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Protocol

COVID-19 Modifications for Remote Teleassessment and Teletraining of a Complementary Alternative Medicine Intervention for People With Multiple Sclerosis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Access to comprehensive exercise and rehabilitation services for people with multiple sclerosis (MS) remains a major challenge, especially in rural, low-income areas. Hence, the Tele-Exercise and Multiple Sclerosis (TEAMS) study aims to provide patient-centered, coordinated care by implementing a 12-week complementary and alternative medicine (CAM) intervention for adults with MS. However, due to the societal impact of coronavirus disease (COVID-19) in mid-March 2020, the University of Alabama at Birmingham announced a limited business model halting all nonessential research requiring on-site visits, which includes the TEAMS study.

Objective: In compliance with the shelter-in-place policy and quarantine guidance, a modified testing and training protocol was developed to allow participants to continue the study.

Methods: The modified protocol, which replaces on-site data collection and training procedures, includes a teleassessment package (computer tablet, blood pressure cuff, hand dynamometer, mini disc cone, measuring tape, an 8” step, and a large-print 8” × 11” paper with ruler metrics and wall-safe tape) and a virtual meeting platform for synchronous interactive training between the therapist and the participant. The teleassessment measures include resting blood pressure and heart rate, grip strength, Five Times Sit to Stand, Timed Up & Go, and the Berg Balance Scale. The teletraining component includes 20 sessions of synchronous training sessions of dual tasking, yoga, and Pilates exercises designed and customized for a range of functional levels. Teletraining lasts 12 weeks and participants are instructed to continue exercising for a posttraining period of 9 months.

Results: The protocol modifications were supported with supplemental funding (from the Patient-Centered Outcomes Research Institute) and approved by the University Institutional Review Board for Human Use. At the time nonessential research visits were halted by the university, there were 759 people enrolled and baseline tested, accounting for 92.5% of our baseline testing completion target (N=820). Specifically, 325 participants completed the 12-week intervention and follow-up testing visits, and 289 participants needed to complete either the intervention or follow-up assessments. A modified analysis plan will include sensitivity analyses to ensure the robustness of the study results in the presence of uncertainty and protocol deviations. Study results are projected to be published in 2021.

Conclusions: This modified remote teleassessment/teletraining protocol will impact a large number of participants with MS who would otherwise have been discontinued from the study.

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KEYWORDS

multiple sclerosis; telerehabilitation; teletraining; physical activity; disability; tele-exercise; telehealth; COVID-19

Introduction

Multiple sclerosis (MS) is an autoimmune-mediated neurological disorder that results in demyelination and transection of axons in the central nervous system, and it affects more than two million people across the world [1,2]. The current literature strongly supports the use of home telerehabilitation or what is commonly referred to as telehealth (to encompass a broader set of uses) as an equally effective alternative to usual care for patients with MS [3-6]. Because exercise has a strong effect in managing health and MS symptoms [7-10], exercise rehabilitation is one of the major applications of telehealth technology. The advantages of telehealth over usual care include increased social support, participant adherence, quality of care, cost-effectiveness, access to services (no need for transportation), and reduced burden on health professionals to allow easier dissemination of services [11]. Since comprehensive exercise and rehabilitation services are not provided on-site across all MS clinics, remote testing and training can make such services more accessible for patients who do not live near center-based programs.

In 2017, our research team began to implement a randomized controlled effectiveness trial comparing two methods of delivering a complementary and alternative medicine (CAM) intervention: CAM delivered at home and on-site at a clinic (the TEAMS [Tele-Exercise and Multiple Sclerosis] study; ClinicalTrials.gov NCT03117881) [12]. The CAM intervention consists of yoga, Pilates, and dual tasking exercises. Participants are randomized into one of two groups: (a) home-based CAM involving the use of a computer tablet with an app to stream 20 prerecorded exercise or rehabilitation video sessions tailored to an individual's functional level [13]; and (b) clinic-based CAM involving 20 supervised exercise training sessions with trained study therapists. The supervised sessions were implemented by 86 therapists at 43 clinics that were spread across three states (Alabama, Mississippi, and Tennessee). The study originally aimed to include 820 people with MS by April 30, 2020.

In response to coronavirus disease (COVID-19), the University of Alabama at Birmingham halted all nonessential research studies that required on-site interaction with research participants. This included the TEAMS study, which had a total of 759 participants enrolled and baseline tested at the time of closure (March 2020); this accounts for 92.5% of our baseline testing target (N=820). Specifically, 325 participants completed the study, and 289 participants were in the process of completing the study (ie, they needed to either complete the intervention or their follow-up data collection visits at 3-, 6-, and 12-months postintervention). Breaking this sample down further, there were 545 remaining data collection (on-site) visits that needed to be completed at the time of the COVID-19 closure. With no apparent end date to COVID-19, the research team requested a modification to the protocol from the study program officer. The teleassessment and training protocol modifications were approved and supported with supplemental funding provided by the funding agency (Patient-Centered Outcomes Research Institute [PCORI]) on March 27, 2020, and the protocol was approved by the University Institutional Review Board for Human Use on March 29, 2020. This paper describes the COVID-19 protocol modifications.

Methods

The TEAMS study is a randomized controlled trial comparing the effectiveness of a 12-week tele-exercise program delivered at home via a computer tablet (TeleCAM) or at the clinic by a therapist (DirectCAM). Further details of the TEAMS study can be found elsewhere [12].

Recruitment

A total of 289 participants are in the process of completing the TEAMS study and will be reconsented to undergo the COVID-19 modified study procedures. Inclusion and exclusion criteria remain the same as the original study (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patient Determined Disease Steps score: 0-7 (mild-to-moderate disability)
- Able to use arms and/or legs for exercise while standing or seated
- Aged 18-70 years
- Physician permission for study participation

Exclusion criteria

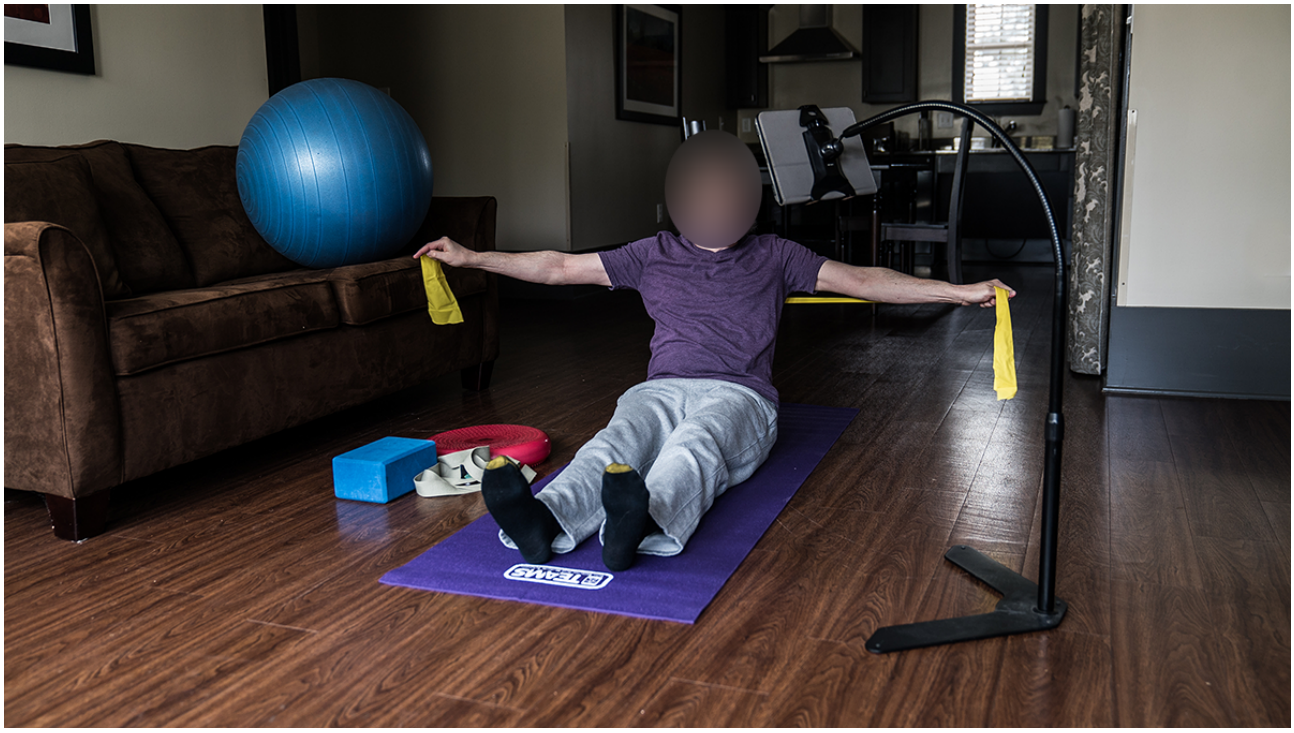
- Significant visual acuity that prevents seeing a tablet screen in order to follow along with the home exercise program (self-reported)
- Event(s) of cardiovascular disease, severe pulmonary disease, or renal failure within the last 6 months
- Active pressure ulcer
- Pregnancy
- Received a rehabilitation session within the last 30 days
- Godin Leisure-Time Exercise Questionnaire score ≥24 (ie, physically active)

The Intervention and COVID-19 Modifications

The 12-week DirectCAM intervention is composed of dual tasking, yoga, and Pilates. Participants in DirectCAM receive in-person instruction from a therapist 2 times a week for the first 8 weeks and then once a week for the last 4 weeks for a total of 20 sessions (1 hr/session). TeleCAM participants receive the same 12-week intervention through exercise videos that are preloaded to a custom-designed tablet app [13]. Figure 1 demonstrates a person with MS performing the intervention using the provided equipment and computer tablet. They also receive phone calls through an Interactive Voice Response system to collect data and enhance adherence to the intervention. After the 12-week intervention, DirectCAM participants receive written instructions and photos of the exercises and are encouraged to continue the program at home for 9-months postintervention. TeleCAM participants are encouraged to continue to exercise using the videos on their tablet 9-months postintervention. Currently, there is a total of 545 participants for whom data collection needs to be completed: 88 participants that need to complete follow-up data collection at 3 months postintervention; 168 at 6 months; and 289 at 12 months. There are 25 participants who were randomized to receive DirectCAM but were unable to because of COVID-19 restrictions.

In response to COVID-19, PCORI provided the study team with supplemental funding, which was used to adapt the on-site intervention into remote testing and training with a licensed occupational or physical therapist. DirectCAM participants are now receiving their remaining intervention sessions with a study therapist through videoconferencing. These participants are categorized into a separate group referred to as remote DirectCAM (rDirectCAM). rDirectCAM participants who decline or are unable to videoconference (eg, no compatible computer or internet access at home) have the option of communicating with their therapist via telephone. Thus, this study includes two methods of teletraining: (1) internet-supervised training (rDirectCAM) and (2) self-regulated training using preloaded videos on a computer tablet (TeleCAM).

Figure 1. An example of a person with multiple sclerosis exercising in their home with the intervention equipment and computer tablet.



Teleassessments

A total of 16 therapists will conduct all assessments through videoconferencing (teleassessments). To ensure strong fidelity across therapists, they will undergo a 30-minute training session directed by the clinical study coordinator (author TT). TT is a licensed occupational therapist with 24 years of training and has been involved with the TEAMS study since its inception. TT will also train and monitor therapists to deliver rDirectCAM through videoconferencing.

A Brief Description of Assessment Measures and Protocols

Participants Who Decline or Are Unable to Participate in Teleassessments

Participants who decline or are unable to participate in the teleassessments will be sent the study questionnaires either through mail or email via the study database (Research Electronic Data CAPture [REDCap]), based on their preference. Questionnaires include the 36-Item Short Form Survey (SF-36), the Modified Fatigue Impact Scale, and the Godin Leisure Time Exercise Questionnaire (for more details refer to our original study protocol [12]).

Protocol for Teleassessment Participants

The goal of the teleassessment protocol is to mirror the on-site assessment protocol [12]. The measures have strong psychometric properties to support their use in people with MS. The measures that participants undergo depend on their Patient Determined Disease Steps (PDDS) score. Participants with a PDDS score between 0-4 (indicative of minimal mobility disability) will complete all measures: the Hand-Grip Strength Test [14], the Five Times Sit to Stand test [15], the Timed Up & Go Test [16-18], and the Berg Balance Scale [19,20]. Participants with a PDDS score between 5-7 complete all measures except the Timed Up & Go Test and Berg Balance Scale (due to safety concerns as noted previously during on-site clinic visits). The teleassessment measures are listed below, and specific details and procedures can be found in the supplemental data collection form and therapist guide (Multimedia Appendices 1 and 2, respectively):

- Height and weight (self-report)
- Changes in medication (self-report)
- Blood pressure/heart rate
  - Equipment: a chair with an arm, a heart rate monitor, and a blood pressure cuff
  - Setup:
    - Camera view: frontal view of the participant's upper body
    - The participant sits quietly for at least 5 minutes prior to assessment
- Hand-grip strength
  - Equipment: a chair with an arm and a digital hand dynamometer
  - Setup:
    - Camera view: frontal view of the participant's upper body
    - The participant sits in a stationary chair or a wheelchair and uses a hand dynamometer; three trials with each hand with the elbow flexed at 90 degrees, with 30-second rest in between trials
- Five Times Sit to Stand (Figure 2)
  - Equipment: a chair (a chair with arms can enhance safety but discourage the participant from using, if unnecessary)
  - Setup:

- Camera view: side view of the participant's entire body (at least shoulders, hip, and knees)
- The participant sits in a chair or a wheelchair
- Three options for where to place the chair:
  - An open space, not supported by a mat or wall
  - An open space, support from a caregiver or family member, if necessary
  - Supported against a wall (if chair movement is an issue)

- Timed Up & Go (Figure 3)
  - Conducted only for people with PDDS Score between 0-4, determined via self-report during prescreening.
  - Equipment: a chair with arms, a mini disc cone, and a 3-meter soft measuring tape
  - Setup:
    - Camera view: diagonal or frontal view to capture the participant's entire body throughout the test (camera view should include the 3-meter walkway and the chair)
    - The participant can place the computer tablet on the floor or on furniture for better view
    - The participant places a chair at the beginning of a 12-foot cleared space, free from obstacles or throw rugs
    - The participant lays down the measuring tape starting at the tip of their toes when sitting in a chair and places the cone at the end of the measuring tape
    - The participant removes the measuring tape
    - Chair setup options:
      - An open space, not supported by a mat or wall
      - An open space, support from a caregiver/or family member, if needed
      - Supported against a wall

- Berg Balance Scale (note: the research team anticipated that the Berg Balance Scale would be the most difficult test to administer via telehealth. Thus, the team incorporated elements from a previous study demonstrating that the Berg could be conducted reliably through teleassessment [21])
  - Conducted only for people with PDDS Score between 0-4, determined via self-report during prescreening.
  - Equipment: two chairs (one with arms and one without), an 8" therapy step, a printed paper with ruler metrics and wall safe tape, and a mini disc cone
  - Setup:
    - Camera view includes the frontal view of the participant's entire body for all tasks
    - Three options for where to place the chair:
      - An open space, not supported by a mat or wall
      - An open space, support from a caregiver/or family member, if possible
      - Supported against a wall

  - Test instructions and modifications:
    - All tasks completed in frontal view
    - After completing all tasks once, repeat the unsupported standing and standing with eyes closed task with a side view (in order to reduce the likelihood of missing data) [21]
    - Perform the functional reach task with a custom print paper with large-numbered metrics and markings to indicate critical scoring criteria for the therapist (Figure 4).

Figure 2. An example of the videoconference view of the starting position for the Five Times Sit to Stand test.

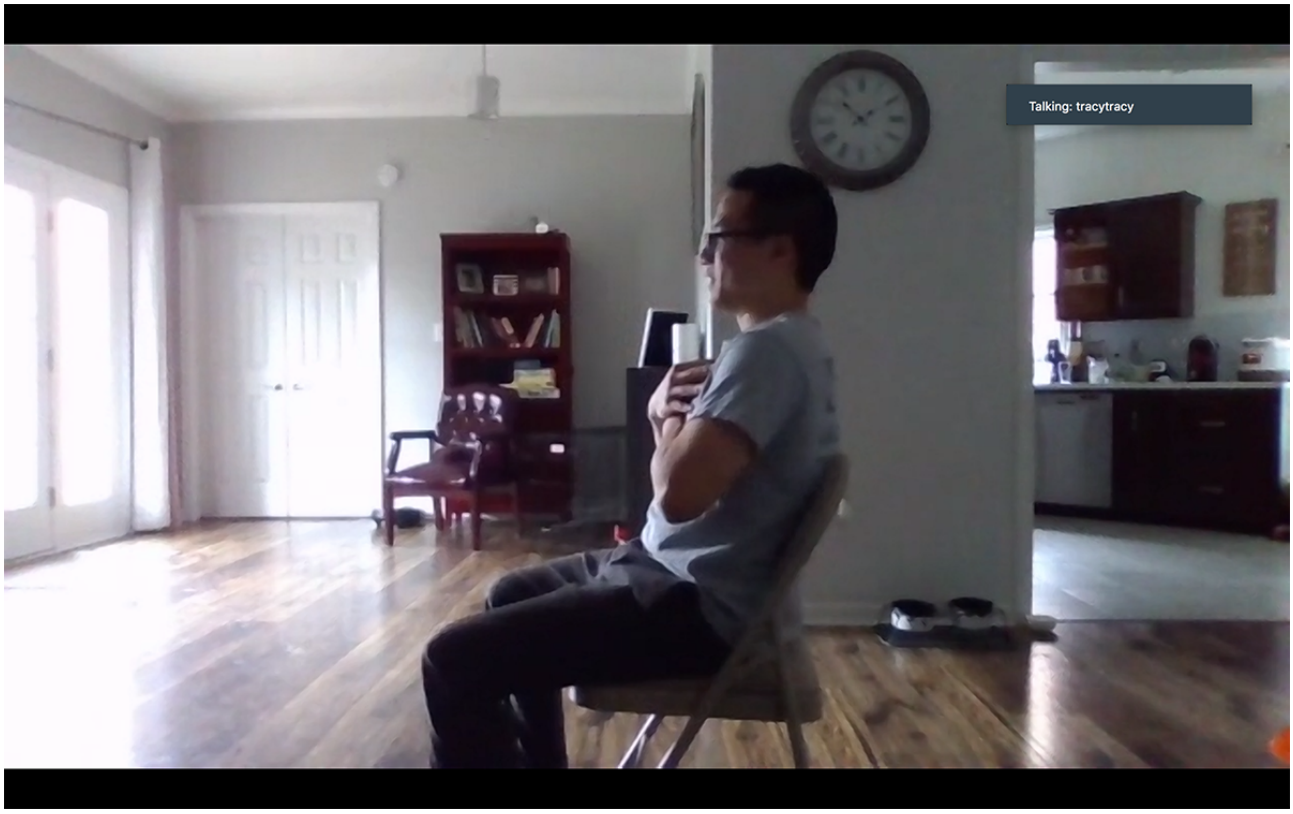


Figure 3. An example of the videoconference view for the Timed Up & Go test.

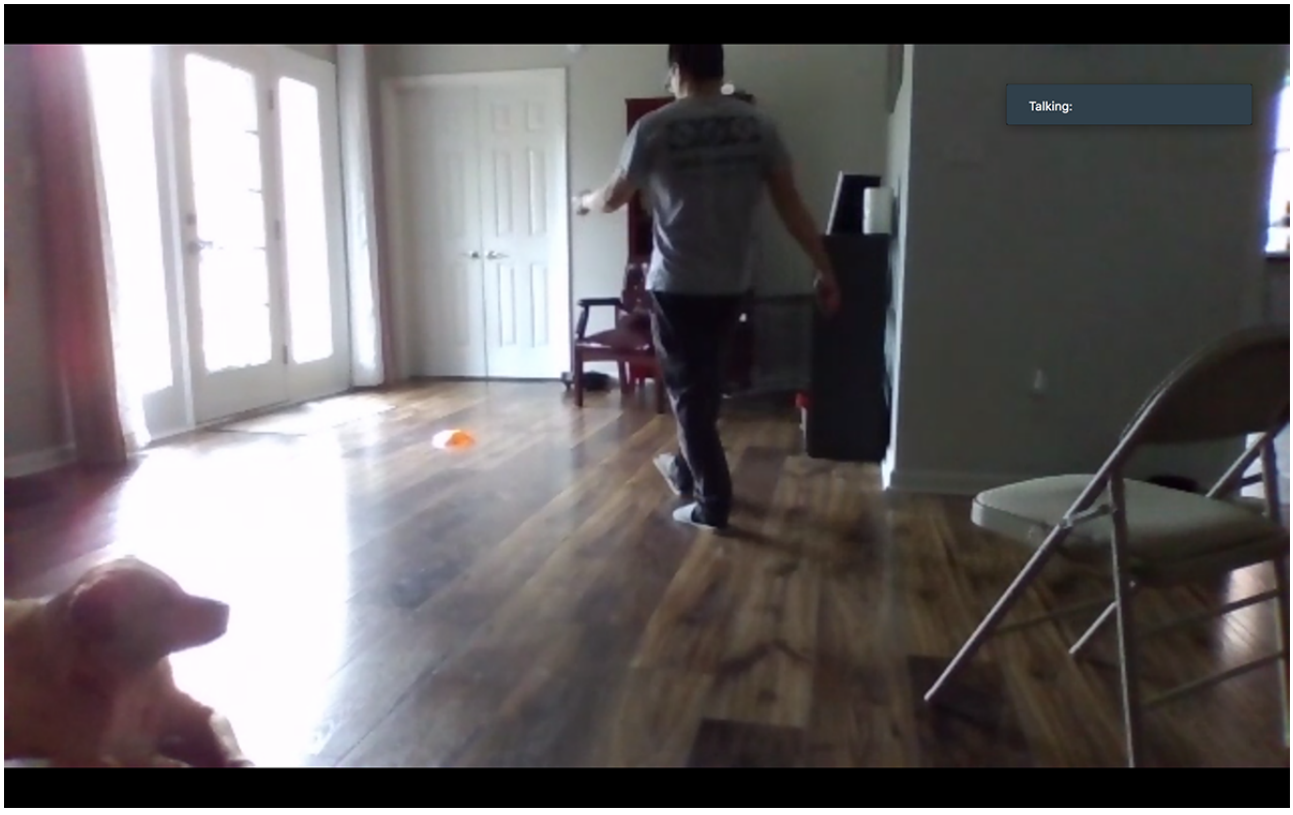
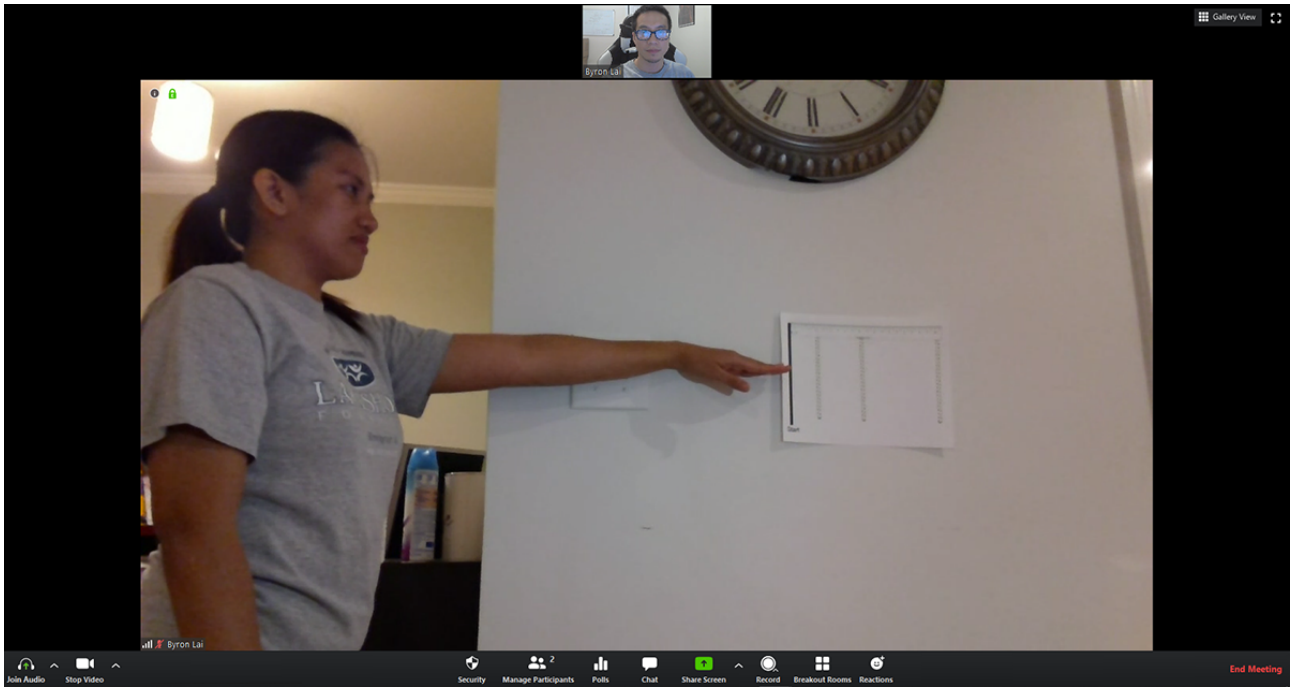


Figure 4. An example of the videoconference view for the starting position of the functional reach task of the Berg Balance Scale.



Teleassessment Equipment

After participants have reconsented, they will be asked whether they would like to participate in the teleassessments. Research personnel will ship interested participants a single package (minimum package dimensions 18.5” × 12.1” × 8.75”) containing the following teleassessment equipment (Figure 5):

- A roll of wall-safe tape;
- Computer tablet (Lenovo S340 81TB0000US);
- Heart rate and blood pressure cuff (A&D Medical Wrist Blood Pressure Monitor, UB-543);
- CAMRY Hand Grip Dynamometer;
- American Challenge Soccer Mini Disc Cones (required to complete the Timed Up & Go test and used for the pick-up task of the Berg Balance Scale);
- Soft measuring tape, precut to a 3-meter length for the Timed Up & Go test;
- An 8” small foldable step stool (required to complete the Berg Balance Scale);
- A large-print 8” × 11” paper with ruler metrics.

Figure 5. A teleassessment package prior to being shipped to a participant's home. The equipment includes an 8" step, a blood pressure cuff, a roll of wall-safe tape, a 3-meter measuring tape, a hand dynamometer, a mini disc cone, a large print paper with ruler metrics, a sheet with participant instructions (under the step), and a computer laptop (bottom).

General Teleassessment Procedures

Teleassessments will be conducted at baseline and at 3, 6, and 12 months postintervention. Given the size of the project and the strong psychometric properties of the teleassessments, the research team was primarily concerned with whether the teleassessments could be delivered reliably across different therapists. Accordingly, the first 8 participants who will receive the teleassessments will participate in a preliminary interrater reliability study. These 8 participants will complete 2 teleassessment sessions (done in the same day). Each teleassessment session will be conducted by one of two therapists. A sample size of 8 was chosen based on an intraclass correlation (ICC) power calculation with the following components: statistical power of 0.8; α=0.05; two raters; minimum acceptable reliability (H0)=0.75, expected reliability (H1)=0.97. The value for expected reliability was based on a systematic review paper of interrater reliability of the Berg Balance Scale in a clinical population [22]. We anticipated that the Berg Balance Scale would be the most difficult test to conduct via teleassessment.

Therapists will schedule the teleassessments with study participants and send them a Zoom meeting link that can be accessed via the provided tablet. During the meeting, therapists will have access to two documents to help guide them through the teleassessments: (1) a manual for quick visual reminders, and (2) a step-by-step data collection form to be completed during the meeting (Multimedia Appendix 2). Therapist interactions with the participant will be guided by the Supportive Accountability Theory [23]. Specifically, therapists will aim to develop a social relationship/bond and present a social presence that provides a sense of accountability to enhance participants' motivation and adherence to the teleassessment protocol. The procedures for the teleassessments are listed in Textbox 2.

Textbox 2. General teleassessment procedures.

1. Open data collection form in the box
2. Start videoconference meeting with the participant
3. Build social bond with the participant (introductions and establish rapport)
4. Brief the participant on what the teleassessment will entail and duration (max 2 hours)
5. Ask the participant if their medication has changed and document additions
6. Ask the participant if they have all the necessary equipment and sufficient space
7. Assess the room for safety hazards or obstacles
8. Ensure the participant has adequate privacy
9. Inform the participant to be careful during teleassessments
10. Complete anthropometrics and functional assessments using the data collection form
11. Remind the participant to complete the questionnaires that were sent to them
12. Inform the participant that research personnel will send them a gift card
13. Schedule the next teleassessment follow-up (if applicable)
14. End the videoconference meeting
15. Upload the data collection forms to Box and notify research personnel that testing is complete and to send a gift card

Statistical Analysis

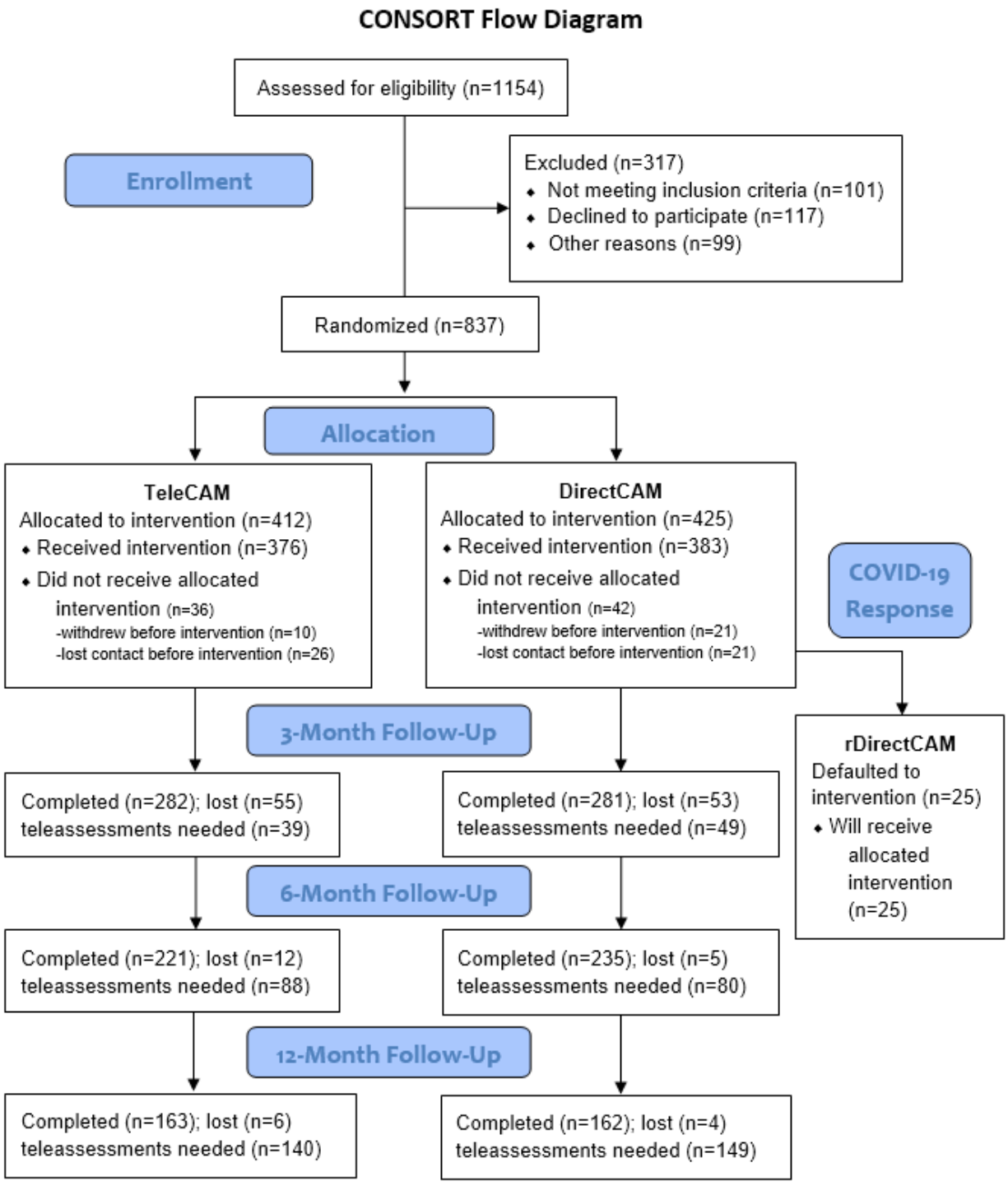
All statistical analyses for the TEAMS study intervention will be conducted in an intent-to-treat manner at the individual level considering the multilevel and repeated nature of the data (participants nested within clinics with 4 time points for every participant). We will conduct analyses with an additional time-varying covariate to account for protocol deviations (rDirectCAM and participants who received teleassessments). Contrasts and estimate statements will be used to draw inferences pooling estimates from the original intervention types (DirectCAM versus TeleCAM). We will conduct sensitivity analyses with and without the rDirectCAM participants. Given that the rDirectCAM group was created unexpectedly in response to COVID-19, this group may not be adequately powered to detect changes in outcomes.

Regarding the teleassessment interrater reliability examination, ICC values of 0.5-0.75 will be interpreted as moderate reliability; 0.75-0.9 good reliability; and 0.9 excellent reliability [24]. We will also collect feasibility data related to participant uptake and implementation processes throughout the remainder of the TEAMS study and publish this in a future paper. These data will include the (1) number of participants who volunteer for the teleassessments; (2) number of participants who complete the follow-up teleassessments at months 3, 6, and 12 postintervention; (3) number of teleassessment tasks completed; (4) total time in minutes required to complete the teleassessments; and (5) adverse events.

Results

Recruitment commenced on March 16, 2020, using a multipronged recruitment strategy. Participants were recruited via study brochures or word of mouth from MS clinics and specialists, a large three-state (Alabama, Mississippi, and Tennessee) community organization network, and through the networks of a diverse MS stakeholder team that was engaged in the project [12]. Recruitment is now complete and there are 837 individuals with MS randomized into the study. Data collection is ongoing. Details on data collected for participant characteristics (eg, type of MS, disability severity, and functional mobility) and outcomes are reported elsewhere [12]. The modified CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 6) displays consented, enrolled, and completed participants, as well as the number of teleassessments required to complete the study.

Figure 6. Modified CONSORT (Consolidated Standards of Reporting Trials) diagram reporting the number of teleassessments that need to be completed and participants who need to undergo rDirectCAM. COVID-19: coronavirus disease.



Discussion

This paper describes a modified teleassessment and teletraining protocol for the TEAMS intervention due to COVID-19 restrictions on on-site visits. To the best of our knowledge, this study will also include the largest number of teleassessments ever conducted in a telerehabilitation/exercise trial for people with MS.

The study findings will be of great relevance to health professionals who aim to conduct similar remote, synchronous telerehabilitation/tele-exercise trials for people with MS and other disability groups. While the research team matched as closely as possible the standardized on-site assessment procedures with the remote teleassessment protocol, the psychometric properties (ie, validity and reliability) of the specific teleassessment procedures have not yet been tested. We aim to establish the psychometric properties of these tests

once COVID-19 restrictions are lifted. General feasibility data will be recorded for all participants who undergo the teleassessments (eg, participants volunteering for the teleassessments, percentage of tasks completed/not completed, and time to implement the tests). These findings will be used to support evidence-based policy decisions regarding telerehabilitation implementation, development, and programming.

Acknowledgments

BL, C-YC, EP, and TT created the initial manuscript draft. BL and TT developed the teleassessment protocol. EP, TT, H-JY, TM, and JR designed the study procedures related to the teleassessments. All authors contributed equally to later manuscript drafts.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Teleassessment data collection form.
[DOCX File , 195 KB - resprot_v9i7e18415_app1.docx]

Multimedia Appendix 2
Therapist instruction guide.
[DOCX File , 2400 KB - resprot_v9i7e18415_app2.docx]

References

1. Wallin M, Culpepper W, Nichols E, Bhutta Z, Gebrehiwot T, Hay S, et al. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology 2019 Mar;18(3):269-285. [doi: 10.1016/S1474-4422(18)30443-5] [Medline: 6372756]
2. Trapp BD, Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? Annu Rev Neurosci 2008 Dec;31(6):247-269 [FREE Full text] [doi: 10.1146/annurev.neuro.30.051606.094313] [Medline: 18558855]
3. Amatya B, Galea MP, Kesselring J, Khan F. Effectiveness of telerehabilitation interventions in persons with multiple sclerosis: A systematic review. Mult Scler Relat Disord 2015 Jul;4(4):358-369. [doi: 10.1016/j.msard.2015.06.011] [Medline: 26195057]
4. Rintala A, Hakala S, Paltamaa J, Heinonen A, Karvanen J, Sjögren T. Effectiveness of technology-based distance physical rehabilitation interventions on physical activity and walking in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. Disabil Rehabil 2018 Feb 15;40(4):373-387. [doi: 10.1080/09638288.2016.1260649] [Medline: 27973919]
5. Robb JF, Hyland MH, Goodman AD. Comparison of telemedicine versus in-person visits for persons with multiple sclerosis: A randomized crossover study of feasibility, cost, and satisfaction. Mult Scler Relat Disord 2019 Nov;36:101258. [doi: 10.1016/j.msard.2019.05.001] [Medline: 31472419]
6. Bove R, Garcha P, Bevan CJ, Crabtree-Hartman E, Green AJ, Gelfand JM. Clinic to in-home telemedicine reduces barriers to care for patients with MS or other neuroimmunologic conditions. Neurol Neuroimmunol Neuroinflamm 2018 Nov;5(6):e505 [FREE Full text] [doi: 10.1212/NXI.0000000000000505] [Medline: 30775409]
7. Razazian N, Kazeminia M, Moayedi H, Daneshkhah A, Shohaimi S, Mohammadi M, et al. The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. BMC Neurol 2020 Mar 13;20(1):93 [FREE Full text] [doi: 10.1186/s12883-020-01654-y] [Medline: 32169035]
8. Motl RW, Gosney JL. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult Scler 2008 Jan;14(1):129-135. [doi: 10.1177/1352458507080464] [Medline: 17881388]
9. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. J Psychosom Res 2014 Jun;76(6):465-471. [doi: 10.1016/j.jpsychores.2014.03.014] [Medline: 24840141]
10. Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of Exercise Training on Fitness in Multiple Sclerosis: A Meta-Analysis. Arch Phys Med Rehabil 2016 Sep;97(9):1564-1572. [doi: 10.1016/j.apmr.2016.01.023] [Medline: 26896750]

11. Jennett PA, Affleck Hall L, Hailey D, Ohinmaa A, Anderson C, Thomas R, et al. The socio-economic impact of telehealth: a systematic review. J Telemed Telecare 2003 Oct 13;9(6):311-320. [doi: 10.1258/135763303771005207] [Medline: 14680514]
12. Rimmer JH, Thirumalai M, Young HJ, Pekmezi D, Tracy T, Riser E, et al. Rationale and design of the tele-exercise and multiple sclerosis (TEAMS) study: A comparative effectiveness trial between a clinic- and home-based telerehabilitation intervention for adults with multiple sclerosis (MS) living in the deep south. Contemp Clin Trials 2018 Aug;71(6):186-193 [FREE Full text] [doi: 10.1016/j.cct.2018.05.016] [Medline: 29859267]
13. Thirumalai M, Rimmer JH, Johnson G, Wilroy J, Young H, Mehta T, et al. TEAMS (Tele-Exercise and Multiple Sclerosis), a Tailored Telerehabilitation mHealth App: Participant-Centered Development and Usability Study. JMIR Mhealth Uhealth 2018 May 24;6(5):e10181 [FREE Full text] [doi: 10.2196/10181] [Medline: 29798832]
14. Guclu-Gunduz A, Citaker S, Nazliel B, Irkec C. Upper extremity function and its relation with hand sensation and upper extremity strength in patients with multiple sclerosis. NRE 2012 Jun 01;30(4):369-374. [doi: 10.3233/nre-2012-0768]
15. Fry DK, Pfalzer LA. Reliability of Four Functional Tests and Rating of Perceived Exertion in Persons with Multiple Sclerosis. Physiotherapy Canada 2006 Jul;58(3):212-220. [doi: 10.3138/ptc.58.3.212]
16. Kalron A, Dolev M, Givon U. Further construct validity of the Timed Up-and-Go Test as a measure of ambulation in multiple sclerosis patients. Eur J Phys Rehabil Med 2017 Dec;53(6):841-847 [FREE Full text] [doi: 10.23736/S1973-9087.17.04599-3] [Medline: 28290192]
17. Sebastião E, Sandroff BM, Learmonth YC, Motl RW. Validity of the Timed Up and Go Test as a Measure of Functional Mobility in Persons With Multiple Sclerosis. Arch Phys Med Rehabil 2016 Jul;97(7):1072-1077. [doi: 10.1016/j.apmr.2015.12.031] [Medline: 26944709]
18. Learmonth YC, Paul L, McFadyen AK, Mattison P, Miller L. Reliability and clinical significance of mobility and balance assessments in multiple sclerosis. International Journal of Rehabilitation Research 2012;35(1):69-74. [doi: 10.1097/mrr.0b013e328350b65f]
19. Cattaneo D, Regola A, Meotti M. Validity of six balance disorders scales in persons with multiple sclerosis. Disabil Rehabil 2006 Jun 30;28(12):789-795. [doi: 10.1080/09638280500404289] [Medline: 16754576]
20. Cattaneo D, Jonsdottir J, Repetti S. Reliability of four scales on balance disorders in persons with multiple sclerosis. Disabil Rehabil 2007 Dec 30;29(24):1920-1925. [doi: 10.1080/09638280701191859] [Medline: 17852286]
21. Venkataraman K, Morgan M, Amis KA, Landerman LR, Koh GC, Caves K, et al. Tele-Assessment of the Berg Balance Scale: Effects of Transmission Characteristics. Arch Phys Med Rehabil 2017 Apr;98(4):659-664.e1 [FREE Full text] [doi: 10.1016/j.apmr.2016.10.019] [Medline: 27894732]
22. Downs S, Marquez J, Chiarelli P. The Berg Balance Scale has high intra- and inter-rater reliability but absolute reliability varies across the scale: a systematic review. Journal of Physiotherapy 2013 Jun;59(2):93-99 [FREE Full text] [doi: 10.1016/S1836-9553(13)70161-9] [Medline: 23663794]
23. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res 2011 Mar 10;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]
24. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of Chiropractic Medicine 2016 Jun;15(2):155-163 [FREE Full text] [doi: 10.1016/j.jcm.2016.02.012] [Medline: 27330520]

Abbreviations

CAM: complementary alternative medicine
CONSORT: Consolidated Standards of Reporting Trials
COVID-19: coronavirus disease
ICC: intraclass correlation
MS: multiple sclerosis
PCORI: Patient-Centered Outcomes Research Institute
PDDS: Patient Determined Disease Steps
RCT: randomized controlled trial
REDCap: Research Electronic Data CAPture
SF-36: 36-Item Short Form Survey
TEAMS: Tele-Exercise And Multiple Sclerosis

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Protocol

Preventing Cardiovascular Disease Among Urban African Americans With a Mobile Health App (the MOYO App): Protocol for a Usability Study

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Abstract

Background: Cardiovascular disease (CVD) disparities are a particularly devastating manifestation of health inequity. Despite advancements in prevention and treatment, CVD is still the leading cause of death in the United States. Additionally, research indicates that African American (AA) and other ethnic-minority populations are affected by CVD at earlier ages than white Americans. Given that AAs are the fastest-growing population of smartphone owners and users, mobile health (mHealth) technologies offer the unparalleled potential to prevent or improve self-management of chronic disease among this population.

Objective: To address the unmet need for culturally tailored primordial prevention CVD–focused mHealth interventions, the MOYO app was cocreated with the involvement of young people from this priority community. The overall project aims to develop and evaluate the effectiveness of a novel smartphone app designed to reduce CVD risk factors among urban-AAs, 18-29 years of age.

Methods: The theoretical underpinning will combine the principles of community-based participatory research and the agile software development framework. The primary outcome goals of the study will be to determine the usability, acceptability, and functionality of the MOYO app, and to build a cloud-based data collection infrastructure suitable for digital epidemiology in a disparity population. Changes in health-related parameters over a 24-week period as determined by both passive (eg, physical activity levels, sleep duration, social networking) and active (eg, use of mood measures, surveys, uploading pictures of meals and blood pressure readings) measures will be the secondary outcome. Participants will be recruited from a majority AA “large city” school district, 2 historically black colleges or universities, and 1 urban undergraduate college. Following baseline screening for inclusion (administered in person), participants will receive the beta version of the MOYO app. Participants will be monitored during a 24-week pilot period. Analyses of varying data including social network dynamics, standard metrics of activity, percentage of time away from a given radius of home, circadian rhythm metrics, and proxies for sleep will be performed. Together with external variables (eg, weather, pollution, and socioeconomic indicators such as food access), these metrics will be used to train machine-learning frameworks to regress them on the self-reported quality of life indicators.

Results: This 5-year study (2015-2020) is currently in the implementation phase. We believe that MOYO can build upon findings of classical epidemiology and longitudinal studies like the Jackson Heart Study by adding greater granularity to our knowledge of the exposures and behaviors that affect health and disease, and creating a channel for outreach capable of launching interventions, clinical trials, and enhancements of health literacy.

Conclusions: The results of this pilot will provide valuable information about community cocreation of mHealth programs, efficacious design features, and essential infrastructure for digital epidemiology among young AA adults.

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KEYWORDS

African Americans; mHealth; community-based participatory research; agile design; cardiovascular

Introduction

Background

Health inequity is a vast and complex problem, which defies simplistic solutions. Cardiovascular disease (CVD) disparities are a particularly devastating manifestation of health inequity. Despite advancements in prevention and treatment, CVD is still the leading cause of death in the United States [1]. It has a disproportionately worse impact on African Americans, with approximately 65,000 more deaths annually than projections based on age and gender alone would predict [2]. Additionally, research indicates that African American and other US minority populations are affected by CVD earlier than white American adults [3,4]. Many factors contribute to this disparity, including prevalence of CVD risk factors, psychosocial and economic determinants of health (including education, wealth or income, literacy, numeracy neighborhood environment, and others), and insufficient access to quality health and social services [5].

Longitudinal observational studies such as the Framingham Heart Study and the Jackson Heart Study (JHS) have been instrumental in identifying CVD risk factors and tracking outcomes [6]. The JHS in particular has pioneered innovative participant engagement approaches to assess CVD risk factors [7]. This study has focused comprehensively on a marginalized group suffering from health disparities, yielding enhanced understanding of risk and increased precision of risk stratification [8]. The JHS has further emphasized community input and community activism for health and research. The JHS has demonstrated that deep involvement of the target community in building a research initiative can facilitate long-term commitment and retention. A particularly novel and highly successful aspect of the JHS is its training programs [9]. African American high school, college, and graduate students are engaged in subject matter and practicums in epidemiology, bioethics, statistics, and other disciplines essential to the work of the JHS. Graduates of these programs have emerged as a new African American cohort of epidemiologists, physicians, bioethicists, lawyers, and other professionals. They benefited from the affiliation with the JHS and are positioned to impact health disparities across generations.

The lessons of the JHS, learned in the final decade of the 20th century, are timeless and potentially adaptable and scalable in light of rapidly advancing technological developments, which have birthed an age of "digital epidemiology." Given that mobile phone ownership is near ubiquitous among Americans [10,11], mobile health (mHealth) technologies offer unparalleled potential to prevent or improve self-management of chronic disease. Co-design with the community, an echo of the JHS approach, may hold potential for enhanced cultural congruence, acceptability, and trust of this 21st century approach to population research in marginalized communities. The successful community-driven JHS model suggests an important emergent opportunity to leverage advancements in mobile technology to better identify environmental and behavioral risks as well as design and launch interventions that may be efficacious in reducing risk and improving outcomes. As with the JHS Scholars Program, intentional involvement of young people in the cocreation of this initiative (termed "MOYO," after the Kiswahili word for heart) will not only introduce them to the potential of connected technology in health but serve to demystify and motivate many of them toward science, technology, economics, and mathematics careers.

Objectives

MOYO will develop an mHealth approach to eliminating health disparities by (1) co-designing the MOYO app using community-based participatory and agile design methods; (2) integrating electronic health record data generated by traditional methods with data collected "in the wild" (eg, wearables, mobile phone use, local weather, pollution, and geographic location); (3) creating a cloud-based system to allow users to view and track their integrated data over time and improve health care outcomes; and (4) providing educational and community outreach to empower participants to cocreate apps for deployment within the digital ecosystem.

Methods

Design

The MOYO study design will be a longitudinal cohort pilot study.

Theoretical Framework

The theoretical underpinnings of this project combine the health belief model (HBM) and social cognitive theory of mass communication (SCT MC). The HBM and the SCT MC will be used to develop the formative evaluation measures. In addition, the community-based participatory research (CBPR) and the agile software development approaches will be combined to define the user experience and to design the user interface. Multimedia Appendix 1 summarizes the similarities and differences among the principles of these complementary paradigms. These principles provide a framework and guidelines that inform the methodology, development, and design of the MOYO app and the formation of the MOYO app (adapted from the Agile Alliance's Manifesto [12-14]).

Health Belief Model

The HBM will be used to allow for a systematic exploration to understand the target population's attitudes and beliefs toward the capacity of mobile apps to facilitate behavior change, identify the features of health-focused apps that are the most and least desirable, and define the health-focused app elements that encourage long-term app use. The five relevant constructs of the HBM that will be used are perceived benefits, perceived barriers, perceived threats, self-efficacy, and cues to action. Adhering to CBPR methodology, the Morehouse School of Medicine, the Prevention Research Center, and the Community Coalition Board will work with the MOYO team to develop validated, culturally tailored focus group questions.

Social Cognitive Theory of Mass Communication

The SCT MC approaches will augment the use of CBPR and agile design approaches to gain a comprehensive understanding of the design features desired by the target population. The SCT MC, which is based on the original four constructs of the social cognitive theories (ie, self-efficacy, use of incentive motivation, social environment, and reciprocal determinism) will provide a framework for the analysis of psychological mechanisms through which media and communication influences human behavior [15].

Community-Based Participatory Research

CBPR is a research approach that emphasizes community-academic partnership and shared leadership in the planning, implementation, evaluation, and dissemination of initiatives [14]. Persons representing our target population will be invited to join the MOYO Project Advisory Board (MPAB). The function of the project advisory board will be to involve community members in all phases of the research process. The MOYO-community partnership will implement the nine principles of CBPR to answer our research questions related to community relevance while addressing community-identified social, structural, physical environmental, and policy priorities. To achieve this measure, the study team will have members of the MPAB define the opportunities and threats to community adoption of the MOYO app. Further, we will use the agile software development framework to address the opportunities and threats presented by the MPAB.

Agile Software Development Framework

Consistent with CBPR principles, we did not make a priori assumptions about community needs or preferences in a health-focused app. Therefore, the conventional Waterfall method, typically employed in app design, was rejected in favor of an adaptive software development methodology known as *Agile Design*. A series of "sprints" and "scrums" define the process, with sprints representing the individuals in the process working on focused individual components [16]. Weekly, the research and design teams will assemble (in a scrum) to merge code, refine concepts, and produce an intermediate product for testing. This process will be repeated until a stable minimum viable product is produced. Table 1 compares and contrasts the principles of CBPR and the agile software development framework.

Table 1. Key and complementary principles of agile software development and community-based participatory research.

Principles	Community-based participatory research	Agile software development
Promotes collaborative and equitable partnerships in all research phases and involves an empowering and power-sharing process	✓	N/A[a]
Customer (user) satisfaction through early and continuous delivery of useful software	N/A	✓
Recognizes community as a unit of identity	✓	N/A
Builds on strengths and resources within the community	✓	N/A
Welcomes changing requirements, even late in development	N/A	✓
Frequently delivered software (weeks rather than months)	N/A	✓
Facilitates colearning and capacity building among all partners (eg, integrates knowledge and action for mutual benefit of all partners)	✓	✓
Projects are built around motivated individuals who should be trusted to complete the task(s)	N/A	✓
Focuses on problems of relevance to the local community using an ecological approach that attends to multiple determinants of health and disease	✓	N/A
Balances research and action for the mutual benefit of all partners	✓	N/A
Face-to-face conversation is the best form of communication	N/A	✓
Disseminates findings and knowledge gained to the broader community and involves all partners in the dissemination process	✓	N/A
Working software is the primary measure of progress	N/A	✓
Promotes a long-term process and commitment to sustainability	✓	N/A
Sustainable development, able to maintain a constant pace (eg, agile processes promote sustainable development)	N/A	✓
Continuous attention to technical excellence and good design enhances agility	N/A	✓
Simplicity—the art of maximizing the amount of work not done—is essential	N/A	✓
Self-organizing team	N/A	✓
Regular adaptation to changing circumstance	N/A	✓

[a]Not applicable.

Research Population

African Americans 18-29 years of age who frequent our recruitment locations in Atlanta, Georgia will be invited to participate in the MOYO study.

To be enrolled in the study, potential participants must meet all of the following inclusion criteria: (1) be self-identified as black or African American; (2) be between the ages of 18 and 29 years, inclusively; and (3) own an iOS or Android-based smartphone. Potential study participants will be excluded if they are younger than 18 years.

Recruitment and Data Collection Procedure

To recruit persons toward the lower end of our age inclusion criteria, we plan to engage high school seniors enrolled in one Atlanta, Georgia-based school district. The school district is characterized as a "large city" school district serving 79.15% self-identified black or African American students [17], and 74.44% of the students receive free or reduced lunch [18]. Additionally, recruitment will take place at the undergraduate serving institutions in Atlanta, Georgia. Each historically black college or university recruitment location is a 4-year institution, where the average cost of attendance is US $34,130 and average estimated salary after attending is US $41,433 [19-21]. In addition, the state college recruitment site is a 4-year institution, where the annual cost of tuition is approximately US $5346, and the estimated salary after attending is US $28,000 [22]. To engage an "out-of-school" population, participants will be recruited from city of Atlanta job placement and vocational skills training initiatives, which serve Atlanta residents 17-24 years of age.

Furthermore, MOYO will implement community-wide, event-based recruitment strategies. Similar to a *hack-a-thon*, MOYO's events-based recruitment strategy will convene age-eligible participants to engage in health disparity-based problem solving. At each of these "HealthTech Events," the participants will be introduced to the impact of national and local disparities in CVD outcomes among urban-African Americans. They will also engage in the design-thinking process to problem solve through the application of technology and analyze key features of mobile- or internet-based development to design, prototype, and implement systems for human-centered computing. The design-thinking process is a problem-solving framework, which was adopted to emphasize human-centered research, diverse teamwork, and rapid prototyping. [23] This

user-centered design strategy will result in prototypes of the end user's version of an optimally designed and maximally functional MOYO app.

Prospective Data Collection

Prior to entry into the study, participants will be screened for inclusion and exclusion criteria. Once eligibility criteria are met, participants will complete a baseline assessment to be administered via email. The baseline assessment will include questions on demographics (age, gender, self-reported race, education, parents' education, socioeconomic status); personal and family health history; medication history (prescription and over-the-counter medications); other medical problems, particularly diabetes or uncontrolled hypertension; medical or surgical events and illness history; and history of current mania, psychotic disorder, or substance dependence.

Physical Activity

Activity is logged several times a second from the phone's accelerometer to provide information on sleep and changes in physical activity levels. Notably, we do not collect absolute location to preserve privacy.

Mental Health and Well-Being

We will measure the complexity of social network and mood or behavior from phone call logs and text messages. Again, the identity of the sender and recipient, and the content of the conversation or text message is not recorded, only the type of word in a text message as represented in the Linguistic Inquiry and Word Count dictionary [24,25]. Apart from these automatic measures, the user can self-report using standard scales such as the Patient Health Questionnaire-9 [26].

Environment

The app also includes data triggered from the user's location including relative distance travelled from home, weather, pollution levels, local restaurant proximity, and the degree to which the current location is a food desert.

Nutrition

Food choices will be logged via text description or photograph.

Sleep Quality

Sleep quality metrics will be collected from activity and heart rate data using low-cost wearables.

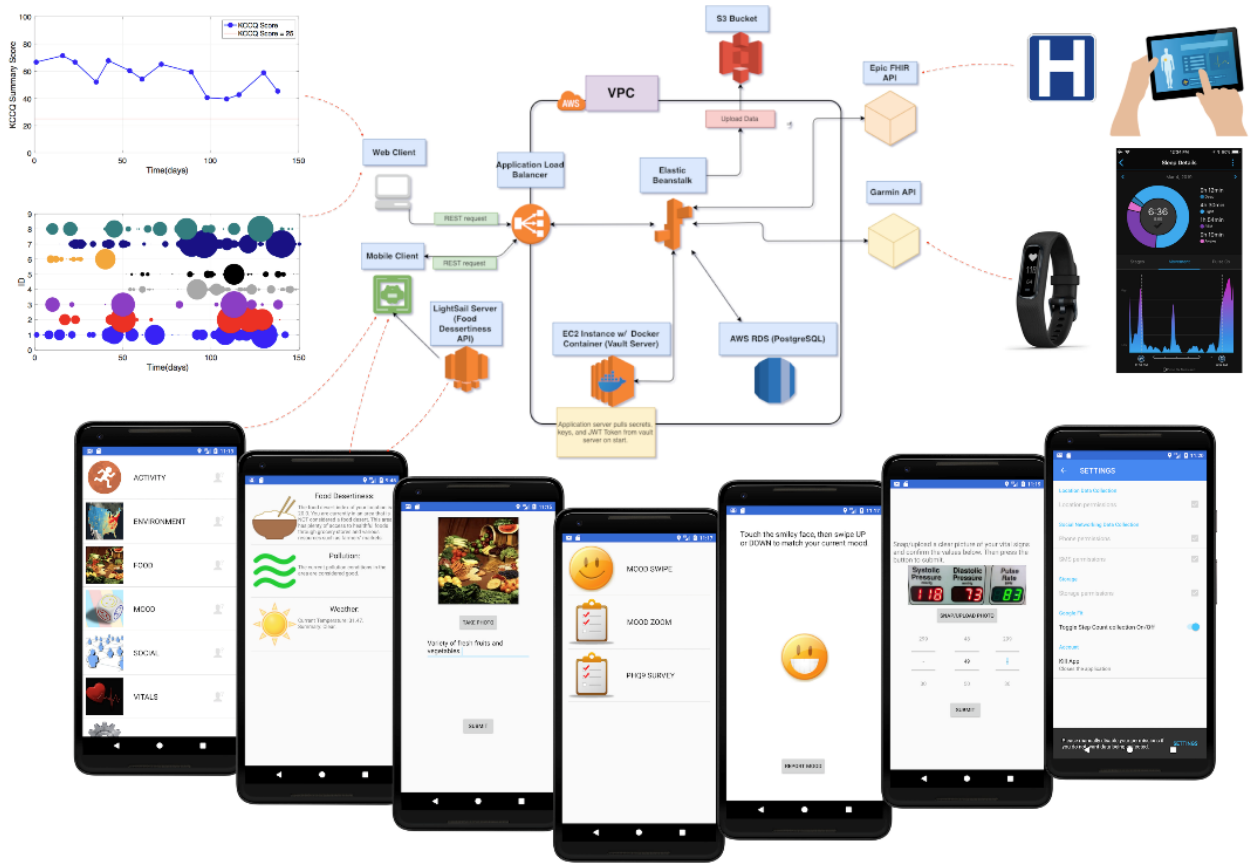
Vital Signs

Blood pressure and heart rate will be collected by typing text or taking a picture of the device such as a health kiosk in a pharmacy. In addition to the app, heart rate and activity can be captured using a wearable.

Electronic Health Records

Finally, electronic medical record data can be captured via the Fast Healthcare Interoperability Resource protocol [27]. All data will be pushed to Amazon Web Services in a deidentified manner, and users can log on to see a basic dashboard of their data. At a later date, we intend to engage the users to learn how to manipulate their data via the cloud to build personalized models and improve the dashboard for individuals. Figure 1 illustrates the MOYO smartphone app framework for data collection and secure storage in the cloud.

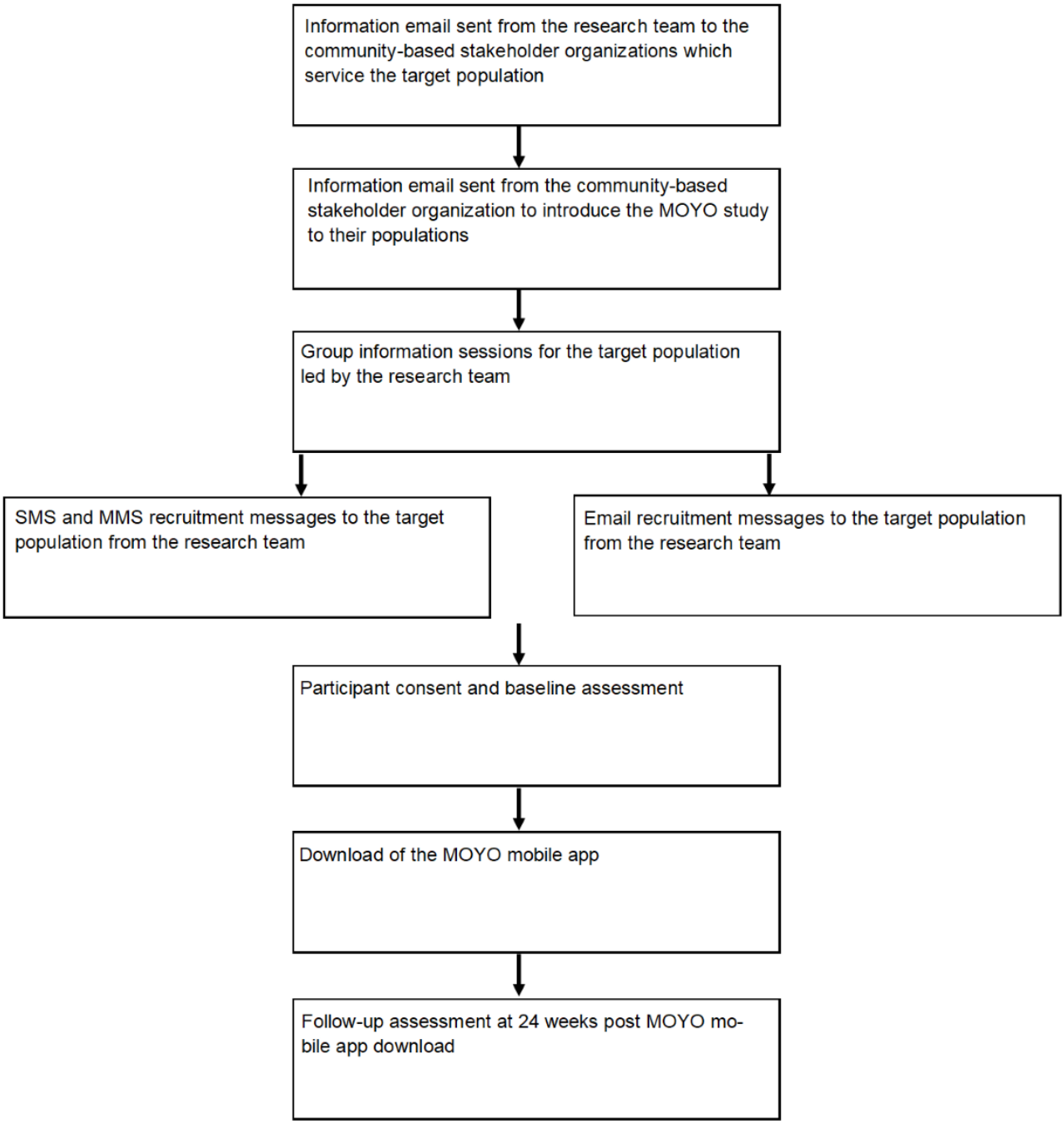
Figure 1. Schematic of app-cloud framework for securely collecting health and activity data. API: application programming interface; AWS: Amazon Web Services; EC2: Amazon Elastic Compute Cloud; FHIR: Fast Healthcare Interoperability Resources; JWT: JSON Web Token; REST: representational state transfer; RDS: Relational Database Service; S3: Amazon Simple Storage Service; SQL: Structured Query Language; VPC: virtual private cloud.



Outcome Measures

The primary outcome measures will assess changes in health-related parameters over a 24-week period as determined by both passive (eg, physical activity levels, sleep duration, social networking) and active (eg, use of mood measures, surveys, uploading of pictures of meals and blood pressure readings) measures. Figure 2 details the participant flow through the MOYO pilot study.

Figure 2. Participant flow and pilot study procedures and assessments. MMS: multimedia messaging service.



Statistical Analysis

Data from social network dynamics will standardized metrics of activity, percentage of time away from a given radius of home, circadian rhythm metrics, and proxies for sleep [28]. Together with environment variables (ie, weather, pollution, and socioeconomic indicators such as food quality access), these metrics will be used to train machine-learning frameworks to regress them on the self-reported quality of life indicators. Because this is the first time this has been done in this type of population, it is impossible to estimate effect size and perform a power calculation. In recent works, we showed that this type of approach is powerful in estimating the self-reported quality of life (using a standard scale) in heart failure and patients with bipolar disorder [28,29]. We intend to perform similar analyses on this current cohort to identify changes in mental and physical health as defined by the validated self-report scales.

Results

This 5-year funded study (2015-2020) is currently in the implementation phase and will run through August 2020. To date, we have enrolled and collected ongoing data from 112 individuals, providing data continuously over a period of up to two years, indicating that there are few barriers to the use of the framework described here. We believe that MOYO can build upon findings of classical epidemiology and longitudinal studies like the JHS by adding greater granularity to our knowledge of the exposures and behaviors that affect health and disease, and creating a channel for outreach capable of launching

interventions, clinical trials, and enhancement of health literacy. The study findings will be communicated through peer-reviewed publications and webinars.

Discussion

We have demonstrated in this phase of our MOYO project that community-based participatory principles can be effectively combined with Agile Design approaches to allow novel mHealth interventions for marginalized communities. This phase of our work is a prologue to the broader deployment and testing of the health app, which aims to better define risk and promote prevention among marginalized groups suffering health inequity.

Health disparities are a persistent, pernicious fact of American life that, in the words of former HHS Secretary Margaret Heckler, are an affront both to our ideals and to the ongoing genius of American medicine [30]. The last 3 decades have seen a growth of literature documenting this problem. Potential solutions to these issues have been far less frequently set forth and realized.

mHealth capabilities and the nearly universal adoption of the cell phone represent a potential "leveling of the (health) playing field." The collection of critical individual, biometric, and environmental data, at a previously unachievable granularity and scale, combined with uniform and broad access to possible intervention are made possible through technology.

Unlike the often inequitable and spotty American system of health care, cell phone use covers a much wider proportion of the population with increasingly smaller differences in adoption among American ethnoracial groups. Although the digital divide persists, African Americans (and the Latinx population) rely heavily on smartphones for health information and educational material [28]. If leveraged wisely, mHealth could influence bio-psychobehavioral aspects of health and wellness on an unprecedented scale. If applied early in the lifespan, we may disrupt the morbid trajectory, which can take hold in youth and produce excess death and disability by middle age among blacks and other disadvantaged minorities. MOYO is an early effort to establish a platform that will have high rates of use in health disparity communities by adopting the principles that embrace community engagement from inception to implementation. Furthermore, the deep involvement of young users from a historically marginalized group (including training of a selected subset in basic programming) stimulates interest and broadens knowledge in technology for both academic and career opportunities in this underrepresented group.

MOYO leverages four distinct but related research methodologies: CBPR, Agile Design, HBM, and SCT MC. It fuses modern approaches to intervention and technology design to address health inequities and empowers a new generation to improve their health, health literacy, technical literacy, and, as a result, their educational and economic potential. An app designed for deep insights into health requires deep data mining and, therefore, deep trust toward ownership and sustainability among the target population. We adopted a cocreation approach, which involves the young African American population in the technology from the ground-up. By imparting programming skills to a subset of the target demographic, they are becoming advocates and vested creators in the technology. With nonpermissive open-source licensing, it also provides a substrate for the target population to create sustainable and profitable innovations, potentially providing further economic empowerment and technology training opportunities.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Key and complementary principles of agile software development and community-based participatory research. These principles provide a framework and guidelines that inform the methodology, development, and design of the MOYO app and the formation of the MOYO app.
[DOCX File , 19 KB - resprot_v9i7e16699_app1.docx]

References

1. Heron M. Deaths: leading causes for 2016. Natl Vital Stat Rep 2018 Jul;67(6):1-77 [FREE Full text] [Medline: 30248017]

2. Satcher D, Fryer GE, McCann J, Troutman A, Woolf SH, Rust G. What if we were equal? A comparison of the black-white mortality gap in 1960 and 2000. Health Aff (Millwood) 2005;24(2):459-464. [doi: 10.1377/hlthaff.24.2.459] [Medline: 15757931]
3. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016 Jan 26;133(4):e38-360. [doi: 10.1161/CIR.0000000000000350] [Medline: 26673558]
4. Rodriguez CJ, Allison M, Daviglus ML, Isasi CR, Keller C, Leira EC, American Heart Association Council on Epidemiology and Prevention, American Heart Association Council on Clinical Cardiology, American Heart Association Council on Cardiovascular and Stroke Nursing. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. Circulation 2014 Aug 12;130(7):593-625 [FREE Full text] [doi: 10.1161/CIR.0000000000000071] [Medline: 25098323]
5. Davis AM, Vinci LM, Okwuosa TM, Chase AR, Huang ES. Cardiovascular health disparities: a systematic review of health care interventions. Med Care Res Rev 2007 Oct;64(5 Suppl):29S-100S [FREE Full text] [doi: 10.1177/1077558707305416] [Medline: 17881625]
6. Taylor HA. The Jackson Heart Study: an overview. Ethn Dis 2005;15(4 Suppl 6):S6-S1. [Medline: 16317981]
7. Sempos CT, Bild DE, Manolio TA. Overview of the Jackson Heart Study: a study of cardiovascular diseases in African American men and women. Am J Med Sci 1999 Mar;317(3):142-146. [doi: 10.1097/00000441-199903000-00002] [Medline: 10100686]
8. Fox ER, Samdarshi TE, Musani SK, Pencina MJ, Sung JH, Bertoni AG, et al. Development and validation of risk prediction models for cardiovascular events in black adults: the Jackson Heart Study cohort. JAMA Cardiol 2016 Apr 01;1(1):15-25 [FREE Full text] [doi: 10.1001/jamacardio.2015.0300] [Medline: 27437649]
9. Taylor HA, Henderson F, Abbasi A, Clifford G. Cardiovascular disease in African Americans: innovative community engagement for research recruitment and impact. Am J Kidney Dis 2018 Nov;72(5 Suppl 1):S43-S46 [FREE Full text] [doi: 10.1053/j.ajkd.2018.06.027] [Medline: 30343723]
10. Pew Research Center. 2014 Feb 08. Emerging nations embrace internet, mobile technology URL: https://www.pewresearch.org/global/2014/02/13/emerging-nations-embrace-internet-mobile-technology/ [accessed 2016-05-12]
11. Anderson M. Pew Research Center. 2015 Apr 15. Racial and ethnic differences in how people use mobile technology URL: https://www.pewresearch.org/fact-tank/2015/04/30/racial-and-ethnic-differences-in-how-people-use-mobile-technology/ [accessed 2017-06-11]
12. Israel BA, Schulz AJ, Parker EA, Becker AB, Community-Campus Partnerships for Health. Community-based participatory research: policy recommendations for promoting a partnership approach in health research. Educ Health (Abingdon) 2001;14(2):182-197. [doi: 10.1080/13576280110051055] [Medline: 14742017]
13. Beck K. Agile Manifesto. Principles behind the Agile Manifesto URL: http://agilemanifesto.org/principles.html [accessed 2019-02-03]
14. Paulk MC. Agile methodologies and process discipline. J Defense Software Eng 2002:15 [FREE Full text]
15. Bandura A. Social cognitive theory of mass communication. Media Psychol 2001 Aug;3(3):265-299. [doi: 10.1207/s1532785xmep0303_03]
16. Cusumano MA, Smith S. MIT Libraries. 1995 Aug 16. Beyond the Waterfall: software development at Microsoft URL: https://dspace.mit.edu/bitstream/handle/1721.1/2593/SWP-3844-33836288.pdf [accessed 2019-03-06]
17. National Center for Educational Statistics. Common core of data: public school district data URL: https://tinyurl.com/y9yutpzg [accessed 2018-11-15]
18. Georgia Department of Education. 2019 May 07. Atlanta Public Schools (761) free and reduced lunch (FRL) - fiscal year 2019 data report URL: https://www.atlantapublicschools.us/cms/lib/GA01000924/Centricity/Domain/2754/1819_fte_pack_frl001_public.pdf
19. US Department of Education College Scorecard. Morehouse College URL: https://collegescorecard.ed.gov/search/?name=morehouse%20college&sort=salary:desc [accessed 2019-01-25]
20. US Department of Education College Scorecard. Spelman College URL: https://collegescorecard.ed.gov/search/?name=spelman%20college&sort=salary:desc [accessed 2019-01-17]
21. US Department of Education College Scorecard. Clark Atlanta University URL: https://collegescorecard.ed.gov/school/?138947-Clark-Atlanta-University [accessed 2019-01-22]
22. US Department of Education College Scorecard. Atlanta Metropolitan State College URL: https://collegescorecard.ed.gov/school/?138901-Atlanta-Metropolitan-State-College [accessed 2019-01-22]
23. McCurdie T, Taneva S, Casselman M, Yeung M, McDaniel C, Ho W, et al. mHealth consumer apps: the case for user-centered design. Biomed Instrum Technol 2012;Suppl:49-56. [doi: 10.2345/0899-8205-46.s2.49] [Medline: 23039777]
24. Pennebaker JW, Booth RJ, Francis ME. LIWC.net. 2001. Linguistic Inquiry and Word Count: LIWC2007 URL: http://www.depts.ttu.edu/psy/lusi/files/LIWCmanual.pdf
25. Pennebaker JW, Mehl MR, Niederhoffer KG. Psychological aspects of natural language. use: our words, our selves. Annu Rev Psychol 2003;54:547-577. [doi: 10.1146/annurev.psych.54.101601.145041] [Medline: 12185209]

26. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
27. HL7 International. 2014 Feb 02. HL7 Fast Healthcare Interoperability Resources Specification (FHIR®), DSTU Release 1 URL: https://tinyurl.com/y8vxdwsg
28. Cakmak A, Reinertsen E, Taylor H, Shah AG. Personalized heart failure severity estimates using passive smartphone data. 2018 Oct 13 Presented at: IEEE International Conference on Big Data; 2018; Seattle, WA p. 10-13. [doi: 10.1109/bigdata.2018.8621980]
29. Tsanas A, Saunders K, Bilderbeck A, Palmius N, Osipov M, Clifford G, et al. Daily longitudinal self-monitoring of mood variability in bipolar disorder and borderline personality disorder. J Affect Disord 2016 Nov 15;205:225-233. [doi: 10.1016/j.jad.2016.06.065] [Medline: 27449555]
30. US Department of Health and Human Services. 2018 Aug 07. HHS Secretary Azar statement on passing of former HHS Secretary Margaret Heckler URL: https://www.hhs.gov/about/news/2018/08/07/hhs-secretary-azar-statement-on-passing-of-former-hhs-secretary-margaret-heckler.html [accessed 2018-10-11]

Abbreviations

AA: African American
CBPR: community-based participatory research
CVD: cardiovascular disease
HBM: health belief model
JHS: Jackson Heart Study
mHealth: mobile health
MPAB: MOYO Project Advisory Board
SCT MC: social cognitive theory of mass communication

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Protocol

Development of "Advancing People of Color in Clinical Trials Now!": Web-Based Randomized Controlled Trial Protocol

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Abstract

Background: Participation in clinical trials among people of color remains low, compared with white subjects. This protocol describes the development of "Advancing People of Color in Clinical Trials Now!" (ACT Now!), a culturally tailored website designed to influence clinical trial decision making among people of color.

Objective: This cluster randomized study aims to test the efficacy of a culturally tailored website to increase literacy, self-efficacy, and willingness to enroll in clinical trials among people of color.

Methods: ACT Now! is a randomized trial including 2 groups: (1) intervention group (n=50) with access to the culturally tailored website and (2) control group (n=50) exposed to a standard clinical recruitment website. Clinical trial literacy and willingness to enroll in a clinical trial will be measured before and after exposure to the website corresponding to their assigned group (intervention or control). Surveys will be conducted at baseline and during the 1-month postintervention and 3-month follow-up. Website architecture and wireframing will be informed by the literature and experts in the field. Statistical analysis will be conducted using a two-tailed *t* test, with 80% power, at .05 alpha level, to increase clinical trial literacy, self-efficacy, and willingness to enroll in clinical trials 3 months post intervention.

Results: We will design a culturally tailored website that will provide leverage for community stakeholders to influence clinical trial literacy, self-efficacy, and willingness to enroll in clinical trials among racial and ethnic groups. ACT Now! applies a community-based participatory research approach through the use of a community steering committee (CSC). The CSC provides input during the research study conception, development, implementation, and enrollment. CSC relationships help foster trust among communities of color. ACT Now! has the potential to fill a gap in clinical trial enrollment among people of color through an accessible web-based website. This study was funded in July 2017 and obtained institutional review board approval in spring 2017. As of December 2019, we had enrolled 100 participants. Data analyses are expected to be completed by June 2020, and expected results are to be published in fall 2020.

Conclusions: ACT Now! has the potential to fill an important gap in clinical trial enrollment among people of color through an accessible web-based website.

Trial Registration: ClinicalTrials.gov NCT03243071; https://clinicaltrials.gov/ct2/show/NCT00102401

International Registered Report Identifier (IRRID): DERR1-10.2196/17589

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KEYWORDS

health communication; health care disparities; eHealth

Introduction

Clinical Trials Health Disparities

Racial and ethnic minority individuals in the United States are consistently underrepresented in clinical trials [1]. Paradoxically, these groups are disproportionately affected by the leading causes of chronic disease and mortality compared with whites [2]. Participants in clinical trials are typically educated, white, and from the middle class [3,4], limiting the external generalizability to people of color (ie, African American, Hispanic, Asian, and Native American) [5,6]. Limited scientific evidence on effective solutions to address the health of racial and ethnic minority groups contributes to the health disparities gap. Identifying treatments to ameliorate the burden of disease experienced by people of color requires increased participation in clinical trials. This study will investigate the effectiveness of a culturally tailored website to increase knowledge, self-efficacy, and willingness to enroll in clinical trials among people of color in the New York City area.

Background

Factors that may affect racial and ethnic group decision making to participate in clinical trials include the following: patient mistrust, perceived racial discrimination, transparency, awareness, culture and language, health literacy, invitation to participate in a clinical trial, social support, health insurance coverage, and pre-existing comorbidities [7-18]. Research suggests that African American and Hispanic enrollment in pharmacology clinical trials for cancer drugs and cystic fibrosis are particularly low [19,20]. Addressing the many barriers to clinical trial enrollment is critical to increasing minority enrollment in clinical trials research. We particularly aim to increase the health literacy of the many types of clinical trials that go beyond pharmacological drug testing. To that end, we aim to increase minority willingness to enroll in evidence-based interventions, including mechanistic, exploratory, pilot studies; interventional trials; and behavioral trials [21]. To engender higher decision making among people of color to enroll in clinical trials, we propose an accessible, culturally adapted, electronic health (eHealth) educational tool to enhance clinical trial literacy among racial and ethnic groups. Pew Research Center reported that 88% of blacks and Hispanics use the internet, broadly serving as an opportune channel for clinical trial health education [22]. Through focus groups among people of color, we plan to address collective concerns and lean into cultural learning and concerns about research engagement among people of color, as part of developing a representative tool for collective decision making [23]. A culturally tailored website may be an optimal strategy for influencing clinical trial decision making to enroll in clinical trials through a channel the target population is already engaged with, the internet [22]. Educational tools that address the issues and concerns related to clinical trial enrollment may aid in bridging the gap between academic research institutions and communities of color.

Health literacy is a key indicator that influences the decision to participate in clinical trials [24]. Health literacy is the ability to understand and act upon information to make recommended health decisions. Examples of proficient health literacy include understanding food labels, prescription medication use, and navigating the health care system [25]. Unfortunately, only 12% of American adults show proficiency in broad health literacy [26]. This is an important finding, as individuals with low health literacy are challenged by web-based clinical trial search engines [27]. Health literacy is a key social determinant of identifying and enrolling in clinical trials and has been associated with poor health outcomes among population subgroups, including people of color [27-29]. Given the low national health literacy rates, we decided to specifically focus on clinical trial literacy domain knowledge gains, as they predict the related outcomes of clinical trial literacy and willingness to enroll in a clinical trial.

In this study, we describe the process of developing and testing Advancing People of Color in Clinical Trials Now! (ACT Now!), a culturally tailored website to promote clinical trial participation among minority groups. Through the involvement of community members, academic researchers, and clinicians, this study will bridge the gap between groups to develop and disseminate a culturally tailored website to increase clinical trial decision making to enroll in clinical trials among people of color.

Objective

This study will evaluate the effectiveness of a culturally tailored website to influence clinical trial decision making among people of color. Given the individual interface with the website, intrapersonal factors related to clinical trial literacy and self-efficacy were identified as predictors of how willing participants are to enroll in a clinical trial. Self-efficacy, one's confidence in carrying out a behavior, has been consistently identified as a predictor of behavior change [30]. To this end, we identified self-efficacy and clinical trial health literacy as predictors of health behavior change. The multidisciplinary team will study the following aims:

1. To evaluate the efficacy of a culturally tailored website, compared with the New York University (NYU) Langone Health's standard clinical trial website, using a randomized group design, to assess decision making related to willingness to enroll in clinical trials. We hypothesize that participants exposed to the culturally tailored intervention website will increase their clinical trial literacy and self-efficacy and thereby increase their decision making related to willingness to enroll in clinical trials, compared with those exposed to the standard NYU website (control).
2. To determine if intrinsic psychosocial factors (clinical trial awareness, health literacy, and self-efficacy), demographic factors (including socioeconomic, gender, and age), and medical factors (risk behavior, history of preventive behavior, and clinical diagnoses) would moderate the likelihood of enrolling in a clinical trial when exposed to the culturally tailored intervention website. We hypothesize that participants' decision making to enroll in a clinical trial will be mediated by increased health literacy and self-efficacy, independent of their knowledge, attitudes/beliefs, intrinsic motivation, social support, and socioeconomic position.

Methods

Framework

Our design and testing of ACT Now! are based on the National Institutes of Health (NIH) behavior change consortium and consolidated standards of reporting trials (CONSORT) statements to inform its development [31]. Following a community-based informed approach, the guidelines of the CONSORT statements will ensure implementation fidelity and thereby enhance internal validity and generalizability. Formative evaluation, including ongoing qualitative feedback on process evaluation with the community steering committee (CSC) members and qualitative debriefing sessions for participants to provide open-ended feedback, along with quantitative surveys, will ensure that the study components are feasible and acceptable to participants and stakeholders.

Study Design

ACT Now! uses a randomized controlled trial design to assess the following patient outcomes: (1) willingness to enroll in clinical trials and (2) behavioral intention to enroll in clinical trials. The participants' recommendations to others about clinical trials will evaluate exposure before and after the culturally tailored clinical trial literacy intervention website. Participants will be randomized into two groups: (1) the intervention group (n=50), which will have access to the culturally tailored website in the study setting [32]; and (2) the control group (n=50), which will have access to the NYU Langone's standard clinical trial website in the study setting [33].

At the onset of the 2-year study time frame, starting from July 2017 and ending in June 2019, refinement of study components with stakeholders, community leaders, researchers, and clinicians will be decided based on mutually agreed consensus. The formative period will allow for staff training, standardization of procedures, identification and onboarding of CSC members, and endorsement of the recruitment and implementation plan during focus groups. On development of the culturally tailored clinical trial website, participants who may be equally eligible for any NYU study will be recruited through community health fairs or the CSC member referrals. Alternate-sequencing random order will be used to randomly assign participants to the intervention or control website. The participants' viewership and engagement with the website will be monitored using Google Analytics and Squarespace metrics. An institutional review board (IRB)–approved informed consent form was administered before study participation.

Community stakeholder partnerships will engender trust, which is necessary to ensure the implementation of our protocol and sustainability beyond study completion [34]. Through the engagement of our standing CSC led by a senior health educator, we will make inroads toward sustainable relationships for community-based research by engaging our CSC. Trusted members of the community liaise between academic and health care settings to translate concerns of the people they represent. The CSC members represent a gender-balanced, racially diverse group of people who are active on their community boards, in churches, and in the field of public health. Thus, we will employ community-based participatory research [35], an approach that works with the community as equal partners in research, to formulate project aims and develop and execute our research implementation plan.

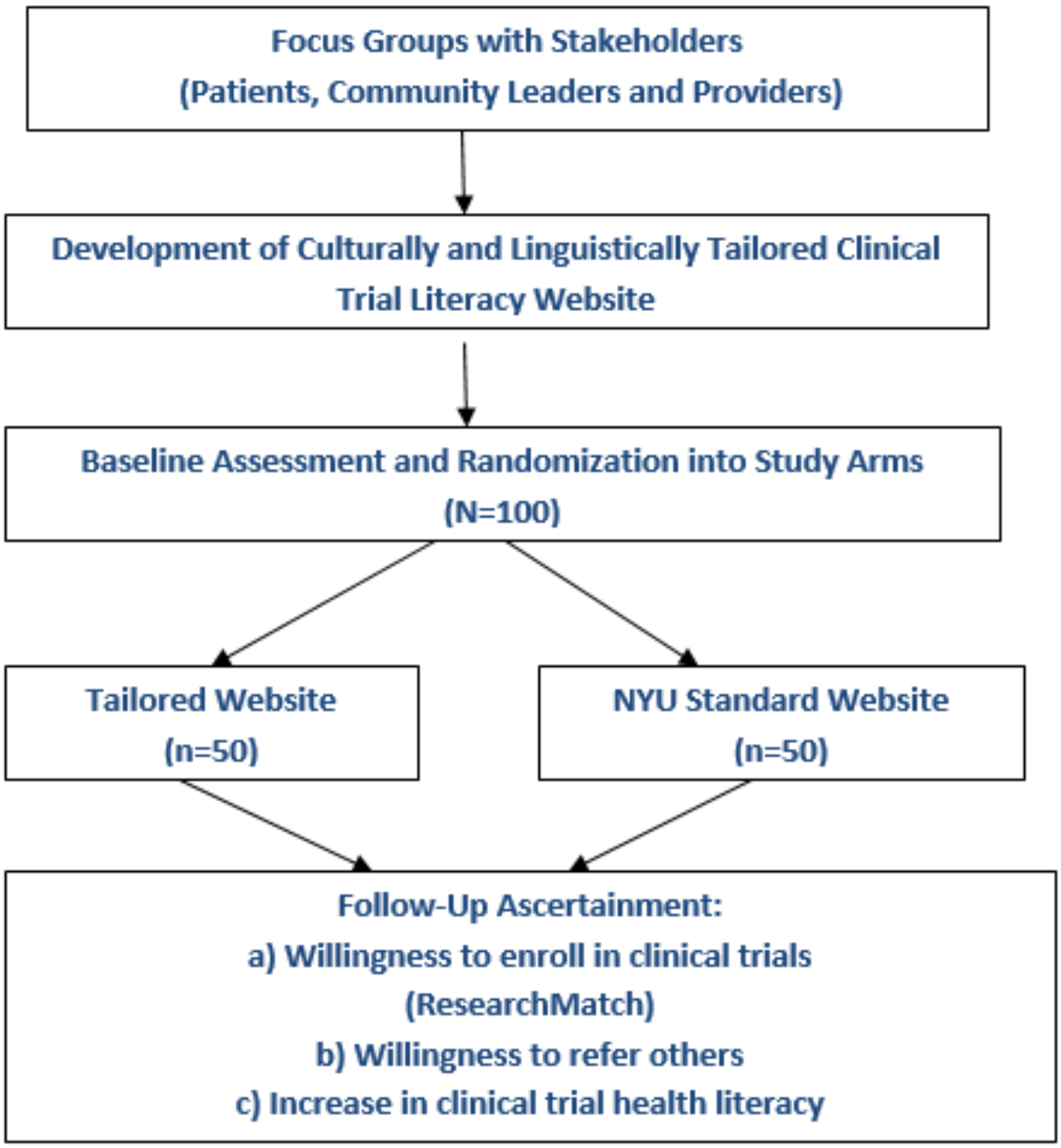
Partnership with the CSC will be instrumental in developing a website that resonates with our target population. Quarterly meetings with the CSC are critical to website development and recruitment. CSC members will recruit participants at a neutral place of their choosing or a community site (ie, library, church, their home, or NYU Center for Healthful Behavior Change). This approach includes standardization of recruitment procedures by training CSC members and complying with a checklist of procedures during participant enrollment.

Participants will be eligible for the study based on the following criteria: self-identified as a person of color, ≥18 years old, literate, and resident in the New York area for at least three months after enrollment. On enrollment, IRB consent and baseline surveys will be completed via Qualtrics, lasting about 25 min. At baseline, participants will receive a US $25 gift card and a Wi-Fi–enabled iPad, preloaded with intervention or control materials on the browser. A research assistant will familiarize participants with the iPad, including how to access the intervention or control websites. Participants who have access to the intervention website will be granted a password-protected log-in to prevent cross-contamination exposure to both websites. After participants complete the study, voluntary debriefing sessions will be offered. They will then be scheduled for their 1-month follow-up visit, and the researchers will thank them for their time.

At the 1-month follow-up, participants will return their iPads to the NYU Langone's Center for Healthful Behavior Change and receive US $50 as compensation for their participation and time. The participants will complete the surveys 1 month post intervention and during their 3-month follow-up.

During the final 3-month visit, participants will receive US $25 and complete the final surveys. Participants will have the opportunity to voluntarily debrief about their experience in the study. The research associate will thank them for their time. Participants assigned to the control arm will receive access to intervention resources no later than 3 months after their last visit. Figure 1 shows the study flowchart with the main study outcome measures.

Figure 1. Study diagram illustrating participant flow throughout the study cycle.



Ethics Approval and Consent to Participate

This study received approval from the NYU IRB in 2017. Study modifications are communicated to the IRB as modifications occur. We will communicate the IRB-approved amendments to trial participants.

Community Steering Committee

In total, 3 CSC members will be identified by the lead health educator of the Center for Healthful Behavior Change. The CSC members will complete the collaborative institutional training initiative certification and be trained on study responsibilities and expectations. The CSC members will receive US $150 for each session, for a total of 6 meetings over the course of the 2-year study. The CSC members will participate in focus groups to aid the research team in identifying the following information: (1) beliefs and attitudes about clinical trials, (2) beliefs and attitudes about minority involvement in clinical trials, and (3) beliefs and attitudes regarding clinical trials from people in their community. They will also provide feedback on the culturally tailored website landing page, study materials, video testimonials, and the recruitment process.

Culturally Tailored Intervention Website Development

Website design will begin with storyboarding, an outline of the digital story elements on the website [36], and information architecture, the way website content is displayed and affects user interactions with the website [37] that are informed by

previous findings in the literature and expert knowledge of NYU faculty. This process will begin by reviewing data previously collected from clinical trials, which led to improved prevention strategies, treatment approaches, and recommendations for the medical management of people of color. We will identify key themes and brainstorm ideas that craft the appropriate message for the target audience at a sixth-grade reading level. This might include describing the data in the form of visual pictures, infographics on health disparities, and videos, while minimizing the use of words. We will survey web-based resources to guide the innovative creative process and development of additional content. Furthermore, we will discuss website design in an attempt to plan the layout according to how the user will navigate and process the information on the website.

After viewing the educational health materials, we will create a rough draft using concepts from the storyboard and wireframing session. We will visit this over several days before the CSC and expert panel reviews it. Finally, we will create infographics for the subheading section titled, *What is a Clinical Trial?* Video interviews with NYU faculty members of color will be included to reflect diverse representations of researchers and clinicians who could speak about the importance of including people of color in clinical trials, including benefits to the community. In addition, a video animation welcoming people to the website and providing an overview of the website will be a part of the welcome page.

Cognitive walk-through, how a person applies problem-solving techniques to learn through their interactions with a website and discover system limitations [38] and heuristic usability, evaluating the website design and literacy [39] testing will be conducted by an informatics specialist (YI). The specialist will address technical issues, layout, design, and literacy level appropriateness of the website. Consistent with previous research and testing of culturally tailored websites [40], think-aloud sessions, where participants verbalize their thought process when interacting with the website [41], will be held with 12 people reflective of the target population demographics, with a diverse age, gender, and race sample, to examine website navigation and content validation concerns [41,42]. Cognitive walk-through of study surveys allows for editing and troubleshooting corrections and time determination of approximately 25 to 30 min to complete the study.

Participants enrolled in the intervention condition will be exposed to the tailored website, which will have 7 sections of content including the welcome page: *Disparities and Research*, *Clinical Trials*, *Research Success*, *Words Used in Research*, *Clinical Trial Resources*, and *Our Mission*. In addition to the *ACT Now!* landing page, each page explains the content in the video and print format. The *ACT Now!* landing page (Figure 2) includes a video animation welcoming the user to the website and providing a summary of the website content and the importance of increasing enrollment in clinical trials among racial and ethnic groups. The cartoon characters depict different ages, skin tones, cultural and religious markers (eg, the hijab), and disability status. Infographics on disparities in clinical trials and the need for minority representation in research to address chronic conditions (ie, breast cancer and diabetes), images of people of color interacting with health care professionals, and an iPad include pictures of patients and providers interacting as well as descriptive narrative content.

The *Disparities and Research* section includes 3 paragraphs describing how social determinants such as race, ethnicity, age, education, and income affect health outcomes and how increasing diversity in research may help identify solutions to reducing health disparities. This information will explain health disparities in research by an NYU faculty member and physician embedded in video format on the website. Similarly, the *Clinical Trials* section includes the following subheadings: *What is a clinical trial?*, *What are the steps of a clinical trial?*, *Common barriers in a clinical trial?*, *Reluctance to participate in clinical trials?*, and *Importance of participation in clinical trials?* (Figure 3) Each subheading page will include 1 to 3 paragraphs on the page topic and a video of an NYU faculty member of color. Each page will have information explaining what takes place during clinical trial research and explain clinical trial involvement from the participant's point of view. Website topics include the role of the IRB, participant time, compensation, and acknowledging historical events in America that may have led to patient mistrust, such as the Syphilis Study at Tuskegee. This section will explain that research participation is voluntary and that safeguards are in place to protect the rights of the participant.

The *Research Success* section of the website will include 3 subheadings: *How has research benefited my community?Areas of needed improvement*, and *Testimonials*. The *How has research benefited my community?* section will include information on the role of research in neighborhoods of people of color, such as Harlem, to provide screenings and behavioral health interventions to reduce chronic disease risk factors. This section provides information regarding successful behavioral health interventions in the community, such as barbershops, that have increased screening and treatment rates for African American men, who are typically underserved. The *Words Used in Research* section includes definitions of a glossary of terms used throughout the website. The *Clinical Trial Resources* section explains the safeguards in place to protect a person enrolled in clinical trial research, with hyperlinks to the NIH and ClinicalTrials.gov as additional sources that explain the process. The *Find a Clinical Trial* section will include hyperlinks to clinical trials at NYU and the NIH organized by the hyperlink disease state. The final *Our Mission* section will an image of the Center for Healthful Behavior Change staff, the name and contact information of the principal investigator, key faculty and staff, and acknowledgment of the funding source.

On study completion, all participants in the control arm of the study will have access to the intervention site via a partner community website.

Figure 2. Landing page screenshot of study including subheading menus and cartoon animation describing clinical trials.

Figure 3. Joseph Ravenell, MD describing the different types of clinical trials, including community-based research.

Measures

Screening questions will take about 5 min. Participants will complete the survey measures at baseline, 1-month follow-up, and 3-month follow-up. Baseline data collection and subsequent measures will take approximately 25 min each for eligible participants enrolled in the study. We will use Qualtrics software to capture survey data entry in real time. Secured access to participant data is only available through the NYU Langone Health password log-in–required secure portal. We will code surveys before statistical analysis using validated survey tools. The clinical trial sponsor did not deem that a data monitoring committee was necessary.

Sociodemographic Variables

Sociodemographic variables will include age, race, insurance status, level of education, employment status, marital status, and annual household income.

Health Status and Chronic Conditions

The medical outcomes study questionnaire short form 36 health survey is a validated 36-item instrument that serves as an indicator of overall health status. This survey has a Cronbach alpha reliability score of approximately .80. Estimates of reliability in the physical and mental sections are typically above 0.90. The eight sections of the tool examine vitality; physical functioning; bodily pain; general health perceptions; physical, emotional, and social role functioning; and mental health [43]. These eight sections include scaled scores that are weighted sums of questions in each section.

Clinical Trial Literacy

Researchers at the NYU Center for Healthful Behavior Change and the University of California, Los Angeles, developed and validated a 24-item survey instrument to assess clinical trial literacy and attitudes across a diverse sample of 400 participants. Survey items will be developed in partnership with the CSC members to help assess literacy level appropriateness. Likert scale responses ranged from definitely false to definitely true. Sample survey items include "A clinical trial is a research study that involves people." and "Research is important to improve the health of people of color." Item score correlations ranged from 0.45 to 0.68, and Cronbach alpha based on Pearson correlations was .93.

Message Effectiveness Scale

Culturally tailored messages are more effective when they resonate well with specific populations to improve targeted behavior outcomes [44]. An assessment of website content will ascertain what was more influential in increasing the willingness of the participants to enroll in a clinical trial. The 14-item message effectiveness scale [45] will be completed 1 month postintervention to assess user acceptance.

Internet Self-Efficacy Scale

The internet self-efficacy scale will measure the self-confidence of users in using the iPad and the internet based on a 5-point Likert scale response option. The 8-item survey reported a Cronbach alpha of .93 [46].

Willingness to Enroll in a Clinical Trial

The willingness of the participants to enroll in a clinical trial will be assessed based on 3 hypothetical trials on a scale from 1 (*not willing*) to 5 (*very willing*). Clinical trial vignettes are based on weight loss, hypertension treatment, and cancer treatment [47]. Cronbach alphas of .6 and .8 were reported for the Corbie-Smith distrust in clinical research index and the primary care assessment survey trust subscales, respectively. Table 1 displays an overview of the study measures at baseline, 1 month, and 3 months.

Table 1. Study outcome measures.

Measures	Baseline	1 month	3 months
Demographic and clinical variables	X[a]	—[b]	—
Medical outcomes study questionnaire short form 36	X	—	—
National assessment for adult literacy	X	—	—
Clinical trials literacy	X	X	X
Message effectiveness scale	X	X	X

[a]X denotes what measure to ascertain.

[b]Empty cells signify not to capture the measure at the timepoint.

Recruitment

The CSC members will be recruited via the word-of-mouth snowball method and will occur at a place of their choosing in a neutral community site (ie, library or faith-based organization). Although effective eHealth frameworks exist for eHealth clinical trial recruitment [47], the CSC took ownership of the study recruitment process. Eligible participants enter into a research arm based on a predetermined randomization spreadsheet. Nondisclosure of group assignment during enrollment blinds trial participants to intervention arm assignment. This randomized approach includes standardizing recruitment procedures by training the CSC members and complying with a checklist of procedures during participant enrollment. The CSC members will be trained in study recruitment procedures before launching the study, including thorough role-playing of participant enrollment and troubleshooting of iPad equipment. NYU staff accompany the CSC members during participant enrollment to ensure consent forms are signed in compliance with the NYU Langone Health regulations.

Power

Using a medium effect size (d=0.32) and a sample size of 100, this study will be adequately powered (>80%) to detect significant differences between participants with improvements in health literacy scores. A significant increase in the number of participants in the intervention arm who are willing to register for clinical trials can also be detected. Actual registration in a clinical trial is not measured.

Statistical Analysis

Paired t tests and chi-square tests will be conducted to compare participants who exhibited improvement in health literacy compared with those who did not. A logistic regression model will determine which factors are associated with a higher likelihood of (1) enrolling in a clinical trial and (2) referring others to participate in clinical trials as well, based on baseline factors. A two-tailed test, at 80% power and an alpha of .05, comparing 25% with 45% would require 50 participants enrolled in each arm. This will allow for differences to be assessed in participation rates. In addition, a 23% attrition rate is taken into account when considering the mediating and contextual factors between tailored clinical trial messages and participation rates. The attrition rate is based on our previous study experience with a similar study design. We plan to prevent study attrition with biweekly check-ins with participants regarding iPad troubleshooting, website engagement, and/or general study questions.

Communication on trial results will be disseminated to the scientific community via a peer-reviewed publication. A CSC meeting will be held at study completion to share trial results with community stakeholders.

Results

We will design a culturally tailored website that will provide leverage for community stakeholders to influence clinical trial literacy, self-efficacy, and willingness to enroll in clinical trials among racial and ethnic groups. ACT Now! applies a community-based participatory research approach through the use of a CSC. The CSC provides input during the research study conception, development, implementation, and enrollment. CSC relationships help foster trust among communities of color. ACT Now! has the potential to fill a gap in clinical trial enrollment among people of color through an accessible web-based website. Funded in July 2017 and obtained IRB approval in spring 2017. As of December 2019, we had enrolled 100 participants. Data analyses are expected to be completed by June 2020, and expected results are to be published in fall 2020.

Discussion

Principal Findings

The significance of this study is its patient-centered approach to addressing minority enrollment in clinical trials. Building the intervention website in partnership with community leaders in a way that values their perspective is an important cornerstone of our study. Eliciting community feedback throughout the process of website development and recruitment is crucial to ensure acceptability and dissemination of the message regarding the importance of participation in clinical trials. Logistical challenges with administrative onboarding of the CSC members slowed down study initiation. In addition, securing iPads with the appropriate access restrictions and image permissions and website vendors were operational hurdles. However, building inroads in the community can erect bridges where barriers once existed and allow for involvement in community-based research in the future.

Previous interventions to increase minority enrollment in clinical trials have focused on just one racial or ethnic group (ie, African American or Asian) [5,48], gender [49], or are heavily focused on drug or biologic testing (ie, cancer) [50,51]. ACT Now! uses an inclusive approach, targeting all groups of color (ie, African American, Asian American, and Hispanic). This study could be adapted by different interest groups to be used for future clinical trials for recruitment efforts, awareness platforms, and education efforts, such as the *All of Us* research program, which aims to create a diverse racial and ethnic database of patient health information [52]. In addition, this study is neither gender specific nor age specific, aiming to address women and nongender binary people of color who are typically not represented in clinical trial research as well [53]. ACT Now! is inclusive of individuals of varying racial, gender, age, and sexual orientation to reduce misconceptions and address barriers to research [7].

Engaging people of color in the study process has effectively increased knowledge about clinical trial research, such as in the Asian American community. Ma et al [5] applied the community-based participatory research approach for the development, tailoring, implementation, and evaluation of an intervention to increase Asian American representation in clinical trials. Community-based organizations and community health educators significantly increased clinical trial knowledge among 247 participants. Benefits to science and the larger Asian American community were found to be the most important factors to emphasize when aiming to enhance Asian American participation in clinical trials [5]. Similarly, ACT Now! will include people of color as part of the CSC to provide feedback on key content areas, layout, and design of the culturally tailored website, to better resonate with the target population.

ACT Now! aims to address clinical trial literacy across a diverse group of racial and ethnic minority groups, as well as self-efficacy and decision making to enroll in clinical trial research, using a CSC to guide development and recruitment. Wells et al [49] applied a cultural competency and recruitment training program (CCRTP) to increase minority enrollment in cancer clinical trials. Significant improvements were found in knowledge and attitude measures post intervention. Minority participation in clinical trials increased by 1.2% (an additional 300 minority patients) 1 year after the CCRTP. Both studies reported significant increases in knowledge gains but only modest improvements in minority enrollment in clinical trials [49].

Study Limitations

Although our study aims to increase the literacy of all types of clinical trial research, including nonpharmacological observational studies, we do not measure actual participant enrollment in clinical trials after study intervention. Future research should consider the effect of clinical trial literacy tools to influence actual study enrollment. In addition, other barriers to enrollment should be considered, such as religion.

Conclusions

ACT Now! will apply a community-based participatory research approach through the use of a CSC, providing input during the intervention website development and a study referral source for participant enrollment. Each CSC member will serve as a community representative that the participants trust. CSC members will ensure the safe return of iPads disseminated in the community, which sparked the recruitment referral snowball approach. In addition, NYU staff members will join CSC members at community recruitment events throughout New York City, meeting participants where they are and ensuring their onboarding process addresses any technical issues or study concerns.

ACT Now! has the potential to fill an important gap in clinical trial enrollment among people of color through an accessible web-based website. Literacy level–appropriate text, infographics, videos, and cartoon videos aim to educate people of color on clinical trial research via a web-based intervention. The culturally tailored approach, endorsed and codeveloped by trusted community leaders, strengthens the partnership between the community, academia, and the private sector.

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Authors' Contributions

All authors made significant contributions to the conception and implementation of the study as well as the final manuscript. GL, JR, and AS contributed to the study conception and methods. AC, VG, RR, NW, and YI contributed to study development. AC contributed to the introduction and discussion. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. US Food and Drug Administration. 2015 - 2016 Global Participation in Clinical Trials Report URL: https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM570195.pdf [accessed 2018-11-27]
2. National Academies of Sciences Engineering and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on Community-Based Solutions to Promote Health Equity in the United States. In: Baciu A, Negussie Y, Geller A, Weinstein JN, editors. Communities in Action: Pathways to Health Equity. Washington, DC: National Academies Press; 2017.
3. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control 2016 Oct;23(4):327-337 [FREE Full text] [doi: 10.1177/107327481602300404] [Medline: 27842322]
4. Rochon P, Mashari A, Cohen A, Misra A, Laxer D, Streiner D, et al. The inclusion of minority groups in clinical trials: problems of under representation and under reporting of data. Account Res 2004;11(3-4):215-223. [doi: 10.1080/08989620490891412] [Medline: 15812967]
5. Ma GX, Tan Y, Blakeney NC, Seals BF, Ma XS, Zhai S, et al. The impact of a community-based clinical trial educational intervention among underrepresented Chinese Americans. Cancer Epidemiol Biomarkers Prev 2014 Mar;23(3):424-432 [FREE Full text] [doi: 10.1158/1055-9965.EPI-13-0773] [Medline: 24092627]
6. Hussain-Gambles M. Ethnic minority under-representation in clinical trials. Whose responsibility is it anyway? J Health Organ Manag 2003;17(2):138-143. [doi: 10.1108/14777260310476177] [Medline: 12916177]
7. Langford AT, Resnicow K, Dimond EP, Denicoff AM, Germain DS, McCaskill-Stevens W, et al. Racial/ethnic differences in clinical trial enrollment, refusal rates, ineligibility, and reasons for decline among patients at sites in the national cancer institute's community cancer centers program. Cancer 2014 Mar 15;120(6):877-884 [FREE Full text] [doi: 10.1002/cncr.28483] [Medline: 24327389]
8. Langford A, Resnicow K, An L. Clinical trial awareness among racial/ethnic minorities in HINTS 2007: sociodemographic, attitudinal, and knowledge correlates. J Health Commun 2010;15(Suppl 3):92-101 [FREE Full text] [doi: 10.1080/10810730.2010.525296] [Medline: 21154086]

9. Rivers D, August EM, Sehovic I, Lee Green B, Quinn GP. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. Contemp Clin Trials 2013 Jul;35(2):13-32. [doi: 10.1016/j.cct.2013.03.007] [Medline: 23557729]
10. Shavers VL, Lynch CF, Burmeister LF. Racial differences in factors that influence the willingness to participate in medical research studies. Ann Epidemiol 2002 May;12(4):248-256. [doi: 10.1016/s1047-2797(01)00265-4] [Medline: 11988413]
11. Langford AT, Larkin K, Resnicow K, Zikmund-Fisher BJ, Fagerlin A. Understanding the role of message frames on African-American willingness to participate in a hypothetical diabetes prevention study. J Health Commun 2017 Aug;22(8):647-656. [doi: 10.1080/10810730.2017.1339146] [Medline: 28749729]
12. Shaw R, McKenzie S, Taylor T, Olafiranye O, Boutin-Foster C, Ogedegbe G, et al. Beliefs and attitudes toward obstructive sleep apnea evaluation and treatment among blacks. J Natl Med Assoc 2012;104(11-12):510-519 [FREE Full text] [doi: 10.1016/s0027-9684(15)30217-0] [Medline: 23560353]
13. Williams NJ, Jean-Louis G, Ravenell J, Seixas A, Islam N, Trinh-Shevrin C, et al. A community-oriented framework to increase screening and treatment of obstructive sleep apnea among blacks. Sleep Med 2016 Feb;18:82-87 [FREE Full text] [doi: 10.1016/j.sleep.2015.07.019] [Medline: 26652238]
14. Svensson K, Ramírez OF, Peres F, Barnett M, Claudio L. Socioeconomic determinants associated with willingness to participate in medical research among a diverse population. Contemp Clin Trials 2012 Nov;33(6):1197-1205 [FREE Full text] [doi: 10.1016/j.cct.2012.07.014] [Medline: 22885788]
15. Brondolo E, Gallo LC, Myers HF. Race, racism and health: disparities, mechanisms, and interventions. J Behav Med 2009 Feb;32(1):1-8. [doi: 10.1007/s10865-008-9190-3] [Medline: 19089605]
16. Blendon RJ, Aiken LH, Freeman HE, Corey CR. Access to medical care for black and white Americans. A matter of continuing concern. J Am Med Assoc 1989 Jan 13;261(2):278-281. [Medline: 2909026]
17. Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. J Behav Med 2009 Feb;32(1):20-47 [FREE Full text] [doi: 10.1007/s10865-008-9185-0] [Medline: 19030981]
18. Smedley BD, Nelson AR, Stith AY. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academic Press; 2003.
19. -. Diversifying clinical trials. Nat Med 2018 Dec;24(12):1779. [doi: 10.1038/s41591-018-0303-4] [Medline: 30523324]
20. McGarry M, McColley SA. Minorities are underrepresented in clinical trials of pharmaceutical agents for cystic fibrosis. Ann Am Thorac Soc 2016 Oct;13(10):1721-1725 [FREE Full text] [doi: 10.1513/AnnalsATS.201603-192BC] [Medline: 27410177]
21. Grants & Funding: National Institutes of Health (NIH). 2017. NIH's Definition of a Clinical Trial URL: https://grants.nih.gov/policy/clinical-trials/definition.htm [accessed 2020-03-28]
22. Pew Research Center. 2019. Internet/Broadband Fact Sheet URL: http://www.pewinternet.org/fact-sheet/internet-broadband/ [accessed 2018-02-05]
23. Alden DL, Friend J, Schapira M, Stiggelbout A. Cultural targeting and tailoring of shared decision making technology: a theoretical framework for improving the effectiveness of patient decision aids in culturally diverse groups. Soc Sci Med 2014 Mar;105:1-8. [doi: 10.1016/j.socscimed.2014.01.002] [Medline: 24606791]
24. Evans KR, Lewis MJ, Hudson SV. The role of health literacy on African American and Hispanic/Latino perspectives on cancer clinical trials. J Cancer Educ 2012 Jun;27(2):299-305 [FREE Full text] [doi: 10.1007/s13187-011-0300-5] [Medline: 22203466]
25. Dias S, Gama A. [Community-based participatory research in public health: potentials and challenges]. Rev Panam Salud Publica 2014 Feb;35(2):150-154. [Medline: 24781097]
26. US Department of Health and Human Services. Health Literacy Online URL: https://health.gov/communication/literacy/quickguide/factsbasic.htm [accessed 2018-11-27]
27. The National Center for Education Statistics. NAAL Fact Sheets: Overview URL: http://nces.ed.gov/NAAL/fct_overview.asp [accessed 2018-11-27]
28. Utami D, Bickmore TW, Barry B, Paasche-Orlow MK. Health literacy and usability of clinical trial search engines. J Health Commun 2014;19(Suppl 2):190-204. [doi: 10.1080/10810730.2014.938842] [Medline: 25315593]
29. The National Center for Education Statistic. 2006. The Health Literacy of America's Adults: Results From the 2003 National Assessment of Adult Literacy URL: https://nces.ed.gov/pubs2006/2006483.pdf [accessed 2018-11-12]
30. Strecher V, DeVellis BM, Becker MH, Rosenstock IM. The role of self-efficacy in achieving health behavior change. Health Educ Q 1986;13(1):73-92. [doi: 10.1177/109019818601300108] [Medline: 3957687]
31. Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, Treatment Fidelity Workgroup of the NIH Behavior Change Consortium. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH behavior change consortium. Health Psychol 2004 Sep;23(5):443-451. [doi: 10.1037/0278-6133.23.5.443] [Medline: 15367063]
32. ACT NOW! - Squarespace. URL: https://actnownyu.squarespace.com/ [accessed 2020-04-29]
33. NYU Grossman School of Medicine. Clinical Research URL: https://med.nyu.edu/research/office-science-research/clinical-research/ [accessed 2020-04-29]

34. Anderson-Lewis C, Darville G, Mercado RE, Howell S, di Maggio S. mHealth technology use and implications in historically underserved and minority populations in the united states: systematic literature review. JMIR Mhealth Uhealth 2018 Jun 18;6(6):e128 [FREE Full text] [doi: 10.2196/mhealth.8383] [Medline: 29914860]
35. Holkup P, Tripp-Reimer T, Salois E, Weinert C. Community-based participatory research: an approach to intervention research with a native American community. ANS Adv Nurs Sci 2004;27(3):162-175 [FREE Full text] [doi: 10.1097/00012272-200407000-00002] [Medline: 15455579]
36. Casida D, VanderMolen J. Using storyboarding pedagogy to promote learning in a distance education program. J Nurs Educ 2018 May 1;57(5):319. [doi: 10.3928/01484834-20180420-14] [Medline: 29718526]
37. Pugatch J, Grenen E, Surla S, Schwarz M, Cole-Lewis H. Information architecture of web-based interventions to improve health outcomes: systematic review. J Med Internet Res 2018 Mar 21;20(3):e97 [FREE Full text] [doi: 10.2196/jmir.7867] [Medline: 29563076]
38. Georgsson M, Staggers N, Årsand E, Kushniruk A. Employing a user-centered cognitive walkthrough to evaluate a mhealth diabetes self-management application: a case study and beginning method validation. J Biomed Inform 2019 Mar;91:103110 [FREE Full text] [doi: 10.1016/j.jbi.2019.103110] [Medline: 30721757]
39. Walsh L, Hemsley B, Allan M, Adams N, Balandin S, Georgiou A, et al. The e-health literacy demands of Australia's my health record: a heuristic evaluation of usability. Perspect Health Inf Manag 2017;14(Fall):1f [FREE Full text] [Medline: 29118683]
40. Robbins R, Senathirajah Y, Williams NJ, Hutchinson C, Rapoport DM, Allegrante JP, et al. Developing a tailored website for promoting awareness about obstructive sleep apnea (OSA) among blacks in community-based settings. Health Commun 2019 May;34(5):567-575 [FREE Full text] [doi: 10.1080/10410236.2018.1423865] [Medline: 29338353]
41. Richardson S, Mishuris R, O'Connell A, Feldstein D, Hess R, Smith P, et al. 'Think aloud' and 'near live' usability testing of two complex clinical decision support tools. Int J Med Inform 2017 Oct;106:1-8 [FREE Full text] [doi: 10.1016/j.ijmedinf.2017.06.003] [Medline: 28870378]
42. Cotton D, Gresty K. Reflecting on the think-aloud method for evaluating e-learning. Br J Educ Technol 2006 Jan;37(1):45-54. [doi: 10.1111/j.1467-8535.2005.00521.x]
43. Brandeis University. Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36) URL: https://www.brandeis.edu/roybal/docs/SF-36_website_PDF.pdf [accessed 2018-11-11]
44. Kreuter M, Farrell DW, Olevitch LR, Brennan LK. Tailoring Health Messages: Customizing Communication With Computer Technology. Mahwah, NJ: Lawrence Erlbuam; 1999.
45. Rice RE, Atkins CK, editors. Public Communication Campaigns. Thousand Oaks, CA: Sage Publications; 2001.
46. Eastin M, Larose R. Internet self-efficacy and the psychology of the digital divide. J Comput Mediat Commun 2006;6(1):-. [doi: 10.1111/j.1083-6101.2000.tb00110.x]
47. Lattie EG, Kaiser SM, Alam N, Tomasino KN, Sargent E, Rubanovich CK, et al. A practical do-it-yourself recruitment framework for concurrent ehealth clinical trials: identification of efficient and cost-effective methods for decision making (part 2). J Med Internet Res 2018 Nov 29;20(11):e11050 [FREE Full text] [doi: 10.2196/11050] [Medline: 30497997]
48. Durant RW, Legedza AT, Marcantonio ER, Freeman MB, Landon BE. Willingness to participate in clinical trials among African Americans and whites previously exposed to clinical research. J Cult Divers 2011;18(1):8-19 [FREE Full text] [Medline: 21526582]
49. Wells JS, Pugh S, Boparai K, Rearden J, Yeager KA, Bruner DW. Cultural competency training to increase minority enrollment into radiation therapy clinical trials-an NRG oncology RTOG study. J Cancer Educ 2017 Dec;32(4):721-727 [FREE Full text] [doi: 10.1007/s13187-016-1051-0] [Medline: 27209044]
50. Killien M, Bigby J, Champion V, Fernandez-Repollet E, Jackson R, Kagawa-Singer M, et al. Involving minority and underrepresented women in clinical trials: the national centers of excellence in women's health. J Womens Health Gend Based Med 2000 Dec;9(10):1061-1070. [doi: 10.1089/152460900445974] [Medline: 11153102]
51. Eggly S, Hamel LM, Heath E, Manning MA, Albrecht TL, Barton E, et al. Partnering around cancer clinical trials (PACCT): study protocol for a randomized trial of a patient and physician communication intervention to increase minority accrual to prostate cancer clinical trials. BMC Cancer 2017 Dec 2;17(1):807 [FREE Full text] [doi: 10.1186/s12885-017-3804-5] [Medline: 29197371]
52. Clinical Trials. Trends, Charts, and Maps URL: https://clinicaltrials.gov/ct2/resources/trends [accessed 2018-09-27]
53. National Institutes of Health (NIH) — All of Us. URL: https://allofus.nih.gov/ [accessed 2020-03-28]

Abbreviations

ACT Now!: Advancing People of Color in Clinical Trials Now!
CCRTP: cultural competency and recruitment training program
CONSORT: consolidated standards of reporting trials
CSC: community steering committee
eHealth: electronic health
IRB: institutional review board

NIH: National Institutes of Health
NYU: New York University

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Protocol

A Web-Based Program for Cannabis Use and Psychotic Experiences in Young People (Keep It Real): Protocol for a Randomized Controlled Trial

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Abstract

Background: Young Australians (16-25 years) have the highest rates of past-month cannabis use in the world. Cannabis use increases the risk of alcohol and other drug disorders and depressive disorders, and has a robust dose-response association with psychotic experiences (PEs) and disorders. PEs are subthreshold positive psychotic symptoms, including delusions and hallucinations, which increase the risk of substance use, depressive or anxiety disorders, and psychotic disorders. Access to effective web-based early interventions targeting both cannabis use and PEs could reduce such risk in young people.

Objective: The objective of this study is to determine the efficacy and cost-effectiveness of the *Keep it Real* web-based program compared to an information-only control website among young cannabis users (16-25 years) with PEs.

Methods: Participants are recruited online, and consenting individuals meeting inclusion criteria (aged 16-25 years, who have used cannabis in the past month and experienced PEs in the past 3 months) are automatically randomized to either the *Keep it Real* web-based program (n=249) or an information-only control website (n=249). Both websites are self-guided (fully automated). The baseline and follow-up assessments at 3, 6, 9, and 12 months are self-completed online. Primary outcome measures are weekly cannabis use, PEs, and the relative cost-effectiveness for quality-adjusted life years. Secondary outcomes include other substance use and related problems, PE-related distress, cannabis intoxication experiences, severity of cannabis dependence, depression/anxiety symptoms, suicidality, and mental well-being and functioning.

Results: Recruitment commenced in February 2019, and the results are expected to be submitted for publication in mid-2021.

Conclusions: This study protocol describes a large randomized controlled trial of a new web-based program for young cannabis users experiencing PEs. If effective, the accessibility and scalability of *Keep it Real* could help reduce growing public health concerns about the significant social, economic, and health impacts of cannabis use.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618001107213; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374800

International Registered Report Identifier (IRRID): DERR1-10.2196/15803

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KEYWORDS

cannabis; marijuana; substance use; psychotic; psychotic experiences; psychosis; digital intervention; web-based program; eHealth; adolescent; CBT; motivational interviewing; mindfulness; education; well-being

Introduction

Young adults aged 18-24 years (23%) have the highest rates of past-year cannabis use in Australia [1]. This is alarming as cannabis influences cognitive and affective brain development [2,3], and accounts for 10.8% and 6.2% of the health burden in males and females, respectively [4]. It is estimated that one in six adolescents who try cannabis will develop dependence and daily users are at 18 times the risk [2,5,6]. Cannabis users are also at 3-4 times the risk of developing alcohol and other drug (AOD) use disorders, which increases to 8 times among daily users [2,5,6]. Any use and heavy use of cannabis also increase the risk of later depression symptoms and disorders (OR 1.17-1.62) [7]. Long-term use is associated with poor cognitive, educational, social, psychological, and physical health outcomes, which can have profound and lasting effects on the individual, his/her family, and the community [2,3,6].

Cannabis has a robust dose-response association with psychotic symptoms and disorders. A meta-analysis of 11 longitudinal population-based studies found that cannabis users were 40% more likely to report psychotic symptoms, and had *2.6 times* the risk of developing a psychotic disorder, with the level of risk increasing in a dose-response manner [8]. Heavy cannabis users have a fourfold risk of developing psychotic disorders [9]. Between 40% and 74% of young people with first-episode psychosis use cannabis, which has been associated with poorer clinical, social, and functional outcomes [10]. Cannabis use also increases the risk of psychotic relapse and hospital readmission, and cannabis cessation reduces the risk to the same level as nonusers [11-13]. Treatment-seeking samples of young people meeting ultrahigh-risk criteria for psychosis (ie, a family history of psychosis, brief intermittent psychotic symptoms, or attenuated psychotic symptoms) who heavily use cannabis and/or meet criteria for DSM-IV cannabis abuse or dependence are also more likely to develop a psychotic disorder (OR 1.75) [14,15].

Cannabis use has been strongly linked to psychotic experiences (PEs), which are subthreshold psychotic symptoms, including delusions and hallucinations. PEs are familial, heritable, and share many genetic, social, and environmental risk factors with the clinical phenotype of psychosis [16]. They are much more common in the general population than psychotic disorders (whose lifetime prevalence is 1%-3%), with an 11.9% median lifetime prevalence of self-reported PEs reported across 13 epidemiological general population cohort studies [17]. A 12-month prevalence rate of up to 28% have been reported in community samples of adolescents and young adults [18]. This is concerning, as a meta-analysis of six studies reported that people with PEs have 3.5 times the risk of developing later a psychotic disorder over a 3- to 24-year period, with the level of risk increasing with the severity/persistence of PEs [19]. PEs are also an important marker for other adverse mental health outcomes [16]. They have been found to triple the risk of later substance use disorders in a dose-response manner [20]. Young people with PEs are also at increased risk of current depression (6.5 times) or anxiety disorders (5 times), suicidal thoughts (3 times), and suicide attempts (4 times) [21-23].

Cannabis use has been strongly associated with PEs in general population samples. Up to 90% of past-week cannabis users reported PEs in the same week in an experience sampling method study [24]. A growing number of prospective studies have demonstrated a dose-response relationship between cannabis use and PEs in young people [25-27]. Changes in cannabis use have also been found to result in concomitant increases or decreases in PEs in a 5-year study among young adults [28]. A 20-year follow-up study found that weekly and occasional cannabis use in adolescence was associated with 4.3 and 2.3 times the relative risk of continuously high PEs, respectively [29]. This dose-response relationship between cannabis use and PEs has also been confirmed in biological and experimental studies using hair samples following smoking or intravenous administration of tetrahydrocannabinol (THC) [30].

Together, this research indicates that cannabis use is a preventable risk factor for PEs as well as for a range of other adverse substance use and mental health symptoms and disorders in young people [3]. A targeted early intervention that provides optimal treatment for cannabis use and PEs could reduce the risk of these adverse outcomes, and their associated personal, social, economic, and health costs [31]. However, less than 8% of people with cannabis use disorders [32], 13% of 18-year olds with PEs, and 52% of those with psychotic disorders have ever sought professional help [33]. Young cannabis users with PEs may be even less likely to seek help due to concerns about confidentiality and stigma. It is also unclear where young cannabis users with PEs should seek help. Mental health services may view PEs as substance related or not serious enough to warrant treatment. AOD services may also turn them away as their PEs may be considered too severe for AOD treatment settings. Web-based and mobile phone–based treatments provide an anonymous, and highly accessible way of delivering evidenced-based, high-quality psychological treatment to young people who are the most frequent users of the internet (United Kingdom: 100% males, 98% females; United States: 98%; Australia: 100%, 90% ≥3 times/day) [34-36].

Cognitive behavior therapy (CBT) has an established evidence base for multiple mental health difficulties. CBT effectively treats cannabis use when delivered face-to-face or via the web [37,38]. Web-based CBT programs also effectively reduce anxiety and depression symptoms and disorders [39]. Although systematic reviews have found web-/mobile-based programs for people with psychosis to be highly acceptable, usable, and engaging, and reduced the severity of psychotic symptoms and risk of transition to psychotic disorders among help-seeking patients at ultrahigh-risk for psychosis [40,41], no web-based

early interventions for PEs have been tested in a randomized controlled trial (RCT) to date.

To address this gap, we developed the stand-alone *Keep it Real* (Version 1) web-based program which targets cannabis use and PEs in young people. The feasibility and outcomes of *Keep it Real* were tested in a pilot study among 213 young people (16-25 years), who had used cannabis in the past month and reported subthreshold PEs in the past 3 months (Community Assessment of Psychic Experience [CAPE-15] score of >18). The pilot study recruited 1089 past-month cannabis users over a period of 6 months using university student emails and social media and website posts. Almost all young people (95%) accessed the CAPE-15 PE feedback as well as a mean of 2.94 (SD 1.82) of the six *Keep it Real* modules. On average, they gave the program a rating of 4 out of 5 for overall objective quality on the eHealth Rating Scale (mean total score=3.82, SD 0.57), with good engagement (mean 3.29, SD 0.63) and high levels of functionality (mean 4.13, SD 0.72), aesthetics (mean 4.11, SD 0.68), and information (mean 4.14, SD 0.65) quality. High retention rates were achieved in the 3-month (n=200, 88.5%) and 6-month (n=180, 84.5%) follow-ups. Participants achieved significant reductions (all $P<.001$) in the frequency of cannabis use (Cohen *d* effect size=0.36, $d=0.46$) and related problems (*d* effect size=0.45, $d=0.48$) as well as the frequency of PEs (*d* effect size=0.67, $d=0.70$) and their associated distress (*d* effect size=0.33, $d=0.40$) at 3- and 6-months follow-up, respectively. Moderate effect sizes were found for reductions in cannabis use and related problems and PE-related distress, and large reductions in the frequency of PEs were found. Neither the frequency of cannabis use nor PEs at baseline had an impact on website engagement, retention rates, or treatment outcomes. Together, these results provide preliminary evidence that the *Keep it Real* web-based program could be effective and acceptable among young cannabis users with PEs.

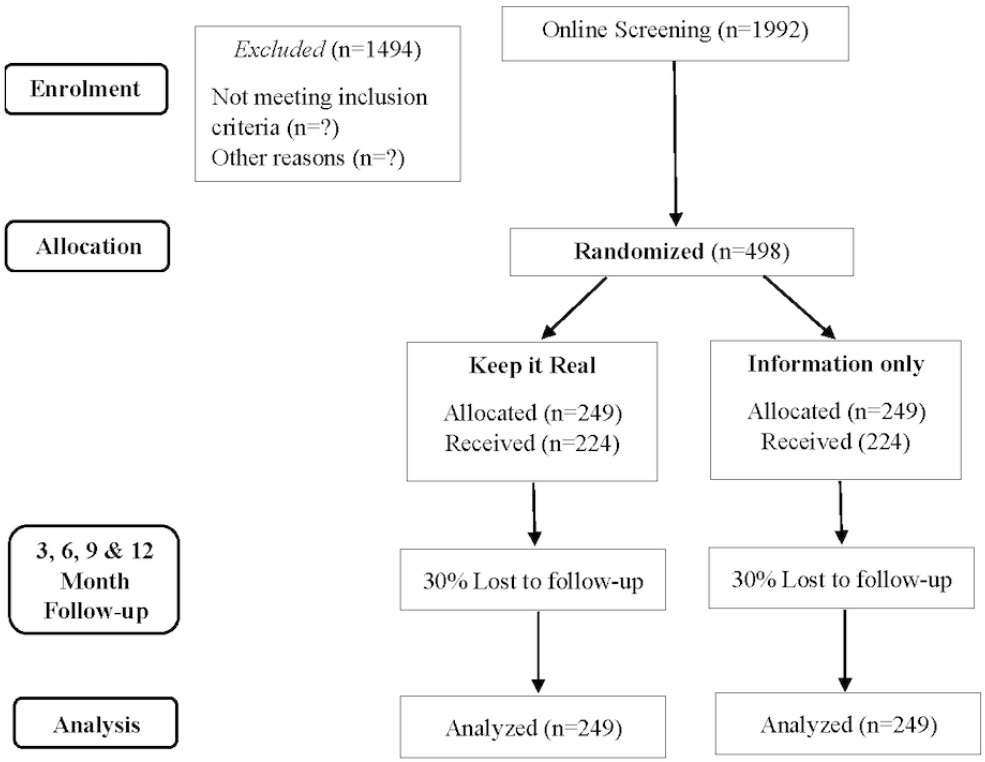
This protocol paper describes an RCT aimed at determining the efficacy and cost-effectiveness of *Keep it Real* (Version 2) compared to an information control website (ICW) among young people: (i) aged 16-25 years, who have (ii) used cannabis in the past month, and (iii) experienced PEs in the past 3 months. It is hypothesized that *Keep it Real* will result in significantly greater improvements in primary outcome variables of cannabis use and PEs, and will be more cost-effective than the ICW control condition. Secondary outcomes such as cannabis, alcohol, tobacco, and other substance use and related problems, including PE-related distress, cannabis intoxication experiences, the severity of cannabis dependence, depression/anxiety symptoms, suicidality, mental well-being, and functioning; and baseline moderators of intervention effects (eg, childhood trauma, impulsivity, urbanicity, lifetime psychotic disorder) will also be examined.

Methods

Trial Design

The trial is a two-arm, parallel group (1:1 ratio) superiority RCT that will determine the efficacy and cost-effectiveness of the *Keep it Real* web-based program, compared to an ICW. Assessments are completed at baseline, and at 3, 6, 9, and 12 months follow-up. The trial has ethics committee approval, is registered (ACTRN12618001107213), and follows Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) research protocol guidelines (see supplementary materials) as well as Consolidated Standards of Reporting Trials (CONSORT) eHealth guidelines (see Figure 1) [42,43].

Figure 1. Anticipated CONSORT (Consolidated Standards of Reporting Trials) diagram.



Recruitment and Procedures

This project will utilize a secure, automated web-based project and data management system for RCTs. A two-step recruitment and informed consent process will be used. Young people aged 16-25 years who have used cannabis in the past month will be first asked to complete an online survey on *Cannabis and Psychotic Experiences*, and repeat the survey 6 and 12 months later. They are recruited online via university student emails and posts and paid advertising to social media (eg, Facebook) and substance use-related websites (eg, Cannabis Information Service) containing a link to an online consent form and survey. Snowballing techniques will be used and participants will be offered a reimbursement incentive of Aus $10 for referring a friend to the study. Consenting participants (via a checkbox) self-complete all baseline and follow-up assessments online. Survey logic automatically screens participants for eligibility. Participant contact details (name, email address, mobile number) and the IP address of respondents will be manually checked to identify repeat or duplicate surveys. Participants who give contact details that appear false, for example, multiple similar names or email addresses, will be excluded. All baseline, 6-, and 12-month survey completers will be entered in a draw to win 1 out of 10 Aus $100 gift vouchers.

Young people are asked if they are interested in trialing the *Keep it Real* website (via a checkbox) on the online survey consent form, and again at the end of the baseline survey. Those who express interest in trialing the website and score a minimum of 18 on the CAPE-15, which is indicative of at least three PEs "sometimes" or one PE "nearly always" in the past 3 months, are eligible to participate in the RCT. They are also required to have internet access and to provide a mobile number and email address. People who use alcohol or other illicit drugs are included as long as cannabis is the most frequently used drug (other than tobacco). Exclusion criteria will be (i) history of traumatic brain injury or organic brain disease, (ii) current acute suicide risk, and (iii) insufficient English fluency. Eligible participants are automatically sent the consent form for the RCT, and those who provide consent (via a checkbox) are randomized and sent an email and SMS link to either the *Keep it Real* web-based program or information-only control website. They are not informed about which website program they are allocated to. The study information sheet states that both programs provide information on PEs, psychosis, and cannabis use. They differ by their level of interactivity.

Young people who are ineligible for the RCT remain participants in the original survey study and are provided with immediate access to the *Keep it Real* website. Those in the RCT are automatically sent follow-up surveys at 3, 6, 9, and 12 months postbaseline via SMS and email. Noncompleters will be contacted via telephone by outcome assessors blind to treatment allocation to remind them to complete the survey online or over the phone. Participants are reimbursed Aus $20 for completing each follow-up survey (maximum of Aus $80). If a participant chooses to withdraw from the study, they will still be able to continue using *Keep it Real* or the ICW. The trial statistician will be blind to treatment group allocation.

Measures

All measures are self-reported and the follow-up frequency is provided in Table 1. Demographic variables include sex, gender, occupation, education, employment, living arrangements, urbanicity, relationship status, migration status, ethnicity, estimated hours of internet use/day, family and personal history of mental and substance use disorders, and history of traumatic brain injury or organic brain disease.

Table 1. Assessment timeline.

Measure	Baseline	3 months	6 months	9 months	12 months
1. (Screen) Cannabis use in past month, age	✓				
2. (Screen) CAPE-15[a]	✓	✓	✓	✓	✓
3. Demographics	✓				
4. Psychosis screen	✓	✓	✓	✓	✓
5. Suicidality screen	✓	✓	✓	✓	✓
6. OTI[b] for cannabis	✓	✓	✓	✓	✓
7. ASSIST[c]	✓	✓	✓	✓	✓
8. GAD-7[d], PHQ-9[e]	✓	✓	✓	✓	✓
9. Cannabis knowledge	✓	✓	✓	✓	✓
10. SDS[f]	✓	✓	✓	✓	✓
11. SUPPS-P[g]	✓				✓
12. CEQ-I[h]	✓	✓	✓	✓	✓
13. MHC-SF[i]	✓	✓	✓	✓	✓
14. MAFS[j]	✓	✓	✓	✓	✓
15. CTQ[k]	✓				
16. EQ-5D-5L[l] scale	✓	✓	✓	✓	✓
17. Health and service utilization	✓	✓	✓	✓	✓
18. eHRS[m]		✓			

[a]CAPE-15: Community Assessment of Psychic Experiences.
[b]OTI: Opiate Treatment Index.
[c]ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test.
[d]GAD-7: Generalized Anxiety Disorder.
[e]PHQ-9: Patient Health Questionnaire.
[f]SDS: Severity of Dependence Scale.
[g]SUPPS-P: Short UPPS-P Impulsive Behavior Scale.
[h]CEQ-I: Cannabis Experiences Questionnaire-Intoxication.
[i]MHC-SF: Mental Health Continuum-Short Form.
[j]MAFS: Multidimensional Adolescent Functioning Scale.
[k]CTQ: Childhood Trauma Questionnaire.
[l]EQ-5D-5L: 5-dimension version of the European Quality of Life 5-level.
[m]eHRS: eHealth Rating Scale.

Primary Outcomes

The primary outcome measures for cannabis use and psychotic like experiences are described below:

1. Cannabis use: The AOD section of the Opiate Treatment Index (OTI) will be used to assess the frequency (≤once a week; >once a week; ≥daily) and the mean amount of cannabis (in 1/4 gram standard units) per day in the past month [44]. As cannabis use is difficult to quantify, young people will be able to select their own cannabis unit (grams/cones/pipes/joints/$ spent/mixed with tobacco/shared), which will be converted into 0.25 gram cannabis units using standardized criteria [45].
2. Psychotic-like experiences: PEs are assessed with the 15-item version of the 20-item positive scale of the Community Assessment of Psychic Experiences (CAPE) measure. The CAPE-15 measures the frequency (1=never to 4=nearly always) and level of distress (1=not distressed to 4=very distressed) related to PLEs in the past 3 months [46]. This version has high levels of internal consistency and a more optimal three-factor structure, consisting of persecutory ideation, bizarre experiences, and perceptual abnormalities [46]. This 3-factor structure was replicated in a meta-analysis [47].

Secondary Outcomes

A number of secondary outcomes will also be measured, as outlined below:

1. AOD-related problems: The 8-item Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) provides a measure of the frequency of substance use and related problems in the past 3 months for 10 substance classes [48]. It has well-established reliability and validity across a range of age groups and populations, including people with first-episode psychosis [48,49].
2. Depression/anxiety symptoms: The 9-item Patient Health Questionnaire (PHQ-9) and the 7-item Generalized Anxiety Disorder (GAD-7) scales will be used to assess depression and general anxiety symptoms in the previous 2 weeks. PHQ-9 and GAD-7 have been validated across a number of populations including adolescents, young adults, and substance users [50-53].
3. Suicidality: Suicidal ideation, plans, and attempts will be assessed using the 6-item Suicidality Scale of the Mini-International Neuropsychiatric Interview (MINI) [54].
4. Well-being: The 14-item version of the Mental Health Continuum-Short Form (MHC-SF) [55] ask participants about their emotional, psychological, and social well-being in the past month. The MHC-SF has been found to be reliable and valid in young adults [56].
5. Cannabis experiences: The Cannabis Experiences Questionnaire-Intoxication (CEQ-I) scale is a 13-item measure of the paranoid-dysphoric (PEs) and euphoric effects of cannabis intoxication validated in young adults [57].
6. Dependence: The Severity of Dependence Scale (SDS), a 5-item measure, will be used to assess the severity of psychological dependence on cannabis in the past 3 months. The SDS is validated for use in cannabis users and people with early psychosis [58,59].
7. Functioning: The Multidimensional Adolescent Functioning Scale (MAFS) is a 23-item self-reported measure of general, family, and peer-related functioning with good psychometric properties [60].

Cost-Effectiveness

Health-related quality of life will be assessed using the 5-dimension version of the European Quality of Life 5-level (EQ-5D-5L) scale [61]. Information on other health care service use including medical and psychological treatment for substance use and other issues in the month prior to each assessment point will be collected.

Other Measures

A number of other measures will also be included in the survey:

1. Lifetime psychotic disorders: The psychosis screen (patient form), which contains 6 items and up to 4 supplementary items for positive responses, will be used to identify lifetime psychotic disorders [62]. A cutoff score of ≥2, which has 67% sensitivity and 84% specificity, will be used [62]. Participants who answer positively to any of the items will also be asked to describe their experience in more detail in an open-ended response format. All responses will be checked prior to randomization to reduce the likelihood of false positives. A 3-month version of the psychosis screen will be used at follow-up.
2. Knowledge: In all, 19 questions will assess the young person's level of knowledge about cannabis and its effects, with response options of "true" or "false." The total score reflects the number of correct answers.
3. Impulsivity: The 20-item Short UPPS-P Impulsive Behavior Scale (SUPPS-P) provides a measure of the 5-factor model of impulsivity consisting of: (i) negative urgency (tendency to act rashly under extreme negative emotions), (ii) lack of premeditation (tendency to act without thinking), (iii) lack of perseverance (inability to remain focused on a task), (iv) sensation seeking (tendency to seek out novel and thrilling experiences), and (v) positive urgency (tendency to give into impulses when experiencing high positive affect) [63]. Higher levels of impulsivity and sensation seeking have been reported in first-episode psychosis in patients with rather than without cannabis abuse; and has been associated with PEs among young cannabis [64,65].
4. Childhood trauma: The Childhood Trauma Questionnaire (CTQ) is a valid and reliable 28-item measure of childhood abuse and neglect [66]. Childhood trauma will be included as a potential moderator, due to evidence that it may increase the risk of cannabis use, PEs, and other mental health issues [67].
5. Website evaluation: The 26-item eHealth Rating Scale, which is based on the Mobile App Rating Scale user version, will be utilized to measure the usability, engagement, aesthetics, information quality, and perceived impact of web-based programs at the 3-month follow-up [68]. Participants are also asked to provide a written feedback on the website.

Randomization

A computerized random number sequence generator incorporating random permuted blocks will be used to allocate participants to: (i) *Keep it Real* or (ii) ICW. Stratification will be by cannabis usage (daily or less), sex, age (16-20 years and 21-25 years), and psychosis screen result (present vs not present). The randomization sequence is concealed within the secure website and the allocation is automatically released when full eligibility criteria are met.

Interventions

Young cannabis users who meet RCT inclusion criteria and consent to participate are automatically randomized to either the *Keep it Real* or ICW program, and are sent an email and SMS link to the relevant program. Both programs are accessible via login on any computer, tablet, or mobile device with an internet connection. They are password protected and are sited on parallel, secure servers. Both programs are self-guided (fully automated), and all website modules are unlocked and can be accessed by the user at any time. SMS reminders to access both programs will be sent on day 7, 14, and 21 after baseline. Participants' "backend" usage data will be automatically captured by the website, including logins, modules accessed/completed, inserted text, and dates of data entry. All participants have continuous access to the Get Help section of the website, which provides the contact details of mental health and AOD services (including crisis care).

Keep It Real Web-Based Program

The *Keep it Real* program (Version 2) consists of seven modules that can be completed in 30-90 minutes over 1-3 sessions (via login). Version 1 of *Keep it Real*, which was tested in the initial pilot study, only targeted cannabis use. Version 2 targets cannabis, alcohol, methamphetamine, and heroin use. Each module ends with a printable summary screen. PEs are targeted first, given young people are more likely to be concerned about PEs than their cannabis use. The first three modules aim to increase the users' ability to identify, understand, and reduce distress associated with PEs. The program content was informed by the *Think You're Crazy? Think Again* [69] self-help book, based on Morrison's evidence-based CBT treatment for people at "ultrahigh risk" for psychosis (including those with PEs) [70-72]. Module 1 defines PEs and provides a detailed personal feedback on self-reported PEs relative to age-related and gender-specific norms. Module 2 provides information on risk factors for PEs (including cannabis use, trauma, stress, anxiety/depression), psychotic symptoms, and disorders using fact sheets and videos. Module 3 provides information and normative data on different subtypes of PEs and suggests a number of simple CBT techniques for their management. These modules were originally developed for the *Get Real* web-based program for young people with PEs. A small pilot study in 12 young people found that the program had high levels of acceptability and perceived utility, and resulted in significant reductions in the frequency and level of distress associated with PEs at the 3-month follow-up [73].

Modules 4 and 5 use motivational interviewing techniques to target cannabis, alcohol, methamphetamine, and heroin use. The program content was informed by evidence-based brief motivational interviewing interventions for cannabis use, including web-based programs [37,38,74]. A series of participatory design workshops with young people in residential treatment for substance use problems were also conducted to develop and refine the program content. Interactive quizzes on cannabis, alcohol, methamphetamine, and heroin use are included to increase their substance use knowledge. Young people are also given personal feedback on their substance use and related problems, relative to age-related and gender-specific norms. Participants can complete and receive normative feedback on the CEQ-I to increase awareness of the relationship between cannabis use and PEs [57]. They are then encouraged to set harm minimization or change goals and develop a plan for achieving them using harm minimization skill and change goal checklists.

Module 6 targets users' coping skills by providing training in cognitive behavioral techniques including stress management, problem solving, behavioral activation, and attention control retraining (mindfulness). Module 7 encourages appropriate help seeking for PEs and/or cannabis use and addresses any barriers to doing so.

Participants can track their PEs (CAPE-15), cannabis intoxication effects (CEQ-I), substance use and related problems over time, and receive feedback on age-related and gender-specific norms each time they complete the measures. An interactive graphical summary of their PE, CEQ-I, cannabis, alcohol, methamphetamine, and heroin use and related problems over various time frames (self-selected) is also available to increase participants' awareness of the relationship between their substance use and PEs.

Information Control Website

This program delivers the information sheets from the *Keep it Real* program in a 4-module web-based format including: (i) What are weird experiences? (ii) How does cannabis affect me? (iii) How does other substance use affect me? (iv) Should I seek help? Further reading sheets are also available from a "Fact Sheets" menu containing: (i) What is psychosis? (ii) Am I at risk of developing psychosis? (iii) What is schizophrenia? (iv) What is bipolar disorder? (v) Facts about cannabis/alcohol/amphetamines/heroin. This control condition was designed to provide participants with access to the type of web-based information they may have found naturally online. It does not provide personal feedback from assessments or normative feedback on substance use or PEs at baseline or follow-up. No information is given on how to manage PEs nor do the resources focus on building motivation to change substance use or increasing users' understanding of the relationship between their substance use and PEs.

Project and Risk Management

Weekly meetings monitor project implementation, clinical (including study withdrawals, adverse events), and research integrity (including data safety, important harms or unintended effects, blindness violations). Email or telephone consultations will be used to determine urgent issues, and a record of decision precedents will be kept to ensure consistency. Suicide and psychosis safety protocols identify and manage risk at all survey time points. Participants with a positive psychosis screen or who report a low level of suicide risk (MINI Suicidality Scale score of 1-5) receive a message in the online survey and an email providing details of appropriate support services and helplines. They are also asked to contact the research team if they have additional questions or would like assistance finding support. Those who report a moderate (Suicidality Scale score of 6-9) or high (10+) level of suicide risk are asked if they are receiving adequate support and if their feelings have recently improved (due to the 1-month time frame of the measure). If the participant answers yes to both questions, no further action is taken. If they answer yes to one of these questions or request further support, they are called within 48 hours by a research assistant to assess how further support can be provided (using a call script). Those who report a suicide plan or a suicide attempt within the past month are contacted by a trained clinical psychologist, who assesses the level of risk and helps the participant connect with appropriate supports.

Sample Size Calculation

Power calculations to determine sample size were based on the effects found in the *Keep it Real* pilot study, which found a moderate effect size for reductions in the frequency of cannabis use (d=0.46). Due to the uncontrolled nature of the pilot study, a conservative approach using small to moderate effects was used. To measure a moderate effect size of f=.20, alpha (α) set at 0.025, and power set at 0.95, we would require 191

participants per group (a total of 382 participants). If baseline covariates accounting for about 40% of the variability in the outcome model were included in the calculations, then we would have 0.99 power to detect a small to moderate treatment effect. We predict a 20%-30% attrition rate at 12 months based on our pilot data and previous work and will therefore need to randomize a total of 498 participants.

The pilot study recruited 1089 past-month cannabis users over a period of 6 months (using the same recruitment strategies) to identify 860 monthly cannabis users meeting our PE inclusion criterion (CAPE-15≥18). Of these, 295 (34%) expressed interest in participating in the *Keep it Real* pilot trial (66 [7%] no interest; 503 [58%] no response) and 213 (72% of those interested; 25% of the total sample) were randomized. We will, therefore, need to recruit 1992 cannabis users in order to randomize 498 participants (see Figure 1).

Data Analyses

The independent variable is a treatment condition with two levels: (i) *Keep it Real* and (ii) the ICW. The primary outcome variable is the frequency and average amount of cannabis/day (in 1/4 gram standard units) in the past month (on the OTI) and the frequency of PEs (CAPE-15, including subscales) in the past 3 months. Secondary outcome variables include the typical quantity and frequency of alcohol, tobacco, cannabis, and other drug use and related problems in the past 3 months (ASSIST), cannabis knowledge, PE-related distress (CAPE-15), cannabis intoxication experiences (CEQ-I), severity of cannabis dependence (SDS), depression (PHQ-9)/anxiety (GAD-7) symptoms, suicidality (MINI), mental well-being (MHC-SF), and functioning (MAFS). To determine whether there are group differences in the primary and secondary outcome measures at 3, 6, 9, and 12 months, a series of mixed effects models for repeated measures (MMRM) will be employed. The within-groups factor will be time (baseline, 3, 6, 9, 12 months) and group (*Keep it Real*, ICW) will be the between-subjects factor to examine the timexgroup interaction. This technique can also control for potential confounds (eg, other drug use and related problems) and examine potential baseline moderators of intervention effects (eg, age, gender, childhood trauma [CTQ], impulsivity [SUPPS-P], urbanicity, cannabis knowledge, lifetime psychotic disorder). Missing data will be handled using full information maximum likelihood estimation and an intention-to-treat analysis is performed.

A two-pronged economic analysis comparing *Keep it Real* and ICW will be conducted, taking a societal perspective, including costs of treatment provision and intervention (including website development and maintenance) as well as productivity costs. The analysis will display the cost-effectiveness in both natural units and as QALYs (based on the EQ-5D-5L). Models will assess *Keep it Real*'s offset on reduced health care service use and productivity losses are avoided. In a second modeled cost-effectiveness analysis (CEA), the estimated change in cannabis consumption from the trial will be extrapolated to the general Australian population of 16-25-year olds. Uncertainty will be assessed using a combination of nonparametric bootstrapping for the effect size (cannabis frequency) and Monte Carlo simulation for all other variables (with sampling uncertainty).

Results

Recruitment commenced in February 2019, and is now closed for recruitment. The results are expected to be submitted for publication in mid-2021.

Discussion

Overview

Large numbers of young cannabis users report PEs, which increase their risk of developing psychotic, substance use, and depressive/anxiety disorders. Current services are failing to engage these young people—and would struggle to meet the need if they did seek help. An effective, safe, low-cost, nonstigmatizing accessible intervention is needed. Our pilot data showed that the *Keep it Real* program resulted in substantial reductions in both PEs and cannabis use, and young people found the program engaging and easy to use. This study protocol describes a large RCT that will determine if *Keep it Real* is more efficacious and cost-effective than the minimal web-based information they may otherwise receive.

Strengths and Limitations

Engaging large numbers of young nonhelp-seeking cannabis users into web-based treatment is challenging, as they are unlikely to view their cannabis use as problematic or responsible for their PEs. However, the pilot study clearly demonstrated the feasibility of recruiting young cannabis users with PEs (79% of survey completers), with 72% of the 34% who expressed interest agreeing to be randomized to the trial. The pilot study also highlighted the acceptability of *Keep it Real*, as young people gave the program an average rating of 4 out of 5 for overall objective quality, and the functionality, aesthetics, and information subscales and a 3 out of 5 rating for engagement. Moreover, the pilot study provided preliminary evidence for the efficacy of *Keep it Real* as well as valuable data on the participation/retention rates and effect sizes to inform sample size which was used to ensure that this RCT is well powered.

Young people will be asked if they were interested in participating in the RCT prior to receiving feedback on their PEs. While this recruitment strategy will ensure that all young people are given the opportunity to participate, it may increase the risk of selection bias by potentially excluding those with little insight into their PEs. Nevertheless, the inclusion of people with a lifetime history of a psychotic disorder and the stratification of the randomization sequence by psychosis screen result may help reduce such risk of bias.

The inclusion of a range of potential control variables and moderators of treatment outcomes is a further strength of the study. However, mediators were not included due to concerns about potential assessment reactivity, the existing length of the assessment schedule, and participant burden. *Keep it Real* participants are able to monitor their PEs and substance use within the program. The extent of monitoring observed in this study will provide an indication of young cannabis users'

willingness to engage in regular assessments for future studies exploring potential mediators of change.

The number of modules in the *Keep it Real* and ICW programs are not matched, but the ICW program contains the same number of information sheets as the *Keep it Real* program. While it could be argued that the smaller amount of content in the ICW may be insufficient to produce an effect, this control condition was designed to control access to a web-based program and the minimal amount and type of information users may otherwise receive online. Nevertheless, it is possible that the overlap in content may wash out any differential treatment effects between programs.

Conclusion

Web-based programs are ideal platforms for delivering self-guided treatments to nonhelp-seeking young people with PEs. *Keep it Real* is the first web-based program to target PEs in cannabis users. The program content is based on evidence-based CBT treatments for people at ultrahigh risk for psychosis (which includes a subgroup with PEs) [41] and motivational interviewing interventions for cannabis use [37,38]. *Keep it Real* will be freely available and users will have unlimited 24/7 access to the program, including the PE and substance use monitoring and feedback, enabling the user to engage in continuous self-management. The program also has broad applicability as it can be used as a stand-alone treatment or as an adjunct to usual treatment for help-seeking cannabis users with PEs accessing clinical services. Different components of the program can also be used to address cannabis, alcohol, methamphetamine, or heroin use, PEs, cannabis intoxication effects, and to provide coping skills training. If *Keep it Real* demonstrates a substantial and cost-effective impact on cannabis use and PEs, its low unit cost and scalability would mean that it has substantial potential to make a population-wide impact on both immediate and longer term consequences of cannabis use and their significant social, economic, and health costs.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 816 KB - resprot_v9i7e15803_app1.pdf]

References

1. Australian Institute of Health and Welfare. 2016 National Drug Strategy Household Survey Detailed Report. Canberra: AIHW; 2017. ISBN:9781760541941.
2. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370(23):2219-2227 [FREE Full text] [doi: 10.1056/NEJMra1402309] [Medline: 24897085]
3. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiat 2016;73(3):292-297 [FREE Full text] [doi: 10.1001/jamapsychiatry.2015.3278] [Medline: 26842658]
4. Degenhardt L, Stockings E, Patton G, Hall WD, Lynskey M. The increasing global health priority of substance use in young people. Lancet Psychiatry 2016;3(3):251-264 [FREE Full text] [doi: 10.1016/S2215-0366(15)00508-8] [Medline: 26905480]
5. Blanco C, Hasin DS, Wall MM, Flórez-Salamanca L, Hoertel N, Wang S, et al. Cannabis use and risk of psychiatric disorders prospective evidence from a US national longitudinal study. JAMA Psychiatry 2016;73(4):388-395 [FREE Full text] [doi: 10.1001/jamapsychiatry.2015.3229] [Medline: 26886046]
6. Silins E, Horwood LJ, Patton GC, Fergusson DM, Olsson CA, Hutchinson DM, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. Lancet Psychiatry 2014;1(4):286-293 [FREE Full text] [doi: 10.1016/S2215-0366(14)70307-4] [Medline: 26360862]
7. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med 2014;44(4):797-810 [FREE Full text] [doi: 10.1017/S0033291713001438] [Medline: 23795762]
8. Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370(9584):319-328 [FREE Full text] [doi: 10.1016/S0140-6736(07)61162-3]
9. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophr Bull 2016;42(5):1262-1269 [FREE Full text] [doi: 10.1093/schbul/sbw003] [Medline: 26884547]

10. Zammit S, Moore THM, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, et al. Effects of cannabis use on outcomes of psychotic disorders: systematic review. Br J Psychiatry 2008;193(5):357-363 [FREE Full text] [doi: 10.1192/bjp.bp.107.046375] [Medline: 18978312]
11. Rømer Thomsen R, Thylstrup B, Pedersen MM, Pedersen MU, Simonsen E, Hesse M. Drug-related predictors of readmission for schizophrenia among patients admitted to treatment for drug use disorders. Schizophr Res 2018;195:495-500 [FREE Full text] [doi: 10.1016/j.schres.2017.09.026]
12. Hides L, Dawe S, Kavanagh D, Young RM. Psychotic symptom and cannabis relapse in recent-onset psychosis Prospective study. Br J Psychiatry 2006;189(2):137-143 [FREE Full text] [doi: 10.1192/bjp.bp.105.014308] [Medline: 16880483]
13. Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, et al. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 2016;3(3):215-225 [FREE Full text] [doi: 10.1016/S2215-0366(15)00363-6] [Medline: 26777297]
14. McHugh MJ, McGorry PD, Yung AR, Lin S, Wood SJ, Hartmann JA, et al. Cannabis-induced attenuated psychotic symptoms: implications for prognosis in young people at ultra-high risk for psychosis. Psychol Med 2017;47(4):616-626 [FREE Full text] [doi: 10.1017/S0033291716002671] [Medline: 27821204]
15. Kraan T, Velthorst E, Koenders L, Zwaart K, Ising HK, van den Berg D, et al. Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. Psychol Med 2015;46(4):673-681 [FREE Full text] [doi: 10.1017/S0033291715002329] [Medline: 26568030]
16. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry 2016;15(2):118-124 [FREE Full text] [doi: 10.1002/wps.20310] [Medline: 27265696]
17. Linscott RJ, van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med 2013;43(6):1133-1149 [FREE Full text] [doi: 10.1017/S0033291712001626] [Medline: 22850401]
18. Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. Arch Gen Psychiatry 1996;53(11):1022-1031 [FREE Full text] [doi: 10.1001/archpsyc.1996.01830110060007] [Medline: 8911225]
19. Kaymaz N, Drukker M, Lieb R, Wittchen HU, Werbeloff N, Weiser M, et al. Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. Psychol Med 2012;42(11):2239-2253 [FREE Full text] [doi: 10.1017/S0033291711002911] [Medline: 22260930]
20. Cederlöf M, Kuja-Halkola R, Larsson H, Sjölander A, Östberg P, Lundström S, et al. A longitudinal study of adolescent psychotic experiences and later development of substance use disorder and suicidal behavior. Schizophr Res 2016;181:13-16. [doi: 10.1016/j.schres.2016.08.029] [Medline: 27615409]
21. Varghese D, Scott J, Welham J, Bor W, Najman J, O'Callaghan M, et al. Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. Schizophr Bull 2011;37(2):389-393 [FREE Full text] [doi: 10.1093/schbul/sbp083] [Medline: 19687152]
22. Saha S, Scott JG, Johnston AK, Slade TN, Varghese D, Carter GL, et al. The association between delusional-like experiences and suicidal thoughts and behaviour. Schizophr Res 2011;132(2-3):197-202 [FREE Full text] [doi: 10.1016/j.schres.2011.07.012] [Medline: 21813264]
23. Nishida A, Sasaki T, Nishimura Y, Tanii H, Hara N, Inoue K, et al. Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in adolescents aged 12-15 years. Acta Psychiatr Scand 2010;121(4):301-307 [FREE Full text] [doi: 10.1111/j.1600-0447.2009.01439.x] [Medline: 19614622]
24. Verdoux H, Gindre C, Sorbora F, Tournier M, Swendsen JD. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. Psychol Med 2003;33(1):23-32 [FREE Full text] [doi: 10.1017/S0033291702006384] [Medline: 12537033]
25. Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. Schizophr Bull 2005;31(3):608-612 [FREE Full text] [doi: 10.1093/schbul/sbi027]
26. Kuepper R, van Os J, Lieb R, Wittchen H, Hofler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year followup cohort study. BMJ 2011;342:d738. [doi: 10.1136/bmj.d738] [Medline: 21363868]
27. Mackie CJ, Castellanos-Ryan N, Conrod PJ. Developmental trajectories of psychotic-like experiences across adolescence: impact of victimization and substance use. Psychological Medicine 2011;41(1):47-58 [FREE Full text] [doi: 10.1017/S0033291710000449] [Medline: 20346196]
28. van Gastel WA, Vreeker A, Schubart CD, MacCabe JH, Kahn RS, Boks MP. Change in cannabis use in the general population: a longitudinal study on the impact on psychotic experiences. Schizophr Res 2014;157(1–3):266-270 [FREE Full text] [doi: 10.1016/j.schres.2014.04.023] [Medline: 24930951]
29. Rössler W, Riecher-Rössler A, Angst J, Murray R, Gamma A, Eich D, et al. Psychotic experiences in the general population: a twenty-year prospective community study. Schizophr Res 2007;92(1-3):1-14 [FREE Full text] [doi: 10.1016/j.schres.2007.01.002]

30. Morgan CJA, Gardener C, Schafer G, Swan S, Demarchi C, Freeman TP, et al. Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychol Med 2012;42(2):391-400 [FREE Full text] [doi: 10.1017/S0033291711001322] [Medline: 21798112]
31. Dominguez MDG, Wichers M, Lieb R, Wittchen H, van Os J. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. Schizophr Bull 2011;37(1):84-93 [FREE Full text] [doi: 10.1093/schbul/sbp022] [Medline: 19460881]
32. Hasin DS, Kerridge BT, Saha TD, Huang B, Pickering R, Smith SM, et al. Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: findings from the National Epidemiologic Survey on Alcohol and Related Conditions–III. Am J Psychiatry 2016;173(6):588-599 [FREE Full text] [doi: 10.1176/appi.ajp.2015.15070907] [Medline: 26940807]
33. Zammit S, Kounali D, Cannon M, David AS, Gunnell D, Heron J, et al. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry 2013;170(7):742-750 [FREE Full text] [doi: 10.1176/appi.ajp.2013.12060768]
34. Australian Communications and Media Authority. ACMA Communications Report 2017–18. Melbourne: Australian Communications and Media Authority; 2019.
35. Statista Research Department. 2018. Internet Usage in the United Kingdom URL: https://www.statista.com/topics/3246/internet-usage-in-the-uk/
36. Statista Research Department. 2019. Internet Usage in the United States URL: https://www.statista.com/topics/2237/internet-usage-in-the-united-states/
37. Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L. Psychosocial interventions for cannabis use disorder. Cochrane Database Syst Rev 2016;5(5):CD005336. [doi: 10.1002/14651858.CD005336.pub4] [Medline: 27149547]
38. Hoch E, Preuss UW, Ferri M, Simon R. Digital interventions for problematic cannabis users in non-clinical settings: findings from a systematic review and meta-analysis. Eur Addic Res 2016;22(5):233-242 [FREE Full text] [doi: 10.1159/000445716]
39. Ebert DD, Zarski AC, Christensen H, Stikkelbroek Y, Cuijpers P, Berking M, et al. Internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. PLoS ONE 2015;10(3):e0119895 [FREE Full text] [doi: 10.1371/journal.pone.0119895] [Medline: 25786025]
40. Alvarez-Jimenez M, Alcazar-Corcoles MA, González-Blanch C, Bendall S, McGorry PD, Gleeson JF. Online, social media and mobile technologies for psychosis treatment: a systematic review on novel user-led interventions. Schizophr Res 2014;156(1):96-106 [FREE Full text] [doi: 10.1016/j.schres.2014.03.021] [Medline: 24746468]
41. Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. Psychol Med 2014;44(3):449-468 [FREE Full text] [doi: 10.1017/S0033291713000354] [Medline: 23521867]
42. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Karmela K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
43. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
44. Darke S, Hall W, Wodak A, Heather N, Ward J. Development and validation of a multi-dimensional instrument for assessing outcome of treatment among opiate users: the Opiate Treatment Index. Br J Addict 1992;87(5):733-742 [FREE Full text] [doi: 10.1111/j.1360-0443.1992.tb02719.x] [Medline: 1591524]
45. Norberg N, Mackenzie J, Copeland J. Quantifying cannabis use with the Timeline Followback approach: a psychometric evaluation. Drug Alcohol Depend 2012;121(3):247-252 [FREE Full text] [doi: 10.1016/j.drugalcdep.2011.09.007] [Medline: 21955364]
46. Capra C, Kavanagh DJ, Hides L, Scott J. Current CAPE-15: a measure of recent psychotic-like experiences and associated distress. Early Interv Psychiatry 2017;11(5):411-417 [FREE Full text] [doi: 10.1111/eip.12245] [Medline: 25962504]
47. Winifred M, Toulopoulos T. Psychometric properties of “community assessment of psychic experiences”: review and meta-analysis. Schizophr Bull 2016;42(1):34-44 [FREE Full text] [doi: 10.1093/schbul/sbv175] [Medline: 27460616]
48. Humeniuk R, Ali R, Babor TF, Farrell M, Formigoni ML, Jittiwutikarn J, et al. Validation of the alcohol, smoking and substance involvement screening test (ASSIST). Addiction 2008;103(6):1039-1047 [FREE Full text] [doi: 10.1111/j.1360-0443.2007.02114.x] [Medline: 18373724]
49. Hides L, Cotton SM, Berger G, Gleeson J, O'Donnell C, Proffitt T, et al. The reliability and validity of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in first-episode psychosis. Addict Behav 2009;34(10):821-825 [FREE Full text] [doi: 10.1016/j.addbeh.2009.03.001] [Medline: 19324499]
50. Hides L, Lubman DI, Devlin H, Cotton S, Aitken C, Gibbie T, et al. Reliability and validity of the Kessler 10 and patient health questionnaire among injecting drug users. Aust N Z J Psychiatry 2007;41(2):166-168 [FREE Full text] [doi: 10.1080/00048670601109949]
51. Johnson JG, Harris ES, Spitzer RL, Williams JBW. The patient health questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. J Adolesc Health 2002;30(3):196-204 [FREE Full text] [doi: 10.1016/S1054-139X(01)00333-0] [Medline: 11869927]

52. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
53. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
54. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22-33. [Medline: 9881538]
55. Keyes CLM. Mental illness and/or mental health? Investigating axioms of the complete state model of health. J Consult Clin Psychol 2005;73(3):539-548 [FREE Full text] [doi: 10.1037/0022-006X.73.3.539] [Medline: 15982151]
56. Hides L, Quinn C, Stoyanov SR, Cockshaw W, Mitchell T, Kavanagh D. Is the mental wellbeing of young Australians best represented by a single, multidimensional or bifactor model? Psychiatry Res 2016;241:1-7 [FREE Full text] [doi: 10.1016/j.psychres.2016.04.077] [Medline: 27152903]
57. Quinn CA, Wilson H, Cockshaw W, Barkus E, Hides L. Development and validation of the cannabis experiences questionnaire–Intoxication effects checklist (CEQ-I) short form. Schizophr Res 2017;189:91-96 [FREE Full text] [doi: 10.1016/j.schres.2017.01.048] [Medline: 28189531]
58. Swift W, Copeland J, Hall W. Choosing a diagnostic cut-off for cannabis dependence. Addiction 1998;93(11):1681-1692 [FREE Full text] [doi: 10.1046/j.1360-0443.1998.931116816.x] [Medline: 9926531]
59. Hides L, Dawe S, Young RM, Kavanagh DJ. The reliability and validity of the Severity of Dependence Scale for detecting cannabis dependence in psychosis. Addiction 2007;102(1):35-40 [FREE Full text] [doi: 10.1111/j.1360-0443.2006.01669.x] [Medline: 17207121]
60. Wardenaar KJ, Wigman JTW, Lin A, Killackey E, Collip D, Wood SJ, et al. Development and validation of a new measure of everyday adolescent functioning: the multidimensional adolescent functioning scale. J Adolesc Health 2013;52(2):195-200 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.06.021] [Medline: 23332484]
61. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
62. Jablensky A, McGrath J, Herrman H, Castle D, Gureje O, Morgan V. People Living with Psychotic Illness: An Australian Study 1997-98. Canberra: National Survey of Mental Health and Wellbeing: Report 4, Mental Health Branch, Australian Commonwealth Department of Health and Aged Care; 1999. ISBN:0642367027.
63. Cyders MA, Littlefield AK, Coffey S, Karyadi KA. Examination of a Short Version of the UPPS-P Impulsive Behavior Scale. Addict Behav 2014;9(9):1372-1376 [FREE Full text] [doi: 10.1016/j.addbeh.2014.02.013] [Medline: 24636739]
64. Katz G, Kunyvsky Y, Lurie TH, Raskin S, Abramowitz MZ. Impulsivity, sensation seeking and anhedonia as possible explanations for cannabis abuse comorbidity among first psychotic episode inpatients. J Addict Res Ther 2017;8(02):318. [doi: 10.4172/2155-6105.1000318]
65. Spriggens L, Hides L. Patterns of cannabis use, psychotic-like experiences and personality styles in young cannabis users. Schizophr Res 2015;165(1):3-8 [FREE Full text] [doi: 10.1016/j.schres.2015.03.023] [Medline: 25868934]
66. Scher CD, Stein MB, Asmundson GJ, McCreary DR, Forde DR. The childhood trauma questionnaire in a community sample: psychometric properties and normative data. J Trauma Stress 2001;14(4):843-857 [FREE Full text] [doi: 10.1023/A:1013058625719] [Medline: 11776429]
67. Shevlin M, Murphy J, Houston JE, Adamson G. Childhood sexual abuse, early cannabis use, and psychosis: testing the effects of different temporal orderings based on the National Comorbidity Survey. Psychosis 2009;1(1):19-28. [doi: 10.1080/17522430802546640] [Medline: 18024467]
68. Stoyanov SR, Hides L, Kavanagh DJ, Wilson H. Development and validation of the user version of the Mobile Application Rating Scale (uMARS). JMIR Mhealth Uhealth 2016;4(2):e72 [FREE Full text] [doi: 10.2196/mhealth.5849] [Medline: 27287964]
69. Morrison AP, Renton JC, French P, Bentall RP. Think you're crazy? Think again: a resource book for cognitive therapy for psychosis. New York, NY: Routledge/Taylor & Francis Group; 2008. ISBN: 9781583918364.
70. Morrison AP, French P, Walford L, Lewis SW, Kilcommins A, Green J, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. Br J Psychiatry 2004;185(4):291-297 [FREE Full text] [doi: 10.1192/bjp.185.4.291] [Medline: 15458988]
71. Morrison AP, French P, Parker S, Roberts M, Stevens H, Bentall RP, et al. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. Schizophr Bull 2007;33(3):682-687 [FREE Full text] [doi: 10.1093/schbul/sbl042] [Medline: 16973786]
72. Morrison AP, French P, Stewart SLK, Birchwood M, Fowler D, Gumley AI, et al. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ 2012;344(7852):e2233. [doi: 10.1136/bmj.e2233] [Medline: 22491790]
73. Stafford E, Hides L, Kavanagh DJ. The acceptability, usability and short-term outcomes of Get Real: a web-based program for psychotic-like experiences (PLEs). Internet Interventions 2015;2(3):266-271 [FREE Full text] [doi: 10.1016/j.invent.2015.05.004]

74. Hides L, Carroll S, Scott R, Baker AL, Lubman D. Quik Fix: a randomised controlled trial of a brief motivational interviewing intervention for alcohol/cannabis and psychological distress in young people. Psychother Psychosom 2013;82(2):122-124. [doi: 10.1159/000341921] [Medline: 23295899]

Abbreviations

AOD: alcohol and other drug
ASSIST: alcohol, smoking, and substance involvement screening test
CAPE: community assessment of psychic experiences
CBT: cognitive behavior therapy
CEQ-I: Cannabis Experiences Questionnaire-Intoxication
CTQ: Childhood Trauma Questionnaire
eHRS: eHealth Rating Scale
EQ-5D-5L: 5-dimension version of the European Quality of Life 5-level
GAD: Generalized Anxiety Disorder
ICW: information control website
MAFS: Multidimensional Adolescent Functioning Scale
MHC-SF: Mental Health Continuum-Short Form
MINI: Mini-International Neuropsychiatric Interview
OTI: Opiate Treatment Index
PE: psychotic experience
PHQ: Patient Health Questionnaire
RCT: randomized controlled trial
SDS: Severity of Dependence Scale
SUPPS-P: Short UPPS-P Impulsive Behavior Scale

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Protocol

Effectiveness of a Theory- and Web-Based Adaptive Implementation Intervention on Nurses' and Nursing Students' Intentions to Provide Brief Counseling: Protocol for a Randomized Controlled Trial

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Abstract

Background: Brief counseling can motivate patients to initiate health behavior change. However, increasing the provision of brief counseling by nurses is difficult due to contextual and practitioner-level factors impeding nurses' motivation and intentions to provide brief counseling (eg, unfavorable attitude toward brief counseling, lack of perceived control linked to barriers). Theory-based implementation interventions could address these practitioner-level factors and support evidence-based practice in the context of brief counseling. Web-based, adaptive e-learning (electronic learning) programs are a novel type of implementation intervention that could address the limitations of current brief counseling training programs, such as accessibility and personalization.

Objective: This paper presents a study protocol for evaluating the effectiveness of the E_MOTIV$_A$ implementation intervention—a theory- and web-based adaptive e-learning program—to increase nurses' and nursing students' intentions to provide brief counseling for smoking, an unbalanced diet, and medication nonadherence.

Methods: A two-group, single-blind, randomized controlled trial will be conducted with nurses and nursing students enrolled in a Bachelor of Science in Nursing program in Quebec, Canada. Participants in the experimental group will be allocated to the E_MOTIV$_A$ intervention—a theory- and web-based adaptive e-learning program—while participants in the active control group will be allocated to the E_MOTIV$_B$ intervention, a knowledge- and web-based standardized e-learning program. The E_MOTIV$_A$ intervention was designed to influence the constructs of the Theory of Planned Behavior (eg, attitude, subjective norms, and perceived behavioral control) in the context of brief counseling. The Cognitive Load Index and User Engagement Scale will be used to assess participants' cognitive load and engagement related to e-learning. Participants will complete the Brief Counseling Nursing Practices Questionnaire–Abridged Version at baseline and follow-up. All study measures will be completed online.

Results: The study is ongoing. The results of the study will provide answers to the primary hypothesis (H1) that experimental group participants will demonstrate a greater change in the score of intentions to provide brief counseling between baseline (–T1) and follow-up (T4). Secondary hypotheses include greater improvements in scores of attitude (H2), subjective norms (H3), perceived control (H4), behavioral beliefs (H5), normative beliefs (H6), and control beliefs (H7) regarding brief counseling in the experimental group between baseline and follow-up. We also anticipate lower intrinsic and extrinsic cognitive loads (H8, H9), higher germane cognitive load (H10), and higher engagement (H11, H12) in the experimental group.

Conclusions: This study will be among the first in evaluating a novel type of implementation intervention, a theory- and web-based adaptive e-learning program, in nurses and nursing students. This type of intervention has the potential to support evidence-based practice through accessible, personalized training in wide-ranging domains in nursing.

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KEYWORDS

brief counseling; implementation science; knowledge translation; eLearning; clinical practice improvement; nursing education

Introduction

Noncommunicable Diseases and Behavioral Risk Factors

Noncommunicable diseases, including cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases, are major contributors to global morbidity and mortality [1]. In Canada, noncommunicable diseases were responsible for 88% of deaths in 2017 [1]. These diseases are caused mainly by behavioral risk factors, such as smoking, an unbalanced diet, and medication nonadherence [2]. The prevalence of smoking among Canadians was 17.9% in 2014 [3]. Through hemodynamic, hemostatic, and inflammatory mechanisms, smoking leads, on average, to a life expectancy of 10 years lower [2]. The prevalence of an unbalanced diet among Canadians, defined as a failure to meet the fruit and vegetable consumption threshold according to Canada's food guide [4], was 60.3% in 2014 [3]. Diet plays an important role in the pathophysiology associated with noncommunicable diseases through several mechanisms of action [2]. Finally, while medication adherence varies by population and context, a meta-analysis highlighted that 40% of patients do not take their recommended treatment for their cardiovascular problem (defined by adherence 80%) [5]. Thus, these behavioral risk factors should be targeted by interventions initiated by health care professionals, including nurses [6].

Brief Behavior Change Counseling

When provided by trained health care professionals, motivational approaches such as brief behavior change counseling, hereafter called brief counseling, can help patients initiate and maintain health behavior change [6]. Brief counseling, lasting from 1 to 15 minutes, aims to explore the individual's motivation and capabilities and to intervene to encourage and support behavior change [7-9]. Brief counseling is associated with modest but clinically significant effects for smoking cessation, the adoption of a balanced diet, and medication adherence [10,11].

Nurses and nursing students are well-positioned across the continuum of care to provide brief counseling to explore patients' beliefs, assess their level of motivation for change, and intervene to elicit behavior change [12]. However, brief counseling requires specific knowledge and skills [12]. While nursing students acquire foundational knowledge about health communication and develop relational skills (eg, active listening, reformulation), training does not generally cover specific abilities to explore patients' motivation and ambivalence and to intervene accordingly. In addition, nurses and nursing students' attitudes toward brief counseling can be variable and may alter their motivation in providing brief counseling in different care settings. Some may believe these settings are not conducive to brief counseling and health behavior change [13].

Similarly, the subjective norm (ie, the perceived social pressure onwards) toward brief counseling is influenced by the attitudes and behaviors of nurses and other professionals [13]. There is also a need to increase nurses' and nursing students' perceived behavioral control over brief counseling by addressing barriers, highlighting facilitators, and providing knowledge and skills to intervene [14]. According to the Theory of Planned Behavior (TPB), these sociocognitive determinants (ie, attitude, subjective norm, perceived behavioral control) are predictors of nurses' and nursing students' intentions to provide brief counseling, and of its actual provision in clinical practice [15].

Theory-Based Implementation Interventions

Sociocognitive determinants may be used for designing a theory-based *implementation intervention* to increase the provision of brief counseling by nurses and nursing students [16]. An implementation intervention is defined as any strategy or program "aimed at increasing the use of research-based knowledge in healthcare practice (pg 2)" [17]. Examples of these interventions, sometimes called "implementation strategies," including audit and feedback, educational materials, e-learning (electronic learning), educational games, communities of practice, local opinion leaders, and reminders [18]. Practitioner-level implementation interventions target behavior change at the level of individual health care professionals and teams (ie, nurses and nursing students in this context) [17]. These interventions may be based on a wide range of theories, models, and frameworks, including theories of behavior and behavior change, such as the TPB [19]. Studies that evaluate implementation interventions based on the TPB have become more common in recent years [20-22]. For example, a study by Welch [22] used the TPB to design an implementation intervention, a web-based e-learning program, aiming to influence the moral norm, or sense of professional responsibility, to promote the uptake of brief counseling by nurses. Additional studies are warranted to solidify the evidence base [16,21].

Adaptive e-Learning Programs

Studies have shown the benefits of e-learning and the use of technology to support learning and clinical practice change [23,24]. Recently, adaptive e-learning has emerged has a novel type of practitioner-level implementation intervention [24]. Adaptive e-learning programs collect data at different points

during a training program (eg, attitude of each learner) to determine, from multiple pathways conceptualized by a team of experts or by computer algorithms, the optimal learning path for each learner [24]. Adaptive e-learning programs mimic face-to-face learner-teacher interactions, where the teacher adapts learning content and format based on learners' feedback. Adaptive e-learning programs could alleviate the current limitations of most brief counseling training programs. Indeed, most brief counseling training programs assessed with nurses and nursing students have been mainly face-to-face, limiting accessibility, and group-based, reducing personalization [12].

Two main cognitive processes have been studied to optimize human-computer interaction in the context of adaptive e-learning: engagement and cognitive load. Engagement, the learner's investment when interacting with an e-learning program, should be maximized [25]. The cognitive load refers to how much the learner's working memory is solicited during learning [26]. Three types of cognitive loads have different effects on learning: 1) intrinsic load, linked to the complexity of the learning task, should be adapted to the learner; 2) extrinsic load, linked to superfluous or confusing elements during learning, should be minimized; 3) germane load, linked to the integration of the programs' concepts, should be maximized. Considering learners' engagement and cognitive load is crucial when developing and evaluating an adaptive e-learning program. More specifically, considering engagement is important in this context since giving learners control over their learning path in an adaptive e-learning program may increase their engagement. In addition, personalizing instruction through data collected at multiple time points during the training may also increase the learner's engagement in the e-learning program. Regarding cognitive load, it is hypothesized that personalizing instruction in an adaptive e-learning program may reduce extrinsic load and increase germane load [24].

To our knowledge, only one prior study evaluated a theory- and web-based adaptive e-learning program targeting sociocognitive determinants to support the provision of brief counseling by nurses, and none was conducted with nursing students. The study was conducted in The Netherlands to support the provision of brief counseling by primary care nurses for smoking cessation [21]. Results showed that the e-learning program increased the provision of brief counseling for smoking cessation among a subset of these nurses [21]. Thus, this paper adds to the emerging literature by presenting a protocol for evaluating the E_MOTIV$_A$ implementation intervention—a theory- and web-based adaptive e-learning program—to increase nurses' and nursing students' intentions to provide brief counseling.

Study Objective and Hypotheses

The objective of this randomized controlled trial (RCT) is to evaluate the effect of a theory- and web-based adaptive e-learning program targeting the constructs of the TPB (E_MOTIV$_A$ intervention; experimental group), versus a knowledge- and web-based standardized e-learning program (E_MOTIV$_B$ intervention; active control group), on nurses' and nursing students' intentions to provide brief counseling for smoking cessation, the adoption of a balanced diet and medication adherence. Our primary hypothesis (H1) is that experimental group participants will demonstrate a greater change in the score of intentions to provide brief counseling between baseline (–T1) and follow-up (T4).

Secondary hypotheses include greater improvements in scores of attitude (H2), subjective norm (H3), perceived behavioral control (H4), behavioral beliefs (H5), normative beliefs (H6), and control beliefs (H7) regarding brief counseling in the experimental group between baseline and follow-up. We also anticipate lower intrinsic and extrinsic cognitive loads (H8, H9), higher germane cognitive load (H10), and higher experiential and behavioral engagement (H11, H12) in experimental group participants compared with control group participants.

We will also explore links between theoretical constructs of the study model—ie, what sociocognitive determinants at baseline (–T1) are correlated with the intentions to provide brief counseling at the follow-up (T4).

Methods

Trial Design

A two-group, single-blind, parallel RCT will be conducted to evaluate the effectiveness of the E_MOTIV$_A$ experimental intervention compared to the E_MOTIV$_B$ control intervention. This protocol is presented according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guideline [27]. The Consolidated Standards of Reporting Trials (CONSORT) eHEALTH checklist is presented in Multimedia Appendix 1. The protocol was prospectively registered on October 14, 2019 (ISRCTN32603572).

Study Setting and Eligibility Criteria

The study will be conducted entirely online at a Faculty of Nursing in a major university in Quebec, Canada. In the province of Quebec, nurses can practice with a 3-year College Diploma in Nursing, or with a 3-year Bachelor of Science in Nursing (BSN) degree achieved at the university level. However, nurses with a College Diploma can still pursue university-level education with a shorter, 2-year BSN program. Thus, BSN programs in Quebec include both nurses and nursing students. For this reason, while the study will be conducted in a BSN program, it targets both nurses and nursing students (hereafter called "participants").

The inclusion criteria are: (1) to be a BSN student in a primary health care course; (2) to be able to perform computer tasks (eg, taking emails); (3) to understand French. There is no exclusion criterion.

Interventions

This section provides a high-level summary of the interventions. An in-depth description of both interventions will be published in a forthcoming paper.

Experimental Group (E_MOTIV$_A$)

Participants (ie, nurses and nursing students) in the experimental group will receive access to the "E_MOTIV$_A$ intervention," a web- and theory-based adaptive e-learning program incorporating learning content delivered through text, pictures,

and videos on (1) smoking, unbalanced diet, medication nonadherence; (2) treatment options; and (3) brief counseling (Table 1). This content was piloted with 31 nurses [9,28]. Moreover, the E_MOTIV$_A$ intervention incorporates content based on an integrative theoretical framework including (1) the TPB [15]; (2) Cognitive Load Theory [29]; (3) the concept of engagement [25] (Figure 1). The TPB posits that *sociocognitive determinants* (ie, attitude, subjective norms, and perceived behavioral control) influence participants' *intentions*, which in turn, with *actual behavioral control* (eg, external factors), influences participants' *behavior* in clinical practice. The second component is the Cognitive Load Theory, which describes principles aimed at linking the E_MOTIV$_A$ intervention to the cognitive architecture of learners. The third component is the concept of engagement, acting as a mediator between the E_MOTIV$_A$ intervention and its effects on sociocognitive determinants in participants. The E_MOTIV$_A$ intervention targets 7 sociocognitive determinants amenable to change in participants regarding brief counseling (Table 1). To change these determinants and increase participants' intentions to provide brief counseling in clinical practice, the E_MOTIV$_A$ program incorporates 19 strategies (ie, behavior change techniques) (Table 1). The e-learning program was developed with a web agency near Montreal, Canada.

More specifically, E_MOTIV$_A$ consists of 3 adaptive training sessions. Each session includes a fixed number of "navigation adaptation points" consisting of questions asked to participants. There are two types of these adaptation points:

1. *Suggested* navigation adaptation points, where the participant can determine the preferred learning path from multiple options. This is operationalized as a question asked to participants, for example, "Which cardiovascular risk factor do you wish to see first in this training program from the options presented below?" The participant can then select one of three options (smoking, unhealthy eating habits, medication nonadherence), and the platform will dynamically adapt the learning path.
2. *Enforced* navigation adaptation points, where the participant answers a question with a 4-point response scale (agree, agree slightly, disagree slightly, disagree), for example, "Helping patients change their health behaviors (like smoking) is complex." Depending on their answers, participants are automatically sent to different learning paths. In this specific example, if the participant answers "Agree," "Agree slightly" or "Disagree slightly," they are sent to a video of a nurse practitioner explaining that while health behavior change can be complex and difficult, it can also often be spontaneous and does not necessarily involve a long process (eg, quitting smoking).

The first training session focuses on noncommunicable diseases, cardiovascular risk factors, the foundations of health behavior change, and the 5 As brief counseling approach. It includes three navigation adaptation points: (1) one focusing on cardiovascular risk factors; (2) one focusing on the participant's beliefs about brief counseling (eg, the effectiveness of brief counseling); and (3) one focusing on the participant's perceived ability or control over the provision of brief counseling (eg, how much time it takes to provide brief counseling). The second training session focuses on strategies and resources for smoking cessation, the adoption of a balanced diet and medication adherence, as well as on multiple role-playing videos of brief counseling with a nurse and patients presenting different levels of motivation toward behavior change. It includes four navigation adaptation points: (1) one focusing on normative beliefs about brief counseling (eg, what do doctors think about brief counseling); (2) one focusing on role-playing videos of brief counseling with unmotivated patients; (3) one focusing on role-playing videos of brief counseling with motivated patients; and (4) one focusing on participants' intention to provide brief counseling. The third training session allows students to review any content from previous sessions but does not include new content.

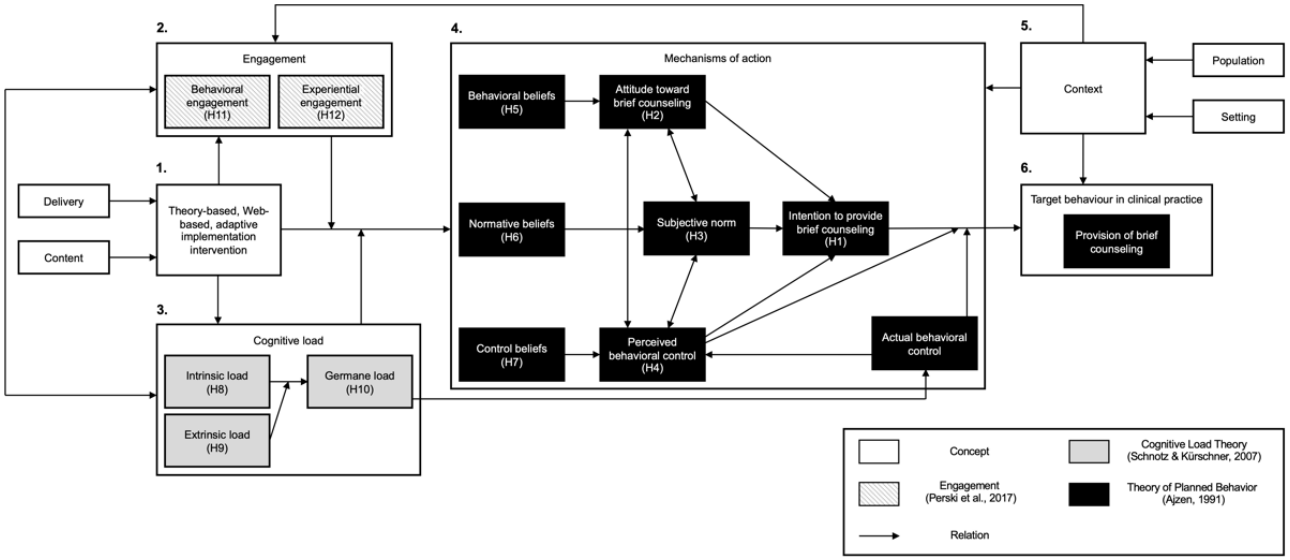
Control Group (E_MOTIV$_B$)

Participants in the control group will access the "E_MOTIV$_B$ intervention," a knowledge- and web-based standardized e-learning program (Table 1), including learning content on risk factors, treatment options, and brief counseling. The E_MOTIV$_B$ intervention targets primarily 2 sociocognitive determinants in participants regarding brief counseling. However, the intervention may also affect other sociocognitive determinants (eg, attitude, behavioral beliefs). To change these determinants, E_MOTIV$_B$ includes 6 strategies frequently used in nursing education [31].

Table 1. A high-level description of the E_MOTIV$_A$ and E_MOTIV$_B$ interventions.

Characteristic	E_MOTIV$_A$ intervention (experimental group)	E_MOTIV$_B$ intervention (control group)
Description	A theory- and web-based adaptive e-learning program focusing on brief counseling	A knowledge- and web-based standardized e-learning program focusing on brief counseling
Training Sessions		
Number of sessions	3	3
Duration of each session	Session duration will vary in function of the learning paths. • Session 1: ~50 min • Session 2: ~60 min • Session 3: ~20 min	Session duration is fixed for sessions 1 and 2, and variable for session 3. • Session 1: ~40 min • Session 2: ~50 min • Session 3: ~20 min
Clinical focus of the e-learning program	Brief counseling for smoking, unbalanced diet and medication nonadherence	Brief counseling for smoking, unbalanced diet and medication nonadherence
Brief counseling approach taught	5 As (Ask-Assess-Advise-Agree-Assist)	5 As (Ask-Assess-Advise-Agree-Assist)
Sociocognitive determinants targeted by the training program in participants	The E_MOTIV$_A$ intervention is personalized to 7 sociocognitive determinants in participants to increase the provision of brief counseling in clinical practice 1. Intention 2. Attitude 3. Subjective norm 4. Perceived behavioral control (eg, knowledge, skills) 5. Behavioral beliefs 6. Normative beliefs 7. Control beliefs	The E_MOTIV$_B$ intervention targets primarily 2 sociocognitive determinants in participants to increase the provision of brief counseling in clinical practice 1. Perceived behavioral control (eg, knowledge, skills) 2. Control beliefs To a lesser extent, the intervention may affect other sociocognitive determinants.
Strategies (ie, behavior change techniques) to change the sociocognitive determinants in participants	To increase participants' intentions to provide brief counseling in clinical practice, the E_MOTIV$_A$ intervention incorporates 19 strategies, including the 6 of the E_MOTIV$_B$ program. Examples of these strategies include 1. Encouraging the substitution of existing practices (information-giving) for brief counseling. 2. Providing information on the approval of other care team members regarding providing brief counseling.	The E_MOTIV$_B$ intervention includes 6 strategies frequently used in nursing continuing education 1. Role modeling, ie, the demonstration of brief counseling skills by an expert nurse with patients in videotaped simulated clinical encounters. 2. Instructions on how to provide brief counseling for smoking, unbalanced diet, and medication nonadherence.

Figure 1. The integrative theoretical framework of the study, based on the Theory of Planned Behavior [15], Cognitive Load Theory [29], and the concept of engagement with digital interventions [32].



Variables, Measures, and Data Collection

Study variables and measures are presented in Table 2. First, a 15-item sociodemographic questionnaire will be completed at the baseline. Second, we will use the Brief Counseling Nursing Practices Questionnaire Abridged Version (BCNPQ–AV) at baseline [33] and at the follow-up to measure nurses' intentions (H1), and other sociocognitive determinants regarding brief counseling (H2-H7). The BCNPQ was developed originally in French based on the TPB [33]. The BCNPQ–AV has 7 subscales and 48 items. Items have an 8-point (0-7) Likert-type response scale. Third, after two training sessions, we will use the French version of the Cognitive Load Index (CLI) [34] to measure participants' cognitive load related to the e-learning programs. The 10-item French version of the CLI measures 3 types of cognitive load. All items have an 11-point (0-10) Likert response scale. Mid-range intrinsic load scores, low extrinsic load scores, and high germane load scores are desired. Fourth, we will use the French version of the User Engagement Scale–Short Form (UES–SF) [35] to measure participants' experiential engagement with e-learning programs. The French version of the UES–SF measures four dimensions of experiential engagement with the e-learning program: (1) focused attention, (2) perceived usability, (3) aesthetic appeal, and (4) reward. All items have a 6-point (0-5) Likert-type response scale. The higher scores are, the more users are engaged with the e-learning program. Psychometric properties of the French versions of the CLI and the UES–SF tested in 57 nursing students [36]. Finally, we will collect usage data through the E_MOTIV$_A$ and E_MOTIV$_B$ programs. We will collect the duration of use (minutes), the frequency of use (number of logins per user), and the percentage of participants who complete training sessions and who consult each page.

Table 2. Study variables and measures.

Study variable	Definition	Instrument/measure	Items, n	Sample question	Internal consistency (α)
Sociodemographic and professional characteristics	N/A[a]	Study-specific questionnaire, self-administered online	15	"How many online courses have you taken in the past?"	N/A
Sociocognitive determinants					
H1: Intention to provide brief counseling	General disposition of the participant to provide brief counseling for smoking, unbalanced diet, and medication nonadherence.	Brief Counseling Nursing Practices Questionnaire—Abridged Version (BCNPQ—AV), self-administered online	15	"Over the next few months, I have the intention to provide brief counseling to my smoking patients."	.92
H2: Attitude toward behavior	Latent disposition toward brief counseling based on their emotional response to it and their evaluation of its consequences.	BCNPQ—AV	6	"For me, it is important to provide brief counseling to my patients."	.81
H3: Subjective norms	Perceived social pressure toward brief counseling, as a function of the behavior of others (eg, other team members) in the environment.	BCNPQ—AV	4	"Nursing managers believe that I should provide brief counseling to my patients."	.89
H4: Perceived behavioral control	Perceived degree of control (capability, opportunity) over the integration of brief counseling in clinical practice.	BCNPQ—AV	7	"I have the skills required to help patients initiate change for the reduction of a cardiovascular risk factor."	.70
H5: Behavioral beliefs	Subjective probability of perceiving that brief counseling has favorable or unfavorable attributes.	BCNPQ—AV	4	"If I provided brief counseling, it would make my patients aware of the consequences of cardiovascular risk factors (examples: smoking, poor diet) on their health."	.84
H6: Normative beliefs	Subjective probability of perceiving positively or negatively the attitude/behavior of others regarding brief counseling.	BCNPQ—AV	6	"Doctors would disapprove/approve of the fact that I provide brief counseling to my patients."	.84
H7: Control beliefs	Subjective probability of considering having the capability and opportunity necessary to perform brief counseling based on the facilitators and barriers.	BCNPQ—AV	5	"I will have the support of my nursing team members to provide brief counseling to my patients."	.74
Cognitive load					
H8: Intrinsic cognitive load	Cognitive load associated with the task and the learning content.	French version of the Cognitive Load Index (CLI), self-administered online	3	"The subject(s) covered during this activity were very complex."	.83
H9: Extrinsic cognitive load	Cognitive load associated with superfluous, unnecessary, or confusing elements are added to the learning task.	CLI	3	"The directions or explanations were ineffective for my learning."	.70
H10: Germane cognitive load	Cognitive load reflecting the understanding and integration of the programs' concepts.	CLI	4	"The activity really improved my understanding of the subject(s) covered."	.96

Study variable	Definition	Instrument/measure	Items, n	Sample question	Internal consistency (α)
Engagement					
H11: Experiential engagement	Subjective experience that emerges from interaction with the e-learning[b] program characterized by attention, interest, and affect.	French version of the User Engagement Scale—Short Form (UES—SF), self-administered online	12	"The EMOTIV platform was visually pleasing."	.76 to .89
H12: Behavioral engagement with e-learning programs	Objective measure of the use of the e-learning program characterized by the number, duration, and period of contacts.	Usage data collected in both e-learning programs	N/A	N/A	N/A

[a]N/A: not applicable.

[b]e-learning: electronic learning.

Timeline and Procedures

All study procedures are identical in both study groups, apart from the experimental and control e-learning programs which have different structures, contents, and durations (Figure 2). Participants will be enrolled in the study for up to 21 days, from recruitment (–T2) to follow-up (T4) (Table 3). We estimate that it will take approximately two and a half hours for participants in both groups to participate in the study. After consenting to participate in the study (–T2), participants will immediately be redirected to the online questionnaire to complete baseline measures (–T1). Within 24 hours of completing the baseline measures, participants will be randomized (T0). They will receive an email containing a link to the E_MOTIV_A or E_MOTIV_B intervention, as well as their user code and password to access the e-learning program. Training sessions 1 (T1), 2 (T2), and 3 (T3) will be completed on the E_MOTIV_A or E_MOTIV_B web-based platforms within 14 days following randomization. If participants do not want to complete the optional session 3, they will be able to complete the follow-up (T4) measures (ie, the CLI, UES–SF, and BCNPQ–AV online questionnaires) immediately after session 2 by clicking on an embedded link at the end of the session. Otherwise, once participants have completed session 3, they will receive an email containing a link to the follow-up (T4) online questionnaires. Participants will be able to complete follow-up measures until 21 days postrandomization.

Figure 2. Participant flow diagram.

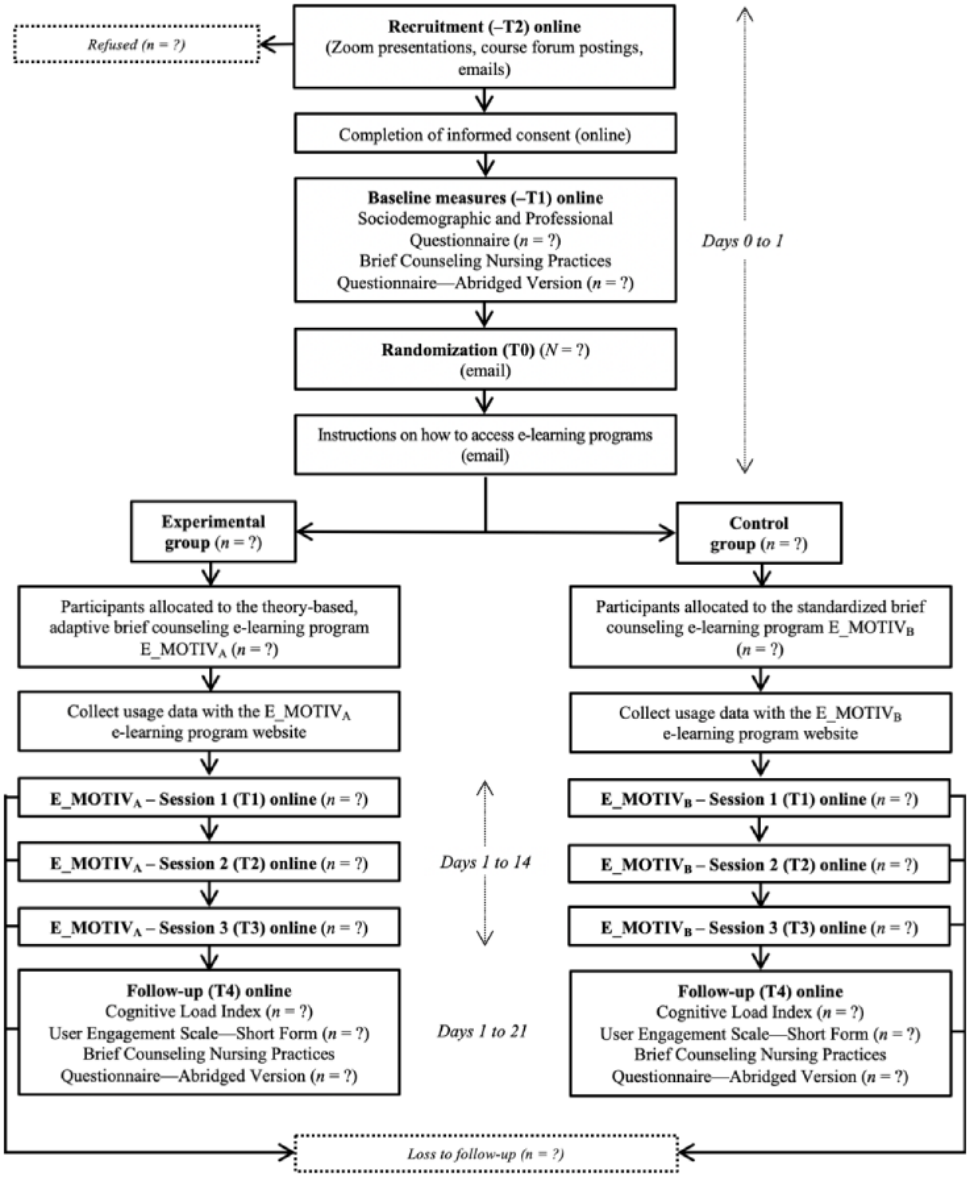


Table 3. Study timeline.

Activity	Items, n	Day 0		Days 0 to 1	Days 1 to 14			Days 1 to 21
		Recruitment (−T2)	Baseline measures (−T1)	Randomization (T0)	Training session 1 (T1)	Training session 2 (T2)	Training session 3 (T3, optional)	Follow-up (T4)
Recruitment and randomization								
Eligibility evaluation		✓						
Log of the selection procedure		✓						
Informed consent		✓						
Randomization				✓				
Instructions for training sessions (access)				✓				
Training sessions								
Access to the E_MOTIV$_A$ intervention (experimental group) or E_MOTIV$_B$ intervention (control group)					✓	✓	✓	
Measures collected with online questionnaires								
Sociodemographic questionnaire	15		✓					
H1 to H7—Brief Counseling Nursing Practices Questionnaire—Abridged Version	48		✓					✓
H8 to H10—Cognitive Load Index	10							✓
H11—User Engagement Scale—Short Form	12							✓
Collected with the e-learning[a] programs								
H12—Usage data (eg, frequency, duration)					✓	✓	✓	

[a]e-learning: electronic learning.

Sample Size and Recruitment

This study seeks to enroll 25 participants per group (BSN students, including nurses and nursing students), for a total of 50 participants (0.75 power; 0.05 bilateral significance level). The calculation is based on the comparison of the change in *intentions to provide brief counseling* (ie, H1; follow-up [T4] score minus the baseline score [−T1]) between the experimental and control groups. We estimate that the standard deviation of the change in intentions will be 6.5. This sample size will allow us to detect a difference of 5 in the score of intentions to provide brief counseling between the two groups. Given the context of the study, carried out as part of a Bachelor of Science in Nursing course, we will not refuse participants once the N is reached to offer all students equal opportunity.

Participants will be recruited through two large group Zoom presentations, course forum postings, and email invitations.

Randomization and Allocation

The randomization scheme will be generated by the Offsite Coordinating Center (the Montreal Health Innovations Coordinating Center, MHICC). Random assignment will follow a 1:1 allocation with random block sizes to minimize group imbalances.

Blinding

Both interventions, ie, both e-learning programs, will be completed individually and have the same appearance, name, and main contents to increase the blinding of participants to group allocation. The E_MOTIV$_A$ intervention being adaptive, participants will have different learning pathways in that group. This variability in the content and pathways in half of the participants will attenuate contamination between groups if participants discuss their learning experience. The Study Coordinator will be aware of group assignment to (1) create accounts on the E_MOTIV web-based platform for each participant and (2) assign each participant to the experimental or control e-learning program in the E_MOTIV web-based platform.

Data Analysis

Study variables will be presented by group. The mean, standard deviation, median, minimum, and maximum will be presented

for continuous variables, while categorical variables will be described as frequencies and percentages. All statistical tests will be bilateral and with a 0.05 significance level. The Statistical Package for the Social Sciences version 25 will be used to produce intention-to-treat analyses (ie, analysis of all participant data, regardless of study completion) under the supervision of the MHICC.

For the primary outcome, the change in the score of intentions to provide brief counseling (T4-−T1) will be analyzed with a covariance model (ANCOVA), including the group factor and the intentions score at baseline (−T1). This model will allow a comparison of the adjusted mean change in participants' intentions to provide brief counseling between groups.

Continuous secondary outcomes measured in terms of change between baseline and follow-up (H2 to H7) will be analyzed similarly to the primary outcome. Continuous secondary outcomes measured at follow-up (H9 to H12) will be compared between groups using Student *t* tests or Mann-Whitney tests if variables are not normally distributed.

In terms of exploratory analyzes, the associations between sociocognitive determinants at baseline (−T1) and intentions (H1) will be evaluated using Pearson coefficients or with Spearman coefficients if data are not normally distributed. Multivariate models may be used if data are suitable.

Ethical Considerations

This protocol has been approved by the University of Montreal Science and Health Research Ethics Board (#20-052-CERSES-D).

Results

Participant recruitment and enrollment began in spring 2020. Analysis of study results is expected in the summer of 2020 at the end of data collection.

Discussion

This paper describes a study protocol for evaluating the effectiveness of a theory- and web-based adaptive e-learning program on nursing students' and nurses' intentions to provide brief counseling.The E_MOTIV$_A$ intervention, which is one of the first of its kind, has important implications for both research and practice. In terms of research, the E_MOTIV$_A$ program could be modified to train nurses and nursing students in a wide range of clinical domains. The navigation adaptation points could focus on additional psychological and social constructs for other clinical practices, such as physical assessment, and test ordering. Moreover, additional studies could be conducted to evaluate the E_MOTIV$_A$ program, which is an entirely digital intervention, paired with co-interventions implemented directly in care settings, such as local opinion leaders or academic detailing. In terms of practice, E_MOTIV$_A$ has the potential to increase the effectiveness and efficiency of learning in nurses and nursing students. Through the adaptivity process, the program can account for the particularities inherent to each learner and provide personalized instruction, potentially increasing engagement and reducing cognitive load.

We remark on two limitations of the present study. First, participants will be randomized individually to the experimental and control groups. Thus, participants in both groups may discuss the project among themselves. Participants will be blinded to group assignment to minimize the risk of contamination. Second, we anticipate that participant retention may present a challenge, given the 10% dropout rate observed with a shorter training program in a previous study. To maximize retention, we will send up to three standardized email reminders will be sent to participants at each study time point (T1, T2, T3, and T4). For example, the reminder for completing the first training session will read as follows: "This email is only a brief courtesy reminder that you can start the first session of the E_MOTIV training program now. You can also start the second training session as soon as you have time. Here is a reminder of the information to log in: […]".

In conclusion, this study will be among the first in evaluating a theory- and web-based adaptive e-learning program in nurses and nursing students. These programs have the potential to support evidence-based practice through accessible, personalized training in wide-ranging domains in nursing [32,37].

Acknowledgments

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Conflicts of Interest

GF and SC have developed and own the E_MOTIV web-based e-learning platform.

Multimedia Appendix 1
CONSORT-eHEALTH Checklist (V 1.6.1).
[PDF File (Adobe PDF File), 332 KB - resprot_v9i7e18894_app1.pdf]

References

1. World Health Organization. Noncommunicable Diseases Progress Monitor 2017. Geneva, Switzerland: World Health Organization; 2017. URL: http://www9.who.int/nmh/publications/ncd-progress-monitor-2017/en/ [accessed 2020-07-11]
2. De Lemos JA, Omland T. Chronic Coronary Artery Disease: A Companion to Braunwald's Heart Disease. Philadelphia, PA: Elsevier; 2018.
3. Agence de la santé publique du Canada. Quel est l'état de santé des canadiens? Analyse des tendances relatives à la santé des canadiens du point de vue des modes de vie sains et des maladies chroniques. Ottawa, Canada: Government of Canada; 2016. URL: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/how-healthy-canadians/pub1-fra.pdf [accessed 2020-07-11]
4. Government of Canada. Canada's Food Guide. Ottawa, Canada: Government of Canada; 2020. URL: https://food-guide.canada.ca/en/ [accessed 2020-07-11]
5. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 2013 Oct 01;34(38):2940-2948. [doi: 10.1093/eurheartj/eht295] [Medline: 23907142]
6. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. Cochrane Database of Systematic Reviews 2015;Art. No CD006936. [doi: 10.1002/14651858.cd006936.pub3]
7. Karvinen K, Balneaves L, Courneya K, Perry B, Truant T, Vallance J. Evaluation of Online Learning Modules for Improving Physical Activity Counseling Skills, Practices, and Knowledge of Oncology Nurses. ONF 2017 Nov 1;44(6):729-738. [doi: 10.1188/17.onf.729-738]
8. Aveyard P, Begh R, Parsons A, West R. Brief opportunistic smoking cessation interventions: a systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction 2012 Jun;107(6):1066-1073. [doi: 10.1111/j.1360-0443.2011.03770.x] [Medline: 22175545]
9. Fontaine G, Cossette S, Heppell S, Boyer L, Mailhot T, Simard M, et al. Evaluation of a Web-Based E-Learning Platform for Brief Motivational Interviewing by Nurses in Cardiovascular Care: A Pilot Study. J Med Internet Res 2016 Aug 18;18(8):e224 [FREE Full text] [doi: 10.2196/jmir.6298] [Medline: 27539960]
10. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation 2010 Jul 27;122(4):406-441 [FREE Full text] [doi: 10.1161/CIR.0b013e3181e8edf1] [Medline: 20625115]
11. Rees K, Dyakova M, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. Cochrane Database of Systematic Reviews 2013;Art. No.:CD002128. [doi: 10.1002/14651858.cd002128.pub4]
12. Fontaine G, Cossette S, Maheu-Cadotte M, Mailhot T, Heppell S, Roussy C, et al. Behavior change counseling training programs for nurses and nursing students: A systematic descriptive review. Nurse Educ Today 2019 Nov;82:37-50. [doi: 10.1016/j.nedt.2019.08.007] [Medline: 31425931]
13. Engström M, Skytt B, Ernesäter A, Fläckman B, Mamhidir A. District nurses' self-reported clinical activities, beliefs about and attitudes towards obesity management. Appl Nurs Res 2013 Nov;26(4):198-203. [doi: 10.1016/j.apnr.2013.06.009] [Medline: 23928123]
14. Lepage M, Dumas L, Saint-Pierre C. [Do we teach the smoking cessation intervention to future nurses? Result of a descriptive study]. Glob Health Promot 2014 Sep;21(3):54-62. [doi: 10.1177/1757975914523456] [Medline: 24658424]
15. Ajzen I. The theory of planned behavior. Organizational Behavior and Human Decision Processes 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-t]
16. Côté F, Gagnon J, Houme PK, Abdeljelil AB, Gagnon MP. Using the theory of planned behaviour to predict nurses' intention to integrate research evidence into clinical decision-making. J Adv Nurs 2012 Oct;68(10):2289-2298. [doi: 10.1111/j.1365-2648.2011.05922.x] [Medline: 22229522]
17. Cahill LS, Carey LM, Lannin NA, Turville M, O'Connor D. Implementation interventions to promote the uptake of evidence-based practices in stroke rehabilitation. Cochrane Database of Systematic Reviews 2017;Art. No.: CD012575. [doi: 10.1002/14651858.cd012575]
18. Effective Practice and Organization of Care (EPOC) Cochrane Group. EPOC Taxonomy; 2015. 2015. URL: https://epoc.cochrane.org/epoc-taxonomy [accessed 2020-07-11]
19. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci 2015 Apr 21;10(53):53-13 [FREE Full text] [doi: 10.1186/s13012-015-0242-0] [Medline: 25895742]
20. Sinclair PM, Kable A, Levett-Jones T, Holder C, Oldmeadow CJ. The CKD-DETECT study: An RCT aimed at improving intention to initiate a kidney health check in Australian practice nurses. J Clin Nurs 2019 Aug 13;28(15-16):2745-2759. [doi: 10.1111/jocn.14882] [Medline: 30970152]
21. de Ruijter D, Candel M, Smit ES, de Vries H, Hoving C. The Effectiveness of a Computer-Tailored E-Learning Program for Practice Nurses to Improve Their Adherence to Smoking Cessation Counseling Guidelines: Randomized Controlled Trial. J Med Internet Res 2018 May 22;20(5):e193 [FREE Full text] [doi: 10.2196/jmir.9276] [Medline: 29789278]
22. Welch J. Building a foundation for brief motivational interviewing: communication to promote health literacy and behavior change. J Contin Educ Nurs 2014 Dec 20;45(12):566-572. [doi: 10.3928/00220124-20141120-03] [Medline: 25401341]

23. Clark R, Mayer R. E-Learning and the science of instruction: proven guidelines for consumers and designers of multimedia learning. Hoboken, NJ: John Wiley & Sons; 2016.
24. Fontaine G, Cossette S, Maheu-Cadotte M, Mailhot T, Deschênes M, Mathieu-Dupuis G, et al. Efficacy of adaptive e-learning for health professionals and students: a systematic review and meta-analysis. BMJ Open 2019 Aug 28;9(8):e025252 [FREE Full text] [doi: 10.1136/bmjopen-2018-025252] [Medline: 31467045]
25. O'Brien HL. Theoretical perspectives on user engagement. In: O'Brien HL, Cairns P, editors. Why Engagement Matters: Cross-Disciplinary Perspectives, Innovations on User Engagement. Cham, Switzerland: Springer; 2016:1-26.
26. Sweller J. Cognitive load during problem solving: effects on learning. Cognitive Science 1988;12(2):257-285. [doi: 10.1207/s15516709cog1202_4]
27. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
28. Fontaine G. Évaluation de la plateforme de formation en ligne MOTIV@CŒUR sur les interventions motivationnelles brèves auprès d'infirmières en soins aigus cardiovasculaires. Faculty of Nursing, Université de Montréal 2016 [FREE Full text]
29. Schnotz W, Kürschner C. A Reconsideration of Cognitive Load Theory. Educ Psychol Rev 2007 Sep 19;19(4):469-508. [doi: 10.1007/s10648-007-9053-4] [Medline: 25762908]
30. Perski O, Blandford A, West R, Michie S. Conceptualising engagement with digital behaviour change interventions: a systematic review using principles from critical interpretive synthesis. Transl Behav Med 2017 Jun;7(2):254-267 [FREE Full text] [doi: 10.1007/s13142-016-0453-1] [Medline: 27966189]
31. Pearson E, Byrne-Davis L, Bull E, Hart J. Behavior change techniques in health professional training: developing a coding tool. Transl Behav Med 2020 Feb 03;10(1):96-102. [doi: 10.1093/tbm/iby125] [Medline: 30535181]
32. Wuchner SS. Integrative Review of Implementation Strategies for Translation of Research-Based Evidence by Nurses. Clinical Nurse Specialist 2014;28(4):214-223. [doi: 10.1097/nur.0000000000000055]
33. Lepage M, Champagne F, Renaud L. Un outil pour évaluer les pratiques cliniques des infirmières auprès des patients fumeurs en cessation tabagique à l'hôpital. Recherche en soins infirmiers 2013;112:36-45. [doi: 10.3917/rsi.112.0036]
34. Leppink J, Paas F, Van der Vleuten CPM, Van Gog T, Van Merriënboer JJG. Development of an instrument for measuring different types of cognitive load. Behav Res Methods 2013 Dec;45(4):1058-1072. [doi: 10.3758/s13428-013-0334-1] [Medline: 23572251]
35. O'Brien HL, Cairns P, Hall M. A practical approach to measuring user engagement with the refined user engagement scale (UES) and new UES short form. International Journal of Human-Computer Studies 2018 Apr;112:28-39. [doi: 10.1016/j.ijhcs.2018.01.004]
36. Fontaine G, Cossette S, Maheu-Cadotte MA, Mailhot T, Lavoie P, Gagnon MP, et al. Traduction, adaptation et évaluation psychométrique préliminaire d'une mesure d'engagement et d'une mesure de charge cognitive en contexte d'apprentissage numérique. Pédagogie Médicale 2019;20(2):79-90 [FREE Full text] [doi: 10.1051/pmed/2020009]
37. Fontaine G, Cossette S, Maheu-Cadotte M, Deschênes M, Rouleau G, Lavallée A, et al. Effect of implementation interventions on nurses' behaviour in clinical practice: a systematic review, meta-analysis and meta-regression protocol. Syst Rev 2019 Dec 05;8(1):305 [FREE Full text] [doi: 10.1186/s13643-019-1227-x] [Medline: 31806051]

Abbreviations

BCNPQ: Brief Counseling Nursing Practices Questionnaire
BCNPQ–AV: Brief Counseling Nursing Practices Questionnaire–Abridged Version
CLI: Cognitive Load Index
CONSORT–eHEALTH: Consolidated Standards of Reporting Trials E-Health
e-learning: electronic learning
MHICC: Montreal Health Innovations Coordinating Center
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TPB: Theory of Planned Behavior
UES–SF: User Engagement Scale—Short Form

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Protocol

Effectiveness of the InCharge Prevention Program to Promote Healthier Lifestyles: Protocol for a Randomized Controlled Trial

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Abstract

Background: InCharge is a newly developed school-based health intervention aimed at older adolescents. It aims to promote a healthier lifestyle by increasing self-regulation skills. After the InCharge program's effectiveness was previously investigated in a pilot study, the content of the program was adapted.

Objective: This study describes the protocol of a cluster randomized controlled trial that aims to investigate the effectiveness of the InCharge program.

Methods: A cluster randomized controlled trial including 70 classes with older adolescents (aged 16 years or older) in the Netherlands will be conducted to test the effectiveness of the InCharge program. After schools are recruited, randomization occurs at the class level. The trial consists of the following two conditions: an experimental condition and a control condition. Participants in the experimental condition will be given the InCharge intervention, consisting of four lessons of 50 minutes, with each lesson containing three assignments of approximately 15 minutes. While participants in the experimental condition will receive InCharge, participants in the control condition will receive regular academic school courses. Surveys are administered 1 week before the intervention (baseline), 1 week after the intervention (posttest), and 12 weeks after the intervention (follow-up). Variables of interest include, but are not limited to, self-regulation; predictors of snack intake, physical activity, and alcohol use; and interpersonal communication regarding these health behaviors. In addition to surveys, observations will be conducted during the first and fourth lessons, teachers will be interviewed, and focus groups will be held with a selection of students from the intervention condition.

Results: Enrollment started in September 2017. As of June 2019, a total of 1216 participants were enrolled for this trial. Findings will be published in peer-reviewed journals and presented at conferences. The trial has been approved by the Ethics Review Board of the Faculty of Social and Behavioral Sciences of the University of Amsterdam (reference no.: 2017-PC-8244).

Conclusions: In this study protocol, the design of a cluster randomized controlled trial is described, which assesses how effectively the school-based intervention InCharge stimulates healthier lifestyles in late adolescents. We hypothesize that participants in the experimental condition will consume less alcohol, eat fewer unhealthy snacks, and be more physically active compared with participants in the control condition.

Trial Registration: Netherlands Trial Register (NL6654); https://www.trialregister.nl/trial/6654

International Registered Report Identifier (IRRID): RR1-10.2196/17702

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KEYWORDS

school-based health intervention; adolescents; health behavior; healthy lifestyle; quality of life; behavior change

Introduction

Background

Health and mortality are strongly affected by behaviors such as excessive alcohol use, a poor diet, and physical inactivity [1]. Some health-risk behaviors, such as a poor diet, originate early in life and continue to deteriorate as children grow older [2]. Most health-risk behaviors, however, develop in adolescence. When children move into adolescence, they become less dependent on their parents, peer relationships gain importance, and exposure to high-risk behaviors increases [3]. Generally, unhealthy lifestyle behaviors steadily increase through adolescence, with a peak in late adolescence (age 16 years or older) [4,5]. During this developmental period, several changes in adolescents' social environment contribute to the accumulation of unhealthy lifestyle behaviors. For example, in late adolescence, most individuals transition from secondary schooling to further education, and the number of adolescents with a part-time job increases with age. Furthermore, older adolescents spend less time in their family home and are increasingly allowed to make their own choices. At the same time, more social activities occur in drinking contexts, and together these changes are associated with unhealthy lifestyle behaviors, such as an escalation of alcohol use [6], a poor diet [7], and decreases in physical activity [8].

Effectiveness of Health Promotion Programs

In the past decades, numerous health promotion programs have been developed in order to prevent the rapid increase of unhealthy behaviors during adolescence. The majority of these programs take place in the school environment, because many adolescents can easily be reached by school-based health interventions. Several studies have suggested that these interventions can indeed promote healthier lifestyles, such as a healthy diet [9] and physical activity [10], and prevent health-risk behaviors, such as alcohol use [11]. However, most systematic reviews and meta-analyses demonstrated large heterogeneity in effectiveness [10,12].

Furthermore, most health promotion programs include several different components, and in most evaluation studies, the exact relationship between these intervention components and their effects remains unclear. In order to understand which program components contribute to healthier lifestyle behaviors and which components do not, several authors conducted meta-regression analyses. For example, previous research demonstrated that self-regulation, which is defined as the capacity needed to resist temptations and impulses [13], was an effective component in health interventions [14]. Among all prevention strategies that were included in the meta-regression, self-monitoring (ie, observing and recording a target behavior [15]) contributed the most to program effectiveness, and combining self-monitoring with at least one other technique based on self-regulation resulted in the largest effect sizes for both healthy eating and physical activity. Furthermore, research showed that health programs based on improving self-regulation skills were especially effective in late adolescence [12].

Therefore, the school-based health intervention investigated in this protocol study also incorporated self-regulation as the main prevention strategy to promote healthier lifestyles. The intervention, called "InCharge," is newly developed by the Trimbos Institute (the Netherlands Institute for Mental Health and Addiction). The InCharge program is developed for older adolescents and aims to promote healthier lifestyles by improving self-regulation skills (ie, through elaborating on and practicing self-regulation). The program helps students realize what is important to them and how certain temptations can hinder them from achieving these goals, teaches them that self-regulation can be used to resist certain temptations (eg, peer pressure), trains self-regulation skills by formulating an action plan, and helps them practice self-regulation through various assignments. Finally, alcohol is introduced as a temptation, and students formulate action plans for responsible alcohol use in order to stimulate healthier drinking behaviors.

This protocol study also investigates potential factors that determine the effectiveness of the InCharge school-based health intervention, because previous studies have found large heterogeneity in the effectiveness of these types of interventions [12]. In particular, this protocol study investigates the role of interpersonal communication during the InCharge school-based health intervention. In the context of mass-mediated health interventions, previous studies have shown that interpersonally communicating about health-related topics is strongly related to health behavior [16,17] and that health interventions can indirectly influence health behaviors through stimulating interpersonal communication about a health behavior [18]. This protocol study will investigate similar purposes of interpersonal communication in a school-based health context. Furthermore, as most school-based health interventions are taught by school teachers, this study protocol will also investigate the role of teacher-related communication during the InCharge program.

Theoretical Basis

The InCharge program is based on several psychological theories such as the social cognitive theory (SCT) [19], the theory of planned behavior (TPB) [20], and the goal-setting theory [21]. The SCT explains behavior by the interaction of personal factors, such as outcome expectancies, self-efficacy, and environmental factors, such as the behavior of others. According to the SCT, behavior change can occur through both active learning and modeling (ie, vicarious reinforcement by learning from the experiences of others). Both mechanisms are incorporated in InCharge; the 7-day challenge offers the opportunity to actively learn through practicing self-control, discussing experiences of classmates with the challenge, and watching several video fragments, resulting in vicarious reinforcement. The TPB is commonly used to explain health behavior and postulates that intention, the most important determinant of behavior, is in turn influenced by the following three constructs: attitude, subjective norms, and perceived behavioral control, which is comparable to self-efficacy in SCT. InCharge mainly aims to influence perceived behavioral control by elaborating on and practicing self-regulation skills. As research has shown that outcome expectancies are related to attitudes [22], the program is expected to influence attitudes by linking the consequences of giving in to health-related temptations to personal goals. Subjective norms are influenced through discussions about social acceptability (regarding alcohol

use). Finally, the goal-setting theory explains behavior change by means of an action sequence of wishing, planning, acting, and evaluating [23]. Goals should be both challenging and feasible [24], and plans should connect a certain goal-directed activity with an anticipated situation [25] in order to be successful. These principles are incorporated in the 7-day challenge, which is one of the components of InCharge.

The InCharge program is developed by taking into account the developmental characteristics of older adolescents. The primary developmental tasks of late adolescence are forming an identity, planning the future, and acquiring the necessary skills to transition into adulthood [26]. As older adolescents experience fundamental changes in their self-definition and identity by exploring new philosophies, lifestyles, and behaviors [6], late adolescence is ideally suited to introduce a healthy lifestyle. Previous research on substance use prevention demonstrated that older adolescents benefit from a social influence approach [12], which makes them aware of the various social pressures to use substances in order to be psychologically prepared to resist these influences. The InCharge program also creates awareness of peer pressure by showing and discussing different examples of peer pressure. In late adolescence, the brain considerably matures, improving executive functions, such as planning, thinking ahead, response inhibition, and more advanced self-regulation and impulse control [27,28]. As a result, older adolescents are capable of mastering self-regulation skills, which has been proven to be an effective prevention strategy in this developmental period [12]. Therefore, improving students' self-regulation skills is one of the core prevention strategies of InCharge.

Aim and Hypotheses

This study describes the protocol of a randomized controlled trial (RCT) including 70 classes with older adolescents, which aims to evaluate the effectiveness of the InCharge program. Baseline, posttest, and 3-month follow-up measures will be conducted to determine whether the program successfully influences the determinants of health behaviors. After completing the program, students in the intervention condition are expected to refrain more from binge drinking and eating unhealthy foods, such as snacks and sweets, and to be more physically active than students in the control condition.

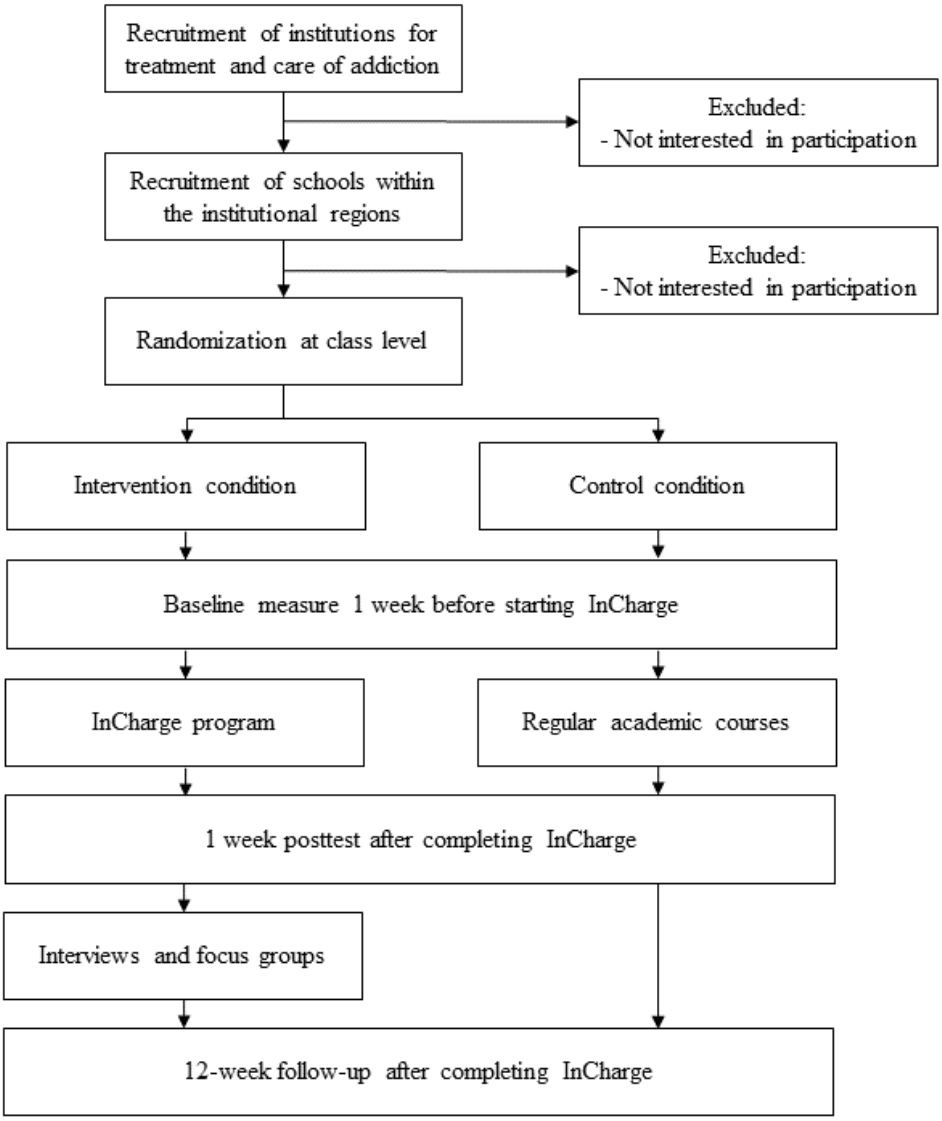
Other aims of our study are to understand the mechanisms through which the InCharge program has its effects. We investigate whether the effects of the program on health behaviors can be explained by increased self-regulation, which is expected to be one of the core mechanisms of the program. Additionally, as previous research has shown the importance of interpersonal communication in mass-mediated health interventions [18], our study aims to investigate interpersonal communication in the context of a school-based health intervention.

Methods

Study Design

The InCharge effectiveness study is a cluster RCT including the following two conditions: an experimental condition (the InCharge program) and a control condition (no intervention) (Figure 1). Participants are older adolescents (aged 16 years or older) in schools for intermediate vocational education, schools for higher general secondary education, and schools for preuniversity education. After initial recruitment and enrollment of schools in the trial, randomization takes place at the class level. In each school, measurements in both experimental and control classes are scheduled 1 week before the four lessons of the InCharge program are implemented in the experimental classes (baseline), and 1 week (posttest) and 3 months (follow-up) after the experimental classes have completed the InCharge program. In addition, the first and fourth lessons of the program are observed by two independent coders in order to obtain information on how the program is delivered, interviews are conducted with teachers about their experiences with the program, and focus groups are conducted with small groups of students about their experiences with the program (both interviews and focus groups are conducted 1 week after the posttest assessment). After all data have been collected within a school, control classes will also receive the intervention.

Figure 1. Design of the cluster randomized controlled trial.



Participants

Recruitment

The Municipal Health Services and prevention departments of regional institutions for the treatment and care of addiction help to implement the InCharge program in schools. From these Municipal Health Services and regional institutions, 47 prevention practitioners are trained by the Trimbos Institute to instruct teachers on how to deliver the program and are asked to provide us with a list of schools in their region interested in participating in the InCharge study. The research team contacts these schools to explain the objective and design of the study. First, schools receive an invitation and an information brochure via email, and thereafter, schools are contacted by phone to discuss participation in the study. Schools are allowed to select the number of classes participating in the study, with a minimum of two classes because randomization occurs within schools. To create comparable research conditions, schools are instructed that a minimum number of two classes should be from the same educational level of the field of study. Classes are eligible for inclusion in the study if they contain older adolescents and the level of education is intermediate vocational education, higher general secondary education, or preuniversity education. Students are recruited by class participation. In collaboration with the schools, students' parents are informed about the study objectives and receive passive informed consent forms. Written active informed consent is obtained from all participating students.

Randomization

We randomize the participants at the class level, and classes within schools are matched on the school level in order to obtain more comparable research conditions. Classes are randomly allocated to the experimental or control condition by means of repeated coin tossing. For each selection of matched classes within schools, classes are assigned to the experimental condition if the coin toss shows heads and to the control condition if the coin toss shows tails. The coin toss procedure is continued until all matched classes are assigned to a research condition, such that as many matched classes as possible are assigned to the experimental and control conditions. Randomization is carried out centrally, with two researchers present to monitor the procedure.

Sample Size Calculation

Effect sizes are difficult to estimate for the InCharge program because the program is newly developed. As school-based prevention programs generally have small effects [12], we based the estimation of the sample size on a small effect size (d=0.2) [29]. In order to reliably detect a small-sized effect in a two-sided test with a conventional significance threshold of α=.05 and a power of (1–β)=0.80, 393 students are required per condition. However, as students are nested in classes and the program is delivered to classes of students, observations of students in the same class are not independent. Therefore, the required sample size is corrected for clustering. Assuming an intraclass correlation of 0.025 and an average class size of 16 participating students, the required sample size increases to 560 students in 35 classes per condition. Calculations are made using the downloadable procedure "clustersampsi" from Stata (StataCorp).

Study Intervention

The experimental intervention is a school-based program named InCharge, which has been designed for older adolescents. The main objective of the program is to stimulate healthy lifestyle behaviors, such as increased physical activity, and to decrease unhealthy behaviors, such as binge drinking and eating unhealthy foods. These objectives should mainly be obtained by means of increasing students' self-regulation skills.

InCharge Program

The InCharge program consists of four 50-minute lessons, and each lesson contains three assignments of approximately 15 minutes. Teachers are trained on how to work with the program material by prevention professionals from Municipal Health Services or regional institutions for the treatment and care of addiction. Materials, such as worksheets, videos, and a web-based quiz tool, are available on a digital teacher platform. In addition, a specially designed app for the smartphone (the 7-day challenge) is used to help students complete the program.

In the first assignment of the first lesson, students visualize their goals for the next 5 years by thinking about what they want to achieve in life and why this is important to them. In the second assignment, students discuss the biggest temptations in their lives. For this assignment, the teacher clears a space in the classroom and draws an imaginary line. Students are asked to position themselves alongside this imaginary line according to how tempting they assess certain temptations, such as chocolate or sweets, alcohol, and staying in bed in the morning. After each temptation, the teacher asks the students to explain their position. In the third assignment, students visualize how their goals would be affected by repeatedly giving in to their biggest temptations or repeatedly resisting their biggest temptations.

In the second lesson, the concept of self-regulation is introduced (for students, self-regulation is called willpower). First, students watch and discuss a video of the marshmallow experiment to understand the role of self-regulation [30]. In this experiment, young children are offered a choice between one marshmallow provided immediately or two marshmallows after waiting for a short period of time. The second assignment focuses on previous experiences with willpower. Students are asked to discuss their own experiences with succeeded challenges, together with the applied strategies that helped them succeed. Finally, all students prepare a challenge to complete during the next week to train their self-regulation abilities. First, they set a realistic goal for themselves related to a chosen health behavior, after which they create a specific plan to achieve this goal. This plan includes the identification of difficult situations and the selection of coping strategies to address these situations accordingly. The actual challenge is completed as a homework assignment. With the help of a specially designed smartphone app (the 7-day challenge), students monitor their progress.

In the third lesson, first, the results of the 7-day challenge are discussed. During the second assignment, students reflect on their original plan to complete the challenge and discuss how these plans could further be improved. The third assignment addresses peer pressure, as peers have been shown to strongly influence the health behaviors of adolescents [31,32]. In order to grasp the influence of peer pressure, students watch and discuss a video of an experiment with a test subject sitting in a room with confederates. As the room fills up with smoke, all confederates remain calm as if nothing happens. As a result, the test subject also remains seated, which could actually be life threatening in case of a real fire.

The final lesson elaborates on alcohol use. At first, students watch a video of partying adolescents who are consuming large amounts of alcohol. The video shows a group of friends who are having fun at first, but the situation ends with a conflict and an injury as a result of excessive alcohol use. Thereafter, students discuss the role of peer pressure in excessive drinking. Second, in order to make them aware of current social norms, students discuss the social acceptability of binge drinking by means of an interactive web-based quiz. Finally, the students identify situations in their own life, where it is important to be careful with alcohol, and come up with strategies to do so. A more thorough description of the assignments can be found in Multimedia Appendix 1.

Data Collection

An overview of all measurements is provided in Table 1. Data are collected by means of paper questionnaires, which are answered during school hours under the supervision of a teacher. In addition, observational data are collected during the first and fourth lessons, complemented with qualitative data from individual interviews with teachers and focus groups with a selection of students.

Table 1. Overview of measurements.

Measurement	Baseline	Posttest	Follow-up
Demographic variables	X[a]	X	X
Self-control variables			
Perceived self-control/impulsivity	X	X	X
Perceived temptations	X	X	X
Motivation to resist temptations	X	X	X
Alcohol, snacking, and physical activity			
Actual behavior	X	X	X
Intentions	X	X	X
Attitudes	X	X	X
Social norms	X	X	X
Negative outcome expectancies	X	X	X
Self-efficacy	X	X	X
Perceived parental rules	X	__[b]	—
Communication about the program			
Frequency (with friends, classmates, and parents)	—	X	—
Valence (with friends, classmates, and parents)	—	X	—
Communication about alcohol, snacking, and physical activity			
Frequency (with friends, classmates, and parents)	X	X	X
Valence (with friends, classmates, and parents)	X	X	X
Program evaluation			
Teacher evaluation (student questionnaire)	—	X	—
Intervention evaluation			
Student questionnaire	—	X	—
Student focus group	—	X	—
Teacher interview	—	X	—

[a]Measurement performed.

[b]Measurement not performed.

Outcomes

Questionnaire Data

The InCharge program aims to stimulate a healthier lifestyle in general among older adolescents by increasing self-regulation skills. In terms of outcome measures, the study focuses on the following three outcome behaviors: alcohol use, snack intake, and lack of physical activity. A pilot study of the program has shown that these behaviors are most prevalent among older adolescents. The main outcomes that are measured for alcohol use, snack intake, and physical activity are the actual behaviors and predictors of the behaviors. Snack behavior and physical activity are operationalized as the number of times adolescents consume snacks and are physically active in an ordinary week as well as in the past 7 days [33]. Alcohol use is operationalized as the number of times adolescents drink alcohol and engage in binge drinking in the past 4 weeks (ie, frequency), as well as the number of drinks adolescents usually consume on one occasion (ie, quantity). Moreover, the predictors of these behaviors are operationalized according to the TPB as attitudes, subjective norms, perceived behavioral control, and behavioral intention [20]. As an additional predictor, negative outcome expectancies are defined as the anticipated negative result of a certain behavior [34]. We operationalized negative outcome expectancies as the probability that exercising less than once a week or daily snacking will lead to weight increase, a poor condition, and health-related problems. For alcohol use, negative outcome expectancies are operationalized as the probability that drinking more than five glasses of alcohol on one occasion will lead to sickness, loss of control, blackouts, regret, and violence (including sexual violence). Finally, parental rules for the three behaviors are assessed.

Additional measures are general self-control, assessments of various temptations, interpersonal communication about the three health behaviors and the intervention, and evaluation of the program and teacher. First, we assess self-control using an adapted version of the Brief Self-Control Scale [35], which assesses deliberative action and impulse control using the

following items: “I am good at resisting temptations,” “I have a hard time breaking bad habits,” “I do certain things that are bad for me, if they are fun,” “I wish I had more self-discipline,” “People would say that I have iron self-discipline,” “Pleasure and fun sometimes keep me from getting work done,” “Sometimes I can’t stop myself from doing something, even if I know it is wrong,” and “I often act without thinking through all the alternatives.” Second, we assess the perceived strength of the temptations with respect to alcohol use, snack intake, and lack of physical activity, as well as the motivation to resist these behavioral temptations. Third, we operationalized interpersonal communication as the frequency of discussions about the intervention (intervention condition only) and the three health behaviors outside class, and how positive or negative adolescents talk about the intervention and these three behaviors. The conversational frequency and valence are separately asked for conversations with friends, classmates, parents, and the teacher who taught InCharge. Fourth, regarding the program evaluation, we assess student perceptions of both the teacher and the prevention program InCharge. The included teacher-related measure is teacher communication, which is operationalized as a selection of variables assessing teacher clarity, verbal immediacy, and content relevance [36-38]. Evaluations of the program consist of an affective (eg, fun) and cognitive component (eg, informative).

Observational Data

Observations are conducted during delivery of the first and fourth lessons of InCharge to provide information on the classroom processes and how the program is delivered (Multimedia Appendices 2 and 3). The main outcomes of the observations are treatment integrity (ie, adherence to the protocol), interpersonal communication during the intervention, classroom interactional processes, teaching style, and student participation. First, treatment integrity or adherence is operationalized as the extent to which the delivered intervention resembles the intended intervention [39]. Additionally, we assess whether the teacher appears to support the intervention. Second, interpersonal communication is operationalized as the number of times a student or teacher talks about the three outcome behaviors during plenary discussions. We also assess whether a student or teacher initiates these discussions about the three outcome behaviors, whether comments during the plenary discussions are based on own experiences, and whether a student or teacher gives suggestions to increase self-efficacy regarding the three behaviors. Third, classroom interactional processes consist of three dimensions, namely emotional support (eg, positive climate), classroom organization (eg, behavior management), and instructional support (eg, quality of feedback [40]). Fourth, teaching style consists of the two components warmth and control [41]. Finally, we code several characteristics referring to student behavior, such as student participations, disruptive behaviors, and general class atmosphere.

Qualitative Data

The topic list of the focus groups with students includes interpersonal communication about temptations, evaluations of the InCharge program, and evaluations of the teacher. For interpersonal communication, we investigate the motivation to discuss temptations with the teacher, friends, classmates, and parents, and reasons why students did not discuss temptations with these conversational partners. The content as well as the valence of the conversations about temptations is investigated for interpersonal communication both within class and outside class. For the evaluation of the program, we aim to understand what parts of the intervention students find helpful or not, whether students actively complete in-class and homework assignments, and whether students think the intervention helps them to deal with temptations in the future. Lastly, we ask students about whether their teacher clearly explains the assignments during the intervention, who should ideally be given these interventions, and their perceptions of their teacher’s support for the intervention.

The topic list of interviews with teachers includes interpersonal communication, teacher perception of students, and evaluation of InCharge. For interpersonal communication, we assess the content and valence of conversations with students about the InCharge program, both during the intervention and outside class, as well as conversations that teachers have overheard among students. For teacher perception of students, we investigate how teachers perceive students’ participation and enjoyment. Finally, we discuss the health intervention with the teacher in order to find improvements for the program.

Statistical Analysis

The background variables of the students (eg, gender, age, and educational level) will be checked to assess whether these variables are successfully randomized across the experimental and control conditions. Unsuccessfully randomized variables will be included as covariates in further analyses to control for potential confounding. Our data have a multilevel structure because participants are nested within classes, and these classes are nested within schools. Therefore, participants in one class or school are more similar than participants in other classes or schools. To account for this potential dependency in the data, we will correct standard errors and parameter estimates for clustering.

In order to determine the effectiveness of the health intervention, an intention-to-treat procedure and completers-only framework will be used to analyze the data. An intention-to-treat analysis of the data implies that participants will be analyzed under the condition that they are initially assigned, whereas completers-only framework analyzes only participants who are present at all time points. Using multilevel analyses, the three behavioral outcomes (snack intake, physical activity, and alcohol use) will be compared between participants in the experimental condition and those in the control condition at posttest and follow-up to determine the effects of the program. In the experimental condition only, multilevel analyses will be conducted to investigate the influence of treatment integrity on the predictors of the three health behaviors at posttest and follow-up. For missing data in multilevel models, maximum likelihood estimation will be used. As self-regulation is an important concept in InCharge, we will test whether the potential effects of InCharge on the health behaviors are explained by self-control. Additionally, relations between interpersonal communication with teachers, friends, classmates, and parents

(ie, frequency and valence) and health-related outcomes, such as a mediating role between the conditions and outcomes, will be tested. As the program is delivered by teachers, we will also test in the experimental condition whether teacher communication relates to the evaluations of the health intervention and the three behavioral outcomes, using structural equation modeling. For structural equation models, expectation maximization will be used to impute the data.

For the qualitative data, interviews with teachers and focus groups with students will be analyzed on the strengths and weaknesses of the program in order to adapt the program. Furthermore, qualitative data will be used to determine the content of interpersonal communication with regard to the InCharge program and various temptations.

Patient and Public Involvement

No patient is involved in this study.

Ethics and Dissemination

The trial has been approved by the Ethics Review Board of the Faculty of Social and Behavioral Sciences of the University of Amsterdam (reference no.: 2017-PC-8244), and the trial is registered with the Netherlands Trial Register (NL6654). Manuscripts reporting the effectiveness of the health intervention and our other aims will be submitted to peer-reviewed journals for publication.

Results

The recruitment, inclusion, and randomization of participants (ie, schools) started in the spring of 2017 and was continued in the spring of 2018, and data are being collected during the following two consecutive school years: 2017-2018 and 2018-2019. As of June 2019, a total of 1216 participants have been enrolled for this trial. This study is part of a PhD project and is expected to be completed in November 2020.

Discussion

Goals of the Study

The goal of this paper is to describe the study protocol of a cluster RCT that aims to evaluate the effectiveness of a school-based health intervention named InCharge. The goal of this program is to stimulate healthier lifestyles by improving the self-regulation skills of older adolescents. We expect that adolescents will be more inclined to refrain from binge drinking and eating unhealthy foods and to be more physically active after following the InCharge program compared with adolescents in the control condition.

Strengths and Limitations

Given that InCharge is a school-based health intervention, the potential to reach a large number of adolescents is an important strength of the program. Second, the underlying mechanisms of InCharge are based on several often successfully tested and relevant theories such as the SCT [19] and the TPB [20], indicating that the program is theoretically well-founded. In addition to the theoretical foundation of the program, the content of InCharge is tailored to the developmental phase of older adolescents by including self-regulation as a core mechanism, which has been proven as one of the most effective prevention strategies during this developmental phase [12]. Furthermore, the study uses a mixed-method design with both quantitative and qualitative data to evaluate the effectiveness of the program. Another strength of the design is that it includes measures for immediate outcomes and measures for follow-up at 3 months, enabling us to assess both the short-term and medium-term effects of the prevention program in comparison with a control group. Lastly, research has shown that interpersonal communication about health topics strongly influences health behavior [16,17]. In our design, we investigate similar purposes of interpersonal communication, as well as the role of teacher communication, in the context of a school-based health intervention.

Our study has some limitations as well. The unit of randomization was classes instead of schools. The presence of both experimental classes and control classes within the same school could result in contamination between conditions because students from the experimental and control condition could have shared information about the intervention. However, as classes within the same school are generally more similar than classes from different schools, we expect that randomization at the class level will result in more comparable research conditions than randomization at the school level. Another limitation relates to the fact that the questionnaire data are obtained through self-reports. A disadvantage of self-reported data is that participants likely want to present themselves favorably, and hence, this might influence how they respond to surveys [42]. One example of such a bias in self-reports is the social desirability bias [43], which means that participants respond in a way that they believe would be perceived as socially desirable by others. This bias could, for example, lead participants to wrongly estimate the frequency of their health behaviors. To limit the incentive for social desirability, we assure participants about complete confidentiality and anonymity of their data.

Practical Relevance

The InCharge study evaluates the effectiveness of the program, and its findings will help to further improve the program. The study also investigates whether including self-regulation as a key component in a school-based health intervention promotes healthier lifestyles among older adolescents. If findings reveal that improving self-regulation skills decreases unhealthy behaviors, such as alcohol use and snack intake, and increases healthy behaviors, such as physical exercise, the findings may aid the developers of health interventions in designing effective behavior change programs for older adolescents. In addition to the content of the intervention, investigating how teacher communication relates to the three health behaviors can provide information on how to communicate for a school-based health intervention. This information can be used to formulate communication guidelines in order to improve the delivery of school-based health interventions and, ultimately, healthier lifestyles. Promoting healthier lifestyles is especially important for older adolescents because unhealthy behaviors generally peak during late adolescence [4,5]. Finally, this study aims to provide information on how interpersonal communication during the intervention and outside the classroom could improve or

hamper the effectiveness of school-based health interventions. These findings may help health care professionals in designing interventions that elicit desired conversations about health-related topics in order to stimulate healthier lifestyles.

Conclusion

This protocol study uses an RCT to assess the effectiveness of InCharge, a newly developed school-based health intervention for older adolescents. As previous research has shown that utilizing self-regulation is an important prevention strategy, the goal of InCharge is to promote healthier behaviors, such as physical activity, and discourage unhealthy behaviors, such as alcohol use, by enhancing self-regulation skills. The program will be improved based on the findings of the effectiveness study.

Authors' Contributions

MM: design of the work; acquisition, analysis, and interpretation of data; and drafting and revision of the work. BVdP: conception and design of the work; interpretation of data; and revision of the work. HH: conception and design of the work; interpretation of data; and revision of the work. SO: conception and design of the work; interpretation of data; and drafting and revision of the work. RV: acquisition of data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of the assignments of the InCharge program.
[DOCX File , 17 KB - resprot_v9i7e17702_app1.docx]

Multimedia Appendix 2
Observation form of lesson 1.
[DOCX File , 24 KB - resprot_v9i7e17702_app2.docx]

Multimedia Appendix 3
Observation form of lesson 4.
[DOCX File , 20 KB - resprot_v9i7e17702_app3.docx]

References

1. Noncommunicable diseases: progress monitor 2017. World Health Organization. 2017 Sep 01. URL: https://apps.who.int/iris/rest/bitstreams/1088594/retrieve [accessed 2017-10-01]
2. Hulshof K, Ocke MC, van Rossum CT, Buurma-Rethans EJ, Brants HA, Drijvers JJ, et al. Results of the national food consumption survey 2003. RIVM. 2004 Oct 14. URL: https://www.rivm.nl/bibliotheek/rapporten/350030002.pdf [accessed 2017-10-01]
3. Forehand R, Wierson M. The role of developmental factors in planning behavioral interventions for children: Disruptive behavior as an example. Behavior Therapy 1993;24(1):117-141. [doi: 10.1016/s0005-7894(05)80259-x]
4. Kwan MY, Cairney J, Faulkner GE, Pullenayegum EE. Physical activity and other health-risk behaviors during the transition into early adulthood: a longitudinal cohort study. Am J Prev Med 2012 Jan;42(1):14-20. [doi: 10.1016/j.amepre.2011.08.026] [Medline: 22176841]
5. Mahalik JR, Levine Coley R, McPherran Lombardi C, Doyle Lynch A, Markowitz AJ, Jaffee SR. Changes in health risk behaviors for males and females from early adolescence through early adulthood. Health Psychol 2013 Jun;32(6):685-694. [doi: 10.1037/a0031658] [Medline: 23477574]
6. Schulenberg JE, Maggs JL. A developmental perspective on alcohol use and heavy drinking during adolescence and the transition to young adulthood. J Stud Alcohol Suppl 2002 Mar(14):54-70. [doi: 10.15288/jsas.2002.s14.54] [Medline: 12022730]
7. Draper CE, Grobler L, Micklesfield LK, Norris SA. Impact of social norms and social support on diet, physical activity and sedentary behaviour of adolescents: a scoping review. Child Care Health Dev 2015 Sep;41(5):654-667. [doi: 10.1111/cch.12241] [Medline: 25809525]
8. Deforche B, Van Dyck D, Deliens T, De Bourdeaudhuij I. Changes in weight, physical activity, sedentary behaviour and dietary intake during the transition to higher education: a prospective study. Int J Behav Nutr Phys Act 2015 Feb 15;12:16 [FREE Full text] [doi: 10.1186/s12966-015-0173-9] [Medline: 25881147]
9. Silveira JA, Taddei JA, Guerra PH, Nobre MR. Effectiveness of school-based nutrition education interventions to prevent and reduce excessive weight gain in children and adolescents: a systematic review. J Pediatr (Rio J) 2011;87(5):382-392 [FREE Full text] [doi: 10.2223/JPED.2123] [Medline: 22012577]

10. Dobbins M, De Corby K, Robeson P, Husson H, Tirilis D. School-based physical activity programs for promoting physical activity and fitness in children and adolescents aged 6-18. Cochrane Database Syst Rev 2009 Jan 21(1):CD007651. [doi: 10.1002/14651858.CD007651] [Medline: 19160341]
11. Foxcroft D, Tsertsvadze A. Universal school-based prevention programs for alcohol misuse in young people. Cochrane Database Syst Rev 2011 May 11(5):CD009113. [doi: 10.1002/14651858.CD009113] [Medline: 21563171]
12. Onrust SA, Otten R, Lammers J, Smit F. School-based programmes to reduce and prevent substance use in different age groups: What works for whom? Systematic review and meta-regression analysis. Clin Psychol Rev 2016 Mar;44:45-59 [FREE Full text] [doi: 10.1016/j.cpr.2015.11.002] [Medline: 26722708]
13. Carver C, Scheier M. Self-regulation of action and affect. In: Vohs KD, Baumeister RF, editors. Handbook of Self-Regulation: Research, Theory and Application. New York: Guilford Press; 2016:3-23.
14. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. Health Psychol 2009 Nov;28(6):690-701. [doi: 10.1037/a0016136] [Medline: 19916637]
15. Kanfer FH. Self-monitoring: Methodological limitations and clinical applications. Journal of Consulting and Clinical Psychology 1970;35(2):148-152. [doi: 10.1037/h0029874]
16. Korhonen T, Uutela A, Korhonen HJ, Puska P. Impact of mass media and interpersonal health communication on smoking cessation attempts: a study in North Karelia, 1989-1996. J Health Commun 1998;3(2):105-118. [doi: 10.1080/108107398127409] [Medline: 10977248]
17. Rimal RN, Flora JA, Schooler C. Achieving Improvements in Overall Health Orientation. Communication Research 2016 Jun 30;26(3):322-348. [doi: 10.1177/009365099026003003]
18. van den Putte B, Yzer M, Southwell BG, de Bruijn G, Willemsen MC. Interpersonal communication as an indirect pathway for the effect of antismoking media content on smoking cessation. J Health Commun 2011 May;16(5):470-485. [doi: 10.1080/10810730.2010.546487] [Medline: 21337250]
19. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewoods Cliff, NJ: Prentice Hall; 1986.
20. Ajzen I. Attitudes, Personality, and Behavior. Chicago, IL: Dorsey Press; 1998.
21. Carver C, Scheier M. On the Self-Regulation of Behavior. New York, NY: Cambridge University Press; 1998.
22. Stacy AW, Widaman KF, Marlatt GA. Expectancy models of alcohol use. J Pers Soc Psychol 1990 May;58(5):918-928. [doi: 10.1037//0022-3514.58.5.918] [Medline: 2348377]
23. Gollwitzer PM. Goal Achievement: The Role of Intentions. European Review of Social Psychology 1993 Jan;4(1):141-185. [doi: 10.1080/14792779343000059]
24. Locke E, Latham G. A Theory of Goal Setting & Task Performance. Englewood Cliffs, NJ: Prentice Hall; 1990.
25. Gollwitzer PM. Implementation intentions: Strong effects of simple plans. American Psychologist 1999;54(7):493-503. [doi: 10.1037/0003-066x.54.7.493]
26. Zarrett N, Eccles J. The passage to adulthood: challenges of late adolescence. New Dir Youth Dev 2006(111):13-28, 7. [doi: 10.1002/yd.179] [Medline: 17225644]
27. Steinberg L. Risk Taking in Adolescence. Curr Dir Psychol Sci 2016 Jun 23;16(2):55-59. [doi: 10.1111/j.1467-8721.2007.00475.x]
28. Steinberg L. A dual systems model of adolescent risk-taking. Dev Psychobiol 2010 Apr;52(3):216-224. [doi: 10.1002/dev.20445] [Medline: 20213754]
29. Cohen J. A power primer. Psychol Bull 1992 Jul;112(1):155-159. [doi: 10.1037//0033-2909.112.1.155] [Medline: 19565683]
30. Mischel W, Ebbesen EB, Zeiss AR. Cognitive and attentional mechanisms in delay of gratification. J Pers Soc Psychol 1972 Feb;21(2):204-218. [doi: 10.1037/h0032198] [Medline: 5010404]
31. Glaser B, Shelton KH, van den Bree MB. The moderating role of close friends in the relationship between conduct problems and adolescent substance use. J Adolesc Health 2010 Jul;47(1):35-42 [FREE Full text] [doi: 10.1016/j.jadohealth.2009.12.022] [Medline: 20547290]
32. Salvy S, de la Haye K, Bowker JC, Hermans RC. Influence of peers and friends on children's and adolescents' eating and activity behaviors. Physiol Behav 2012 Jun 06;106(3):369-378 [FREE Full text] [doi: 10.1016/j.physbeh.2012.03.022] [Medline: 22480733]
33. de Looze M, van Dorsselaer S, de Roos S, Verdurmen J, Stevens G, Gommans R, et al. Gezondheid, welzijn en opvoeding van jongeren in Nederland. HBSC. 2013 Jan. URL: https://hbsc-nederland.nl/wp-content/uploads/2018/08/hbsc-rapport-2013-herzien.pdf [accessed 2019-10-01]
34. Feather N. Expectations and Actions. Hillsdale, NJ: Lawrence Erlbaum; 1982.
35. Tangney JP, Baumeister RF, Boone AL. High self-control predicts good adjustment, less pathology, better grades, and interpersonal success. J Pers 2004 Apr;72(2):271-324. [doi: 10.1111/j.0022-3506.2004.00263.x] [Medline: 15016066]
36. Chesebro JL, McCroskey JC. The development of the teacher clarity short inventory (TCSI) to measure clear teaching in the classroom. Communication Research Reports 1998 Jun;15(3):262-266. [doi: 10.1080/08824099809362122]
37. Frymier A, Shulman G. "What's in it for me?": Increasing content relevance to enhance students' motivation. Communication Education 1995 Jan;44(1):40-50. [doi: 10.1080/03634529509378996]

38. Gorham J. The relationship between verbal teacher immediacy behaviors and student learning. Communication Education 1988 Jan;37(1):40-53. [doi: 10.1080/03634528809378702]
39. Perepletchikova F. On the Topic of Treatment Integrity. Clin Psychol (New York) 2011 Jun;18(2):148-153 [FREE Full text] [doi: 10.1111/j.1468-2850.2011.01246.x] [Medline: 21769167]
40. Pianta R, Hamre B, Hayes N. Classroom Assessment Scoring System — Secondary (CLASS-S). Charlottesville, VA: University of Virginia; 2008.
41. Ertesvåg SK. Measuring authoritative teaching. Teaching and Teacher Education 2011 Jan;27(1):51-61. [doi: 10.1016/j.tate.2010.07.002]
42. Richter L, Johnson PB. Current Methods of Assessing Substance Use: A Review of Strengths, Problems, and Developments. Journal of Drug Issues 2016 Aug 03;31(4):809-832. [doi: 10.1177/002204260103100401]
43. van de Mortel TF. Faking it: Social desirability response bias in self-report research. Aust J Adv Nurs. 2008. URL: https://www.ajan.com.au/archive/Vol25/Vol_25-4_vandeMortel.pdf

Abbreviations

RCT: randomized controlled trial
SCT: social cognitive theory
TPB: theory of planned behavior

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Protocol

HIV Self-Testing to Promote Serostatus Disclosure Among Men Who Have Sex With Men in China: Protocol for a Stepped Wedge Randomized Controlled Trial

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Abstract

Background: Disclosure of HIV serostatus is important for the prevention of HIV infection among men who have sex with men (MSM). However, knowledge of sexual partners' HIV status among MSM in China is low. As a complement to HIV testing services, HIV self-testing (HIVST) has considerable potential to promote serostatus disclosure.

Objective: The primary objective of our trial is to evaluate the effect of HIVST on improving serostatus disclosure to sexual partners. We hypothesize that MSM in an intervention condition will have a higher awareness of the HIV status of their sexual partners compared with MSM in the control condition. The secondary aims are to evaluate (i) changes in sexual behaviors after disclosure of HIV status by sexual partners, (ii) promotion of the frequency of HIV and syphilis testing on participants and their sexual partners, and (iii) factors that restrict the disclosure of HIV infection to sexual partners. We hypothesize that MSM in the intervention condition will exhibit safer sexual decision making and a higher rate of HIV testing uptake compared with MSM in the control condition.

Methods: A stepped wedge randomized controlled trial will be conducted throughout China. Study recruitment of 800 MSM will be promoted through advertisements released on WeChat public accounts. Individuals who are born biologically male, aged ≥18 years, HIV negative, and who have not undergone HIV testing in the past 3 months will be recruited. Eligible men will be randomly divided (1:1:1:1) into four groups and randomized. The group cluster will initiate the intervention so that participants will be provided with 2-4 free finger prick–based HIVST kits until trial completion. The intervention period for participants in each of the four groups will be initiated at 3-month intervals. Men in both groups will be required to complete a baseline and four follow-up surveys every 3 months. The primary intervention outcome will evaluate the effect of the distribution of HIVST kits on improvement in the disclosure of sexual partners' HIV status. The secondary outcomes will be changes in sexual behaviors after disclosure of HIV status from sexual partners, the promotion of the frequency of HIVST on participants and their sexual partners, and the factors that restrict disclosure of HIV status to sexual partners.

Results: Subject recruitment began in August 2018. The first round of follow-up surveys post intervention is complete, with three rounds remaining to be done. Data analysis was scheduled for April 2020 and the results will be disseminated through conferences and peer-reviewed publications.

Conclusions: Few studies have evaluated interventions to increase knowledge of sexual partners' HIV status among MSM. Our trial will provide information on the link between HIVST and HIV serostatus disclosure. The findings of this trial will facilitate the implementation of HIVST services to help control the spread of HIV among MSM in China.

Trial Registration: Chinese Clinical Trial Registry ChiCTR1800019453; http://www.chictr.org.cn/showproj.aspx?proj=30158
International Registered Report Identifier (IRRID): DERR1-10.2196/17788

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KEYWORDS

HIV; HIV self-testing (HIVST), HIV serostatus disclosure; men who have sex with men (MSM); stepped wedge randomized controlled trial; China

Introduction

Background

The HIV epidemic is a significant public health problem worldwide, especially among men who have sex with men (MSM) [1,2]. Of all new HIV infections worldwide in 2017, MSM accounted for 18% but reached 29% in the Asia-Pacific region [3]. National surveillance data have indicated that HIV prevalence among MSM in China increased from 0.9% in 2003 to 8% in 2015 [4,5]. Despite considerable efforts, HIV-positive MSM comprise an increasing proportion of newly infected individuals infected through regular or casual sexual partners [6]. Thus, HIV serostatus disclosure from sexual partners is essential for the prevention and control of HIV infection among MSM [7].

There are several benefits of HIV serostatus disclosure between sexual partners. It facilitates serosorting, promotes safer sexual behavior, and reduces the risk of HIV acquisition [8-10]. For example, women in Kenya are more likely to use condoms after receiving the HIV-positive results of male partners [11]. However, the practice of HIV serostatus disclosure remains uncommon among MSM in low- and middle-income countries (LMICs) [12,13]. A recent study among MSM in China found that the knowledge of sexual partners' HIV status for most "regular" and "casual" male partners was only 20.6% and 17.8%, respectively [14]. This low prevalence may be due to fear of violence [15], concerns about upsetting family numbers and rejection [16,17], or lack of social support [18]. Low uptake of HIV testing is another critical concern with the disclosure of HIV status [19]. However, a meta-analysis in China showed that only 38% of MSM had taken an HIV test in the previous 12 months and that 53% of MSM had never undertaken an HIV test in their lifetime [20].

HIV self-testing (HIVST) is a complement to conventional facility-based HIV testing services and has been recommended by the World Health Organization (WHO) since 2015 [21]. Individuals who use HIVST can collect their blood or saliva privately, conduct a test, and read the results themselves. With the characteristics of privacy, convenience, and confidentiality, HIVST is attractive to MSM [22-24]. Studies have indicated that HIVST has high acceptability among MSM, and a considerable proportion of MSM have expressed great interest and are willing to use it [25-27]. Two randomized controlled trials (RCTs) conducted in developed countries demonstrated that HIVST increases the frequency of HIV testing among MSM [28,29].

Many studies have primarily focused on the process [30], benefits and barriers [16], and factors associated with HIV serostatus disclosure [9]. One prospective cohort study and an RCT in Kenya indicated that HIVST kits distributed by sexually active females could promote HIV status disclosure from their heterosexual partners, and subsequently safer sexual decisionmaking [11,31]. However, few studies have explored the intervention effect of HIVST to promote HIV status disclosure among MSM. Further studies are urgently needed to fill the current gap and evaluate the effect of HIVST intervention on improvement of HIV serostatus disclosure among MSM in China.

Objective

The primary objective of our trial is to evaluate the effect of HIVST on improving HIV serostatus disclosure between sexual partners. The hypothesis is that MSM receiving free HIVST test kits and counseling will have a higher awareness of the HIV status of their sexual partners compared with MSM in the control condition. The secondary aims are to determine the: (i) changes in sexual behaviors after disclosure of HIV status from sexual partners; (ii) promotion of the frequency of HIV and syphilis testing on participants and their sexual partners; (iii) factors that restrict the disclosure of HIV infection to sexual partners. The hypotheses are that MSM in the intervention condition will exhibit safer sexual decisionmaking and a higher rate of HIV testing compared with MSM in the control condition.

Methods

Trial Design

Given the significantly higher risk of acquiring HIV among MSM than the general heterosexual population, an RCT is not appropriate on ethical grounds. Therefore, this study was designed as a stepped wedge RCT. This design will ensure that all participants have an equal chance to initiate the intervention, though each group will begin the intervention at different times. Also, a pragmatic stepped wedge RCT design will allow the evaluation of the intervention in different groups rather than in a single group.

Study Setting and Recruitment

An online cohort will be established. All information, including surveys and HIVST results, will be collected through Gold Data, an online platform dedicated to data collection [32]. A few personal WeChat (Tencent) public accounts that are active in the MSM social circle will release an advertisement to invite MSM to participate in the trial. The advertisement will explain the study objectives, content, and procedures. Restrictions on the use of Internet Protocol addresses will ensure that all participants can complete the survey only once. A 20 RMB (2.84 USD) incentive will be delivered to each participant for

the first baseline, and 20 RMB (2.84 USD) for each follow up. Participants who complete all five surveys (baseline and four follow-ups) will earn an extra 200 RMB (28.39 USD) to compensate for their time.

A baseline survey will be used to assess eligibility. Eligible men will be randomly divided into four groups at a ratio of 1:1:1:1. Intervention for the four groups will be randomized and initiated at 3-month intervals. Participants who reach the intervention period will be provided with 2-4 free HIVST kits. The trial will last for 1 year. All individuals who enroll in the trial will be required to complete four follow-up surveys every 3 months. The trial will not be blinded because researchers will be aware of the assignment and sequence with which intervention materials are delivered to each participant. A flowchart describing the trial design is presented in Table 1.

Table 1. Study schedule.

Timepoint	Enrollment	Allocation	Post allocation			
Enrollment	Aug 2018-Feb 2019	Aug 2018-Feb 2019	T1[a]	T2[b]	T3[c]	T4[d]
Online recruitment	X					
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Intervention initiated						
Group A			I[e]	I	I	I
Group B			C[f]	I	I	I
Group C			C	C	I	I
Group D			C	C	C	I
Assessments						
Online surveys			X	X	X	X

[a]T1: 1-3 months after enrollment.

[b]T2: 3-6 months after enrollment.

[c]T3: 6-9 months after enrollment.

[d]T4: 9-12 months after enrollment.

[e]I: Intervention condition.

[f]C: Control condition.

Inclusion Criteria

Men who provide written informed consent and meet all of the following criteria will be regarded as eligible and invited to participate: born biologically male; age ≥18 years; HIV-negative; had oral or anal sex with men in the previous 6 months; no HIV testing in the past 3 months; willing to provide their telephone number and address (for follow-up and delivery of HIVST kits); willing to accept HIVST kits; willing to share truthful information regarding sexual behavior and HIV testing; willing to accept consultation before and after HIVST and links to HIV care.

Exclusion Criteria

MSM will be excluded if they are participating in other research projects, unable to speak or read the Chinese language, unable to complete the online questionnaire using a mobile telephone, or cannot provide written informed consent.

Randomization and Allocation

The Mersenne Twister pseudo-random number generator will generate 200 groups of 1-4 random number tables using SAS (SAS Institute) to determine each participant's group assignment. Then, researchers will randomly select four balls marked 1, 2, 3, and 4 from a closed container to determine the intervention sequence (A-B-C-D). Interventions will be initiated at 3-month intervals.

Intervention Implementation

When MSM participants reach the intervention period, researchers will send a Quick Response (QR) barcode to each participant to request delivery of 2-4 HIVST kits. The survey is nationwide, and participants will be asked to provide their telephone number and address for delivery of the requested kits.

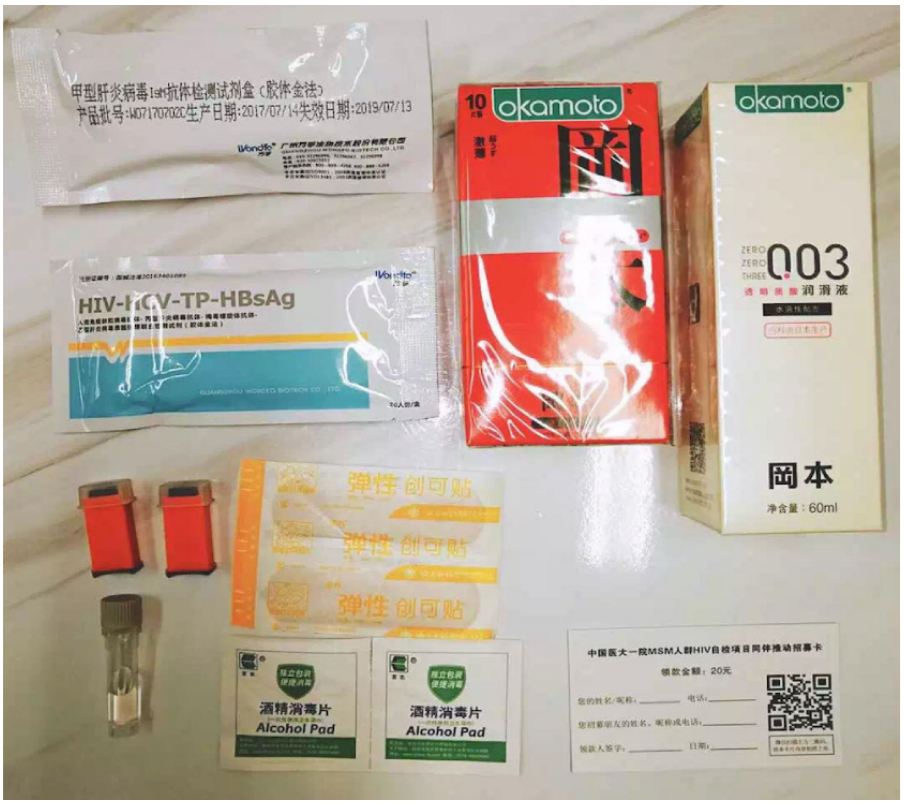
The HIVST kits will be sent 1-2 days after request and can be used for HIV testing by the participants themselves and their sexual partners. To confirm that participants have used their HIVST kits and help researchers provide consultations, photographs of all HIVST results must be uploaded and submitted through the online survey platform within 20 min after testing. If participants have shared the HIVST kits with their sexual partners, the latter will also be asked to upload a photograph of their HIVST results and complete a questionnaire. The telephone number of participants who share the HIVST kits will also be required for indemnification matching. Participants will be permitted to apply for repeat delivery of 2-4 HIVST kits if previously delivered kits have been used,

with no restrictions on the number of HIVST kits permitted during the research period. For participants' convenience and privacy, the HIVST kits will be delivered by express mail in discreet packaging without visible text mentioning HIVST. Participants will not have to pay for HIVST kits or postage.

HIVST Kit Components

Finger prick HIVST kits (Wondfo) approved by the Food and Drug Administration of China will be used. Antibodies against HIV 1/2 will be detected 6 weeks post infection using blood specimens [33]. In addition to HIV, the assay also contains reagents to test for antibodies against syphilis, the hepatitis C virus, and surface antigens of the hepatitis B virus, which are prevalent among MSM in China (Figure 1). Consumables needed for testing (alcohol, cotton, disposable blood needles, EDTA capillary tubes, and bandages) will be provided in each kit. Video and written instructions will provide detailed procedures for testing and an explanation of possible results. Participants can contact the study administrators through a 24-h telephone number or WeChat account if they encounter problems or difficulties during testing.

Figure 1. HIVST kits used in the study.



Consultation and Referral Services

Researchers will provide consultation via WeChat, the platform used to enroll in the study, before and after testing. Trained researchers will provide pretest consultation for all participants, informing them of the purpose and significance of HIV testing at the time participants make their test kit request. In addition to sending HIVST kits, test kit instructions (written and video) will be distributed. For those participants who cannot use the self-testing kits after reading the instructions, WeChat and telephone support will be provided. Posttest counseling will be provided within 24 hours after the test results are uploaded. Test results uploaded by participants and their sexual partners will be reviewed daily. Individuals whose test results are "positive" or "indeterminate" will be contacted immediately by telephone or WeChat. Posttest consultation for those who upload HIV-negative results will consist of a reminder of the meaning of a negative test result and how to prevent HIV infection. Those who have positive self-test results will receive HIV posttest consultation services, including interpretation of the test results and referral to services for clinical confirmation testing and antiviral treatment. Materials for dried-blood spot (DBS) testing will be recommended and freely provided for further testing, including western blotting and nucleic-acid detection, at the Key Laboratory of AIDS Immunology of Liaoning Province (First Affiliated Hospital of China Medical University, Shenyang, China) [34]. HIV laboratory test result confirmation will be provided to participants, and counseling and referral will be suggested.

Contamination Control

The initial screen will ask whether the applying participant's partners or friends have participated in this HIVST study. To reduce the potential for contamination between groups, participants who indicate their partners or friends have participated in the study will be deemed ineligible to participate.

Study Measures and Outcomes

Baseline and follow-up surveys will be completed via mobile telephone and collected through Gold Data, the most popular online data collection system platform in China. Study administrators will establish an online survey form and generate

a QR code link to the survey questionnaire. Study subjects will scan the QR code provided and complete the survey, indicating their willingness to participate in the project and the conditions for participation. A link to the questionnaire is also included in the HIVST kit instruction manual mailed to the respondent. After completing the HIVST, participants scan the QR code and provide their identification numbers, social background, and behavioral information, and uploaded photos of self-test results.

Data privacy is assured by contractual agreement with Gold Data, as well as Gold Data's encryption systems. Participants are asked to use pseudonyms rather than their real names. A secondary identifier is provided with each participant's questionnaire. Study administrators also used physical controls, such as locked storage for study data, to ensure participants' privacy and data security.

A baseline questionnaire will be used to screen candidates for inclusion eligibility. Eligible participants will be required to complete the remaining questions in the surveys. Data collection will include social background (age, level of education, monthly income, occupation, marital status, and sexual orientation), high-risk sexual behaviors, and experience of HIV testing. High-risk sexual behaviors, including the number and type of sexual partners, number of condom-less oral or anal sex encounters, and knowledge of sexual partners' HIV status during the past 3 months, will be documented. HIV testing history, including the number of self-reported HIV tests, experience with HIVST, and variables, will also be recorded.

Participants will be asked to complete follow-up surveys within one week after being notified via WeChat message. Follow-up surveys will be performed at 3, 6, 9, and 12 months after enrollment. The distribution of HIVST kits, sexual partners' willingness to use the kits, and the rate of HIV status disclosure by sexual partners will be collected. In addition to high-risk sexual behaviors and HIV testing experience in the baseline survey, sexual decision making will also be measured to evaluate the effect of HIV status disclosure. Questions regarding sexual decisionmaking will focus mainly on whether to have sex and condom use (never/sometimes/usually/always using) for oral or anal sex after knowing the HIV status of sexual partners (negative/positive/unknown). Participants who report that they are unwilling to disclose their HIV status to sexual partners will be asked questions about sexual orientation, HIV status, type of sexual partners, HIV testing-related violence, and HIV testing history.

Reminder messages will be sent via WeChat for 3 weeks to ensure the completion of follow-up surveys. Participants will be considered lost to follow-up if they do not complete their survey within 1 month.

Sample Size

To calculate sample size, we used the calculation tool for the stepped wedge RCT design developed by Hussey et al [35]. Tang and colleagues found that in China, the proportions of MSM being told of their partners' HIV status were 20.6% and 17.8% for most regular and casual male partners, respectively [14]. Assuming that the effect of the intervention period was superior to that of the control period, an overall growth of 10%, four intervention periods, a coefficient of variation of 0.40 (usually between 0.15 and 0.40), a two-sided α of 0.05, and 90% power, the total sample sizes of 620 and 560 for the most recent regular and casual male partners were significant. Given a loss to follow-up of 20%, we made a conservative estimate that 200 men in each group would be sufficient to detect differences between the intervention and control conditions.

Data Management

Survey data and photographs of testing results will be collected through an online survey platform. Only researchers will have an account and password, so the safety and privacy of participants are ensured. Data will be downloaded directly and saved in an identifiable format on a computer. When the data are transmitted, some identifiable variables, such as name, telephone number, and address, will be encrypted for privacy protection. A specific telephone will be used for daily contact with participants during the trial and will be locked in a document cabinet after work every day.

Analysis Plan

Survey data will be imported into SAS for data management and analysis. The primary outcome will be the self-reported disclosure of HIV status by sexual partners during the past 3 months. Generalized linear mixed models will be used to compare the differences between intervention and control conditions for primary outcome analysis. Intervention status and time will be treated as fixed effects, whereas group clusters and individuals will be estimated as random effects. The effects of the intervention will be reported with 95% confidence intervals and *P* values. $P<.05$ will be considered significant.

Similar methods will be used to measure secondary outcomes, including the frequency of HIV testing uptake, frequency of syphilis testing, number of sexual partners, and unprotected sex. In addition, logistic regression analysis will be used to explore the relationship between the HIVST results of sexual partners and condom use during sexual intercourse. Factors such as sexual orientation, HIV status, type of sexual partners, HIV testing-related violence, history of HIV testing, and others will be measured to examine their association with disclosure of HIV status to sexual partners.

Patient and Public Involvement

We invited a community-based organization worker from the Shenyang Sunny organization and two MSM to participate in revising the structure and content of our recruitment advertisement, guaranteeing it would be attractive and relevant to the MSM community. These individuals were not involved in conducting the study. As the intervention will be initiated at different times, all participants have the right to seek other HIV testing services during the study, regardless of the group to which they have been assigned. The results will be disseminated to the public and study population after study completion.

Ethics and Dissemination

The research program and procedures have been approved by the ethics committee of the First Affiliated Hospital of China Medical University (2018-174-2). The study was registered

with the Chinese Clinical Trial Registry (trial ID: ChiCTR1800019453) on November 12, 2018. Informed consent forms will be provided to each participant before the questionnaire and distribution of HIVST kits. Participants will be able to withdraw from the study at any time. We will use a mobile telephone to contact respondents. The findings of the study will be made available to local and national government agencies in China and disseminated through academic publications and international conferences.

The study was retrospectively registered under ID ChiCTR1800019453 on Chinese Clinical Trial Registry because the authors were unaware of the definition of a clinical trial per the International Committee of Medical Journal Editors.

Results

At the time of publication, recruitment and intervention are complete for all participants. Data for the baseline and initial investigation have been added to Chinese Clinical Trial Registry.

Discussion

HIV serostatus disclosure has important implications for the prevention and control of HIV epidemics. Studies have suggested that HIV testing (especially for couples) is critical for disclosure of HIV status [36]. The situation is similar in China. A recent observational study of eight cities showed that HIV testing and HIVST were positively associated with HIV status disclosure for regular and casual male partners [14]. Studies have demonstrated that HIVST can promote the disclosure of HIV status among heterosexual couples, but no scholars have evaluated the impact among MSM. A nationwide, large-scale, stepped wedge RCT is necessary to evaluate the ability of HIVST to facilitate HIV status disclosure among MSM in China. If successful, evidence derived from our trial could be used to expand the implementation of HIVST services. The trial outcome will also provide policy and intervention strategies for this key population in government and community organizations.

Our trial will also explore the impact of HIVST intervention on HIV testing uptake among participants and their sexual partners. Since 2012, the WHO has recommended MSM to undergo HIV testing with their partners [37]. Our trial will provide multiple HIVST kits to each participant and permit them to share those kits with their sexual partners. This form of secondary distribution may aid in our understanding of how to improve the level of HIV testing uptake in MSM.

Our trial has four main limitations. First, a 12-month research period is relatively long, and to maintain compliance from participants (especially during follow-up) will be challenging. To compensate for this anticipated loss, we will enlarge the sample size by 20%. Second, because the survey interval is 3 months, recall bias may occur during information collection. To compensate, researchers will assess whether some questionnaire variables are consistent with subsequent feedback from participants. Third, migration of participants may occur during the long study period. To circumvent this problem, we will remind participants to contact us and update their mobile telephone number and residence address. Other information will be used to match identification if necessary. Finally, participants will be recruited through the internet; MSM who lack access to the internet will not be recruited, which may limit the generalizability of study results.

Acknowledgments

We thank the staff in Yi Gui and Rainbow Harbor of the First Affiliated Hospital of China Medical University for helping in the recruitment of trial participants.

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Authors' Contributions

TL, HL, YJ, and JX initiated this research plan and designed this protocol. TL, XM, EP, and JZ helped with the design of the questionnaire and recruitment methods. YG, ZC, and WD provided expertise on the collection of questionnaires, DBS samples, HIV post counseling, and referral. All authors edited the protocol and agreed with the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT checklist.
[PDF File (Adobe PDF File), 347 KB - resprot_v9i7e17788_app1.pdf]

References

1. van Griensven F, de Lind van Wijngaarden JW. A review of the epidemiology of HIV infection and prevention responses among MSM in Asia. AIDS 2010 Sep;24 Suppl 3(Suppl 3):S30-S40. [doi: 10.1097/01.aids.0000390087.22565.b4] [Medline: 20926926]

2. Global Health Observatory (GHO) data. Geneva, Switzerland: World Health Organization; 2017.
3. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. The Lancet 2012 Jul;380(9839):367-377. [doi: 10.1016/s0140-6736(12)60821-6]
4. UNAIDS DATA 2018. Geneva: Joint United Nations Programme on HIV/AIDS; 2018.
5. Qin Q, Tang W, Ge L, Li D, Mahapatra T, Wang L, et al. Changing trend of HIV, Syphilis and Hepatitis C among Men Who Have Sex with Men in China. Sci Rep 2016 Aug 18;6(1):31081 [FREE Full text] [doi: 10.1038/srep31081] [Medline: 27535092]
6. Tang S, Tang W, Meyers K, Chan P, Chen Z, Tucker JD. HIV epidemiology and responses among men who have sex with men and transgender individuals in China: a scoping review. BMC Infect Dis 2016 Oct 20;16(1):588 [FREE Full text] [doi: 10.1186/s12879-016-1904-5] [Medline: 27765021]
7. UNAIDS. The global HIV/AIDS epidemic. Geneva, Switzerland: UNAIDS 2017.
8. Beyrer C, Wirtz A, Walker D, Johns B, Frangiscos S, Baral S. The global HIV epidemics among men who have sex with men. Washington DC: World Bank Publications 2011. [doi: 10.1596/9780821387269_ch08]
9. Xia Q, Molitor F, Osmond DH, Tholandi M, Pollack LM, Ruiz JD, et al. Knowledge of sexual partner's HIV serostatus and serosorting practices in a California population-based sample of men who have sex with men. AIDS 2006 Oct 24;20(16):2081-2089. [doi: 10.1097/01.aids.0000247566.57762.b2] [Medline: 17053354]
10. Deribe K, Woldemichael K, Wondafrash M, Haile A, Amberbir A. Disclosure experience and associated factors among HIV positive men and women clinical service users in Southwest Ethiopia. BMC Public Health 2008 Feb 29;8(1):81 [FREE Full text] [doi: 10.1186/1471-2458-8-81] [Medline: 18312653]
11. Bikaako-Kajura W, Luyirika E, Purcell DW, Downing J, Kaharuza F, Mermin J, et al. Disclosure of HIV status and adherence to daily drug regimens among HIV-infected children in Uganda. AIDS Behav 2006 Jul 22;10(4 Suppl):S85-S93. [doi: 10.1007/s10461-006-9141-3] [Medline: 16791525]
12. Thirumurthy H, Masters SH, Mavedzenge SN, Maman S, Omanga E, Agot K. Promoting male partner HIV testing and safer sexual decision making through secondary distribution of self-tests by HIV-negative female sex workers and women receiving antenatal and post-partum care in Kenya: a cohort study. The Lancet HIV 2016 Jun;3(6):e266-e274. [doi: 10.1016/s2352-3018(16)00041-2]
13. Carballo-Diéguez A, Balán IC, Dolezal C, Ibitoye M, Pando MA, Marone R, et al. HIV status disclosure among infected men who have sex with men (MSM) in Buenos Aires, Argentina. AIDS Educ Prev 2013 Dec;25(6):457-467 [FREE Full text] [doi: 10.1521/aeap.2013.25.6.457] [Medline: 24245593]
14. Edwards-Jackson N, Phanuphak N, Van Tieu H, Chomchey N, Teeratakulpisarn N, Sathienthammawit W, et al. HIV serostatus disclosure is not associated with safer sexual behavior among HIV-positive men who have sex with men (MSM) and their partners at risk for infection in Bangkok, Thailand. AIDS Res Ther 2012 Dec 23;9(1):38 [FREE Full text] [doi: 10.1186/1742-6405-9-38] [Medline: 23259683]
15. Tang W, Liu C, Cao B, Pan SW, Zhang Y, Ong J, SESH Study Group. Receiving HIV Serostatus Disclosure from Partners Before Sex: Results from an Online Survey of Chinese Men Who Have Sex with Men. AIDS Behav 2018 Dec 22;22(12):3826-3835 [FREE Full text] [doi: 10.1007/s10461-018-2062-0] [Medline: 29470809]
16. Hampanda KM, Rael CT. HIV Status Disclosure Among Postpartum Women in Zambia with Varied Intimate Partner Violence Experiences. AIDS Behav 2018 May 3;22(5):1652-1661 [FREE Full text] [doi: 10.1007/s10461-017-1909-0] [Medline: 28975510]
17. Maman S, Medley A. Gender dimensions of HIV status disclosure to sexual partners: rates barriers and outcomes. A review paper 2003.
18. Medley A, Garcia-Moreno C, McGill S, Maman S. Rates, barriers and outcomes of HIV serostatus disclosure among women in developing countries: implications for prevention of mother to-child transmission programmes. Bull World Health Organ ? 2004;82(4):307.
19. Smith R, Rossetto K, Peterson BL. A meta-analysis of disclosure of one's HIV-positive status, stigma and social support. AIDS Care 2008 Nov 13;20(10):1266-1275. [doi: 10.1080/09540120801926977] [Medline: 18608080]
20. Yoshioka MR, Schustack A. Disclosure of HIV status: cultural issues of Asian patients. AIDS Patient Care STDS 2001 Feb;15(2):77-82. [doi: 10.1089/108729101300003672] [Medline: 11224933]
21. Zou H, Hu N, Xin Q, Beck J. HIV testing among men who have sex with men in China: a systematic review and meta-analysis. AIDS Behav 2012 Oct 8;16(7):1717-1728. [doi: 10.1007/s10461-012-0225-y] [Medline: 22677975]
22. Marcus U, Schink SB, Sherriff N, Jones A, Gios L, Folch C, Sialon II Network. HIV serostatus knowledge and serostatus disclosure with the most recent anal intercourse partner in a European MSM sample recruited in 13 cities: results from the Sialon-II study. BMC Infect Dis 2017 Nov 25;17(1):730 [FREE Full text] [doi: 10.1186/s12879-017-2814-x] [Medline: 29178847]
23. WHO. WHO Guidelines on HIV self-testing and partner notification URL: http://www.who.int/hiv/pub/vct/hiv-selftesting-guidelines/en [accessed 2019-03-12]
24. Young SD, Daniels J, Chiu CJ, Bolan RK, Flynn RP, Kwok J, et al. Acceptability of using electronic vending machines to deliver oral rapid HIV self-testing kits: a qualitative study. PLoS One 2014 Jul 30;9(7):e103790 [FREE Full text] [doi: 10.1371/journal.pone.0103790] [Medline: 25076208]

25. Lippman SA, Moran L, Sevelius J, Castillo LS, Ventura A, Treves-Kagan S, et al. Acceptability and Feasibility of HIV Self-Testing Among Transgender Women in San Francisco: A Mixed Methods Pilot Study. AIDS Behav 2016 Apr 28;20(4):928-938 [FREE Full text] [doi: 10.1007/s10461-015-1236-2] [Medline: 26511864]
26. World HO. Guidelines on HIV self-testingpartner notification: supplement to consolidated guidelines on HIV testing services. Geneva, Switzerland: WHO 2016.
27. World HO. Consolidated guidelines on HIV testing services: WHO. Consolidated guidelines on HIV testing services 2015:2015.
28. Pant Pai N, Bhargava M, Joseph L, Sharma J, Pillay S, Balram B, et al. Will an unsupervised self-testing strategy be feasible to operationalize in Canada? Results from a pilot study in students of a large canadian university. AIDS Res Treat 2014;2014:747619-747618 [FREE Full text] [doi: 10.1155/2014/747619] [Medline: 24511392]
29. Schnall R, John RM, Carballo-Dieguez A. Do High-Risk Young Adults Use the HIV Self-Test Appropriately? Observations from a Think-Aloud Study. AIDS Behav 2016 Apr 30;20(4):939-948 [FREE Full text] [doi: 10.1007/s10461-015-1240-6] [Medline: 26518679]
30. Figueroa C, Johnson C, Verster A, Baggaley R. Attitudes and Acceptability on HIV Self-testing Among Key Populations: A Literature Review. AIDS Behav 2015 Nov 9;19(11):1949-1965 [FREE Full text] [doi: 10.1007/s10461-015-1097-8] [Medline: 26054390]
31. Bavinton BR, Brown G, Hurley M, Bradley J, Keen P, Conway DP, et al. Which gay men would increase their frequency of HIV testing with home self-testing? AIDS Behav 2013 Jul 23;17(6):2084-2092. [doi: 10.1007/s10461-013-0450-z] [Medline: 23525790]
32. Gold Data. URL: https://cmuvct.jinshuju.com/home [accessed 2020-05-26]
33. Katz DA, Golden MR, Hughes JP, Farquhar C, Stekler JD. HIV Self-Testing Increases HIV Testing Frequency in High-Risk Men Who Have Sex With Men. JAIDS Journal of Acquired Immune Deficiency Syndromes 2018;78(5):505-512. [doi: 10.1097/qai.0000000000001709]
34. Jamil MS, Prestage G, Fairley CK, Grulich AE, Smith KS, Chen M, et al. Effect of availability of HIV self-testing on HIV testing frequency in gay and bisexual men at high risk of infection (FORTH): a waiting-list randomised controlled trial. The Lancet HIV 2017 Jun;4(6):e241-e250. [doi: 10.1016/s2352-3018(17)30023-1]
35. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials 2007 Feb;28(2):182-191. [doi: 10.1016/j.cct.2006.05.007] [Medline: 16829207]
36. Masters SH, Agot K, Obonyo B, Napierala Mavedzenge S, Maman S, Thirumurthy H. Promoting Partner Testing and Couples Testing through Secondary Distribution of HIV Self-Tests: A Randomized Clinical Trial. PLoS Med 2016 Nov 8;13(11):e1002166 [FREE Full text] [doi: 10.1371/journal.pmed.1002166] [Medline: 27824882]
37. Sharma A, Chavez PR, MacGowan RJ, McNaghten A, Mustanski B, Gravens L, et al. Willingness to distribute free rapid home HIV test kits and to test with social or sexual network associates among men who have sex with men in the United States. AIDS Care 2017 Dec 09;29(12):1499-1503. [doi: 10.1080/09540121.2017.1313386] [Medline: 28393612]

Abbreviations

HIVST: HIV self-testing
LMIC: lower- and middle-income countries
MSM: men who have sex with men
QR: quick response (barcode)
RCT: randomized controlled trial
WHO: World Health Organization

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Protocol

Del Nido Cardioplegia Versus Cold Blood Cardioplegia in Adult Cardiac Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Background: The use of cardioplegia solutions as a myocardial protection technique is essential during cardiac surgery with cardiopulmonary bypass. The del Nido cardioplegia solution (DNS) has been widely used as a myocardial preservation technique for pediatric patients undergoing cardiac surgery with cardiopulmonary bypass. Its unique pharmacological features have created growing interest for adult cardiac surgery, especially for elderly patients or those with ventricular dysfunction who are more prone to ischemia-reperfusion injury. Ever since its implementation, several retrospective studies have been published to validate the efficacy, safety, and efficiency of DNS in adult patients undergoing coronary revascularization, valve replacement, or combined procedures. Recently, a meta-analysis based on nine retrospective studies was published claiming the noninferiority of DNS compared to other conventional cardioplegia solutions. Few prospective randomized studies have been conducted whose primary outcome was the assessment of DNS clinical efficacy compared to other solutions commonly used in adult patients.

Objective: The aim of this randomized clinical trial is to assess the benefits of DNS compared to Cardi-Braun blood cardioplegia solution in clinical and biochemical terms regarding myocardial protection during adult cardiac surgery.

Methods: This is the protocol of a controlled, randomized, single-center clinical trial carried out at the Puerta de Hierro Majadahonda University Hospital in Spain. A total of 474 participants over the age of 18 years undergoing elective cardiac surgery with cardiopulmonary bypass will be assigned to groups by simple randomization to receive either DNS or Cardi-Braun blood cardioplegia solution. The primary outcome will be the differences between groups in myocardial protection in biochemical terms (ie, perioperative troponin levels) and clinical terms (ie, presence of the composite variable *acute cardiovascular event*). The clinical trial will be carried out under conditions of respect for the fundamental rights of the person and the ethical principles that affect biomedical research with human beings, as well as in accordance with international recommendations contained in the Declaration of Helsinki and its subsequent revisions.

Results: The inclusion process started in 2018. Data cleaning and analyses are expected to take place in the fall of 2020 and the results are expected in January 2021.

Conclusions: This study is particularly relevant as it will be one of the first to analyze the clinical effects of del Nido cardioplegia on the basis of direct myocardial protection parameters. In light of published studies, carrying out prospective studies based on primary clinical objectives with a larger sample, high-risk patients, and longer cardiopulmonary bypass times continues to be necessary. We believe that our study addresses an important gap in the knowledge of del Nido cardioplegia in adult patient cardiac surgery and will be able to clarify the possible benefits of this method in a large population of patients undergoing these procedures.

Trial Registration: European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) 2017-005144-14; https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-005144-14+; ClinicalTrials.gov NCT04094168; https://clinicaltrials.gov/ct2/show/NCT04094168

International Registered Report Identifier (IRRID): DERR1-10.2196/17826

(JMIR Res Protoc 2020;9(7):e17826) doi:10.2196/17826

KEYWORDS

del Nido cardioplegia; cardiac surgery; myocardial protection

Introduction

Scientific Background and Explanation of Rationale

Myocardial protection during cardiac surgery with cardiopulmonary bypass is essential to avoid detrimental effects of ischemia secondary to aortic cross-clamping. To do so, several strategies have been used throughout the years, such as intermittent aortic occlusion, induced ventricular fibrillation, deep systemic hypothermia, or the administration or cardioplegia solutions.

In 1955, Melrose et al were the first to propose the concept of hyperkalemic cardioplegia, using a high-concentration potassium-citrate solution to afford elective reversible cardiac arrest [1]. Ever since, multiple pharmacological solutions and modes of administration have been studied, without currently having a clear and homogenous model considered a reference standard.

On the other hand, there has been a tangible change in the features of patients undergoing cardiac surgery for the last two decades. Patients are older and, therefore, have increased comorbidity, and they undergo more complex surgical procedures, which entail longer ischemia times. The quest for a cardioplegia solution providing maximal myocardial protection has never been more important.

The del Nido cardioplegia solution (DNS) was first formulated for pediatric cardiac surgery in the early 1990s and has been widely used ever since [2]. It contains the crystalloid Plasmalyte, with an electrolyte composition similar to that of the extracellular space. Its mannitol content reduces myocardial cell inflammation and serves as an ischemia induced-free-radical scavenger. Magnesium sulfate improves ventricular recovery by preventing excessive intracellular calcium to build up by blocking calcium channels. The presence of lidocaine, which blocks sodium channels, prolongs the myocyte refractory period. The formula provides adequate myocardial protection for ischemia periods of up to 90 minutes.

Its pharmacological properties have contributed to its popularity for elderly patients with depleted myocardial reserve undergoing cardiac surgery [3,4]. Experimental studies carried out in aged rabbit hearts showed further accumulation of calcium and, therefore, an undermined ventricular function after prolonged ischemic periods. DNS used with the same experimental population showed decreased intracellular calcium levels and fewer spontaneous ventricular contractions [5].

Several retrospective studies have assessed the safety and efficacy of DNS in adults undergoing coronary revascularization, valve replacement, combined procedures, and cardiac reinterventions [6-8].

In 2017, a meta-analysis comparing the effects of DNS and conventional cardioplegia solutions in adult cardiac surgery was published [9]. It concluded that there were shorter aortic cross-clamp times, reduced cardiopulmonary bypass times, reduced need for mechanical ventilation, and shorter intensive care unit (ICU) lengths of stay for the DNS group. On the other hand, no significant differences were observed as far as the following were concerned: the evolution of cardiac enzymes, postoperative vasoactive needs, the appearance of atrial fibrillation, in-hospital lengths of stay, or mortality. DNS appeared to be noninferior in terms of myocardial protection, morbidity, and mortality. Nevertheless, the results are somewhat restricted due to the lack of randomized prospective studies in the analysis.

Recently, two prospective studies assessing the effects of DNS in adults have been published [10,11], yet their primary outcomes focused on myocardial protection indirectly or on biochemical data (ie, electrical activity, need for ventricular defibrillation after the release of the aortic cross-clamp, and troponin evolution after surgery). Light has yet to be shed on the clinical advantages of DNS in adult patients, including older patients and those with a history of ventricular dysfunction.

Aim of the Study

The aim of this study is to establish the benefits of DNS in clinical and biochemical terms regarding myocardial protection during adult cardiac surgery.

Methods

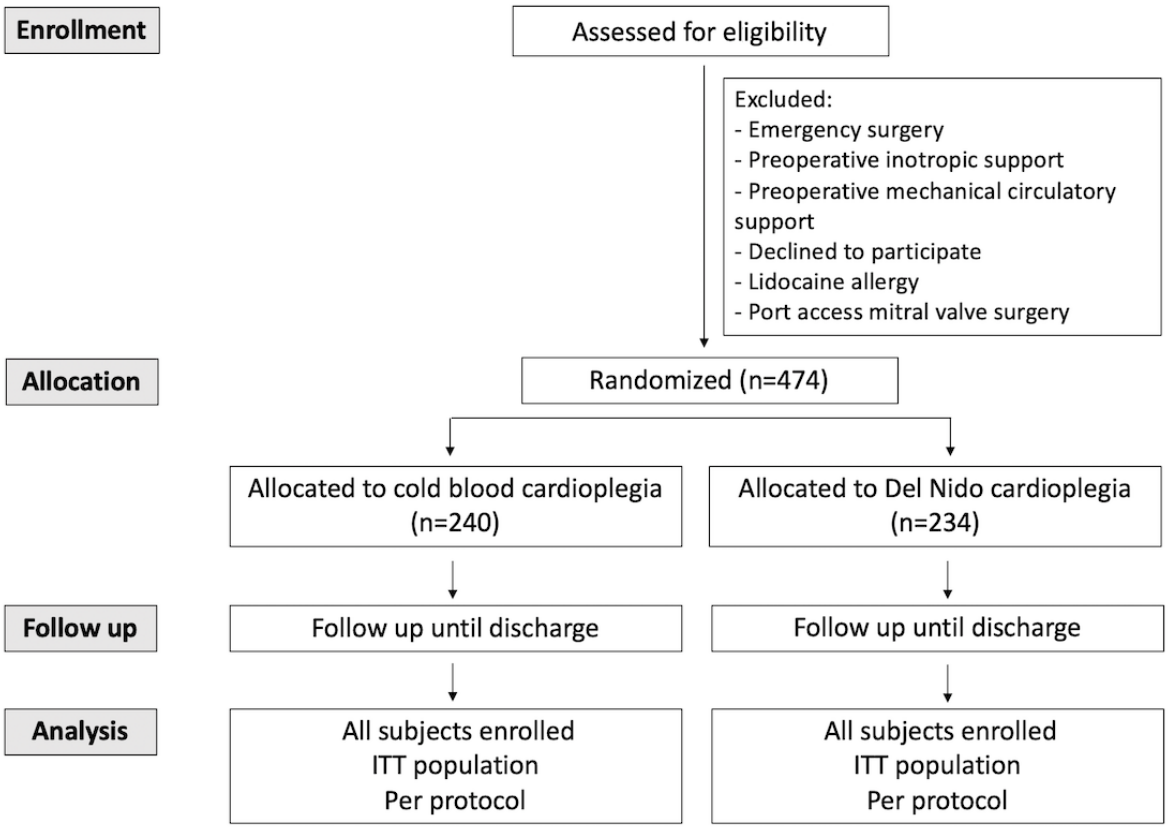
Study Setting

The study was planned according to the updated Consolidated Standards of Reporting Trials (CONSORT) statement, the Declaration of Helsinki, and the Guidelines of Good Clinical Practice issued, as required, by Spanish regulatory authorities. This study will be conducted at one center, the Puerta de Hierro Majadahonda University Hospital.

Trial Design

This study is designed as a single-center, double-blind, controlled clinical trial. Participants will be randomized into a group receiving del Nido cardioplegia (intervention group) or a group receiving Cardi-Braun cold blood cardioplegia (control group; Figure 1). We will conduct a superiority analysis.

Figure 1. CONSORT flow diagram.



Eligibility Criteria for Participants

All patients over the age of 18 years who are scheduled for cardiac surgery may be eligible to participate in the study. The inclusion and exclusion criteria are explained in detail in Textbox 1 below.

Textbox 1. Inclusion and exclusion criteria for study participants.

Inclusion criteria

- Patients over the age of 18 years
- Patients undergoing elective cardiac surgery with cardiopulmonary bypass

Exclusion criteria

- Patients who do not consent to participate in the study
- Patients with a documented allergy to amide-type local anesthetics
- Patients undergoing emergent surgery
- Unstable patients who require pharmacological inotropic support; mechanical circulatory support, such as intra-aortic balloon counterpulsation (IABC) or extracorporeal membrane oxygenation (ECMO); or preoperative intubation
- Patients undergoing mitral valve replacement surgery using the Heartport technique

Study Procedures and Interventions

Within the control group, blood cardioplegia will be administered by means of a cold induction dose at 4-8 °C and a maintenance dose administered every 20 minutes. It will be dispensed via the anterograde or retrograde approach according to the protocol of the center.

Within the intervention group, del Nido cardioplegia will be administered according to the usual practice in a single dose of 1000 cc via the anterograde or retrograde approach according to the protocol of the center. Additional doses (550 mL) will be administered when spontaneous electrical activity appears or, in the case of periods of ischemia, longer than 90 minutes. Common clinical practice will not be modified in the remaining perioperative aspects.

Outcome Measures

The main variables of the study will be the composite clinical variable *acute cardiovascular event* and the biochemical variable *maximum postoperative troponin value*.

The *acute cardiovascular event* variable will consist of one or several of the following events:

1. Early perioperative myocardial infarction: occurring during the first 72 hours after surgery and defined according to the criteria of the Task Force of the European Society of Cardiology, the American Heart Association, and the World Heart Federation.
2. Prolonged low cardiac output: defined as the need to maintain support with two or more inotropic and/or other circulatory mechanical assistance devices—intra-aortic balloon counterpulsation (IABC) or extracorporeal membrane oxygenation (ECMO)—beyond the first 24 postoperative hours.
3. Appearance of ventricular arrhythmias: ventricular tachycardia (VT) and ventricular fibrillation (VF) requiring electrical cardioversion in the first 24 postoperative hours.

To analyze the effect of cardioplegia on myocardial protection at a biochemical level, the level of troponins will be monitored upon arrival at the ICU and during the first 48 hours. Likewise, the maximum troponin peak will be collected during the first 48 postoperative hours.

Other secondary variables of efficacy and safety will be analyzed. Among the intraoperative variables, surgical times (ie, ischemia time and cardiopulmonary bypass times), the volume of cardioplegia solution administered and its route of administration, temperature, average blood pressure, and maximum blood glucose values, as well as the need for electrical cardioversion after aortic cross-clamp release, will be monitored.

Among the postoperative variables, the occurrence of atrial fibrillation will be registered, as well as the requirement for inotropic and mechanical pharmacological support, time to withdrawal, and the occurrence of clinical complications (ie, deterioration of ventricular function upon hospital discharge, surgical reintervention, prolonged mechanical ventilation, acute kidney injury, infectious complications, convulsive activity, or stroke). The need for ICU readmission, ICU and hospital length of stay, and mortality will also be noted.

Subgroup analyses will be carried out in four populations: elderly patients (over 80 years), patients undergoing prolonged cardiopulmonary bypass (longer than 120 minutes), patients with low ventricular ejection fraction (less than 30%), and patients subjected to coronary artery bypass grafting.

Participant Timeline

Follow-up will be carried out from the beginning of the randomization until the participant is discharged. The variables will be collected in the operating room postoperatively; variable collection will occur at a higher frequency within the first 48 hours.

The research team will monitor the possible adverse events, including the time of occurrence, duration, intensity, course, and outcome, in order to make an assessment of the causal relationship between the adverse event and the drug.

Statistical Analyses

Sample Size Calculation

The literature reviewed reflects a need for postoperative inotropic vasoactive support ranging from 35% to 40%. In the sample size calculation, we propose that better myocardial protection will be reflected in a lower need for electrical cardioversion, lower pharmacological inotropic or mechanical support, and a lower incidence of myocardial infarction.

For a hypothetical reduction of inotropic support within the first 24 postoperative hours from 38% to 25%, with an α risk of 5%, at a statistical power of 80% (β=.20), by bilateral test with application of the Fleiss correction factor, and estimating losses of 10%, 474 participants distributed into two groups will be necessary.

Participants will be assigned to groups by simple randomization of the sample, obtaining a computer sequence by Stata 16 (StataCorp). The computer distribution will assign 234 participants to the intervention group (DNS) and 240 participants to the control group (blood cardioplegia). When patients arrive at the theater, perfusionists will enroll participants.

Analyses

A description of the data from each group of the study and the total sample will be carried out. The properties of the original variables will be defined, and the aforementioned composite variables will be created. The main variable—*prolonged low cardiac output syndrome*—will be created from the following original variables: *presence of two or more inotropic agents at 24 hours of admission*, *mechanical support with IABC*, and/or *mechanical support with ECMO or other ventricular assistance*. The main composite variable—*acute cardiovascular event*—will be created from the following variables: *perioperative myocardial infarction*, *prolonged low cardiac output syndrome*, *prolonged vasoplegia*, and/or *VT or VF episodes in the first 24 hours*.

The quantitative variables shall be described through the mean (SD), median (IQR), 95% CI, and minimum and maximum values. Qualitative variables shall be presented as relative and absolute frequencies. To ensure the uniformity of the groups, a detailed analysis will be made by evaluating the association using the Pearson correlation coefficient and the *P* value by means of the Student-Fisher *t* test; correction for unequal variances for the quantitative variables, and the association with the odds ratio and the *P* value, will be obtained with chi-square tests for the categorical variables.

The raw effect of each type of cardioplegia on the acute cardiovascular event will be estimated using a logistic regression model.

Two populations will be defined through intention-to-treat analysis and by biological efficacy. The first population will include all the initially randomized subjects, including all those who leave the study due to noncompliance. The second population will include all those subjects who complete the study within the same group in which they were randomized. An intermediate safety analysis will be performed when approximately 50% of patients have been randomized.

Monitoring and Quality Assurance

The clinical trial is defined as a *low intervention–level trial*, due to the fact that the cardioplegia solutions used are already approved and used in accordance with the terms of the marketing authorization; as well, the solutions are extensively backed up by published scientific evidence on their safety and efficacy (Royal Decree 1090/2015).

The confidentiality of the identity of the volunteers will be respected if the data obtained in this study are published. Subjects' data included in the study will be treated in accordance with Organic Law 15/1999, December 13, on the Protection of Personal Data.

Ethics Approval and Consent to Participate

This study has been registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) (No. 2017-005144-14) and at ClinicalTrials.gov (No. NCT04094168). The study protocol has been approved by the Ethics Committee of Puerta de Hierro Majadahonda University Hospital and was approved by the Spanish Medicines and Health Products Agency (AEMPS).

This clinical trial will be carried out under conditions of respect for the fundamental rights of the person and the ethical principles that affect biomedical research with human beings, as well as in accordance with international recommendations contained in the Declaration of Helsinki and its subsequent revisions. Likewise, national recommendations will be followed in accordance with the guidelines of the AEMPS.

Participants will receive information, both orally and in writing, regarding the manner in which the study will be carried out, the study aims, possible risks that may arise from the study, and the rules that must be observed during the follow-up period. If the patient fulfils the inclusion criteria and agrees to participate in the study, she or he will provide written informed consent; providing consent will not prevent the patient from withdrawing such consent and abandoning the study at any time and for any reason.

Availability of Data and Materials

The datasets used and/or analyzed during the study will be available from the corresponding author upon reasonable request.

Results

The inclusion process started in 2018. Data cleaning and analyses are expected to take place in the fall of 2020 and the results are expected in January 2021.

Discussion

Overview

This study is expected to expand knowledge of DNS in adult cardiac surgery. DNS is assumed to be beneficial in terms of myocardial protection, and it is expected to corroborate a reduction in VF after declamping the aorta and in the number of defibrillations. Also, it is presumed to result in a reduction in postoperative troponin levels and inotropic support for low cardiac output syndrome. Although it is not the main objective of the study, the trial will provide information regarding the benefits of DNS in high-risk subpopulations, such as elderly patients and those with longer periods of cross-clamping or low ventricular ejection fraction.

This study is particularly relevant as it will be the first to analyze the clinical effects of del Nido cardioplegia on the basis of direct myocardial protection parameters. Although the meta-analysis published in 2017 highlighted some clinical benefits in favor of del Nido cardioplegia, there was a fundamental limitation, which is that data collection was based on retrospective studies.

Further published prospective studies also failed to focus their primary objectives on the analysis of the possible clinical effects of del Nido cardioplegia. Ad et al analyzed the postoperative troponin peak and the need for electrical cardioversion after aortic cross-clamp release in a population of 89 patients; in addition to its small sample size, this study excluded high-risk patients over 80 years of age, and the data showed short aortic clamp times [10].

Sanetra et al analyzed troponin peak and electrical activity after aortic cross-clamp release in a population of 150 patients undergoing aortic valve replacement. All clinical outcomes detailed in the study were part of the secondary objectives. Likewise, they excluded from their analysis reoperated patients with ejection fractions under 30% or with coronary artery disease susceptible to percutaneous interventionism or surgery [11].

In light of the above studies, carrying out prospective studies based on primary clinical objectives with a larger sample, high-risk patients, and longer cardiopulmonary bypass times continues to be necessary [12]. We believe that our study addresses an important gap in the knowledge of del Nido cardioplegia in adult patient cardiac surgery and will be able to clarify the possible benefits of this method in a large population of patients undergoing these procedures.

Strengths and Limitations of This Study

This clinical trial has several strengths. The calculated sample size is large and includes elderly patients with a history of ventricular dysfunction. It does not exclude complex procedures that may involve longer cardiopulmonary bypass times.

The trial also has some limitations. Although surgical procedures will be performed by different surgeons, the single-center design may generate external validation problems. The exclusion of emergent interventions and of patients with preoperative vasoactive support also limits extrapolation of results to unstable patients.

In developing the methodology, we have aimed to reduce bias as much as possible. The compilation of other myocardial protection variables has been fundamental in addressing bias.

Acknowledgments

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Authors' Contributions

JGS designed the study. SS and DML performed the literature search. Discrepancies were discussed with JGS, JGF, and AFG. LRG recorded the intraoperative data. JGS and AFG were the major contributors in writing this manuscript. All the authors participated in the design of the study and read, commented upon, and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Melrose DG, Dreyer B, Bentall H, Baker JB. Elective cardiac arrest. Lancet 1955 Jul 02;266(6879):21-22. [doi: 10.1016/s0140-6736(55)93381-x] [Medline: 14382605]
2. Matte GS, del Nido PJ. History and use of del Nido cardioplegia solution at Boston Children's Hospital. J Extra Corpor Technol 2012 Sep;44(3):98-103 [FREE Full text] [Medline: 23198389]
3. O'Blenes SB, Friesen CH, Ali A, Howlett S. Protecting the aged heart during cardiac surgery: The potential benefits of del Nido cardioplegia. J Thorac Cardiovasc Surg 2011 Mar;141(3):762-770 [FREE Full text] [doi: 10.1016/j.jtcvs.2010.06.004] [Medline: 20656301]
4. Vázquez A, Favieres C, Pérez M, Valera F, Torregrosa S, Doñate L, et al. Del Nido cardioplegia: A safe, effective and cheap myocardial protection strategy [Article in Spanish]. Cirugía Cardiovascular 2015 Nov;22(6):287-293 [FREE Full text] [doi: 10.1016/j.circv.2015.05.003]
5. Ataka K, Chen D, Levitsky S, Jimenez E, Feinberg H. Effect of aging on intracellular Ca2+, pHi, and contractility during ischemia and reperfusion. Circulation 1992 Nov;86(5 Suppl):II371-II376. [Medline: 1424026]
6. Guajardo Salinas GE, Nutt R, Rodriguez-Araujo G. Del Nido cardioplegia in low risk adults undergoing first time coronary artery bypass surgery. Perfusion 2017 Jan;32(1):68-73. [doi: 10.1177/0267659116661051] [Medline: 27451052]
7. Yerebakan H, Sorabella RA, Najjar M, Castillero E, Mongero L, Beck J, et al. Del Nido cardioplegia can be safely administered in high-risk coronary artery bypass grafting surgery after acute myocardial infarction: A propensity matched comparison. J Cardiothorac Surg 2014 Oct 30;9:141 [FREE Full text] [doi: 10.1186/s13019-014-0141-5] [Medline: 25359427]
8. Sorabella RA, Akashi H, Yerebakan H, Najjar M, Mannan A, Williams MR, et al. Myocardial protection using del Nido cardioplegia solution in adult reoperative aortic valve surgery. J Card Surg 2014 Jul;29(4):445-449 [FREE Full text] [doi: 10.1111/jocs.12360] [Medline: 24861160]
9. Li Y, Lin H, Zhao Y, Li Z, Liu D, Wu X, et al. Del Nido cardioplegia for myocardial protection in adult cardiac surgery: A systematic review and meta-analysis. ASAIO J 2018;64(3):360-367. [doi: 10.1097/MAT.0000000000000652] [Medline: 28863040]
10. Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM, Fitzgerald D. The use of del Nido cardioplegia in adult cardiac surgery: A prospective randomized trial. J Thorac Cardiovasc Surg 2018 Mar;155(3):1011-1018 [FREE Full text] [doi: 10.1016/j.jtcvs.2017.09.146] [Medline: 29246552]
11. Sanetra K, Gerber W, Shrestha R, Domaradzki W, Krzych Ł, Zembala M, et al. The del Nido versus cold blood cardioplegia in aortic valve replacement: A randomized trial. J Thorac Cardiovasc Surg 2020 Jun;159(6):2275-2283.e1. [doi: 10.1016/j.jtcvs.2019.05.083] [Medline: 31358336]
12. Lazar HL. Del Nido cardioplegia: Passing fad or here to stay? J Thorac Cardiovasc Surg 2018 Mar;155(3):1009-1010 [FREE Full text] [doi: 10.1016/j.jtcvs.2017.09.126] [Medline: 29110949]

Abbreviations

AEMPS: Spanish Medicines and Health Products Agency
CONSORT: Consolidated Standards of Reporting Trials
DNS: del Nido cardioplegia solution
ECMO: extracorporeal membrane oxygenation
EudraCT: European Union Drug Regulating Authorities Clinical Trials Database
IABC: intra-aortic balloon counterpulsation
ICU: intensive care unit

VF: ventricular fibrillation
VT: ventricular tachycardia

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Protocol

Evidence-Based Decision Aid for Patients With Parkinson Disease: Protocol for Interview Study, Online Survey, and Two Randomized Controlled Trials

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Abstract

Background: Shared decision making is particularly important in situations with different treatment alternatives. For the treatment of idiopathic Parkinson disease, both pharmacological and surgical approaches can be applied.

Objective: In this research project, a series of studies will be conducted to investigate how decision aids for patients with idiopathic Parkinson disease should be designed in order to support the decision-making process.

Methods: In Study 1a, qualitative interviews will be conducted to determine which needs frequently occur for patients with idiopathic Parkinson disease. In Study 1b, the identified needs will then be rated for personal relevance by an independent group of patients in an online survey. In Study 2, a randomized controlled trial will be used to pretest different decision aids in a sample group of people who do not have a medical background and who do not have Parkinson disease. In Study 3, a randomized controlled trial will be used to investigate the effect of the decision aids that had been evaluated as positive in Study 2 with patients who have idiopathic Parkinson disease.

Results: This series of studies received ethical approval in January 2020. As of June 2020, data collection for Study 1a has started, and it is estimated that Studies 1a, 1b, 2, and 3 will take approximately 4, 4, 6, and 6 months to complete, respectively. It is planned to present the results and analyses at international conferences and to submit the results to peer-reviewed journals for publication, once the studies have been completed. The findings will also be shared with clinicians and patients through presentations at information events.

Conclusions: This series of studies is intended to result in an evidence-based decision aid for patients with idiopathic Parkinson disease in order to support the informed and reflected shared decision-making process. We further intend to contribute to a deeper understanding of the individual preferences of patients with idiopathic Parkinson disease and the impact of those preferences on treatment decisions.

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KEYWORDS

decision aids; Parkinson disease; interview study; online survey; randomized controlled trial; patients

Introduction

Background

Shared decision making has become increasingly common in the context of medical consultations [1-3]. While in any medical consultation it is useful and ethically necessary to inform and educate a patient thoroughly, participatory decisions are particularly appropriate in situations where different alternatives need to be considered and for which no one treatment is superior to the others. In these situations, a preference-sensitive decision should be made based on the personal circumstances and individual preferences of the patient [4-6]. Research indicates that patient participation in the medical decision-making process has positive effects. A meta-analysis [7] with a total of 105 studies showed that shared decision making led to increased knowledge, higher confidence in decisions, and more active patient participation. Studies [7,8] found that the use of shared decision making could reduce health care system costs, because patients often chose less invasive (and therefore, less expensive) treatment options. In addition, most patients would like to be more involved in the medical decision-making process [9]. But, despite these promising findings, shared decision making has not yet been sufficiently implemented in clinical practice [10,11]. The Revised Program Theory for shared decision making [12] identified relevant factors influencing engagement in shared decision making. The authors of that paper [12] explicitly foster future research using this theory and examining additional key mechanisms of shared decision making. Based on these theoretical considerations, herein we will examine the influence of health care system support through decision aids.

Treatment of Parkinson Disease

For the treatment of idiopathic Parkinson disease, both pharmacological and surgical methods can be used. The 2016 *Leitlinien für Diagnostik und Therapie in der Neurologie–Idiopathisches Parkinsonsyndrom(Guidelines for Diagnosis and Therapy in Neurology–Idiopathic Parkinson Disease)* of the *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)* and the *Deutsche Gesellschaft für Neurologie (German Society of Neurology)* [13] recommended offering subthalamic nucleus–deep brain stimulation to patients with a confirmed diagnosis of idiopathic Parkinson disease who, despite best medical treatments, have motor fluctuations and dyskinesia that cannot be treated with medication, or tremor that cannot be controlled with medication (recommendation 47 in [13]). In addition, deep brain stimulation of the subthalamic nucleus can be offered to patients 60 years of age or younger with confirmed idiopathic Parkinson disease in the first three years after the onset of motor fluctuations or dyskinesia (recommendation 48 in [13]).

Furthermore, it was emphasized that when data suggest deep brain stimulation rather than best medical treatment, surgical treatment should remain an individual decision as long as medical alternatives exist [13]—even if the outcome of drug treatment may be worse than that of subthalamic nucleus–deep brain stimulation in such cases. Nevertheless, since subthalamic nucleus-deep brain stimulation may be more effective than pharmacological treatment, this surgical alternative should be discussed with the patient. When deciding between subthalamic nucleus–deep brain stimulation or drug therapy, patients should be involved in the decision-making process in order to be able to make a preference-sensitive decision with the physician (recommendation 66 in [13]).

Shared Decision Making

Doctors in clinical practice often have too little time for lengthy conversations and tend to overestimate the understanding and health literacy of patients [14,15]. Low health literacy of patients with idiopathic Parkinson disease has been shown to correlate with an increased risk of hospitalization [16]. A meta-analysis showed that the perception of traditional role models, in which doctors are the experts whose instructions are followed, represents a barrier for many patients to actively participating in the decision-making process [17]. One way to deal with this barrier is to use decision aids. They are often used to provide information about illnesses and treatment options and have shown their value in various medical fields [18,19]. Decision guidance is an opportunity to support both patient education and informed decision-making in cooperation with attending physicians and therapists. It is explicitly emphasized that decision aids should not claim to replace patient to doctor direct contact or conversations. Rather, they should be viewed as a supplement that makes it easier to take individual needs into account. The guidelines [13] also recommended that patients with idiopathic Parkinson disease should be provided with individually adapted need-based enhanced communication throughout the course of their disease (recommendation 67 in [13]). According to the Revised Program Theory [12] of shared decision making, giving patients support for shared decision making (for example, by means of a well-designed decision aid) may result in higher confidence in their decision-making abilities and in stronger engagement in shared decision making. Studies [20-22] showed that many patients with Parkinson disease want to play a more active role in treatment decisions [20]. As one study [21] that interviewed patients with Parkinson disease showed, patients often had to take the initiative themselves to be referred to a deep brain stimulation center. Only 10% to 15% of patients for whom deep brain stimulation might be considered a suitable therapy option were, in fact, referred to specialist centers. This finding can be attributed, among other reasons, to insufficient information on the part of patients and neurologists alike [22].

Decision Aids

There are many ways to support patients in their decision-making process and to inform them about the disease and its possible treatment alternatives. Experience reports (ie, narratives) from other patients are an important source of information in addition to exchanges with medical specialists. Patients exchange information about their situation with other people and use the internet in their search for medical information often finding testimonials from other patients [23]. Patient reports are also often integrated into decision-making aids. The use of narratives in decision aids is critically discussed in the literature [24-26]. Narratives have the advantage that they are vivid, easy to understand, and not too abstract, which can

make it easier for patients to process and remember the information conveyed [24,27]; therefore, this format appears to be particularly suitable for patients with idiopathic Parkinson disease, as their cognitive abilities may also be limited. Entwistle et al [28] concluded, in a qualitative interview study, that the personal experiences of others combined with the imparting of factual knowledge can be very helpful for decision making. The patients who were interviewed stated that the reports helped them to better imagine the different options, to become clear about what was important to them personally, and to handle their negative emotions; however, narratives can also have the disadvantage of encouraging the activation of heuristics and generating additional emotions, which can lead to a distorted perception of the information given [25]. In a study [29] with a focus on persuasion, it was found that information mediation with narratives, when compared with scientific information mediation, led to more knowledge gained, more emotions, and stronger persuasion. Narratives also partly influenced the decisions of people who do not have a medical background [30]. In preference-sensitive decision situations, where the needs of the patient should be a key factor in the decision, the persuasive effect of decision support would be considered problematic. The decision-making process of patients should be supported in the preference-sensitive situations that occur in patients with idiopathic Parkinson disease, without convincing them of any one of the possible treatment options. According to the Expected Utility Theory [31,32], it is easier for patients to engage in shared decision making if outcome probabilities of a given treatment are presented. But in preference-sensitive situations, no treatment is superior to the other. As a result, decision difficulty in these situations would be perceived as rather high [12]. The question arises as to whether it makes sense in this situation to report clinical outcomes at all, or whether it is more useful to provide information about possible personal motives and preferences. Decision aids and narratives can be designed very differently and can exert various positive or negative influences on decision making as a result of their design. It is important to understand how decision aids should be designed to help patients take their knowledge, their personal preferences, and their needs into account when making decisions, without pushing them in any specific direction.

Goals of the Research Project

In this research project, a series of studies will be conducted to investigate how decision aids for patients with idiopathic Parkinson disease should be designed in order to support the decision-making process. The goal is to support patients in taking their individual preferences into account when making a decision and to make them feel confident with their decision. We will use a participatory design process for the development of the decision aid [33]. Feedback and ideas for improvement will be requested from health care professionals before the prototype is used in the studies.

It is an open question whether the presentation of possible preferences has a positive influence on the decision-making process. In addition, it has not yet been clarified whether patient narratives can strengthen patient decisions in difficult decision situations. Moreover, we will act on the suggestion of the Revised Program Theory and examine additional key mechanisms of shared decision making. We aim to compare the impact of presenting motives that affect a decision with the impact of presenting treatment outcomes.

In Study 1a, qualitative interviews will be conducted to determine which needs frequently occur for patients with idiopathic Parkinson disease. In Study 1b, the identified needs will then be assessed for personal relevance by other patients in an online survey. In Study 2, a randomized controlled trial will be used to pretest different decision aids with people who do not have a medical background and who do not have Parkinson disease. In Study 3, a randomized controlled trial will be used to investigate the effect of the decision aids that were evaluated as positive in Study 2 in patients with idiopathic Parkinson disease.

Methods

Ethical Approval

These proposed studies have been reviewed and approved by the ethics committee of the Faculty of Medicine of the Eberhard Karls University Tübingen.

Studies 1a and 1b: Expectations and Wishes Regarding Medical Treatment Options for Parkinson

Study Design

A qualitative interview study (Study 1a) with 6 patients with idiopathic Parkinson disease will identify the common needs, expectations, wishes, and preferences that play a role in the decision to opt for drug-only treatment over deep brain stimulation. Patients with idiopathic Parkinson disease who qualify for deep brain stimulation treatment according to recommendations 47 and 48 in [13] will be invited to a screening week as part of regular clinical care.

During this 1-week inpatient stay, the medical, cognitive, and psychological condition of patients will be examined in preparation for potential deep brain stimulation surgery. From a certain date onward, all patients who meet the inclusion criteria (see below) will be asked by the treating physician whether they agree to participate in a qualitative interview. A semistandardized interview lasting approximately 30 minutes will be conducted with those who agree to participate in order to identify the personal needs, hopes, fears, and expectations associated with drug treatment and deep brain stimulation treatment options. In an online survey study (Study 1b), a different group of patients with idiopathic Parkinson disease will rate the needs, hopes, fears, and expectations that were identified in Study 1a according to personal relevance. Patients with idiopathic Parkinson disease who are at different stages of their disease will be recruited for Study 1b. Patient assessment of their stage and burden of the disease will be measured using a validated questionnaire (Parkinson Disease Questionnaire, PDQ-39) [34].

Participants

In order to achieve a representative rating, a total of 60 patients will be recruited for the online survey study (Study 1b). Recruitment will be carried out with the support of the

specialized outpatient units of the University Hospital Tübingen, neurologists in private practice, and self-help groups for patients with idiopathic Parkinson disease. Patients will be included if they have been diagnosed with Parkinson disease, have had Parkinson disease for at least 5 years, are between 18 and 80 years of age; have taken prescribed dopaminergic medication consistently for at least two weeks before inclusion in the study; have a very good knowledge of German, and have signed a written declaration of consent. Patients will be excluded if they have been diagnosed with dementia.

Study 1a: Interview Guide

During the interview, each area will be introduced with an open question (Textbox 1). Further questions will follow only if the answer is unclear or the question has not been answered.

Textbox 1. Open-ended questions and topics for semistructured interview.

Satisfaction with the current situation

- How satisfied are you with the current situation? (scaling question: 0 = very dissatisfied, 100 = very satisfied)
- What should remain the same?
- What should change?

Other: mobility and motor skills, faculty of speech, sleep, memory and concentration ability, previous treatment, general state of health, execution of profession and hobbies, participation in social life

Reasons and expectations

- What are your main reasons for deep brain stimulation?
- What are your main reasons for a purely pharmacological therapy?
- What are other reasons?
- What should change?
- How would you know if the decision was good?
- In which area (eg, work, social life, hobbies) do you hope to have a positive influence?
- What are your plans for the time after the deep brain stimulation/drug changeover?
- What positive expectations/worries do you associate with a deep brain stimulation/drug changeover regarding your social environment, your self-reliance, your well-being?

Study 1b: Questionnaire

The needs, wishes, and worries that are identified in Study 1a will be evaluated in Study 1b. Patients who wish to participate will also have to confirm that they are currently in the process of deciding between further treatment with medication or deep brain stimulation. The questionnaire will initially present questions pertaining to inclusion and exclusion criteria, and if their responses indicate they are eligible, questions about personal needs, wishes, and worries will be provided.

A maximum of 20 statements such as (the following are example items only) “I hope to be able to maintain more personal contacts through a successful treatment”, “It is important to me that the treatment has as few side effects as possible,” and “I hope that the treatment will improve my independence” will be evaluated. In addition, participant knowledge about treatment options will be evaluated with maximum of 20 statements or questions such as (the following are example items only) “The danger that deep brain stimulation can lead to psychological impairment is very high” and “The danger that a purely pharmacological treatment can lead to psychological impairment is very high” where participants will indicate whether the statements are true or false and how confident they are in their answers:. Since patients with idiopathic Parkinson disease may display neuropsychiatric symptoms, such as apathy or emotional instability, the German version of the Apathy Evaluation Scale [35] and a German version of a short-scale for assessing the personality traits in the five-factor model (big five) [36] will be administered.

Study 2: Effects of Decision Aids on the Decision-Making Process (People With Nonmedical Background)

Study Design

Based on the patient preferences identified in Study 1, online decision aids will be designed in close collaboration with health professionals. We will use a participatory design process to increase the later acceptance and use of the decision aids, and thus, facilitate the implementation process in clinical practice. The impact of the decision aids on the decision-making process will be investigated in a randomized controlled trial with a 1×3 between-subject design with the following 3 groups: condition 1, decision aid with factual information (control); condition 2, decision aid with factual information and patient reports on the individual motives underlying the decision-making process; and condition 3, decision aid with factual information and patient reports on the outcomes achieved through the treatment option.

In condition 3, positive and negative outcomes will be presented according to the actual success rate of the treatment options, that is, both successful and less successful treatment outcomes will be shown for both treatment options. The information provided to the participants regarding the success rates of the

treatment options will be based upon existing literature in line with institutional history.

We hypothesize that the conditions containing patient reports on motives or outcomes will have a beneficial effect compared to the condition with only factual information; participants to whom decision aids with patient reports are presented will feel better prepared for decision making (Hypothesis 1) and will evaluate the decision more positively (Hypothesis 2). It is an open research question whether the two conditions with patient reports on individual motives and patient reports on outcomes will also differ with respect to preparation for decision making and decision evaluation.

In addition, this study will be used to evaluate and refine the factual information part of the decision aid. Participant knowledge about treatment options will be evaluated pre and posttest to identify which facts are difficult to understand (and which, perhaps, even result in misunderstandings or irrational fears). This information will influence the design of the factual information and will be re-evaluated in the subsequent study (Study 3).

Participants

Healthy individuals who are neither active in the medical field nor studying a medical subject will be recruited via the Leibniz Institut für Wissensmedien database of test subjects and the University of Tübingen email distribution list, where individuals who are not studying medical-related subjects can be preidentified. Participants at least 18 years old, not affected by Parkinson disease, and with a very good knowledge of German will be eligible for inclusion.

Since only medium to large effect sizes are relevant for our purposes, a sample size of 37 participants per condition will be targeted. The sample size was determined using G*Power [37] and is based on an alpha error probability of .05, a test power of .90, and an expected effect size of f=0.30 for an analysis of variance with repeated measurements and between-subject factors.

Procedure

After basic demographic data (age, gender, education) and individual prior experiences with Parkinson disease have been collected, the study participants will be asked to put themselves in the position of a patient with idiopathic Parkinson disease with the help of a case description. The following dependent variables will be measured as target variables before and after the use of the decision support: decisional conflict [38]; hypothetical decision (which treatment option would be preferred); attitude toward both treatment options (modified according to [39]); and knowledge about risks and side effects of treatment options, mode of action of treatment options, and possible advantages and disadvantages of treatment options.

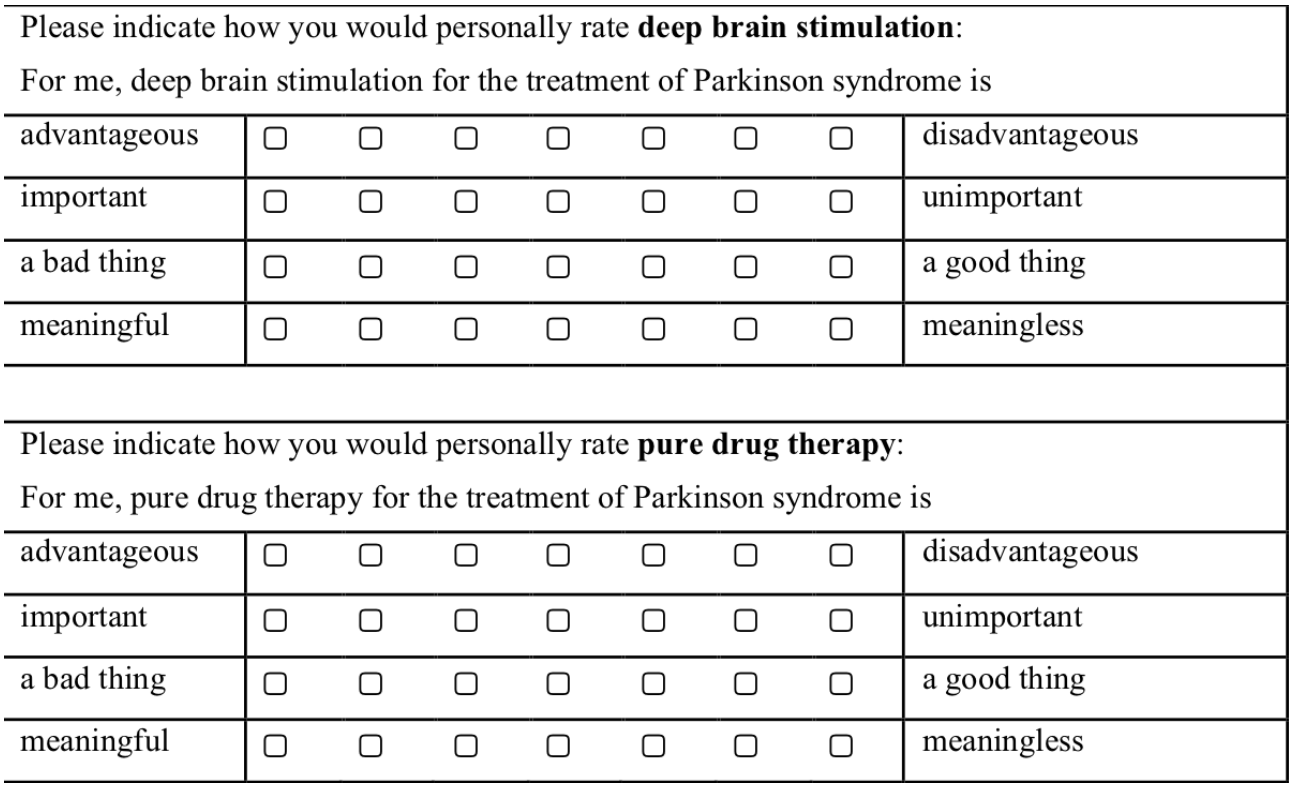
Subsequently, participants will be randomly assigned (computer-generated assignments) to the 3 conditions. Based on the results of Study 1a and Study 1b, a text- and video-based decision aid will be designed with a maximum reception time of 15 minutes.

In addition, the following are to be completed after the decision aid has been used: preparation for decision making (based on [40]); evaluation of the preferences or motives identified in Study 1 with regard to the importance for the decision made, decision evaluation scale [41]; reflection on one's own reasons for the decision; suggestions for improvement (open answer format), and the knowledge test.

Measures

A pre-existing decisional conflict questionnaire will be used [38]. Participants will be asked, "How sure are you about your decision for surgical or non-surgical treatment?" and will reply to three statements using a 7-point Likert scale for each: "It's hard for me to make that decision"; "I'm not sure how to act on this decision"; "It's clear which choice is best for me." They will also be asked "How do you feel about this decision?" and reply to 4 statements using a 7-point Likert scale: "I feel like I made an informed decision"; "My decision shows what is most important to me"; "I expect to stick to my decision"; "I'm satisfied with my decision." Attitude toward both treatment options will be measured with a 4-item scale (modified following [39]; Figure 1). The knowledge test will be based on the results of Study 1b. The aim will be to provide information on any existing misconceptions or false information regarding the treatment options for Parkinson disease and to test the efficacy of the information provided (a maximum of 10 items). The postintervention preparation for decision making scale is based on [40] (Figure 2). The numerical scale has treatment options ranging from deep brain stimulation on one end of the scale to pure drug therapy on the other end. A decisional conflict questionnaire [38], ratings of feelings about the decision, ratings of attitude toward both treatment options [39], and the decision evaluation scale [41] (Figure 3) will be used.

Figure 1. Attitude toward treatment options.



Please indicate how you would personally rate **deep brain stimulation**: For me, deep brain stimulation for the treatment of Parkinson syndrome is								
advantageous	☐	☐	☐	☐	☐	☐	☐	disadvantageous
important	☐	☐	☐	☐	☐	☐	☐	unimportant
a bad thing	☐	☐	☐	☐	☐	☐	☐	a good thing
meaningful	☐	☐	☐	☐	☐	☐	☐	meaningless

Please indicate how you would personally rate **pure drug therapy**: For me, pure drug therapy for the treatment of Parkinson syndrome is								
advantageous	☐	☐	☐	☐	☐	☐	☐	disadvantageous
important	☐	☐	☐	☐	☐	☐	☐	unimportant
a bad thing	☐	☐	☐	☐	☐	☐	☐	a good thing
meaningful	☐	☐	☐	☐	☐	☐	☐	meaningless

Figure 2. Preparation for decision making scale.

Please indicate how helpful this information material was to you. Did this information material...							
	Not at all						Very much
Help you realize that a decision has to be made?	☐	☐	☐	☐	☐	☐	☐
Prepare you to make a better decision?	☐	☐	☐	☐	☐	☐	☐
Help you think about the pros and cons of each treatment option?	☐	☐	☐	☐	☐	☐	☐
Help you think about which advantages and disadvantages are most important?	☐	☐	☐	☐	☐	☐	☐
Make it clear to you that your decision depends on what means the most to you?	☐	☐	☐	☐	☐	☐	☐
Help you organize your thoughts about the decision?	☐	☐	☐	☐	☐	☐	☐
Help you think about how much you want to be involved in this decision?	☐	☐	☐	☐	☐	☐	☐
Help you come up with questions you want to ask the doctor?	☐	☐	☐	☐	☐	☐	☐
Prepare you to talk to your doctor about what is most important to you?	☐	☐	☐	☐	☐	☐	☐
Prepare you for your next appointment with your doctor?	☐	☐	☐	☐	☐	☐	☐

Figure 3. Decision evaluation scale.

Please think now about your decision and the decision-making process and choose how strongly you agree with the following statements.							
	I don't agree at all						I fully agree
I expect to stick to my decision.	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my decision.	☐	☐	☐	☐	☐	☐	☐
I still have doubts about my choice.	☐	☐	☐	☐	☐	☐	☐
This is my own decision.	☐	☐	☐	☐	☐	☐	☐
I find it difficult to make that decision.	☐	☐	☐	☐	☐	☐	☐
I am satisfied with the information I have received.	☐	☐	☐	☐	☐	☐	☐
I know the advantages and disadvantages of the treatment methods.	☐	☐	☐	☐	☐	☐	☐
I need more information for this decision.	☐	☐	☐	☐	☐	☐	☐
I want clearer advice.	☐	☐	☐	☐	☐	☐	☐
I have made a well-informed decision.	☐	☐	☐	☐	☐	☐	☐
This decision will be made without me.	☐	☐	☐	☐	☐	☐	☐
I feel pressure from others in this decision.	☐	☐	☐	☐	☐	☐	☐
I wish someone else would decide for me.	☐	☐	☐	☐	☐	☐	☐
My decision frightens me.	☐	☐	☐	☐	☐	☐	☐
I regret my decision.	☐	☐	☐	☐	☐	☐	☐

A maximum of 16 items will be used to evaluate the preferences and motives that were identified in Study 1 with regard to the importance for the decision made such as (the following items are example items only since the items are not yet known): “Please rate the extent to which you agree with the following statements. There is no right or wrong answer. We are only interested in your personal opinion and assessment.”; “The very small, but existing danger of an irreversible side effect (eg, by a brain hemorrhage) with the deep brain stimulation, influenced my decision strongly.”; “The hope for improvement of my independence in everyday life, through deep brain stimulation, has strongly influenced my decision.”; “The concern about psychological impairment (eg, psychosis, states of confusion) in a pure drug treatment had a strong influence on my decision.”

Analysis

Data analysis will be performed using SPSS statistical software (version 25; IBM Corp) . We will perform an analysis of variance with posthoc tests (for interval-scaled data) and Mann-Whitney tests (for ordinal-scaled data). We will report all data as means and standard deviations (for interval-scaled data) and the median (for ordinal-scaled data). The level of significance will be set at $P<.05$. Cohen d and r will be calculated as effect sizes.

Study 3: Effects of Decision Aids on the Decision-Making Process (Patients With Parkinson Syndrome)

Study Design

Based on the decision aids examined in Study 2, the most suitable format for a preference-sensitive decision will be selected and its efficacy will be compared with that of the use of pure factual information. If the need for further modifications of the decision aids becomes apparent in Study 2, we will implement the modifications in collaboration with health professionals. All of the participating patients will be given the opportunity to use the information material of the other condition immediately after the data collection. This ensures that none of

the study participants will have any disadvantages, despite the randomized between-subject design.

Participants

Recruitment will be carried out with the support of the special outpatient units of the University Hospital Tübingen, neurologists in private practices, and Parkinson self-help groups. The same inclusion and exclusion criteria used in Studies 1a and 1b will be used for Study 3. Since, in this case, only medium to large effect strengths (d=.70) have clinical relevance, a sample size of 36 participants per condition will be targeted.

Procedure

Basic demographic data (age, sex, education) and the individual perception of the limitations caused by the disease will be collected with the PDQ-39 [34]. Participants will be asked to complete the following questionnaires before and after the use of the decision support: decisional conflict [38]; hypothetical decision ("which treatment option would you probably choose in this situation?"); attitude toward both treatment options (modified following [39]); study-designed knowledge test on risks and side effects of treatment options, mode of action of treatment options, possible advantages and disadvantages of treatment options questionnaires will be used. In addition, the following will be completed after the decision aid has been used: preparation for decision making (based on [40]); evaluation of the preferences and motives identified in Study 1 with regard to the importance for the decision made; decision evaluation scale (based on [41]; reflection on one's own reasons for the decision; suggestions for improvement (open answer format).

Measures

Personal assessment of the current stage and burden of the disease will be measured using the validated questionnaire PDQ-39 [28]. Moreover, the German version of the Apathy Evaluation Scale [35] and the German version of the short-scale for assessing the personality traits in the five-factor model (big five) [36] will be used. In addition, all of the scales in Study 2 will be used. Differences will be only in the introduction to the topic (in Study 3 the participants are patients who are actually affected) and the study design. At the end of the study, the participants will also be given the opportunity to use the information material of the other condition.

Analysis

Data analysis will be performed using SPSS statistical software (version 25.0; IBM Corp). We will perform t tests (for interval-scaled data) and Mann-Whitney tests (for ordinal-scaled data). We will report all data as means and standard deviations (for interval-scaled data) and as the median (for ordinal-scaled data). The level of significance will be set at P<.05. Cohen d and r will be calculated as effect sizes.

Data Protection

Personal data will be collected and processed in these studies. For the patients diagnosed with idiopathic Parkinson disease (Studies 1 and 3) the data include their name, sex, age, duration of the disease, other diagnoses, and personal experiences with the disease. In the case of patients, disease data from medical documents (regarding diagnoses and duration of disease) will also be included in the evaluation if necessary. For the medical laypeople (Study 2) the data will include sex, age, and personal experiences with Parkinson disease.

Data will be pseudonymized in a protected electronic database accessible only to authorized staff members, who are bound by professional and data secrecy obligations. In order to verify the correct transfer of the treatment data from the medical file to the encrypted study database, authorized people may inspect the personal disease data related to the study. All employees are bound to secrecy.

The research results from the studies will be published in anonymized form in scientific journals or databases. For the collection, storage, and use of the data, the consent of the participants is required and will be obtained by having them sign the declaration of consent to data protection.

Results

This study received ethical approval in January 2020. As of June 2020, data collection for Study 1a has begun, and it is estimated that Studies 1a, 1b, 2, and 3 will take approximately 4, 4, 6, and 6 months to complete, respectively. It is planned to present the study results and analyses at international conferences and to submit them to peer-reviewed journals. The study results will additionally be shared with clinicians and patients by presenting them at information events.

Discussion

This series of studies is intended to shed light on how an evidence-based decision aid for patients with idiopathic Parkinson disease should be designed, in order to facilitate an informed and reflected shared decision-making process. Moreover, the series of studies seeks to contribute to a deeper understanding of individual preferences of patients with idiopathic Parkinson disease and the impact of those preferences on treatment decisions. It is idiosyncratic that the decision-process for patients with idiopathic Parkinson disease may take a relatively long period of time (possibly several years). Idiopathic Parkinson disease is a slowly progressing neurodegenerative disease that makes it possible to protract any final decision through a series of continuous re-evaluations of the patients' current status and reassessments of their quality of life. During this prolonged decision period, evidence and preferences may develop gradually.

The outcomes from this series of studies will provide valuable new insights into the potential of decision aids for supporting a reflective and informed decision about idiopathic Parkinson disease treatment, and the studies will also help to discover barriers to making an informed decision. The findings would be directly applicable to clinical situations such as (1) results about what kind of information is especially misleading can help physicians and therapists to focus on these aspects in their consultations; (2) knowledge about common patient needs, wishes, and fears can help to tailor the given information to individuals, and (3) if the decision aids have been shown to support shared decision making, physicians can use the tools

as additional support for patients. In this case, the information could potentially be provided before medical consultation as preparation. Physicians could then use the consultation time to respond specifically to patient questions and concerns. It is open for discussion whether the findings of this series of studies could be generalized to other fields and contribute to theory with regard to decision situations where empirical evidence (eg, potential superiority of an invasive therapy) and personal preferences (eg, avoidance of surgical intervention) contradict each other.

The strengths of this series of studies are the combination of research methods (qualitative and quantitative methods), the combination of study settings (field and laboratory studies), the adherence to the Revised Program Theory of shared decision making, and the combination of study populations (patients and healthy participants). These strengths will help to produce a broad and more complete view of decision aids for patients with idiopathic Parkinson disease as well as a deeper insight into principal underlying processes of decision-making.

There are limitations to our studies. One issue is that the significance of any potential findings is restricted to patients who suffer from idiopathic Parkinson disease and have not been diagnosed with dementia. Since the decision aids will target this population, the findings will not be generalizable for patients with other diagnoses. Our studies will aim to explore the presentation of motives and outcomes regarding shared decision making for patients with idiopathic Parkinson disease, so we will not be able to make recommendations on how to design and implement other decision support systems in different contexts. Nevertheless, the fine-grained participatory procedure applied here for the design and evaluation of decision aids can also be used for designing decision aids in other contexts or systems. An indepth analysis of patient state of knowledge, needs, wishes, and fears before designing a support system would streamline the design process.

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Conflicts of Interest

For authors MB, JK, ME, IC, none declared. AG was supported by research grants from Medtronic, Abbott, Boston Scientific, the German Federal Ministry of Education and Research, and the Baden-Württemberg Foundation. DW was supported by research grants from Medtronic, Abbott, Boston Scientific, German Research Council, and travel grants and speakers' honoraria from Medtronic, Abbott, Boston Scientific, Abbvie, STADA, Bial. The funding had no involvement in study design, the writing of the report, and in the decision to submit the article for publication.

References

1. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med 1997 Mar;44(5):681-692. [Medline: 9032835]
2. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012 Oct;27(10):1361-1367 [FREE Full text] [doi: 10.1007/s11606-012-2077-6] [Medline: 22618581]
3. Eggeling M, Bientzle M, Cress U, Shiozawa T, Kimmerle J. The impact of physicians' recommendations on treatment preference and attitudes: a randomized controlled experiment on shared decision-making. Psychol Health Med 2020 Mar;25(3):259-269. [doi: 10.1080/13548506.2019.1687917] [Medline: 31707838]
4. Keirns CC, Goold SD. Patient-centered care and preference-sensitive decision making. JAMA 2009 Oct 28;302(16):1805-1806. [doi: 10.1001/jama.2009.1550] [Medline: 19861674]
5. Elwyn G, Frosch D, Rollnick S. Dual equipoise shared decision making: definitions for decision and behaviour support interventions. Implement Sci 2009 Nov 18;4:75 [FREE Full text] [doi: 10.1186/1748-5908-4-75] [Medline: 19922647]
6. Veroff D, Marr A, Wennberg DE. Enhanced support for shared decision making reduced costs of care for patients with preference-sensitive conditions. Health Affairs 2013 Feb;32(2):285-293. [doi: 10.1377/hlthaff.2011.0941]
7. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2017 Dec 12;4:CD001431. [doi: 10.1002/14651858.CD001431.pub5] [Medline: 28402085]
8. Oshima LE, Emanuel EJ. Shared decision making to improve care and reduce costs. N Engl J Med 2013 Jan 03;368(1):6-8. [doi: 10.1056/NEJMp1209500] [Medline: 23281971]
9. Chewning B, Bylund CL, Shah B, Arora NK, Gueguen JA, Makoul G. Patient preferences for shared decisions: a systematic review. Patient Educ Couns 2012 Jan;86(1):9-18 [FREE Full text] [doi: 10.1016/j.pec.2011.02.004] [Medline: 21474265]
10. Kayyali R, Gebara SN, Hesso I, Funnell G, Naik M, Mason T, et al. Shared decision making and experiences of patients with long-term conditions: has anything changed? BMC Health Serv Res 2018 Oct 10;18(1):763 [FREE Full text] [doi: 10.1186/s12913-018-3575-y] [Medline: 30305085]

11. Ford S, Schofield T, Hope T. Are patients' decision-making preferences being met? Health Expect 2003 Mar;6(1):72-80 [FREE Full text] [doi: 10.1046/j.1369-6513.2003.00211.x] [Medline: 12603630]
12. Waldron T, Carr T, McMullen L, Westhorp G, Duncan V, Neufeld S, et al. Development of a program theory for shared decision-making: a realist synthesis. BMC Health Serv Res 2020 Jan 23;20(1):59 [FREE Full text] [doi: 10.1186/s12913-019-4649-1] [Medline: 31973754]
13. Arbeitsgemeinschaft D. Leitlinien für Diagnostik und Therapie in der Neurologie - Idiopathisches Parkinsonsyndrom. Available. URL: https://www.awmf.org/uploads/tx_szleitlinien/030-010l_S3_Parkinson_Syndrome_Idiopathisch_2016-06.pdf [accessed 2020-06-15]
14. Weinman J, Yusuf G, Berks R, Rayner S, Petrie KJ. How accurate is patients' anatomical knowledge: a cross-sectional, questionnaire study of six patient groups and a general public sample. BMC Fam Pract 2009 Jun 12;10:43 [FREE Full text] [doi: 10.1186/1471-2296-10-43] [Medline: 19523189]
15. Cosic F, Kimmel L, Edwards E. Patient comprehension of common orthopedic terminology. Health Lit Res Pract 2019 Jul;3(3):e187-e193 [FREE Full text] [doi: 10.3928/24748307-20190624-04] [Medline: 31428736]
16. Fleisher JE, Shah K, Fitts W, Dahodwala NA. Associations and implications of low health literacy in Parkinson's Disease. Mov Disord Clin Pract 2016;3(3):250-256 [FREE Full text] [doi: 10.1002/mdc3.12272] [Medline: 27331078]
17. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014 Mar;94(3):291-309. [doi: 10.1016/j.pec.2013.10.031] [Medline: 24305642]
18. Scalia P, Durand MA, Berkowitz JL, Ramesh NP, Faber MJ, Kremer JAM, et al. The impact and utility of encounter patient decision aids: systematic review, meta-analysis and narrative synthesis. Patient Educ Couns 2019 May;102(5):817-841. [doi: 10.1016/j.pec.2018.12.020] [Medline: 30612829]
19. Eggeling M, Bientzle M, Shiozawa T, Cress U, Kimmerle J. The impact of visualization format and navigational options on laypeople's perception and preference of surgery information videos: randomized controlled trial and online survey. J Participat Med 2018 Nov 22;10(4):e12338. [doi: 10.2196/12338]
20. Weernink MGM, van Til JA, van Vugt JPP, Movig KLL, Groothuis-Oudshoorn CGM, IJzerman MJ. Involving patients in weighting benefits and harms of treatment in Parkinson's disease. PLoS One 2016;11(8):e0160771 [FREE Full text] [doi: 10.1371/journal.pone.0160771] [Medline: 27575744]
21. Hamberg K, Hariz G. The decision-making process leading to deep brain stimulation in men and women with parkinson's disease - an interview study. BMC Neurol 2014 Apr 25;14:89 [FREE Full text] [doi: 10.1186/1471-2377-14-89] [Medline: 24761767]
22. Lange M, Mauerer J, Schlaier J, Janzen A, Zeman F, Bogdahn U, et al. Underutilization of deep brain stimulation for Parkinson's disease? a survey on possible clinical reasons. Acta Neurochir (Wien) 2017 May;159(5):771-778. [doi: 10.1007/s00701-017-3122-3] [Medline: 28258308]
23. Kimmerle J, Bientzle M, Cress U. Personal experiences and emotionality in health-related knowledge exchange in internet forums: a randomized controlled field experiment comparing responses to facts vs personal experiences. J Med Internet Res 2014 Dec 04;16(12):e277 [FREE Full text] [doi: 10.2196/jmir.3766] [Medline: 25486677]
24. Bekker HL, Winterbottom AE, Butow P, Dillard AJ, Feldman-Stewart D, Fowler FJ, et al. Do personal stories make patient decision aids more effective? a critical review of theory and evidence. BMC Med Inform Decis Mak 2013;13 Suppl 2:S9 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S9] [Medline: 24625283]
25. Winterbottom A, Bekker HL, Conner M, Mooney A. Does narrative information bias individual's decision making? a systematic review. Soc Sci Med 2008 Dec;67(12):2079-2088. [doi: 10.1016/j.socscimed.2008.09.037] [Medline: 18951673]
26. Osaka W, Nakayama K. Effect of a decision aid with patient narratives in reducing decisional conflict in choice for surgery among early-stage breast cancer patients: a three-arm randomized controlled trial. Patient Educ Couns 2017 Mar;100(3):550-562. [doi: 10.1016/j.pec.2016.09.011] [Medline: 28277290]
27. Mazor KM, Baril J, Dugan E, Spencer F, Burgwinkle P, Gurwitz JH. Patient education about anticoagulant medication: is narrative evidence or statistical evidence more effective? Patient Educ Couns 2007 Dec;69(1-3):145-157. [doi: 10.1016/j.pec.2007.08.010] [Medline: 17942268]
28. Entwistle VA, France EF, Wyke S, Jepson R, Hunt K, Ziebland S, et al. How information about other people's personal experiences can help with healthcare decision-making: a qualitative study. Patient Educ Couns 2011 Dec;85(3):e291-e298. [doi: 10.1016/j.pec.2011.05.014] [Medline: 21652162]
29. Betsch C, Ulshöfer C, Renkewitz F, Betsch T. The influence of narrative v. statistical information on perceiving vaccination risks. Med Decis Making 2011;31(5):742-753. [doi: 10.1177/0272989X11400419] [Medline: 21447730]
30. Winterbottom AE, Bekker HL, Conner M, Mooney AF. Patient stories about their dialysis experience biases others' choices regardless of doctor's advice: an experimental study. Nephrol Dial Transplant 2012 Jan;27(1):325-331. [doi: 10.1093/ndt/gfr266] [Medline: 21642512]
31. Tversky A. A critique of expected utility theory: descriptive and normative considerations. Erkenntnis 1975 Jun;9(2):163-173. [doi: 10.1007/bf00226380]
32. Briggs R. Normative theories of rational choiceexpected utility. The Stanford Encyclopedia of Philosophy (edition Fall 2019;Edward N. Zalta (ed.). Available:E [FREE Full text]

33. Al-Itejawi HHM, van UCF, Vis AN, Nieuwenhuijzen JA, Hofstee MJA, van MRJA, et al. Development of a patient decision aid for the treatment of localised prostate cancer: a participatory design approach. J Clin Nurs 2016 Apr;25(7-8):1131-1144. [doi: 10.1111/jocn.13120] [Medline: 26880526]
34. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997 Sep;26(5):353-357. [Medline: 9351479]
35. Lueken U, Seidl U, Schwarz M, Völker L, Naumann D, Mattes K, et al. [Psychometric properties of a German version of the Apathy Evaluation Scale]. Fortschr Neurol Psychiatr 2006 Dec;74(12):714-722. [doi: 10.1055/s-2006-932164] [Medline: 17167730]
36. Rammstedt B, Kemper C, Klein M, Beierlein C, Kovaleva A. A short scale for assessing the big five dimensions of personalityitem Big Five Inventory (BFI-10). MDA 2013;7(2):10. [doi: 10.12758/mda.2013.013]
37. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007 May;39(2):175-191. [Medline: 17695343]
38. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making 1995;15(1):25-30. [Medline: 7898294]
39. Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect 2001 Jun;4(2):99-108. [Medline: 11359540]
40. Bennett C, Graham ID, Kristjansson E, Kearing SA, Clay KF, O'Connor AM. Validation of a preparation for decision making scale. Patient Educ Couns 2010 Jan;78(1):130-133. [doi: 10.1016/j.pec.2009.05.012] [Medline: 19560303]
41. Stalmeier PFM, Roosmalen MS, Verhoef LCG, Hoekstra-Weebers JEHM, Oosterwijk JC, Moog U, et al. The decision evaluation scales. Patient Educ Couns 2005 Jun;57(3):286-293. [doi: 10.1016/j.pec.2004.07.010] [Medline: 15893210]

Abbreviations

PDQ: Parkinson Disease Questionnaire

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Protocol

Self-Myofascial Release Intervention and Mobile App in Patients With Hemophilic Ankle Arthropathy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Hemophilic ankle arthropathy is manifested by degenerative functional alterations and chronic pain. Myofascial release techniques are used to treat soft tissue adhesions, relieve pain, and reduce tissue sensitivity.

Objective: This study aims to evaluate the safety and efficacy of a protocol using self-myofascial release with a foam roller to be applied in patients with hemophilic ankle arthropathy.

Methods: Patients with ankle arthropathy (N=70) will be recruited, enrolled, and assigned to one of two groups—experimental or control—in a 1:1 allocation ratio. Patients will be recruited from 5 centers in different regions of Spain. Patient data will be collected at baseline, posttreatment, and follow-up. The primary outcome will be frequency of ankle joint bleeding (self-reported). The secondary outcomes will be ankle range of motion (measured with a digital goniometer); joint pain (measured with a visual analog scale and an algometer); joint status (measured using the Hemophilia Joint Health Score); muscle strength (measured with a dynamometer); functionality of lower limbs (measured using the 6-minute walking test); activity (self-reported); and muscle flexibility (measured using the fingertip-to-floor test). The treatment program includes 11 exercises that must be administered bilaterally. A mobile app will be developed where each patient will be able to observe the exercises to be carried out. Each session will last 15 minutes with 5 physiotherapy sessions per week for a period of 3 months. It is expected that patients with hemophilia who receive the foam roller intervention will show improvement in mobility, pain, and status of the ankle joint; muscle strength; and function in the lower extremities.

Results: The study has been approved by the institutional review board of the University of Murcia. Patient recruitment will begin in September 2020, and the intervention period will last until June 2021. Data collection will take place between September 2020 and October 2021.

Conclusions: This protocol describes a randomized clinical trial to examine the safety and efficacy of a self-myofascial release intervention using a foam roller in patients with hemophilic ankle arthropathy.

Trial Registration: ClinicalTrials.gov NCT03914287; http://clinicaltrials.gov/ct2/show/NCT03914287.
International Registered Report Identifier (IRRID): PRR1-10.2196/15612

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KEYWORDS

Hemophilic arthropathy; ankle; self-myofascial release; joint pain; functionality; randomized clinical trial

Introduction

Hemophilia is a congenital coagulopathy characterized by a deficiency of a clotting factor (factor VIII in hemophilia A and factor IX in hemophilia B). Most clinical manifestations are musculoskeletal such as bruising and hemarthrosis. The recurrence of joint bleeding causes degenerative, progressive, and chronic joint deterioration (hemophiliac arthropathy); chronic pain; and a deteriorated perception of the patient's quality of life. Symptoms of hemophilic arthropathy include limited range of motion, decreased periarticular muscle strength, decreased proprioception, and chronic pain [1,2].

The ankle joint, a crucial component of locomotion, is one of the most affected joints (as are the knee and elbow joints) [3], imposing important functional and proprioceptive limitations. These limitations are the result of developing intra-articular alterations such as joint space narrowing, the development of osteophytes, bone deformities, or axial alterations [4]. Prophylactic treatment has been shown to be highly effective in the prevention of hemophilic arthropathy [5]; however, many patients, nevertheless, develop these sequelae as a result of late initiation of treatment, poor adherence to prophylaxis, or the development of inhibitors (antibodies to factor VIII or factor IX concentrates).

The treatment of hemophilic ankle arthropathy includes pharmacologic and orthopedic interventions with the aim of improving symptoms in the patient. The administration of anti-inflammatory and analgesic drugs [6], conducting synoviorthesis to remove the synovial membrane, and ultimately, arthrodesis of the ankle joint are the most common treatments [7].

Physiotherapy can play an extremely important role in the treatment of hemophilic ankle arthropathy. Manual therapy techniques [8], therapeutic exercise [9], or electrotherapy [10] have provided positive results in the control of chronic pain in patients with hemophilic ankle arthropathy.

The degenerative process, itself, is one of the intrinsic mechanisms affecting the fascial system, since it favors loss of elasticity and flexibility, and triggers a process of pathological cross-linking of collagen fibers. Fascial therapy aims to remove fascial tissue restriction through mechanical stimuli applied for 3 to 5 minutes in order to promote the piezoelectric effect in the crystalline matrix of the fascia [11]. The mechanical stimulus to the fascia (in the form of either pressure or tangential compression) triggers a secondary conjunctive cellular response and promotes cellular communication through piezoelectric and mechanotransduction mechanisms [12]. Although pilot and cohort studies [13,14] have proven that this technique is safe in patients with hemophilic arthropathy of the ankle, clinical studies need to be conducted with a large sample size in order to confirm that this technique is indeed suitable.

Fascia is the soft tissue component of the connective tissue matrix that extends through the human body forming a continuous three-dimensional composite of structural support throughout the body [15]. Myofascial release is a physiotherapy technique in which sustained pressure is applied in order to reduce restrictions of the fascia. Mechanical stimulation favors the readjustment of collagen fibers and improves the quality of movement, fluid circulation, and lymphatic drainage [16]. These changes can help break apart adhesions caused by processes such as scarring and fibrosis in the body. Myofascial induction is a manual physiotherapy technique that applies the principles of biomechanical loading of soft tissue and modification of neural reflexes through stimulation of the mechanoreceptors in the fascia to release fascial restrictions and restore healthy tissue [17].

Self-myofascial release with a foam roller is used to treat fascial adhesions and to restore the normal extensibility of soft tissues [18]. Self-myofascial release has similar effects to those provided by manual fascial release techniques. These benefits include easing muscle tension and stiffness, reducing pain, reducing inflammation, alleviating muscle spasms, and increasing joint mobility. Myofascial release techniques have been used to treat adhesions of the soft tissue, to relieve pain and tissue sensitivity, and to reduce edema and inflammation, while improving muscle recovery [19]. In self-myofascial release, patients use their own body weight and materials such as a foam roller to exert pressure on the affected soft tissues [20,21]. Scientific evidence has shown that these types of tools help improve the range of motion as well as pre and postexercise muscle performance [21,22]. The efficacy of these types of exercises to improve joint mobility has been tested in relation to improving mobility in knee flexion [20] and relative to improving ankle joint mobility [23].

The use of foam rollers for myofascial release is based on findings of postintervention changes to joint range of motion and pressure pain thresholds which may be due to a mechanical and neurophysiological responses [24,25]. The direct pressure of the roller may produce local mechanical and global neurophysiological effects that relax the tissues and attenuate pain in the targeted and surrounding area [26]. Local pressure from the roller may affect the viscoelastic properties of the myofascia which may be responsible for such changes within the tissue. Other mechanisms that may be involved include thixotropy (reduced viscosity when stress is applied), reduced myofascial restriction (from the breaking apart of physical adhesions), fluid-related changes (forced fluid displacement within the tissue), and cellular responses (elicited through

mechanotransduction from the applied stress within the tissues) [24]. Researchers have also found that foam-rolling reduces arterial stiffness, increases arterial tissue perfusion, and improves vascular endothelial functions related to tissue relaxation [27].

The objective of this paper is to describe our approach to the design and implementation of a protocol for self-myofascial release using a foam roller for patients with hemophilic ankle arthropathy with the aim of reducing the frequency of joint bleeding; improving range of motion; reducing joint pain; and restoring functionality, structural integrity, muscle flexibility, and muscle strength.

Methods

Study Design

This study is designed as a randomized controlled multicenter clinical trial (ClinicalTrials.gov; NCT03914287) to establish the safety and efficacy of a physiotherapy intervention consisting of self-myofascial release using a foam roller. Once eligibility is determined, participants will be randomized to either the intervention (experimental) group or the control group.

Clinical Record and Selection Criteria

This study has been approved by the research ethics committee of the University of Murcia (2428/2019). Patients will be included if they have been diagnosed with hemophilia A or B, are 18 years of age or older, have been diagnosed with bilateral hemophilic arthropathy of the ankle (more than 3 points of joint damage on the Hemophilia Joint Health Score), and are on prophylactic or on-demand treatment with factor VIII or factor IX concentrates.

Patients will be excluded from the study if they are not able to ambulate; have been found to have inhibitors (antibodies to factor VIII or factor IX), have neurological or cognitive alterations that prevent them from understanding the questionnaires and physical tests, or choose not to give informed consent (have not signed the statement of informed consent).

Sample Size

The target sample size for inclusion in the study is 70 patients. The sample size is justified with respect to the prevalence of patients with congenital coagulopathies; there are 2039 patients with either hemophilia A and B or von Willebrand disease in Spain, of which 612 meet the selection criteria for the study (Spanish Federation of Hemophilia). Based on these data, the sample size at national level would be 236 individuals, with a confidence level of 95% and an expected dropout ratio of 15%. Thus, a sample size of a total of 70 patients from the 5 centers will be used.

Randomization

Participants will be randomly assignment using opaque envelopes to one of two groups—experimental and control. Random assignment of patients will be carried out after cluster recruitment (based on hemophilia type and patient age) to ensure homogeneity of the study groups. This assignment will be carried out by a person who is not involved in the study objectives and who is unaware of the identity of the participants.

Outcome Measures

Baseline assessments will be carried out at Hemophilia Association centers. Measurements will be performed by a physiotherapist who is unaware of patient group assignments.

After the treatment period and 3 months after completion, the patients included in both groups (experimental and control) will be re-evaluated by the same rater under the same conditions as their initial evaluation.

Dependent variables (range of motion, joint pain, functionality, joint state, muscle strength, muscle flexibility, and record of activity) will be measured at each study assessment (baseline, posttreatment, and follow-up). A 10-point visual analog scale will be used to evaluate patient perception of joint pain, ranging from 0 (no pain) to 10 (maximum perceived pain). An algometer (FPN100; Wagner Instruments) will be used for the assessment of pressure-induced pain (the amount of pressure at which the person perceives pain), both at the joint and at other body sites [28]. Pressure will be applied gradually at the site, increasing at rate of 50 kPa/s until the patient reports that the sensation is painful [29]. In patients with ankle arthropathy, bilateral measurements will be taken anterior to the lateral malleolus (ankle) [30] and at two other sites—the spinous process of the L5 vertebra and on the extensor carpi radialis longus muscle of the forearm (5 cm distal to the lateral epicondyle of the humerus) [28]. Using a portable instrument [31] for assessing physical activity, patient physical activity level (average number of steps per day, average distance per day, average amount of active time, and energy consumption) will be recorded. The Hemophilia Joint Health Score [32] will be used to evaluate the joint condition of knees, ankles, and elbows. It includes 8 items (inflammation and its duration, pain, atrophy and muscle strength, crepitus, and reduced flexion and extension) ranging from 0 to 20 points per joint (the higher the score, the greater the joint deterioration).

The 6-minute walking test [33] measures the distance walked over a period of 6 minutes as an assessment of submaximal capacity to perform exercise. This instrument was developed for use in patients with respiratory disease and heart failure, but has been used in children and adults with a variety of chronic conditions, including hemophilia [34-36]. The test is performed on a 30 to 50-meter track, and the use of walking aids or orthopedic devices is permitted. Ankle range of motion will be measured by a digital goniometer using a protocol designed by Thornton et al [37]; the assessment can be performed with the patient standing. The axis of the goniometer will be placed alongside the lateral malleolus of the ankle. The fixed arm will be placed parallel to the fibula while the mobile arm is aligned to be parallel with the fifth metatarsal bone. This measuring instrument allows more accurate measurements than those obtained with a plastic goniometer. The patient will be asked to perform 3 repetitions of each movement. The mean of the 3 measurements will be used [28]. The maximum isometric strength of the plantar flexor muscles of the ankle will be evaluated on both limbs with a manual dynamometer. The patient will be placed in a supine position with 90º ankle dorsiflexion. The dynamometer will be located proximal to the metatarsophalangeal joints on the plantar side) and will be held

by the evaluator [38]. The patient will be asked to perform 3 maximal effort isometric contractions (each for 5 seconds with a 30-second break in between) against the dynamometer and the mean of the 3 measurements will be used [28]. The fingertip-to-floor test [39] assesses the degree of flexibility of the posterior muscles of the lower limbs. The distance between the fingertips and the floor is calculated at maximum hip flexion with knees extended.

Intervention

Patients will continue their factor VIII or factor IX concentrate treatment as prescribed by their referring hematologists. Throughout the study, the prescribed pharmacologic treatment, dosage, and periods of substitute treatment of the participants will not be altered. Participants in the control group will receive no physical therapy using self-myofascial release and will continue with their usual routine of physical activity and exercise. Outcomes will be assessed under the same conditions as those of the experimental group.

At the beginning of the study, the main investigator will explain the characteristics of the intervention to be carried out to the experimental group. Each session will last approximately 15 minutes, with 5 physiotherapy sessions over a period of 3 months. Each patient will perform the interventions at home. Participants will have free access to the mobile app. Access to the platform will be approved after the patient signs the informed consent form. Once the study is complete, the contents of the app (Table 1) will be available on the website of the Hemophilia Physiotherapy research group (InHeFis).

The protocol for self-myofascial release of the lower limbs using a foam roller and solid ball massage, adapted to patients with hemophilic ankle arthropathy, will include self-myofascial release of the plantar, back of the leg, and hamstring regions, as well as adductor, abductor, and pelvitrochanteric muscles. Table 1 shows the physiotherapy protocol. Periodic follow-up will be performed, through phone calls and by SMS text messages, to answer questions from patients regarding the use of the app.

A mobile app (designed by the research group) will be used to demonstrate all the exercises in the self-myofascial release protocol. Each time the patient exercises, he or she will be able to watch a video explaining the characteristics of each exercise (time, repetitions, position, and action). This free app will also collect adherence data recorded as days of exercise by the participant.

Patient will need to have a suitable floor mat. A massage ball will be used for pressure point massage (solid ball massage), typically 40 mm to 50 mm in diameter, made of a hard polyurethane, but slightly padded. Two smooth low-deformability foam rollers (90 cm in length and 15 cm in diameter) will also be used.

Table 1. Physiotherapy protocol using self-myofascial release for patients with hemophilic ankle arthropathy.

Region and exercise aid	Action	Observations	Times
Plantar region			
Solid ball massage	Slow circular movements shall be carried out with slight pressure on the sole of the foot. The stimulus should be applied below the pain threshold.	Three areas shall be worked on: near the heel, in the middle of the sole of the foot and below the metatarsal head. Circular movements shall be carried out.	5 seconds in each area, bilaterally
Solid ball massage	Linear movements shall be carried out on the sole of the foot exerting a slight pressure from the heel to the metatarsals and from the metatarsals to the heel.	The maneuver shall include slight flexion and extension movements of the toes.	15 repetitions shall be performed for each foot
Achilles region			
Foam roller	The movement shall be performed from the most distal part of the leg to the region of myotendinous connection with the calf muscles.	The exercise is to be assisted with slight plantar flexion and extension movements by the patient. The exercise can be enhanced by crossing a leg in extension over the leg subject to the work stimulus	15 slow sliding movements
Soleus and calf muscles			
Foam roller	Movement assisted with slight plantar flexion and extension movements shall be performed. The roller will move over the calf muscle.	The exercise can be enhanced by crossing a leg in extension over the leg subject to the work stimulus.	15 slow sliding movements
Extensor retinaculum of the ankle			
Foam roller	With the foam roller placed in the anterior region of the ankle, a sliding motion while exerting slight pressure on the anterior region of the ankle shall be performed.	Performed with the patient in a quadruped position. Slight plantar and dorsal flexion movements of the ankle can be combined.	15 slow movements
Muscle compartment of the anteroexternal region of the leg			
Foam roller	Movements shall be performed on the anteroexternal region of the leg, with slight compression stimuli and longitudinal release of the tibialis anterior, toe extensor, and peroneal muscles.	Performed with the patient in a quadruped position incorporating a slight hip rotation	15 slow movements
Hamstring region			
Foam roller	Bilateral work on the hamstring region using a foam roller shall be performed by rolling each hamstring on the foam roller bilaterally and attempting the widest possible run.	Performed with the patient seated in such a way that the hamstring muscles are supported on the foam roller.	10 slow movements
Foam roller	Unilateral work on the hamstring region using a foam roller shall be performed focusing the work on one leg while making slight flexion and extension movements of the knee.	Performed with the patient seated in such a way that the hamstring muscles are supported on the foam roller.	10 slow movements
Adductor muscles			
Solid ball massage	The exercise shall be carried out in 3 different areas of the inner thigh region: middle third, proximal third and distal third, starting on the distal third. The ball will be placed between the legs and slight pressure will be applied.	With sustained pressure, slow movements shall be performed with one leg so the solid ball moves in a circle. Movements shall be performed using each leg, changing the position of the ball to the medial third, and then the proximal third.	5 slow movements
Abductor muscles			
Foam roller	The patient shall be positioned in lateral decubitus, with the foam roller on the side of the thigh, applying slow slides on the back of the thigh	The longitudinal run should be as wide as possible.	15 slow movements
Pelvitrochanteric muscles			
Foam roller	The patient shall be seated on the foam roller, flexing a hip while placing the foot with the sole resting on the floor to ensure greater body weight on the gluteal and pelvitrochanteric region on the opposite side.	Perform smooth movements sliding the gluteal region over the foam roller. Then change legs.	15 slow movements

Data Analysis

The distribution of the sample, the changes after the intervention and follow-up period in each group, and the intra and interindividual effect will be analyzed. We will use the intent-to-treat method to include all individuals who were randomized in the final data analysis.

The statistical analysis will be carried out using SPSS statistical software (version 19.0; IBM Corp). The Kolmogorov-Smirnov test will be used to test for normality, and the Levene test will be used to test for homoscedasticity. If the conditions of normality and homoscedasticity are violated, nonparametric tests will be used.

Descriptive statistics (mean and standard deviation) will be calculated for all dependent variables. A one-way repeated measures analysis of variance will be used to compare the groups (experimental and control) at 3 assessment times (baseline, posttreatment, and follow-up). If the interaction is found to be significant, pairwise comparisons will be performed. The significance level will be set at α=.05. To control the error rate, Bonferroni correction will be applied. The results of the *F* test will depend on the significance of Mauchly sphericity. If significant, the Greenhouse-Geisser correction will be used. To assess clinical relevance, we will calculate the standard error of measurement and minimum detectable change for each dependent variable.

Results

The study has been approved by the ethics committee of the University of Murcia (ID: 2428/2019). Patient recruitment will begin in September 2020, and an intervention period will continue until June 2021. Data collection will take place between September 2020 and October 2021.

Discussion

This project is the most ambitious physiotherapy study, in terms of methodology, recorded to date in Spain. The inclusion of 70 patients with hemophilia from 5 different regions for participation in a physiotherapy program will confer on this project a high statistical power, which is unusual in a rare pathology such as hemophilia. Patients with hemophilic ankle arthropathy will undergo treatment with self-myofascial release using a foam roller. The research team is made up of multidisciplinary hemophilia specialists, renowned physiotherapists with extensive clinical experience, and researchers in the field of hemophilia, as well as experts in methodology and statistics. Coordination between different regions of Spain, with the participation of universities, hospitals and associations of patients, is an uncommon effort in the field of hemophilia-related physiotherapy research.

Another potential strength is that this protocol can help to establish a rapid, safe, and effective intervention for patients with hemophilia. In addition to clinical improvements, it could facilitate greater adherence to physiotherapy treatments and improve the quality of life of individuals with hemophilia.

Self-myofascial release requires no economic investment in the case of manual therapy. Validating its safety and efficacy could promote the development of a quick, inexpensive, and simple physiotherapy intervention that can easily be used widely.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V. 1. 6. 1).
[PDF File (Adobe PDF File), 271 KB - resprot_v9i7e15612_app1.pdf]

References

1. Gringeri A, Ewenstein B, Reininger A. The burden of bleeding in haemophilia: is one bleed too many? Haemophilia 2014 Jul;20(4):459-463. [doi: 10.1111/hae.12375] [Medline: 24472015]
2. Valentino LA. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. J Thromb Haemost 2010 Sep;8(9):1895-1902 [FREE Full text] [doi: 10.1111/j.1538-7836.2010.03962.x] [Medline: 20586922]
3. Gouw SC, Timmer MA, Srivastava A, de Kleijn P, Hilliard P, Peters M, et al. Measurement of joint health in persons with haemophilia: a systematic review of the measurement properties of haemophilia-specific instruments. Haemophilia 2019 Jan;25(1):e1-e10. [doi: 10.1111/hae.13631] [Medline: 30427100]
4. Rodriguez-Merchan EC. Prevention of the musculoskeletal complications of hemophilia. Adv Prev Med 2012;2012:201271 [FREE Full text] [doi: 10.1155/2012/201271] [Medline: 22778972]

5. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007 Aug 09;357(6):535-544. [doi: 10.1056/NEJMoa067659] [Medline: 17687129]
6. Holstein K, Klamroth R, Richards M, Carvalho M, Pérez-Garrido R, Gringeri A, European Haemophilia Therapy Standardization Board. Pain management in patients with haemophilia: a European survey. Haemophilia 2012 Sep;18(5):743-752. [doi: 10.1111/j.1365-2516.2012.02808.x] [Medline: 22530627]
7. Rodriguez-Merchan EC. Management of hemophilic arthropathy of the ankle. Cardiovasc Hematol Disord Drug Targets 2017;17(2):111-118. [doi: 10.2174/1871529X17666170908110758] [Medline: 28891453]
8. Cuesta-Barriuso R, Gómez-Conesa A, López-Pina J. Effectiveness of two modalities of physiotherapy in the treatment of haemophilic arthropathy of the ankle: a randomized pilot study. Haemophilia 2014 Jan;20(1):e71-e78. [doi: 10.1111/hae.12320] [Medline: 24251556]
9. Mazloum V, Rahnama N, Khayambashi K. Effects of therapeutic exercise and hydrotherapy on pain severity and knee range of motion in patients with hemophilia: a randomized controlled trial. Int J Prev Med 2014 Jan;5(1):83-88 [FREE Full text] [Medline: 24554996]
10. Gomis M, González L, Querol F, Gallach JE, Toca-Herrera J. Effects of electrical stimulation on muscle trophism in patients with hemophilic arthropathy. Arch Phys Med Rehabil 2009 Nov;90(11):1924-1930. [doi: 10.1016/j.apmr.2009.05.017] [Medline: 19887218]
11. O'Connell JA. Bioelectric responsiveness of fascia: a model for understanding the effects of manipulation. Techniques in Orthopaedics 2003;18(1):67-73. [doi: 10.1097/00013611-200303000-00012]
12. Tutusaus R, Potau JM. Sistema Fascial. Anatomía, valoración y tratamiento. Barcelona: Editorial Médica Panamericana SA; 2015.
13. Donoso-Úbeda E, Meroño-Gallut J, López-Pina JA, Cuesta-Barriuso R. Safety and effectiveness of fascial therapy in adult patients with hemophilic arthropathy. A pilot study. Physiother Theory Pract 2018 Oct;34(10):757-764. [doi: 10.1080/09593985.2018.1425513] [Medline: 29334292]
14. Donoso-Úbeda E, Meroño-Gallut J, López-Pina JA, Cuesta-Barriuso R. Safety of fascial therapy in adult patients with hemophilic arthropathy of ankle. A cohort study. Musculoskelet Sci Pract 2018 Jun;35:90-94. [doi: 10.1016/j.msksp.2018.03.003] [Medline: 29550698]
15. Findlay T, Schleip R. Introduction. In: Findlay T, Schleip R, editors. Fascia Research: Basic Science and Implications for Conventional and Complementary Health Care. Munich: Elsevier; 2007:2-9.
16. Bordoni B, Lintonbon D, Morabito B. Meaning of the solid and liquid fascia to reconsider the model of biotensegrity. Cureus 2018 Jul 05;10(7):e2922 [FREE Full text] [doi: 10.7759/cureus.2922] [Medline: 30197845]
17. Castro-Sánchez AM, Matarán-Peñarrocha GA, Arroyo-Morales M, Saavedra-Hernández M, Fernández-Sola C, Moreno-Lorenzo C. Effects of myofascial release techniques on pain, physical function, and postural stability in patients with fibromyalgia: a randomized controlled trial. Clin Rehabil 2011 Sep;25(9):800-813. [doi: 10.1177/0269215511399476] [Medline: 21673013]
18. Crane JD, Ogborn DI, Cupido C, Melov S, Hubbard A, Bourgeois JM, et al. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. Sci Transl Med 2012 Feb 01;4(119):119ra13 [FREE Full text] [doi: 10.1126/scitranslmed.3002882] [Medline: 22301554]
19. Paolini J. Review of myofascial release as an effective massage therapy technique. Athl Ther Today 2009;14(5):30-34. [doi: 10.1123/att.14.5.30]
20. MacDonald GZ, Penney MDH, Mullaley ME, Cuconato AL, Drake CDJ, Behm DG, et al. An acute bout of self-myofascial release increases range of motion without a subsequent decrease in muscle activation or force. J Strength Cond Res 2013 Mar;27(3):812-821. [doi: 10.1519/JSC.0b013e31825c2bc1] [Medline: 22580977]
21. Sullivan KM, Silvey DBJ, Button DC, Behm DG. Roller-massager application to the hamstrings increases sit-and-reach range of motion within five to ten seconds without performance impairments. Int J Sports Phys Ther 2013 Jun;8(3):228-236 [FREE Full text] [Medline: 23772339]
22. Cheatham SW, Kolber MJ, Cain M, Lee M. The effects of self-myofascial release using a foam roll or roller massager on joint range of motion, muscle recovery, and performance: a systematic review. Int J Sports Phys Ther 2015 Nov;10(6):827-838 [FREE Full text] [Medline: 26618062]
23. Škarabot J, Beardsley C, Štirn I. Comparing the effects of self-myofascial release with static stretching on ankle range-of-motion in adolescent athletes. Int J Sports Phys Ther 2015 Apr;10(2):203-212 [FREE Full text] [Medline: 25883869]
24. Kelly S, Beardsley C. Specific and cross-over effects of foam rolling on ankle dorsiflexion range of motion. Int J Sports Phys Ther 2016 Aug;11(4):544-551 [FREE Full text] [Medline: 27525179]
25. Cheatham SW, Kolber MJ. Does roller massage with a foam roll change pressure pain threshold of the ipsilateral lower extremity antagonist and contralateral muscle groups? an exploratory study. J Sport Rehabil 2018 Mar 01;27(2):165-169. [doi: 10.1123/jsr.2016-0196] [Medline: 28253066]
26. Grabow L, Young JD, Alcock LR, Quigley PJ, Byrne JM, Granacher U, et al. Higher quadriceps roller massage forces do not amplify range-of-motion increases nor impair strength and jump performance. J Strength Cond Res 2018 Nov;32(11):3059-3069. [doi: 10.1519/JSC.0000000000001906] [Medline: 30152808]

27. Okamoto T, Masuhara M, Ikuta K. Acute effects of self-myofascial release using a foam roller on arterial function. J Strength Cond Res 2014 Jan;28(1):69-73. [doi: 10.1519/JSC.0b013e31829480f5] [Medline: 23575360]
28. Skou ST, Simonsen O, Rasmussen S. Examination of muscle strength and pressure pain thresholds in knee osteoarthritis: test-retest reliability and agreement. J Geriatr Phys Ther 2015;38(3):141-147. [doi: 10.1519/JPT.0000000000000028] [Medline: 25594517]
29. Leffler A, Kosek E, Lerndal T, Nordmark B, Hansson P. Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. Eur J Pain 2002;6(2):161-176. [doi: 10.1053/eujp.2001.0313] [Medline: 11900476]
30. Dhondt W, Willaeys T, Verbruggen LA, Oostendorp RA, Duquet W. Pain threshold in patients with rheumatoid arthritis and effect of manual oscillations. Scand J Rheumatol 1999;28(2):88-93. [doi: 10.1080/030097499442540] [Medline: 10229137]
31. Pérez-Alenda S, Carrasco JJ, Megías-Vericat JE, Poveda JL, Bonanad S, Querol F. Quantification of physical activity in adult patients with haemophilic arthropathy in prophylaxis treatment using a fitness tracker. Haemophilia 2018 Jan;24(1):e28-e32. [doi: 10.1111/hae.13388] [Medline: 29271553]
32. Fischer K, de Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: exploring reliability and validity. Haemophilia 2013 Nov;19(6):944-950. [doi: 10.1111/hae.12197] [Medline: 23730725]
33. Balke B. A simple field test for the assessment of physical fitness. rep 63-6. Rep Civ Aeromed Res Inst US 1963 Apr:1-8. [Medline: 14131272]
34. Douma-van Riet DCM, Engelbert RHH, van Genderen FR, Ter Horst-De Ronde MTM, de Goede-Bolder A, Hartman A. Physical fitness in children with haemophilia and the effect of overweight. Haemophilia 2009 Mar;15(2):519-527. [doi: 10.1111/j.1365-2516.2008.01928.x] [Medline: 19347992]
35. Groen W, van der Net J, Lacatusu AM, Serban M, Helders PJM, Fischer K. Functional limitations in Romanian children with haemophilia: further testing of psychometric properties of the Paediatric Haemophilia Activities List. Haemophilia 2013 May;19(3):e116-e125. [doi: 10.1111/hae.12090] [Medline: 23374095]
36. Salim M, Brodin E, Spaals-Abrahamsson Y, Berntorp E, Zetterberg E. The effect of Nordic Walking on joint status, quality of life, physical ability, exercise capacity and pain in adult persons with haemophilia. Blood Coagul Fibrinolysis 2016 Jun;27(4):467-472. [doi: 10.1097/MBC.0000000000000554] [Medline: 27124104]
37. Thornton J, Sabah S, Segaren N, Cullen N, Singh D, Goldberg A. Validated method for measuring functional range of motion in patients with ankle arthritis. Foot Ankle Int 2016 Aug;37(8):868-873. [doi: 10.1177/1071100716645391] [Medline: 27113608]
38. van der Ploeg RJ, Fidler V, Oosterhuis HJ. Hand-held myometry: reference values. J Neurol Neurosurg Psychiatry 1991 Mar;54(3):244-247 [FREE Full text] [doi: 10.1136/jnnp.54.3.244] [Medline: 2030353]
39. Perret C, Poiraudeau S, Fermanian J, Colau MM, Benhamou MA, Revel M. Validity, reliability, and responsiveness of the fingertip-to-floor test. Arch Phys Med Rehabil 2001 Nov;82(11):1566-1570. [doi: 10.1053/apmr.2001.26064] [Medline: 11689977]

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Protocol

A Novel Narrative E-Writing Intervention for Parents of Children With Chronic Life-Threatening Illnesses: Protocol for a Pilot, Open-Label Randomized Controlled Trial

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Abstract

Background: A novel evidence-based Narrative e-Writing Intervention (NeW-I) has been developed and tested in Singapore to advance psychosociospiritual support for parents of children with chronic life-threatening illnesses. NeW-I is informed by an international systematic review and a Singapore-based qualitative inquiry on the lived experience of parental bereavement and supported by literature on anticipatory grief interventions for improving the holistic well-being of parent caregivers of seriously ill children.

Objective: This study's aim was to provide an accessible platform, NeW-I—which is a strengths- and meaning-focused and therapist-facilitated mobile app and web-based counseling platform—that aims to enhance quality of life, spiritual well-being, hope, and perceived social support and reduce depressive symptoms, caregiver burden, and risk of complicated grief among parents of children with chronic life-threatening illnesses.

Methods: The NeW-I therapist-facilitated web-based platform comprises a mobile app and a website (both of which have the same content and functionality). NeW-I has been implemented in Singapore as a pilot open-label randomized controlled trial comprising intervention and control groups. Both primary and secondary outcomes will be self-reported by participants through questionnaires. In collaboration with leading pediatric palliative care providers in Singapore, the trial aims to enroll 36 participants in each group (N=72), so that when allowing for 30% attrition at follow-up, the sample size will be adequate to detect a small effect size of 0.2 in the primary outcome measure, with 90% power and two-sided significance level of at least .05. The potential effectiveness of NeW-I and the accessibility and feasibility of implementing and delivering the intervention will be assessed.

Results: Funding support and institutional review board approval for this study have been secured. Data collection started in January 2019 and is ongoing.

Conclusions: NeW-I aspires to enhance holistic pediatric palliative care services through a structured web-based counseling platform that is sensitive to the unique cultural needs of Asian family caregivers who are uncomfortable with expressing emotion even during times of loss and separation. The findings of this pilot study will inform the development of a full-scale NeW-I protocol and further research to evaluate the efficacy of NeW-I in Singapore and in other Asian communities around the world.

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International Registered Report Identifier (IRRID): DERR1-10.2196/17561

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KEYWORDS

narrative therapy; psychotherapy; pediatric palliative care; end-of-life care; randomized controlled trial; cyber-counseling; mobile phone

Introduction

Background

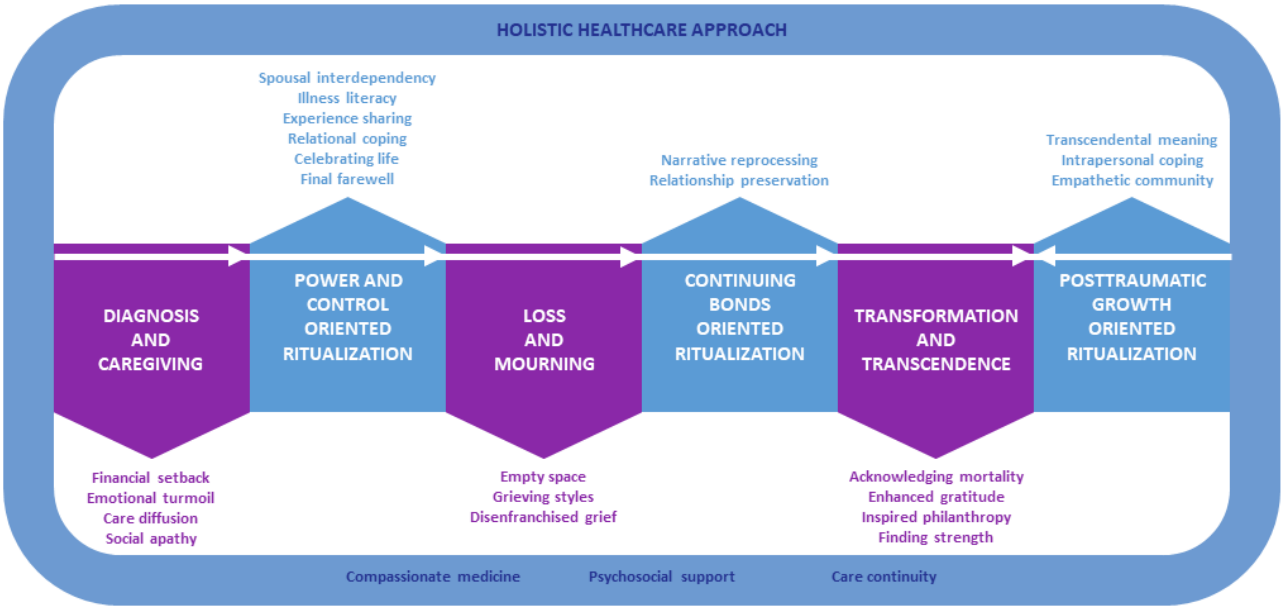
There is a global increase in the number of children living with chronic life-threatening illnesses [1,2]. In Singapore, child deaths (age <19 years) due to chronic conditions increased from 204 per year to 245 per year during the 2014 to 2016 period [3]. In fact, congenital anomalies as well as cardiovascular and cerebrovascular diseases account for over half of all deaths in the 0 to 19 years age range in Singapore [4]. Due to technological developments in medical care, children with chronic life-threatening illnesses can live longer, but they simultaneously face the challenge of being dependent on their caregivers (usually, their parents) and disability for a prolonged period [1]. However, not all seriously ill children and their parents receive adequate palliative support services [3].

Being a parent caregiver of a child with a chronic life-threatening illness is a highly stressful experience [5]. In addition to the typical challenges of parenting, parent caregivers must navigate a complex web of stressors, including the practical and financial burden of caregiving [6], strained marital and social relationships [7], and neglect of other healthy children and family members [8]. Furthermore, parent caregivers of children with chronic life-threatening illnesses need to frequently communicate and engage with medical professionals, but such interactions can increase the anxiety and distress of the parents if they are not adequately involved in making decisions regarding their child's treatment [9,10]. Thus, the stressors associated with caregiving and the elevated demand on resources put parent caregivers at increased risk of depressive symptoms, fatigue, and overall poor quality of life [11].

Parental Bereavement Trajectories of Child Loss

Our research team recently conducted a qualitative systematic review of 25 high-quality research papers published between 2000 and 2017, exploring the lived experience of parental bereavement due to a child's chronic life-threatening illness. A 4-phase parental bereavement trajectory of child loss was developed, highlighting appropriate interventions that help parents identify care needs, elicit caregiving strengths, enhance death preparedness, and foster meaning-making throughout the trajectory of their child's illness to reduce psychoemotional distress during the period of end-of-life caregiving and into bereavement [12]. Our research team conducted a second study to examine the Asian experience of parental bereavement via meaning-oriented strength-focused interviews with 6 couples, 13 mothers, 4 fathers, and 2 primary parental figures (N=25 parental units) who lost their child to a chronic life-threatening illness in Singapore [13,14]. Grounded theory analysis revealed 7 themes and 25 subthemes that were organized into a trauma-to-transformation model of parental bereavement (Figure 1). This culture-specific model shows the milestones of how Asian bereaved parents journeyed through their child's life-threatening illness and eventual death, describing the ritualistic actions as well as family communication and transactional patterns that aided them to better cope with their loss, to regain control over their lives, to sustain a continuing bond with their deceased child, and to move forward with and ultimately transcend their grief through meaning reconstruction [13,14].

Figure 1. Trauma to transformation model of parental bereavement in Asia.



These findings echo previous literature [15-18] positing that parents facing potential child loss could benefit from psychosocial and therapeutic interventions as soon as prognosis is known and throughout the trajectory of the illness, which could ease the transition from caregiving through mortality and bereavement, thus mitigating adverse grief outcomes (Table 1). However, most supportive interventions for parents caring for children with chronic life-threatening illnesses only occur after bereavement [19-21], and a recent systematic review found negligible evidence to support their effectiveness [22]. As such, there is a need to develop a preloss intervention to augment pediatric palliative care and parental bereavement support service—one that empowers parents to reflect on their caregiving experiences, explore and identify resources that could help them better cope with the challenges of caregiving, and support their child to live a meaningful life despite a chronic life-threatening illness.

Table 1. Clinical implications of findings from the qualitative study on the lived experience of parental bereavement in Asia.

Findings from qualitative studies on the lived experience of parental bereavement in Asia	Implications for clinical work
Facing their child's impending mortality is a difficult experience, which can isolate parents. Societal attitudes toward illness can make it difficult for parents to engage with their previous social networks.	Support parents in gaining a greater sense of control over their lives and strengthening resilience during the period of end-of-life caregiving through empathic support and psychoeducational resources for self-care and healthy coping.
Parents seek to understand the medical terminology associated with their child's illness and prognosis of the condition, so that they can evaluate potential risks and benefits of treatment procedures and make informed care decisions.	Empower parents to provide the best possible care to their child through exploration of resources for seeking information about illness and caregiving.
Parents desire to give their children a chance to rise above the difficulties brought on by the illness and display strength to help their child live as fully as possible.	Facilitate meaningful family experiences that allow parents and their children to move away from the drudgery of illness, suffering, and caregiving and focus on building parent-child memories.
Asian parents tend to have a collaborative approach to caregiving for their sick child. They often rely on family members, relatives, and other parents of sick children for support.	Explore sources of support, which participants have within their close social network and how they can be harnessed in care provision.

Elements of a Preloss Intervention for Parents of Children With Chronic Life-Threatening Illnesses

In developing a preloss intervention that could meaningfully impact families throughout their child's trajectory of illness and leading to the final days of their child's life, a number of important therapeutic elements need to be considered and incorporated. First, anticipatory grief, defined as the process of mourning the loss of a loved one before actual loss that enables caregivers to experience and adjust to various grief responses, must be central to such an intervention [17,23]. Anticipatory grief can smoothen the process of coping with death as the individual has the scope to come to terms with the loss in advance [24]. Studies have found that strength-based end-of-life interventions with elements that address anticipatory grief can improve adult patients' quality of life and mitigate poor bereavement outcomes among family caregivers [25]. It is, therefore, possible that an anticipatory grief-based psychotherapeutic intervention for parents of children with chronic life-threatening illnesses could help parents to

understand and regulate their emotions, enhance death preparedness, and thereby build resilience.

Second, it would be useful for a preloss intervention for parents of children with chronic life-threatening illnesses to adopt a meaning reconstruction approach [26-28], with each individual actively constructing a phenomenological world of their experiences in relation to various familial and sociocultural contexts and supporting their sense of loss and grief accordingly. Such a meaning reconstruction approach empowers grievers to choose whether to direct their attention to the loss and process turbulent feelings or to focus on practical adjustments to re-engage with their everyday life. Third, a preloss intervention would benefit from a narrative approach [29,30], which could help individuals connect with emotions that are challenging to accept, generate new meaningful stories about life and loss, and restructure negative emotional appraisal of situations such as end-of-life caregiving into more positive ones, thereby generating a sense of hope.

Two effective examples of applying the meaning reconstruction approach and the narrative approach in supporting holistic end-of-life care are dignity therapy [25,31,32] and family dignity intervention [33]. Both of these are evidence-based psychotherapies that address the physical, psychosocial, and existential issues pertaining to one's dignity at the end-of-life period. Specifically, a family dignity intervention is designed to support the collective experience of grief and loss for Asian families facing mortality, and it could add great value to a preloss intervention for parents of children with chronic life-threatening illnesses. In practice, family dignity intervention comprises a meaning-focused interview with a patient-and-family caregiver dyad that fosters the expression of appreciation and emotional connection through the retelling of important life narratives. The interview is recorded, transcribed, and edited into a legacy document and returned to the dyad for sharing with their loved ones for healing and remembrance.

Finally, a preloss intervention for parents of children with chronic life-threatening illnesses must be mindful of the caregiving responsibilities and limitations that serve as barriers for parents to engage in sit-and-talk therapy [12]. It is possible that a web-based platform that is cost-effective and time-efficient [34] can deliver psychotherapy to such parents. Such therapist-facilitated internet-based platforms are increasingly used for brief and effective psychotherapy for a range of conditions, including depression, anxiety, and stress [35-40]. Moreover, when web-based platforms use writing as the modality for emotional expression and reflection, efficacy is superior compared with audio or video mediums [41]. Finally, the anonymity of an e-writing channel can encourage greater willingness to self-disclose [42,43].

This Study and Objectives

Globally, pediatric palliative care interventions predominantly emphasize the stages of grief and psychological tasks that grieving parents must accomplish after their child's death [22], and in Singapore, there is no known empirically tested intervention to provide psychoemotional support and psychoeducational resources to parents of children with chronic life-threatening illnesses. Singapore is a leading nation in digital readiness, smartphone utilization for communication is ingrained into the everyday life of its people [44], and web-based intervention services for improving well-being have been welcomed by the Singaporean community [45,46]. Hence, it is reasonable to propose that web-based solutions are vitally useful for enhancing pediatric palliative care and parental bereavement support services. Furthermore, in view of the fact that Asian family caregivers can be uncomfortable with explicit emotional expression even during times of loss and separation [47], a web-based platform and the relative anonymity it offers to participants [43] would be appropriate for an Asian population.

The research team of this study integrated the aforementioned elements necessary for a preloss intervention for parents of children with chronic life-threatening illnesses and conceived a Narrative e-Writing Intervention (NeW-I) to address the gap in pediatric palliative care delivery and research in the local context. NeW-I is a novel web-based, therapist-facilitated, strength-focused, and meaning-oriented intervention designed to provide direct service to parents of children with chronic life-threatening illnesses. The development and evaluation of NeW-I is guided by the Medical Research Council Framework for the Development and Evaluation of Complex Interventions, which is widely recognized in the design and evaluation of complex interventions to improve health outcomes [48,49]. NeW-I is also inspired by the meaning reconstruction model [50], the narrative approach to anticipatory grief [51], dignity therapy [31,32], family dignity intervention for holistic end-of-life care [33], and the findings of a recent investigation on Asian parental bereavement experience of child loss by our research team [13,14].

The overarching goal of the novel NeW-I intervention model is to provide an accessible platform for parent caregivers to reflect on their experiences of caring for a child with a chronic life-threatening illness from a new perspective (ie, new eye) as well as to create a renewed sense of self-understanding and empowered identity in the context of their experience (ie, new I). The specific research objectives are three-fold: (1) to develop a standardized protocol for a cultural-specific and meaning-oriented NeW-I for anticipatory grief and bereavement support for parent caregivers of children with chronic life-threatening illnesses and eventual death; (2) to evaluate the efficacy of NeW-I in enhancing quality of life, spiritual well-being, hope, and social support as well as decreasing caregiver burden, depressive symptoms, and risk of complicated grief among parent caregivers; and (3) to examine the challenges and pitfalls in the design and implementation of NeW-I through an integrated feasibility and acceptability study for informing large-scale implementation of the intervention.

Methods

Study Design and Hypotheses

This study utilizes an open-label randomized controlled trial design comprising 2 groups: (1) an intervention group (structured NeW-I protocol) and (2) a control group (journaling activity unrelated to their child's illness). It is hypothesized that intervention participants who successfully complete NeW-I will

experience an enhanced quality of life, spiritual well-being, sense of hope, and perceived social support and decreased depressive symptoms, subjective caregiver burden, and risk of complicated grief as compared with control participants. It is also hypothesized that NeW-I is deemed as an accessible and user-friendly service by participants.

Sample

The sample comprises 72 individual parents of varying ethnicity in Singapore (N=72). Where both parents of a child participate in the study, their group allocation is randomly determined, and assessments are completed by both parents independently. To be eligible for participation in this study, the individual must be a parent whose child has been diagnosed with a chronic life-threatening illness and has a prognosis of more than 3 months at the time of enrollment. For the purpose of this study, a *child* has been defined as children and young persons between the ages of 0 and 19 years [52]. The individual must be able to speak, read, and write in English and provide informed consent. Individuals are excluded from this study if they are suffering from severe depressive symptoms and psychological distress, as identified by 2 screening tools. Specifically, to protect participants' well-being during the pilot testing of NeW-I, those who do not meet the stated cutoff scores of the Patient Health Questionnaire – 9 (PHQ-9; >19) and Kessler psychological distress scale (K-10; >29) are excluded, as formal treatment and therapy would be more beneficial [53,54]. Additionally, if participants cease to meet the inclusion criteria during the study (eg, due to their child's untimely death), they are excluded from the study and provided with alternative resources for psychosocial support. However, the data that have been collected until the time of their participation will be kept and analyzed so that a complete and comprehensive evaluation of the study will be possible.

Sample Size Calculation

For a main trial designed with 90% power and two-sided significance level of at least .05, a pilot sample size of 25 per arm is needed to detect a small effect size of 0.2 in the primary outcome measure [55]. A meta-analysis suggested that many high-quality psychotherapy studies (high quality studies defined by a proficiently trained therapist, treatment integrity, N>50) on the treatment of depression have a mean effect size of 0.22 [56]. Allowing for an attrition rate of 30% at follow-up (a larger estimate due to end-of-life context), the sample size must be inflated by a factor of $1/(1-0.3)=1.43$. Therefore, the minimum sample size required for this study was 72 or 36 in each group.

Recruitment Procedures

Purposive sampling was adopted to achieve a target sample size of 72. Potential participants are identified and contacted by the collaborating organization (leading pediatric palliative care providers in Singapore, including KK Women's and Children's Hospital, Club Rainbow Singapore, Muscular Dystrophy Association Singapore, and Rare Disorders Society Singapore) to introduce the study to their beneficiaries. This sampling strategy allows the recruitment of participants whose children suffer from a wide range of chronic life-threatening conditions, thus allowing for maximum variation in the sampling. If verbal consent is obtained from potential participants, their contact details are passed to the research team at Nanyang Technological University, who subsequently establish telephone contact, explain study procedures, and introduce the NeW-I web-based platform. All personal information pertaining to potential participants are kept confidential, and only the responsible researchers have access to such information.

Open recruitment is also carried out so that all parents of children with chronic life-threatening illnesses have equal opportunity to participate in a potentially beneficial study and to examine the feasibility of implementing this free and easily accessible intervention in the community. Posters have been placed in strategic locations across Singapore (such as offices of leading pediatric palliative care providers) that provide information regarding the study. When interested participants contact the research team, the study procedures are explained, the NeW-I platform is introduced, and registration information is provided.

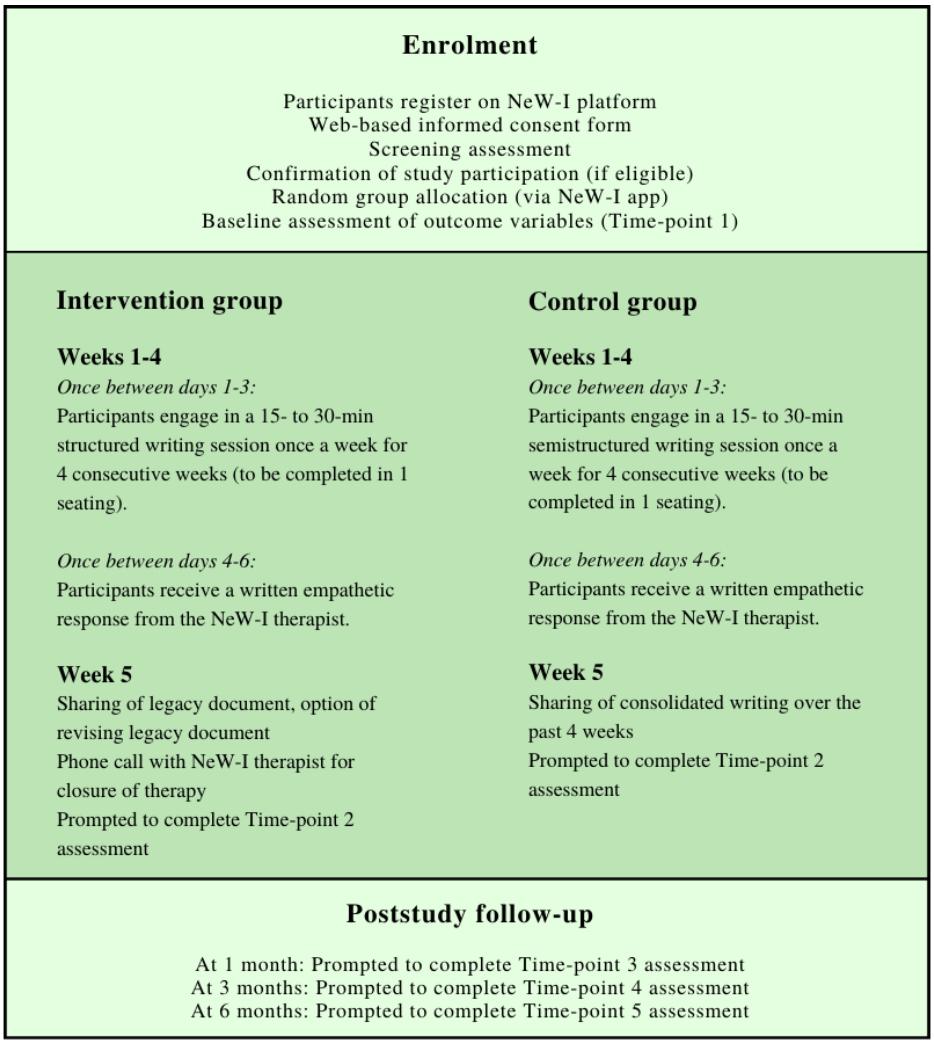
App and Intervention Procedure

The NeW-I therapist-facilitated web-based platform comprises a mobile app and a website (both of which have the same content and functionality). Participants can download the app free of cost from the Apple App Store and the Google Play Store by keying in the relevant keywords or scanning the quick response code provided on the NeW-I study advertisement posters. The NeW-I website is under construction. As shown in Multimedia Appendix 1, when participants initially log in to the app, they are directed to a study participation and informed consent page that provides details about study procedures, institutional affiliations of the research team, rights of research participants, and protection of confidentiality. After participants endorse this web-based informed consent form on the NeW-I platform, they are directed to a demographic information page. Participants are also requested to provide their contact details and last few digits of their national identification number to ensure that only 1 user account is created by each individual.

Following this, participants are directed to a screening page where participants complete the PHQ-9 and the K-10. Those who pass the screening assessments receive confirmation of study participation and are requested to wait for a phone call from the research team. Those who do not pass the screening assessments are thanked for their time and provided with resources for psychosocial support. Individuals who pass the screening assessments receive a phone call from the NeW-I team as a means of identity checking. Following this, participants complete baseline measures (time point 1 assessment). This is followed by a random allocation of participants to either the intervention group or the control group, which is performed via the NeW-I platform using computer-generated random numbers. Participants are then directed to the first writing session. Participants have the option to choose to begin the first writing session immediately or delay for a maximum of 3 days. The day on which participants begin their first writing session is day 1 of week 1. Participants who do not begin their first writing session within 3 days are excluded from the study. However, a concession period of 7 days is given to participants who have a genuine reason for their

inability to adhere to the protocol (such as unexpected changes in their child's health condition) and have expressed keen interest in participating in the study. A similar concession period of 7 days is also maintained for participants who are unable to adhere to the study protocol in weeks 2, 3, and 4 (such that each participant can only be given 1 concession during the entire duration of their study participation). Detailed study procedures are described in Figure 2.

Figure 2. Description of Narrative e-Writing Intervention (NeW-I) procedures.



NeW-I is delivered by trained therapists in the research team who are experts in death education and grief counseling and have the clinical competence to work with family caregivers in pediatric palliative settings. All team members have successfully completed research integrity modules under the provisions of Nanyang Technological University's institutional review board and adhere to the board's guidelines for safeguarding participants' identity and confidentiality.

Intervention and Control Groups

Both intervention and control group participants follow the procedures described in Figure 2. There are 4 weekly sessions of writing. A template has been provided to ensure that the participants' writings tie in with the session objectives. To improve participants' adherence to the study protocol, they receive an automated notification on their phone app and email each time a fresh writing session becomes available to them. Participants were assured of anonymity and confidentiality of their writing to encourage open and honest self-expression. The structured writing for each session requires 15 to 30 min, as exposure and time to process ideas through written disclosure over at least three sessions of 15 min each can produce effective outcomes [57].

For the intervention group participants, each weekly session has a unique objective (Table 2). Briefly, in week 1, participants reflect on the demands of caring for a child with a chronic life-threatening illness and the means to cope with these challenges. In week 2, participants consider avenues where they could seek more information about their child's illness and resources for caregiving. In week 3, participants examine the sources of support that they have within their network of family and friends. In week 4, participants explore how they (and their children) could rise above illness-related challenges and live their lives as fully as possible.

For control group participants, the objective is consistent across the 4 weeks, that is, participants engage in a weekly writing session that is unrelated to their child's illness and allows them to experience the therapeutic benefits of narrative writing (Table 3).

Table 2. Content and questions for reflective writing for intervention group.

Session structure	Week 1	Week 2	Week 3	Week 4
Objective	• To provide participants with a platform to reflect on the emotional, practical, and financial demands of caring for a child with a chronic life-threatening illness and the means to cope with these challenges.	• To explore avenues where participants can seek more information about their child's illness and resources for caregiving.	• To explore the sources of support that participants have within their close network of family and friends.	• To explore how participants (and their children) can rise above illness-related challenges and live their lives as fully as possible.
Questions for reflective writing	• Tell us a little about your child and what you love about him or her. • Tell us about the challenges that you have encountered when caring for your child. • What has been your biggest challenge so far? How have you coped with it? • What are three things that have helped you cope in your caregiving journey?	• How satisfied are you with the knowledge and information that you have about your child's condition? • What has been helpful in providing you with the knowledge and information? • What are some forms of support that have been helpful for you in providing quality care to your child? How were these forms of support helpful? • What would help you to feel more competent as your child's caregiver? What is one thing you could do to make that difference?	• Tell us about some people who have been helpful or supportive in your caregiving journey. How have they helped you to cope during difficult times? • On a scale of 1 to 10, with 1 being "Not at All" and 10 being "Very Much," how satisfied are you with your spousal relationship? (Please omit this question if it does not apply to you.) What might make that score a little higher? • What are some things that others could do for you that could further help you in your caregiving journey?	• Tell us what you love best about your child. What quality about him or her makes you proud? • What would a good day for your child look like right now? What makes it a good day? • Tell us about an enjoyable moment with your child. • What are some things you can do to make an enjoyable moment happen?
Counseling goals	• To affirm the strengths that have helped participants to survive and thrive. • To provide psychoeducation about local social welfare organizations that can provide them with support.	• To acknowledge participants' efforts to seek power and control over their seemingly uncontrollable lives through illness literacy. • To provide psychoeducation about sources for seeking more information about their child's illness, treatment options, and resources for caregiving.	• To reframe that they are indeed blessed to have the support of their spouse or family or friends to help them to cope with this challenging period. • To reframe participants' sharing from sessions 1, 2, and 3 by taking the semantic content as it is but providing an alternative viewpoint of perceiving the situation.	• To assist participants (and their children) in building meaningful and cherished memories through reflecting on achievements and fulfillment of dreams. • To examine ways in which participants can enhance quality of life in their child's final days.

Table 3. Content and questions for reflective writing for control group.

Session structure	Week 1	Week 2	Week 3	Week 4
Questions for reflective writing	This week, we'd love to know a little bit about you. Tell us what an average day in your life looks like. Feel free to share with us any and every detail that you find comfortable to talk about!	This week, we'd like to know about what has the past week been like for you? Feel free to share with us in as much detail as you like!	This week, we'd like to know what is the biggest challenge (e.g. emotional, financial, practical etc.) that you are facing right now? Do feel free to add on anything else about this challenge that you would like us to know!	This week, we'd like to know what you find most comforting right now (e.g. family, relationships, work, hobbies and other activities etc.). Tell us about what makes this thing comforting for you?

Evaluation of Outcomes

Quantitative Assessments

Via the NeW-I platform, both intervention and control group participants fill out a sociodemographic form at baseline and are then assessed on a battery of self-reported standardized and validated measures across 5 time points. The primary outcome measure is the participants' quality of life, as measured by the Kemp Quality of Life scale (KQOL) [58]. Secondary outcomes are assessed using (1) a modified version of the Functional Assessment of Chronic Illness Therapy - Spiritual Well-Being scale (FACIT-Sp-12) [59], (2) the Herth Hope Index (HHI) [60], (3) Patient Health Questionnaire – 9 [53], (4) the Burden Scale for Family Caregivers-Short (BSFC-s) [61], (5) the Inventory of Social Support (ISS) [62], and (6) a modified version of the Brief Grief Questionnaire (BGQ) [63] (Table 4).

Table 4. Quantitative outcome measures.

Measure	Number of items	Rating scale; factor
Kemp Quality of Life scale	1	7-point Likert scale; 1 factor
Functional Assessment of Chronic Illness Therapy - Spiritual Well-Being (adapted version)	12	5-point Likert scale; 3 factors: meaning, peace, and faith
Herth hope index	12	4-point Likert scale; 1 factor
Patient Health Questionnaire - 9 (also serves as a screening assessment)	9	4-point Likert scale; 1 factor
Burden Scale for Family Caregivers-Short	10	4-point Likert scale; 1 factor
Inventory of Social Support	5	5-point Likert scale; 1 factor
Brief Grief Questionnaire (adapted version)	5	3-point Likert scale; 1 factor

Assessment for both intervention and control groups takes place at 5 time points: baseline (time point 1), immediately after completion of the intervention or control protocol (time point 2), 1 month after completion of the intervention or control protocol (time point 3), 3 months after completion of the intervention or control protocol (time point 4), and a final follow-up 6 months after completion of the intervention or control protocol (time point 5). Participants receive an automated notification on their phone app and email each time an assessment set becomes available to them. For each completed assessment, participants receive a voucher worth Singapore $30 (approximately US $21).

Acceptability and Feasibility Study

To evaluate the acceptability and effectiveness of NeW-I, all intervention participants are invited to participate in a semistructured interview at the completion of all intervention components at time point 2, which explores the impact of the intervention, aspects of the intervention found to be helpful, aspects of the intervention found to be unhelpful and how they could be improved, challenges encountered in completing the intervention, and scope for enhancing intervention usability. To assess the feasibility of implementing and delivering NeW-I, the research team maintains an audit trail of the time needed to provide feedback to participants and restructure their narrative writing; deviations from the intervention protocol (if any); uncompleted interventions and their reasons; and NeW-I therapists' perceptions of competence, observations of participants' experiences and responses, and difficult or deviant cases. All feedback provided to participants will be vetted by at least two members of the research team for data monitoring, quality, and safety assurance.

Data Analysis

Quantitative Data

The statistical analysis plan for the quantitative data in this study was designed according to the Consolidated Standards of Reporting Trials guidelines [64] and recommendations made by Gamble et al [65] for clinical trials. Quantitative parameters will be presented as mean (SD) or median (IQR), and categorical variables will be presented as numbers and proportions. The internal consistency of psychometric scales will be assessed using Cronbach alpha. To compare the primary quantitative outcome (KQOL) and secondary quantitative outcomes (FACIT-Sp-12, HHI, PHQ-9, BSFC-s, ISS, and BGQ) between the intervention and control groups over time (time point 1 to time point 5, with time point 2 being the primary time point of comparison), multilevel mixed-effect regression analysis will be used with time as a random effect. All demographic and other relevant covariates measured at baseline will be adjusted in the model. Mixed models allow us to include all available data in the presence of dropouts occurring into the analysis [66]. Individual multivariable models will be constructed for each outcome to estimate the effect sizes and corresponding CIs. Clinically meaningful interactions will also be checked and included in the model if $P<.10$. Marginal effects will be used to predict mean outcome scores for the intervention and control groups. For this study, a two-sided significance level of at least .05 will be considered a statistically significant finding. All analyses will be conducted using Statistical Package for the Social Sciences (SPSS) (version 22.0; IBM Corp) and Stata (version 15.1; StataCorp) statistical software.

The intention-to-treat principle will be followed in the data analysis. However, an additional sensitivity analysis will be conducted to handle missing data during the analysis, where fully conditional multiple imputation with *n (% missing)* imputations and 1000 iterations using the Markov Chain Monte

Carlo method will be used [67]. Model summary estimates will be calculated based on the Rubin rule [68].

Qualitative Data

All qualitative data are stored and analyzed using the NVivo (QSR International) computer software. Phenomenological analysis will be used to obtain an in-depth and comprehensive view of the data set from an insider's perspective [69]. Unique or minority voices will be elicited to illuminate counterpoints to the stated views. Throughout the data analysis process, strategies to maximize research rigor and trustworthiness will be prioritized. The use of such a method of data analysis has been demonstrated in previous research involving grief therapy with bereaved parents [70].

Ethical Considerations

This study has been approved by the institutional review board of Nanyang Technological University, Singapore (IRB-2018-07-009). Web-based, endorsed informed consent was obtained from all participants before study participation. Participants' confidentiality, safety from unintended outcomes, and right to withdraw without any adverse consequences are safeguarded under the ethical provisions of Human Biomedical Research Act studies reviewed by the institutional review board of Nanyang Technological University, Singapore.

As such, there is minimal risk of engaging in a web-based narrative writing activity. The experienced NeW-I therapist will be available to participants to offer web-based support, in the event that some aspects of the intervention cause them distress or discomfort. If participants need further support, a referral system has been set up such that participants who are recruited via purposive sampling would be referred to their health and social care provider for follow-up assistance. Finally, any deviations from or changes to the study protocol, unexpected breaches in privacy, or major technical difficulties will be promptly reported to the institutional review board of Nanyang Technological University, Singapore, and further steps will be taken after seeking advice from the board.

Results

Foundational research leading to this study received funding support from the Singapore Ministry of Education in 2017, and further funding support for pilot implementation of the intervention was obtained from the Temasek Foundation Innovates' Singapore Millennium Foundation Grant in 2018. The study was approved by the institutional review board of Nanyang Technological University in 2018. The recruitment of participants started in January 2019 and is ongoing. Data collection is expected to be completed in September 2020.

Discussion

Research Synopsis and Implications

NeW-I is a first-of-its-kind, web-based, therapist-facilitated, strength-focused, and meaning-oriented intervention for parents of children with chronic life-threatening illnesses, thereby filling in a critical service gap in local pediatric palliative care. Through an open-label randomized control trial, the efficacy of NeW-I for improving such parents' quality of life, spiritual well-being, hope, and social support and decreasing depressive symptoms, caregiver burden, and risk of complicated grief is investigated across 5 time points. It is expected that parents who successfully complete the structured NeW-I intervention protocol will experience enhanced quality of life, spiritual well-being, sense of hope, and perceived social support and decreased depressive symptoms, subjective caregiver burden, and risk of complicated grief as compared with parents who engage in a journaling activity unrelated to their child's illness (control group). It is also expected that parents will find NeW-I to be an accessible and user-friendly service.

In addition to improving the psychosociospiritual well-being of parent caregivers, this study creates opportunities for (1) a longitudinal assessment of the mental states of 36 parents (ie, control group) to obtain a naturalistic trajectory of anticipatory grief, (2) an evaluation of the extent to which the intervention is successful in improving the mental well-being of 36 parents (ie, intervention group), and (3) an evaluation of the extent to which these potential positive effects are sustained over time. The findings will inform the development of a full-scale NeW-I protocol that will be disseminated via research papers and presentations. This will form the foundation for further empirical research to test the effectiveness, acceptability, and feasibility of NeW-I in Singapore and in other Asian communities around the world.

The web-based narrative writing model of NeW-I and the relative anonymity it offers to participants [43] supports the unique needs of Asian family caregivers who are uncomfortable with emotional expression even during times of loss and separation [47]. It is hoped that NeW-I is perceived by parents to be a safe platform for engaging in intimate dialogue regarding their child's caregiving, thereby enhancing parents' experience of their child's illness trajectory, empowering them to harness available resources to provide the best possible care to their child, while simultaneously reducing psychosocial distress and caregiver burden. Evidence from a recent systematic review [71] suggests that the guided web-based intervention protocol of NeW-I is likely to be cost-effective. Additionally, the web-based intervention protocol is convenient to access, allows expression of disenfranchised emotions, and promotes meaning ascription to traumatic experiences. Finally, the current format of NeW-I is tailored for parents of children with chronic life-threatening illnesses. However, after a detailed examination of the structural and implementation strengths and challenges of NeW-I, its effectiveness in enhancing mental health as well as feasibility and accessibility, the web-based therapeutic protocol can be adapted to deliver psychotherapy to diverse populations including young adults who are diagnosed with a life-limiting condition, siblings of terminally ill young persons, and caregivers of patients with dementia, to name a few.

Limitations and Conclusions

Presently, NeW-I can only be implemented with participants who speak, read, and write English. Singapore is a multicultural and multilinguistic nation [72], and future research should expand the delivery language of NeW-I and assess its acceptability and effectiveness among different linguistic and

ethnic groups in Singapore and globally. Despite this limitation, NeW-I could enhance participants' wellness by drawing attention away from their illness narrative and instead emphasize areas that research has demonstrated to be most meaningful at the end of life. Expected study outcomes can generate new knowledge to inform research and practice in pediatric palliative care and parental bereavement support locally and globally.

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Authors' Contributions

AH and OD conceived and designed the study, obtained funding, and drafted the paper. OD, GT, BT, and CL participated in designing the study and operationalizing procedures. GT also contributed to training and skills development. JC, RH, CY, and SG helped in study planning and study execution. All authors have made substantial contributions to the development and editing of the manuscript and have approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshots of the narrative e-writing intervention app.
[PDF File (Adobe PDF File), 318 KB - resprot_v9i7e17561_app1.pdf]

Multimedia Appendix 2
CONSORT‐EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 125 KB - resprot_v9i7e17561_app2.pdf]

References

1. Fraser LK, Miller M, Hain R, Norman P, Aldridge J, McKinney PA, et al. Rising national prevalence of life-limiting conditions in children in England. Pediatrics 2012 Apr;129(4):e923-e929. [doi: 10.1542/peds.2011-2846] [Medline: 22412035]
2. Herbert A. Faculty of Medicine: University of Queensland. 2017. Palliative Care for Children Often Involves Treating the Whole Family URL: https://medicine.uq.edu.au/article/2017/10/palliative-care-children-often-involves-treating-whole%C2%A0family [accessed 2020-04-24]
3. Committee on the Rights of the Child. REACH. 2017. Public Consultation on Singapore's 4th/5th Periodic Report on The UNCRC URL: https://www.reach.gov.sg/participate/public-consultation/ministry-of-social-and-family-development/rehabilitation-and-protection-group/public-consultation-on-singapores-periodic-report-on-the-uncrc [accessed 2020-04-28]
4. Chong PH, Chan MY, Yusri LI. Do children die? A retrospective review of deaths in a children's hospital. Singapore Med J 2012 Mar;53(3):192-195 [FREE Full text] [Medline: 22434294]
5. Cadell S, Kennedy K, Hemsworth D. Informing social work practice through research with parent caregivers of a child with a life-limiting illness. J Soc Work End Life Palliat Care 2012;8(4):356-381. [doi: 10.1080/15524256.2012.732021] [Medline: 23194170]
6. Doka K. Ethics, end-of-life decisions and grief. Mortality 2005 Feb;10(1):83-90. [doi: 10.1080/13576270500031105]
7. Bergstraesser E, Inglin S, Hornung R, Landolt MA. Dyadic coping of parents after the death of a child. Death Stud 2015;39(1-5):128-138. [doi: 10.1080/07481187.2014.920434] [Medline: 25204680]
8. Alam R, Barrera M, D'Agostino N, Nicholas DB, Schneiderman G. Bereavement experiences of mothers and fathers over time after the death of a child due to cancer. Death Stud 2012 Jan;36(1):1-22. [doi: 10.1080/07481187.2011.553312] [Medline: 24567992]
9. Jordan J, Price J, Prior L. Disorder and disconnection: parent experiences of liminality when caring for their dying child. Sociol Health Illn 2015 Jul;37(6):839-855. [doi: 10.1111/1467-9566.12235] [Medline: 26216375]
10. Meert KL, Eggly S, Pollack M, Anand KJ, Zimmerman J, Carcillo J, National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Parents' perspectives on physician-parent communication near the time of a child's death in the pediatric intensive care unit. Pediatr Crit Care Med 2008 Jan;9(1):2-7 [FREE Full text] [doi: 10.1097/01.PCC.0000298644.13882.88] [Medline: 18477906]

11. Dellve L, Samuelsson L, Tallborn A, Fasth A, Hallberg LR. Stress and well-being among parents of children with rare diseases: a prospective intervention study. J Adv Nurs 2006 Feb;53(4):392-402. [doi: 10.1111/j.1365-2648.2006.03736.x] [Medline: 16448482]
12. Dutta O, Tan-Ho G, Choo P, Ho A. Lived experience of a child's chronic illness and death: a qualitative systematic review of the parental bereavement trajectory. Death Stud 2019;43(9):547-561. [doi: 10.1080/07481187.2018.1503621] [Medline: 30285557]
13. Dutta O, Tan-Ho G, Choo PY, Low XC, Chong PH, Ng C, et al. Trauma to transformation: the lived experience of bereaved parents of children with chronic life-threatening illnesses in Singapore. BMC Palliat Care 2020 Apr 6;19(1):46 [FREE Full text] [doi: 10.1186/s12904-020-00555-8] [Medline: 32252753]
14. Ho AH, Dutta O, Tan-Ho G, Choo PY, Low XC, Chong PH, et al. Thematic analysis of spousal interaction patterns among Asian parents of children with chronic life-threatening illness. BMJ Open 2019 Nov 19;9(11):e032582 [FREE Full text] [doi: 10.1136/bmjopen-2019-032582] [Medline: 31748309]
15. Tan JS, Docherty SL, Barfield R, Brandon DH. Addressing parental bereavement support needs at the end of life for infants with complex chronic conditions. J Palliat Med 2012 May;15(5):579-584 [FREE Full text] [doi: 10.1089/jpm.2011.0357] [Medline: 22512806]
16. Rini A, Loriz L. Anticipatory mourning in parents with a child who dies while hospitalized. J Pediatr Nurs 2007 Aug;22(4):272-282. [doi: 10.1016/j.pedn.2006.08.008] [Medline: 17645955]
17. Al-Gamal E, Long T. Anticipatory grieving among parents living with a child with cancer. J Adv Nurs 2010 Sep;66(9):1980-1990. [doi: 10.1111/j.1365-2648.2010.05381.x] [Medline: 20626475]
18. Kreicbergs UC, Lannen P, Onelov E, Wolfe J. Parental grief after losing a child to cancer: impact of professional and social support on long-term outcomes. J Clin Oncol 2007 Aug 1;25(22):3307-3312. [doi: 10.1200/JCO.2006.10.0743] [Medline: 17664479]
19. Harvey S, Snowdon C, Elbourne D. Effectiveness of bereavement interventions in neonatal intensive care: a review of the evidence. Semin Fetal Neonatal Med 2008 Oct;13(5):341-356. [doi: 10.1016/j.siny.2008.03.011] [Medline: 18514602]
20. Contro N, Sourkes BM. Opportunities for quality improvement in bereavement care at a children's hospital: assessment of interdisciplinary staff perspectives. J Palliat Care 2012;28(1):28-35. [Medline: 22582469]
21. Murray JA, Terry DJ, Vance JC, Battistutta D, Connolly Y. Effects of a program of intervention on parental distress following infant death. Death Stud 2000 Jun;24(4):275-305. [doi: 10.1080/074811800200469] [Medline: 11010730]
22. Endo K, Yonemoto N, Yamada M. Interventions for bereaved parents following a child's death: a systematic review. Palliat Med 2015 Jul;29(7):590-604. [doi: 10.1177/0269216315576674] [Medline: 25805741]
23. William) WJ. Grief Counseling and Grief Therapy: A Handbook for the Mental Health Practitioner. London, UK: Routledge; 2003.
24. Ivancovich D. Trinity Western University. 2004. The Role of Existential Coping and Spiritual Coping in Anticipatory Grief URL: https://www.twu.ca/sites/default/files/ivancovichdebra.pdf [accessed 2020-04-23]
25. Chochinov H, Kristjanson L, Breitbart W, McClement S, Hack T, Hassard T, et al. Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial. Lancet Oncol 2011 Aug;12(8):753-762 [FREE Full text] [doi: 10.1016/S1470-2045(11)70153-X] [Medline: 21741309]
26. Neimeyer R, Keesee N. Dimensions of diversity in the reconstruction of meaning. In: Doka K, editor. Living With Grief: Who We Are How We Grieve. New York, USA: Routledge; 1998:223-227.
27. Stroebe M, Schut H. The dual process model of coping with bereavement: rationale and description. Death Stud 1999;23(3):197-224. [doi: 10.1080/074811899201046] [Medline: 10848151]
28. Gilbert K. 'We've had the same loss, why don't we have the same grief?' loss and differential grief in families. Death Stud 1996 May;20(3):269-283 [FREE Full text] [doi: 10.1080/07481189608252781]
29. Dysvik E, Natvig G, Furnes B. A narrative approach to explore grief experiences and treatment adherence in people with chronic pain after participation in a pain-management program: a 6-year follow-up study. Patient Prefer Adherence 2013 Aug;7:751-756. [doi: 10.2147/ppa.s46272] [Medline: 23990710]
30. Morris C, Simpson J, Sampson M, Beesley F. Emotion and self-cutting: narratives of service users referred to a personality disorder service. Clin Psychol Psychother 2015;22(2):125-132. [doi: 10.1002/cpp.1870] [Medline: 24115508]
31. Chochinov H, Hack T, Hassard T, Kristjanson L, McClement S, Harlos M. Dignity therapy: a novel psychotherapeutic intervention for patients near the end of life. J Clin Oncol 2005 Aug 20;23(24):5520-5525. [doi: 10.1200/JCO.2005.08.391] [Medline: 16110012]
32. McClement S, Chochinov HM, Hack T, Hassard T, Kristjanson LJ, Harlos M. Dignity therapy: family member perspectives. J Palliat Med 2007 Oct;10(5):1076-1082. [doi: 10.1089/jpm.2007.0002] [Medline: 17985964]
33. Ho AH, Car J, Ho MR, Tan-Ho G, Choo PY, Patinadan PV, et al. A novel family dignity intervention (FDI) for enhancing and informing holistic palliative care in Asia: study protocol for a randomized controlled trial. Trials 2017 Dec 4;18(1):587 [FREE Full text] [doi: 10.1186/s13063-017-2325-5] [Medline: 29202863]
34. Griffiths K, Christensen H. Review of randomised controlled trials of internet interventions for mental disorders and related conditions. Clin Psychol 2006;10(1):16-29. [doi: 10.1080/13284200500378696]

35. Newman MG, Szkodny LE, Llera SJ, Przeworski A. A review of technology-assisted self-help and minimal contact therapies for anxiety and depression: is human contact necessary for therapeutic efficacy? Clin Psychol Rev 2011 Feb;31(1):89-103. [doi: 10.1016/j.cpr.2010.09.008] [Medline: 21130939]
36. Barak A, Hen L, Boniel-Nissim M, Shapira N. A comprehensive review and a meta-analysis of the effectiveness of internet-based psychotherapeutic interventions. J Technol Hum Serv 2008 Jul 3;26(2-4):109-160 [FREE Full text] [doi: 10.1080/15228830802094429]
37. Gainsbury S, Blaszczynski A. A systematic review of internet-based therapy for the treatment of addictions. Clin Psychol Rev 2011 Apr;31(3):490-498. [doi: 10.1016/j.cpr.2010.11.007] [Medline: 21146272]
38. Kaltenthaler E, Parry G, Beverley C. Computerized cognitive behaviour therapy: a systematic review. Behav Cogn Psychother 2004 Feb 18;32(1):31-55. [doi: 10.1017/S135246580400102X]
39. Ploeg J, Ali MU, Markle-Reid M, Valaitis R, Bartholomew A, Fitzpatrick-Lewis D, et al. Caregiver-focused, web-based interventions: systematic review and meta-analysis (part 2). J Med Internet Res 2018 Oct 26;20(10):e11247 [FREE Full text] [doi: 10.2196/11247] [Medline: 30368439]
40. Sherifali D, Ali MU, Ploeg J, Markle-Reid M, Valaitis R, Bartholomew A, et al. Impact of internet-based interventions on caregiver mental health: systematic review and meta-analysis. J Med Internet Res 2018 Jul 3;20(7):e10668 [FREE Full text] [doi: 10.2196/10668] [Medline: 29970358]
41. Williams A, Duggleby W, Eby J, Cooper RD, Hallstrom LK, Holtslander L, et al. Hope against hope: exploring the hopes and challenges of rural female caregivers of persons with advanced cancer. BMC Palliat Care 2013 Dec 17;12(1):44 [FREE Full text] [doi: 10.1186/1472-684X-12-44] [Medline: 24341372]
42. Perle J, Langsam L, Nierenberg B. Controversy clarified: an updated review of clinical psychology and tele-health. Clin Psychol Rev 2011 Dec;31(8):1247-1258. [doi: 10.1016/j.cpr.2011.08.003] [Medline: 21963670]
43. Suler J. The online disinhibition effect. Cyberpsychol Behav 2004 Jun;7(3):321-326. [doi: 10.1089/1094931041291295] [Medline: 15257832]
44. Digital News Asia. 2017. Singapore Consumers Digitally Savvy; Demand Secure, Affordable, High-Quality Experiences URL: https://www.digitalnewsasia.com/digital-economy/singapore-consumers-digitally-savvy-demand-secure-affordable-high-quality [accessed 2020-04-23]
45. Moon EW, Tan NC, Allen JC, Jafar TH. The use of wireless, smartphone app-assisted home blood pressure monitoring among hypertensive patients in Singapore: pilot randomized controlled trial. JMIR Mhealth Uhealth 2019 May 28;7(5):e13153 [FREE Full text] [doi: 10.2196/13153] [Medline: 30905872]
46. Haldane V, Tan YG, Teo KW, Koh JJ, Srivastava A, Cheng RX, et al. Perspectives on acceptance and use of a mobile health intervention for the prevention of atherosclerotic cardiovascular disease in Singapore: mixed-methods study. JMIR Mhealth Uhealth 2019 Mar 14;7(3):e11108 [FREE Full text] [doi: 10.2196/11108] [Medline: 30869651]
47. Ho AH. University of Hong Kong. 2013. Living and Dying With Dignity: An Interpretive-systemic Framework in Hong Kong URL: https://hub.hku.hk/handle/10722/193427 [accessed 2020-04-28]
48. Campbell M, Fitzpatrick R, Haines A, Kinmonth A, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. Br Med J 2000 Sep 16;321(7262):694-696 [FREE Full text] [doi: 10.1136/bmj.321.7262.694] [Medline: 10987780]
49. Lakshman R, Griffin S, Hardeman W, Schiff A, Kinmonth A, Ong K. Using the medical research council framework for the development and evaluation of complex interventions in a theory-based infant feeding intervention to prevent childhood obesity: the baby milk intervention and trial. J Obes 2014;2014:646504 [FREE Full text] [doi: 10.1155/2014/646504] [Medline: 25143830]
50. Neimeyer R. Bereavement and the quest for meaning: rewriting stories of loss and grief. Hellenic J Psychol 2006;3:181-188 [FREE Full text]
51. Toyama H, Honda A. Using narrative approach for anticipatory grief among family caregivers at home. Glob Qual Nurs Res 2016;3:2333393616682549 [FREE Full text] [doi: 10.1177/2333393616682549] [Medline: 28462354]
52. Government of Singapore. Singapore Statutes Online. 2019. Children and Young Persons Act URL: https://sso.agc.gov.sg/Act/CYPA1993 [accessed 2020-04-24]
53. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
54. Andrews G, Slade T. Interpreting scores on the Kessler psychological distress scale (K10). Aust N Z J Public Health 2001 Dec;25(6):494-497. [doi: 10.1111/j.1467-842x.2001.tb00310.x] [Medline: 11824981]
55. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 2016 Jun;25(3):1057-1073 [FREE Full text] [doi: 10.1177/0962280215588241] [Medline: 26092476]
56. Cuijpers P, van Straten A, Bohlmeijer E, Hollon SD, Andersson G. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. Psychol Med 2010 Feb;40(2):211-223. [doi: 10.1017/S0033291709006114] [Medline: 19490745]
57. Frattaroli J. Experimental disclosure and its moderators: a meta-analysis. Psychol Bull 2006 Nov;132(6):823-865. [doi: 10.1037/0033-2909.132.6.823] [Medline: 17073523]

58. Siebens HC, Tsukerman D, Adkins RH, Kahan J, Kemp B. Correlates of a single-item quality-of-life measure in people aging with disabilities. Am J Phys Med Rehabil 2015 Dec;94(12):1065-1074 [FREE Full text] [doi: 10.1097/PHM.0000000000000298] [Medline: 25888654]
59. Bredle J, Salsman J, Debb S, Arnold B, Cella D. Spiritual well-being as a component of health-related quality of life: the functional assessment of chronic illness therapy—spiritual well-being scale (FACIT-Sp). Religions 2011;2(1):77-94 [FREE Full text] [doi: 10.3390/rel2010077]
60. Herth K. Abbreviated instrument to measure hope: development and psychometric evaluation. J Adv Nurs 1992 Oct;17(10):1251-1259. [doi: 10.1111/j.1365-2648.1992.tb01843.x] [Medline: 1430629]
61. Graessel E, Berth H, Lichte T, Grau H. Subjective caregiver burden: validity of the 10-item short version of the burden scale for family caregivers BSFC-s. BMC Geriatr 2014 Feb 20;14:23 [FREE Full text] [doi: 10.1186/1471-2318-14-23] [Medline: 24555474]
62. Hogan N, Schmidt L. Testing the grief to personal growth model using structural equation modeling. Death Stud 2002 Oct;26(8):615-634. [doi: 10.1080/07481180290088338] [Medline: 12243195]
63. Shear K, Jackson C, Essock S, Donahue S, Felton C. Screening for complicated grief among project liberty service recipients 18 months after September 11, 2001. Psych Serv 2006;57(9):1291-1297 [FREE Full text] [doi: 10.1037/t62516-000]
64. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010 Mar 24;8:18 [FREE Full text] [doi: 10.1186/1741-7015-8-18] [Medline: 20334633]
65. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the content of statistical analysis plans in clinical trials. J Am Med Assoc 2017 Dec 19;318(23):2337-2343. [doi: 10.1001/jama.2017.18556] [Medline: 29260229]
66. Rabe-Hesketh S, Skrondal A. Multilevel and Longitudinal Modeling Using Stata. Texas, USA: Stata Press; 2012.
67. Johnson D, Young R. Toward best practices in analyzing datasets with missing data: comparisons and recommendations. J Marriage Fam Couns Internet 2019;73(5):926-945. [doi: 10.1111/j.1741-3737.2011.00861.x]
68. Rubin D. Multiple Imputation for Nonresponse in Surveys. New York, USA: John Wiley & Sons; 1987.
69. Groenewald T. A phenomenological research design illustrated. Int J Qual Methods 2016 Nov 29;3(1):42-55 [FREE Full text] [doi: 10.1177/160940690400300104]
70. Yelvington D. Capella University. 2013. Parents' Perceptions About Their Participation in an Equine Assisted Grief-Group Experience URL: https://search.proquest.com/docview/1491162909 [accessed 2020-04-28]
71. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, Christensen H. Economic evaluations of internet interventions for mental health: a systematic review. Psychol Med 2015 Dec;45(16):3357-3376. [doi: 10.1017/S0033291715001427] [Medline: 26235445]
72. Singapore Department of Statistics (DOS). 2017. Population Trends URL: https://www.singstat.gov.sg/-/media/files/publications/population/population2017.pdf [accessed 2020-04-24]

Abbreviations

BGQ: brief grief questionnaire
BSFC-s: Burden Scale for Family Caregivers-Short
FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy - Spiritual Well-Being scale
HHI: Herth hope index
ISS: inventory of social support
K-10: Kessler psychological distress scale
KQOL: Kemp quality of life scale
NeW-I: Narrative e-Writing Intervention
PHQ-9: Patient Health Questionnaire – 9

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Protocol

Yoga and Aerobic Dance for Pain Management in Juvenile Idiopathic Arthritis: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is one of the most common types of arthritis among children. According to JIA guidelines for physical activity (PA), structured PA interventions led to improved health outcomes. However, many PA programs, such as yoga and aerobic dance, have not been studied in this population despite being popular among youth. Web-based PA programs could provide patients with accessible and affordable interventions.

Objective: The primary aims of the proposed pilot randomized controlled trial (RCT) are to examine (1) the feasibility of conducting a full-scale RCT to evaluate the effectiveness of two popular types of PA: a yoga training program and an aerobic dance training program, in female adolescents (aged 13-18 years) with JIA compared with an electronic pamphlet control group; and (2) the acceptability of these interventions.

Methods: A three-arm prospective randomized open-label study with a parallel group design will be used. A total of 25 female adolescents with JIA who have pain will be randomized in a ratio of 2:2:1 to one of the 3 groups: (1) online yoga training program (group A: n=10); (2) online aerobic dance training program (group B: n=10); and (3) electronic pamphlet control group (group C: n=5). Participants in groups A and B will complete 3 individual 1-hour sessions per week using online exercise videos, as well as a 1-hour virtual group session per week using a videoconferencing platform for 12 weeks. Participants from all groups will have access to an electronic educational pamphlet on PA for arthritis developed by the Arthritis Society. All participants will also take part in weekly online consultations with a research coordinator and discussions on Facebook with participants from their own group. Feasibility (ie, recruitment rate, self-reported adherence to the interventions, dropout rates, and percentage of missing data), acceptability, and usability of Facebook and the videoconferencing platform will be assessed at the end of the program.

Pain intensity, participation in general PA, morning stiffness, functional status, fatigue, self-efficacy, patient global assessment, disease activity, and adverse events will be assessed using self-administered electronic surveys at baseline and then weekly until the end of the 12-week program.

Results: This pilot RCT has been funded by the Arthritis Health Professions Association. This protocol was approved by the Children's Hospital of Eastern Ontario Research Ethics Board (#17/08X). As of May 11, 2020, recruitment and data collection have not started.

Conclusions: To our knowledge, this is the first study to evaluate the effectiveness of yoga and aerobic dance as pain management interventions for female adolescents with JIA. The use of online programs to disseminate these 2 PA interventions may facilitate access to alternative methods of pain management. This study can lead to a full-scale RCT.

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KEYWORDS

juvenile idiopathic arthritis; yoga; aerobic exercise; dance; pain management; pilot

Introduction

Juvenile Idiopathic Arthritis and Physical Activity

Juvenile idiopathic arthritis (JIA) is one of the most common types of arthritis among children [1-3]. Symptoms, which include joint pain, stiffness, swelling, and fatigue [4-6], can significantly affect most children's health-related quality of life (HRQOL). Although adolescents in the general population spend on average 57% of their time engaging in sedentary behavior after school [7], youths with JIA tend to be less active than their healthy peers and meet the national recommendations for physical activity (PA) less often [8]. Physical inactivity associated with JIA may lead to poor bone mineral density, increased fatigue, decreased muscle strength, reduced cardiorespiratory fitness capacity, reduced endurance, loss of functional independence, and diminished quality of life [9-13]. Prolonged physical inactivity may increase the risk of coronary heart disease, diabetes, hypertension, and obesity in adolescents with JIA [14,15]. It is important to help ensure that these symptoms are managed and to promote PA to reduce these long-term consequences [16]. According to recent guidelines for PA in JIA based on a systematic review of the literature [16], structured PA interventions compared with a control were, in general, effective in the self-management of JIA for numerous health outcomes, such as a reduced number of active joints [17,18], diminished pain intensity [19], increased joint range of motion [18,19], increased muscle strength [20,21], improved functional status [19,22], and enhanced quality of life [19,22].

Yoga and Aerobic Dance

Many specific PA programs, such as yoga and aerobic dance, have not yet been studied in this population [16] despite being recommended by several rheumatology organizations such as the Arthritis Foundation and being popular among youths, especially females [23,24]. The fact that yoga and aerobic dance appeal to female adolescents may encourage them to adopt and adhere to these programs longer [23-25].

Yoga has been found to be beneficial for adults of both sexes with rheumatoid arthritis (RA) in reducing pain, pain disability, and swollen and tender joints, increasing functional status and enhancing quality of life, general health, and vitality as well as self-efficacy regarding pain [26-29]. Although no randomized controlled trial (RCT) has demonstrated the effectiveness of yoga in the management of JIA, a single-case design study found yoga (practiced by following a DVD) to be safe and feasible for 2 female adolescents with JIA [25].

There are currently no RCTs on the effectiveness of structured aerobic dance programs for the management of JIA, although it was found that a Zumba program improved the quality of life (P<.001) and aerobic cardiovascular capacity (P<.001) of female college students aged between 19 and 23 years from the general population [30]. Other studies showed that a dance intervention improved self-rated health and reduced emotional distress among adolescent girls with internalizing problems (eg, depressed mood, low self-worth) [24,31].

Disseminating Physical Activity Through Information and Communication Technologies

Although PA interventions may be effective, there is a need to disseminate them to patients in a feasible and cost-effective way. A recent systematic review [32] revealed that information and communication technologies (ICTs) such as a Facebook offer for an exciting dissemination strategy by providing users continuous self-monitoring and self-management as well as real time feedback and information exchange [33-36]. ICTs are particularly appealing to young people as they enhance accessibility and acceptability [34,37-39]. Although ICTs have been successfully used to engage the youth, change behaviors, and provide support and education [32,39-42], few RCTs have used them to deliver information on health-related interventions [43-47]. One study successfully delivered videos of effective PA interventions to adults with arthritis via Facebook [48]. Facebook is one of the most popular and frequently used social media platforms among adolescents [34,38,39,41,49,50]. It has many features that can collect data on content popularity and audience response [51,52]. However, a similar RCT has not been conducted in JIA. Given the high prevalence of JIA among females (ie, 2-4 times more than males) [2,53,54], there is a need to disseminate potentially effective PA activities such as yoga and aerobic dance to this population in an accessible and affordable manner.

Objectives

The primary objectives of the proposed single-blind three-arm pilot RCT with a parallel group will be to examine (1) the feasibility of a 12-week full-effectiveness trial of two popular types of PA and an electronic pamphlet control group: group A: an online yoga training program and a PA electronic educational pamphlet; group B: an online aerobic dance training program and a PA electronic educational pamphlet; group C: an electronic pamphlet control group (PA electronic educational pamphlet) postintervention; and (2) the acceptability of the yoga and aerobic dance PA interventions. The secondary objective of this pilot RCT will be to examine the initial effectiveness of a yoga training program (group A) and an aerobic dance training program (group B) on pain intensity, participation in PA, morning stiffness, functional status, self-efficacy, fatigue, patient global assessment, disease activity, and adverse events in female adolescents (aged 13 to 18 years) with JIA compared with an electronic pamphlet control group (group C) postintervention.

Methods

The following methodology is in full agreement with the Standard Protocol Items for Randomized Trials recommendations for RCTs [55-57] to ensure methodological rigor.

Study Design

This study will use a three-arm prospective randomized open-label study. Participants will be randomized to one of the 3 following groups in a ratio of 2:2:1: group A: an online yoga training program (and a PA electronic educational pamphlet; n=10); group B: an online aerobic dance training program (and a PA electronic educational pamphlet; n=10); and group C: an electronic pamphlet control group (PA electronic educational pamphlet; n=5). The total intervention period will be of 12 consecutive weeks. The frequency and duration of the interventions are based on other trials of yoga and PA interventions in pediatric and adult rheumatology [18,20,22,26,58]. As this pilot RCT involves physical interventions (ie, yoga and aerobic dance training programs), the participants and the research coordinator administering the program will not be blinded. However, the use of anonymous online self-reported questionnaires administered at baseline and postintervention will reduce potential detection bias. With training and standard operating procedures in place, it is anticipated that any performance bias due to not blinding will be minimized.

Study Population

Participants will be included in the study based on the following criteria: (1) female adolescents aged between 13 and 18 years; (2) diagnosis of JIA by a rheumatologist according to the International League of Associations for Rheumatology (ILAR) criteria; (3) absence of serious comorbidities or chronic diseases or of chronic pain that is unrelated to JIA (eg, cancer, fibromyalgia), which may impact the ability to understand and use the exercise program or complete outcome assessments (as determined by the treating rheumatologist); (4) presence of arthritis-related pain during regular activities of at least 30 on a 100-mm visual analog scale (VAS) in the past month; (5) JIA-specific medication regimen not expected to change during the study period; (6) self-reported as not meeting Health Canada's and American College of Sports Medicine's guidelines for PA (<60 minutes of moderate-to-vigorous PA per day) and not using physical interventions/treatments other than medication prescribed for JIA pain relief or over-the-counter medication; (7) capable of using and accessing the internet weekly for the study duration; (8) no contraindications to exercise (according to the treating rheumatologist); and (9) ability to understand English. Participants will be excluded from the study if they do not meet the inclusion criteria.

Interventions

Group A

Participants assigned to this group will be invited to complete a yoga training program. The yoga training program, an evidence-based educational program, is a structured low-intensity Vishwas Raj [26]. This yoga program consists of stretching, strengthening, meditation, and deep breathing and has been shown to be acceptable and effective among adults with RA. Participants will be asked to complete 3 individual 1-hour sessions per week for 12 consecutive weeks by watching a previously filmed session led by a qualified yoga instructor and posted on Facebook. They will also take part in a 1-hour virtual group session per week using a video-conferencing platform. Participants will also participate in weekly online consultations with a research coordinator and discussions on Facebook with other participants in group A. Finally, participants will receive an electronic pamphlet on physical exercise developed by the Arthritis Society. The electronic pamphlet, which groups B and C will also receive, explains how PA can help manage arthritis. It includes valuable tips and a detailed list of the various types of PA and exercises.

Group B

Participants assigned to this group will receive the electronic pamphlet on physical exercise and will be invited to complete an aerobic dance program. The aerobic dance program is a low-to-moderate intensity–level program and will also use a video. The video, adapted for youths with JIA, was developed with feedback from a JIA patient with experience in aerobic dance and a physiotherapist with experience in pediatric rheumatology. The aerobic dance program will have the same characteristics in terms of frequency, total number of sessions, and total duration as the yoga program (ie, three 1-hour individual sessions and one 1-hour virtual group session per week for 12 weeks). Participants will also participate in weekly online consultations with a research coordinator and discussions on Facebook with other participants in group B.

Group C

Participants assigned to this group will receive the electronic pamphlet on physical exercise and will participate in weekly online consultations with a research coordinator to discuss their use of all types of PA in the past, the electronic pamphlet on PA, and their future use of PA. They will also participate in discussions on Facebook with other participants in group C. After the completion of the study, the yoga and aerobic dance

training videos will be available to all participants, including those in the control group. In recruitment documents, this group will be termed the electronic pamphlet group.

Outcomes

The feasibility of a full trial will be monitored throughout the study (eg, randomization, recruitment and retention of participants, data collection, and self-reported adherence). The acceptability of the interventions will be assessed using online questionnaires at the end of the study.

Clinical outcomes will be evaluated at baseline, weekly, and postintervention (at 12 weeks) through the use of online questionnaires in REDCap (Vanderbilt University). At baseline, pain intensity, functional status, fatigue, and self-efficacy will be assessed. Pain intensity and fatigue will be monitored weekly. Finally, all of these outcomes as well as the patient's global assessment will be assessed postintervention. Outcomes were selected based on a JIA core set of outcomes to assess in trials [59]. Outcomes that were found to be essential include pain, functional status, patients' overall well-being (global assessment), joint inflammation signs, and adverse events [59]. Other outcomes that were found to be important but not essential include fatigue, joint stiffness, and PA [59]. Other outcomes need more research to be endorsed, such as coping with the illness, which is related to self-efficacy [59].

Recruitment

The recruitment of a convenience sample of 25 participants (in a ratio of 2:2:1) will be performed at the Children's Hospital of Eastern Ontario (CHEO) Pediatric Rheumatology Clinic. Rheumatologists at the CHEO Rheumatology Clinic will be provided with the inclusion and exclusion criteria for the study. During regular scheduled visits, treating rheumatologists will identify and direct eligible participants with JIA (and their parents) to the research coordinator who will explain the study in detail. Eligible participants will be invited to complete a screening questionnaire to ensure that they meet the study selection criteria before central randomization. If eligible, participants will be asked to sign either a consent form if they are able to consent or an assent form and their parent/guardian will be asked to sign a consent form. They will also complete a questionnaire that will gather sociodemographic and medical information as well as a validated questionnaire on participation in PA. They will also be asked about their preference in terms of PA.

Participant Allocation

Once informed consent is obtained, participants will be randomly assigned to one of the 3 groups using the central randomization scheme [60] and based on a sequence of computer-generated random numbers using a blocking factor (randomly varying between 6 and 9). The central stratified randomization process will be based on age (between 13 and 15 years and between 16 and 18 years).

Before running the randomization program, the data manager will document the participant's initials (first and last names) and date of birth (month and year). After running the program, the data manager will prepare sealed opaque envelopes with the group allocation and study ID number for each patient and will provide it to the research coordinator. Participants will open the sealed opaque envelope containing their group assignment and a confidential link to access their Facebook group page where further instructions can be found. The research coordinator will explain the procedures related to the group assigned and will ask participants to indicate their availability for an initial individual online consultation as well as for virtual group sessions. Participants will be asked not to change their usual level of PA during the study except for following the program to which they were assigned.

At the clinic, participants will complete a questionnaire that will gather the following information:

- Sociodemographic information: partial date of birth (month/year), age, gender, ability to understand English, and ability to use and access the internet weekly for the study duration.
- Medical information: diagnosis, partial date of diagnosis (month/year), disease duration, presence of serious chronic diseases (eg, cancer or other illnesses) or cognitive impairments, presence of contraindications to exercise (as determined by the treating rheumatologist), current use of JIA-specific medication, anticipated change in JIA-specific medication in the next 12 weeks, and use of physical interventions/treatments other than the prescribed medication for JIA pain relief and pain level when performing regular activities. A chart review will help verify this information.
- PA information: the amount of PA performed weekly using a validated exercise log [61] and preferences in terms of PA (eg, yoga, Zumba, or other types).

At baseline, all the participants will be asked to do the following:

1. Create a new Facebook account: All participants will be asked to create an account specifically for the study and select a username that is meaningful to them but does not contain their first or last name, allowing them to remain anonymous.
2. Access the group Facebook page: All participants will be invited to access the link to their group Facebook page, which they will be provided during their group assignment. Participants will be invited to follow the REDCap link provided on the Facebook page and answer baseline questionnaires about their participation in PA, pain, morning stiffness, functional status, fatigue, self-efficacy, and patient global assessment. This will take about 20 to 30 min to complete. The Facebook page will also contain the electronic pamphlet on PA (for all groups), the exercise videos (for groups A and B), and other information.

Following these steps, participants will be asked to complete the training program:

Groups A and B:

- Participants will be invited via Facebook and email to attend an individual online consultation with the research coordinator using a videoconferencing platform. During this consultation, participants can ask questions related to their group assignment, voice their concerns, and establish

a plan of action. For the remainder of the study duration, participants will be encouraged to attend, when possible, individual 10-minute online consultations weekly. During these consultations, participants can provide their feedback and discuss their use of the PA program as well as facilitators and barriers to participating. Private meetings are less difficult to schedule than group meetings and provide greater privacy. They may also be more motivating and less intimidating for participants who may feel their voice really matters and has an impact.

- For the study duration, participants will be asked to complete 3 individual exercise sessions as well as 1 virtual group session each week. The links to the videos will be posted on Facebook and sent by email for participants to use for their individual exercise sessions. For group sessions, the videoconferencing platform link will be posted on Facebook and sent to participants via email. Virtual group sessions will help ensure that they perform the exercises that they observe in the video safely and that they do not hurt themselves. They will also be able to see other participants and be seen if they wish, which will be a motivating factor to perform the PA. A schedule of virtual group sessions offered in the morning or afternoon will be posted on the Facebook group page or sent by email.
- Participants will be asked to record their PA using a validated exercise log [61] as well as their pain intensity and fatigue by completing a brief online questionnaire that regroups valid instruments on a weekly basis. They will be reminded to do so via Facebook, email, and during their online consultations.

Group C: Participants will be invited via Facebook and email to attend an individual online consultation with the research coordinator using a video-conferencing platform. During this consultation, participants can ask questions related to their group assignment, voice their concerns, and discuss PA in general and their plan for PA in the future. They will also be invited to consult the electronic pamphlet on PA each week. For the remainder of the study duration, participants will be encouraged to attend, when possible, individual weekly 10-min online consultations. During these consultations, participants can discuss their use of PA, as well as facilitators and barriers to participating in PA. Participants will be asked to record their PA using a validated exercise log [61] as well as their pain intensity and fatigue by completing a brief electronic questionnaire that regroups valid instruments on a weekly basis.

Throughout the study, the Facebook pages will provide a means of communication for participants who will be able to share their experiences, post comments on the videos, and ask questions of each other and the research coordinator. Access to Facebook group pages will be restricted to study participants. Adolescents who cannot or do not want (or are not granted parental permission) to access Facebook will be given a link to the CHEO webpage that will contain information related to the study and their group. However, they will not be able to interact (ie, leave comments or questions) using this platform.

At 6 and 12 weeks, all participants will be asked to complete online questionnaires about the program that they were allocated to as well as the acceptability of Facebook to deliver PA programs. They will also be asked if they used any other PA during the study. They will also complete online questionnaires assessing their pain intensity, functional status, fatigue, self-efficacy, and well-being (using a patient global assessment). This will take about 20 to 30 minutes to complete.

As a compensation for the time given by participants, they will receive a US $21.40 gift certificate for completing baseline questionnaires and a US $21.40 gift certificate for completing postintervention questionnaires. They will also receive a personalized certificate of participation (community hours for school).

Outcome Measures

The electronic questionnaires will be made accessible to all participants on each group's Facebook page with a URL link or on the CHEO webpage for those who do not wish to create a Facebook account. Participants in groups A, B, and C will be emailed the same URL link to access the questionnaires. Using the *wall* on the Facebook page for all groups, or the CHEO webpage, the research team will provide updates and reminders to all participants regarding deadlines to complete the questionnaires.

The following outcome measures will be used to answer the primary objective:

1. Feasibility will be assessed by the recruitment rate, the randomization process, and self-reported adherence and measured using a questionnaire, as well as protocol deviations, dropout rates, and percentage of missing data in the questionnaires.
    - Recruitment rate: The number of participants recruited in the trial and the time used for recruitment will be documented in a feasibility form. The number of participants will be divided by the duration of recruitment. This will be measured on a continuous basis for up to 12 weeks.
    - Randomization process: The ease at which the randomization process is conducted will be described by researchers in a feasibility form. This will be measured on a continuous basis for up to 12 weeks.
    - Number of protocol deviations: The number of protocol deviations, the time at which they occur, the group in which they occur, and the potential reasons for these will be documented in a feasibility form. Participants will be asked why they deviated from the protocol by researchers using a feasibility form. This will be measured on a continuous basis for up to 12 weeks.
    - Dropout rates: The number of participants who dropped out of the trial, the time at which they dropped out, the group in which they belonged, and the reasons for these will be documented in a feasibility form. Participants will be asked why they dropped out by researchers. The number of dropouts in each group will be divided by the duration of the trial. This will be measured on a continuous basis for up to 12 weeks.
    - Percentage of missing data in the questionnaires: The percentage of missing data in the questionnaires, the time at which they occur, and potential reasons for these will be documented in a feasibility form. This

will be measured on a continuous basis for up to 12 weeks.

- Self-reported adherence: Self-reported adherence to the training programs will be assessed by monitoring the number and length of sessions and dividing the time spent performing the program by the duration of prescribed sessions of either yoga or aerobic dance. Self-reported adherence will be recorded weekly using an adapted online version of the validated 7-day PA Report calendar (in minutes) [62]. This will be measured each week for up to 12 weeks.

2. The acceptability of the yoga or aerobic dance interventions will be assessed using a questionnaire-administered postintervention. Questions will explore the acceptability of online consultations, virtual group sessions, PA videos (either yoga or aerobic dance programs), electronic pamphlet, and training programs (content and duration of the yoga and aerobic dance programs), as well as facilitators and barriers to participating. This questionnaire will be administered at 6 and 12 weeks.
3. The usability of Facebook will be assessed by the System Usability Scale (SUS) [63,64]. The SUS is composed of 10 items using a 5-point scoring system ranging from Strongly Disagree (a score of 1 out of 5 for each question) to Strongly Agree (a score of 5 out of 5 for each question). The total score ranges from 5 (low usability) to 50 (high usability). The usability will be measured at 6 and 12 weeks.
4. The usability of the videoconferencing platform will be assessed by the SUS [63,64]. The SUS is composed of 10 items using a 5-point scoring system ranging from Strongly Disagree (a score of 1 out of 5 for each question) to Strongly Agree (a score of 5 out of 5 for each question). The total score ranges from 5 (low usability) to 50 (high usability). The usability will be measured at 6 and 12 weeks.
5. The use of Facebook will be assessed by the number of posts, live online discussions, and views of the videos. The use will be measured at 6 and 12 weeks.

The following outcome measures will be used to answer the secondary objective:

1. *Pain intensity* will be assessed using the electronic Childhood Health Assessment Questionnaire (CHAQ) 100-mm pain VAS subscale [65]. It uses a scoring system where 0 mm represents no pain and 100 mm represents very severe pain the past week. This measure has already been validated in the JIA population [65,66]. Pain intensity will be measured at baseline, 6 weeks, and 12 weeks.
2. *Participation in PA (level of PA)* will be assessed by using the electronic Physical Activity Questionnaire for adolescents (PAQ-A) aged 14 to 18 years, a 7-day recall instrument measuring the level of PA within the last 7 days [67-69]. The PAQ-A is composed of 8 items using a 5-point scoring system. The total score is calculated by taking the mean score out of 5, with 1 indicating low PA and 5 indicating high PA. The PAQ-A has been reported to be a valid and reliable measure of general PA levels in youths and adolescents [67-69]. Participation in PA will be measured at baseline, 6 weeks, and 12 weeks.
3. *Participation in PA (duration and intensity)* will be assessed by using an exercise log, based on the 7-day PA Recall calendar [62], which will be used weekly. The PA level will be reported in terms of minutes and intensity levels (3 subscales: moderate, hard, and very hard intensity; subscale total scores in minutes) and will be transformed into the metabolic equivalent of tasks, which are units of the basal metabolic rate and express the energy cost of PA. Participation in PA will be measured at baseline, 6 weeks, and 12 weeks.
4. *Morning stiffness* will be assessed by using electronic self-reported questions asking about the presence (Yes/No) and duration of morning stiffness in minutes. It will be measured at baseline, 6 weeks, and 12 weeks.
5. *Functional status* will be assessed using the electronic CHAQ. The CHAQ contains 8 domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities), and items are scored using a 4-point Likert scale of 0 to 3, where 0 represents the ability to perform the activity with no difficulty, 1 represents the ability to perform with some difficulty, 2 represents the ability to perform with much difficulty, and 3 represents the inability to perform over the past week. The mean of the 8 scores will determine the total CHAQ score ranging from 0 to 3, with a lower score indicating higher functional status and a higher score indicating lower functional status. It is the most widely used functional health status measure in JIA, which is a reliable and valid tool for the functional, physical, and psychosocial assessment of children with JIA [65]. It will be measured at baseline, 6 weeks, and 12 weeks.
6. *Fatigue* will be assessed by using an electronic version of a subset of the Patient-Reported Outcomes Measurement Information System Pediatric Short Form version 1.0—Fatigue 10a [70], which measures fatigue and its impact, scored from 1 to 5, where 1 represents never tired and 5 represents almost always tired in the past week. It will be measured at baseline, 6 weeks, and 12 weeks.
7. *Self-efficacy* will be assessed by using the Children's Arthritis Self-Efficacy Scale (CASE), a specific, valid and reliable tool for JIA [71]. CASE is an 11-item self-report scale that is divided into 3 concepts: activity, symptom, and emotion. A 5-point Likert scale is used to rate responses for each item, where 1 represents not at all sure and 5 represents very sure based on the confidence of the child to manage disease effects. It will be measured at baseline, 6 weeks, and 12 weeks.
8. *Patient Global Assessment* will be assessed by using an item used in the Juvenile Arthritis Quality of Life Questionnaire (JAQQ). JAQQ was designed to assess HRQOL in children aged 2 to 18 years JIA or juvenile spondylarthritides [72-75]. JAQQ includes 4 subscales (gross motor function, fine motor function, psychosocial function, and systemic symptoms) as well as a pain and patient global assessment. The patient global assessment asks how youths have been since the last assessment (prior week) on a 5-point Likert scale, scored from 1 to 5, where 1 represents much better and 5 represents much worse. It will be measured at 6 weeks and 12 weeks.

9. *Disease activity* will be assessed by using the active joint count, the number of joints with active disease according to the rheumatologist [1].
10. Adverse events will be reported by participants in answers to open questions.

Data Analysis

Descriptive statistics, such as proportions, means, and standard deviations, will be used to summarize the baseline and end-of-study variables across the 3 study groups (groups A, B, and C) and to assess the distributional assumptions of the statistical techniques used. For the primary objective, data on recruitment rate, randomization process, interventions, clinical and ICT outcome measures, dropout rates, and adherence rates for the interventions will be collected. For the secondary objective, a repeated measures analysis of variance with the fixed-factor study group (A, B, or C) and the within-factor assessment time (0, 6, and 12 weeks) will be conducted to compare groups for the clinical outcome measures at 0, 6, and 12 weeks. An intention-to-treat analysis will be conducted and mixed model repeated measures will be considered to accommodate missing data.

Sample Size Calculation for Future Full-Scale RCT

The current sample size is adequate for pilot studies involving group comparisons to assess feasibility and to estimate the variance to determine the sample size for a definitive trial [76].

Results

This pilot RCT has been funded by the Arthritis Health Professions Association (AHPA). This protocol was approved by the CHEO Research Ethics Board (#17/08X). As of May 11, 2020, recruitment and data collection have not yet started.

Discussion

Strengths

This multidisciplinary and multidimensional rehabilitation study is a rigorous, accessible, single-blind, three-arm pilot RCT using the prospective randomized open blinded endpoint design. It involves web-based, innovative, accessible self-management programs for adolescents with JIA similar to those used in previous studies [41,77,78]. The first strength of this study design is that it will include PA activities that are recommended by several rheumatology organizations and may meet adolescent females' activity preferences. To our knowledge, this is the first study to assess the effectiveness of aerobic dance and yoga on pain management in female adolescents with JIA. It also aims to reduce daily pain intensity and fatigue severity and improve the functional status, self-efficacy, and PA adherence among female adolescents with JIA. The second major strength of this study is that it will use ICTs to deliver these activities and information to youths. The rapid increase in eHealth will appeal to young participants who are already consulting online resources for self-management [79]. This design will be able to overcome time, geographical, and financial constraints. Furthermore, online questionnaires will increase the accessibility and confidentiality of collected outcome measures.

The involvement of a research coordinator, who will be mentored by a team of rehabilitation specialists, is a strength of the study. Rehabilitation specialists play an essential role in supporting community-based self-management programs targeting youths living with chronic conditions, such as JIA [16].

Separate Facebook group pages and individual online consultations using a video-conferencing platform minimized the potential risk of contamination between comparison study groups. Central randomization is ideal for minimizing the potential risk of biases. This proposed pilot RCT is necessary to address the questions of clinical and scientific importance for rehabilitation specialists in improving the health of female adolescents with JIA through the use of PA-based interventions.

Challenges (or Weaknesses)

The blinding of participants is impossible in this type of study, as is generally the case with physical rehabilitation RCTs [80].

There is an increased risk of Type 1 error, rejecting the null hypothesis when it is actually true, due to the presence of multiple outcomes (ie, multicollinearity). The results of this study will likely only be generalizable to female adolescents (ie, those aged 13 to 18 years) with JIA who consult at a pediatric rheumatology clinic in a tertiary care center.

Due to financial limitations, we will use low-cost, accessible ICTs. Although a virtual gym with a live PA instructor would be ideal, participants will have access to recorded sessions led by PA instructors and approved by rehabilitation specialists in rheumatology and will receive support from a research coordinator trained in PA at least once a week.

Hospital-based recruitment may attract more severe cases of JIA. However, central randomization will be implemented as it is ideal to minimize the potential risk of biases.

This study will examine the effectiveness of yoga among female adolescents with JIA, as outcomes will be assessed at 12 weeks.

Population

To minimize the potential misclassification bias, rheumatologists involved in this project will ensure that each participant enrolled in this pilot RCT has a diagnosis of JIA, using ILAR criteria [81].

Although participants cannot be blinded to the group assignment given the nature of the intervention, the investigator who will analyze the data will be blinded.

Intervention

Aerobic dance [30] and yoga exercise programs [26-28,58] are promising for managing JIA pain in young women because they are popular among female adolescents [23-25,30]. These programs will be accessible and inexpensive through Facebook and YouTube [51,79,82].

Comparator

The use of an electronic pamphlet control group is acceptable as they will have access to Facebook and will have online consultations on PA. Furthermore, participants will receive the

same yoga or aerobic dance exercise videos that were offered to the intervention groups after study completion.

Outcomes

Assessments will include a range of clinical outcome measures validated in JIA. Although pain and other outcomes are self-reported, they represent important unwanted symptoms that have functional consequences that affect the activities of daily living of youths with JIA. Furthermore, objective measures of these symptoms are difficult to obtain. However, it is important to be mindful that self-reported measures may lead to reporting bias.

There is also the potential to include further measurements such as PA level (using a questionnaire or an accelerometer) and aerobic exercise testing (ie, assessment of submaximal oxygen consumption: PWC_{170}, physical working capacity at a heart rate of 170 beats per min) to determine potential differences between treatment arms in the full-scale RCT.

Time

The study duration will be 12 consecutive weeks. The frequency and duration of the intervention is based on other trials of yoga and PA interventions in pediatric and adult rheumatology. This length is sufficient to see improvements among adolescents.

Providing participants with weekly online consultations with the research coordinator and providing them with 1 virtual group session each week will help ensure that the participants perform the exercises properly and may also potentially facilitate adherence.

If the proposed PA interventions are effective, we will produce videos to enrich the People Getting a Grip program, an online educational program comprising informational videos and practical videos that provide information on various PA programs for arthritis. These videos will also be freely available on the Arthritis Society webpage and could eventually be used for the full-scale RCT.

Conclusions

This pilot RCT has substantial potential to enhance our understanding of the potential effectiveness of popular PA interventions disseminated to patients with JIA using ICTs, making it a novel study. This will help understand which PA intervention has the most potential for improved outcomes. It will also help determine whether these PAs and ICTs are acceptable to youths with JIA and whether a larger trial would be feasible. The proposed pilot RCT will contribute to the knowledge of the effect of a specific functional activity on self-reported pain relief, functional status, and self-efficacy as well as PA adherence, daily pain, and fatigue intensity.

This study could also set the standard for community-based care for female adolescents with JIA. Moreover, other rehabilitation or functional interventions could be examined for youths with other chronic diseases**.**

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Authors' Contributions

KA, GW, JS, CD, SC, TH, PL, and LB conceptualized the intervention. All authors read and made comments on the previous drafts of the manuscript and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report AHPA.
[PDF File (Adobe PDF File), 72 KB - resprot_v9i7e12823_app1.pdf]

References

1. Petty R, Laxer R, Lindsley C, Wedderburn L. Chronic arthritis in childhood. In: Textbook of Pediatric Rheumatology. Seventh Edition. Philadelphia, USA: Saunders; 2015.
2. Palman J, Shoop-Worrall S, Hyrich K, McDonagh JE. Update on the epidemiology, risk factors and disease outcomes of juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol 2018 Apr;32(2):206-222. [doi: 10.1016/j.berh.2018.10.004] [Medline: 30527427]
3. Harrold LR, Salman C, Shoor S, Curtis JR, Asgari MM, Gelfand JM, et al. Incidence and prevalence of juvenile idiopathic arthritis among children in a managed care population, 1996-2009. J Rheumatol 2013 Jul;40(7):1218-1225 [FREE Full text] [doi: 10.3899/jrheum.120661] [Medline: 23588938]

4. Rashid A, Cordingley L, Carrasco R, Foster HE, Baildam EM, Chieng A, et al. Patterns of pain over time among children with juvenile idiopathic arthritis. Arch Dis Child 2018 May;103(5):437-443 [FREE Full text] [doi: 10.1136/archdischild-2017-313337] [Medline: 29175824]
5. Bromberg MH, Connelly M, Anthony KK, Gil KM, Schanberg LE. Self-reported pain and disease symptoms persist in juvenile idiopathic arthritis despite treatment advances: an electronic diary study. Arthritis Rheumatol 2014 Mar;66(2):462-469 [FREE Full text] [doi: 10.1002/art.38223] [Medline: 24504820]
6. Armbrust W, Siers NE, Lelieveld OT, Mouton LJ, Tuinstra J, Sauer P. Fatigue in patients with juvenile idiopathic arthritFatigue in patients with juvenile idiopathic arthritis: a systematic review of the literatureis: a systematic review of the literature. Semin Arthritis Rheum 2016 Apr;45(5):587-595. [doi: 10.1016/j.semarthrit.2015.10.008] [Medline: 26656031]
7. Arundell L, Fletcher E, Salmon J, Veitch J, Hinkley T. A systematic review of the prevalence of sedentary behavior during the after-school period among children aged 5-18 years. Int J Behav Nutr Phys Act 2016 Aug 22;13:93 [FREE Full text] [doi: 10.1186/s12966-016-0419-1] [Medline: 27549588]
8. Cavallo S, April KT, Grandpierre V, Majnemer A, Feldman DE. Leisure in children and adolescents with juvenile idiopathic arthritis: a systematic review. PLoS One 2014;9(10):e104642 [FREE Full text] [doi: 10.1371/journal.pone.0104642] [Medline: 25329390]
9. Houghton K. Physical activity, physical fitness, and exercise therapy in children with juvenile idiopathic arthritis. Phys Sportsmed 2012 Sep;40(3):77-82. [doi: 10.3810/psm.2012.09.1979] [Medline: 23528624]
10. Lien G, Selvaag AM, Flatø B, Haugen M, Vinje O, Sørskaar D, et al. A two-year prospective controlled study of bone mass and bone turnover in children with early juvenile idiopathic arthritis. Arthritis Rheum 2005 Mar;52(3):833-840 [FREE Full text] [doi: 10.1002/art.20963] [Medline: 15751052]
11. Maggio AB, Hofer MF, Martin XE, Marchand LM, Beghetti M, Farpour-Lambert NJ. Reduced physical activity level and cardiorespiratory fitness in children with chronic diseases. Eur J Pediatr 2010 Oct;169(10):1187-1193. [doi: 10.1007/s00431-010-1199-2] [Medline: 20411275]
12. Stagi S, Masi L, Capannini S, Cimaz R, Tonini G, Matucci-Cerinic M, et al. Cross-sectional and longitudinal evaluation of bone mass in children and young adults with juvenile idiopathic arthritis: the role of bone mass determinants in a large cohort of patients. J Rheumatol 2010 Sep;37(9):1935-1943. [doi: 10.3899/jrheum.091241] [Medline: 20516020]
13. van Brussel M, van Doren L, Timmons BW, Obeid J, van der Net J, Helders PJ, et al. Anaerobic-to-aerobic power ratio in children with juvenile idiopathic arthritis. Arthritis Rheum 2009 Jun 15;61(6):787-793 [FREE Full text] [doi: 10.1002/art.24536] [Medline: 19479700]
14. Markula-Patjas KP, Ivaska KK, Pekkinen M, Andersson S, Moilanen E, Viljakainen HT, et al. High adiposity and serum leptin accompanied by altered bone turnover markers in severe juvenile idiopathic arthritis. J Rheumatol 2014 Dec;41(12):2474-2481. [doi: 10.3899/jrheum.131107] [Medline: 25320222]
15. Pohjankoski H, Kautiainen H, Korppi M, Savolainen A. Simultaneous juvenile idiopathic arthritis and diabetes mellitus type 1-a Finnish nationwide study. J Rheumatol 2012 Mar;39(2):377-381. [doi: 10.3899/jrheum.110654] [Medline: 22174196]
16. Cavallo S, Brosseau L, Toupin-April K, Wells GA, Smith CA, Pugh AG, et al. Ottawa panel evidence-based clinical practice guidelines for structured physical activity in the management of juvenile idiopathic arthritis. Arch Phys Med Rehabil 2017 May;98(5):1018-1041. [doi: 10.1016/j.apmr.2016.09.135] [Medline: 27932265]
17. Takken T, van der Net J, Kuis W, Helders PJ. Physical activity and health related physical fitness in children with juvenile idiopathic arthritis. Ann Rheum Dis 2003 Sep;62(9):885-889 [FREE Full text] [doi: 10.1136/ard.62.9.885] [Medline: 12922964]
18. Singh-Grewal D, Schneiderman-Walker J, Wright V, Bar-Or O, Beyene J, Selvadurai H, et al. The effects of vigorous exercise training on physical function in children with arthritis: a randomized, controlled, single-blinded trial. Arthritis Rheum 2007 Oct 15;57(7):1202-1210 [FREE Full text] [doi: 10.1002/art.23008] [Medline: 17907238]
19. Mendonça TM, Terreri MT, Silva CH, Neto MB, Pinto RM, Natour J, et al. Effects of pilates exercises on health-related quality of life in individuals with juvenile idiopathic arthritis. Arch Phys Med Rehabil 2013 Nov;94(11):2093-2102. [doi: 10.1016/j.apmr.2013.05.026] [Medline: 23806610]
20. Sandstedt E, Fasth A, Eek MN, Beckung E. Muscle strength, physical fitness and well-being in children and adolescents with juvenile idiopathic arthritis and the effect of an exercise programme: a randomized controlled trial. Pediatr Rheumatol Online J 2013 Mar 22;11(1):7 [FREE Full text] [doi: 10.1186/1546-0096-11-7] [Medline: 23432796]
21. Sandstedt E, Fasth A, Fors H, Beckung E. Bone health in children and adolescents with juvenile idiopathic arthritis and the influence of short-term physical exercise. Pediatr Phys Ther 2012;24(2):155-161. [doi: 10.1097/PEP.0b013e31824cce6e] [Medline: 22466383]
22. Tarakci E, Yeldan I, Baydogan SN, Olgar S, Kasapcopur O. Efficacy of a land-based home exercise programme for patients with juvenile idiopathic arthritis: a randomized, controlled, single-blind study. J Rehabil Med 2012 Nov;44(11):962-967 [FREE Full text] [doi: 10.2340/16501977-1051] [Medline: 23027068]
23. Lawler M, Heary C, Nixon E. Variations in adolescents' motivational characteristics across gender and physical activity patterns: a latent class analysis approach. BMC Public Health 2017 Aug 17;17(1):661 [FREE Full text] [doi: 10.1186/s12889-017-4677-x] [Medline: 28818063]

24. Duberg A, Hagberg L, Sunvisson H, Möller M. Influencing self-rated health among adolescent girls with dance intervention: a randomized controlled trial. JAMA Pediatr 2013 Jan;167(1):27-31. [doi: 10.1001/jamapediatrics.2013.421] [Medline: 23403597]
25. Feinstein AB, Cohen LL, Masuda A, Griffin AT, Gamwell KL, Stiles MT, et al. Yoga intervention for an adolescent with juvenile idiopathic arthritis: a case study. Adv Mind Body Med 2018;32(1):13-20. [Medline: 29406303]
26. Badsha H, Chhabra V, Leibman C, Mofti A, Kong KO. The benefits of yoga for rheumatoid arthritis: results of a preliminary, structured 8-week program. Rheumatol Int 2009 Oct;29(12):1417-1421. [doi: 10.1007/s00296-009-0871-1] [Medline: 19184028]
27. Moonaz SH, Bingham CO, Wissow L, Bartlett SJ. Yoga in sedentary adults with arthritis: effects of a randomized controlled pragmatic trial. J Rheumatol 2015 Jul;42(7):1194-1202 [FREE Full text] [doi: 10.3899/jrheum.141129] [Medline: 25834206]
28. Dash M, Telles S. Improvement in hand grip strength in normal volunteers and rheumatoid arthritis patients following yoga training. Indian J Physiol Pharmacol 2001 Jul;45(3):355-360. [Medline: 11881576]
29. Bosch PR, Traustadóttir T, Howard P, Matt KS. Functional and physiological effects of yoga in women with rheumatoid arthritis: a pilot study. Altern Ther Health Med 2009;15(4):24-31. [Medline: 19623830]
30. Donath L, Roth R, Hohn Y, Zahner L, Faude O. The effects of zumba training on cardiovascular and neuromuscular function in female college students. Eur J Sport Sci 2014;14(6):569-577. [doi: 10.1080/17461391.2013.866168] [Medline: 24320999]
31. Duberg A, Jutengren G, Hagberg L, Möller M. The effects of a dance intervention on somatic symptoms and emotional distress in adolescent girls: a randomized controlled trial. J Int Med Res 2020 Mar;48(2):300060520902610 [FREE Full text] [doi: 10.1177/0300060520902610] [Medline: 32019389]
32. Yonker LM, Zan S, Scirica CV, Jethwani K, Kinane TB. 'Friending' teens: systematic review of social media in adolescent and young adult health care. J Med Internet Res 2015 Jan 5;17(1):e4 [FREE Full text] [doi: 10.2196/jmir.3692] [Medline: 25560751]
33. Ritterband LM, Tate DF. The science of internet interventions. Introduction. Ann Behav Med 2009 Aug;38(1):1-3. [doi: 10.1007/s12160-009-9132-5] [Medline: 19816750]
34. Aragão JM, Gubert FD, Torres RA, Silva AS, Vieira NF. The use of Facebook in health education: perceptions of adolescent students. Rev Bras Enferm 2018;71(2):265-271 [FREE Full text] [doi: 10.1590/0034-7167-2016-0604] [Medline: 29412282]
35. Schwinn T, Hopkins J, Schinke SP, Liu X. Using Facebook ads with traditional paper mailings to recruit adolescent girls for a clinical trial. Addict Behav 2017 Feb;65:207-213 [FREE Full text] [doi: 10.1016/j.addbeh.2016.10.011] [Medline: 27835860]
36. Earle E. Development of JIA matters: a parent-led peer support network across England and Wales in collaboration with paediatric rheumatology centres. Rheumatology 2019;58(Supplement 4):415. [doi: 10.1093/rheumatology/kez415.011]
37. Park BK, Calamaro C. A systematic review of social networking sites: innovative platforms for health research targeting adolescents and young adults. J Nurs Scholarsh 2013 Sep;45(3):256-264. [doi: 10.1111/jnu.12032] [Medline: 23676115]
38. van Dyck D, D'Haese S, Plaete J, de Bourdeaudhuij I, Deforche B, Cardon G. Opinions towards physical activity interventions using Facebook or text messaging: focus group interviews with vocational school-aged adolescents. Health Soc Care Community 2019 May;27(3):654-664. [doi: 10.1111/hsc.12679] [Medline: 30398291]
39. Frison E, Eggermont S. Gender and Facebook motives as predictors of specific types of Facebook use: a latent growth curve analysis in adolescence. J Adolesc 2016 Oct;52:182-190. [doi: 10.1016/j.adolescence.2016.08.008] [Medline: 27585534]
40. Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res 2010 Mar 17;12(1):e4 [FREE Full text] [doi: 10.2196/jmir.1376] [Medline: 20164043]
41. Wójcicki TR, Grigsby-Toussaint D, Hillman CH, Huhman M, McAuley E. Promoting physical activity in low-active adolescents via Facebook: a pilot randomized controlled trial to test feasibility. JMIR Res Protoc 2014 Oct 30;3(4):e56 [FREE Full text] [doi: 10.2196/resprot.3013] [Medline: 25357008]
42. Korda H, Itani Z. Harnessing social media for health promotion and behavior change. Health Promot Pract 2013 Jan;14(1):15-23. [doi: 10.1177/1524839911405850] [Medline: 21558472]
43. Bossen D, Veenhof C, van Beek KE, Spreeuwenberg PM, Dekker J, de Bakker DH. Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial. J Med Internet Res 2013 Nov 22;15(11):e257 [FREE Full text] [doi: 10.2196/jmir.2662] [Medline: 24269911]
44. Bull SS, Levine DK, Black SR, Schmiege SJ, Santelli J. Social media-delivered sexual health intervention: a cluster randomized controlled trial. Am J Prev Med 2012 Nov;43(5):467-474 [FREE Full text] [doi: 10.1016/j.amepre.2012.07.022] [Medline: 23079168]
45. Cavallo DN, Tate DF, Ries AV, Brown JD, DeVellis RF, Ammerman AS. A social media-based physical activity intervention: a randomized controlled trial. Am J Prev Med 2012 Nov;43(5):527-532 [FREE Full text] [doi: 10.1016/j.amepre.2012.07.019] [Medline: 23079176]
46. Napolitano MA, Hayes S, Bennett GG, Ives AK, Foster GD. Using Facebook and text messaging to deliver a weight loss program to college students. Obesity (Silver Spring) 2013 Jan;21(1):25-31 [FREE Full text] [doi: 10.1002/oby.20232] [Medline: 23505165]

47. Patrick K, Marshall SJ, Davila EP, Kolodziejczyk JK, Fowler JH, Calfas KJ, et al. Design and implementation of a randomized controlled social and mobile weight loss trial for young adults (project SMART). Contemp Clin Trials 2014 Jan;37(1):10-18 [FREE Full text] [doi: 10.1016/j.cct.2013.11.001] [Medline: 24215774]
48. Brosseau L, Wells GA, Brooks S, de Angelis G, Bell M, Egan M, et al. People getting a grip on arthritis II: an innovative strategy to implement clinical practice guidelines for rheumatoid arthritis and osteoarthritis patients through Facebook. Health Educ J 2013 Jan 25;73(1):109-125. [doi: 10.1177/0017896912471031]
49. Anderson M, Jiang J. Pew Research Center. 2018 May 31. Teens, Social Media & Technology URL: https://www.pewresearch.org/internet/2018/05/31/teens-social-media-technology-2018/ [accessed 2020-05-11]
50. Moreno MA, Grant A, Kacvinsky L, Moreno P, Fleming M. Older adolescents' views regarding participation in Facebook research. J Adolesc Health 2012 Nov;51(5):439-444 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.02.001] [Medline: 23084164]
51. Tse CK, Bridges SM, Srinivasan DP, Cheng BS. Social media in adolescent health literacy education: a pilot study. JMIR Res Protoc 2015 Mar 9;4(1):e18 [FREE Full text] [doi: 10.2196/resprot.3285] [Medline: 25757670]
52. Paek H, Kim K, Hove T. Content analysis of antismoking videos on YouTube: message sensation value, message appeals, and their relationships with viewer responses. Health Educ Res 2010 Dec;25(6):1085-1099. [doi: 10.1093/her/cyq063] [Medline: 20923913]
53. Solau-Gervais E, Robin C, Gambert C, Troller S, Danner S, Gombert B, et al. Prevalence and distribution of juvenile idiopathic arthritis in a region of Western France. Joint Bone Spine 2010 Jan;77(1):47-49. [doi: 10.1016/j.jbspin.2009.11.002] [Medline: 20034832]
54. Modesto C, Antón J, Rodriguez B, Bou R, Arnal C, Ros J, et al. Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scand J Rheumatol 2010 Nov;39(6):472-479. [doi: 10.3109/03009741003742722] [Medline: 20858139]
55. Agha RA, Altman DG, Rosin D. The SPIRIT 2013 statement--defining standard protocol items for trials. Int J Surg 2015 Jan;13:288-291 [FREE Full text] [doi: 10.1016/j.ijsu.2014.12.007] [Medline: 25498499]
56. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Mar 5;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
57. Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Br Med J 2013 Jan 8;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
58. Evans S, Moieni M, Lung K, Tsao J, Sternlieb B, Taylor M, et al. Impact of iyengar yoga on quality of life in young women with rheumatoid arthritis. Clin J Pain 2013 Nov;29(11):988-997 [FREE Full text] [doi: 10.1097/AJP.0b013e31827da381] [Medline: 23370082]
59. Morgan EM, Munro JE, Horonjeff J, Horgan B, Shea B, Feldman BM, et al. Establishing an updated core domain set for studies in juvenile idiopathic arthritis: a report from the OMERACT 2018 JIA workshop. J Rheumatol 2019 Aug;46(8):1006-1013. [doi: 10.3899/jrheum.181088] [Medline: 30770499]
60. van Tulder MW, Assendelft WJ, Koes BW, Bouter LM. Method guidelines for systematic reviews in the cochrane collaboration back review group for spinal disorders. Spine (Phila Pa 1976) 1997 Oct 15;22(20):2323-2330. [doi: 10.1097/00007632-199710150-00001] [Medline: 9355211]
61. Sallis JF, Haskell WL, Wood PD, Fortmann SP, Rogers T, Blair SN, et al. Physical activity assessment methodology in the five-city project. Am J Epidemiol 1985 Jan;121(1):91-106. [doi: 10.1093/oxfordjournals.aje.a113987] [Medline: 3964995]
62. Sallis JF, Haskell WL, Fortmann SP, Wood PD, Vranizan KM. Moderate-intensity physical activity and cardiovascular risk factors: the Stanford five-city project. Prev Med 1986 Nov;15(6):561-568. [doi: 10.1016/0091-7435(86)90061-7] [Medline: 3797388]
63. Sauro J. MeasuringU. 2012. Measuring Usability with the System Usability Scale (SUS) URL: https://measuringu.com/sus/ [accessed 2018-04-04]
64. Brooke J. SUS-a quick and dirty usability scale. In: Jordan PW, Thomas B, McClelland IL, Weerdmeester B, editors. Usability Evaluation In Industry. New York, USA: CRC Press; 1996:4-7.
65. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994 Dec;37(12):1761-1769. [doi: 10.1002/art.1780371209] [Medline: 7986222]
66. Pouchot J, Ruperto N, Lemelle I, Sommelet D, Grouteau E, David L, Paediatric Rheumatology International Trials Organisation. French Study Group for Quality of Life in Rheumatology. The French version of the childhood health assessment questionnaire (CHAQ) and the child health questionnaire (CHQ). Clin Exp Rheumatol 2001;19(4 Suppl 23):S60-S65. [Medline: 11510333]
67. Crocker PR, Bailey DA, Faulkner RA, Kowalski KC, McGrath R. Measuring general levels of physical activity: preliminary evidence for the physical activity questionnaire for older children. Med Sci Sports Exerc 1997 Oct;29(10):1344-1349. [doi: 10.1097/00005768-199710000-00011] [Medline: 9346166]
68. Kowalski KC, Crocker PR, Faulkner RA. Validation of the physical activity questionnaire for older children. Pediatr Exerc Sci 1997;9(2):174-186. [doi: 10.1123/pes.9.2.174]

69. Kowalski KC, Crocker P, Kowalski N. Convergent validity of the physical activity questionnaire for adolescents. Pediatr Exerc Sci 1997;9(4):342-352. [doi: 10.1123/pes.9.4.342]
70. Lai J, Stucky BD, Thissen D, Varni JW, DeWitt EM, Irwin DE, et al. Development and psychometric properties of the PROMIS pediatric fatigue item banks. Qual Life Res 2013 Nov;22(9):2417-2427 [FREE Full text] [doi: 10.1007/s11136-013-0357-1] [Medline: 23378106]
71. Barlow JH, Shaw KL, Wright CC. Development and preliminary validation of a children's arthritis self-efficacy scale. Arthritis Rheum 2001 Apr;45(2):159-166 [FREE Full text] [doi: 10.1002/1529-0131(200104)45:2<159::AID-ANR169>3.0.CO;2-2] [Medline: 11324780]
72. Degotardi P. Pediatric measures of quality of life: the juvenile arthritis quality of life questionnaire (JAQQ) and the pediatric quality of life (PedsQL). Arthritis Rheum 2003 Oct 15;49(S5):S105-S112. [doi: 10.1002/art.11400]
73. Duffy CM, Arsenault L, Watanabe DK, Paquin J, Strawczynski H. Relative sensitivity to change of the juvenile arthritis quality of life questionnaire (JAQQ) on sequential follow-up. Arthritis Rheum 1995;38(-):S178.
74. Duffy CM, Arsenault L, Watanabe DK, Paquin J, Strawczynski H. Validity and sensitivity to change of the juvenile arthritis quality-of-life questionnaire (JAQQ). Arthritis Rheum 1993;36:S144.
75. Duffy CM, Arsenault L, Duffy KN, Paquin J, Strawczynski H. The juvenile arthritis quality of life questionnaire-development of a new responsive index for juvenile rheumatoid arthritis and juvenile spondyloarthritides. J Rheumatol 1997 Apr;24(4):738-746. [Medline: 9101511]
76. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008 Apr;31(2):180-191. [doi: 10.1002/nur.20247] [Medline: 18183564]
77. Cavallo DN, Brown JD, Tate DF, DeVellis RF, Zimmer C, Ammerman AS. The role of companionship, esteem, and informational support in explaining physical activity among young women in an online social network intervention. J Behav Med 2014 Oct;37(5):955-966 [FREE Full text] [doi: 10.1007/s10865-013-9534-5] [Medline: 24081454]
78. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. J Cancer Surviv 2013 Sep;7(3):355-368 [FREE Full text] [doi: 10.1007/s11764-013-0279-5] [Medline: 23532799]
79. Vance K, Howe W, Dellavalle RP. Social internet sites as a source of public health information. Dermatol Clin 2009 Apr;27(2):133-136. [doi: 10.1016/j.det.2008.11.010] [Medline: 19254656]
80. Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. Am J Phys Med Rehabil 1990 Mar;69(1):6-10. [doi: 10.1097/00002060-199002000-00003] [Medline: 2137345]
81. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, International League of Associations for Rheumatology. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004 Mar;31(2):390-392. [Medline: 14760812]
82. Norman CD, Yip AL. eHealth promotion and social innovation with youth: using social and visual media to engage diverse communities. Stud Health Technol Inform 2012;172:54-70. [Medline: 22910502]

Abbreviations

AHPA: Arthritis Health Professions Association
CASE: Children's Arthritis Self-Efficacy Scale
CHAQ: Childhood Health Assessment Questionnaire
CHEO: Children's Hospital of Eastern Ontario
HRQOL: health-related quality of life
ICT: information and communication technology
ILAR: International League of Associations for Rheumatology
JAQQ: Juvenile Arthritis Quality of Life Questionnaire
JIA: juvenile idiopathic arthritis
PA: physical activity
PAQ-A: Physical Activity Questionnaire for adolescents
RA: rheumatoid arthritis
RCT: randomized controlled trial
SUS: system usability scale
VAS: visual analog scale

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Protocol

A Web-Based Decision Aid (myAID) to Enhance Quality of Life, Empowerment, Decision Making, and Disease Control for Patients With Ulcerative Colitis: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Patients with ulcerative colitis (UC) often face complex treatment decisions. Although shared decision making (SDM) is considered important, tools to facilitate this are currently lacking for UC. A recent pilot study of a novel Web-based decision aid (DA), my Actively Informed Decision (myAID), has suggested its acceptability and feasibility for informing treatment decisions and facilitating SDM in clinical practice.

Objective: This paper describes the study protocol of the myAID study to assess the clinical impact of systematic implementation of myAID in routine UC management.

Methods: The myAID study is a multicenter, cluster randomized controlled trial (CRCT) involving 22 Australian sites that will assess the clinical efficacy of routine use of myAID (intervention) against usual care without access to myAID (control) for UC patients. Participating sites (clusters) will be randomly allocated in a 1:1 ratio between the 2 arms. Patients making a new treatment decision beyond 5-aminosalicylate agents will be eligible to participate. Patients allocated to the intervention arm will view myAID at the time of recruitment and have free access to it throughout the study period. The effect of the myAID intervention will be assessed using the results of serial Web-based questionnaires and fecal calprotectin at baseline, 2 months, 6 months, and 12 months. A Web-based questionnaire within 2-4 weeks of referral will determine early change in quality of decision making and anxiety (both arms) and intervention acceptability (intervention arm only).

Results: Study recruitment and funding began in October 2016, and recruitment will continue through 2020, for a minimum of 300 study participants at baseline at the current projection. The primary outcome will be health-related quality of life (Assessment of Quality of Life-8D), and secondary outcomes will include patient empowerment, quality of decision making, anxiety, work productivity and activity impairment, and disease activity. In addition, we aim to determine the predictors of UC treatment decisions and outcomes and the cost-effectiveness of implementing myAID in routine practice. Feedback obtained about myAID will be used to determine areas for improvement and barriers to its implementation. Completion of data collection and publication of study results are anticipated in 2021.

Conclusions: myAID is a novel Web-based DA designed to facilitate SDM in UC management. The results of this CRCT will contribute new evidence to the literature in comparing outcomes between patients who routinely access such decision support intervention versus those who do not, across multiple large inflammatory bowel disease centers as well as community-based private practices in Australia.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12617001246370 http://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617001246370

International Registered Report Identifier (IRRID): DERR1-10.2196/15994

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KEYWORDS

shared decision making; decision aid; ulcerative colitis

Introduction

Background

Ulcerative colitis (UC) is a chronic disabling inflammatory bowel disease (IBD). It affects about 40,000 people in Australia [1], with its incidence and burden rising globally [2]. Although half of these patients may be managed with 5-aminosalicylates (5-ASAs) alone [3], the rest will face decisions about other treatments that require long-term immunosuppression and even colectomy. These decisions are complex because they involve not only the identification of the best treatment strategy to prevent symptoms and progression of the disease but also consideration of the trade-offs of the available treatment options that differ in their efficacy and potential risks, modes of delivery, and dosing intervals. Therefore, patients' values and preferences heavily influence treatment choice and adherence, and a more collaborative and empowering approach to help navigate the complex benefit-risk profiles of these treatment options is important in guiding the decision-making process [4,5].

A recent survey confirmed that such a process of patient engagement or shared decision making (SDM) is desired by patients with UC [6]. SDM helps the doctor and the patient to collaborate on management decisions, which can lead to improved quality of life (QoL) and likelihood of achieving health goals, while lowering the demand for health care resources and improving patients' health care experience [7]. Many health care organizations have embraced SDM as an important part of health care standards and patient-centered care [8-10].

Decision aids (DAs) are tools developed to facilitate SDM by presenting patients with evidence-based information in a patient-friendly format and encouraging active engagement in the decision-making process. A recent Cochrane review indicates that their use in other chronic diseases can improve patient knowledge and reduce decisional conflict and the number of patients remaining undecided or being passive in the decision-making process [11]. With increasing acceptance and familiarity of online tools, Web-based DAs are gaining popularity [6,12,13].

Although using DAs use has the potential to facilitate SDM and participatory medicine in UC management, their uptake and application in clinical practice to date have been limited. Available electronic health technologies have suffered from high attrition rates [14], and patient and clinician perspectives on the best approach to the use of these tools in routine clinical practice remain poorly understood. A participatory health research design to increase involvement of patients and clinicians in their development and subsequent implementation has been suggested as a potential way of increasing their effectiveness and overcoming these limitations.

Recently, a new Web-based DA was developed for use in UC, which, for the first time, includes an interactive video discussing both medical and surgical treatment options in UC management, with the aim of facilitating SDM. Patients and a multidisciplinary panel of clinical experts were involved in its design, with a rigorous evaluation process [15] and close reference to the International Patient Decision Aids Standards checklist [16]. Originally developed in the United States, the DA was modified for use by an Australian audience in this study and named myAID (for my Actively Informed Decision; Emmi Solutions). A pilot study confirmed the acceptability of myAID to both patients and clinicians as a feasible SDM tool for UC management (Kim AH et al, unpublished data, 2020). To investigate whether routine use of myAID to promote SDM will translate to improvement of meaningful outcomes for patients, we designed a national cluster randomized controlled trial (CRCT) to test its efficacy against usual care. The CRCT is hereafter referred to as *the myAID study*.

Research Objectives

The overall aim of this study is to assess the impact of systematic use of myAID by eligible patients with UC on patient-reported UC clinical outcomes over a period of up to 12 months. Specific objectives of this study are as follows:

1. Comparison of changes in health-related QoL (primary outcome) from baseline to 6-month follow-up in patients accessing myAID (intervention arm) versus patients receiving usual care.
2. Comparison of differences in patient empowerment, quality of decision making, anxiety, work productivity, and disease activity including steroid use, hospital visits, and colectomy (secondary outcomes) in patients accessing myAID versus patients receiving usual care at the 6-month follow-up.
3. Determine the predictors of health literacy in patients with UC and the relationship between health literacy, decisional conflict, and treatment choices.
4. Determine the cost-effectiveness of implementing myAID in routine practice.

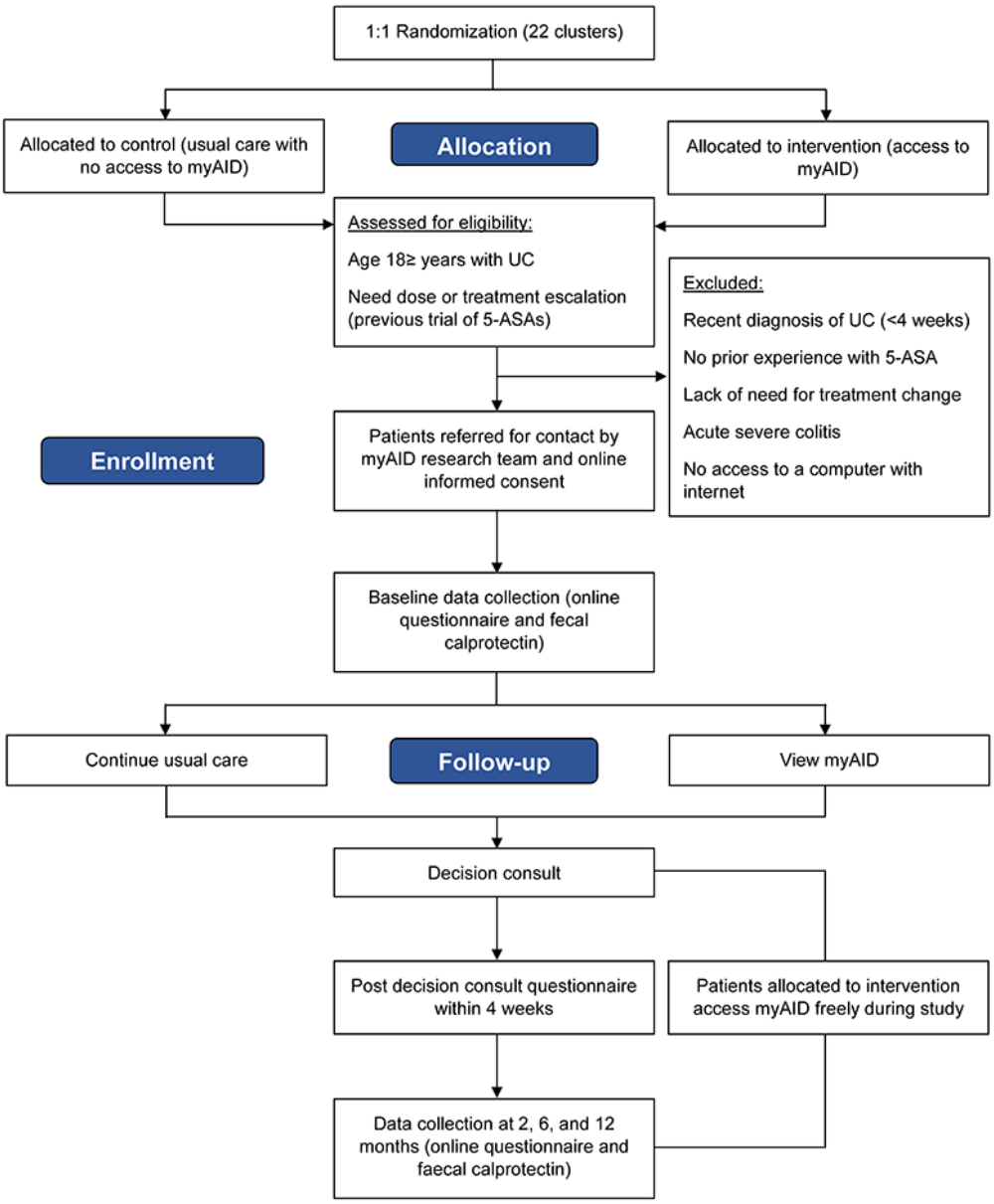
5. Investigate the views of study participants about myAID and determine areas for improvement or barriers to implementation in clinical practice.

Methods

Trial Design

The myAID study is a multicenter CRCT (see Figure 1) using a parallel arm design. Sites will be randomly allocated in a 1:1 ratio between intervention (routine use of myAID) and control (usual care without access to myAID) arms, with each site constituting a single cluster. Patients managed privately by the clinicians practicing at that site will also be grouped into the same cluster. As the intervention requires viewing and interacting with myAID, this is an open-label study with participants and their treating clinician and team being aware of their group allocation. Although only the patients, their family, and clinicians allocated to the intervention arm will be able to access and view myAID during the course of the study, participants from both groups may access other resources either sought independently or as recommended by their treating team, such as printed or online resources via patient organization websites. The use of such resources will be documented via participant questionnaires.

Figure 1. myAID study flowchart. 5-ASA: 5-aminosalicylates; UC: ulcerative colitis; myAID: my Actively Informed Decision. *Decision consult, if arranged, will be arranged within 2-4 weeks of referral. **Post decision consult (if arranged) or follow-up questionnaire to be completed within 2-4 weeks of referral.



Setting

This study will be undertaken at 22 sites in 5 of the 6 states in Australia, including large public IBD clinics and community-based private practices in urban and regional areas. Patient enrollment commenced in October 2016, with 21 of the 22 sites currently enrolling participants. All data collection (all participants) and viewing of myAID (intervention participants) will be undertaken off-site.

Study Population and Eligibility

Trial Inclusion Criteria

Patients presenting to the outpatient clinic at the participating sites will be eligible if they (1) have a diagnosis of UC, (2) are 18 years or older, (3) need to make a new decision about their UC management following a lack of response to (previous or current) 5-ASA treatment, and (4) can consent and read the myAID information online in English.

New decisions about management will have to specifically involve discussions around dose escalation, addition or change in treatment. This may include 5-ASA dose increase or addition of either oral and topical treatment, addition or dose increase of steroids, thiopurines, methotrexate, tofacitinib, and biologic agents as well as discussion regarding better treatment adherence. Consented patients could continue as study participants if they underwent colectomy after study enrollment, provided that this decision was made after baseline assessment and viewing of myAID (for the intervention group).

Trial Exclusion Criteria

The exclusion criteria will be as follows:

1. New diagnosis of UC (diagnosis within 4 weeks before referral) or no prior experience with 5-ASA
2. Lack of need for treatment escalation, addition or change in treatment (including patients who have already undergone colectomy at the time of referral),
3. Current episode of acute severe colitis requiring inpatient treatment
4. Not having access to a computer with internet outside of the clinic.

Study Procedure

Randomization

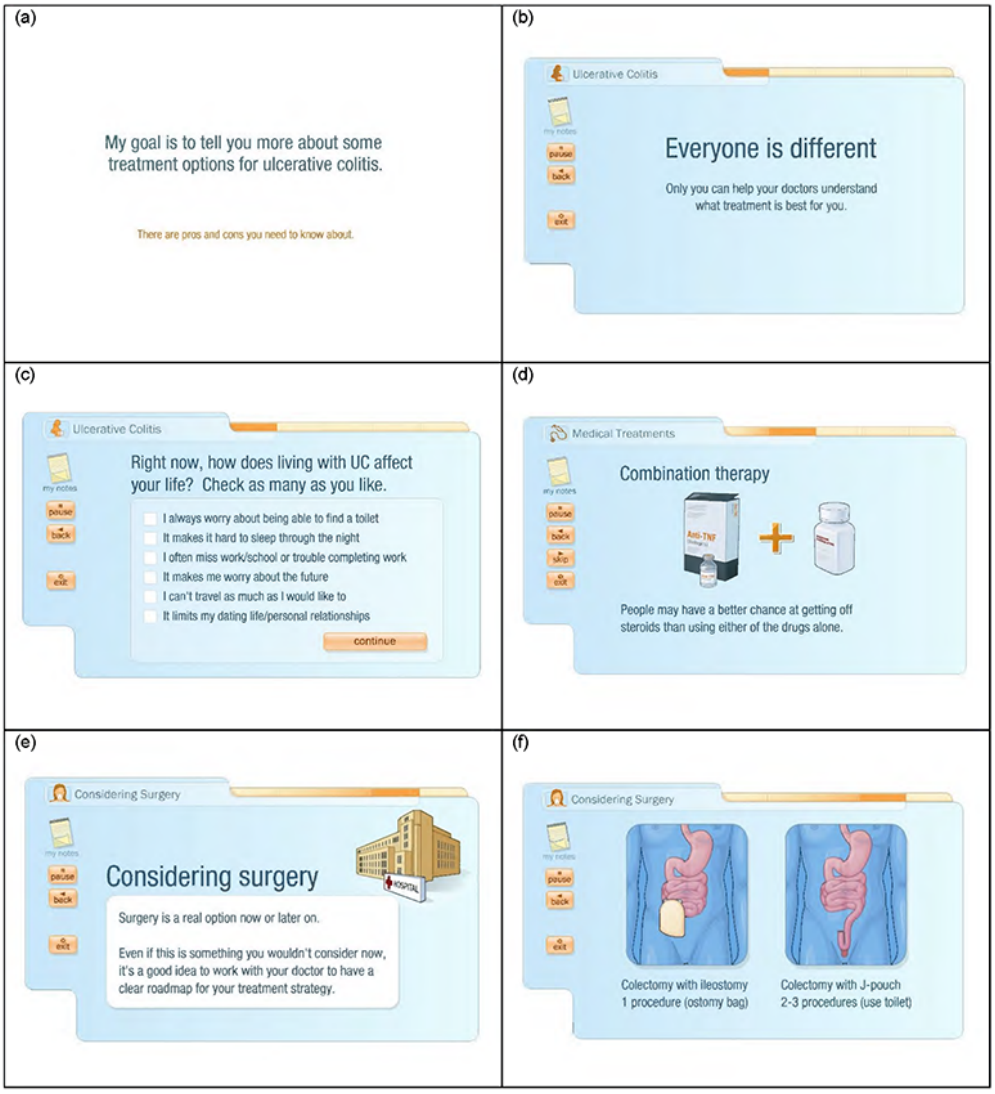
Given the cluster randomization design, all patients are allocated to either the intervention or control arm depending on the allocation of their referring site. When this project was conceptualized, block randomization was used to randomly allocate the original 14 invited sites equally into the intervention and control groups. Since the beginning of the study, 8 additional sites have joined recruitment and were allocated in pairs to the intervention or control group using predetermined block randomization, stratified by size and practice type. The block randomization was developed by the team statistician (JD), and the master copy, which informs the group allocation of site pairs, is held by the only investigator who is not directly involved in any study-related contact (eg, recruitment) or clinical care of participants (AG). Sites were informed of their allocation only after study approval by their local ethics governance.

Intervention—my Actively Informed Decision

The development, key features, and feasibility testing of the myAID intervention were previously described in a pilot study (Kim AH et al, unpublished data, 2020). In brief, myAID (Emmi Solutions) is a Web-based multimedia DA incorporating an interactive video (Figure 2), which has been designed to help prepare viewers for decision making about their UC treatment. Its content has been structured to deliver information aimed at improving the viewer's understanding of UC as well as the available medical and surgical treatments, including their potential benefits and risks, and to elicit the viewer's treatment goals and preferences through a series of interactive questions. The current version is accessible using a computer with an internet connection but is not downloadable or accessible on a mobile device. It takes approximately 32 min to view uninterrupted, with the actual time varying with content watched and time taken with interactive elements.

Patients (and their invited family members) allocated to the intervention arm will have free access to myAID during the period of the study through their designated URL, which will be provided to them upon completion of their baseline Web-based questionnaire. They will be able to view myAID at any location using a computer, provided there is internet access. All patients will confirm their first complete viewing of myAID via their Web-based questionnaire. Patients will report any technical issues with regard to access or use of myAID via email for assistance by the research team. myAID access by these study participants will also be tracked by Emmi Solutions and reported back to the myAID study group on a monthly basis. The treating clinicians allocated to the intervention arm will similarly have free access to myAID during the study period.

Figure 2. Screenshots of myAID (myAID@2015 Emmi Solutions, LLC). myAID: my Actively Informed Decision.



Recruitment and Informed Consent

Patients who are eligible for the study will be identified by their respective consultant gastroenterologist who will obtain verbal consent (or written consent, if specifically required by their local ethics governance) for the interested patient's contact details to be forwarded onto the myAID study group. Referred patients will then receive a study invitation email with an attached electronic participant information booklet, followed by a phone call from the study research assistant to confirm receipt of the study information and provide a verbal explanation of the study. A chance to win an Aus $200 (US $123) gift voucher will be used as an incentive for participation and completion of questionnaires. Those who wish to proceed will then be sent a further email with their unique study ID and a URL, which they will use to provide online consent and complete the baseline questionnaire and a laboratory request form for fecal calprotectin (FC) testing within 3 weeks from the time of the referral to the study. Patients who did not comply with the required timeframe can be re-referred provided they still meet the study inclusion criteria.

Study Flow and Data Collection

All patients completing their baseline Web-based questionnaire will be entered into the study database and continue to be followed up by the myAID study group for 12 months unless they withdraw their consent. All participating sites will continue to provide usual care, although we will ask that a brief follow-up, either in the form of a face-to-face or telephone consultation (referred to as a *decision consult*), be arranged at 2-4 weeks after patient referral to the study if possible. Although not mandated for the study, this was felt to be important by clinicians in our pilot study to facilitate SDM.

Web-based questionnaires (using the SurveyMonkey platform) are administered to study participants at baseline, 2-4 weeks (or following the *decision consult* if arranged), 2 months, 6 months (primary and secondary outcome assessment), and 12 months (long-term impact). Table 1 summarizes the outcome measures captured at each timepoint. Study participants will be sent a URL for the questionnaires via email at each of these time points, as this was deemed acceptable and feasible from the pilot study (Kim AH et al, unpublished data, 2020).

All participants will be asked to submit their stool samples at baseline, 2 months, 6 months, and 12 months. Each site will provide the study participant with a preassembled stool sampling kit at the time of referral. Study participants will be asked to submit their samples to their local Sonic Healthcare pathology laboratory (nationwide pathology provider owned by Sonic Healthcare Limited), where the FC will be measured using a quantitative fluoroenzyoimmunoassay (EliA Calprotectin 2; Thermo Fisher). Participants residing outside of Adelaide in South Australia will use the SA Pathology laboratory (statewide pathology provider for the public health sector in South Australia) that uses the same assay for FC testing. Participants who do not have access to either of these labs will be asked to submit their samples to an alternative local pathology lab. All FC measurements will be performed according to the manufacturer's instructions without knowledge of patient data. Concentrations will be expressed as micrograms per gram of stool.

We will accept patient referrals until 2020 to reach our target recruitment sample and follow-up participants for up to 12 months, thereby completing data collection in 2021.

Table 1. myAID study outcome measures.

Outcome measures	Baseline (within 3 weeks of referral)	Within 4 weeks	2 months	6 months	12 months
Assessment of Quality of Life-8D	✓[a]	N/A[b]	✓	✓	✓
Health Education Impact Questionnaire	✓	N/A	✓	✓	✓
Health Literacy Questionnaire	✓	N/A	✓	✓	✓
Decisional Conflict Scale	✓	✓	✓	✓	✓
Trust in Physician Scale	✓	✓	✓	✓	✓
Hospital Anxiety and Depression Scale-Anxiety	✓	✓	✓	✓	✓
Simple Clinical Colitis Activity Index	✓	N/A	✓	✓	✓
Fecal calprotectin	✓	N/A	✓	✓	✓
Clinical outcomes	✓	N/A	✓	✓	✓
Work productivity and activity index	✓	N/A	✓	✓	✓
myAID acceptability	N/A	✓	N/A	N/A	N/A

[a]✓: included.

[b]N/A: not applicable.

Measures

Patient Demographics, Disease, and Treatment Characteristics

Upon consenting, all patients will complete a Web-based questionnaire to provide the following:

1. Socioeconomic data—age, gender, ethnicity, postal code, language spoken at home, relationship, education, employment and smoking status, and health insurance coverage.
2. Clinical data—time since diagnosis, disease extent, previous hospital visits and admissions for UC, comorbidities, UC-related surgical history, previous and current treatment history including systemic corticosteroid use, main setting for clinical care (public vs private), and access to an IBD nurse.

Review

Outcome Measures

The primary outcome for the study is *QoL* as measured by the 35-item Assessment of Quality of Life-8D (AQoL-8D) [17]. AQoL-8D is a health-related multi-attribute utility QoL instrument that measures 8 dimensions within 2 *super-dimensions*: Physical (independent living, pain, and senses) and psychosocial (mental health, happiness, coping, relationships, and self-worth). AQoL-8D has previously been used in economic evaluation studies in both Crohn disease (CD) [18] and UC [19]. Each item is scored on a 4- to 6-point Likert scale based on a recall period of 7 days, and these are reduced to a single utility score using an algorithm that also generates an index number for each of the 8 dimensions and for the 2 *super-dimensions*.

The secondary outcomes for the study are as follows:

1. *Empowerment*. This will be measured by the Health Education Impact Questionnaire 3.0 (heiQ) [20] using 4 of its dimensions (32 items): positive and active engagement in life, constructive attitudes and approaches, self-monitoring and insight, and emotional well-being. Items are recorded on a 4-point Likert scale from 1 to 4, where 1=strongly disagree and 4=strongly agree. The items in each dimension are summed, and the sum is divided by the number of items to generate a score for each dimension. The heiQ was developed to assess the outcomes of patient education programs, with higher scores indicating better self-management and knowledge, except for the emotional well-being scale, which is reversed.
2. *Health literacy*. This will be measured by the 44-item Health Literacy Questionnaire (HLQ) [21]. The HLQ covers 9 domains, each consisting of 4 to 6 items measured on either 4- or 5-point Likert scales. There is no one overall summative score; the score for each domain is generated by following a computerized algorithm using SPSS or

Microsoft Excel. The included domains capture how the patients engage, access, and use health information and services and provide an opportunity for reflection of the quality of health and social service provision.

3. *Quality of decision making*. This will be measured by the 16-item Decisional Conflict Scale (DCS) [22] and the 11-item Trust in Physician Scale (TPS) [23]. DCS measures uncertainty in making a choice, modifiable factors contributing to the uncertainty, and perceived effective decision making, with a score of 1 indicating low decisional conflict and 5 indicating high decisional conflict. All items are based on a 5-point Likert scale ranging from strongly disagree to strongly agree. Total scores and subscale scores can be summed, divided by the number of items, and then converted to a 0 to 100 scale. TPS, on the other hand, measures the degree of interpersonal trust in a physician with regard to dependability, confidence, and confidentiality of information. All items are scored on a 5-point Likert scale ranging from *strongly agree* (5) to *strongly disagree* (1), and a summary measure of trust can be obtained by taking the unweighted mean of the responses (negatively worded items are reverse-scored) and transforming that value to a 0 to 100 scale.
4. *Anxiety*. This will be measured by the 7-item Hospital Anxiety and Depression Scale-Anxiety (HADS-A) [24]. The HADS-A is a self-assessment mood scale scored on a 4-point Likert scale and reported as a sum score ranging from 0 to 21, with a higher score indicating a greater level of anxiety symptoms.
5. *UC disease activity*. This will be measured by the patient-reported 13-item Simple Clinical Colitis Activity Index (SCCAI) [25] and FC. SCCAI is a symptom-based clinical score for UC with a score range of 0 to 19, with a higher score indicating greater disease activity. Although originally intended for clinician use, recent studies have allowed patients to complete the SCCAI themselves [26,27]. FC is an increasingly accepted biomarker for the assessment of disease activity in IBD. The upper limit of the normal range of FC in patients without gut inflammation is well defined as less than 50 μg/g [28].
6. *Clinical outcomes*. These will be captured by 4 items included in the Web-based questionnaire asking patients to report on their use of systemic corticosteroids, need for UC-related surgery, emergency department visits, and hospital admissions. Responses to these items will be used to initiate chart reviews for validation and to calculate: (1) proportion of patients taking steroids, (2) proportion of patients requiring surgery, and (3) number and days of unplanned emergency department visits and hospital admissions.
7. *Work productivity*. This will be measured by the 6-item Work Productivity and Activity Impairment questionnaire (WPAI) [29]. The WPAI measures 4 domains of the impact of disease on impairment in work or other activities (absenteeism, presenteeism, overall work productivity loss, and activity impairment). It is self-reported using a 1-week recall period, and domain scores are expressed as percentage of impairment, with higher scores indicating worse work-related outcomes.
8. *Acceptability of myAID*. This will be measured by a Web-based questionnaire at 2 to 4 weeks from the time of referral (or following the *decision consult* if arranged) for the intervention group. We will seek intervention group participants' views about the ease of viewing myAID, adequacy of its content, optimal timing for receipt of myAID, and the extent to which it facilitated understanding of their condition and the available treatment options, and ultimately, whether it aided in the discussion of treatment with their clinician. We will also determine whether additional resources were sought or prescribed and whether a *decision consult* was considered necessary in the decision-making process.

Patients who undergo colectomy during the study will complete a modified questionnaire that does not include the SCCAI and will no longer submit stool samples for FC measurement.

Trial Management

The myAID study group, consisting of 2 gastroenterologists, 1 IBD clinical nurse consultant, 1 psychologist, and 1 research assistant, provides day-to-day oversight of the trial and meets at 1 to 2 weekly intervals to address any queries regarding the patient's eligibility at the time of referral or logistical issues raised by participating sites. Each study site will have 1 lead clinician to oversee local patient referral activity and act as the liaison for the myAID study group, but sites will not be directly involved in any patient consent, data collection, or follow-up procedures, which will be entirely managed by the myAID study group. The myAID study group will not be involved in any test result interpretation, for example, colonoscopy or FC, treatment decisions, or advice about management, and any such queries from participants will be forwarded directly to the treating team.

Safety Monitoring and Reporting

As the intervention in this trial does not include drug treatment or procedures, we do not anticipate any safety issues, although we will keep track of the treatment options being selected based on study participants' reports.

Withdrawal

Study participants will be able to withdraw from the study whenever they wish without giving a reason and without affecting their care. We will document their reasons for withdrawal if provided as well as any feedback regarding myAID. If a participant misses 1 assessment, we will encourage them to continue the study and complete the subsequent questionnaires and FC testing at the designated time points. Patients who undergo colectomy during the study period will remain in the study unless they specifically choose to withdraw. Data collection from these patients will be altered as previously described.

Data Management and Record Keeping

The data acquired during the study will be coded and stored as deidentified data on a secure, password-protected computer located at the Ingham Institute for Applied Medical Research and accessed over a secure, virtual private network. Only the members of the myAID study group not directly involved in the participant's care will have access to identifiable data except

for the results of the FC, which will be forwarded directly to the referring clinicians.

Sample Size and Power

The myAID study design is based on an assumption of 0.5 SD difference between the intervention and control groups for the primary outcome of QoL using the AQoL-8D utility score at 6 months. This estimate fares well with the published study by Gibson et al using AQoL-8D, which identified the scores between those in clinical remission and those with active UC [19]. The sample size has been adjusted for the design effect due to the cluster randomization assuming unequal cluster sizes and can accommodate an intraclass correlation coefficient (ICC) as high as 0.05 to achieve 80% power. Adjusting for this ICC, the estimated required sample size for the full study is 238 patients (119 per group), which will require a minimum of 14 clusters for sufficient recruitment. Assuming 70% of eligible patients consent to study participation and a loss to follow-up rate of 20% at the 6-month end point, we then aim to approach a minimum of 426 patients (213 per group) and recruit 298 patients at baseline.

Analysis

Missing Data

General Principles

We will exclude patients for whom only baseline data has been collected. To remain within the primary outcome analysis, patients will need to have completed the Web-based questionnaires across at least three time points (including baseline measures). For each measure, we will summarize the frequency of missing data and assess how this affects the effective sample size and statistical power. If systematic issues are identified, the study statistician and the chief investigator will discuss the findings. Otherwise, appropriate statistical imputation methods will be used to address missing data.

Internal Imputation Within a Questionnaire

None of the questionnaires has an official algorithm for imputing individual missing answers. Given the design of the Web-based questionnaire and the results of the pilot study, we anticipate very few patients providing incomplete responses. Any incomplete questionnaires will be immediately flagged on the Web-based platform, and the patient will be contacted to request completion within the designated period. To additionally reduce missing data and make good use of available information, we will impute missing responses within the included measures and will use multiple imputation methods to achieve this depending on the frequency of missing data.

External Imputation of Outcome Measures

If the entire questionnaire at a specific time point is missing, we will impute missing scores by appropriate regression models using all available values of that score at other time points for the individual and other participants belonging to the same allocated group. We will also consider using other predictors from patient demographics and disease activity, although they may only play a limited role in predicting missing values.

Outcome Data Analysis

The primary analysis will be by *intention to treat* and conducted using multilevel models to account for the correlation of outcomes within a cluster (site). For the primary outcome, the dependent variable will be the AQoL-8D utility score and the exposure variable will be the intervention status (intervention vs control). The unit of analysis will be at the patient level to accommodate the weighting required by unequal cluster (site) sizes. Other independent variables will be added to the models if they are independently associated with AQoL-8D. Multilevel models will also be used to evaluate secondary outcomes.

Multilevel models will further be used to analyze each of the health literacy scores, adjusting for the participant's age, ethnicity, educational/work status, location (rural vs urban), insurance status, and health status including anxiety and disease activity. All statistical analyses will be performed using SAS 9.4 (SAS Institute).

Health Economics Analysis

We will evaluate the additional costs and health outcomes of myAID intervention compared with usual care from the perspectives of the Australian health care system and society within the trial period. This will include all direct costs related to UC, cost of delivering the intervention over 12 months, downstream costs due to selected treatment, hospital visits, and health care utilization and all indirect costs related to the productivity of the participants. Unit costs for health care utilization and medication use will be estimated from chart reviews and linkage to the Medicare Benefits Schedule and the Pharmaceutical Benefits Scheme national databases. Participants' total health care cost will be the aggregation from the number of services used by the unit cost for the service plus medication costs. All costs will be expressed in 2016 Australian dollars (Aus $) and effects in quality-adjusted life years (QALYs). The AQoL-8D will provide utilities for the estimation of QALYs in the cost-utility analysis. WPAI will provide an estimation of the indirect cost. No discounting will be applied as follow-up is for 12 months only.

Patient and Public Involvement

We received input from patients and clinicians from a feasibility pilot study, which guided the design of this study and confirmed the suitability of the intervention, as assessed by patients themselves and by clinicians. The research question and outcome measures were influenced by reviewing other clinical studies examining the role of SDM in patients with IBD, including a similar study assessing the use of a DA in CD. Patients were not involved in the decision of the research question or outcome measures. Patients will not be involved in the recruitment of participants or the conduct of the study. We will gather information about the acceptability of the intervention through a Web-based questionnaire, as part of the study. We plan to disseminate the results of the research to study participants and to the rest of the community through national and international conferences and via publications in peer-reviewed journals.

Ethics and Dissemination

The completed pilot study and this CRCT were approved by the Human Research Ethics Committee of South Western

Sydney Local Health District (HREC/15/LPOOL/358) and relevant site-specific ethics committees. We will report the study findings in accordance with the Consolidated Standards of Reporting Trials guidelines, with appropriate acknowledgment and/or authorship for those who have worked on the trial (as per journal authorship guidelines).

Results

Study recruitment and funding began in October 2016, and recruitment will continue through 2020 at the current projection to ensure adequate numbers are recruited to both arms. Completion of data collection and publication of study results are anticipated in 2021.

Discussion

With increasing complexity of treatment choices, supporting SDM and effective communication in UC management have become even more important. Studies on other chronic diseases suggest that the use of DAs may be beneficial to both facilitate SDM and improve communication, although there has been only limited experience in UC. Even if available, to implement such a tool on a wider scale, more evidence is required regarding its potential usability, efficacy, and cost-effectiveness.

The results from the myAID study will, therefore, contribute important new evidence to the literature, with comparison of outcomes between patients who routinely access myAID and those who do not, across multiple large IBD centers as well as community-based private practices in Australia. Furthermore, it will provide insight into the decision-making process utilized by Australian patients with UC using specifically designed questionnaires measuring health literacy, empowerment, and quality of decision making. Information gathered from the study will then be used to guide further revisions of the myAID tool and its wider implementation to the rest of Australia and internationally, to support SDM and provide better outcomes for patients with UC.

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Authors' Contributions

SC conceived the trial and obtained funding. SC, AG, JA, CS, and AS designed the original protocol. AK, NK, and JD contributed to subsequent protocol development. JD leads the statistical aspects of the trial. All authors have contributed to the general conduct of the study as members of the myAID study, commented on drafts of the manuscript, and agreed to the final published protocol.

Conflicts of Interest

AK, AG, NK, and JD have no relevant competing interests. AS has served as a consultant for AbbVie, Janssen, and Pfizer and received travel support from AbbVie, Ferring, Janssen, Orphan, Shire, and Takeda. JA is on advisory boards, has received speakers' fees and research support, and/or has coordinated education meetings for Abbott, AbbVie, Allergan, Bayer, Celgene, Ferring, Gilead, Janssen, MSD, Pfizer, Shire, and Takeda. All money has been received by her employer to support investigator-initiated research. CS has served as a key advisor to the development of the Ulcerative Colitis Treatment Options program in the United States by Emmi Solutions, Inc; has served as a consultant and is on the advisory boards for AbbVie, Amgen, Celgene, Janssen, Lilly, Pfizer, Prometheus, Salix, Sandoz, Sebela, and Takeda; has received speaker fees from AbbVie, Janssen, Pfizer, and Takeda; has received grant support from AbbVie, Janssen, Pfizer, Takeda, Broad Medical Research Program, Crohn's and Colitis Foundation of America (CCFA), and AHRQ (1R01HS021747-01); and is the co-chair of the CCFA quality of care program. SC is on advisory boards; has received speaker fees, educational support, and research support; and/or has coordinated education meetings for AbbVie, Celgene, Ferring, Gilead, Janssen, MSD, Orphan/Aspen, Pfizer, and Takeda.

Multimedia Appendix 1

Reviewers' report - 2015 GESA AbbVie IBD Clinical Research Grant.
[PDF File (Adobe PDF File), 104 KB - resprot_v9i7e15994_app1.pdf]

References

1. Crohn's & Colitis Australia. 2013. Improving Inflammatory Bowel Disease Care Across Australia URL: https://www.crohnsandcolitis.com.au/site/wp-content/uploads/PwC-report-2013.pdf [accessed 2020-04-07]
2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018 Dec 23;390(10114):2769-2778. [doi: 10.1016/S0140-6736(17)32448-0] [Medline: 29050646]
3. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2016 May 9(5):CD000544 [FREE Full text] [doi: 10.1002/14651858.CD000544.pub4] [Medline: 27158764]
4. Lenti MV, Selinger CP. Patients' beliefs and concerns about the necessity of long-term therapies are crucial for medication adherence for inflammatory bowel disease. J Crohns Colitis 2017 Jun 1;11(6):764-765. [doi: 10.1093/ecco-jcc/jjw213] [Medline: 27932452]
5. Selinger CP, Eaden J, Jones DB, Katelaris P, Chapman G, McDonald C, et al. Modifiable factors associated with nonadherence to maintenance medication for inflammatory bowel disease. Inflamm Bowel Dis 2013 Sep;19(10):2199-2206. [doi: 10.1097/MIB.0b013e31829ed8a6] [Medline: 23899547]
6. Thompson KD, Connor SJ, Walls DM, Gollins J, Stewart SK, Bewtra M, et al. Patients with ulcerative colitis are more concerned about complications of their disease than side effects of medications. Inflamm Bowel Dis 2016 Apr;22(4):940-947. [doi: 10.1097/MIB.0000000000000740] [Medline: 26950308]
7. Hoffmann TC, Légaré F, Simmons MB, McNamara K, McCaffery K, Trevena LJ, et al. Shared decision making: what do clinicians need to know and why should they bother? Med J Aust 2014 Jul 7;201(1):35-39. [doi: 10.5694/mja14.00002] [Medline: 24999896]
8. Jackson B, Begun J, Gray K, Churilov L, Liew D, Knowles S, et al. Clinical decision support improves quality of care in patients with ulcerative colitis. Aliment Pharmacol Ther 2019 Apr;49(8):1040-1051. [doi: 10.1111/apt.15209] [Medline: 30847962]
9. Joseph-Williams N, Lloyd A, Edwards A, Stobbart L, Tomson D, Macphail S, et al. Implementing shared decision making in the NHS: lessons from the MAGIC programme. Br Med J 2017 Apr 18;357:j1744 [FREE Full text] [doi: 10.1136/bmj.j1744] [Medline: 28420639]
10. Frosch DL, Moulton BW, Wexler RM, Holmes-Rovner M, Volk RJ, Levin CA. Shared decision making in the United States: policy and implementation activity on multiple fronts. Z Evid Fortbild Qual Gesundhwes 2011;105(4):305-312. [doi: 10.1016/j.zefq.2011.04.004] [Medline: 21620326]
11. Stacey D, Légaré F, Lewis KB. Patient decision aids to engage adults in treatment or screening decisions. J Am Med Assoc 2017 Aug 15;318(7):657-658. [doi: 10.1001/jama.2017.10289] [Medline: 28810006]
12. Siegel CA. Embracing the internet for progress in shared decision-making. Inflamm Bowel Dis 2007 Dec;13(12):1579-1580. [doi: 10.1002/ibd.20259] [Medline: 17879279]
13. Siegel CA, Lofland JH, Naim A, Gollins J, Walls DM, Rudder LE, et al. Gastroenterologists' views of shared decision making for patients with inflammatory bowel disease. Dig Dis Sci 2015 Sep;60(9):2636-2645 [FREE Full text] [doi: 10.1007/s10620-015-3675-z] [Medline: 25939543]
14. Jackson BD, Gray K, Knowles SR, de Cruz P. eHealth technologies in inflammatory bowel disease: a systematic review. J Crohns Colitis 2016 Sep;10(9):1103-1121. [doi: 10.1093/ecco-jcc/jjw059] [Medline: 26928960]
15. Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Ng CJ, van der Weijden T. A systematic development process for patient decision aids. BMC Med Inform Decis Mak 2013;13(Suppl 2):S2 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S2] [Medline: 24625093]
16. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, International Patient Decision Aids Standards (IPDAS) Collaboration. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. Br Med J 2006 Aug 26;333(7565):417 [FREE Full text] [doi: 10.1136/bmj.38926.629329.AE] [Medline: 16908462]
17. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. Patient 2014;7(1):85-96 [FREE Full text] [doi: 10.1007/s40271-013-0036-x] [Medline: 24271592]
18. Gibson PR, Weston AR, Shann A, Florin TH, Lawrance IC, Macrae FA, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. J Gastroenterol Hepatol 2007 Aug;22(8):1306-1312. [doi: 10.1111/j.1440-1746.2007.04930.x] [Medline: 17559375]
19. Gibson PR, Vaizey C, Black CM, Nicholls R, Weston AR, Bampton P, et al. Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: a cross-sectional, observational study. J Crohns Colitis 2014 Jul;8(7):598-606. [doi: 10.1016/j.crohns.2013.11.017] [Medline: 24345767]

20. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns 2007 May;66(2):192-201. [doi: 10.1016/j.pec.2006.12.002] [Medline: 17320338]
21. Osborne RH, Batterham RW, Elsworth GR, Hawkins M, Buchbinder R. The grounded psychometric development and initial validation of the Health Literacy Questionnaire (HLQ). BMC Public Health 2013 Jul 16;13:658 [FREE Full text] [doi: 10.1186/1471-2458-13-658] [Medline: 23855504]
22. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making 1995;15(1):25-30. [doi: 10.1177/0272989X9501500105] [Medline: 7898294]
23. Anderson LA, Dedrick RF. Development of the trust in physician scale: a measure to assess interpersonal trust in patient-physician relationships. Psychol Rep 1990 Dec;67(3 Pt 2):1091-1100. [doi: 10.2466/pr0.1990.67.3f.1091] [Medline: 2084735]
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
25. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998 Jul;43(1):29-32 [FREE Full text] [doi: 10.1136/gut.43.1.29] [Medline: 9771402]
26. Marín-Jiménez I, Nos P, Domènech E, Riestra S, Gisbert JP, Calvet X, et al. Diagnostic performance of the simple clinical colitis activity index self-administered online at home by patients with ulcerative colitis: CRONICA-UC Study. Am J Gastroenterol 2016 Feb;111(2):261-268. [doi: 10.1038/ajg.2015.403] [Medline: 26753886]
27. Evertsz' FB, Nieuwkerk PT, Stokkers PC, Ponsioen CY, Bockting CL, Sanderman R, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis 2013 Dec;7(11):890-900. [doi: 10.1016/j.crohns.2012.11.007] [Medline: 23269224]
28. von Roon AC, Karamountzos L, Purkayastha S, Reese GE, Darzi AW, Teare JP, et al. Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. Am J Gastroenterol 2007 Apr;102(4):803-813. [doi: 10.1111/j.1572-0241.2007.01126.x] [Medline: 17324124]
29. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993 Nov;4(5):353-365. [doi: 10.2165/00019053-199304050-00006] [Medline: 10146874]

Abbreviations

5-ASA: 5-aminosalicylates
AQoL-8D: Assessment of Quality of Life-8D
CD: Crohn disease
CRCT: cluster randomized controlled trial
DA: decision aid
DCS: Decisional Conflict Scale
FC: fecal calprotectin
HADS-A: Hospital Anxiety and Depression Scale-Anxiety
heiQ: Health Education Impact Questionnaire
HLQ: Health Literacy Questionnaire
IBD: inflammatory bowel disease
ICC: intraclass correlation coefficient
QALYs: quality-adjusted life years
QoL: quality of life
SCCAI: Simple Clinical Colitis Activity Index
SDM: shared decision making
TPS: Trust in Physician Scale
UC: ulcerative colitis
WPAI: work productivity and activity impairment questionnaire

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Protocol

Integration of Mobile Health Into Sickle Cell Disease Care to Increase Hydroxyurea Utilization: Protocol for an Efficacy and Implementation Study

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Abstract

Background: Hydroxyurea prevents disease complications among patients with sickle cell disease (SCD). Although its efficacy has been endorsed by the National Health Lung and Blood Institute evidence-based guidelines, its adoption is low, both by patients with SCD and providers. Mobile health (mHealth) apps provide benefits in improving medication adherence and self-efficacy among patients with chronic diseases and have facilitated prescription among medical providers. However, mHealth has not been systematically tested as a tool to increase hydroxyurea adherence nor has the combination of mHealth been assessed at both patient and provider levels to increase hydroxyurea utilization.

Objective: This study aims to increase hydroxyurea utilization through a combined two-level mHealth intervention for both patients with SCD and their providers with the goals of increasing adherence to hydroxyurea among patients and improve hydroxyurea prescribing behavior among providers.

Methods: We will test the efficacy of 2 mHealth interventions to increase both patient and provider utilization and knowledge of hydroxyurea in 8 clinical sites of the NHLBI-funded Sickle Cell Disease Implementation Consortium (SCDIC). The patient mHealth intervention, *InCharge Health*, includes multiple components that address memory, motivation, and knowledge barriers to hydroxyurea use. The provider mHealth intervention, *Hydroxyurea Toolbox* (*HU Toolbox*), addresses the clinical knowledge barriers in prescribing and monitoring hydroxyurea. The primary hypothesis is that among adolescents and adults with SCD, adherence to hydroxyurea, as measured by the proportion of days covered (the ratio of the number of days the patient is covered by the medication to the number of days in the treatment period), will increase by at least 20% after 24 weeks of receiving the *InCharge Health* app, compared with their adherence at baseline. As secondary objectives, we will (1) examine the change in health-related quality of life, acute disease complications, perceived health literacy, and perceived self-efficacy in taking hydroxyurea among patients who use *InCharge Health* and (2) examine potential increases in the awareness of hydroxyurea benefits and risks, appropriate prescribing, and perceived self-efficacy to correctly administer hydroxyurea therapy among SCD providers between baseline and 9 months of using the *HU Toolbox* app. We will measure the reach, adoption, implementation, and maintenance of both the *InCharge Health* and the *HU Toolbox* apps using the reach, effectiveness, adoption, implementation, and maintenance framework and qualitatively evaluate the implementation of both mHealth interventions.

Results: The study is currently enrolling study participants. Recruitment is anticipated to be completed by mid-2021.

Conclusions: If this two-level intervention, that is, the combined use of InCharge Health and HU Toolbox apps, demonstrates efficacy in increasing adherence to hydroxyurea and prescribing behavior in patients with SCD and their providers, respectively, both apps will be offered to other institutions outside the SCDIC through a future large-scale implementation-effectiveness study.

Trial Registration: ClinicalTrials.gov NCT04080167; https://clinicaltrials.gov/ct2/show/NCT04080167

International Registered Report Identifier (IRRID): DERR1-10.2196/16319

(JMIR Res Protoc 2020;9(7):e16319) doi:10.2196/16319

KEYWORDS

sickle cell anemia; digital medicine; adherence; hydroxycarbamide; RE-AIM; implementation science; health innovation; mobile phone

Introduction

Sickle Cell Disease and Hydroxyurea Therapy

Sickle cell disease (SCD) is a genetic disorder affecting approximately 100,000 Americans [1]. The effects of SCD are devastating, including severe acute and chronic pain, cognitive disability, renal failure, and lung disease. In controlled clinical trials, hydroxyurea reduces SCD complications (acute pain and acute chest syndrome events) and costs [2-5]. In uncontrolled population studies, hydroxyurea reduces hospitalizations and mortality, supporting the effectiveness of hydroxyurea outside of research studies [6-11]. Hydroxyurea is prescribed in a once-daily dosing, and blood counts are monitored every 1 to 3 months and titrated to reach a maximum tolerated dose defined by mild, reversible myelosuppression [12]. Given the evidence of its benefit, in 2014, the National Institutes of Health/National Heart, Lung, and Blood Institute (NHLBI) released guidelines recommending the use of hydroxyurea [13].

Hydroxyurea Underutilization and Efforts to Improve Its Use

Despite overwhelming evidence of its positive effects, hydroxyurea is vastly underutilized [14,15]. In analyses conducted using Medicaid claims data, fewer than 50% of adults were ever prescribed or initiated hydroxyurea, and only about 30% of those who initiated treatment achieved adequate adherence levels [16-19]. Among children, adherence was higher; however, the number of children who were prescribed hydroxyurea was low [20-22]. Barriers to prescribing hydroxyurea include providers' reluctance due to lack of knowledge about the drug and appropriate dosing, low patient acceptance due to insufficient knowledge or misconceptions about risks and benefits, and forgetfulness leading to poor adherence [14,15,20,23-28]. Patient forgetfulness related to daily hydroxyurea use is a common barrier [29] and may be exacerbated by the prevalence of cognitive dysfunction in patients with SCD, including working memory deficits and low motor processing speed [30-32]. Additionally, negative perceptions toward hydroxyurea are strongly associated with lower adherence to this medication [33]. Among prescribers, the anticipation of poor patient adherence dissuades medical providers from prescribing hydroxyurea [19,20,34].

Improved adherence to hydroxyurea achieves higher fetal hemoglobin (HbF) levels (thereby decreasing polymerization of the sickle hemoglobin), fewer hospital admissions, a higher health-related quality of life, and reductions in health care costs, resulting in major improvements in overall clinical outcomes [35,36].

In an effort to address the underutilization of evidence-based recommendations, including that of hydroxyurea, the NHLBI established the Center for Translation Research and Implementation Science in 2014 [37], and in 2016, the NHLBI funded the SCD Implementation Consortium (SCDIC) [38]. The goal of the SCDIC is to support multilevel and multicomponent interventions to address the quality gap in the delivery of evidence-based treatments for patients with SCD between the ages of 15 and 45 years (when the gap in care delivery is the greatest) employing implementation science strategies. The Integration of mHealth into SCD Care to Increase Hydroxyurea Utilization study is one of the planned multicenter studies within the SCDIC that utilizes the implementation

science framework and evaluation strategies to increase the adaptation and dissemination of evidence-based treatments among individuals with SCD.

Mobile Health Technology and Its Potential for Sickle Cell Disease Care and Hydroxyurea Utilization

The existing body of research provides support for mHealth interventions to improve treatment adherence across a variety of chronic conditions, including SCD [39-42]. Among patients with SCD, approximately 85% to 97% of patients own smartphones [29,43], and some use this technology to monitor pain [44,45].

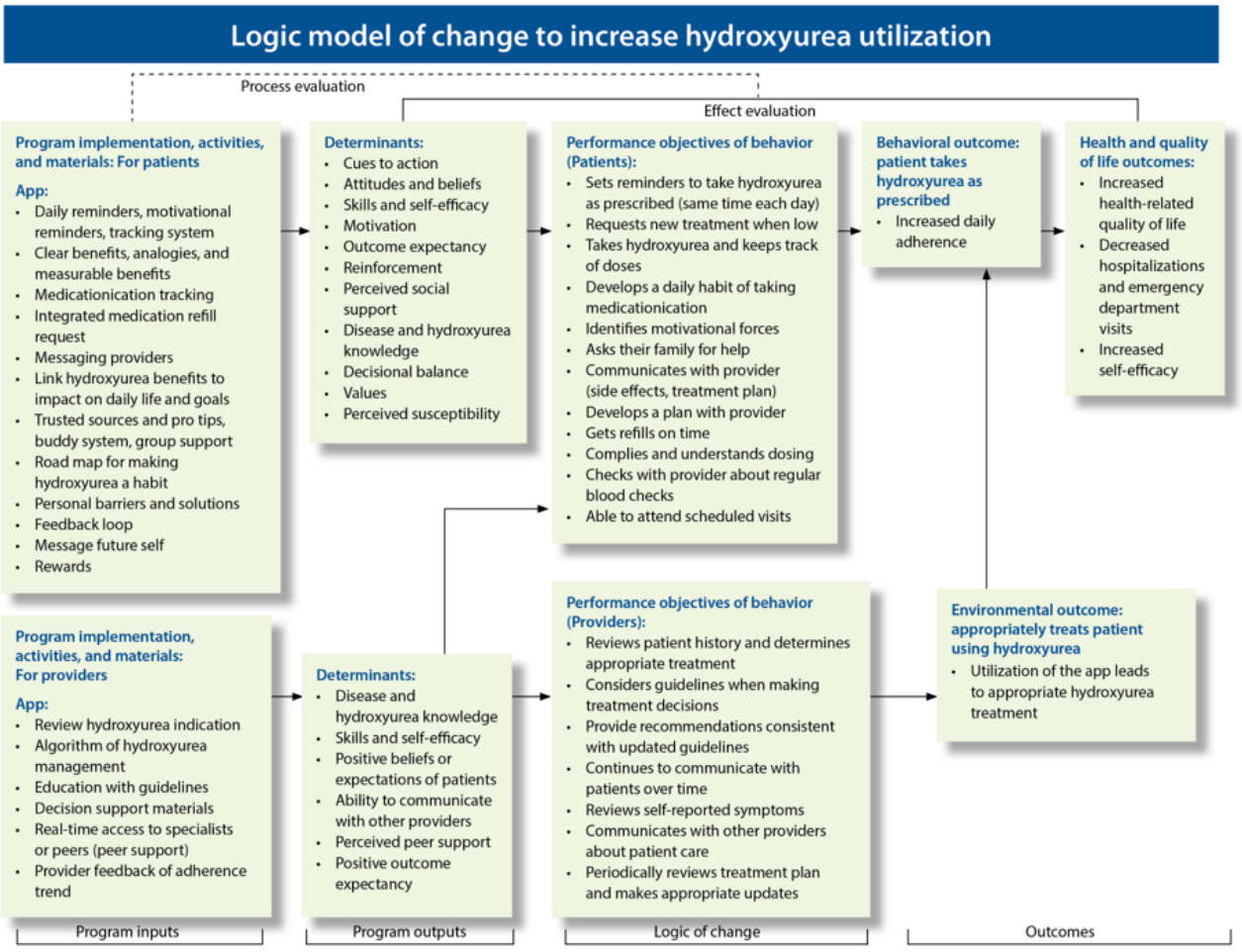
Preliminary studies suggest that mHealth interventions can specifically be used to improve hydroxyurea adherence. In children with SCD, the use of text message reminders combined with direct-observed therapy (via video recording) and financial incentives for 6 months significantly increased hydroxyurea adherence and hematologic markers [46,47]. In a study of 81 adolescents with SCD who received text messaging to improve hydroxyurea adherence, significant increases in relevant hematological indices (HbF, mean corpuscular volume [MCV], hemoglobin [Hb]) and significant reduction of hemolysis markers (absolute reticulocyte count [ARC], bilirubin, and lactate dehydrogenase [LDH]) were observed [43]. Collectively, these findings suggest that hydroxyurea use can be improved with the use of mHealth via improved adherence. A systematic review of mHealth apps for SCD has confirmed these findings but observed that the sample size of most studies was not large, and the studies were mostly observational or retrospective [42].

mHealth is also increasingly used to aid physicians in their medical decision making [48] and to facilitate consultations with other providers and experts in their areas of expertise [49,50], highlighting the broad applicability of mHealth, not only for patients but also for medical providers. In a survey of health care providers, more than 70% of physicians had smartphones, and 77% of nurses and doctors used medical apps [51]. The ease of access and increasing familiarity with apps has led to a growing focus on developing disease-specific medical apps for health care providers.

Logic Model of Change to Increase Hydroxyurea Utilization

We conceptualized a logic model that guided the development of mHealth apps to foster hydroxyurea utilization among patients and improve provider prescribing behaviors. This logic model used intervention mapping methods to develop and adapt behavioral models for testing mHealth as an intervention to increase hydroxyurea use. Intervention mapping is a systematic framework for developing, implementing, and adapting theory- and evidence-based interventions [52]. Using the knowledge of barriers to the uptake and adherence to hydroxyurea therapy, we mapped the determinants of hydroxyurea utilization (Figure 1). These determinants are hypothesized to drive the behaviors involved in patients' and providers' use of hydroxyurea and correspond to the barriers of hydroxyurea use that were identified through literature review and the results of a needs assessment within the study participating sites. Importantly, the patient and provider interventions were developed and aimed at the determinants that could affect the behavior involved in taking and prescribing hydroxyurea; the ultimate goal (the behavioral outcome) is to foster greater patient adherence to hydroxyurea (Figure 1).

Figure 1. Logic model of change to increase hydroxyurea utilization. This logic model maps all barriers identified by literature review and needs assessment analysis, with a focus on the determinants of the behaviors to hydroxyurea use. The intervention addresses the determinants of hydroxyurea use at both the patient and provider levels. If this two-level intervention is successful, hydroxyurea utilization will increase, as reflected by increased hydroxyurea adherence, resulting in improved health-related quality of life and reduction in acute health care utilization.



Hydroxyurea Adherence Behaviors for Patients

To guide the development of the mHealth app for patients, we used the health belief model (HBM) as the framework [53] for behavioral change. The HBM explains health behaviors and focuses on the attitudes and beliefs of individuals. The health-related action driving the increased use of hydroxyurea includes 5 constructs: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and self-efficacy. Notably, these 5 constructs represent modifiable factors that, together, can influence the increased use of hydroxyurea. The patient intervention focuses on these 5 constructs as the specific mechanisms to address the change in behavior (ie, medication adherence).

Behavioral Model for Mobile Health Utilization Among Medical Providers

The acceptance of new technology by users, including new mHealth innovations, determines its successful adaptation and, therefore, its intended effects. The perceptions of health care professionals regarding their ability to use mobile health care systems to accomplish a health care task is an important determinant that should also be considered when new technology is implemented. The technology acceptance model [54,55] is a conceptual model that explains the intent to use new information technology (eg, mHealth) or information science among users, including medical providers. Perceived usefulness, perceived ease of use, compatibility, and mobile health care systems self-efficacy are the most important determinants of the behavior intent of providers [56]. We considered all of these drivers and assessed them in the context of the hydroxyurea prescriber to develop the provider *HU Toolbox* as follows:

- *Perceived usefulness*: SCD providers require concise information to support clinical decision making while prescribing hydroxyurea.
- *Compatibility*: The previous experience SCD providers have in using mobile technology was considered.
- *Perceived ease of use*: The perception of SCD providers that mobile technology can be integrated with their electronic health system and their daily clinical routine.
- *Mobile health care systems self-efficacy*: SCD providers' perception that mHealth could help with the task of prescribing hydroxyurea.

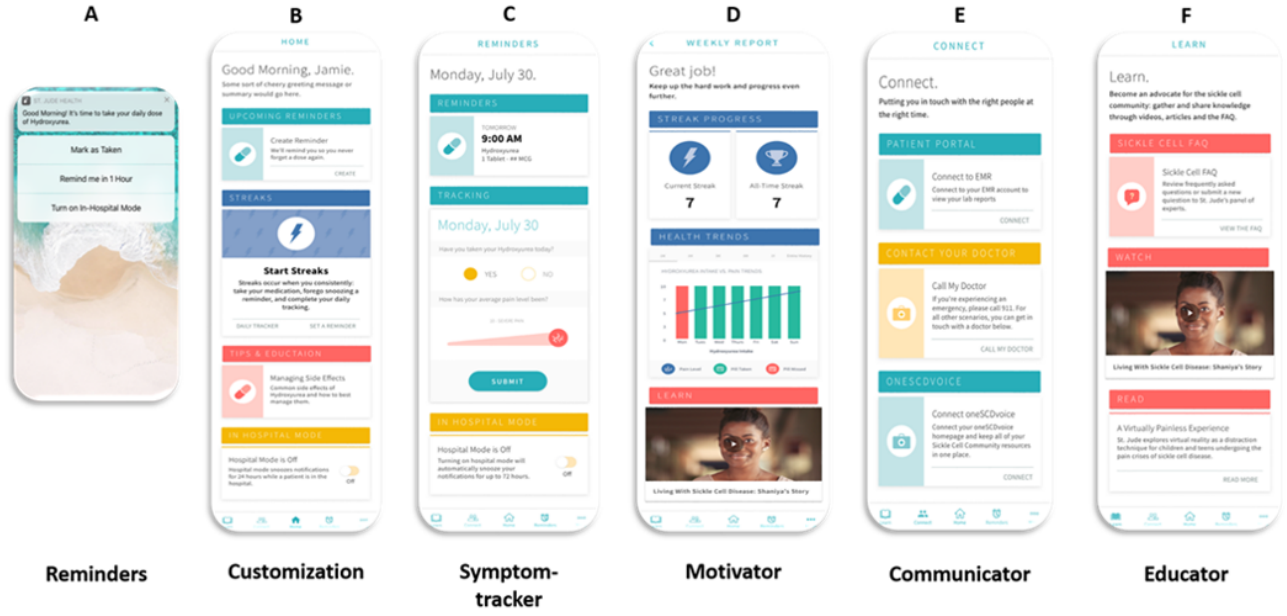
Description of the Mobile Health Interventions

InCharge Health Mobile App

InCharge Health was developed using a user-centered design approach, in which the patients' input in its development was obtained through an iterative process that started with a design-thinking session, followed by surveys and interviews that investigated barriers and facilitators of hydroxyurea use and preferences for its use [57]. A prototype was developed and further refined using information derived from focus groups with patients with SCD.

The *InCharge Health* mobile app includes several features to increase patient engagement, including the following: (1) daily customizable text message reminders that can be sent if the patient is hospitalized, (2) a daily recording of hydroxyurea adherence and pain score, (3) a 7-day streak that tracks daily adherence and graphing of adherence against pain symptoms, (4) a communication feature that allows the patient to connect to the health care provider and other patients, and (5) an education bank that provides information about SCD and hydroxyurea risks and benefits in layman's terms (Figure 2). Additionally, *InCharge Health* has an accountability partner feature that specifies a person (eg, friend, family member) who will receive notifications if the user has not documented the use of hydroxyurea for >4 hours (from the time of receipt of the daily reminder) and is encouraged to remind the patient to take their medication. The *InCharge Health* app does not collect any protected health information and functions in places with Wi-Fi accessibility or using the phone's data plan.

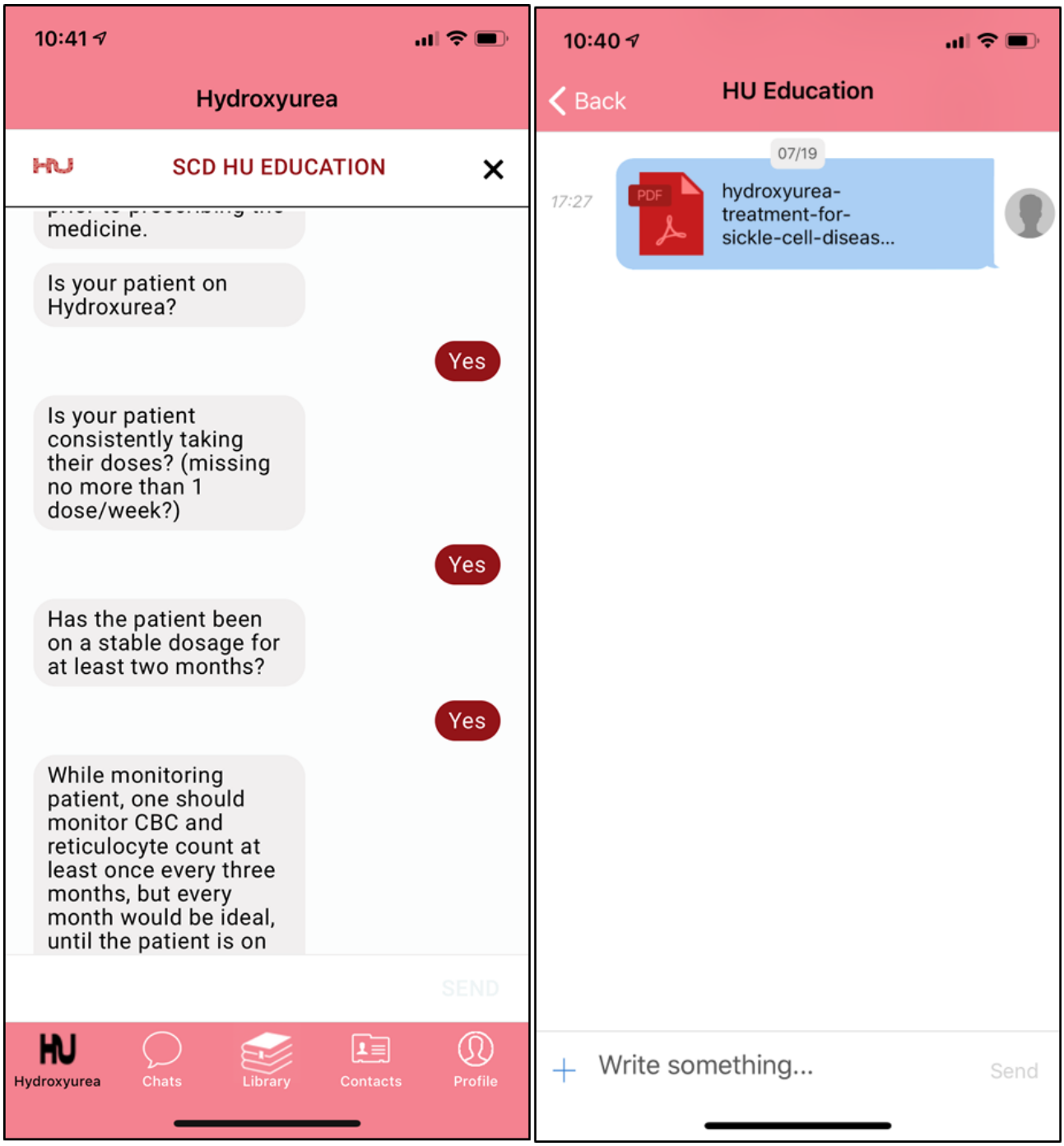
Figure 2. Features of the InCharge Health app for patients. (A) Push notifications will come daily and will prompt the patient participant to mark if the dose was taken, not taken, or be reminded later. (B) Customization of the push notification messages, time of the day, and choice of the accountability partner. (C) A daily pain and mood tracker is available and captures pain level and mood changes. (D) Graphing of pain level versus pain is available for the past 7 days. (E) A link to the patient portal accesses the patient's electronic medical chart, clinic numbers, and patient-led discussion forums. (F) A large resource bank is available with links to vetted educational websites, educational material, and educational videos and is included.



Hydroxyurea Toolbox Mobile App

The *HU Toolbox* is a decision-support tool developed with input from pediatricians, internists, and hematologists from several academic centers in North Carolina and members of the Community Care of North Carolina medical home system. The *HU Toolbox* app contains NHLBI guidelines adapted for pediatric and adult providers (guidelines and recommendations stratified by age). In addition to being an information source, the app contains artificial intelligence algorithms guiding the clinician on how to prescribe hydroxyurea and monitor its effects through a chatbot feature, which simulates a human conversation using text messaging. The *HU Toolbox* chatbot feature guides clinicians on how to recognize hydroxyurea side effects and how to manage them (Figure 3). Finally, a built-in SCD specialist feature is available, allowing providers to reach and consult SCD experts in their region, who respond to enquiries within 24 hours.

Figure 3. Features of the HU Toolbox mobile app: The HU Toolbox provides tools for medical providers prescribing hydroxyurea. The app provides a chatbot for users to ask questions about how to dose and monitor hydroxyurea effects and side effects (left panel). In addition, there is educational material available in a library (right panel) as well as the ability to chat directly with a local SCD specialist. HU Toolbox: Hydroxyurea Toolbox; SCD: sickle cell disease.



Specific Aims and Objectives

Aim 1: Improve Patient Adherence to Hydroxyurea

We will compare adherence to hydroxyurea at baseline with adherence after 6 months of *InCharge Health* among adolescents and adults with SCD. Our primary hypothesis is that, among patients with SCD, hydroxyurea therapy adherence will increase by 20% at 24 weeks after receiving the *InCharge Health* intervention, compared with their hydroxyurea adherence measured at baseline. Adherence will be measured by the proportion of days covered (PDC; the ratio of the number of days the patient is covered by the medication to the number of days in the treatment period) [58]. The rationale for choosing the primary end point is because a 20% increase in PDC is a clinically meaningful change and represents an increment of approximately 1.4 additional days of hydroxyurea use in a week's period. Our conservative estimated increase of 20% refill is based on previous studies that used text messages to increase hydroxyurea adherence and observed adherence increases as high as 60% [59]. The timing of the primary end point (at 24 weeks) is such that it will allow sufficient time to observe clinical and laboratory changes from increased

hydroxyurea adherence, as it may take an average of 4 to 6 months to observe full hydroxyurea effects.

Aim 1a: To Assess Patient Engagement and Behaviors Related to Use of InCharge Health

We will evaluate the consistent use of the app, patient satisfaction, and continued use of the app beyond the study period.

Aim 1b: To Examine the Improvement in Clinical and Patient Outcomes Related to the Use of InCharge Health

We will investigate changes in the proportion of patients with PDC >80%, hematologic indices, acute health care utilization, health-related quality of life, and perceived self-efficacy for medication use between baseline and 24 weeks after receiving the InCharge Health intervention.

Aim 2: Improve Provider Hydroxyurea Prescribing Behaviors

Among providers using the HU Toolbox app, we will examine the changes in knowledge of hydroxyurea benefits and risks as well as perceived self-efficacy to correctly prescribe hydroxyurea therapy between baseline and after 9 months of using the HU Toolbox intervention.

Aim 2a: To Examine Clinical Characteristics and Provider Engagement and Behaviors Related to the Use of the HU Toolbox

We will evaluate the frequency with which providers use the app and provider satisfaction and continued use of the app beyond the study period.

Aim 2b: To Assess Combined Effects of the Patient and Provider Mobile Health Interventions on Hydroxyurea Adherence and Acute Health Care Utilization.

We will examine if the changes in hydroxyurea adherence, emergency department visits, and hospitalizations are enhanced by the use of InCharge Health and HU Toolbox concomitantly.

Aim 3

We will qualitatively evaluate the barriers and facilitators of the implementation of mHealth interventions. We will examine the strategies used to support the implementation of mHealth interventions and evaluate the facilitators and barriers to implementation from multiple stakeholder perspectives: patients, providers, and administrators.

Methods

The study protocol is reported in accordance with the Standard Protocol Items for Clinical Trials (SPIRIT), where applicable (SPIRIT checklist; Multimedia Appendix 1) [60].

Evaluation Framework

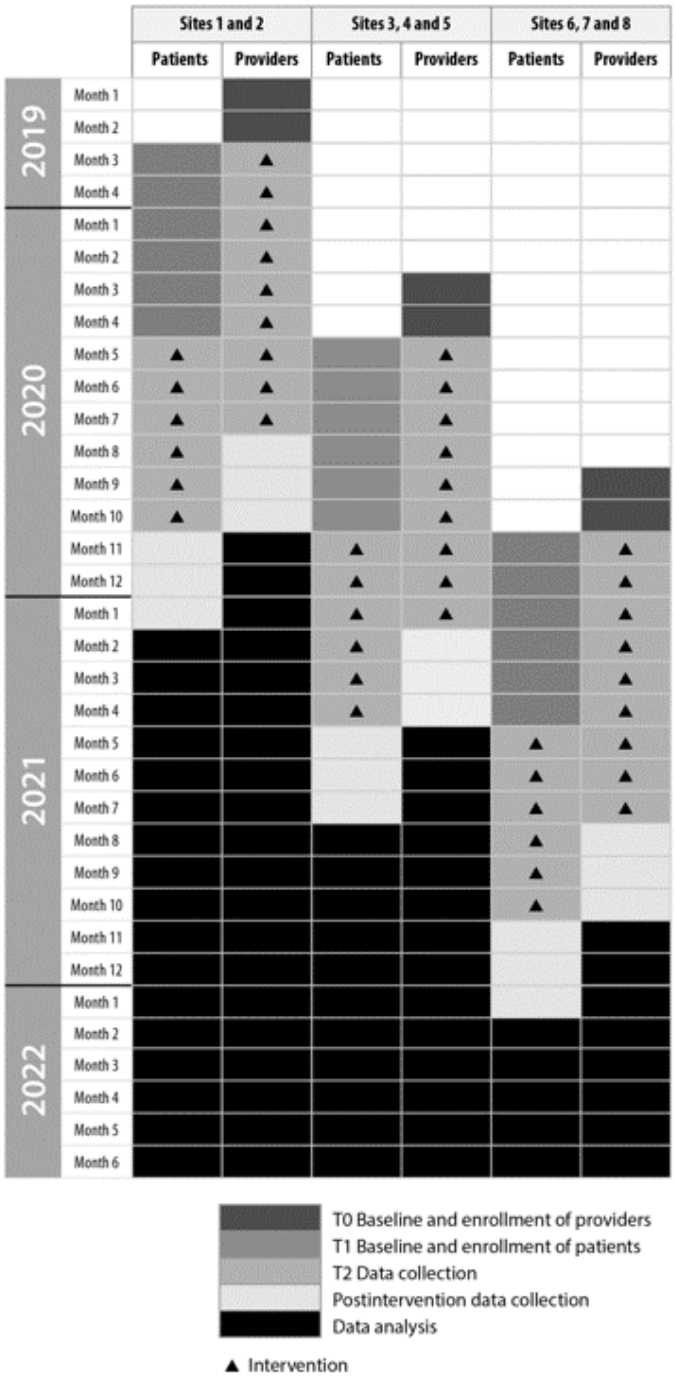
Key considerations to begin implementing mHealth for hydroxyurea utilization include recruitment in diverse care settings and estimating the reach, effectiveness, adoption, implementation, and maintenance of the apps, which are the 5 components of the RE-AIM framework [61]. RE-AIM is a useful framework to evaluate the utility of mHealth to foster hydroxyurea utilization and to broaden the future applicability and dissemination of the apps [62,63]. RE-AIM will be used in this study to measure the overall impact and robustness of apps to achieve improved patient adherence to hydroxyurea and better prescribing practices of this drug.

Study Design

The study design is a nonrandomized, closed cohort trial where the 2 mHealth apps will be introduced sequentially in 8 participating clinic sites over 3 time periods (Figure 4). A cohort of subjects recruited from within each site will be followed over each time period in which the unit of analysis will be the patient. Within each site, there will be one or more treatment clinics.

Each provider within a participating clinic will receive the *HU Toolbox* intervention for 9 months, while each patient participant will receive the *InCharge Health* app intervention for 6 months. The providers (physicians and advance care practitioners) will begin receiving the provider app 2 months before patients (at the same site) initiate the use of the patient app. There will be a staggered 6 months between groups of sites (Figure 4). The study rollout will allow for a baseline evaluation, followed by preparation and introduction of the provider app (education of providers and remaining staff), followed by implementation of the apps, and evaluation postimplementation (Figure 4). Implementing the interventions at the first 2 sites will allow us to determine any challenges and adapt to ensure increased uptake and implementation for the following sites.

Figure 4. Study time periods: 2 or 3 groups of sites will enter the study at each of the 3 time periods, and 4 study phases will take place during each study period. T0: introduction of HU Toolbox to providers, provider enrollment, and baseline data collection. T1: introduction of InCharge Health to patients, patient enrollment, and baseline data collection. T2: All enrolled patients and provider participants were followed as active study participants. Each patient will use the InCharge Health app for 6 months, and each provider will use the HU Toolbox app for 9 months. Postintervention data collection: this phase reflects the sustainability of the interventions. We will continue to provide technical support for both patient and provider applications and measure continued utilization of the applications and adherence to hydroxyurea. Solid triangle denotes InCharge Health and HU Toolbox interventions. HU Toolbox: Hydroxyurea Toolbox.



Study Setting

The study will be carried out at 8 diverse SCDIC participating clinical sites and their subsites. The study settings are variable and include academic and nonacademic sites within urban, suburban, and rural settings. The context for the program is diverse and presents an opportunity to test mHealth in different

settings, with not only geographical but also structural differences using the RE-AIM evaluation framework.

Participants

Potential participants will be approached during a nonemergent clinic visit. The study coordinator will verify that the participant (patient or provider) meets the study eligibility criteria (Textboxes 1 and 2), and will approach them in person, phone, or via electronic media about enrolling in the study. Participants will sign an informed consent before study participation (unless a waiver of consent is granted by the local institutional review board). If the participant is a minor, the legal guardian will sign the consent and assent will be obtained. Participants will be considered enrolled when consent is obtained, and inclusion criteria have been confirmed. All providers within each practice will be approached and invited to participate. All clinics will have each provider register within the app to allow provider-specific data. Each site will maintain a local enrollment log and will also confirm enrollment status in the data management system.

Textbox 1. Inclusion and exclusion criteria for patient participants.

Inclusion criteria

- Between 15 and 45 years
- Treated at or affiliated with one of the sickle cell diseases implementation consortium sites
- English speaking
- Confirmed sickle cell disease diagnosis by a hemoglobin fractionation test
- Owns a cellular/mobile smartphone (either Android or iOS)
- Hydroxyurea therapy:
  - Already receiving hydroxyurea therapy (at least one previous prescription for hydroxyurea in the past 3 months) or
  - Initiating hydroxyurea therapy (the first prescription must be written on the same day as study enrollment). Patient participants who initiate hydroxyurea on the same day of study enrollment will not contribute to the total target accrual for the site, but rather will be analyzed as a separate group

Exclusion criteria

- Known current pregnancy
- A red blood cell transfusion in the past 60 days. This is necessary as transfusions will mask laboratory markers and clinical changes from hydroxyurea
- Currently using consistency. another cellphone app or a web-based tool (electronic health tool) to increase hydroxyurea adherence

Textbox 2. Inclusion criteria and the exclusion criterion for provider participants.

Inclusion criteria

- Physician (including physician in training) or advanced practice provider (nurse practitioner or physician assistant) who cares for at least one patient with sickle cell disease for an anticipated minimum of 12 months from study enrollment
- Access to a cellular/mobile smartphone (either Android or iOS) or access to a computer with internet connectivity (*HU Toolbox* app can be accessed via the internet on any device)
- Exclusion criterion
- Currently using another phone app or a web-based tool to increase hydroxyurea adherence for patients with SCD in his/her practice

Implementation Strategies

To promote the uptake of both the patient and provider mHealth apps into practice, we will employ multiple implementation strategies. Sites will be provided with a list of discrete strategies (eg, education strategies such as conducting ongoing training and regular check-ins with patients and providers regarding app functionality). Each clinical site will be able to select a strategy or strategies that best fit their context. All sites will be required to provide training on the apps for both patients and providers using a standard training protocol, which is detailed in the study standard operating procedure document. Research staff will guide the participants on the installation of *InCharge Health* and *HU toolbox* on the participants' mobile devices (or computer in the case of providers). Using a developed script, the research team will provide instructions about app settings, explain how to use the app, and answer any questions. Before participants leave the clinic, patients will be asked to demonstrate their knowledge and ability to use the app. Centralized technical assistance (by the app developers) will be provided for both apps to ensure a high level of fidelity in their implementation. Specifically, patients and providers will be given a number to call and an email address if they have questions regarding the app or the study in general. Data related to technical problems related to the apps will be tracked to evaluate their functionality.

Study Outcome Measures

Primary Outcome

Efficacy will be determined by assessing the impact of *InCharge Health* on hydroxyurea by measuring the change in PDC from baseline (before intervention) to week 24 (primary outcome). For the PDC, the pharmacy that fills the most prescription claims within the target therapeutic category for a specific patient within the calendar range will be assigned responsibility for the patient. The pharmacy name and number where hydroxyurea is filled will be collected by the research coordinators at each study visit, and refill information will be requested from these pharmacies. All prescription drug refills, from all dispensing pharmacies, will be ascertained.

Secondary Outcomes

These include daily recorded adherence on the app; proportion of patients with PDC ≥80%; laboratory markers of hydroxyurea response (HbF, Hb concentration, MCV, ARC, absolute neutrophil count, indirect bilirubin, LDH); health care utilization (hospitalizations and emergency department visits); health-related quality of life; perceived health literacy, patient medication self-efficacy, and implementation outcomes.

Data Collection

After enrolling, patient participants will return at 12 and 24 weeks for study visits, where study-related procedures will be conducted (Table 1). Provider participants will complete an assessment of self-confidence in prescribing hydroxyurea at baseline and at the study exit (Table 2). Three months after study completion, *InCharge Health* and *HU Toolbox* usage will be assessed via analysis of app statistics. Additionally, at study completion, we will solicit feedback from patients and providers regarding the clinical usefulness of the apps and their usability and impact. (Tables 1 and 2). Clinical and implementation measures will be assessed using the RE-AIM framework, both for *InCharge Health* (Table 3) and *HU Toolbox* (Table 4).

We will conduct 15 semistructured key-informant interviews (30-60 min) with multiple key stakeholders toward the end of app implementation at each of the study sites. We will purposively sample and interview patients and providers (physicians and advance care practitioners) from each site according to mHealth app use (low uptake vs high uptake). The RE-AIM framework was used to develop the interview guides and systematically assess barriers and facilitators. For example, patients will be asked how using *InCharge Health* impacts the way they take hydroxyurea, whereas providers will be asked how using the *HU Toolbox* impacts the way they prescribe hydroxyurea. Patients and providers will also be asked about why they chose to participate in the study, training received for the apps, and whether they would continue to use the apps after the study is complete. We also plan interviews with clinic administrators to gain a clinic-level perspective on factors that influenced implementation.

Table 1. Schedule of evaluations for patient participants.

Measures and definition	Week 24 (retrospectively collected)	Baseline	Week 12	Week 24 (study exit)	Week 36 (poststudy)
Socio d emographic					
Age, sex, race, ethnicity, marital status, educational attainment, health insurance type, income, occupation	—[a]	x[b]	—	—	—
Informed consent	—	x	—	—	—
Patient adherence to hydroxyurea (Aim 1) and the combined effects of the patient and provider mHealth [c] interventions (Aim 2b)					
Hydroxyurea adherence					
Proportion of daily coverage	x	x	x	x	x
App daily adherence statistics and 7-day recall measure using the brief medication questionnaire	—	x		x	—
Clinical influence of the InCharge Health app; (Aim 1b) and the combined effects of the patient and provider mHealth interventions (Aim 2b)					
Hydroxyurea effect					
Date hydroxyurea initiated	—	x	—	—	—
MTD[d] dose (mg/kg/day) and date reached	—	x	—	—	—
Current dose (mg/kg/day and mg/day)	—	x	x	x	x
Biomarkers of hydroxyurea effect (HbF[e]%, Hb[f], MCV[g], ANC[h], ARC[i], indirect bilirubin, LDH[j])	x	x	x	x	x
Health care utilization					
Date and discharge diagnosis of ED[k] visits, acute care/infusion visit hospitalizations	x	x	x	x	x
Self-efficacy and health literacy					
PROMIS[l] self-efficacy for medication short form	—	x	—	x	—
Perceived health literacy	—	x	—	x	—
Health-related quality of life and pain report					
ASCQ-Me[m] pain impact, ASCQ-Me pain episode frequency and severity, PROMIS pain quality	—	x	—	x	—
Engagement of patients related to the use of InCharge Health app (Aim 1a)					
Implementation measures					
See Tables 3 and 4	—	—	—	x	—
mHealth satisfaction					
Perceived usability and acceptability of mHealth intervention (MARS[n]) [64]	—	—	x	x	—
Evaluation of facilitators and barriers to implementation of the mHealth app (Aim 3)					
Barriers and facilitators to implementation					
Qualitative interviews[o]	—	—	—	x	x

[a]Denotes not done at this timepoint.

[b]x denotes done at this timepoint.

[c]mHealth: mobile health.

[d]MTD: maximum tolerated dose.

[e]HbF: fetal hemoglobin.

[f]Hb: hemoglobin.

[g]MCV: mean corpuscular volume.

[h]ANC: absolute neutrophil count.

[i]ARC: absolute reticulocyte count.

[j]LDH: lactate dehydrogenase.

[k]ED: emergency department.

[l]PROMIS: Patient-Reported Outcomes Measurement Information System.

[m]ASCQ-Me: adult sickle cell quality of life measurement information system.

[n]MARS: mobile app rating scale.

[o]Conducted at the end of the study at each site.

Table 2. Schedule of evaluations for provider participants.

Measure and definition	Baseline	Week 36 (study exit)	Week 48 (poststudy)
Sociodemographic			
Age, sex, race, ethnicity, type of professional (physician, nurse practitioner, physician assistant), years in practice	x[a]	—[b]	—
Informed consent	—	—	—
Improve provider hydroxyurea awareness, prescribing, and monitoring behaviors (Aim 2)			
Self-efficacy and hydroxyurea knowledge			
Perceived confidence in prescribing hydroxyurea to patients with SCD[c], including correct daily dosing	x	x	—
Engagement of providers related to the use of the HU Toolbox app (Aim 2a)			
Implementation and mHealth satisfaction			
Perceived usability and acceptability of mHealth intervention (MARS[d] scale) [64]	—	x	—
Hydroxyurea prescribing practices (clinic-level measures)			
Total number of patients with SCD	x	x	x
Number of patients eligible to receive hydroxyurea therapy at provider participant's site[e]	x	x	x
Number of hydroxyurea-eligible patients who are prescribed hydroxyurea (all sickle genotypes)[e]	x	x	x
Evaluation of facilitators and barriers to implementation of the mHealth app (Aim 3)			
Barriers and facilitators to implementation			
Qualitative interviews[f]	—	x	—

[a]x denotes done at this time point.

[b]Denotes not done at this time point.

[c]SCD: sickle cell disease.

[d]MARS: mobile app rating scale.

[e]Hydroxyurea eligibility will follow the 2014 National Health Lung and Blood Institute guidelines as follows: hydroxyurea should be offered to all children with homozygous sickle hemoglobin mutation (HbSS) and compound heterozygous sickle hemoglobin and null beta thalassemia (HbSβ^0-thalassemia) age ≥9 months and prescribed to all symptomatic adults with HbSS/HbSβ^0-thalassemia, that is, >3 episodes of severe vaso-occlusion in the preceding 9 months [13].

[f]Conducted at the end of the study at each site.

For additional information on Implementation and mHealth satisfaction, please refer to Tables 3 and 4

Table 3. The reach, effectiveness, adoption, implementation, and maintenance evaluation measures of InCharge Health implementation.

Domains and measures		Data sources
Reach	• Sociodemographic characteristics of patients at each site • Proportion and representativeness of patients screened for the study (numerator) among all patients who receive hydroxyurea treatment (denominator) at each site • Proportion and representativeness of patients eligible for the study (numerator) among all patients who receive hydroxyurea treatment (denominator) at each site • Proportion and representativeness of patients participating/enrolled in the study (numerator) among all patients who receive hydroxyurea treatment and were eligible (denominator) at each site	• Clinic data collection forms • Clinic population demographics and treatment data, study database • Screening log • Qualitative interviews
Effectiveness	• Primary outcome • >20% improvement in the PDC[a] for hydroxyurea among those receiving the intervention	• Prescription drug claims (PDC for hydroxyurea refills)
	• Secondary outcomes • Change in Quality of life, self-efficacy, perceived health literacy • Change in percentage of patients with ED[b] visits, hospitalizations since the last study visit • Change in biomarkers of hydroxyurea effect (MCV[c], ANC[d], ARC[e], indirect bilirubin, HbF[f], Hb[g], LDH[h])	• Patient surveys (ASCQ-Me[i], PROMIS[j], Perceived health literacy, self-efficacy) • Medical chart abstraction • Qualitative interviews
Adoption	• Proportion and description of clinics in each site agreeing to support *InCharge Health* • Proportion and description of providers in each clinic agreeing to support *InCharge Health* (ie, proportion enrolled on the study)	• Clinic administrative data and data collection forms • Qualitative interviews
Implementation	• Consistency with which sites are able to implement the app as planned • Qualitative assessment of any adaptations or enhancement to recruitment strategies needed to meet enrollment by the clinic, by site • Assess adaptation of training needed to improve *InCharge Health* implementation at each site • Engagement with the app: percentage, number, and representativeness of patients who used *InCharge Health* during the study period (low, medium-low, medium, or high use; in the entire practice) • Proportion, number, and characteristics of patients who complete the study among those who initiate the use of the app but then later discontinue at each site • Percentage and characteristics of patients who reported satisfaction with the *InCharge Health* app (MARS[k] scale) • Clinic/provider assessment of perceptions of *InCharge Health* app for further scale-up or sustainability—ease of use, preferred features, and so on	• App usage statistics • Patient surveys • Qualitative interviews
Maintenance/sustainability	• Extent to which program leaders express a desire or intent to continue providing the app with patients at the conclusion of the research • Percentage of patients who continue to use the app beyond the study period and their representativeness	• Pharmacy claims data (PDC for hydroxyurea refills) • App use statistics • Clinic data collection forms • Qualitative interviews

[a]PDC: proportion of days covered.

[b]ED: emergency department.

[c]MCV: mean corpuscular volume.

[d]ANC: absolute neutrophil count.

[e]ARC: absolute reticulocyte count.

[f]HbF: fetal hemoglobin.

[g]Hb: hemoglobin.

[h]LDH: lactate dehydrogenase.

[i]ASCQ-Me: adult sickle cell quality of life measurement information system.

[j]PROMIS: Patient-Reported Outcomes Measurement Information System.

[k]MARS: mobile app rating scale.

Table 4. The reach, effectiveness, adoption, implementation, and maintenance evaluation measures of Hydroxyurea Toolbox implementation.

Domains	Measures	Data sources
Adoption—clinic	• Proportion and representativeness of clinics that agree to support the *HU*[a]*Toolbox*	• Institutional data to describe clinics (eg, size, case mix, years in service, regional sociodemographics of SCD[b] patients) • Clinic data collection form • Qualitative interviews
Adoption—provider	• Characteristics of providers at each site (eg, specialty, years in practice, sociodemographics, level of expertise) • Proportion and representativeness of eligible providers approached in the study (numerator) among all providers (denominator) • Proportion and representativeness of enrolled providers in the study (numerator) among all eligible providers (denominator) at each site	• Provider survey • Clinic data collection form
Effectiveness	• Number and proportion of providers demonstrating improved knowledge and self-efficacy in hydroxyurea administration • Percentage of patients who were prescribed hydroxyurea per provider	• Provider survey • Medical chart abstraction • Qualitative interviews
Implementation	• Consistency with which sites are able to implement the use of the Toolbox app as planned • Engagement with the app: Percentage, number, and representativeness of providers that appropriately used *HU Toolbox* app (low or high use; in the entire practice) • Percentage of providers who reported satisfaction with *HU Toolbox* app (MARS[c] scale) • Percentage of patients whose provider used the Toolbox at each site • App usage statistics	• App usage statistics • Provider survey • Qualitative interviews
Maintenance/sustainability	• Extent to which program leaders express a desire or intent to offer or encourage the use of the Toolbox app by their clinical providers at the conclusion of the research • Percentage of providers who continue to use the provider app beyond the study period, and representativeness • Percentage of providers who continue to prescribe hydroxyurea to their patients	• App usage statistics • Clinic data collection form • Qualitative interviews

[a]HU: Hydroxyurea.

[b]MARS: mobile app rating scale.

[b]SCD: sickle cell disease.

Sample Size

Sample sizes were calculated for the primary outcome, PDC, using simulations based on the linear mixed model in the analysis plan. First, we modeled the baseline values. Results from Candrilli et al [18] indicated a left-skewed distribution for adherence measured by medication possession ratio. We expect a similarly left-skewed distribution for PDC. The baseline PDC was therefore modeled as PDC=100 × X, where X follows a beta distribution with parameters 1.0 and 0.6667. This produced a left-skewed distribution with a mean of 60% (SD 30%), closely paralleling a mean of 0.60 (SD 0.32) reported by Candrilli et al [18] for the medication possession ratio. We included site-to-site variation in baseline PDC by adding a site-specific random variate, drawn from a normal distribution with a mean of 0 (SD 0.2) to the 2 parameters. The resulting site-specific means are between 56% and 69%, with a probability of .95. Baseline values were modeled by drawing random samples from these beta distributions.

To model treatment response, including site-to-site variation in response, we added the expected response of 12% plus a site-specific random variable drawn from a normal distribution with a mean of 0 (SD 5.48) to each baseline value for PDC. Residual intrasubject variation at each time point (in the linear mixed model) was included by adding a separate random variable drawn from a normal distribution with a mean of 0 to each simulated PDC value. Assuming that approximately 25% of 24-week PDC values will be missing, each 24-week observation was randomly deleted with a probability of .25.

The treatment effect is measured against noise, which includes residual intrasubject variation and site-to-site variation in treatment response. Therefore, power was investigated by specifying SDs for the 2 variance components, generating

simulated data sets of 8 sites with 46 subjects recruited per site, and fitting the linear mixed model to each data set. Power was estimated as the percentage of simulated data sets producing a statistically significant increase in PDC among 1000 simulated data sets.

Baseline and posttreatment PDC are expected to be moderately to strongly correlated (ie, subjects with lower baseline PDC will tend to have lower posttreatment PDC than those with higher starting values). This expectation places limits on the variance components because the correlation varies inversely with the variance of the measurements. Variance components that result in a correlation of 0.50 also result in approximately 90% power to detect a treatment effect under the conditions specified in the simulations. A correlation of 0.50 is well below expectations, indicating that the study will have considerable power to detect the posited treatment effect under the specified conditions.

Patients who initiate hydroxyurea on the same day of enrollment will not contribute to the primary aim but will be analyzed as a separate subset of participants for the secondary outcomes only, as no baseline PDC will be able to be calculated for them. The total number of physicians and advanced practitioners in all participating sites is approximately 100. All of them will be approached, and the total number of those who agree to participate will be computed.

Methods of Analysis

Aim 1: Improve Patient Adherence to Hydroxyurea

Changes in PDC in response to treatment will be evaluated using a linear mixed model. Predictors will include a random effect for the study site, a fixed binary indicator for treatment, the interaction of the site with treatment, and a random effect for the subject nested within the site. The interaction is included to test for differences in PDC changes among sites. The random subject effect is included to account for the correlation induced by repeated observations of the same subjects. If the interaction is not statistically significant, then it will be dropped from the model, and inferences about treatment response will be based on the main effect of treatment. If the treatment does indicate site-to-site variation in change in PDC, then pairwise comparisons between changes at the sites will be made using the Tukey honestly significant difference to control the type I error rate.

Aim 1a: To Assess Patient Engagement and Behaviors Related to the Use of InCharge Health

Counts and scores of the measures in Textboxes 1 and 2 will be graphed with box plots by month. Using the box plots from the last month, patients will be classified into 4 levels of app usability: *low* (<25% of the daily app usage), *medium-low* (25%-49% of the daily app usage), *medium-high* (50%-74% of the daily app usage) or *high* (75%-100% of the daily app usage) by initially using quartiles of the implementation measures, then examining the box plots of the measures and adjusting as needed to create 4 clinically meaningful groupings of app users. App uptake will be computed at the end of the study at each site.

Aim 1b: To Examine the Improvement in Clinical and Patient Outcomes Related to the Use of InCharge Health

The linear mixed model will also be employed to evaluate changes in laboratory biomarkers of hydroxyurea effect, quality of life, health literacy, self-efficacy, and satisfaction with the app (as listed in Textboxes 1 and 2) between baseline and 24 weeks. The models will include the treatment indicator and site as usual, a 4-level categorical predictor of use of the app (low, medium-low, medium-high, and high) and the interaction of app use with the treatment. A statistically significant interaction will be interpreted to mean that changes in an outcome in response to the treatment varied with use of the app. The Tukey HSD test will then be employed to identify the pairwise differences that contributed to the significant effect. If no variation with use of the app is found, then the interaction will be dropped from the model as described earlier. The models for laboratory biomarkers will also include time since starting hydroxyurea and sickle cell genotype as covariates. Models, including site-level characteristics of urban versus rural and academic versus community will also be created to determine if heterogeneity in the site characteristics impacts intervention efficacy. For dichotomous outcomes, such as PDC ≥80% versus <80% and hospitalization and emergency room visits during the study, generalized linear mixed models (GLMM) will be employed with a logit link to relate the outcome to the predictors [65]. The GLMM models will follow the same format as the linear mixed model above with fixed effects for intervention/app use and random effects for sites and subjects within sites.

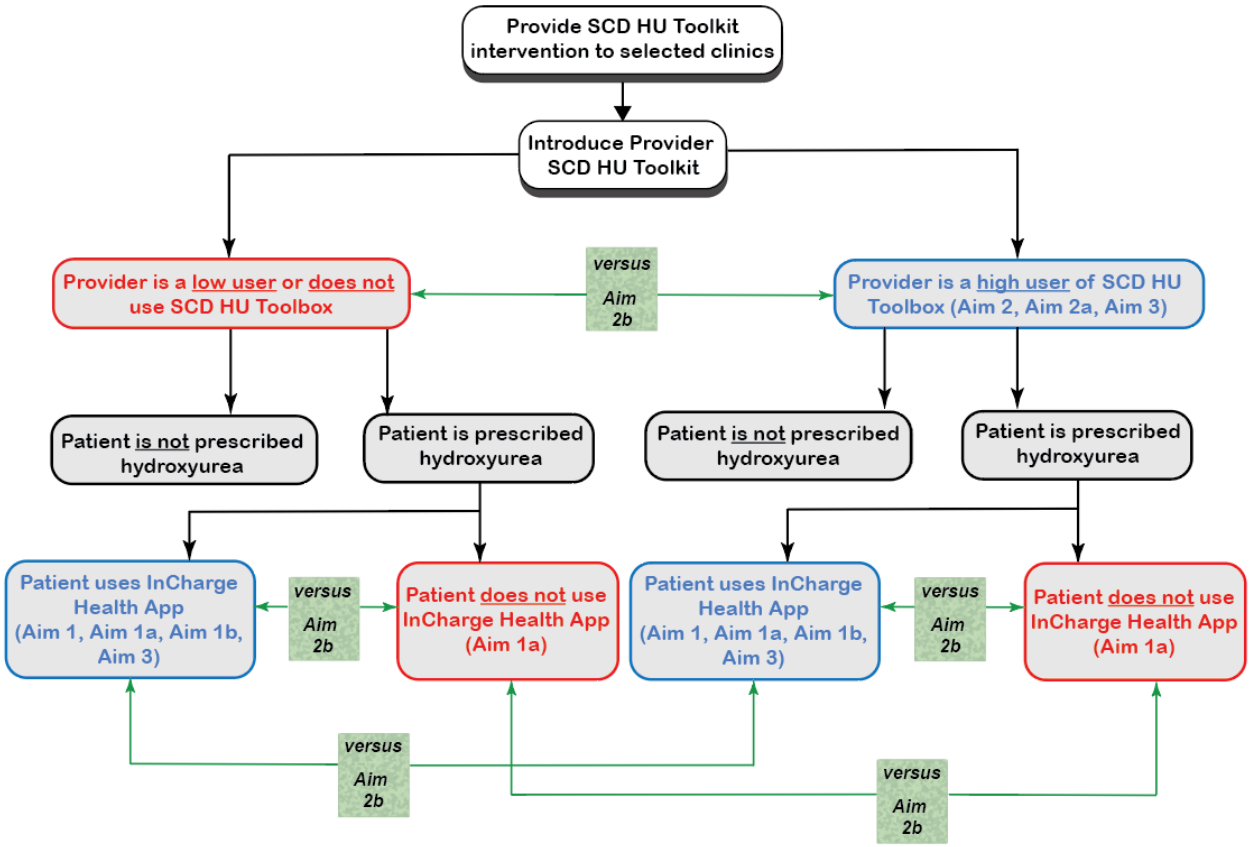
Aim 2: Improve Provider Hydroxyurea Prescribing Behaviors

Given the limited number of providers expected to enroll in the study, many of the analyses are simplified and do not account for the across the site and across time complexities of the study design. As such, the results should be considered exploratory. Using baseline data, providers will be classified into 4 categories, according to the level of comfort and expertise in caring for patients with SCD (Multimedia Appendix 2). We will attempt to evaluate the implementation and effectiveness outcomes stratified by this provider categorization to better understand how expertise impacts the implementation and effectiveness of the *HU Toolbox* app.

Aim 2a: To Examine Clinic Characteristics and Provider Engagement and Behaviors Related to the Use of the HU Toolbox

Uptake of the *HU Toolbox* by providers after 9 months will be assessed using the implementation measures identified in Table 4 (under implementation). Box plots for each measure for all participants will be combined and stratified by expertise level. One-way analysis of variance or Kruskal-Wallis tests will examine differences in the uptake of the *HU Toolbox* across expertise levels (Figure 5). If the null hypothesis is rejected, Dunn's test will be employed for multiple comparisons. If an experience level has fewer than 5 providers, it will be combined with the closest lower experience level. The results of these analyses will be used to identify clinically meaningful *low* and *high* toolbox app uptake groups for Aim 2b.

Figure 5. Study group comparisons according to each aim. The introduction and investigation of each intervention is performed sequentially. A total of 4 possible intervention combinations will be evaluated and compared: provider and patient use the intervention (patient and provider blue boxes), neither provider nor patient uses the intervention (patient and provider blue boxes), provider uses the intervention, but the patient does not (provider: blue box and patient: red box), and the patient uses the intervention, but the provider does not (provider red box and patient blue box). HU Toolbox: Hydroxyurea Toolbox; SCD: sickle cell disease.



Aim 2b: To Assess the Combined Effects of the Patient and Provider Mobile Health Interventions on Hydroxyurea Adherence and Health Care Utilization

Figure 5 shows the sequential introduction and investigation of each intervention. A total of 4 possible intervention combinations will be evaluated and compared: provider and patient use the intervention, neither provider nor patient uses the intervention, the provider uses the intervention, but the patient does not, and the patient uses the intervention, but the provider does not. Comparisons within and across groups will be conducted. This analysis seeks to identify the impact of both the patient and provider interventions on hydroxyurea adherence and acute health care utilization (count of emergency department visits and hospitalizations per patient) at baseline and at 6 months. These outcomes will be treated as Poisson variables in GLMMs with log link functions. Predictors will include an indicator for time (baseline vs 6 months), a categorical predictor for the 4 levels of *InCharge Health* app uptake defined in Aim 1a, an indicator for low (less than one day per month use of the app in a 6-month period) versus high provider (one or more days per month use of the app in a 6-month period) toolkit app uptake, the interaction between patient and provider uptake, and a random effect to account for clustering of baseline and 9-month measures within providers. The Tukey HSD test will be employed for pairwise comparisons among predictor categories if statistically significant effects of patient characteristics, provider characteristics, or interactions are found. App uptake will be computed at the end of the study at each site.

Aim 3: Qualitatively Evaluate the Barriers and Facilitators of the Implementation of Mobile Health Interventions

Sufficient understanding of the contextual factors in the implementation of mHealth interventions is critical to ensuring future scale-up and translation of study findings [66]. As such, for Aim 3, we will build on the RE-AIM quantitative findings by using qualitative inquiry to identify common barriers and facilitators across the sites and to support the development of implementation strategies for use in future studies. Data will be collected and analyzed concurrently using a mixed methods approach, where qualitative data will be secondary to the quantitative assessment [67].

Results

The study is currently enrolling participants (NCT 04080167). Recruitment is anticipated to be completed by mid-2021. The results are expected to be submitted for publication toward the end of the project in early 2022.

Discussion

Hydroxyurea has proven its efficacy in treating patients with SCD, but its utilization in real-world settings is suboptimal. mHealth interventions have increasingly been used to foster greater adherence to medication and to facilitate the use of therapies by prescribers. In this study, we propose to overcome the barriers to hydroxyurea utilization by using a 2-level mHealth intervention: the *InCharge Health* app for patients and the *HU Toolbox* app for providers. We will examine the uptake of these 2 interventions using implementation science strategies. Although acknowledging the multilevel barriers to hydroxyurea utilization, our approach will address the main barriers affecting hydroxyurea adoption and use among patients with SCD and focus on improving prescribing practices among providers. This 2-level approach will allow us to demonstrate the clinical effect of mHealth interventions to improve adherence among patients (the main outcome of the study) and, at the same time, address and evaluate other barriers to optimal care among providers. Our findings will enhance the subsequent implementation of mHealth in diverse settings and populations, as the participating sites are substantially different in geographical settings (eg, urban, suburban, and rural) and population characteristics. The study will provide preliminary data on the integration of mHealth into clinical care, its clinical influence, and evaluate how well this strategy is accepted, adopted, and sustained in diverse clinical settings.

The Integration of mHealth into SCD Care to Increase Hydroxyurea Utilization study will be the first large-scale prospective trial to investigate mHealth interventions for SCD using an implementation science framework to improve hydroxyurea effectiveness and adaptation while incorporating implementation strategies to maximize the integration of the apps into clinical practice. If successful, this model may create a new paradigm in which mHealth interventions can be integrated into routine clinical practice in real-world settings. This approach focuses on the complexity of therapies for chronic diseases in which the lack of widespread adaptation is multifactorial and should account for multiple stakeholders.

This study has some limitations. PDC is one of the multiple measures of medication adherence; however, it allows us to pragmatically estimate adherence as it approximates optimal adherence when PDC is ≥80%. PDC is an accepted quality measure of adherence and the metric used by the Centers for Medicare and Medicaid Services as the process measure of adherence [68]. PDC best reflects the *real-world* setting as opposed to the use of electronic bottles or video-recorded daily dose ingestion (ie, directly observed adherence measure). The Integration of mHealth into SCD Care to Increase Hydroxyurea Utilization study does not include randomization of mHealth interventions, and this approach may be considered as the next step in our research.

Few prospective intervention studies to improve hydroxyurea adherence in SCD using mHealth have been undertaken [42]. In general, they have shown positive results in improving daily hydroxyurea utilization and other outcomes, such as health-related quality of life [69,70]. The Integration of mHealth into SCD Care to Increase Hydroxyurea Utilization study expands the existing studies because it (1) addresses all the important behavior determinants of suboptimal hydroxyurea utilization at both the patient and provider levels, (2) incorporates them into mHealth apps for both patients and providers, and (3) studies a large population of patients with SCD and their providers in different geographic and clinical settings. Finally, engagement with mHealth interventions will be of particular importance during the study, as sustained use of mHealth intervention may decrease over time. Our study plans to evaluate engagement with mHealth interventions by monitoring app usability (frequency of use and specific features used) in addition to performing qualitative analysis to better ascertain factors influencing engagement with mHealth.

In summary, the Integration of mHealth into SCD Care to Increase Hydroxyurea Utilization study is the first study investigating the efficacy and implementation of mHealth interventions on 2 levels to improve hydroxyurea utilization, namely the patient and the provider, in a large multicenter prospective study. Importantly, the development of both mHealth interventions was informed by the stakeholders involved (patients with SCD and their providers). If successful, this study will help define the role of mHealth in increasing hydroxyurea utilization at multiple levels and will allow for a large-scale implementation trial that will rigorously test which strategies are most effective in disseminating mHealth to more patients with SCD and their providers.

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Authors' Contributions

JH, NS, LD, DB, MF, RG, VG, RL, AK, CM, JS, TW, MT, CC, AB, MP, LK, and HB conceived the study. All authors contributed to refining the study design and finalizing the protocol. JH drafted the initial and final versions of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

JH receives research funds from Global Blood Therapeutics and Novartis, and consultant fees from MJH Life Sciences. NS receives research funding from Global Blood Therapeutics, Imara and Novartis, is a paid speaker for Novartis, Global Blood Therapeutics, Alexion, and is a consultant for Novartis and Commonwealth Serum Laboratories Behring. HB receives research funding from Sanofi, Otsuka, Improved Patient Outcomes, Novo Nordisk, and is a consultant for Novartis, Sanofi, and Abbott.

Multimedia Appendix 1
SPIRIT checklist.
[DOC File , 123 KB - resprot_v9i7e16319_app1.doc]

Multimedia Appendix 2
Categorization of providers according to expertise level (classification developed by Dr Wally R Smith and Dr Richard Lottenberg).
[PNG File , 44 KB - resprot_v9i7e16319_app2.png]

Multimedia Appendix 3
List of sickle cell disease implementation consortium investigators.
[DOCX File , 26 KB - resprot_v9i7e16319_app3.docx]

References

1. Hassell K. Population estimates of sickle cell disease in the US. Am J Prev Med 2010 Apr;38(4 Suppl):S512-S521. [doi: 10.1016/j.amepre.2009.12.022] [Medline: 20331952]
2. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. N Engl J Med 1995 May 18;332(20):1317-1322. [doi: 10.1056/NEJM199505183322001] [Medline: 7715639]
3. Wang WC, Oyeku SO, Luo Z, Boulet SL, Miller ST, Casella JF, BABY HUG Investigators. Hydroxyurea is associated with lower costs of care of young children with sickle cell anemia. Pediatrics 2013 Oct;132(4):677-683 [FREE Full text] [doi: 10.1542/peds.2013-0333] [Medline: 23999955]
4. Wang W, Ware R, Miller S, Iyer R, Casella J, Minniti C, BABY HUG Investigators. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet 2011 May 14;377(9778):1663-1672 [FREE Full text] [doi: 10.1016/S0140-6736(11)60355-3] [Medline: 21571150]
5. Thornburg CD, Files BA, Luo Z, Miller ST, Kalpatthi R, Iyer R, BABY HUG Investigators. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood 2012 Nov 22;120(22):4304-10; quiz 4448 [FREE Full text] [doi: 10.1182/blood-2012-03-419879] [Medline: 22915643]
6. Nottage KA, Hankins JS, Smeltzer M, Mzayek F, Wang WC, Aygun B, et al. Hydroxyurea use and hospitalization trends in a comprehensive pediatric sickle cell program. PLoS One 2013;8(8):e72077 [FREE Full text] [doi: 10.1371/journal.pone.0072077] [Medline: 23967276]
7. Stallworth JR, Jerrell JM, Tripathi A. Cost-effectiveness of hydroxyurea in reducing the frequency of pain episodes and hospitalization in pediatric sickle cell disease. Am J Hematol 2010 Oct;85(10):795-797 [FREE Full text] [doi: 10.1002/ajh.21772] [Medline: 20645429]
8. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. J Am Med Assoc 2003 Apr 2;289(13):1645-1651. [doi: 10.1001/jama.289.13.1645] [Medline: 12672732]
9. Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood 2010 Mar 25;115(12):2354-2363. [doi: 10.1182/blood-2009-05-221333] [Medline: 19903897]
10. Lobo CL, Pinto JF, Nascimento EM, Moura PG, Cardoso GP, Hankins JS. The effect of hydroxcarbamide therapy on survival of children with sickle cell disease. Br J Haematol 2013 Jun;161(6):852-860. [doi: 10.1111/bjh.12323] [Medline: 23590693]
11. Lê PQ, Gulbis B, Dedeken L, Dupont S, Vanderfaeillie A, Heijmans C, et al. Survival among children and adults with sickle cell disease in Belgium: benefit from hydroxyurea treatment. Pediatr Blood Cancer 2015 Nov;62(11):1956-1961. [doi: 10.1002/pbc.25608] [Medline: 26173735]
12. Ware R. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood 2010 Jul 1;115(26):5300-5311 [FREE Full text] [doi: 10.1182/blood-2009-04-146852] [Medline: 20223921]
13. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. J Am Med Assoc 2014 Sep 10;312(10):1033-1048. [doi: 10.1001/jama.2014.10517] [Medline: 25203083]

14. Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, et al. National institutes of health consensus development conference statement: hydroxyurea treatment for sickle cell disease. Ann Intern Med 2008 Jun 17;148(12):932-938. [doi: 10.7326/0003-4819-148-12-200806170-00220] [Medline: 18458271]
15. Lanzkron S, Strouse JJ, Wilson R, Beach MC, Haywood C, Park H, et al. Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med 2008 Jun 17;148(12):939-955 [FREE Full text] [doi: 10.7326/0003-4819-148-12-200806170-00221] [Medline: 18458272]
16. Ritho J, Liu H, Hartzema AG, Lottenberg R. Hydroxyurea use in patients with sickle cell disease in a medicaid population. Am J Hematol 2011 Oct;86(10):888-890 [FREE Full text] [doi: 10.1002/ajh.22134] [Medline: 21922530]
17. Lanzkron S, Haywood C, Fagan PJ, Rand CS. Examining the effectiveness of hydroxyurea in people with sickle cell disease. J Health Care Poor Underserved 2010 Feb;21(1):277-286. [doi: 10.1353/hpu.0.0272] [Medline: 20173269]
18. Candrilli SD, O'Brien SH, Ware RE, Nahata MC, Seiber EE, Balkrishnan R. Hydroxyurea adherence and associated outcomes among medicaid enrollees with sickle cell disease. Am J Hematol 2011 Mar;86(3):273-277 [FREE Full text] [doi: 10.1002/ajh.21968] [Medline: 21328441]
19. Lanzkron S, Haywood C, Hassell KL, Rand C. Provider barriers to hydroxyurea use in adults with sickle cell disease: a survey of the sickle cell disease adult provider network. J Natl Med Assoc 2008 Aug;100(8):968-973. [Medline: 18717150]
20. Lebensburger JD, Sidonio RF, Debaun MR, Safford MM, Howard TH, Scarinci IC. Exploring barriers and facilitators to clinical trial enrollment in the context of sickle cell anemia and hydroxyurea. Pediatr Blood Cancer 2013 Aug;60(8):1333-1337 [FREE Full text] [doi: 10.1002/pbc.24486] [Medline: 23418000]
21. Patel NG, Lindsey T, Strunk RC, DeBaun MR. Prevalence of daily medication adherence among children with sickle cell disease: a 1-year retrospective cohort analysis. Pediatr Blood Cancer 2010 Sep;55(3):554-556 [FREE Full text] [doi: 10.1002/pbc.22605] [Medline: 20658630]
22. Reeves SL, Jary HK, Gondhi JP, Raphael JL, Lisabeth LD, Dombkowski KJ. Hydroxyurea use among children with sickle cell anemia. Pediatr Blood Cancer 2019 Jun;66(6):e27721. [doi: 10.1002/pbc.27721] [Medline: 30900800]
23. Haywood C, Beach MC, Bediako S, Carroll CP, Lattimer L, Jarrett D, et al. Examining the characteristics and beliefs of hydroxyurea users and nonusers among adults with sickle cell disease. Am J Hematol 2011 Jan;86(1):85-87 [FREE Full text] [doi: 10.1002/ajh.21883] [Medline: 21117058]
24. Crosby LE, Barach I, McGrady ME, Kalinyak KA, Eastin AR, Mitchell MJ. Integrating interactive web-based technology to assess adherence and clinical outcomes in pediatric sickle cell disease. Anemia 2012;2012:492428 [FREE Full text] [doi: 10.1155/2012/492428] [Medline: 22701785]
25. Thornburg CD, Calatroni A, Telen M, Kemper AR. Adherence to hydroxyurea therapy in children with sickle cell anemia. J Pediatr 2010 Mar;156(3):415-419 [FREE Full text] [doi: 10.1016/j.jpeds.2009.09.044] [Medline: 19880135]
26. Walsh KE, Cutrona SL, Kavanagh PL, Crosby LE, Malone C, Lobner K, et al. Medication adherence among pediatric patients with sickle cell disease: a systematic review. Pediatrics 2014 Dec;134(6):1175-1183 [FREE Full text] [doi: 10.1542/peds.2014-0177] [Medline: 25404717]
27. Strouse JJ, Heeney MM. Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. Pediatr Blood Cancer 2012 Aug;59(2):365-371 [FREE Full text] [doi: 10.1002/pbc.24178] [Medline: 22517797]
28. Oyeku SO, Driscoll MC, Cohen HW, Trachtman R, Pashankar F, Mullen C, et al. Parental and other factors associated with hydroxyurea use for pediatric sickle cell disease. Pediatr Blood Cancer 2013 Apr;60(4):653-658 [FREE Full text] [doi: 10.1002/pbc.24381] [Medline: 23129068]
29. Badawy SM, Thompson AA, Liem RI. Technology access and smartphone app preferences for medication adherence in adolescents and young adults with sickle cell disease. Pediatr Blood Cancer 2016 May;63(5):848-852. [doi: 10.1002/pbc.25905] [Medline: 26844685]
30. Smith KE, Schatz J. Working memory in children with neurocognitive effects from sickle cell disease: contributions of the central executive and processing speed. Dev Neuropsychol 2016;41(4):231-244 [FREE Full text] [doi: 10.1080/87565641.2016.1238474] [Medline: 27759435]
31. Vichinsky EP, Neumayr LD, Gold JI, Weiner MW, Rule RR, Truran D, Neuropsychological Dysfunction and Neuroimaging Adult Sickle Cell Anemia Study Group. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. J Am Med Assoc 2010 May 12;303(18):1823-1831 [FREE Full text] [doi: 10.1001/jama.2010.562] [Medline: 20460621]
32. Jorgensen D, Metti A, Butters M, Mettenburg J, Rosano C, Novelli E. Disease severity and slower psychomotor speed in adults with sickle cell disease. Blood Adv 2017 Sep 26;1(21):1790-1795 [FREE Full text] [doi: 10.1182/bloodadvances.2017008219] [Medline: 29296825]
33. Badawy SM, Thompson AA, Lai J, Penedo FJ, Rychlik K, Liem RI. Adherence to hydroxyurea, health-related quality of life domains, and patients' perceptions of sickle cell disease and hydroxyurea: a cross-sectional study in adolescents and young adults. Health Qual Life Outcomes 2017 Jul 5;15(1):136 [FREE Full text] [doi: 10.1186/s12955-017-0713-x] [Medline: 28679417]
34. Brandow AM, Jirovec DL, Panepinto JA. Hydroxyurea in children with sickle cell disease: practice patterns and barriers to utilization. Am J Hematol 2010 Aug;85(8):611-613 [FREE Full text] [doi: 10.1002/ajh.21749] [Medline: 20658592]

35. Zhou J, Han J, Nutescu EA, Gordeuk VR, Saraf SL, Calip GS. Hydroxycarbamide adherence and cumulative dose associated with hospital readmission in sickle cell disease: a 6-year population-based cohort study. Br J Haematol 2018 Jul;182(2):259-270 [FREE Full text] [doi: 10.1111/bjh.15396] [Medline: 29767446]
36. Badawy SM, Thompson AA, Holl JL, Penedo FJ, Liem RI. Healthcare utilization and hydroxyurea adherence in youth with sickle cell disease. Pediatr Hematol Oncol 2018;35(5-6):297-308. [doi: 10.1080/08880018.2018.1505988] [Medline: 30636474]
37. Mensah GA, Engelgau M, Stoney C, Mishoe H, Kaufmann P, Freemer M, Trans-NHLBI T4 Translation Research Work Groups. News from NIH: a center for translation research and implementation science. Transl Behav Med 2015 Jun;5(2):127-130 [FREE Full text] [doi: 10.1007/s13142-015-0310-7] [Medline: 26029274]
38. DiMartino LD, Baumann AA, Hsu LL, Kanter J, Gordeuk VR, Glassberg J, Sickle Cell Disease Implementation Consortium. The sickle cell disease implementation consortium: translating evidence-based guidelines into practice for sickle cell disease. Am J Hematol 2018 Dec;93(12):E391-E395 [FREE Full text] [doi: 10.1002/ajh.25282] [Medline: 30203558]
39. Palmer M, Barnard S, Perel P, Free C. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Database Syst Rev 2018 Jun 22;6:CD012675 [FREE Full text] [doi: 10.1002/14651858.CD012675.pub2] [Medline: 29932455]
40. Farzandipour M, Nabovati E, Sharif R, Arani M, Anvari S. Patient self-management of asthma using mobile health applications: a systematic review of the functionalities and effects. Appl Clin Inform 2017 Oct;8(4):1068-1081 [FREE Full text] [doi: 10.4338/ACI-2017-07-R-0116] [Medline: 29241254]
41. Mohammadi R, Tafti MA, Hoveidamanesh S, Ghanavati R, Pournik O. Reflection on mobile applications for blood pressure management: a systematic review on potential effects and initiatives. Stud Health Technol Inform 2018;247:306-310. [Medline: 29677972]
42. Badawy SM, Cronin RM, Hankins J, Crosby L, DeBaun M, Thompson AA, et al. Patient-centered ehealth interventions for children, adolescents, and adults with sickle cell disease: systematic review. J Med Internet Res 2018 Jul 19;20(7):e10940 [FREE Full text] [doi: 10.2196/10940] [Medline: 30026178]
43. Estepp JH, Winter B, Johnson M, Smeltzer MP, Howard SC, Hankins JS. Improved hydroxyurea effect with the use of text messaging in children with sickle cell anemia. Pediatr Blood Cancer 2014 Nov;61(11):2031-2036. [doi: 10.1002/pbc.25177] [Medline: 25132074]
44. Schatz J, Schlenz AM, McClellan CB, Puffer ES, Hardy S, Pfeiffer M, et al. Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. Clin J Pain 2015 Jun;31(6):536-547 [FREE Full text] [doi: 10.1097/AJP.0000000000000183] [Medline: 25503599]
45. Shah N, Jonassaint J, de Castro L. Patients welcome the sickle cell disease mobile application to record symptoms via technology (SMART). Hemoglobin 2014;38(2):99-103. [doi: 10.3109/03630269.2014.880716] [Medline: 24512633]
46. Creary SE, Gladwin MT, Byrne M, Hildesheim M, Krishnamurti L. A pilot study of electronic directly observed therapy to improve hydroxyurea adherence in pediatric patients with sickle-cell disease. Pediatr Blood Cancer 2014 Jun;61(6):1068-1073. [doi: 10.1002/pbc.24931] [Medline: 24436121]
47. Creary S, Chisolm D, Stanek J, Hankins J, O'Brien SH. A multidimensional electronic hydroxyurea adherence intervention for children with sickle cell disease: single-arm before-after study. JMIR Mhealth Uhealth 2019 Aug 8;7(8):e13452 [FREE Full text] [doi: 10.2196/13452] [Medline: 31397291]
48. Silveira DV, Marcolino MS, Machado EL, Ferreira CG, Alkmim MB, Resende ES, et al. Development and evaluation of a mobile decision support system for hypertension management in the primary care setting in Brazil: mixed-methods field study on usability, feasibility, and utility. JMIR Mhealth Uhealth 2019 Mar 25;7(3):e9869 [FREE Full text] [doi: 10.2196/mhealth.9869] [Medline: 30907740]
49. Klingberg A, Wallis LA, Hasselberg M, Yen P, Fritzell SC. Teleconsultation using mobile phones for diagnosis and acute care of burn injuries among emergency physicians: mixed-methods study. JMIR Mhealth Uhealth 2018 Oct 19;6(10):e11076 [FREE Full text] [doi: 10.2196/11076] [Medline: 30341047]
50. Lim J, Cloete G, Dunsmuir DT, Payne BA, Scheffer C, von Dadelszen P, et al. Usability and feasibility of PIERS on the move: an mhealth app for pre-eclampsia triage. JMIR Mhealth Uhealth 2015 Apr 17;3(2):e37 [FREE Full text] [doi: 10.2196/mhealth.3942] [Medline: 25887292]
51. Moore S, Jayewardene D. The use of smartphones in clinical practice. Nurs Manag (Harrow) 2014 Jul;21(4):18-22. [doi: 10.7748/nm.21.4.18.e1225] [Medline: 24967805]
52. Fernandez ME, Ruiter RA, Markham CM, Kok G. Intervention mapping: theory- and evidence-based health promotion program planning: perspective and examples. Front Public Health 2019;7:209 [FREE Full text] [doi: 10.3389/fpubh.2019.00209] [Medline: 31475126]
53. Stretcher V, Rosenstock I. The health belief model. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: Theory, Research, and Practice. San Francisco, CA: Jossey-Bass; 1997.
54. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Q 1989 Sep;13(3):319. [doi: 10.2307/249008]
55. Venkatesh V, Davis FD. A model of the antecedents of perceived ease of use: development and test. Decis Sci 1996 Sep;27(3):451-481. [doi: 10.1111/j.1540-5915.1996.tb01822.x]

56. Wu J, Wang S, Lin L. Mobile computing acceptance factors in the healthcare industry: a structural equation model. Int J Med Inform 2007 Jan;76(1):66-77. [doi: 10.1016/j.ijmedinf.2006.06.006] [Medline: 16901749]
57. Alberts NM, Badawy SM, Hodges J, Estepp JH, Nwosu C, Khan H, et al. Development of the InCharge Health Mobile App to Improve Adherence to Hydroxyurea in Patients With Sickle Cell Disease: User-Centered Design Approach. JMIR Mhealth Uhealth 2020 May 08;8(5):e14884-e14821 [FREE Full text] [doi: 10.2196/14884] [Medline: 32383683]
58. Bijlsma MJ, Janssen F, Hak E. Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method. Pharmacoepidemiol Drug Saf 2016 Mar;25(3):325-332. [doi: 10.1002/pds.3935] [Medline: 26687394]
59. Pernell B, DeBaun M, Becker K, Rodeghier M, Bryant V, Cronin R. Improving medication adherence with two-way short message service reminders in sickle cell disease and asthma. A feasibility randomized controlled trial. Appl Clin Inform 2017 May 24;8(2):541-559 [FREE Full text] [doi: 10.4338/ACI-2016-12-RA-0203] [Medline: 28536723]
60. Chan A, Tetzlaff J, Altman D, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 5;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
61. Shoup JA, Gaglio B, Varda D, Glasgow RE. Network analysis of RE-AIM framework: chronology of the field and the connectivity of its contributors. Transl Behav Med 2015 Jun;5(2):216-232 [FREE Full text] [doi: 10.1007/s13142-014-0300-1] [Medline: 26029284]
62. Quanbeck A, Gustafson DH, Marsch LA, Chih MY, Kornfield R, McTavish F, et al. Implementing a mobile health system to integrate the treatment of addiction into primary care: a hybrid implementation-effectiveness study. J Med Internet Res 2018 Jan 30;20(1):e37 [FREE Full text] [doi: 10.2196/jmir.8928] [Medline: 29382624]
63. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM planning and evaluation framework: adapting to new science and practice with a 20-year review. Front Public Health 2019;7:64 [FREE Full text] [doi: 10.3389/fpubh.2019.00064] [Medline: 30984733]
64. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. JMIR Mhealth Uhealth 2015 Mar 11;3(1):e27 [FREE Full text] [doi: 10.2196/mhealth.3422] [Medline: 25760773]
65. Baio G, Copas A, Ambler G, Hargreaves J, Beard E, Omar RZ. Sample size calculation for a stepped wedge trial. Trials 2015 Aug 17;16(1):354 [FREE Full text] [doi: 10.1186/s13063-015-0840-9] [Medline: 26282553]
66. Bakken S, Ruland CM. Translating clinical informatics interventions into routine clinical care: how can the RE-AIM framework help? J Am Med Inform Assoc 2009;16(6):889-897 [FREE Full text] [doi: 10.1197/jamia.M3085] [Medline: 19717799]
67. Palinkas LA, Aarons GA, Horwitz S, Chamberlain P, Hurlburt M, Landsverk J. Mixed method designs in implementation research. Adm Policy Ment Health 2011 Jan;38(1):44-53 [FREE Full text] [doi: 10.1007/s10488-010-0314-z] [Medline: 20967495]
68. Bosworth HB. Enhancing Medication Adherence: The Public Health Dilemma. New York, USA: Springer Healthcare; 2012.
69. Green NS, Manwani D, Matos S, Hicks A, Soto L, Castillo Y, et al. Randomized feasibility trial to improve hydroxyurea adherence in youth ages 10-18 years through community health workers: the HABIT study. Pediatr Blood Cancer 2017 Dec;64(12):e26689 [FREE Full text] [doi: 10.1002/pbc.26689] [Medline: 28643377]
70. Smaldone A, Findley S, Manwani D, Jia H, Green NS. HABIT, a randomized feasibility trial to increase hydroxyurea adherence, suggests improved health-related quality of life in youths with sickle cell disease. J Pediatr 2018 Jun;197:177-85.e2 [FREE Full text] [doi: 10.1016/j.jpeds.2018.01.054] [Medline: 29571930]

Abbreviations

ANOVA: analysis of variance
ED: emergency department
GLMM: generalized linear mixed models
HbF: fetal hemoglobin
HBM: health belief model
HU Toolbox: Hydroxyurea Toolbox
LDH: lactate dehydrogenase
LMM: linear mixed model
MARS: mobile app rating scale
MCV: mean corpuscular volume
mHealth: mobile health
MTD: maximum tolerated dose
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institutes of Health

PDC: proportion of daily coverage
PROMIS: Patient-Reported Outcomes Measurement Information System
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
SCD: sickle cell disease
SCDIC: sickle cell disease implementation consortium
SPIRIT: Standard Protocol Items for Clinical Trials

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Protocol

Assessment of the Effectiveness and Cost-Effectiveness of Tailored Web- and Text-Based Smoking Cessation Support in Primary Care (iQuit in Practice II): Protocol for a Randomized Controlled Trial

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Abstract

Background: The prevalence of smoking is declining; however, it continues to be a major public health burden. In England, primary care is the health setting that provides smoking cessation support to most smokers. However, this setting has one of the lowest success rates. The iQuit in practice intervention (iQuit) is a tailored web-based and text message intervention developed for use in primary care consultations as an adjunct to routine smoking cessation support with the aim of increasing success rates. iQuit has demonstrated feasibility, acceptability, and potential effectiveness.

Objective: This definitive trial aims to determine the effectiveness and cost-effectiveness of iQuit when used as an adjunct to the usual support provided to patients who wish to quit smoking, compared with usual care alone.

Methods: The iQuit in Practice II trial is a two-arm, parallel-group, randomized controlled trial (RCT) with a 1:1 individual allocation comparing usual care (ie, pharmacotherapy combined with multisession behavioral support)—the control—with usual care plus iQuit—the intervention. Participants were recruited through primary care clinics and talked to a smoking cessation advisor. Participants were randomized during the initial consultation, and those allocated to the intervention group received a tailored advice report and 90 days of text messaging in addition to the standard support provided to all patients.

Results: The primary outcome is self-reported prolonged abstinence biochemically verified using saliva cotinine at 6 months after the quit date. A sample size of 1700 participants, with 850 per arm, would yield 90% power to detect a 4.3% difference in validated quit rates between the groups at the two-sided 5% level of significance. The Cambridge East Research Ethics Committee approved the study in February 2016, and funding for the study was granted from May 2016. In total, 1671 participants were recruited between August 2016 and July 2019. Follow-up for all participants was completed in January 2020. Data analysis will begin in the summer of 2020.

Conclusions: iQuit in Practice II is a definitive, pragmatic RCT assessing whether a digital intervention can augment the impact of routine smoking cessation support in primary care. Previous research has found good acceptability and feasibility for delivering iQuit among smoking cessation advisors working in primary care. If demonstrated to be cost-effective, iQuit could be delivered across primary care and other settings, such as community pharmacies. The potential benefit would likely be highest where less behavioral support is delivered.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 44559004; http://www.isrctn.com/ISRCTN44559004.

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KEYWORDS

text messaging; smoking cessation; internet-based intervention; adults; smokers; tobacco; primary care

Introduction

Public Health Burden of Smoking

In 2015, the total estimated smoking-related cost to the UK National Health Service (NHS) was GB £2.6 billion (US $3.3 billion), of which GB £1.1 billion (US $1.4 billion) was within primary care settings [1]. Smoking-related morbidity accounts for 489 300 hospital admissions and 77,800 deaths in England each year. About 14.4% of adults in England currently smoke [2], and despite the fact that smoking prevalence has fallen over recent years, this equates to approximately 6.4 million adults aged >20 years [3]. Prevalence has reduced mostly in the 18- to 24-year age group; however, the proportion of adults still smoking is highest among the unemployed and those of a lower economic status. There has been some improvement in the quit success rate of this population, which may be due to the European Union tobacco products directive, which was finalized in 2017 [4]. Prohibition of smoking in public spaces and the use of smoking cessation services may have contributed to the reduction in smoking prevalence over the last 15 years [5]. However, to achieve the Department of Health's vision of a smoke-free generation by 2035 [6], there is a strong need to increase the effectiveness and cost-effectiveness of existing interventions embedded within health care in addition to other tobacco control initiatives.

Primary Care as a Setting for Smoking Interventions

Since 2012, when revisions were made to the quality and outcomes framework's reporting of smoking status, general practitioners (GPs) have been incentivized to offer and record stop-smoking support to all registered patients [7]. Therefore, primary care is an important setting for smoking cessation support. Physicians, nurses, and other health care practitioners are in a prime position to engage with and provide smoking cessation support to patients presenting at specialized health clinics (eg, asthma, hypertension, diabetes) and general consultations. Many practices train at least one health care practitioner to offer and deliver smoking cessation support, and the two most commonly trained practitioners to deliver support (ie, health care assistants and nurses) are equally effective at delivering this support [8].

The stop smoking services (SSS) follow the National Institute for Health and Care Excellence recommendations [9] to provide one-to-one behavioral support, discussing and providing pharmacotherapy for smokers wishing to quit. Although the number of people attending NHS stop smoking services in primary care and general practice has fallen in recent years [2,10], the proportion of successful quit attempts (self-report at 4 weeks after a quit attempt) remains steady at 51% [10]. A systematic review of 44 studies showed that patients receiving cessation support from nurses or other health care practitioners offering advice, counseling, and other strategies increased their chances of a successful quit attempt (at 6 months after quit date) by 29% (relative risk [RR] 1.29; 95% CI 1.21 to 1.38), 15.7% in the treatment arm (nursing intervention) versus 12.2% in the control arm (minimal intervention) [11]. In this review, *nursing intervention* was defined as the provision of any kind of support or advice by nurses, and the control group comprised those who saw the same nurse but received only brief advice and self-help materials. In addition, increasing the amount of behavioral support can further aid the smoker to quit (RR 1.15; 95% CI 1.08 to 1.22) [12].

Text Messaging and Tailored Interventions for Smoking Cessation (Effectiveness and Cost-Effectiveness)

Tailored interventions use data collected on or about an individual to make the information provided to them more personally relevant, increasing the likelihood that it will be read, understood, and acted upon. Tailored self-help interventions can be more effective than nontailored materials (RR 1.28; 95% CI 1.18 to 1.37) [13] and are better than no help at all (RR 1.34; 95% CI 1.19 to 1.51) [13]. In addition, text messaging programs can increase quit rates (RR 1.54; 95% CI 1.19 to 2.00) [14].

Currently, 96% of adults in the United Kingdom have access to a mobile phone, and in 2017, 6.4 billion SMS text messages were sent [15]. A Cochrane review of 12 studies assessing the effectiveness of text-based mobile phone interventions to support a quit attempt found a positive effect of mobile phone interventions on abstinence compared with controls at 6 months (RR 1.67; 95% CI 1.46 to 1.90), 9.3% in the treatment arm versus 5.6% in the control arm [16]. The majority of interventions in these trials were SMS text message based, whereas the control arms varied from daily nontailored text messages to no intervention.

The York Health Economics Consortium [17] concluded that there was not enough evidence concerning the cost-effectiveness of NHS-related smoking interventions. Their review showed some cost benefits, but the studies analyzed were far-reaching and included smoking cessation support in hospital settings, some very old studies, and studies that were of both low- and high-intensity interventions.

However, smoking cessation interventions have been shown to be cost-effective in many populations, including low-income populations [18] and people with chronic obstructive pulmonary disease (COPD) [19]. Tailored smoking cessation interventions have also been shown to be cost-effective [20], with the cost

benefit increasing the older the smoker is at the time of quitting (Table 1—data adapted from the txt2stop trial) [20]. However, although quitters in the txt2Stop trial had access to NHS SSS, the intervention was delivered as an adjunct to these services and not through them.

Table 1. A summary of incremental costs and quality-adjusted life years gained per 1000 participants.

Characteristics	Age (years)		
	<30	30-40	>40
Incremental cost, GB£ (US$)	−11,066 (−13,682)	−30,320 (−37,487)	−74,214 (−91,756)
Incremental quality-adjusted life years	20	27	38

The intervention in this trial (iQuit in practice intervention [iQuit]) is a tailored smoking cessation system designed for use by health care practitioners during the delivery of routine cessation support. iQuit is the culmination of research into the effectiveness of tailored smoking cessation advice reports [21-24] and evidence from trials using SMS text messages as a means of delivering tailored messages to smokers to assist them in their quit attempt [20,25-31]. Using a web-based questionnaire, the practitioner asks smokers a series of questions that are used to tailor an advice report. iQuit also delivers a 90-day program of automated, tailored, and interactive text messages, designed to support the smoker in their quit attempt.

The iQuit in Practice Pilot Trial

iQuit has previously been assessed for feasibility, acceptability, and short-term effectiveness in a randomized controlled trial (RCT) [32]. In the trial, we found good acceptability for iQuit from participants and advisors. A total of 93.7% of participants found the texts easy to understand, 67.7% felt receiving support by text message acceptable, and 44.8% said that the text messages had helped them to quit smoking. It took advisors approximately 8 min (mean 7.7 min SD 4.0) to deliver the intervention and gave a mean score of 4.6 (SD 0.7, 5-point scale) for ease of using the web-based questionnaire within a consultation [32]. In terms of its effect on short-term abstinence (Table 2), the primary focus of the trial, we found no significant between-group differences. However, although not prespecified, we found statistically significant between-group differences for both self-reported 6-month prolonged abstinence at the 6-month follow-up and for continuous abstinence.

Table 2. Summary of smoking outcomes from the iQuit in Practice pilot trial.

Smoking outcomes for the iQuit in Practice pilot trial	Control arm, n (%)	Intervention arm, n (%)	Absolute difference, % (95% CI)	Odds ratio (95% CI)
Primary outcome				
Self-reported 2-week point-prevalence abstinence at 8-week follow-up	122 (40.3)	135 (45.2)	4.9 (−3.0 to 12.7)	1.22 (0.88 to 1.69)
Secondary outcomes				
Carbon monoxide–verified 2-week point-prevalence abstinence at 4-week follow-up after quit date	71 (23)	81 (27)	3.7 (−3.3 to 10.6)	1.21 (0.84 to 1.76)
Self-reported 3-month prolonged abstinence at 6-month follow-up	70 (23)	76 (25)	2.3 (−4.5 to 9.1)	1.13 (0.78 to 1.65)
Additional outcomes				
Self-reported 6-month prolonged abstinence at 6-month follow-up	27 (9)	45 (15)	6.1 (0.9 to 11.4)	1.81 (1.09 to 3.01)
Continuous abstinence (4-week, 8-week, and 6-month follow-ups)	19 (6)	34 (11)	5.1 (0.6 to 9.8)	1.92 (1.07 to 3.45)

The RR for the long-term intervention effect at 6 months was 1.69 (95% CI 1.08 to 2.65). The estimated probability that the intervention would produce a small intervention effect equivalent to an RR of at least 1.2 is 93%, and the probability of a medium effect size of 1.5 is 70%.

This trial is therefore a definitive, pragmatic RCT in primary care to assess the effectiveness and cost-effectiveness of iQuit on biochemically validated abstinence at a 6-month follow-up. It will be assessed against the *usual practice* for smoking cessation consultations.

Trial Objectives

The study aims to assess the effectiveness and cost-effectiveness of iQuit when delivered alongside usual care compared with usual care alone.

Design

iQuit in Practice II is a two-arm, parallel-group RCT with 1:1 individual allocation comparing usual care (control) with usual care plus iQuit (intervention).

Methods

Practices: Recruitment

Participants were recruited from general practices in the East of England under the remit of the Eastern and North Thames clinical research networks. Our pilot study [32] suggested that 22 is a feasible minimum target of participating smokers per practice; therefore, we set out to approach 66 practices over 36 months to achieve our initial proposed sample size of 1452 participants. However, participant recruitment was monitored and reported monthly to the study team by the trial coordinator. Detailed graphs and charts of overall and per practice activity informed whether more or fewer general practices were needed to achieve the target.

General practices were eligible if they had at least one smoking cessation advisor trained to deliver level 2 smoking cessation advice (or were willing to be trained to that level). Practices were not to be participating in any other smoking cessation research studies, and all smoking cessation advisors had to have internet access from a computer in their consultation room and access to a printer. Training and site initiation took place in a single 2-hour session. Training included informed consent, using the iQuit web-based questionnaire, and an explanation of RCTs.

Participants: Inclusion and Exclusion Criteria

Patients were eligible for the study if they met all of the following criteria: (1) a current tobacco smoker (ie, they usually smoked at least one cigarette a day and had smoked in the past 7 days), (2) able to read and understand English and could provide written informed consent, (3) ≥18 years, (4) had a mobile phone and were familiar with sending and receiving text messages, (5) willing to participate in the study and follow study procedures, and (6) not enrolled in another formal smoking cessation study or treatment program at the time.

Health care practitioners were prompted to check whether patients met the eligibility criteria when they signed on to the iQuit in Practice computer program. The ability to read and understand English was a subjective decision by the practitioner based on their knowledge of the patient and the patient's medical records.

Patients were excluded if they were considered by their GP to be unsuitable for the study for any reason. There was no proforma of ineligible conditions. It was at the discretion of the GP and health care practitioner to decide whether or not the patient should take part in the study. GPs were asked to screen lists of known smokers before invitation letters were sent. Reasons for noninclusion included mental illness, terminal illness, or dementia. Patients with existing medical conditions such as COPD or heart disease were not excluded unless their GP considered them unsuitable. As individual allocation worked effectively in the pilot trial, with no contamination found [32], patients were also not excluded if more than one person per household was participating in the trial.

Participants were not re-enrolled into the trial if they had not been successful in their quit attempt. However, this did not exclude them from receiving further support from their smoking cessation advisor.

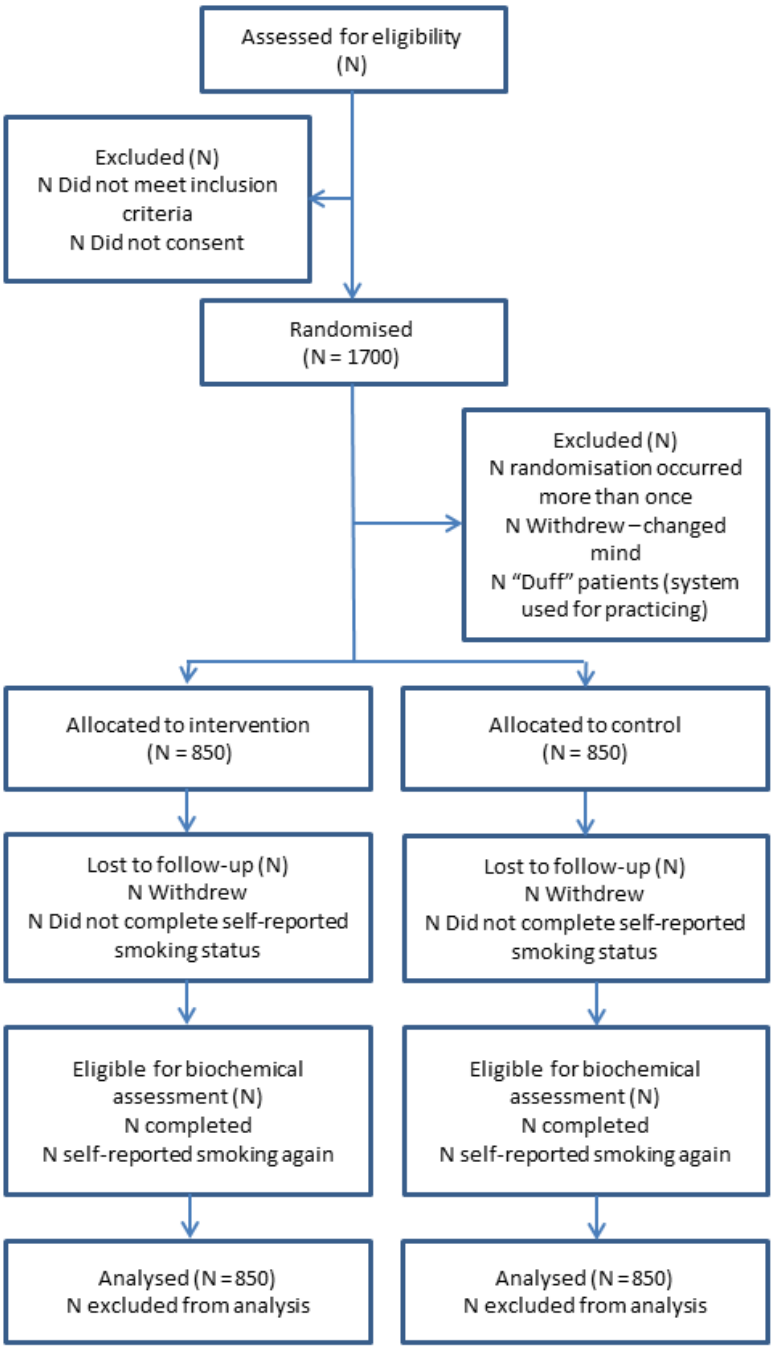
Participants: Recruitment

Participants were recruited using 3 methods (Figure 1 shows the projected trial profile):

1. Opportunistic recruitment: All health care practitioners in participating practices were encouraged to identify potential participants. Smokers presenting at other clinics (eg, health checks, asthma clinics, COPD clinics) and expressing a desire to quit smoking were advised to make an appointment with the smoking cessation advisor.
2. Self-referral: Patients could refer themselves for smoking cessation support.
3. Proactive recruitment: Practices were encouraged to mail study invitations to smokers identified from their database. In addition to a covering letter, patients received an information sheet and were encouraged to make an appointment with the smoking cessation advisor at the surgery.

Participant recruitment in GP practices was monitored (as previously described), and a number of strategies were used to ensure the sample size was achieved (eg, regular newsletters [sometimes tailored to the practice]). Further support and training for underperforming practices was available. Practices were also encouraged to use national promotions (eg, Stoptober and national no smoking day) to encourage recruitment. Posters and leaflets were available for practices to display in their waiting rooms.

Figure 1. Projected trial profile.



Interventions

Control

In-person SSS support, which is mainly delivered one to one, is usual practice for smoking cessation consultations in primary care. During the first session, the advisor discusses with the patient the reasons for why they smoke and why they wish to quit. They also assess the patient's level of nicotine dependence using validated tools such as the Fagerstrom test for nicotine dependency, the heaviness of smoking index, or the Urge to Smoke Questionnaire. They discuss past quit attempts and support the patient to set a quit date. To aid the quit attempt, patients are offered pharmacotherapy: varenicline, buproprion, or nicotine replacement therapy (NRT) products (eg, patches, gum, lozenges, inhalators, mouth, and nasal sprays). The patient's expired-air carbon monoxide (CO) level is also measured using the practice's own Smokerlyzer. Follow-up appointments by the smoking cessation advisor are offered at 1, 2, 3, and 4 weeks after the quit date to monitor progress and to offer advice on handling withdrawal symptoms and difficult situations, to monitor CO levels, and to ensure that the patient has an adequate supply of medication [33].

All participants in our trial received this level of support (*usual care*).

Intervention

In addition to the *usual care* described earlier, participants allocated to the intervention arm received the following.

Tailored Advice Report

iQuit uses participant answers to the iQuit web-based questionnaire to instantly generate a highly tailored detailed advice report (Multimedia Appendix 1), approximately 4 A4 pages in length. The program is informed by (1) theories of smoking cessation and behavior change, including social cognitive theory [34] and the perspectives of change model [35]; (2) findings from previous studies; (3) feedback from the iQuit in Practice I trial [32]; and (4) best practice guidance from the National Centre for Smoking Cessation Training [36]. To ensure adequate tailoring, iQuit asks detailed questions about an individual's smoking habits and history, including nicotine dependence, motivation and determination to quit, reasons for quitting, self-image, pros and cons of quitting, perceived difficult situations, children, living with other smokers, social support, and current health problems. The advice report contains detailed advice on quitting tailored to 25 items from the web-based questionnaire. The program can generate over 3300 million different reports.

Tailored Text Messages

A 90-day program of automatically generated tailored text messages (Multimedia Appendix 2) is sent to the participant's mobile phone, beginning the day before their quit date. Participants receive either 0, 1, or 2 messages each day (approximately 1.2 on average), with fewer messages toward the end of the 90 days. The messages are a further refinement of those developed for the version evaluated in the first trial with some additional features [32]. Texts were amended to reflect the current trend in SMS messaging (eg, the return of full length rather than abbreviated words, ie, text instead of txt). However, content, style, and frequency remained unchanged, as 64.1% of participants in the pilot trial found them useful and 93.7% of participants found them easy to understand. The texts are designed to remind participants about their quit attempt, provide information about reasons for quitting, increase and maintain motivation, boost confidence at quitting, and provide coping strategies for difficult situations. Messages are individually tailored using baseline information collected through the web-based questionnaire with additional information obtained via interactive messages sent to participants at 4, 5, and 8 weeks during the program. The 4- and 8-week messages ask about current smoking status (ie, have they smoked in the last week. Participants respond by texting *Y* or *Yes*, *N* or *No* and those that have smoked in the last week are invited to text in a new quit date). The 5-week message asks participants about their confidence in quitting for good using a 5-point scale and provides feedback in response. Participants can text *STOP*, email, or telephone the study team at any time to stop receiving further messages. For added distraction, participants can text *QUIZ* to receive a general knowledge quiz question. After submitting their answer, they receive a text telling them whether their answer is correct or incorrect. If they do not respond, they will automatically receive the correct answer after approximately 5 min. Participants can also text *HELP* if they are tempted to smoke, or *SLIP* if they have had a lapse to receive further support. If participants want to increase or decrease the frequency of the text messages, they can text *MORE* or *LESS*.

Sample Size, Power, and Precision

In the iQuit in Practice I trial, the quit rates (self-reported prolonged abstinence at 6 months) were 8.9% and 15.1% in the control and intervention groups, respectively [32]. If we assume a 90% response rate to biochemical verification and that 90% of these are confirmed as nonsmokers (as advised by the chair of the trial steering committee, Dr Jamie Brown from University College London), this gives the estimated validated quit rates of 7.1% and 12.1% for control and intervention, respectively. An absolute increase of 5% quitting would be a worthwhile and scalable effect for this low-cost intervention. Detecting an effect of this size with 90% power using a two-sided chi-square test at the 5% significance level requires 726 participants per arm (nonresponders at follow-up assumed to be smoking), and 1452 in total.

In the first 12 months of recruitment, the response rate to biochemical validation was lower than expected. The observed response rates suggested that we would fall short of the 282 biochemically validated nonsmokers required to maintain 90% power (column 3 of Table 3 gives further details). On the basis that, we needed the same number (n=282) of validated nonsmokers. Using the observed response rates of participants to biochemical validation (64%), a revised sample size of 1700 participants was proposed. With 850 participants per arm, the study has 90% power to detect a 4.3% difference in validated quit rates of 10.3% versus 6.0% at the two-sided 5% level of significance. The trial steering committee (TSC) and the research ethics committee approved the revised sample size of 1700 participants.

Table 3. Sample size assumptions.

Raw numbers	Scenario 1, n	Scenario 2, n	Scenario 3, n
Sample size	1452	1452	1700
Self-reported abstinence at 6 months postquit date	348	479	561
Response to biochemical validation	314	307	287
Validated nonsmoker	282	245	287

Randomization

Randomization was stratified by smoking cessation advisor, so that each advisor would see approximately equal numbers of intervention and control participants. The allocation sequence is generated by a computer-based random number generator using random permuted blocks with block sizes of 4 and 6 to make the sequence difficult to predict, while avoiding a major imbalance between intervention and control groups if a block is incomplete at the end of recruitment. The sequence is stored

on the web server database, accessible only to the data manager and the chief investigator. Allocation is made after the questions in part 1 of the web-based iQuit program have been completed.

Procedure: Initial Consultation

At the start of the initial appointment, the smoking cessation advisor logs onto the web-based iQuit program, talks through the information sheet (Multimedia Appendix 3) and goes through the set of 6 eligibility questions with the patient. If eligible, the advisor obtains written consent (Multimedia Appendix 4) from the patient following good clinical practice guidelines [37].

Once informed consent has been obtained, participants complete a short health utility questionnaire (EQ-5D-5L) [38] in which they report any problems with mobility, self-care, usual activities, pain, anxiety, and depression. Following this, the smoking cessation advisor continues with *usual care* before returning to the iQuit program. There are 2 parts to the iQuit program. Part 1 includes questions on gender, age, cigarette consumption, the longest period of abstinence, strength of motivation, and determination to quit smoking. A quit date (which must be within 2 weeks of the consultation) is also recorded in this section along with the CO reading taken earlier in the consultation. It is only after these questions have been completed that the computer randomly allocates the participant to either the control or the intervention group (Multimedia Appendix 5).

For participants allocated to the control group, there are no further questions. They are reassured that even though they are in the control group, their contribution to the research study is still valuable. They are also reminded that the research team will follow them up in 6 months. The smoking cessation advisor finishes the appointment in the usual way, making clinical follow-up appointments with the participant wherever possible.

For participants randomized to the intervention group, there is a further set of questions (part 2). These questions include the tailoring questions described in the intervention section earlier. Finally, the participant's mobile phone number is entered, and their preferred way of being referred to in the text messages. At the end of part 2, the smoking cessation advisor prints the generated advice report and hands it to the participant to take away and read. Intervention participants start receiving the 90-day program of text message support beginning the day before their quit date.

Procedure: Follow-Up

All participants in the control and intervention groups are followed up 6 months after their initial quit date. The follow-up comprises 3 parts:

1. A question to ascertain the success of their quit attempt: Participants are asked to respond to the question "have you smoked at all since your quit attempt" with either A1, A2, or A3 meaning that they have had no cigarettes, not more than five cigarettes in total or smoked more than five cigarettes in total, respectively.
2. A saliva sample for biochemical validation: Participants who respond to the first question with A1 or A2 also receive a saliva sampling kit for biochemical validation (cotinine and anabasine in saliva are important biomarkers for determining a participant's smoking status) [39,40].
3. A more detailed questionnaire (Multimedia Appendix 6) that participants can complete on the web, on a printed copy, or over the telephone.

The preferred method for asking about smoking status is indirectly through either a text message or via email. However, if neither of these contact details were available, but the participant had given a landline telephone number, a researcher, blind to group allocation, called the participant to ask the question over the phone. Participants who had not provided a telephone number or an email address were sent the detailed questionnaire, which included the primary outcome question, through the post.

Participants who responded to the first question by text or email were sent a link to complete the questionnaire on the web. Participants who responded to the question over the telephone were given the option of completing the questionnaire at that time, were sent the questionnaire by post, or completed it on the web. All participants who answered with either A1 or A2 to the initial question were sent a saliva sampling kit through the post for biochemical validation of their quit attempt.

All participants were followed up with a telephone call (where possible) if there was a missing follow-up component (ie, the saliva sample has not been received by the laboratory within 14 days of it being sent and the questionnaire has not been returned). Where it was not possible to reach the participant using these methods, a further sample kit and the questionnaire was sent to the address we held.

If there was no response to any form of communication within 90 days of their quit date, participants were categorized as lost to follow-up and treated as smokers for the statistical analysis.

Data Collection, Management, and Analysis

All personal data are stored on a secure server within the University of Cambridge Clinical School computing services. Access to the trial database is through a 2-factor authentication system (Signify). All data are anonymized before analysis and publication.

Baseline data were collected through the iQuit program, and follow-up data were collected as described earlier. Saliva samples were sent to ABS laboratories (BioPark). Cotinine levels of <15 ng/mL suggest abstinence from smoking by the participant [41]. Cotinine, however, does not distinguish between nicotine obtained through tobacco smoke and nicotine obtained through NRT. Therefore, a second assay to measure anabasine is run if the cotinine concentration is >15 ng/mL.

Data Monitoring

We have not appointed a data monitoring committee as this is a low-risk trial assessing a behavioral intervention. However, a TSC has been formed and meets to oversee recruitment and follow-up and to provide comments and expertise on the statistical analysis plan and significant protocol changes.

Results

In February 2016, the Cambridge East Research Ethics and the Health Research Authority approved the study to begin recruiting. Funding began in May 2016 and between August 2016 and July 2019, 1671 participants were recruited. Follow-up was completed by January 2020 and data collection will commence in the summer of 2020.

The working protocol for the study is version 7, dated March 27, 2018 (Multimedia Appendices 7 and 8)

Outcomes

In line with the Russell Standard, the primary outcome is self-reported prolonged abstinence over the entire 6-month follow-up period (allowing for up to five cigarettes in total), combined with 7-day point prevalence with biochemical verification at 6 months [40]. In the event that a participant was unwilling to provide a saliva sample, they could provide a CO reading instead. CO readings were taken at their physician's surgery (Multimedia Appendices 9 and 10).

Secondary outcomes include (1) CO-verified abstinence at the 4-week quit date follow-up for at least 2 weeks, assessed by the smoking cessation advisor; (2) self-reported prolonged abstinence over the whole of the 6-month follow-up period (allowing for up to five cigarettes in total); (3) self-reported 7-day point-prevalence abstinence at the 6-month follow-up; and (4) cost and utility measures (ie, the time required to complete the iQuit program and resource use, including use of cessation medication).

Process measures, all assessed from the follow-up questionnaire include (1) the number of serious quit attempts lasting ≥24 hours during the 6-month follow-up period, (2) motivation and confidence in quitting, (3) use of strategies to help avoid smoking or lapsing during the 6-month follow-up period, and (4) (intervention group only) evaluation of the tailored advice report and text messaging program (eg, how helpful they found them, how they felt about the number of texts sent).

Statistical Analysis

A detailed statistical analysis plan was completed by the senior trial statistician dated August 16, 2018, and approved by the TSC. The final analysis will be performed after all the follow-up data has been collected; there is no interim analysis. The statistician will be blind to group allocation until data queries have been resolved, and the statistical analysis plan has been followed. The analysis will take an intention-to-treat (ITT) strategy approach. The ITT population comprises all patients that have been randomized, regardless of finding any participant later to have been ineligible or any controls who have mistakenly received the behavioral intervention, or any intervention arm participants who had not received the behavioral intervention. A per-protocol analysis is not planned because the number of participants not receiving an intervention was very low in our previous study [32]. The focus will be on reporting 95% CIs for estimates of effect size. Statistical tests will be two-tailed and assessed at the 5% significance level. Tests will be used sparingly and restricted largely to addressing stated hypotheses as detailed in the statistical analysis plan, so reporting of *P* values will be limited.

Primary Effectiveness Analysis

The primary analysis of the primary outcome will involve obtaining a point estimate of the intervention effect as the difference in proportions, with 95% CI and the corresponding *P* value for the intervention effect from the Pearson chi-square test. The primary analysis and sensitivity analysis for handling missing primary outcome data (primarily assuming this as *not abstinent*) will together comprise the ITT strategy. The detailed statistical analysis plan describes the secondary reporting of relative effects, such as odds ratio and RR, which should be useful for comparison with other studies and meta-analyses. The statistical analysis plan describes further methods for this sensitivity analysis and for exploratory secondary analysis of the primary outcome, indicated by unexpected covariate imbalance. The statistical analysis plan provides further information as to why, a priori, the primary analysis is decided to be unadjusted for the stratifier (smoking cessation advisor), given the low numbers of primary outcome events per stratifier categories.

Subgroup variables that will be examined as potential moderators of the intervention are medication use (categorized into NRT or varenicline), nicotine dependence (based on the heaviness of smoking index, categories of 7+ and <7), and the Index of Multiple Deprivation (5 quintile-based categories). The approach to subgroup analysis will involve assessing the significance of the interaction of a subgroup variable with arm allocation and summarizing the intervention effect with a 95% CI within each category of the subgroup variable.

Secondary Effectiveness Analyses

The key secondary effectiveness outcomes are binary, and a Pearson chi-square test will be used unless assumptions are unexpectedly contraindicated. Ordinal response outcomes (and their changes from baseline, where collected) will be evaluated between arms using methods for continuous outcomes, in consideration of the large sample size, unless categories are few and sparse, requiring categorical analysis methods outlined further in the statistical analysis plan. Where the baseline is available, analysis of covariance will be used for continuous outcomes. Alternatively, the Student *t* test will be used. If there is evidence of differential variance between arms (eg, Levene F-ratio), then an alternative test based on an appropriate modification to fractional degrees of freedom will be reported if the variance ratio is large enough to materially alter the result and conclusion.

Economic Analyses

The economic evaluation will estimate the incremental cost per incremental individual quitting smoking at 6 months (defined as self-report with biochemical verification: the primary outcome measure) and per incremental quality-adjusted life year (QALY) gained over 6 months.

The setting of the study is English primary care (and is assumed to be generalizable to the United Kingdom as a whole). The analytic perspective is that of the NHS over a time horizon of

6 months. No interim analyses are planned. Costs and outcomes will not be discounted as the follow-up period is less than one year. Cost items comprise the index consultation with the smoking cessation advisor (data derived from the iQuit program), text messages, prescription medications, and other primary care contacts. QALYs will be calculated from the EQ-5D-5L using the recommended set of utility weights at the time of analysis.

Process Evaluation

Many process measures fall into either ordinal or binary categories. Those considered to be potential mediators include motivation, confidence in quitting, use of cognitive behavioral lapse prevention strategies, medication use, and use of additional NHS cessation support. Process measures that are intervention-arm-only are also ordinal or binary, and will be summarized descriptively in terms of averages and percentages, and include reading advice reports, reading advice texts, finding them helpful, and viewing messages (annoying versus pleasing).

For continuous process measures, to obtain valid CIs, the nonparametric bootstrap method will be considered for use when the distribution is highly skewed, and an absolute difference presentation and interpretation is important.

For process measures proximal to the behavior, such as motivation and confidence in quitting, chi-square trend tests for between-arm evaluation will be reported after assumption checking.

For measures proximal to the intervention, such as use of strategies to help avoid smoking or lapsing during the follow-up period of the individual's experience in the trial, Pearson chi-square test, chi-square trend test, Student *t* test will primarily be used depending on response distribution and distributional assumptions, and interpretability of point and ideally interval estimate provision.

Discussion

The purpose of this trial is to evaluate the effectiveness and cost-effectiveness of digital adjunctive support to usual smoking cessation care in primary care. The trial has been designed following the Standard Protocol Items: Recommendations for Interventional Trials [42] and Consolidated Standards of Reporting Trials [43,44] guidelines (Multimedia Appendix 11), and feedback from the pilot trial [32] to maximize both internal and external validities.

Trial Design

A cluster-randomized design was considered for the trial but decided against. The randomization built into the web-based iQuit computer program is easily implemented, maintains allocation concealment, and avoids selection bias. In addition, if there is a clustering of outcomes, an individually randomized design requires a smaller sample size to detect an effect. The computer program randomizes participants during the initial consultation. The allocation sequence is not accessible to smoking cessation advisors or participants in advance, and the advisors and participants remain blinded to group allocation until after the first set of questions.

However, there are disadvantages to individual randomization in trials of behavioral interventions. Participants may be disappointed to learn that they will not be receiving the iQuit intervention and feel they are not active participants in the trial.

This may, in part, be due to a lack of understanding of RCTs and the purpose of control groups. Therefore, in the participant information sheet and with smoking cessation advisors in training, we provide an explanation of RCTs and why people allocated to a control group are as important to research as the group receiving the intervention. Advisors also reassure participants they will still receive support from them during their quit attempt.

However, there is the potential for this to lead to systematic differences between intervention and control conditions in the usual care component as smoking cessation advisors try to compensate for this disappointment. However, participants not receiving the intervention still have access to all available resources in the same way as the group receiving the intervention. Therefore, any additional support given to the control arm would attenuate any intervention effect and thus have a conservative effect on the results.

Recruitment

We encouraged GP practices to recruit opportunistically rather than proactively. Although proactive invitation letters can act as a prompt for participation, this approach was not very successful during our pilot trial [32] and would likely be insufficient to recruit the numbers we require. However, opportunistic recruitment has some disadvantages: (1) more time is needed to talk with potential participants about the study, which in a busy general practice can be a challenge, and (2) recruiting participants who have had to make a quick decision about taking part in the study. We therefore encouraged GP practices to hand out study information to patients attending other consultations (eg, diabetes clinics) and in the waiting room to maximize the time available for reading information and coming to a decision. With increased use of electronic-cigarettes [2], smokers seeking support from smoking cessation services have fallen over recent years [6]. Therefore, recruitment was monitored internally and various strategies used to encourage practices to be more active in their recruitment. Quarterly newsletters of study progression were produced, and regular contact with smoking cessation advisors enabled us to work with them to identify individual issues with recruitment. In the majority of cases, the over-riding problem was a fall in numbers seeking support through the surgery. Therefore, further GP practices were recruited as necessary to ensure we maintained a steady recruitment rate to reach our target.

Outcome Assessment

The preferred method for obtaining the initial response is by text or email. Every attempt is made to obtain self-reported smoking status in this way. However, where there has been no response to initial attempts, participants are called instead. The interviewer is initially blind to the participant's group allocation; however, during the course of the telephone interview, they will become unblinded as details of the participants' quit attempts are discussed. Self-report outcomes, however, are naturally

subject to bias in whichever way they are collected. We will conform to the Russell Standard definitions of abstinence, and a saliva sample will be obtained from all participants who self-report a successful quit attempt to determine their smoking status. This presents further disadvantages; for example, it may yield a lower than expected response rate. However, attrition is monitored along with recruitment, and decisions will be made to compensate for a lower than anticipated return of saliva samples. For example, early on during the trial, we decided to increase the sample size to compensate for a lower than expected return.

External Validity

In this trial, external validity is increased by using smoking cessation advisors, employed by practices, rather than research staff to deliver the intervention and the control intervention. We used minimal inclusion and exclusion criteria for practices and participants, and iQuit was designed to be easily incorporated into usual care, whereas the text messages were delivered independently of the practice. Opportunistic recruitment also had the potential to include smokers who would not necessarily have replied to a study intervention, thereby increasing the diversity of the study population. However, there still remains a limitation in the study design, as smokers with a poor grasp of written English may struggle with the advice report and texts.

Potential Benefits of the iQuit Program

If the iQuit program is demonstrated to be cost-effective, it could be delivered across primary care in all regions. Over 100,000 smokers set a quit date in the NHS each year, of which over 38,000 [45] are seen in primary care. It has the potential to reach a large number of smokers seeking support to quit. It may also be beneficial for smokers receiving cessation support in other settings, such as a pharmacy, which treats over 20,000 smokers per year. The potential benefit would likely be highest where less behavioral support is delivered.

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Cancer Research United Kingdom funds the study. The funder is not involved in the protocol design or study management. Service support costs for GP practices are provided by the NHS in line with AcoRD (Attributing the costs of health and social care Research & Development). The trial sponsor is the University of Cambridge, School of Clinical Medicine. The key contact person is Carolyn Read (Carolyn.Read@admin.cam.ac.uk). The sponsor was advised on the design of the protocol. Participants and GP practices will receive a newsletter summarizing the findings. Results from this trial will be presented at academic conferences and submitted to a peer-reviewed journal.

The East of England—Cambridge East research ethics committee (REC) reviewed and gave approval to undertake this trial. REC reference: 16/EE/0030, Integrated Research Application System (IRAS) project ID, 188824. Informed consent will be obtained from all study participants.

Authors' Contributions

JP coordinated the trial, helped develop the statistical analysis plan, and led the writing of the manuscript. FN contributed to the design of the study, led the refinement of the intervention, helped develop the statistical analysis plan, and helped draft the manuscript. MS and SH contributed to the design of the study, refinement of the intervention, and carried out the telephone interviews. JB is the trial data manager and designed the trial database. AP is the senior trial statistician, advised on the design and statistical analysis, and developed the statistical analysis plan. EW is the health economist and advised on cost-effectiveness analysis. TC is a coinvestigator and contributed to the grant application and design of the study. HG contributed to the design of the study. SS is the chief investigator and grant holder, conceived the study, contributed to its design, and helped draft the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
iQuit example advice report.
[DOC File , 36 KB - resprot_v9i7e17160_app1.doc]

Multimedia Appendix 2

iQuit in Practice example text messages version 1.0, December 16,2015.
[DOCX File , 17 KB - resprot_v9i7e17160_app2.docx]

Multimedia Appendix 3
iQuit in Practice participant information sheet version 6.0, May 24, 2018.
[DOC File , 126 KB - resprot_v9i7e17160_app3.doc]

Multimedia Appendix 4
iQuit in practice participant consent form version 3, December 06,2016.
[DOC File , 102 KB - resprot_v9i7e17160_app4.doc]

Multimedia Appendix 5
Schedule of enrolment and interventions for the iQuit study.
[DOCX File , 17 KB - resprot_v9i7e17160_app5.docx]

Multimedia Appendix 6
iQuit in Practice intervention group 6-month follow-up questionnaire version 5, September 28, 2018.
[DOC File , 402 KB - resprot_v9i7e17160_app6.doc]

Multimedia Appendix 7
iQuit in Practice protocol v7.0_March 27, 2018.
[DOC File , 335 KB - resprot_v9i7e17160_app7.doc]

Multimedia Appendix 8
iQuit in Practice peer review comments.
[PDF File (Adobe PDF File), 283 KB - resprot_v9i7e17160_app8.pdf]

Multimedia Appendix 9
Baseline variables.
[DOCX File , 19 KB - resprot_v9i7e17160_app9.docx]

Multimedia Appendix 10
Outcome variables.
[DOCX File , 19 KB - resprot_v9i7e17160_app10.docx]

Multimedia Appendix 11
Consolidated Standards of Reporting Trials e-HEALTH checklist.
[PDF File (Adobe PDF File), 1529 KB - resprot_v9i7e17160_app11.pdf]

References

1. Government of UK. 2017 Jul 18. Cost of Smoking to the NHS in England: 2015 URL: https://www.gov.uk/government/publications/cost-of-smoking-to-the-nhs-in-england-2015/cost-of-smoking-to-the-nhs-in-england-2015 [accessed 2020-03-09]
2. NHS Digital. 2019. Statistics on Smoking, England - 2019 URL: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-smoking/statistics-on-smoking-england-2019 [accessed 2020-03-09]
3. Office for National Statistics. 2017. Population Estimates: Analysis Tool URL: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesanalysistool [accessed 2020-03-09]
4. Brown J, West R. Smoking In Britain Journal. 2017. Quit Success Rates in England 2007-2017 URL: http://www.smokinginbritain.co.uk/read-paper/draft/8/Quit%20success%20rates%20in%20England%202007-2017 [accessed 2018-12-07]
5. Song F, Elwell-Sutton T, Naughton F. Impact of the NHS stop smoking services on smoking prevalence in England: a simulation modelling evaluation. Tob Control 2018 Dec 5:- epub ahead of print. [doi: 10.1136/tobaccocontrol-2018-054586] [Medline: 30518567]
6. Developer Documentation: Government of UK. 2017. Towards a Smoke Free Generation: A Tobacco Control Plan for England URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/630217/Towards_a_Smoke_free_Generation_-_A_Tobacco_Control_Plan_for_England_2017-2022__2_.pdf [accessed 2020-03-09]

7. Szatkowski L, Aveyard P. Provision of smoking cessation support in UK primary care: impact of the 2012 QOF revision. Br J Gen Pract 2016 Jan;66(642):e10-e15 [FREE Full text] [doi: 10.3399/bjgp15X688117] [Medline: 26639948]
8. Faulkner K, Sutton S, Jamison J, Sloan M, Boase S, Naughton F. Are nurses and auxiliary healthcare workers equally effective in delivering smoking cessation support in primary care? Nicotine Tob Res 2016 May;18(5):1054-1060 [FREE Full text] [doi: 10.1093/ntr/ntv206] [Medline: 26453668]
9. The National Institute for Health and Care Excellence. 2018. Stop Smoking Interventions and Services URL: https://www.nice.org.uk/guidance/ng92 [accessed 2020-04-01]
10. Iacobucci G. Number of people using NHS stop smoking services continues to fall. Br Med J 2017 Aug 18;358:j3936. [doi: 10.1136/bmj.j3936] [Medline: 28821478]
11. Rice VH, Hartmann-Boyce J, Stead LF. Nursing interventions for smoking cessation. Cochrane Database Syst Rev 2013 Aug 12;12(8):CD001188. [doi: 10.1002/14651858.CD001188.pub4] [Medline: 23939719]
12. Hartmann-Boyce J, Hong B, Livingstone-Banks J, Wheat H, Fanshawe TR. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev 2019 Jun 5;6(10):CD009670. [doi: 10.1002/14651858.CD009670.pub4] [Medline: 31166007]
13. Livingstone-Banks J, Ordóñez-Mena JM, Hartmann-Boyce J. Print-based self-help interventions for smoking cessation. Cochrane Database Syst Rev 2019 Jan 9;1:CD001118 [FREE Full text] [doi: 10.1002/14651858.CD001118.pub4] [Medline: 30623970]
14. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y, Dobson R. Mobile phone text messaging and app-based interventions for smoking cessation. Cochrane Database Syst Rev 2019 Oct 22;10:CD006611. [doi: 10.1002/14651858.CD006611.pub5] [Medline: 31638271]
15. Ofcom. 2018. The Communications Market 2018 URL: https://www.ofcom.org.uk/research-and-data/multi-sector-research/cmr/cmr-2018 [accessed 2020-03-09]
16. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev 2016 Apr 10;4:CD006611 [FREE Full text] [doi: 10.1002/14651858.CD006611.pub4] [Medline: 27060875]
17. Flack S, Taylor M, Trueman P. The National Institute for Health and Care Excellence. 2006. A Rapid Review of: The Cost-Effectiveness of National Health Services Treatments for Smoking Cessation in England URL: https://www.nice.org.uk/guidance/ph10/documents/economic-review-nhs-treatments2 [accessed 2020-05-06]
18. Daly AT, Deshmukh AA, Vidrine DJ, Prokhorov AV, Frank SG, Tahay PD, et al. Cost-effectiveness analysis of smoking cessation interventions using cell phones in a low-income population. Tob Control 2019 Jan;28(1):88-94 [FREE Full text] [doi: 10.1136/tobaccocontrol-2017-054229] [Medline: 29886411]
19. Kirsch F. A systematic review of quality and cost-effectiveness derived from Markov models evaluating smoking cessation interventions in patients with chronic obstructive pulmonary disease. Expert Rev Pharmacoecon Outcomes Res 2015 Apr;15(2):301-316. [doi: 10.1586/14737167.2015.1001976] [Medline: 25600470]
20. Free C, Whittaker R, Knight R, Abramsky T, Rodgers A, Roberts IG. Txt2stop: a pilot randomised controlled trial of mobile phone-based smoking cessation support. Tob Control 2009 Apr;18(2):88-91. [doi: 10.1136/tc.2008.026146] [Medline: 19318534]
21. Mason D, Gilbert H, Sutton S. Effectiveness of web-based tailored smoking cessation advice reports (iQuit): a randomized trial. Addiction 2012 Dec;107(12):2183-2190. [doi: 10.1111/j.1360-0443.2012.03972.x] [Medline: 22690882]
22. Sutton S, Gilbert H. Effectiveness of individually tailored smoking cessation advice letters as an adjunct to telephone counselling and generic self-help materials: randomized controlled trial. Addiction 2007 Jun;102(6):994-1000. [doi: 10.1111/j.1360-0443.2007.01831.x] [Medline: 17523995]
23. Gilbert H, Nazareth I, Sutton S, Morris R, Godfrey C. Effectiveness of computer-tailored smoking cessation advice in primary care (ESCAPE): a randomised trial. Trials 2008 Apr 29;9(1):23 [FREE Full text] [doi: 10.1186/1745-6215-9-23] [Medline: 18445279]
24. Gilbert HM, Leurent B, Sutton S, Alexis-Garsee C, Morris RW, Nazareth I. ESCAPE: a randomised controlled trial of computer-tailored smoking cessation advice in primary care. Addiction 2013 Apr;108(4):811-819. [doi: 10.1111/add.12005] [Medline: 23072513]
25. Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin R, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tob Control 2005 Aug;14(4):255-261 [FREE Full text] [doi: 10.1136/tc.2005.011577] [Medline: 16046689]
26. Bramley D, Riddell T, Whittaker R, Corbett T, Lin RB, Wills M, et al. Smoking cessation using mobile phone text messaging is as effective in Maori as non-Maori. N Z Med J 2005 Jun 3;118(1216):U1494. [Medline: 15937529]
27. Brendryen H, Kraft P. Happy ending: a randomized controlled trial of a digital multi-media smoking cessation intervention. Addiction 2008 Mar;103(3):478-84; discussion 485. [doi: 10.1111/j.1360-0443.2007.02119.x] [Medline: 18269367]
28. Brendryen H, Drozd F, Kraft P. A digital smoking cessation program delivered through internet and cell phone without nicotine replacement (happy ending): randomized controlled trial. J Med Internet Res 2008 Nov 28;10(5):e51 [FREE Full text] [doi: 10.2196/jmir.1005] [Medline: 19087949]

29. Guerriero C, Cairns J, Roberts I, Rodgers A, Whittaker R, Free C. The cost-effectiveness of smoking cessation support delivered by mobile phone text messaging: Txt2stop. Eur J Health Econ 2013 Oct;14(5):789-797 [FREE Full text] [doi: 10.1007/s10198-012-0424-5] [Medline: 22961230]
30. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet 2011 Jul 2;378(9785):49-55 [FREE Full text] [doi: 10.1016/S0140-6736(11)60701-0] [Medline: 21722952]
31. Jamison J, Naughton F, Gilbert H, Sutton S. Delivering smoking cessation support by mobile phone text message: what information do smokers want? A focus group study. J Appl Biobehav Res 2013 Mar 8;18(1):1-23 [FREE Full text] [doi: 10.1111/jabr.12004]
32. Naughton F, Jamison J, Boase S, Sloan M, Gilbert H, Prevost AT, et al. Randomized controlled trial to assess the short-term effectiveness of tailored web- and text-based facilitation of smoking cessation in primary care (iQuit in practice). Addiction 2014 Jul;109(7):1184-1193 [FREE Full text] [doi: 10.1111/add.12556] [Medline: 24661312]
33. National Centre for Smoking Cessation and Training. Standard Treatment Programme: A Guide to Providing Behavioural Support for Smoking Cessation URL: https://www.ncsct.co.uk/usr/pub/standard_treatment_programme.pdf [accessed 2020-03-09]
34. Bandura A. Social Foundations of Thought and Action. London, UK: Prentice-Hall; 1986.
35. Borland R, Balmford J, Hunt D. The effectiveness of personally tailored computer-generated advice letters for smoking cessation. Addiction 2004 Mar;99(3):369-377. [doi: 10.1111/j.1360-0443.2003.00623.x] [Medline: 14982550]
36. West R, McEwen A, Lorencatto F, Michie S, Churchill S, Willis N. National Centre for Smoking Cessation and Training. 2018. NCSCT Training Standard: Learning Outcomes for Training Stop Smoking Practitioners URL: https://www.ncsct.co.uk/usr/pub/NCSCT_training_standard.pdf [accessed 2020-03-06]
37. European Medicines Agency. 2016. Guideline for Good Clinical Practice E6(R2) URL: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf [accessed 2020-05-06]
38. EQ-5D. EQ-5D-5L: About URL: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ [accessed 2020-03-09]
39. Jarvis M, Primatesta P, Erens B, Feyerabend C, Bryant A. Measuring nicotine intake in population surveys: comparability of saliva cotinine and plasma cotinine estimates. Nicotine Tob Res 2003 Jun;5(3):349-355. [doi: 10.1080/1462220031000094213] [Medline: 12791530]
40. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005 Mar;100(3):299-303. [doi: 10.1111/j.1360-0443.2004.00995.x] [Medline: 15733243]
41. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res 2002 May;4(2):149-159. [doi: 10.1080/14622200210123581] [Medline: 12028847]
42. Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Br Med J 2013 Jan 8;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
43. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001 Apr 17;134(8):663-694. [doi: 10.7326/0003-4819-134-8-200104170-00012] [Medline: 11304107]
44. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001 Apr 14;357(9263):1191-1194. [Medline: 11323066]
45. NHS Digital. 2018. Statistics on Smoking - England , 2018 URL: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-smoking/statistics-on-smoking-england-2018/content [accessed 2019-03-11]

Abbreviations

CO: carbon monoxide
COPD: chronic obstructive pulmonary disease
CRN: clinical research network
GCP: good clinical practice
GP: general practitioner
iQuit: iQuit in practice intervention
ITT: intention to treat
NHS: National Health Service
NRT: nicotine replacement therapy
PIS: participant information sheet
PPI: patient and public involvement
QALY: quality-adjusted life year
RCT: randomized controlled trial
REC: research ethics committee
RR: relative risk

SCA: smoking cessation advisor
SSS: stop smoking service
TSC: trial steering committee

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Protocol

Acceptability and Usability of the Mobile Digital Health App NoObesity for Families and Health Care Professionals: Protocol for a Feasibility Study

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Abstract

Background: Almost a quarter or more than a fifth of children in the United Kingdom are overweight or obese by the time they start school. The UK Department of Health and Social Care's national policy for combating childhood obesity has critical outcomes centered on sugar and caloric consumption reduction. Health Education England has developed two digital apps for families with children up to 15 years and for their associated health care professionals to provide a digital learning resource and tool aimed at encouraging healthy lifestyles to prevent obesity.

Objective: This feasibility study assesses the usability and acceptability of Health Education England's NoObesity app for undertaking activities to improve families' diet and physical activity. The purpose of the study is to evaluate the app's influence on self-efficacy and goal setting and to determine what can be learnt to improve its design for future studies, if there is evidence of adoption and sustainability.

Methods: The study population will include 20 to 40 families and their linked health care professionals. Considering issues related to digital access associated with socioeconomic status and the impact on information technology use, study recruitment will be regionally focused in a low socioeconomic status area. The study will last for 9 months (3-month intervention period and 6-month follow-up). The evaluations of feasibility, acceptability, and usability will be conducted using the following scales and theoretical frameworks: (1) system usability scale; (2) Reach Effectiveness Adoption Implementation Maintenance framework; (3) Bandura model of health promotion; and (4) Nonadoption, Abandonment, and Challenges to the Scale-up, Spread, and Suitability framework. App use will be captured and quantitatively analyzed for net use patterns (eg, number of screens viewed, number of logins, cumulative minutes using the app, number of plans made, and number of times goals met) and to triangulate qualitative feedback from study participants.

Results: This study was funded in March 2019 by Health Education England and received University of Oxford Medical Sciences Interdivisional Research Ethics Committee approval on January 31, 2020 (R62092/RE001). At manuscript submission, study recruitment is pending, and expected results will be published in 2021.

Conclusions: This study will provide evidence on the NoObesity app's influence on self-efficacy and goal-setting and determine what can be learnt to improve its design for future studies, if there is evidence of adoption and sustainability.

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KEYWORDS

mHealth; mobile health; digital health; digital technology; weight loss; obesity; overweight; child health; cell phone; telecommunication

Introduction

Background

Obesity is a rising concern globally. In the United Kingdom, it is projected that by 2030, 41% to 48% of men and 35% to 43% of women will be obese, and almost a quarter or more than a fifth of children are overweight or obese by the time they start school [1]. It is estimated that obesity-related conditions are currently costing the National Health Service £6.1 billion (US $7.3 billion; £1=US $1.23) per year, with a cost to society of these conditions estimated at £27 billion (US $33.3 billion) per year [2-4]. The UK Department of Health and Social Care updated the national policy for combating childhood obesity in 2018, with critical outcomes centered on sugar and calorie consumption reduction [2].

The rapid development of technology has quickly led to a growing market for various devices and mobile digital software claiming to aid with weight loss, with 102.4 million products sold in 2016, and sales expected to continue to rise [5]. The effectiveness of these technologies has been subject to many studies [6-10], with some results suggesting that they can benefit weight loss temporarily. However, sustained weight loss is often unsuccessful [8,9]. Even when evidence on these interventions demonstrates a relevant weight loss or reduction in weight gain, if this benefit only lasts for a short period, it dramatically reduces the usefulness of these technologies [8,9]. Digital mobile technology for weight loss could be a novelty that wears off over time, rather than an intervention for sustained lifestyle change that can be maintained over the long term. While these technologies have high potential, the limitations noted require further analysis to see how the approaches can be used to make a lasting impact on positive lifestyle change.

Health Education England developed the NoObesity app as a collaborative initiative between the Universities of Bournemouth and Southampton in 2017-2018. This work centered on the development of (1) a family-focused app to enable families to set health goals, identify barriers, and develop strategies to overcome them and (2) a professional-focused app to help health care professionals provide tailored advice to families, provide information on how to handle common objections, and assist families with their lifestyle objectives. The project completed development and user testing on Apple and Android platforms by producing, testing, and finalizing the functionality and structure of the app and also writing, testing, and finalizing the content of the app. User testing consisted of focus groups conducted with professionals and parents or care givers [11]. This feasibility study aims to gather data on the usability and acceptability of the NoObesity app for undertaking activities involving improving family diet, physical activity, and weight.

Solution Overview

NoObesity involves two apps (NoObesity Professional and NoObesity Family) to support the prevention and management of childhood obesity targeting professionals and families. The apps focus on developing the workforce to support families around childhood obesity and enabling families to set behavioral goals to support their own health and wellbeing.

The apps bring both workforce development and service delivery together, which is the result of collaboration that led to the development of this project.

NoObesity Professional App

The NoObesity Professional app has functionality that supports knowledge and skill development of the workforce centered on weight management. Figure 1 outlines the functions in the NoObesity Professional app, and Table 1 outlines the purposes and outcomes.

NoObesity Family App

The NoObesity Family app has functionality that enables families to set behavioral goals to support their own health and wellbeing. These are highlighted in Figure 2. Table 2 outlines the purposes and outcomes of the family app use cases.

Figure 1. Main screen of the NoObesity Professional app.

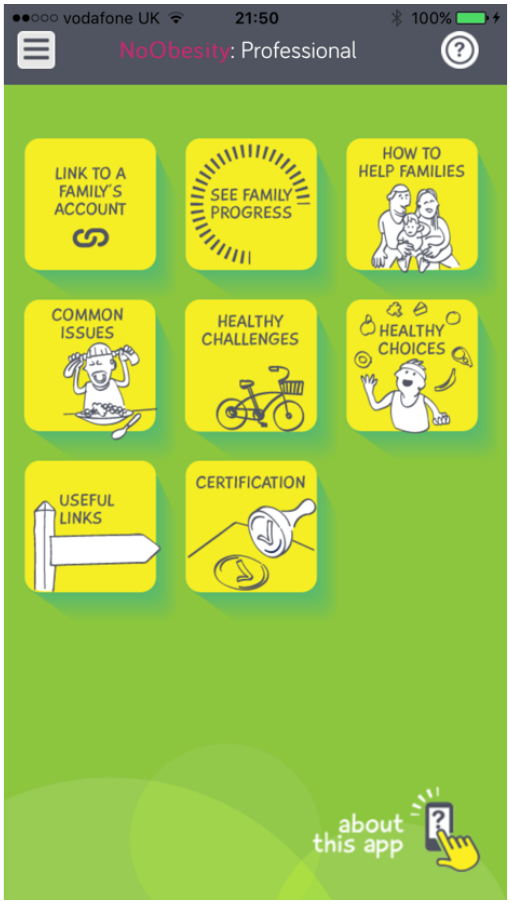


Figure 2. Main screen of the NoObesity Family app.

Table 1. NoObesity Professional app functional overview.

App function	Purpose	Outcome
How to help families	This function enables the professional to follow a family (through a story), where the family comes into contact with a number of different health care workers. The tasks for the professional are as follows: • Read the section of the story. • Score whether the interaction was good. • Reflect on whether there were any missed opportunities to talk about health and wellbeing with the family. The app then provides the professional with information on how interactions with the family can be improved for their own practice.	Professionals will have an increased awareness of the potential opportunities that could be missed in supporting families around health and wellbeing. Professionals will be enabled to reflect on their own practice when coming into contact with families. Professionals will see (read) how a Making Every Contact Count (MECC) approach can be used for their own practice in supporting families.
Common issues	This function provides some of the common issues professionals face when supporting families around healthy eating, diet, and activity. This function offers professionals with some solutions on how they can overcome the common issues and challenges they face. The solutions are developed with MECC principles, which allow professionals to use MECC skills in supporting families.	Professionals are able to learn about solutions they can use to overcome issues and challenges they are presented with. Professionals are enabled to practice MECC skills, as they support families to overcome issues and challenges.
Healthy challenges & healthy choices	These two functions are developed in the form of games within the app that professionals can play as an approach to learning in a fun way about what makes a healthy diet and what level of physical activity is required to burn off calories.	Professionals will gain knowledge of the Eatwell Plate and physical activity to support families.
Useful links	This function provides links to websites for professionals to access for furthering their own learning and Continuing Professional Development.	Professionals will learn about the resources available on specific aspects of health and wellbeing in order to be better informed on the topic and possible signposting.
Certification	This function encourages professionals to do all of the above as they gain bronze, silver, and gold awards on further exploring the content of the app.	Professionals have used the app to develop their knowledge and skills in supporting the prevention and management of childhood obesity with the families they support.

Table 2. NoObesity Family app functional overview.

App function	Purpose	Outcome
Set family goals	This function enables families to set behavioral goals to support them in their health and wellbeing. This function takes them through a Specific, Measurable, Action-oriented, Realistic, Timed, Evaluated, Reviewed (SMARTER) process to make plans and set goals.	Families set goals using a SMARTER process that is part of the MECC program.
Record family progress	This function allows families to record how they have been progressing with family goals and enables them to evaluate and review their goals if they have not progressed as expected.	Families are able to record their progress and review their goals.
Update photo	This function is in place for families to be able to upload pictures of themselves doing healthy things. This could be a meal they have cooked, pictures of them on a health walk, etc.	This is used as an engagement tool allowing families to upload photos of things they have done as a way of encouraging them to come back to the app.
Family survey	This function supports families to take stock of where they are around a number of health-related areas. The family survey includes the following questions: • How much water do you drink? • How much fruit do you eat? • How many vegetables do you eat? • How much physical activity do you do? • How much sleep do you have? • How much screen time do you have? • How often do you brush your teeth? • How happy do you feel? • What is your body size? These questions can be completed by more than one person, so you could end up with a health survey for all members of the family. Once the survey is completed, the app will prompt families to think about setting a goal around one of the areas of the health survey (if they have scored low on it).	It enables collection of baseline data to allow for comparison of change.
Healthy choices & healthy challenges	This function is the same as in the Professional app.	It enables families to learn about the Eatwell Plate and about physical activity.
Parent's survival guide	This function supports families in thinking about how they can overcome the challenges that they face when supporting their children around healthy eating, etc.	Families gain solutions on how they could approach issues and challenges using a MECC approach.
Useful links	This function is the same as in the Professional app.	It enables families to learn about other resources available to support their health and wellbeing.

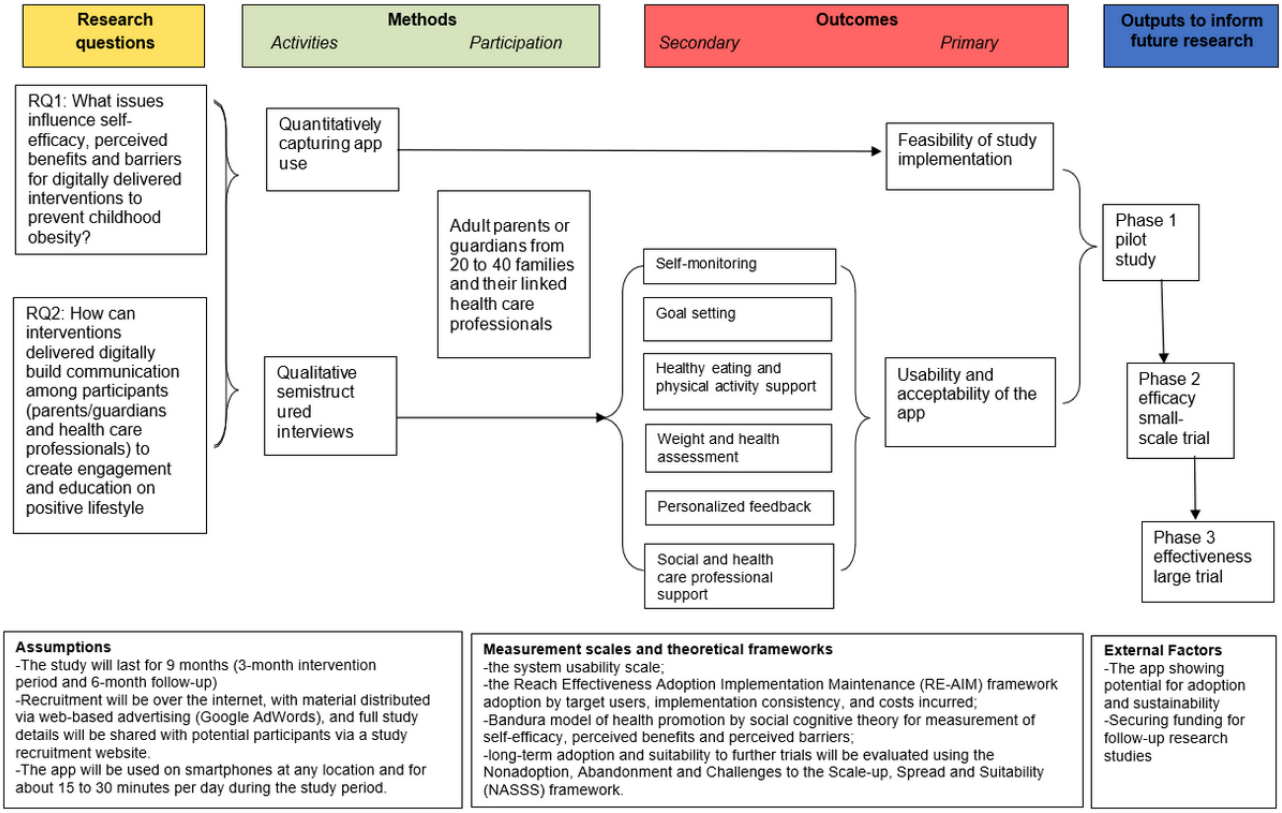
Linking the Apps

The two apps can be linked using a QR code, which is led by the family who may wish to share the goals and progress they have made with a health care worker. For example, this could be during a general practitioner consultation or a visit to the local children's center. The professional will only see the family's survey results, goals, and progress. This will allow the professional to better tailor the support they provide to the family.

Research Questions

The purpose of this study is to investigate the following research questions (Figure 3): (1) What are the issues impacting self-efficacy, perceived benefits, and barriers for digitally delivered interventions to prevent childhood obesity (specifically examining learning and associated actions with regard to diet and physical activity)? (2) How can interventions delivered digitally (eg, NoObesity app) build communication among participants (parents or guardians and health care professionals) to create engagement and education on positive lifestyle habits (parents or guardians and health care professionals)?

Figure 3. Study logic model.



Methods

Design

This investigation will take the form of a feasibility study using mixed methods. To address the study research questions, quantitative monitoring of app users will be supplemented by qualitative interviews with parents or guardians and health care professionals (Multimedia Appendix 1).

Recruitment

We will recruit 20 to 40 families and their associated or linked health care professionals (eg, allied health professionals and health visitors). There will not be separate recruitment of health care professionals; the only included health care professionals will be those whose clients are also using the app in this study. A central objective of this study is to reach demographic saturation (ethnicity, social-economic background, and education) for family study participants; study recruitment will continue until there is a representative sample from each category. Considering issues related to digital access with regard to socioeconomic status and the impact on information technology use, study recruitment will be regionally focused in a low socioeconomic status area. Recruitment material will be distributed via web-based advertising (Google AdWords), with full study details shared to potential participants via a University of Oxford study recruitment webpage. Once identified, potential participants will be sent copies of all consent and study information (Multimedia Appendix 2 and Multimedia Appendix 3). Participants will then have an opportunity to review the material. If they wish to proceed, they can register for the study.

Research Participants

Research participants will be limited to parents or legal guardians and their health care professionals using the app. An Amazon gift voucher will be given as compensation to participants who complete the study.

Inclusion Criteria

The inclusion criteria are centered on adult users (over 18 years) of the app to focus on interactions associated with family goal setting. Children are excluded from the study to focus on the capability of the app to influence adult participants.

The following inclusion criteria will be used: (1) fluency in English; (2) willingness to use the app; (3) parents or legal guardians of a child or children; (4) health care professionals linked to the parent or guardian; and (5) owner of a smartphone to access the app, with 4G data access.

Exclusion Criteria

The following exclusion criteria will be used: (1) individuals who are known to the researchers or staff at Health Education England; (2) deaf or hearing impairment (there is no capability to manage this participant type in this study); (3) prior use of the app before study commencement; (4) refusal to give informed consent; and (5) children, vulnerable young people, or vulnerable adults.

Study Duration and Follow-Up

The study will last for 9 months (3-month intervention period and 6-month follow-up). Participants will be invited to use the NoObesity app for goal setting and monitoring family activities. The app will be used over the internet via their smartphones at

any location during the study period of 3 months. Following a process of informed consent, if participants proceed with the study, they will be given access to links to download and install the app. It is important to note that there are two separate apps, one for families and another for allied health professionals. While the family app is used for family goal planning, the professional app is for monitoring. If health care professionals opt into the study, they will also be interviewed, but separately from the family participants. Interview questions will be asked within the context of how the health care professionals interpreted the impact of the app on their associated client families (same questions will be used but from the perspective of app use and monitoring of outcomes).

Theoretical Framework

The evaluations of feasibility, acceptability, and usability will be conducted using the following scales and theoretical models or frameworks: (1) system usability scale [12]; (2) the Reach Effectiveness Adoption Implementation Maintenance framework [13] will be used to include information regarding target population reach, the potential for solution impact, adoption by target users, implementation consistency, and costs during delivery and maintenance of the intervention; (3) the Bandura model of health promotion [14] described by social cognitive theory will be used in measurement development and validity, with specific emphasis on self-efficacy, perceived benefits, and perceived barriers [15]; and (4) the Nonadoption, Abandonment and Challenges to the Scale-up, Spread and Suitability framework will be used to evaluate long-term adoption and suitability to further trials [16].

Data Collection

Quantitative Data

App use will be captured for net system use patterns; this will include an examination of app usage and engagement throughout the system. The primary method of evaluating factors impacting uptake will be drawn from qualitative investigation, and data concerning system use will be used as a means to triangulate qualitative findings.

Qualitative Data

Surveys and semistructured interviews will be undertaken to evaluate the acceptability and usability of the app. Interviews will be scheduled to last between 40 and 60 minutes (Multimedia Appendix 4). The interviews will be executed at 3-month and 6-month intervals to allow for analysis of the impact of the intervention. Interviews will be conducted through web-based conferencing and telephone conference calls because participants are geographically dispersed. Participants will also be provided with a copy of the study findings that will be published in a peer-reviewed journal.

Data Analysis

Quantitative Data

Web server access logs will be used for analysis of net use patterns (eg, number of screens viewed, number of logins, cumulative minutes using the app, number of plans made, and number of times goals met).

Qualitative Data

All interviews will be audio recorded on a digital recorder, transcribed, and coded using thematic analysis [17]. Interviews (at 3-month and 6-month intervals) will be used to explore the factors influencing topic engagement [17] as follows: (1) self-monitoring; (2) goal setting; (3) physical activity and healthy eating support; (4) weight and health assessment; (5) personalized feedback and motivational strategies (rewards, prompts, or gamification); and (6) social support and health care professional involvement.

Bias

Participants will be asked to provide consent and will be given information on the structure of the study to ensure understanding of the research study. To avoid bias, the criteria to exclude participants who have a relationship with any of the study researchers or who are employed by the university will be enforced. In order to address unconscious bias or other forms of interview recruitment issues, all participants will be included in the study and analysis.

Risks

Interview questions will avoid areas of culturally sensitive issues and will be purely focused on the impact of the intervention. To control any potential perceived issues in this area, participant confidentiality will be protected using data protection procedures complying with European Union data security legislation.

Informed Consent

Prior to completing informed consent, participants will be given information that fully describes the process of the study, including why their participation is necessary, how it will be used, and who the results will be reported to. The research team recognizes the rights of the participants to withdraw from the study at any time and have their data destroyed, and participants will be informed of this. If there are issues identified during the study by study participants, they will be documented and escalated to the Head of the Department, who will take action with the principal investigator. The study will also be overseen by a study steering committee who will monitor adherence to the study protocol. Minutes capturing discussions and key points will be recorded and published.

Data Management

Each participant will be given a unique identifier (ID). The primary key between the unique ID and participant will be held securely on an encrypted secured drive within the university network. The primary key is maintained in the event of a participant wishing to withdraw their data from the study; if such a request is received, all corresponding data and files will be destroyed. Only the research administrators will have access to this file. Although basic demographic information will be captured, the only route to identification will be via this unique ID. Sessions will be recorded and then transcribed by an internal third party (a research assistant trained in transcription) with reference to the unique ID only. The risk of identification will be very low owing to this measure being taken. Only researchers listed in this application and the principal investigator in the research team will have access to the research data. No research

data will be transferred to other organizations, and the results will be disseminated via publications. Records of consent will be kept for 3 years after the publication of the final study results. To comply with the General Data Protection Regulation and the Data Protection Act 2018, personal data will be deleted 3 years after the publication of the final study results. All electronic data will be captured and stored on a password-protected network drive within the University of Oxford network. Access to these files will be limited to the principal investigator, the coinvestigator, a research assistant, and a research associate. Electronic data will be coded using the ID and primary critical pseudonymization process.

Results

This study was funded in March 2019 by Health Education England. A study steering committee was convened in July 2019, where the initial study design was discussed and subsequently reviewed by the principal investigator and the board. After considering feedback, a finalized ethical submission was prepared and approval was received from the University of Oxford Medical Sciences Interdivisional Research Ethics Committee on January 31, 2020 (R62092/RE001). At manuscript submission, study recruitment is pending, and expected results will be published in 2021.

Discussion

Overview

This study will provide evidence on the NoObesity app's influence on self-efficacy and goal setting to improve its design for future studies, if there is evidence of adoption and sustainability. There are gaps in the literature on the lack of effectiveness of mobile apps in improving health behaviors [18] and the need for an iterative design to improve usability [8]. It is hoped that this study will provide variables that can be further evaluated in future studies.

Methodological Limitations

This study is a limited feasibility study observing factors influencing app usage. It is important to note that this study type does not prove effectiveness.

The study methods have been designed proportionate to the resources available for study execution. A higher investment in study resources could lead to a richer set of results; for example, an iterative approach with families and their children would lead to a richer data set and stronger triangulation of results. Owing to limitations of resources, the study does not have provision for parents or guardians who are deaf or hearing impaired.

The study focuses on the recruitment of participants directly via families; however, direct recruitment of health care professionals could have been an alternate recruitment approach that could lead to more robust targeting of prospective family study participants. This is because health care professionals would have informed views on families having the best potential need for the intervention. The study focuses on family recruitment because of the open nature of access of the app via digital stores and the likelihood that families will access the app promptly. These assumptions will be tested within the study.

There is a risk with regard to the nature of the study. The intervention type will not reach low socioeconomic status demographic participants, and there could be bias toward educated and motivated participants. Use of the technology could potentially create further digital access inequality. An attempt has been made to mitigate this in the study approach through recruitment from a low socioeconomic status geographic area.

The study excludes children as study participants and focuses on parents or guardians. An alternate study design could obtain quantitative or qualitative feedback directly from children.

Acknowledgments

This study was funded by Health Education England. Kate King-Hicks, Helena Wehling, and Jamie Blackshaw from Public Health England participated in the program steering committee and provided review feedback for the study design. Nisreen Alwan, Rob Hubbard, Kate King-Hicks, Helena Wehling, Jamie Blackshaw, Peter Rhodes, Matthew Pearce, Jo Lockhart, Kate Slater, Gilly Mancz, and Philippa Darnton participated in the review of materials or as members of the study board. The perspectives and views drawn in the paper are made by the authors and are not necessarily supported by the funders or organizations named.

Authors' Contributions

EM conceived the study topic and designed the review protocol. The protocol was written by EM and MVV, with revisions from all authors.

Conflicts of Interest

Health Education England independently commissioned and developed the NoObesity app. The principal investigator (EM) and the University of Oxford have unrestricted rights to execute the study and publish the findings as independent research entities.

Multimedia Appendix 1
CONSORT eHEALTH Checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1640 KB - resprot_v9i7e18068_app1.pdf]

Multimedia Appendix 2
Participant consent form.
[DOCX File , 81 KB - resprot_v9i7e18068_app2.docx]

Multimedia Appendix 3
Information sheet for participants.
[DOCX File , 79 KB - resprot_v9i7e18068_app3.docx]

Multimedia Appendix 4
Topic guide.
[DOCX File , 26 KB - resprot_v9i7e18068_app4.docx]

Multimedia Appendix 5
Peer review reports from Oxford University (point by point responses).
[DOCX File , 75 KB - resprot_v9i7e18068_app5.docx]

References

1. Behind the headlines: Obesity - Half of UK obese by 2030. NHS. 2011. URL: https://www.nhs.uk/news/obesity/half-of-uk-obese-by-2030/ [accessed 2020-06-15]
2. Childhood obesity: a plan for action, chapter 2. GOV.UK. 2018. URL: https://www.gov.uk/government/publications/childhood-obesity-a-plan-for-action-chapter-2 [accessed 2020-07-06]
3. Pi-Sunyer X. The medical risks of obesity. Postgrad Med 2009 Nov;121(6):21-33 [FREE Full text] [doi: 10.3810/pgm.2009.11.2074] [Medline: 19940414]
4. Caballero B. The global epidemic of obesity: an overview. Epidemiol Rev 2007;29:1-5. [doi: 10.1093/epirev/mxm012] [Medline: 17569676]
5. Wearable Technology Statistics and Trends 2018. Smart Insights. 2017. URL: https://www.smartinsights.com/digital-marketing-strategy/wearables-statistics-2017/ [accessed 2020-06-15]
6. Bardus M, Smith JR, Samaha L, Abraham C. Mobile Phone and Web 2.0 Technologies for Weight Management: A Systematic Scoping Review. J Med Internet Res 2015 Nov 16;17(11):e259 [FREE Full text] [doi: 10.2196/jmir.5129] [Medline: 26573984]
7. Beleigoli AM, Andrade AQ, Cançado AG, Paulo MN, Diniz MD, Ribeiro AL. Web-Based Digital Health Interventions for Weight Loss and Lifestyle Habit Changes in Overweight and Obese Adults: Systematic Review and Meta-Analysis. J Med Internet Res 2019 Jan 08;21(1):e298 [FREE Full text] [doi: 10.2196/jmir.9609] [Medline: 30622090]
8. Singh K, Drouin K, Newmark LP, Filkins M, Silvers E, Bain PA, et al. Patient-Facing Mobile Apps to Treat High-Need, High-Cost Populations: A Scoping Review. JMIR Mhealth Uhealth 2016 Dec 19;4(4):e136 [FREE Full text] [doi: 10.2196/mhealth.6445] [Medline: 27993761]
9. Hu R, van Velthoven MH, Meinert E. Perspectives of People Who Are Overweight and Obese on Using Wearable Technology for Weight Management: Systematic Review. JMIR Mhealth Uhealth 2020 Jan 13;8(1):e12651 [FREE Full text] [doi: 10.2196/12651] [Medline: 31929104]
10. Fawcett E, Van Velthoven MH, Meinert E. Long-Term Weight Management Using Wearable Technology in Overweight and Obese Adults: Systematic Review. JMIR Mhealth Uhealth 2020 Mar 10;8(3):e13461 [FREE Full text] [doi: 10.2196/13461] [Medline: 32154788]
11. Apps being developed to help prevent childhood obesity. Health Education England. 2017 01. URL: https://www.hee.nhs.uk/news-blogs-events/news/apps-being-developed-help-prevent-childhood-obesity [accessed 2020-06-15]
12. Brook J. SUS - A quick and dirty usability scale. Hell - Jens Oliver Meiert. URL: https://hell.meiert.org/core/pdf/sus.pdf [accessed 2020-06-15]
13. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999 Sep;89(9):1322-1327. [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]
14. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
15. Quelly SB. Reliability and Validity of a Tool to Measure School Nurse Perceptions and Practices Associated With Childhood Obesity Prevention. J Nurs Meas 2015;23(2):239-254. [doi: 10.1891/1061-3749.23.2.239] [Medline: 26284838]
16. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies. J Med Internet Res 2017 Nov 01;19(11):e367 [FREE Full text] [doi: 10.2196/jmir.8775] [Medline: 29092808]
17. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]

18. Milne-Ives M, Lam C, De Cock C, Van Velthoven MH, Meinert E. Mobile Apps for Health Behavior Change in Physical Activity, Diet, Drug and Alcohol Use, and Mental Health: Systematic Review. JMIR Mhealth Uhealth 2020 Mar 18;8(3):e17046 [FREE Full text] [doi: 10.2196/17046] [Medline: 32186518]

Abbreviations

ID: identifier

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Protocol

Computer-Based Stratified Primary Care for Musculoskeletal Consultations Compared With Usual Care: Study Protocol for the STarT MSK Cluster Randomized Controlled Trial

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Abstract

Background: Musculoskeletal (MSK) pain is a major cause of pain and disability. We previously developed a prognostic tool (Start Back Tool) with demonstrated effectiveness in guiding primary care low back pain management by supporting decision making using matched treatments. A logical next step is to determine whether prognostic stratified care has benefits for a broader range of common MSK pain presentations.

Objective: This study seeks to determine, in patients with 1 of the 5 most common MSK presentations (back, neck, knee, shoulder, and multisite pain), whether stratified care involving the use of the Keele Start MSK Tool to allocate individuals into low-, medium-, and high-risk subgroups, and matching these subgroups to recommended matched clinical management options, is clinical and cost-effective compared with usual nonstratified primary care.

Methods: This is a pragmatic, two-arm parallel (stratified vs nonstratified care), cluster randomized controlled trial, with a health economic analysis and mixed methods process evaluation. The setting is UK primary care, involving 24 average-sized general practices randomized (stratified by practice size) in a 1:1 ratio (12 per arm) with blinding of trial statistician and outcome data collectors. Randomization units are general practices, and units of observation are adult MSK consulters without indicators of serious pathologies, urgent medical needs, or vulnerabilities. Potential participant records are tagged and individuals invited using a general practitioner (GP) point-of-consultation electronic medical record (EMR) template. The intervention is supported by an EMR template (computer-based) housing the Keele Start MSK Tool (to stratify into prognostic subgroups) and the recommended matched treatment options. The primary outcome using intention-to-treat analysis is pain intensity, measured monthly over 6 months. Secondary outcomes include physical function and quality of life, and an anonymized EMR audit to capture clinician decision making. The economic evaluation is focused on the estimation of incremental quality-adjusted life years and MSK pain–related health care costs. The process evaluation is exploring a range of potential factors influencing the intervention and understanding how it is perceived by patients and clinicians, with quantitative analyses focusing on a priori hypothesized intervention targets and qualitative approaches using focus groups and interviews. The target sample size is 1200 patients from 24 general practices, with >5000 MSK consultations available for anonymized medical record data comparisons.

Results: Trial recruitment commenced on May 18, 2018, and ended on July 15, 2019, after a 14-month recruitment period in 24 GP practices. Follow-up and interview data collection was completed in February 2020.

Conclusions: This trial is the first attempt, as far as we know, at testing a prognostic stratified care approach for primary care patients with MSK pain. The results of this trial should be available by the summer of 2020.

Trial Registration: ISRCTN Registry ISRCTN15366334; http://www.isrctn.com/ISRCTN15366334.

International Registered Report Identifier (IRRID): DERR1-10.2196/17939

(JMIR Res Protoc 2020;9(7):e17939) doi:10.2196/17939

KEYWORDS

musculoskeletal; primary health care; stratified care; randomized controlled trial; therapeutics; economics; outcome and process assessment, health care; prognosis; qualitative research; back pain; osteoarthritis

Introduction

Background

Musculoskeletal (MSK) pain from common conditions such as back pain and osteoarthritis is a major cause of pain and disability. Estimates from the most recent global burden of disease study suggest that it is the leading cause of disability-adjusted life years (DALYs) in Western Europe and Australia [1]. Overall, it accounts for 6.8% of global DALYs, comparable with cancer (7.8%), ischemic heart disease (5.2%), and mental health disorders (7.4%). This burden is reflected in health care use, particularly in UK primary care where MSK pain accounts for around one-fifth of all consultations [2-4]. It also accounts for 8.8 million physiotherapy consultations and over 3.5 million calls annually to emergency services [5]. Usually, general practitioner (GP) care for MSK pain involves a long-term management approach carried out during short 10-min face-to-face consultations during which patients are assessed and treated with advice, education and reassurance, analgesic medication, referral for investigation(s), referral to other services offering conservative treatments such as physiotherapist-led exercise, or referral to secondary care medical specialists such as orthopedic consultants and rheumatologists. For many patients, primary care clinicians should reassure them that their MSK pain is not associated with serious underlying pathology, that the prognosis is usually good, and that further tests are not indicated, combined with advice and support to help them stay active [6]. However, evidence suggests substantial variability in clinical practice, with treatment often not in line with best practice recommendations in guidelines, particularly with respect to opioid medication and x-ray investigation [7].

Due to the high prevalence of these common symptoms, MSK pain has overtaken mental health issues such as stress as the number one reason why people take time off work in Europe and the United States [1]. The early identification and improved management of those at risk of severe disabling MSK pain in primary care, where the majority of these patients are managed, is therefore a high priority [8]. Patients with different MSK pain presentations (eg, back, neck, knee, shoulder, or multisite pain) share common prognostic factors [9]. Co-occurrence of MSK pain located in more than one body region is common [10], with the risk of a poor outcome increasing for those with multisite pain [11]. For example, the Chronic Pain Risk Score [12] has been shown to have predictive validity among patients with MSK pain in different body regions [13-15]. However, previous prognostic questionnaires such as the Chronic Pain Risk Score and the Orebro-MSK Pain Screening Questionnaire [16] were not designed to guide primary care management, and their use in primary care clinical practice is uncommon.

Consequently, we previously developed a prognostic tool (Start Back Tool) specifically for use in primary care to guide the management of patients with low back pain [17]. Prognostic stratified care models involve matching treatments to the patient's prognostic profile to support clinical decision making in an effort to maximize treatment benefits, reduce harm, and increase health care efficiency [18]. The Start Back Tool consists of 9 questions summed into an index score. It utilizes cutoff points to identify 3 prognostic subgroups (patients at low, medium, or high risk of persistent disabling pain). In 2 previous UK studies, stratified care for back pain, based on matching treatment to prognosis, led to superior clinical and economic outcomes compared with best current practice and usual primary care [19,20]. The evidence suggested that patients at low risk received fewer investigations and referral to secondary care, and in contrast, patients at medium or high risk were matched to treatments that could better meet their needs, leading to improved outcomes.

Rationale

A logical next step is to determine whether a similar model of prognostic stratified care might also have benefits for primary care patients with a much broader range of MSK pain presentations. The 5 most common MSK pain presentations in UK primary care are low back pain, knee pain, shoulder pain, neck pain, and multisite pain [2]. In a research program with 4 work packages (the Start MSK program), our team first developed and validated a new 10-item prognostic tool, the Keele Start MSK Tool, to stratify patients with the 5 most common MSK pain presentations into subgroups (those at low, medium, and high risk of persistent pain and disability) [21]. Second, we agreed on evidence-based recommended matched treatment options for patients in each subgroup following a systematic review [22] and expert consensus process [23]. Third, we conducted an external feasibility and pilot randomized trial with 524 patients from 8 general practices (4 intervention and 4 control) [21,24]. The pilot trial confirmed the acceptability of using a stratified care approach in primary care consultations and also helped to refine our recruitment, retention, and sample

size estimates, ahead of the main trial. The findings informed the final wording of the self-report version of the Start MSK Tool, led to a clinician-completed version of the tool, and allowed us to simplify the recommended matched treatment options. All changes made to the main trial protocol following the pilot trial were discussed, shared, and agreed with the trial funder the National Institute for Health Research (NIHR), the Trial Steering Committee (TSC), and the Data Monitoring Committee (DMC).

Aims and Objectives

Primary Objective

The primary objective of the Start MSK main trial is to determine, in patients presenting with 1 of the 5 most common MSK pain presentations in UK primary care, whether stratified care involving the use of the Keele Start MSK Tool to allocate individuals into low-, medium-, and high-risk subgroups, and matching these subgroups to recommended matched clinical management options, is more clinically and cost effective compared with usual nonstratified primary care. The primary clinical outcome is average pain intensity over the past 2 weeks measured each month for 6 months.

Secondary Objectives

The secondary objectives of the trial were as follows:

1. Examining differences in secondary clinical outcomes, clinical decision making and behaviors, and health economic outcomes at the 6-month follow-up:

- Patient outcomes include physical function, confidence in managing their pain (pain self-efficacy), psychological distress, fear-avoidance beliefs, patient-perceived reassurance from their clinician, pain interference with sleep, hobbies/leisure activities, pain interference with work and daily routine, health-related quality of life, and patient satisfaction with care received.
- Clinical decisions and behaviors of interest include identifying whether stratified care changes the primary care management of MSK patients. We anticipate that primary care clinical management will become more consistent for patients within each risk group and be more in line with stratified care, where patients at low risk of persistent disabling pain are less likely to be referred for additional health care, whereas patients at medium or high risk are more likely to be referred for additional health care in ways that match the recommended management options. Using the practices' medical record data, we will examine differences between the trial arms in clinical decision making and behaviors.
- Health economic evaluation will determine the cost-utility of stratified care in comparison with usual, nonstratified care. A cost-consequence analysis will initially be reported, with a subsequent cost-utility analysis from a health care perspective to determine cost per quality-adjusted life years (QALYs) gained, calculated using EuroQol-5D-5L (EQ-5D-5L) responses from the initial and 6-month questionnaires. A broader costing perspective will be considered in a sensitivity analysis, taking into account National Health Service (NHS)/Personal Social Services (PSS) costs and productivity costs associated with time off work. The outcome of interest for the economic analysis will be QALYs. Additional exploratory analyses will consider the cost-effectiveness of stratified care compared with usual nonstratified care for patients at low, medium, and high risk of persistent disabling pain.

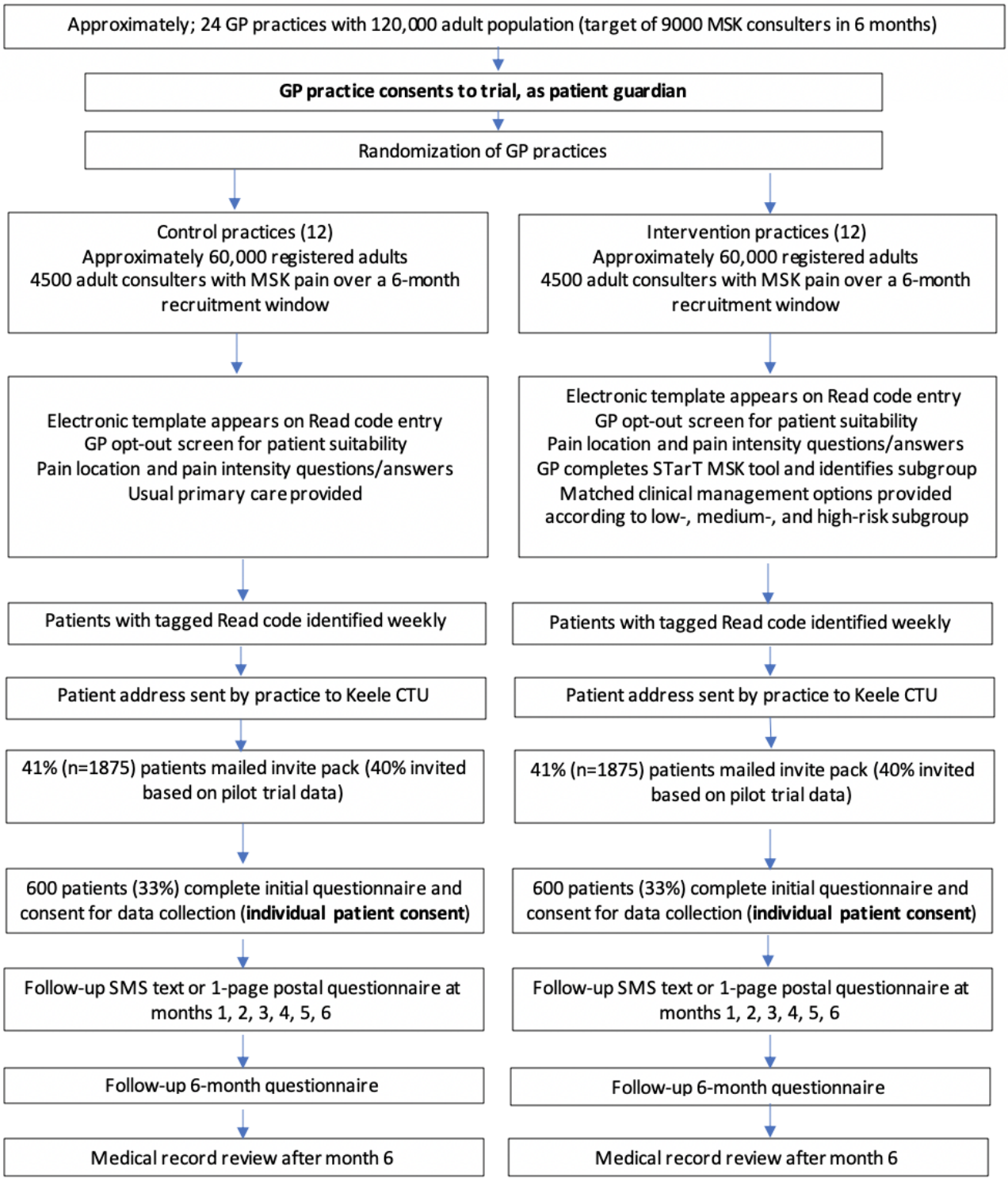
2. Undertaking a process evaluation to explore how stratified care, as a complex intervention, interacts with existing patterns of service organization, professional practice, and professional-patient interaction. The evaluation will use mixed quantitative (eg, a mediation analysis) and qualitative methods, integrating data both at the collection and analysis stages, to generate more detailed and comprehensive findings.

Methods

Study Design and Setting

The Start MSK trial is a pragmatic, two-arm, parallel, cluster randomized controlled trial (RCT), with a linked health economic analysis and mixed methods process evaluation. The setting is UK primary care, and the trial will include approximately 24 average-sized general practices with a total registered adult population of approximately 120,000. General practices will be randomized to either the stratified care intervention (12 practices) or the usual, nonstratified care (12 practices). The units of randomization are the general practices, and the units of observation are adults consulting for MSK pain with 1 of the 5 most common MSK pain presentations (Figure 1).

Figure 1. Flowchart of patient recruitment. CTU: clinical trials unit; GP: general practice; MSK: musculoskeletal.



The intervention in both arms of the trial will include an embedded template within the general practice computer system, which will *pop-up* during the first relevant Read-coded MSK pain consultation within the specified study period (termed the *MSK consultation*; this may be the first consultation or a repeat consultation for MSK pain). However, the content of the template will differ between the 2 arms of the trial. In the control arm, it includes 3 questions: (1) the eligibility of the patient to be invited to participate, (2) the location/site of MSK pain for which the patient is consulting, and (3) the average MSK pain intensity in the past 2 weeks (primary outcome). In the intervention arm, in addition to these 3 questions, the template also includes the Keele Start MSK Tool and recommended matched treatment options [21].

A cluster RCT rather than an individual patient RCT was chosen for both scientific and practical reasons. Stratified care is a new way of working, and the tool, training, and support are delivered at the general practice level (eg, the computer template once installed will *pop-up* on all computers in practice). Primary care clinicians would likely find it difficult to behave differently

toward individuals randomized to control and intervention arms, and therefore, the probability of contamination between the 2 arms would be high using an individual patient randomized trial design. This trial can be thought of as a professional-cluster intervention type [25], in that the stratified care intervention involves changing the professional's behavior during the consultation, in this case, using a prognostic tool and matching patients to clinical management options. Although the patient can opt out of data collection, the intervention is still likely to have an effect on them as it involves introducing specific questions and recommendations about matched treatment options into the consultation.

Minimizing Systematic Bias

The risk of selection bias, specifically of recruitment and participation bias, is a known concern in cluster RCTs [26]. A number of steps have been taken to minimize this, which were tested in the pilot RCT, where we observed no evidence of selection bias:

- The initial part of the computer template to help identify eligible patients is automated based on diagnostic codes entered during the consultation and operates in the same way in both arms of the trial.
- If the clinician deems a patient to be ineligible, they are asked to give a reason for this exclusion so that these reasons can be compared across intervention and control arms. This process is monitored during trial recruitment, with monthly feedback provided to participating practices showing the frequency of template noncompletion, and the proportions of different reasons for ineligibility.
- Patients in both arms of the trial will receive identical study invitation packs comprising the same patient information leaflet (PIL; which does not mention stratified care, only that the study seeks to better understand how common aches and pains affect patients and how primary care can be improved), invitation letter, questionnaire, and consent form for data collection, minimizing the risk of patients in intervention or control arms being more or less likely to participate (participation bias).

General Practice Recruitment and Consent

It is anticipated that an estimated eligible target population of approximately 9000 patients will be identified within a 6-month recruitment window from approximately 24 average-sized general practices (approximately 120,000 registered adults). Practices will include those that range in size (based on patient list size and number of GPs) and a range of settings (urban, semi-urban, and rural). The practice eligibility criteria includes those that use the Egton Medical Information Systems (EMIS) web clinical system (most commonly used electronic medical record [EMR] system in the United Kingdom), those proficient at using Read codes (diagnostic codes) during MSK consultations evidenced through an audit of their recent Read coding behavior, willingness to undergo the training and support sessions needed to become familiar with the stratified care intervention, willingness to participate in anonymized aggregated medical record audits of MSK consultations during the trial recruitment period, and willingness to engage with the process evaluation.

The balance between scientific considerations and the need for consent is a known issue for cluster RCTs [25,26]. Informed consent for practices to participate is formalized through written agreements led by the senior GP partner in each practice acting as a *guardian* for patients in their care, following agreement with their team to provide either usual care or stratified care for the period of the trial (dependent on random allocation). It is anticipated that practices will actively recruit patients for approximately 6 months, with practice recruitment periods staggered over a 12-month period. Reimbursement for the practice time to recruit and participate in the training is provided.

Individual Patient Participants

Potential individual patient participants will consult at a participating practice with 1 of the 5 most common MSK pain presentations (back, neck, knee, shoulder, or multisite pain) as determined by the clinician at the point of consultation.

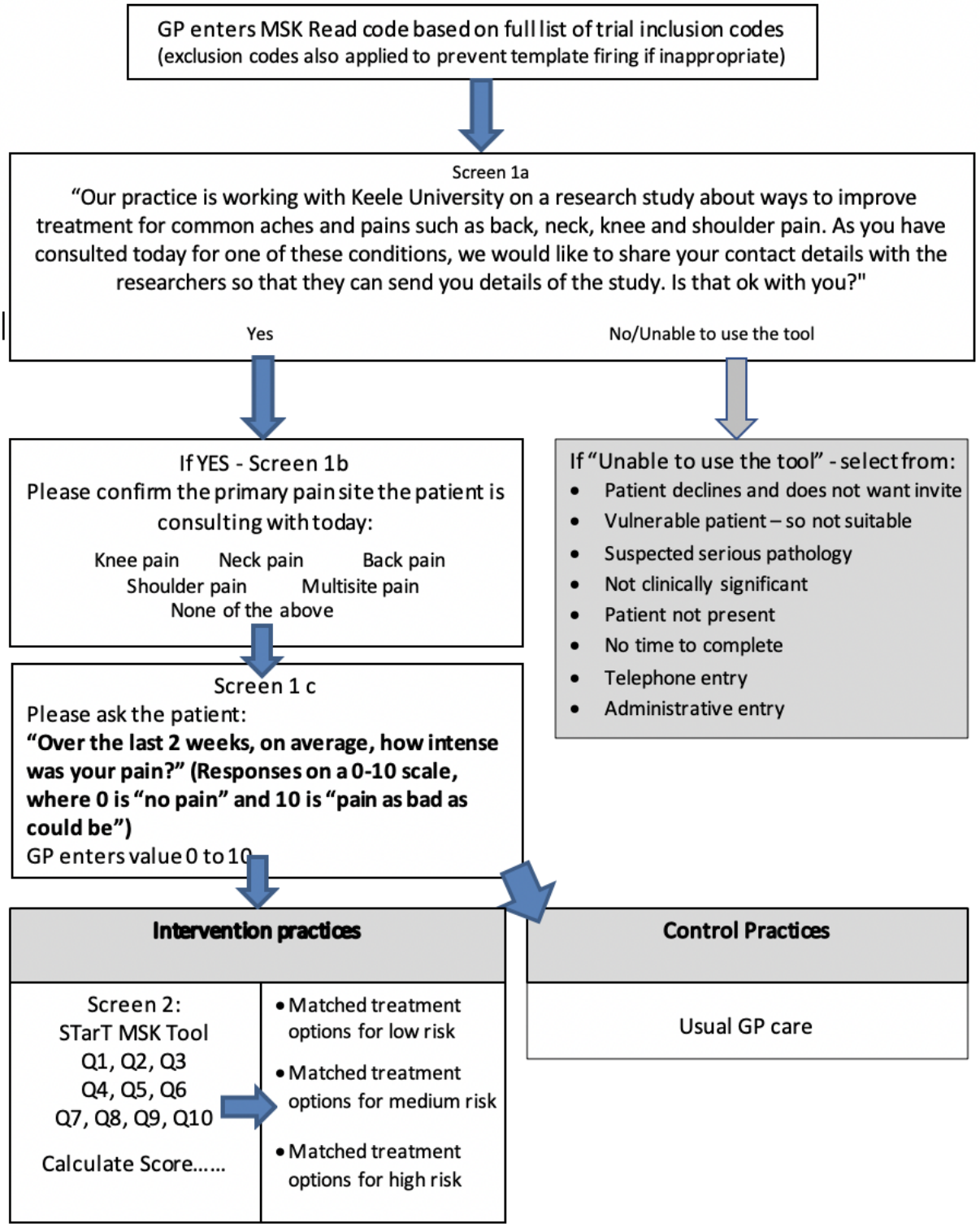
Patient inclusion criteria were aged 18 years and over, registered at the practice during the recruitment period, with a recorded relevant MSK pain Read code entered into the computer system (this may be the first or a repeat consultation), a completed study template, consent to study data collection, consent for research team to have access to their medical record data, and completion of the initial postal questionnaire within 4 weeks of the first mailing.

Patient exclusion criteria were those with indications of serious red flag pathology (eg, recent trauma with significant injury; acute, red, hot swollen joint; suspected fracture; joint infection; cancer; and inflammatory arthropathy such as rheumatoid arthritis, spondyloarthropathy, polymyalgia rheumatica, and crystal disease [gout]), those with urgent medical care needs (eg, cauda equina syndrome), vulnerable patients (including any patients on the severe and enduring mental health register, those who have a diagnosis of dementia, those with a recent diagnosis of a terminal illness, those who have experienced recent trauma or bereavement, or those nearing the end of their life), and those who are unable to communicate in English (both in reading and speaking).

Patient Recruitment for Outcome Data Collection

As described above, an electronic computer template designed to automatically fire to help identify patients will be installed on participating practice computer systems, when 1 of approximately 200 different MSK pain–related Read codes (symptom or diagnostic codes) is entered, as defined by Jordan et al [2] and informed by our pilot RCT (Figure 2). Clinicians will be trained to use this system, but it is already standard practice in NHS primary care since 1985 for clinicians to use this standard vocabulary to record patient findings and procedures in health and social care Information Technology (IT) systems across the United Kingdom. In the consultation, when an MSK-related Read code is entered onto the EMR system, the trial-specific template will be activated. Initially, it prompts the clinician to notify eligible patients about the research study by reading the following:

Figure 2. Details of the trial recruitment template. GP: general practice; MSK: musculoskeletal; Q: question.



Our practice is working with Keele University on a research study about ways to improve treatment for common aches and pains such as back, neck, knee and shoulder pain. As you have consulted today for one these conditions, we would like to share your contact details with the researchers so that they can send you details of the study. Is that ok with you?

Patients who do not give this consent do not have their contact details shared with the research team. Individuals who have previously asked not to be part of any research within the practice are given a Read code that prevents the template from firing in the first place. Retention of identifiable patient data is restricted to the limited period of invitation only, after which, the data of subsequent nonconsenters to the trial will be destroyed. The Keele Clinical Trials Unit (CTU) operates this activity in compliance with the provisions of the Data Protection Act (1998) and adheres to appropriate standards of governance

and security as outlined by the sponsor's (Keele University) standard operating procedures (SOPs).

Practice staff supported by the NIHR Clinical Research Network (CRN), where possible, will regularly (typically weekly) send the contact details of patients for whom the template has been successfully completed to Keele CTU for the purpose of mailing patients their invitation letter, using a secure NHS.net email to transfer data including name, address, Read code for pain site, date of consultation, and EMIS patient identification number. On a monthly basis, the participating practices provide anonymized information about the number of patients for whom the study template is activated and how many of those are not fully completed. This facilitates the provision of a monthly report of their template completion rate and, for intervention practices, additional details about their fidelity to choosing recommended matched clinical management options for patients at low, medium, and high risk.

Eligible participants (from both trial arms) will be sent identical study packs in the post containing a letter from the patient's general practice introducing the study; a PIL, which describes the study and includes instructions on what to do if they wish to take part; an initial questionnaire, including a consent form to record consent for data collection; and a stamped addressed envelope. The following mechanisms will ensure that only eligible and appropriate patients are invited: (1) a list of relevant exclusion Read codes (eg, recent cancer diagnosis) will be used to automatically prevent the template from firing and (2) clinicians will be able to screen individual patients for their suitability at the point of consultation.

In the initial questionnaire sent to patients, participants will provide their written consent for researchers to use their data for this research. A study team member (blind to practice allocation) will support patients who telephone with questions or who need additional support to complete their postal questionnaires, monthly SMS texts, or 1-page questionnaires. The same set of MSK Read codes that trigger the automated template was successfully used as the identification method in our pilot RCT. The electronic identification method is designed to ensure that the template *pop-up* is only activated once per patient, so individuals can only be invited once to participate in this study. Eligible patients who do not respond within 2 weeks of their initial study invitation will be contacted again with another study pack. Patients who do not complete their initial questionnaire within 4 weeks of the initial mailing date will not be contacted again for follow-up data. Patients who return their initial questionnaire and consent to further data collection will be included in the study. The primary outcome (pain intensity) will be collected once a month for 6 months via SMS text or 1-page postal questionnaire (depending on participant preference).

The procedures for reminders for the SMS text monthly communications are as follows: the initial contact will be sent on the next Sunday afternoon that is closest to a calendar month following their initial questionnaire mailing date. If there is no response to this initial contact, a reminder communication will be sent on Tuesday afternoon. If again, there is no response after 48 hours, we will send the monthly 1-page postal questionnaire. On the second consecutive month, we will repeat this procedure; however, if there is no response, in addition to sending the monthly 1-page postal questionnaire, a study team member will telephone the patient to establish what the problem is, seek to resolve it, provide appropriate support, and collect the data where possible. For those receiving the monthly 1-page postal questionnaire, nonresponse after 2 weeks will lead to another 1-page postal questionnaire. Nonresponse on a second consecutive month will lead to a study team member telephoning the patient to establish what the problem is, seek to resolve it, provide appropriate support, and collect the data where possible. Participants will also receive a 6-month follow-up questionnaire to collect further outcomes. Nonresponders to the 6-month follow-up questionnaire will be sent a reminder postcard at 2 weeks and a full questionnaire 2 weeks later (ie, at 4 weeks), and for those who have not responded, a brief questionnaire will be sent after 6 weeks to collect key outcome measures. We will try to collect minimum data over the telephone from participants at 8 weeks where needed. These follow-up methods have been used successfully in previous studies [27-30], including the pilot RCT.

Randomization and Blinding

Practices will be randomized in a ratio of 1:1 to intervention or control using stratified block randomization [31] based on practice patient list size using a Keele CTU computer-generated random sequence and concealment by ensuring that each practice has an anonymized code. The randomization sequence and stratification will be carried out by the senior trial statistician. The block randomization will follow Keele CTU's randomization SOP, and the data sequence will be held on a secure server. Blinding for individual clinicians is not possible, but any staff involved in the collection or database entry of patients' outcome data will be blind to allocation. Access to the allocation sequence will be restricted to those with authorization. Allocation will be shared with the study team (except for the trial statistician and data entry staff who are to remain blind) who will then arrange to inform each practice about their allocation. Data cleaning/checking through stage 1 *data-freeze* and stage 2 *data-lock* reviews will be carried out by the trial statistician, thus maintaining blinding to allocation. The TSC will also be blinded to allocation unless it becomes absolutely necessary to reveal allocation. The DMC trial statistician will be involved in the allocation assignment and, therefore, will not be blinded throughout the study. These processes follow recommendations for cluster trials [26] to reduce selection bias where randomization is before patient data collection.

Interventions

Practice Recruitment Template Installation

Following confirmation that a practice is eligible and willing to take part, an initial setup meeting will be held between the practice, study research team, and a CRN member. This will take place for all practices in both arms of the trial and will be followed by training sessions where the computer template will be installed and demonstrated on the practice's EMIS clinical system. Once the template is installed, the practice is *live*, and potentially eligible participants will be identified in consultations.

Intervention Arm

The recommended matched clinical management options are not new but summarize available evidence-based options into those considered by expert consensus to be appropriate for patients at low, medium, and high risk of persistent pain and disability.

The Start MSK stratified care approach has 2 components: (1) prognostic tool and (2) matched options.

Prognostic Tool

The Keele Start MSK Tool (clinician-completed version) is freely available [32]; is used in the patient consultation [21]; and is supported by an embedded template in the practice's computer system, dedicated training and support sessions, regular audits, peer feedback, and clinical mentoring opportunities using an evidence-based clinician support package to support clinician behavior change [33]. The prognostic tool has 10 questions from which the patient's score and subgroup (low, medium, or high risk of persistent pain and disability) are calculated.

Matched Options

Appropriate matched clinical management options based on an individual's prognosis on the Keele Start MSK Tool will be displayed to support clinical decision making. The matched clinical management options were identified by an evidence synthesis [22], followed by 3 expert consensus workshops [23], during an earlier phase of research, and then further refined following the Start MSK feasibility and pilot [21].

Per Protocol Treatment Decision Rules

Patients at low risk will be considered to be treated *per protocol* if they receive only treatment options 1 or 2 (Figure 3). Patients at medium risk will be *per protocol* if they receive any of options 3-6 (although option 5 is for specific pain sites only). Patients at high risk will be *per protocol* if they receive option 3 or any options between 7 and 11.

Figure 3. Recommended matched treatment options. GP: general practice; MSK: musculoskeletal; NSAIDS: Nonsteroidal anti-inflammatory drugs.

L=Low-risk; M=Medium-risk; H=High-risk	Back			Knee			Multisite			Neck			Shoulder		
Tick mark (✓) denotes matched treatments	L	M	H	L	M	H	L	M	H	L	M	H	L	M	H
1. Education and advice, including exercise, activity modification, weight loss, etc	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Simple oral and topical medications limited to those available over the counter	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Refer to physiotherapy/MSK service		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓
4. Consider weak opioid if acute pain as alternative to NSAIDs		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓
5. Consider corticosteroid injection					✓	✓		✓	✓					✓	✓
6. Refer to supported self-management or locally available community resources (eg, walking group, exercise on prescription/personalized exercise program, expert patient program, dietician, slimming world)		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓
7. Consider atypical analgesia if neuropathic pain present (eg, amitriptyline, pregabalin, gabapentin)			✓			✓			✓			✓			✓
8. Consider referral to pain management service			✓			✓			✓			✓			✓
9. Consider referral to secondary care			✓			✓			✓			✓			✓
10. Consider imaging			✓			✓			✓			✓			✓
11. GP management of comorbidities, distress, frailty, polypharmacy and pain management			✓			✓			✓			✓			✓

The matched options for patients at low risk include advice and education (using printed materials where possible), over-the-counter analgesics, and avoidance of MSK investigations and referrals (where possible). Matched options for patients at medium risk, in addition to the low-risk options, include GPs being encouraged to refer patients to physiotherapy, to review their pain medication, and to consider investigations where necessary. Matched options for patients at high risk, in addition to the medium- and low-risk options, include prescription of atypical analgesia if neuropathic pain is present; referral to specialist services (eg, orthopedics, rheumatology, and pain clinics); imaging; and/or booked reviews to manage complex clinical factors such as comorbidities, polypharmacy, and frailty.

Clinician Support for Delivering Stratified Care

The training and support sessions provided to intervention and control clinicians are designed to equip them with the knowledge and skills to complete the study recruitment template and understand the study inclusion/exclusion criteria. In addition, for intervention practices, a 2-hour intervention training session will be provided. This includes learning about previous stratified care research [19,20], the rationale for developing this new intervention, and investigating whether it will benefit patients

with a broader range of MSK pain. Training will describe the aim to reduce unnecessary health care for patients at low risk, while better targeting health care resources for patients at medium or high risk. Clinicians will have a demonstration of how to use the new approach and have the opportunity to try it out and ask questions and explore how it can be integrated into routine practice. The session will also include discussion and clarification about how the approach differs from usual care and each of the recommended clinical management options. We will also invite a representative from the local MSK physiotherapy service to the training sessions and discuss how best to ensure that patient referrals to physiotherapy include a record of the index consultation and the patient's Start MSK Tool risk group and determine the best method for physiotherapists to communicate with referring GPs if they are concerned about the patient. A feedback meeting will be held with all participating practices (intervention and control) roughly 6 weeks after starting recruitment to discuss the report of their use and completion of the study-specific IT template. For intervention practices, additional feedback on their fidelity to the recommended matched clinical management options will also be provided, comparing each clinician with their colleagues in the same practice and with other clinicians in the trial (anonymized). Monthly email feedback reports will be sent to participating practices.

Physiotherapists linked to intervention practices will also have the opportunity to attend a short training session about the trial and be required to avoid treating patients from control practices for the period of the trial to avoid contamination. However, other key features of physiotherapy care will be as similar as possible for patients irrespective of whether they come from intervention or control practices, including physiotherapy waiting times, treatment session length and number, and the clinical grade of the treating therapist. We will collect these process data from physiotherapy services using a mix of usual clinical record data and standardized case report forms for the study.

Control Arm

In the usual care control arm, patients who consult at their general practice will be assessed and receive advice and treatment as usual (eg, advice and education; medication; referral for investigations or tests; or referral to other services such as physiotherapy, MSK interface clinics, or secondary care specialists such as orthopedics and rheumatology), without the use of formal stratification tools. To keep the control arm as close to *usual care* as possible, clinicians will be advised to follow their usual approach for responding to a patient's pain intensity rating for the presenting MSK problem. Asking a patient the intensity of their pain and where their pain is coming from is common practice [30] and therefore should have little impact on the *usual care* provided.

Data Collection

There will be 3 different types of data collection:

1. Individual patient data, collected from:

- The practices' completed computer templates at the point of consultation
- Initial and 6-month postal questionnaires to participants (full and minimum data versions)
- Monthly SMS text or 1-page postal questionnaire.

2. Clinician decision making and behaviors using data collected from medical records and case report forms

3. Practice-level anonymized aggregated data of MSK Read codes and template use.

Individual Patient Outcomes

General Practice Information Technology Template

The first item on the template asks the primary care clinician to confirm if their patient gives consent to have their contact details shared with the research team. If the answer is yes, then the clinician will record the location of the patient's MSK pain. How this is answered determines which study letter and questionnaire the patient will be sent, as these are slightly different for patients with back, neck, knee, shoulder, or multisite pain. The item reads "Please confirm the primary pain site the patient is consulting with today." Possible response options include *back pain*, neck pain, *knee pain*, *shoulder pain*, *multisite pain*, or *unable to complete template* (which leads to the exit screen). The third question on the template asks the clinician to record the patient's MSK pain intensity by asking "How intense was your pain, on average, over the last 2 weeks?" (Responses are recorded on a scale of 0-10, where 0 is *no pain* and 10 is *worst pain ever*.)

Initial and 6-Month Follow-Up Questionnaires

The initial and 6-month follow-up postal questionnaires are designed to collect information on descriptive characteristics of the participants, pain-related characteristics, and primary and secondary outcome measures (see Table 1 below). Patients are informed in their study invitation that they have been contacted because they recently visited their general practice (the date of their visit will be given) for their MSK pain, which will be prepopulated in the letter (eg, knee pain, shoulder pain) using information from weekly downloaded template codes.

Participants will also be told that it is important they think about their *MSK pain* as they answer the following question: "Thinking about your (eg, neck) pain: Over the last 2 weeks, on average, how intense was your pain?" (Responses were recorded on a scale of 0-10, where 0 is *no pain* and 10 is *worst pain ever*.)

Table 1. A summary of patient-reported data collected.

Conceptual domain	Operational definition	Empirical measure	Number of items	Time
Primary outcome				
Pain intensity	Usual pain intensity	NRS[a] 0-10	1	GPT[b], I[c], 6FU[d], MF[e], and MDC[f]
Secondary outcomes				
Risk status—Start MSK[g] Tool	Risk of persistent disabling pain	Yes/no	9	I and 6FU
MSK health	Impact from MSK symptoms	MSK-HQ[h], 5-point Likert scale	14	I and 6FU
Overall rating of change	Change since MSK pain consultation	−5 to +5 scale	1	I and 6FU
Physical activity level	Days past week of moderate activity	1-7 days	1	I and 6FU
Fear-avoidance beliefs	Fear of movement	Tampa Scale of Kinesiophobia-11	11	I and 6FU
Satisfaction	Satisfaction with care	5-point Likert scale	1	I and 6FU
Perceived reassurance from general practitioner consultation	Patient-perceived reassurance 4 subscales: information gathering, relationship building, generic reassurance, and cognitive reassurance	12 items with 7-point Likert scale	12	I
Receipt of written education material from general practitioner	Single item to ask if patient received written information at their general practitioner visit	Yes/no/don't remember	1	I
Pain self-efficacy	Single item: confidence to manage pain	NRS 0-10	1	I and MF
Psychological distress	Single item regarding level of distress	NRS 0-10	1	I and MF
Site-specific function depending on MSK pain site				
Back pain function	Physical function	RMDQ[i] – original version	24	I and 6FU
Neck pain function	Physical function	NDI[j]	10	I and 6FU
Shoulder pain function	Physical function	SPADI[k]	13	I and 6FU
Knee pain function	Physical function	KOOS-PS[l]	7	I and 6FU
Multisite pain function	Physical function	SF-12 PCS[m]	12	I and 6FU
Quality of life measures				
Health-related quality of life	Utility-based quality of life	EuroQol-5D	5	I, 6FU, and MDC
Health care costs				
Health care resource use	Use of primary care, other National Health Service services, and private health care	Yes/no and if yes details of resources used	3	6FU
Performance at work	How productivity at work is affected	NRS 0-10	1	I and 6FU
Absenteeism from work	Number of days absent from work	Yes/no and details	1	I and 6FU
Patient descriptors				
Age	Age at MSK consultation	Date of birth	1	GP T
Sex	Sex	Male/female	1	GP T
Employment status and absence from work	Employment status at time of questionnaire	Yes/no and details	1	I and 6FU
Socioeconomic status	The individual's current or most recent job title	Job title: categorized as manual/nonmanual	2	I

Conceptual domain	Operational definition	Empirical measure	Number of items	Time
MSK pain location	Site of MSK pain complaint	Choice of anatomical region	1	GP T
Episode duration	Time since last whole month pain free	Episode duration	1	I
Health literacy screen	Health literacy	Single question: Likert scale	1	I
Comorbidities	Other diagnosed comorbidities to select from a list	Yes	1	I
Support needed	Who has completed the questionnaire	Patient/carer/staff/other	1	I
Living arrangements	Lives alone	Yes/no	1	I
Previous episodes	Number of previous pain episodes	Number	1	I

[a]NRS: numerical rating scale.

[b]GP T: GP template.

[c]I: initial questionnaire.

[d]6FU: 6-month follow-up.

[e]MF: monthly follow-up.

[f]MDC: minimal data collection.

[g]MSK: musculoskeletal.

[h]MSK HQ: Musculoskeletal Health Questionnaire.

[i]RMDQ: Roland-Morris Disability Questionnaire.

[j]NDI: Neck Disability Index.

[k]SPADI: Shoulder Pain and Disability Index.

[l]KOOS-PS: Knee Injury and Osteoarthritis Outcome Score-Physical Function Shortform.

[m]SF-12 PCS: Short-Form 12 Physical Component Scale.

Monthly SMS Text or 1-Page Questionnaire for 3 Items, Including the Primary Outcome

In addition to the primary outcome (pain intensity), the monthly SMS text or 1-page questionnaire includes 2 potential mediating variables using the following single items for psychological distress and self-efficacy, which are taken and adapted with permission from the validated MSK Health Questionnaire (MSK-HQ) [34]:

"How much distress have you been experiencing because of your pain, on average, over the last 2 weeks?" (Responses were recorded on a scale of 0-10, where 0 is no distress and 10 is extremely distress.)

"How confident have you felt about managing your pain by yourself (eg, medication, changing lifestyle)?" (Responses were recorded on a scale of 0-10, where 0 is not at all confident and 10 is extremely confident.)

Clinician Behaviors via Linked Medical Records

Clinician decision making and behaviors will be examined through a review of the practice computerized medical records for all patients who give consent for this (at the end of the initial questionnaire). This will allow data to be analyzed from (1) individual patient outcomes, (2) the initial patient-clinician consultation electronic template, and (3) further aspects of their medical record over 6 months following the MSK consultation. Variables of interest from the MSK consultation will include the date of consultation, coded reason for the consultation, MSK pain intensity and location, Start MSK Tool (clinician-completed version) individual items and total score (intervention arm only), and information about the management decisions and other actions taken by the clinician. Other clinical behaviors of interest are described in the *Outcomes* section. The information collected on the patient's risk subgroup and management options in the intervention practices will be audited and fed back to clinicians at regular intervals, allowing them to see how closely they have followed the matched clinical management options. At the end of the trial, we will also report the fidelity of clinicians in the intervention practices in terms of completing the tool and choosing matched treatment options. The template MSK pain intensity score will also provide the initial score for the primary outcome for participants in both arms of the trial.

Physiotherapists treating patients referred from participating practices will complete their usual clinical records. At the end of the trial, we will collect details about the physiotherapy treatment provided for consenting trial participants to compare between intervention and control.

Practice-Level Anonymized and Aggregated Data of Musculoskeletal Read Codes

Each participating general practice will provide anonymized medical record data from potentially eligible patients for whom the template was activated through entry of an MSK Read code (estimated n ≥5000). We will compare the following:

1. The characteristics of those patients in which the template is activated with those who respond to the initial questionnaire and provide individual-level patient outcomes. The information examined will not involve any patient-identifiable data and will not be linked to any other data unless prior patient consent has been provided.

2. Aspects of clinical behaviors for 6 months following the index consultation to compare intervention and control practices for key treatment processes for each risk subgroup. For example, this will include requests for the following:

- Prescriptions (eg, categorized into simple analgesics, nonsteroidal anti-inflammatory drugs, neuromodulators, muscle relaxants, corticosteroid injections, and opioids)
- Referrals (eg, categorized into physiotherapy/MSK interface services, specialist services including orthopedics, pain clinics, and rheumatology)
- Imaging (eg, categorized into x-rays/magnetic resonance imaging (MRI) scans, MSK ultrasound scans, and bone density scans)
- Sick certifications or fit notes (eg, categorized into number per patient and mean length in days)
- Repeat MSK general practice visits.

The collection of anonymized and aggregated medical record data is not uncommon within similar general practice research studies that examine potential recruitment bias [35] or for intervention studies examining clinician decision making and behaviors during the consultation (eg, the Primary Care Osteoarthritis Screening Trial [28] and the Study of Work and Pain trial [30,36]).

Patient and Public Involvement Engagement

This study was discussed and shaped with patient and public involvement engagement (PPIE) through dedicated workshops before the funding submission. The PPIE group agreed with the importance of developing a more robust research base for treatments that can improve the primary care management of MSK pain. Their discussions informed the design and piloting of the text message system and 1-page postal questionnaire used to capture the primary outcome of pain intensity. They also reviewed and improved the patient-facing documentation for the study. Members of the group have expressed an interest in being involved in the analysis of the qualitative data, and it is intended to include them in that process.

Further PPIE meetings were held following the feasibility and pilot trial to identify improvements for the main trial. Their recommendations included the following:

- Updating the invitation pack to provide greater clarity to patients about what is involved in taking part in the trial.
- Simplifying the consent form in the initial patient questionnaire.
- Removing the prize draw system used for participants in the feasibility and pilot trial. This was considered to potentially be confusing for patients and did not appear to lead to a higher response rate to the questionnaires than those in similar research studies.

Outcomes

Primary Outcome

The primary outcome for the trial is the patient-reported clinical outcome of pain intensity, measured monthly over 6 months. Pain intensity is a recommended outcome for trials of MSK pain [37] and had strong face validity among members of the PPIE group. In addition, analysis of our previous MSK cohort data confirmed that this outcome is sensitive to changes in this population.

Secondary Outcomes

Secondary clinical outcomes captured at the initial and 6-month questionnaire include body site–specific physical functional measures, using the Roland-Morris Disability Questionnaire for patients with back pain [38], the Neck Disability Index [39,40] for patients with neck pain, the Shoulder Pain and Disability Index [41] for patients with shoulder pain, the Knee Injury and Osteoarthritis Outcome Score-Physical Function Short form [42] for patients with knee pain, and the Short Form 12v2 Physical Component Scale [43] for patients with multisite pain. Other clinical outcomes will include patients' risk of persistent disabling pain using the Keele Start MSK Tool, and the impact and severity of their MSK pain using the MSK-HQ [34], which includes measures of pain interference with sleep, physical activity level, hobbies/leisure activities, work and daily routine, and quality of life with items for patients' confidence in managing their pain (pain self-efficacy) and emotional health and understanding of how to deal with their condition. We will also collect fear-avoidance beliefs using the 11-item version of the Tampa Scale of Kinesiophobia [44], and the patient-perceived level of reassurance from their clinician will be captured using the Holt and Pincus [45] reassurance scale, which has 4 subscales: information gathering, relationship building, generic reassurance, and cognitive reassurance. Other outcomes will include health-related quality of life using the EQ-5D-5L to calculate QALYs in the health economic evaluation [46] and single-item questions to capture patient satisfaction with care received, receipt of written education material from their clinician, and overall rating of change in their MSK pain since their primary care consultation [47]. As completion of the initial questionnaire can occur up to 4 weeks following the index MSK GP consultation, this means the first measurement of secondary outcomes is after the commencement of treatment. We chose the timing of the final outcome to be at 6 months as our pilot trial [21] demonstrated a plateau in mean outcomes before this time point. A summary of the patient data collection variables is listed in Table 1.

Baseline Population Descriptors

To help describe the population recruited, additional baseline descriptors will capture health literacy using the Single Item Literacy Screener [48], episode duration of MSK pain by asking time since last whole month free from this pain, age, sex, employment, and their most recent paid job title (to calculate their socioeconomic status).

Health Care Resource Use

Questions on additional health care resource use and patient-borne costs including MSK pain–related hospital

inpatient stays, outpatient attendance (eg, physiotherapy), other NHS and private practice health care appointments, and over-the-counter medicines and treatment will be included in the 6-month questionnaire. Work performance will be assessed through a single-item work presenteeism question, and time (days) off work will be aligned to occupational information to ascertain the cost of absenteeism.

Process Evaluation

A process evaluation is planned to explore a range of potential factors that might influence differences between trial arms as well as to better understand how stratified care is used and perceived by patients and clinicians. Following recent Medical Research Council guidance on process evaluations for complex interventions [49], we have designed a mixed methods approach [50]. This will use quantitative analyses focusing on a priori hypothesized intervention targets and qualitative approaches using focus groups and interviews.

A key aim of the process evaluation is to better understand the role of potential intervention targets (mediators) on differences in outcomes between the trial arms [51]. The evidence from our previous stratified care trial (for back pain, the Start Back trial) suggested that the identification and targeting of psychological distress among patients at high risk led to improved outcomes [52]. In addition, a systematic review has recently summarized available evidence and identified pain self-efficacy as another potential mediator [53]. Evidence from the Keele Implementation to Improve Patient Care through Targeted treatment Back study [20], which sought to implement our stratified care approach for patients with low back pain consulting in general practice, suggested that important clinical behavior changes included more systematic identification of patients who are *at risk* of persistent disabling pain who need additional support (leading to more referrals to physiotherapy). After careful consideration by the trial team, a number of potential treatment mediators have been identified a priori, including 3 potential factors at the patient level: (1) reduction in levels of psychological distress measured each month with a single item, (2) increases in pain self-efficacy measured each month with a single item, and (3) the extent of patient-perceived reassurance during the index primary care consultation measured via the initial questionnaire. Changes in these potential patient-level treatment mediators will be examined within a mediation analysis using causal modeling techniques (eg, structural equation modeling) to confirm if they are in the causal pathway explaining any observed between-arm differences in outcome with results also examined at each subgrouping level (low, medium, and high).

In addition, we have identified a number of a priori potential mediators at the level of clinical behavior, measured using the medical record data, including the proportion of patients who receive prescription medications for MSK pain, referrals to other services (eg, physiotherapy and secondary care specialists), referrals for investigations (eg, radiographs, MRI/Computerized Tomography (CT) scans, blood tests), sick certifications (fit notes), and further MSK-related consultations. We will test if there are significant differences in these behaviors between intervention and control practices and whether any of these differences are associated with the results in terms of patients' pain intensity.

Sample Size

In an average-sized UK general practice (6000 registered adults), we expect that about 800 potentially eligible patients will consult with the MSK pain sites of interest per year or 400 over 6 months. The feasibility and pilot trial showed that, on average, the template was activated 375 times over 6 months in each practice, and clinicians fully completed it in 41.1% (154/375) of cases (6 times per week), leading to a letter inviting the patient to participate in the data collection. From this, we expect that 40% of patients invited will return their initial questionnaire in the main trial, be eligible, and consent to further data collection (or 62 over 6 months in 1 practice). However, to be more cautious, given the general uncertainty in data and in generalizability of pilot estimates, we have conservatively estimated the average number of participants recruited per practice within 6 months in the main trial to be around 33% of those invited (or n=50 in 6 months or n=9 per month per practice).

The trial is powered at 90% to test the hypothesis of the overall superiority of stratified primary care versus usual care based on an alpha of 5% (two-tailed) to detect a small *effect size* (standardized mean difference) of 0.2 [54] in the primary outcome (pain intensity). An effect size of 0.2 was considered to be appropriate based on information from the feasibility and pilot trial, in which the proportion of responders in the 3 risk subgroups was 32% at low risk, 55% medium risk, and 13% high risk. Our previous trial of stratified care for patients with low back pain (the Start Back trial) found an effect size of 0.3 and 0.4 in the primary outcome (back pain–related physical function) in patients at medium and high risk, respectively. Therefore, we have assumed these standardized differences in this new trial [19]. In addition, the minimal clinically important difference for the numerical rating scale (NRS) pain intensity scores in MSK pain has been reported to be 1 point [55], which equates to an effect size of about 0.4, relative to an expected SD of about 2.5 [54]. We expect that there would be little or no difference between stratified care and usual care for patients in the low-risk subgroup. Hence, by multiplying these effects by the expected proportion within each subgroup, the overall effect size of interest is 0.2 (equating to an absolute mean difference of approximately 0.5 in pain intensity on a 0-10 scale).

The sample size calculation takes into account the clustering of individual participants by practice and likely participant dropout over a 6-month follow-up (inflationary effects on sample size requirement) as well as repeated measurements and adjustment for corresponding baseline pain intensity score (deflationary effects). We have allowed for an Intraclass correlation coefficient of 0.01 based on previous patient-level data from primary care trials [56] as well as expected variation in recruitment per practice using a guideline coefficient of variation of 0.65 [57], and together with an expected loss to follow-up across all time points of approximately 25%, these factors combine to give a sample size inflation factor of ×2.3 (based on an average cluster size of approximately 50 participants per practice in 6 months). The correlation of data within 6 repeated

measurements and correlation of follow-up scores with baseline score are typically 0.7 and 0.5, respectively [58], which combine to give a sample size deflation factor of ×0.5. The product of inflation and deflation effects results in a magnification of 1.15 compared with a conventional, individual patient, single follow-up comparison, whereby the sample size requirement would be 525 per trial arm (or 1050 in total). The adjusted sample size target is, therefore, 600 patients per arm (1200 in total) from 24 general practices (12 per arm).

Statistical Reporting

Data will be reported according to the Consolidated Standards Of Reporting Trials (CONSORT) 2010 statement [59,60], including extensions to cluster randomized trials [61] and pragmatic trials [62].

Final analysis will be carried out after all the data are collected, entered, and cleaned according to Keele CTU SOPs. A flow diagram will show the flow of participants through the trial, including reasons for not taking part and loss to follow-up (split by trial arm). For trial participants, summaries of continuous variables will comprise the number of observations used, mean, median, SD, and interquartile range as appropriate for the distributional form of the data (in total and split by treatment arm). Summaries of categorical variables will comprise the number of observations used and the number and percentage of observations in each category.

Inferential analyses will include reporting of the main (point) estimate for the mean between-arm difference (numerical outcomes) or odds ratio (categorical outcomes) along with 95% CI and *P* values (two-tailed). Odds ratios will also be converted to absolute risk differences (using the usual care prevalence as the base reference in any conversion). Hypothesis tests will use a two-sided 5% significance level. The main analyses will be performed independently by the trial statisticians using the protocol, and the statistical analysis plan agreed with the TSC. For any results discordance(s), if consensus agreement cannot be reached, then a third (independent) statistician will be asked to review and resolve any differences.

Methods of Analysis

Descriptive Statistics: Baseline Characteristics

The baseline demographics and clinical characteristics of general practices and individual participants will be reported. The CONSORT guidelines generally do not recommend statistical significance testing of baseline imbalances between trial arms. However, a more recent publication suggests baseline testing of individual-level characteristics for cluster RCTs to examine the level of selection bias as indicated by potential imbalances in baseline covariates between arms [63].

Main Analysis of Primary Outcomes

To avoid any potential bias in the analysis, intention to treat (ITT) will be the primary analysis population (including primary and secondary outcomes) unless otherwise stated in the detailed statistical analysis plan (available from the authors). This is defined as general practice clusters (and affiliated participants) being analyzed as they are randomized regardless of the intervention. Data for individuals who withdraw consent to participate in data collection will be included up to the point of withdrawal. Primary analysis will compare mean differences in pain intensity scores between trial arms over a 6-month follow-up using a hierarchical linear mixed regression model evaluating repeated measures data at 1-, 2-, 3-, 4-, 5-, and 6-month follow-up (level 1) within individuals (level 2) and taking into account clustering of individuals within general practices—the unit of randomization (level 3). The analyses will be adjusted for age, sex, and baseline pain intensity score (recorded from the IT template at the point of consultation) at the individual-patient level and general practice size. This analysis fulfills the ITT principle with analysis as randomized and missing data being accounted for under the missing at random assumption. Although the primary analysis will focus on the *average* intervention effect across 1 to 6 months of follow-up, we will also use treatment by time interaction terms to evaluate between-arm differences in mean responses across each of the individual time points of 1, 2, 3, 4, 5, and 6 months. Model fit will be assessed across different covariance structures (unstructured, independence, exchangeable, autoregressive) to ascertain the best-fit model that will be implemented (ie, the model that gives the lowest Bayesian Information Criterion, Akaike Information Criterion, and highest log-likelihood statistics). The monthly pain intensity scores will be used; however, if, for any individual, the last monthly SMS/brief questionnaire response is missing but they have completed the corresponding pain intensity question in their returned 6-month questionnaire (if completed within 20 days of the date of issue of their monthly SMS/brief questionnaire), then the available pain intensity score response will be used (as the 6-month score) for purposes of the primary outcome evaluation.

Analysis of Secondary Outcomes

Analysis of secondary outcomes will be carried out using the ITT approach and using a linear mixed model for numerical outcomes and generalized mixed logistic models for categorical outcomes (adjusted for age, sex, baseline pain, and corresponding baseline score [where applicable] at the individual-patient level and general practice size). For monthly follow-up measures of distress and confidence in managing pain, the analysis will follow that of the primary analysis with initial focus on *average* scores over the 6 months of follow-up and then the time-specific between-arm estimates. The focus of the other secondary measures is on 6-month follow-up data only, with the exception of perceived reassurance, which is captured in the baseline questionnaire.

Sensitivity Analysis of the Primary Outcome

A sensitivity analysis will be carried out using a complier average causal effect analysis (CACE) to provide an unbiased estimate of intervention effect for patients treated according to the stratified care protocol, that is, the intervention arm *protocol* is taken as clinical management in line with the recommended matched treatment options for each risk subgroup. CACE will be performed using a 2-step instrumental variable regression modeling approach where the first step relates to model prediction of *compliance* (at level 2 [individual patient level]) using trial arm only as a fixed-effect predictor and practice and participant IDs as random effects, and the second step estimates

the between-arm difference in outcome (*average* pain intensity) based on predicted compliance—the endogenous (instrumented) variable (from the first step) and the exogenous (instrumental) variables of trial arm, age, sex and point-of-consultation pain score using a mixed effects model as used in the primary analysis.

Subgroup Exploratory Analysis of Primary Outcomes

Subgroup exploratory analysis of the primary outcome (*average* pain intensity) will be carried out by modeling intervention arm interaction terms within the regression models for (1) risk subgroups (low [reference category], medium, and high risk), (2) single MSK pain (reference) site versus multisite pain, and (3) pain site (back [reference], shoulder, knee, and neck). Subgroup analysis was performed regardless of the results of the primary analysis. The mean between-arm difference (and 95% CI and *P* value) will be computed for each subgroup comparison and visually displayed via a forest plot. The main focus will be on the *average* pain intensity rather than on 3-way interactions of intervention-subgroup-time, but the 3-way interaction results will also be examined (and descriptive results produced by subgroup).

Exploratory Mediation Analyses

If there is a significant between-arm difference in the primary outcome (overall pain intensity), then we will carry out exploratory mediation analysis by structural equation modeling to examine (1) which potential mediators are *causal* in effect. (2) if psychological mediators (psychological distress or pain self-efficacy in months 1-5) are on the causal pathway for effect, and (3) if patient-perceived reassurance mediates direct/indirect associations of 6-month pain intensity outcomes.

Evaluation of the Process Outcomes

Process outcomes will be evaluated through comparison of aggregated anonymized data at the level of the participating general practices, by examining, for example, reconsultation rates for MSK pain over 6 months and referral rates to other services between practices in the stratified care versus usual care arms. In intervention practices, we will also investigate the proportions of patients for whom the electronic template is completed, and matched clinical management options are selected overall and by risk subgroup.

A descriptive analysis will be undertaken of physiotherapist data by the intervention arm (eg, waiting times, number of treatment sessions, and clinical grade of treating physiotherapist).

Examination of Bias

Selection bias will be examined through scrutiny of the comparability of recruitment rates per trial arm and comparability in general practice and participant characteristics. Further, a comparison will be performed examining the characteristics of patients in which the electronic template is activated but who did not take part in the data collection (nonparticipants) with those who did participate in terms of practice distribution; pain intensity scores; location of MSK pain; and (within the intervention arm) the proportion of patients at low, medium, and high risk of persistent disabling pain (from the practice consultation IT template). Both crude descriptive and inferential statistics will be reported.

Differential attrition between trial arms will be examined and reported descriptively: frequencies for responses by trial arm will be recorded in the descriptive tables. We will compare baseline sociodemographic and clinical variables and (for response ≥1) monthly NRS pain intensity scores across level of completion of NRS pain intensity (level of completion is 0 to 6, where 0 is nonresponse, 1 responded once, and 6 responded to all 6 monthly follow-ups) to ascertain whether pattern of missingness is likely to be *missing completely at random*, *missing at random*, or *not missing at random*. If the overall follow-up rate of the primary outcome is over 5% different between trial arms and the pattern of missing data is *missing at random*, then we will undertake a multiple imputation (MI; via chained equations) analysis inclusive of baseline variables that are observed to be statistically associated with follow-up response. Further, if the pattern of missingness is seen to suggest that it is nonignorable, the MI sensitivity analysis will address missing data imputations with an incremented or reduced value corresponding to the overall baseline SD (thereby mimicking the nonignorable pattern).

Health Economics

The health economics analysis will determine the cost-effectiveness of stratified care in comparison with usual, nonstratified care over 6 months. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences. Subsequently, cost-utility analysis will be undertaken from an NHS/PSS perspective to determine the cost per additional QALY gained. A broader costing perspective will be considered in a secondary analysis, taking into account NHS/PSS costs, private MSK-related health care costs, and productivity costs associated with time off work.

Costs

Resource use information will be obtained on primary care consultations (eg, general practitioners and practice nurses), secondary care consultations (eg, hospital consultants and physiotherapists), prescriptions, hospital-based procedures (eg, diagnostic tests, injections, and investigations), length of inpatient stay, and surgery. Patients will be asked to distinguish between UK NHS and private provision. Cost data will be collected via a participant questionnaire at 6 months. Unit costs will be obtained from standard sources and health care providers, including the British National Formulary, Unit Costs of Health and Social Care, and NHS Reference costs [64-66]. Given that MSK pain is associated with significant lost productivity, information will also be collected from participants on occupation status, time off work related to their MSK problem, and reduced work performance (presenteeism). This will enable the calculation of productivity costs, allowing analysis from a broader societal cost perspective. The average wage for each respondent will be identified using the UK Standard Occupational Classification coding and annual earnings data for each job type [67].

Outcomes

The outcome of interest for the economic analysis is QALYs and will be generated from participant responses to the EQ-5D-5L questionnaire at baseline and at the 6-month follow-up. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current National Institute for Health and Care Excellence recommendations.

Data Analysis

The cost-utility analysis will be carried out on an ITT basis, with the aim of estimating the difference in costs and QALYs between the stratified care and usual, nonstratified care arms. Missing EQ-5D-5L and cost data will be imputed using MI techniques [68] to ensure that all trial participants are included in the final analysis. For each participant, a QALY score over the 6-month follow-up period will be estimated using the area under the curve approach [69]. Imbalances in baseline utility (EQ-5D-5L) scores between the stratified care and usual nonstratified care arms will be controlled for using a regression approach [70].

The total health care costs over the study period will be calculated by multiplying the resource items used by the respective unit cost and summing over all items. Differences in mean costs and QALYs between the stratified care and usual nonstratified care arms will be estimated. The data for costs are likely to have a skewed distribution; therefore, a nonparametric comparison of means (eg, bootstrapping) will be undertaken to estimate 95% CIs around costs.

Due to the nature of the trial, methods are required to address clustering in both costs and outcomes and to recognize the correlation between individual- and cluster-level costs and outcomes. The methods currently suggested in the health economics literature are multilevel models (MLM) and the 2-stage nonparametric bootstrap, using the Stata 15 [Stata Corp] command TSB) [71]. For the base case scenario, MLM will be used to estimate differential costs, differential QALYs, and incremental net benefits. The analysis will also allow us to control for covariates. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial data itself as well as the methods employed to analyze the data. A cost-effectiveness acceptability curve will be constructed to assess the probability that stratified care is effective at different willingness-to-pay thresholds. To estimate productivity costs, self-reported days off work will be multiplied by the average wage rate. The analysis will use the human capital approach.

Planned sensitivity analysis will include (1) a complete case analysis as an alternative to using an imputed dataset; (2) a broader societal perspective; and (3) additional exploratory analyses that will consider the cost-effectiveness of stratified care versus usual nonstratified care for patients in the low-, medium-, and high-risk subgroups separately. All analyses will be performed using StataCorp 15 software.

Linked Qualitative Study

Theoretical Framework

Two theoretical frameworks will underpin the evaluation. First, the COM-B model [72] offers a way of understanding behavior in the context of complex interventions around 3 key determinants: *capability* (the psychological or physical ability to enact the behavior), *opportunity* (the physical and social environment that enables the behavior), and *motivation* (the reflective and automatic mechanisms that activate or inhibit behavior). Second, normalization process theory provides a framework for understanding how/why some new health care interventions are accepted and taken up, whereas others are less successful [73]. Both frameworks emphasize the broader sociopolitical contexts in which health behaviors and practices are situated and the importance of taking these contexts into account in understanding the adoption of new interventions [73,74].

Aim

This study aims to understand the ways in which stratified care is perceived and operationalized, from the perspectives of health care professionals and patients, taking into account individual, local, and national contexts.

Objectives

The specific objectives of our linked qualitative research will be as follows:

- Identify the acceptability and impact on the consultation of using the clinician-completed version of the Keele Start MSK Tool and the extent to which the matched treatment options are viewed as being in line with clinical judgments on best practice.
- Understand the impact of stratified care on (1) individual clinicians; (2) general practice and physiotherapy services; (3) interprofessional and professional-patient communication; and (4) patients at low, medium, and high risk.
- Document any variation in experiences or views across different practices and services in the trial.

Methods for Linked Qualitative Study

An iterative, mixed methods approach will be adopted [50,75], with the quantitative data informing the qualitative data collection and analysis from both informing the overall findings and conclusions. Data will be drawn from clinicians and patients.

Clinicians

GPs and physiotherapists involved in delivering stratified care will be invited to participate in up to 3 separate focus groups held at approximately 4 GP practices. Where clinicians are unable to attend focus groups, arrangements will be made for individual interviews. Initial focus groups/interviews will explore clinicians' views and experiences of delivering stratified care during the course of the trial. Follow-up focus groups/interviews will be conducted at a later stage once trial results are available to explore views on the trial results and, depending on these results, discuss potential implications for practice, policy, and service provision beyond the trial.

Patients

One-to-one semistructured interviews will be conducted to explore individual patient experiences. Patients at low risk will be interviewed approximately 2 months after their index primary care consultation, whereas patients at medium and high risk will be interviewed at approximately 4 months. This timescale will allow participants to reflect on their experiences of clinical management (including time to access any treatments), communication with the clinicians involved in their care, and their health care resource use over time.

Sampling

Clinicians and patients will be sampled from the stratified care arm of the trial. GPs directly involved in the trial will be identified based on the diversity of practice characteristics, including size and geographic location. A sample of physiotherapists in linked participating services will also be invited to participate. Patients will be purposively sampled from baseline questionnaire responses to capture diverse characteristics, such as pain scores and health-related quality of life, risk subgroup, comorbidity, age, sex, and socioeconomic status.

Sample Size of the Qualitative Study

Data collection will continue until saturation is reached, defined as *informational redundancy*, the point at which additional data no longer offer new insights [76]. We estimate that around 20 to 30 clinicians and approximately 20 to 30 patients will be required.

Recruitment to a Qualitative Study

Clinicians will be informed that as part of their participation in the trial, they may be approached to participate in focus groups or interviews. Additional information explaining confidentiality, anonymity, data storage, and archiving will be distributed ahead of each focus group/interview and individual written consent obtained before the start of the discussion.

Patients will be informed that, as part of their participation in the study, they consented to further research contact. An invitation letter and detailed interview information leaflet will be mailed to the patient, and after 2 to 3 days, a researcher will telephone the patient to check if they are willing to participate and, if so, make arrangements for the interview. Interviews may be face-to-face or by telephone, based on participant preference, and will be arranged at a time/location convenient for the participant. Once an interview has been arranged, a confirmation letter will be sent. Written consent will be obtained at the start of the interview or audio-recorded if the interview is via telephone and checked again at the end. Interviews are estimated to last approximately 1 hour.

Trial Management, Study Administration, and Data Storage

The trial manager assisted by the study coordinator will oversee the day-to-day running of the trial. General practice staff assisted where necessary by the CRN will download details of patients who have a completed template (name, address, MSK pain site, date of MSK consultation, and EMIS patient identification number) on a weekly basis from each practice. Practice staff will arrange transfer of patient details to the dedicated research administrator in Keele CTU using nhs.net-to-nhs.net transfer for mailing of the study invite packs to potential participants. A unique study number will be applied to each potential participant. On return of a completed initial questionnaire, details will be entered into the research database to ensure that no unnecessary reminders are sent. Details of informed consent will be stored in the research database, including participants' names and contact details. In this database, participants will be primarily identified by study number. Data will be entered into the research database by trained members of the administrative team who will be blinded to general practice allocation. Access to the database will be restricted to those members of the team that require access. The coding schedule for the questionnaires will be used to inform the database design and to facilitate data entry. Details of data entry accuracy will be kept by the research data management lead and trial statisticians and reported.

Any requests for access to the anonymized data will follow our data-sharing procedure. Requests for anonymized data will be reviewed by our Data Custodian and Academic Proposals Committee. The full statement on data sharing is publicly available [32]. All information will be held securely and in strict confidence. Each person in this study will be given a study number so that data from the study will not have any identifiable information, such as names and addresses, and cannot be traced. On this basis, these *anonymized* data will be kept electronically and may be used in other research studies.

Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual participating practices or NHS services. One potential issue is that GPs in the intervention arm may feel that the recommended matched clinical management options are not appropriate for an individual patient, in which case they will need to choose a treatment that is not among the recommended options. The clinician training sessions will make it clear that despite being part of a clinical trial, clinicians retain the responsibility to provide appropriate care to their patients. Clinicians will be encouraged to report to the research team where there are consistent difficulties with the stratified care intervention.

Statement of Indemnity and Trial Sponsors

Keele University has in place clinical trial indemnity, which provides coverage to the university for harm that comes about through the university's or its staff's negligence in relation to the design or management of the trial and may alternatively, at the University's discretion, provide cover for nonnegligent harm to participants. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS organization (general practices and other services involved) remains liable for clinical negligence and other negligent harm to patients under this duty of care. The sponsor (Keele University) is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC.

Oversight/Trial Monitoring

The Trial Management Group (TMG) comprises the chief investigator, associate investigator, Keele CTU staff, and other key trial team members. They are responsible for the clinical setup, ongoing management, promotion of the trial, and analysis and interpretation of results. Specifically, the TMG is responsible for (1) protocol completion; (2) study document development; (3) obtaining health research authority approval; (4) completing cost estimates and project initiation; (5) facilitating the TSC and DMC; (6) reporting of serious adverse events (SAEs); (7) monitoring of recruitment, intervention, and follow-up procedures; (8) data collection; and (9) database development. The group will meet on a regular basis, typically monthly, throughout the trial. The trial does not incorporate any a priori stopping rules, and hence, no planned interim analysis of the outcome measures collected in the trial will be carried out.

Financial Arrangements

Clinicians participating in the focus groups/interviews will receive a reimbursement of their time using standard professional rates. Patients participating in an interview will be given a GBP £10 (US $12.2) Love to Shop gift token by way of thanking them for their participation and will only receive remuneration for travel if they participate in an interview at a site other than their home.

Serious Breaches of the Protocol and Good Clinical Practice

Keele CTU has systems in place to ensure that serious breaches of GCP are picked up and reported. A *serious breach* is a breach that is likely to effect to a significant degree: the safety or physical or mental integrity of the participants of the trial or the scientific value of the trial. All protocol deviations or breaches of the GCP will be recorded and reported to the sponsor according to the relevant SOP.

Serious Adverse Events

The NHS Research Committee approval reference is 16/EM/0257. Patient participants gave written consent to participate. SAEs include death, hospitalization, significant disability or incapacity, any life-threatening circumstance, or any other medically significant occurrence that is believed to be related to the trial or interventions. All participating practice staff and physiotherapists will be asked to report as soon as possible to the chief investigator any SAEs among patient participants, that are likely to be related to the trial. We have discussed this issue with the independent TSC and agreed that the potential harms of the study are considered to be minimal and the stratified care information and matched treatment options are considered not only to be evidence-based but also have strong clinical community endorsement and credibility. Any SAEs will be brought to the immediate attention of the trial team. The chief investigator will then assess whether the event was related to or resulted from any of the trial procedures or interventions, according to the process laid out in Keele CTU's SOPs. Any unexpected SAE considered to be related to the trial procedures will be reported to the main research ethics committee by the chief investigator within 15 days of becoming aware of the event. In addition, all such events will be reported to the trial sponsor, TSC, and DMC.

Confidentiality and Anonymity

All information collected during the course of the trial will be kept strictly confidential. All identifying information will be anonymized before being used for analysis. Information will be held securely on paper and managed electronically by Keele University through Keele CTU. Keele CTU complies with all aspects of the 1998 Data Protection Act. The trial data will be held on a database hosted on a secure server by Keele CTU. All research staff involved in this study adhere to robust data security procedures and have explicit duties of confidentiality. These practices are written into their employment contracts and are equivalent to the duties placed on NHS staff. If a participant withdraws consent from further collection of data, their data collected to date will remain on file and will be included in the final study analysis unless requested otherwise.

Results

The trial was funded as part of a 6-year research program in June 2014, the pilot trial was undertaken from October 2016 to May 2017 and the main trial was approved by research ethics committee in February 2018. Data collection for the main trial commenced in May 2018, and ended in July 2019, after a recruitment period of 14 months in 24 GP practices, which successfully recruited 1203 patient participants. All 6-month follow-up and interview data collection was completed in February 2020. Data analysis is currently in progress with expected results to be published in summer 2020. There have been no important changes to methods since trial commencement.

Discussion

This study protocol describes the details of the Start MSK trial, which aims to investigate the clinical and cost effectiveness of stratified primary care for patients with the 5 most common MSK pain presentations compared with usual nonstratified care. The intervention was designed to improve patient outcomes including pain intensity, physical function, and quality of life as well as clinician decision making to reduce treatment variability and improve adherence to best practice. This trial is the first attempt, as far as we know, at testing a prognostic stratified care approach for primary care patients with MSK pain. The results of this trial should be available in the summer of 2020.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1128 KB - resprot_v9i7e17939_app1.pdf]

References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the global burden of disease study 2013. Lancet 2015 Aug 22;386(9995):743-800 [FREE Full text] [doi: 10.1016/S0140-6736(15)60692-4] [Medline: 26063472]
2. Jordan KP, Kadam UT, Hayward R, Porcheret M, Young C, Croft P. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. BMC Musculoskelet Disord 2010 Jul 2;11:144 [FREE Full text] [doi: 10.1186/1471-2474-11-144] [Medline: 20598124]
3. Thomas E, Dunn KM, Mallen C, Peat G. A prognostic approach to defining chronic pain: application to knee pain in older adults. Pain 2008 Oct 15;139(2):389-397. [doi: 10.1016/j.pain.2008.05.010] [Medline: 18583051]
4. Mallen CD, Thomas E, Belcher J, Rathod T, Croft P, Peat G. Point-of-care prognosis for common musculoskeletal pain in older adults. JAMA Intern Med 2013 Jun 24;173(12):1119-1125. [doi: 10.1001/jamainternmed.2013.962] [Medline: 23699833]
5. The National Archives. 2006. The Musculoskeletal Services Framework - A Joint Responsibility: Doing It Differently URL: https://webarchive.nationalarchives.gov.uk/20130124073659/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4138412.pdf [accessed 2020-05-15]
6. Margham T. Musculoskeletal disorders: time for joint action in primary care. Br J Gen Pract 2011 Nov;61(592):657-658 [FREE Full text] [doi: 10.3399/bjgp11X601541] [Medline: 22054314]
7. Somerville S, Hay E, Lewis M, Barber J, van der Windt D, Hill J, et al. Content and outcome of usual primary care for back pain: a systematic review. Br J Gen Pract 2008 Nov;58(556):790-7, i [FREE Full text] [doi: 10.3399/bjgp08X319909] [Medline: 19000402]
8. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health 2011 Oct 6;11:770 [FREE Full text] [doi: 10.1186/1471-2458-11-770] [Medline: 21978149]
9. Henschke N, Ostelo RW, Terwee CB, van der Windt DA. Identifying generic predictors of outcome in patients presenting to primary care with nonspinal musculoskeletal pain. Arthritis Care Res (Hoboken) 2012 Aug;64(8):1217-1224 [FREE Full text] [doi: 10.1002/acr.21665] [Medline: 22422737]
10. Carnes D, Parsons S, Ashby D, Breen A, Foster NE, Pincus T, et al. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. Rheumatology (Oxford) 2007 Jul;46(7):1168-1170. [doi: 10.1093/rheumatology/kem118] [Medline: 17488750]
11. Inouye S, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007 May;55(5):780-791 [FREE Full text] [doi: 10.1111/j.1532-5415.2007.01156.x] [Medline: 17493201]
12. von Korff M, Miglioretti DL. A prognostic approach to defining chronic pain. Pain 2005 Oct;117(3):304-313. [doi: 10.1016/j.pain.2005.06.017] [Medline: 16153772]
13. Dunn KM, Croft PR, Main CJ, von Korff M. A prognostic approach to defining chronic pain: replication in a UK primary care low back pain population. Pain 2008 Mar;135(1-2):48-54. [doi: 10.1016/j.pain.2007.05.001] [Medline: 17570585]
14. Muller S, Thomas E, Dunn KM, Mallen CD. A prognostic approach to defining chronic pain across a range of musculoskeletal pain sites. Clin J Pain 2013 May;29(5):411-416 [FREE Full text] [doi: 10.1097/AJP.0b013e318257099e] [Medline: 23549065]
15. Turner JA, Shortreed SM, Saunders KW, Leresche L, Berlin JA, von Korff M. Optimizing prediction of back pain outcomes. Pain 2013 Aug;154(8):1391-1401. [doi: 10.1016/j.pain.2013.04.029] [Medline: 23688822]
16. Linton SJ, Halldén K. Can we screen for problematic back pain? A screening questionnaire for predicting outcome in acute and subacute back pain. Clin J Pain 1998 Sep;14(3):209-215. [doi: 10.1097/00002508-199809000-00007] [Medline: 9758070]

17. Hill JC, Dunn KM, Lewis M, Mullis R, Main CJ, Foster NE, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. Arthritis Rheum 2008 May 15;59(5):632-641 [FREE Full text] [doi: 10.1002/art.23563] [Medline: 18438893]
18. Foster NE, Hill JC, O'Sullivan P, Hancock M. Stratified models of care. Best Pract Res Clin Rheumatol 2013 Oct;27(5):649-661. [doi: 10.1016/j.berh.2013.10.005] [Medline: 24315146]
19. Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, Foster NE, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. Lancet 2011 Oct 29;378(9802):1560-1571 [FREE Full text] [doi: 10.1016/S0140-6736(11)60937-9] [Medline: 21963002]
20. Foster NE, Mullis R, Hill JC, Lewis M, Whitehurst DG, Doyle C, IMPaCT Back Study team. Effect of stratified care for low back pain in family practice (IMPaCT Back): a prospective population-based sequential comparison. Ann Fam Med 2014;12(2):102-111 [FREE Full text] [doi: 10.1370/afm.1625] [Medline: 24615305]
21. Hill JC, Garvin S, Chen Y, Cooper V, Wathall S, Saunders B, et al. Stratified primary care versus non-stratified care for musculoskeletal pain: findings from the STarT MSK feasibility and pilot cluster randomized controlled trial. BMC Fam Pract 2020 Feb 11;21(1):30 [FREE Full text] [doi: 10.1186/s12875-019-1074-9] [Medline: 32046647]
22. Babatunde OO, Jordan JL, van der Windt DA, Hill JC, Foster NE, Protheroe J. Effective treatment options for musculoskeletal pain in primary care: a systematic overview of current evidence. PLoS One 2017;12(6):e0178621 [FREE Full text] [doi: 10.1371/journal.pone.0178621] [Medline: 28640822]
23. Protheroe J, Saunders B, Bartlam B, Dunn KM, Cooper V, Campbell P, et al. Matching treatment options for risk sub-groups in musculoskeletal pain: a consensus groups study. BMC Musculoskelet Disord 2019 Jun 1;20(1):271 [FREE Full text] [doi: 10.1186/s12891-019-2587-z] [Medline: 31153364]
24. Saunders B, Hill JC, Foster NE, Cooper V, Protheroe J, Chudyk A, et al. Stratified primary care versus non-stratified care for musculoskeletal pain: qualitative findings from the STarT MSK feasibility and pilot cluster randomized controlled trial. BMC Fam Pract 2020 Feb 11;21(1):31 [FREE Full text] [doi: 10.1186/s12875-020-1098-1] [Medline: 32046656]
25. Eldridge SM, Ashby D, Feder GS. Informed patient consent to participation in cluster randomized trials: an empirical exploration of trials in primary care. Clin Trials 2005;2(2):91-98. [doi: 10.1191/1740774505cn070oa] [Medline: 16279130]
26. Eldridge S, Kerry S, Torgerson DJ. Bias in identifying and recruiting participants in cluster randomised trials: what can be done? Br Med J 2009 Oct 9;339:b4006. [doi: 10.1136/bmj.b4006] [Medline: 19819928]
27. Dziedzic KS, Healey EL, Porcheret M, Ong BN, Main CJ, Jordan KP, et al. Implementing the NICE osteoarthritis guidelines: a mixed methods study and cluster randomised trial of a model osteoarthritis consultation in primary care--the management of osteoArthritis in consultations (MOSAICS) study protocol. Implement Sci 2014 Aug 27;9:95 [FREE Full text] [doi: 10.1186/s13012-014-0095-y] [Medline: 25209897]
28. Mallen C. Keele University. 2016. POST Cluster Trial URL: https://www.keele.ac.uk/pcsc/research/ctu/ourresearch/post/ [accessed 2020-05-15]
29. Foster N. Keele University. STEMS Cluster Trial URL: https://www.keele.ac.uk/pcsc/research/researchthemes/musculoskeletalpainandstratifiedcare/stems/ [accessed 2020-05-15]
30. Bishop A, Wynne-Jones G, Lawton SA, van der Windt D, Main C, Sowden G, SWAP Study Team. Rationale, design and methods of the study of work and pain (SWAP): a cluster randomised controlled trial testing the addition of a vocational advice service to best current primary care for patients with musculoskeletal pain (ISRCTN 52269669). BMC Musculoskelet Disord 2014 Jul 10;15:232 [FREE Full text] [doi: 10.1186/1471-2474-15-232] [Medline: 25012813]
31. Carter BR, Hood K. Balance algorithm for cluster randomized trials. BMC Med Res Methodol 2008 Oct 9;8:65 [FREE Full text] [doi: 10.1186/1471-2288-8-65] [Medline: 18844993]
32. Keele University. URL: https://www.keele.ac.uk/startmsk [accessed 2020-05-15]
33. Wensing M, Wollersheim H, Grol R. Organizational interventions to implement improvements in patient care: a structured review of reviews. Implement Sci 2006 Feb 22;1:2 [FREE Full text] [doi: 10.1186/1748-5908-1-2] [Medline: 16722567]
34. Hill J, Kang S, Benedetto E, Myers H, Blackburn S, Smith S, et al. Development and initial cohort validation of the arthritis research UK musculoskeletal health questionnaire (MSK-HQ) for use across musculoskeletal care pathways. BMJ Open 2016 Aug 5;6(8):e012331 [FREE Full text] [doi: 10.1136/bmjopen-2016-012331] [Medline: 27496243]
35. Boardman HF, Thomas E, Ogden H, Millson DS, Croft PR. A method to determine if consenters to population surveys are representative of the target study population. J Public Health (Oxf) 2005 Jun;27(2):212-214. [doi: 10.1093/pubmed/fdi017] [Medline: 15774566]
36. Wynne-Jones G, Artus M, Bishop A, Lawton SA, Lewis M, Jowett S, SWAP Study Team. Effectiveness and costs of a vocational advice service to improve work outcomes in patients with musculoskeletal pain in primary care: a cluster randomised trial (SWAP trial ISRCTN 52269669). Pain 2018 Jan;159(1):128-138. [doi: 10.1097/j.pain.0000000000001075] [Medline: 28976423]
37. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, et al. Report of the NIH Task Force on research standards for chronic low back pain. Phys Ther 2015 Feb;95(2):e1-18 [FREE Full text] [doi: 10.2522/ptj.2015.95.2.e1] [Medline: 25639530]

38. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976) 1983 Mar;8(2):141-144. [doi: 10.1097/00007632-198303000-00004] [Medline: 6222486]
39. BenDebba M, Heller J, Ducker TB, Eisinger JM. Cervical spine outcomes questionnaire: its development and psychometric properties. Spine (Phila Pa 1976) 2002 Oct 1;27(19):2116-23; discussion 2124. [doi: 10.1097/01.BRS.0000025729.35559.28] [Medline: 12394923]
40. MacDermid JC, Walton DM, Avery S, Blanchard A, Etruw E, McAlpine C, et al. Measurement properties of the neck disability index: a systematic review. J Orthop Sports Phys Ther 2009 May;39(5):400-417. [doi: 10.2519/jospt.2009.2930] [Medline: 19521015]
41. Breckenridge JD, McAuley JH. Shoulder pain and disability index (SPADI). J Physiother 2011;57(3):197 [FREE Full text] [doi: 10.1016/S1836-9553(11)70045-5] [Medline: 21843839]
42. Perruccio AV, Lohmander LS, Canizares M, Tennant A, Hawker GA, Conaghan PG, et al. The development of a short measure of physical function for knee OA KOOS-physical function shortform (KOOS-PS) - an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008 May;16(5):542-550 [FREE Full text] [doi: 10.1016/j.joca.2007.12.014] [Medline: 18294869]
43. Ware Jr JE. SF-36 health survey update. Spine (Phila Pa 1976) 2000 Dec 15;25(24):3130-3139. [doi: 10.1097/00007632-200012150-00008] [Medline: 11124729]
44. Archer KR, Phelps KD, Seebach CL, Song Y, Riley LH, Wegener ST. Comparative study of short forms of the tampa scale for Kinesiophobia: fear of movement in a surgical spine population. Arch Phys Med Rehabil 2012 Aug;93(8):1460-1462. [doi: 10.1016/j.apmr.2012.03.024] [Medline: 22481127]
45. Holt N, Pincus T. Developing and testing a measure of consultation-based reassurance for people with low back pain in primary care: a cross-sectional study. BMC Musculoskelet Disord 2016 Jul 12;17:277 [FREE Full text] [doi: 10.1186/s12891-016-1144-2] [Medline: 27405870]
46. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
47. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther 2009;17(3):163-170 [FREE Full text] [doi: 10.1179/jmt.2009.17.3.163] [Medline: 20046623]
48. Morris NS, MacLean CD, Chew LD, Littenberg B. The single item literacy screener: evaluation of a brief instrument to identify limited reading ability. BMC Fam Pract 2006 Mar 24;7:21 [FREE Full text] [doi: 10.1186/1471-2296-7-21] [Medline: 16563164]
49. MRC Guidance. 2008. Developing and Evaluating Complex Interventions: Following Considerable Development in the Field Since 2006, MRC and NIHR Have Jointly Commissioned an Update of This Guidance to Be Published in 2019 URL: https://www.mrc.ac.uk/documents/pdf/complex-interventions-guidance [accessed 2020-05-15]
50. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. Br Med J 2010 Sep 17;341:c4587. [doi: 10.1136/bmj.c4587] [Medline: 20851841]
51. Oakley A, Strange V, Bonell C, Allen E, Stephenson J, RIPPLE Study Team. Process evaluation in randomised controlled trials of complex interventions. Br Med J 2006 Feb 18;332(7538):413-416 [FREE Full text] [doi: 10.1136/bmj.332.7538.413] [Medline: 16484270]
52. Mansell G. British Library EThOS. 2016. Methodological Challenges in Treatment Mediation Analysis : Examples From Studies Targeting Psychological Factors in Patients With Musculoskeletal Pain URL: http://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.695633 [accessed 2020-05-18]
53. Mansell G, Hill JC, Main C, Vowles KE, van der Windt D. Exploring what factors mediate treatment effect: example of the start back study high-risk intervention. J Pain 2016 Nov;17(11):1237-1245 [FREE Full text] [doi: 10.1016/j.jpain.2016.08.005] [Medline: 27565304]
54. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Second Edition. Hillsdale, NJ: Lawrence Earlbaum; 1988.
55. Busse JW, Bartlett SJ, Dougados M, Johnston BC, Guyatt GH, Kirwan JR, et al. Optimal strategies for reporting pain in clinical trials and systematic reviews: recommendations from an OMERACT 12 workshop. J Rheumatol 2015 Oct;42(10):1962-1970. [doi: 10.3899/jrheum.141440] [Medline: 25979719]
56. Adams G, Gulliford MC, Ukoumunne OC, Eldridge S, Chinn S, Campbell MJ. Patterns of intra-cluster correlation from primary care research to inform study design and analysis. J Clin Epidemiol 2004 Aug;57(8):785-794. [doi: 10.1016/j.jclinepi.2003.12.013] [Medline: 15485730]
57. Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. Int J Epidemiol 2006 Oct;35(5):1292-1300. [doi: 10.1093/ije/dyl129] [Medline: 16943232]
58. Vickers AJ. How many repeated measures in repeated measures designs? Statistical issues for comparative trials. BMC Med Res Methodol 2003 Oct 27;3:22 [FREE Full text] [doi: 10.1186/1471-2288-3-22] [Medline: 14580266]
59. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Br Med J 2010 Mar 23;340:c332 [FREE Full text] [doi: 10.1136/bmj.c332] [Medline: 20332509]

60. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Br Med J 2010 Mar 23;340:c869 [FREE Full text] [doi: 10.1136/bmj.c869] [Medline: 20332511]
61. Campbell MK, Piaggio G, Elbourne DR, Altman DG, CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. Br Med J 2012 Sep 4;345:e5661. [doi: 10.1136/bmj.e5661] [Medline: 22951546]
62. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, CONSORT group, Pragmatic Trials in Healthcare (Practihc) Group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. Br Med J 2008 Nov 11;337:a2390 [FREE Full text] [doi: 10.1136/bmj.a2390] [Medline: 19001484]
63. Bolzern J, Mitchell A, Torgerson D. Baseline testing in cluster randomised controlled trials: should this be done? BMC Med Res Methodol 2019 May 17;19(1):106 [FREE Full text] [doi: 10.1186/s12874-019-0750-8] [Medline: 31101078]
64. Joint Formulary Comm. BNF 73 (British National Formulary). London, UK: Pharmaceutical Press; 2017.
65. NHS England and NHS Improvement. Archived Reference Costs URL: https://improvement.nhs.uk/resources/reference-costs/ [accessed 2020-05-15]
66. Curtis L, Burns A. The Unit Costs of Health and Social Care. Canterbury, UK: University of Kent; 2017.
67. Office for National Statistics. 2010. Standard Occupational Classification (SOC) URL: https://www.ons.gov.uk/methodology/classificationsandstandards/standardoccupationalclassificationsoc [accessed 2020-05-15]
68. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, USA: John Willey & Sons; 1987.
69. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. Br Med J 1990 Jan 27;300(6719):230-235 [FREE Full text] [doi: 10.1136/bmj.300.6719.230] [Medline: 2106931]
70. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005 May;14(5):487-496. [doi: 10.1002/hec.944] [Medline: 15497198]
71. Gomes M, Ng ES, Grieve R, Nixon R, Carpenter J, Thompson SG. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. Med Decis Making 2012;32(2):350-361 [FREE Full text] [doi: 10.1177/0272989X11418372] [Medline: 22016450]
72. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci 2012 Apr 24;7:37 [FREE Full text] [doi: 10.1186/1748-5908-7-37] [Medline: 22530986]
73. May CR, Mair FS, Dowrick CF, Finch TL. Process evaluation for complex interventions in primary care: understanding trials using the normalization process model. BMC Fam Pract 2007 Jul 24;8:42 [FREE Full text] [doi: 10.1186/1471-2296-8-42] [Medline: 17650326]
74. Bergold J, Thomas S. Forum Qualitative Sozialforschung. 2012. Participatory Research Methods: A Methodological Approach in Motion URL: http://www.qualitative-research.net/index.php/fqs/article/view/1801/3334 [accessed 2020-05-15]
75. Leech N, Onwuegbuzie AJ. A typology of mixed methods research designs. Qual Quant 2007 Mar 27;43(2):265-275 [FREE Full text] [doi: 10.1007/s11135-007-9105-3]
76. Sandelowski M. Theoretical saturation. In: Given LM, editor. The SAGE Encyclopedia of Qualitative Research Methods. Thousand Oaks, CA: Sage Publications; 2008:875-876.

Abbreviations

CACE: causal effect analysis
CRN: Clinical Research Network
CTU: Clinical Trials Unit
DALYs: disability-adjusted life years
DMC: Data Monitoring Committee
EMIS: Egton Medical Information Systems
EMR: electronic medical record
EQ-5D-5L: EuroQol-5D-5L
GP: general practitioner
ITT: intention to treat
MI: multiple imputation
MLM: multilevel models
MRI: magnetic resonance imaging
MSK: musculoskeletal
MSK-HQ: MSK Health Questionnaire
NHS: National Health Service
NIHR: National Institute for Health Research
NRS: numerical rating scale
PIL: patient information leaflet
PPIE: public involvement engagement

PSS: Personal Social Services
QALYs: quality-adjusted life years
RCT: randomized controlled trial
SAEs: serious adverse events
SOPs: standard operating procedures
TMG: Trial Management Group
TSC: Trial Steering Committee

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Protocol

The Effects of Foot Reflexology on Chemotherapy-Induced Nausea and Vomiting in Patients with Digestive System or Lung Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: The side effects of chemotherapy, specifically chemotherapy-induced nausea and vomiting, are a concern for patients. To relieve these side effects, antiemetic drugs are recommended. However, some patients report that these drugs are not sufficiently effective. Moreover, patients with chronic disease, including cancer, are increasingly interested in complementary and alternative medicines, and express the desire for nonpharmacological treatments to be used in hospitals. Foot reflexology is a holistic approach that is reported to significantly reduce the severity of chemotherapy-induced nausea and vomiting in patients with breast cancer. Some of the chemotherapy treatments for patients with lung and digestive system cancer are moderately or highly emetic.

Objective: The primary objective of this study is to assess the benefits of foot reflexology, together with conventional treatments, on the severity and frequency of chemotherapy-induced nausea and vomiting in patients with lung or digestive system cancer. The secondary objectives to be assessed are quality of life, anxiety, and self-esteem.

Methods: This study is an open-label randomized controlled trial conducted over 22 months (18 months intervention and 4 months follow-up). Eligible participants are patients with a lung or digestive system cancer with an indication for platinum-based chemotherapy. Participants are randomized into two groups: conventional care with foot reflexology and conventional care without foot reflexology. Foot reflexology sessions (30 minutes) are performed on an outpatient or inpatient basis. It was estimated that 40 participants per group will be required. The benefits of foot reflexology will be assessed by comparing the relative change in the severity of nausea and vomiting, as assessed by a visual analogue scale, and the frequency of these side effects between the two groups. The secondary objectives will be assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; Hospital and Anxiety Depression Scale; and Body Image Questionnaire.

Results: This study was approved by the regional ethics committee (Île de France X CPP) on April 3, 2018 (No. ID RCB 2018-A00571-54). Enrollment started in June 2018. Data analysis will be performed during the second quarter of 2020 and results will be published in the last quarter of 2020.

Conclusions: The lack of knowledge regarding the efficacy and safety of foot reflexology limits oncologists to recommend it for this use. This study will provide evidence of the benefits of foot reflexology. If efficacy is confirmed, foot reflexology may be a promising complement to conventional antiemetic drugs.

Trial Registration: Clinicaltrials.gov NCT03508180; https://www.clinicaltrials.gov/ct2/show/NCT03508180.

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KEYWORDS

cancer; randomized controlled trial; foot reflexology; nausea; vomiting; chemotherapy

Introduction

Background

Patients with cancer are increasingly interested in complementary and alternative medicines (CAMs) [1]. According to the systematic review by Keen et al [2], the main reasons patients use CAMs are to treat their cancer, to treat the side effects of treatment, and to improve their quality of life. Patients with chronic disease, including cancer, express the desire for nonpharmacological treatments and CAMs be used in hospitals [3].

At the time of writing, the most frequently provided CAMs in private and public oncology centers in European countries are mind-body techniques, acupuncture, homeopathy, energy therapies, health promotion, traditional herbal medicine, as well as manipulation and body-based practices (kinesiology, osteopathy, physiotherapy, and reflexology) [4]. Foot reflexology is a holistic approach. A systematic review indicated that foot reflexology seems to be effective for patients with cancer but this field requires further rigorous research with a randomized controlled trial [5]. More specifically, foot reflexology improved the quality of life of patients in the palliative stage of cancer [6], significantly decreased pain intensity and anxiety in patients with metastatic cancer [7], and significantly decreased the perceived pain and anxiety of postoperative patients with gastric cancer and hepatocellular cancer [8]. Moreover, a significant decrease in chemotherapy-induced nausea and vomiting (CINV) was observed in patients with breast cancer who received reflexology treatments [9,10]. Foot reflexology, used concomitantly with conventional treatment, shows promise in decreasing the side effects induced by chemotherapy. In particular, it may decrease CINV, which is the side effect that concerns patients the most [11], as it decreases their overall quality of life [12,13] and induces metabolic complications [11]. In addition, CINV can lead to dose reduction, postponement of treatment, and even discontinuation of treatment [14], all of which can decrease the effectiveness of the treatment [15]. To control acute and delayed CINV, antiemetic drugs are prescribed; the main ones used are 5-hydroxytryptamine 3 receptor antagonists, dexamethasone, and neurokinin-1 inhibitor receptor antagonists [11,16,17]. But despite antiemetic therapy, CINV may persist [13]. In addition to the emetogenicity of the chemotherapy, various parameters may be associated, including risk factors (age, gender, alcohol use, history of motion sickness, and history of pregnancy-related vomiting) [12], treatment compliance [18] and the perceptual gap between health professionals and patients [19,20].

In 2018, in both sexes combined, lung cancer was the leading global cause of cancer death (18.4%), followed by digestive system cancer including colorectal (9.2%), stomach (8.2%), and liver (8.2%) [21]. According to national and international recommendations, adjuvant treatment for lung and digestive system cancer is platinum-based chemotherapy [22-26]. Anticancer therapy cisplatin has a high emetic risk (incidence of CINV >90%), while carboplatin and oxaliplatin have a moderate emetic risk (incidence of CINV is from 30% to 90%) [17].

Objective

The aim of this study is to determine whether foot reflexology decreases the side effects induced by chemotherapy (specifically, CINV resulting from platinum-based chemotherapy) in patients with lung or digestive system cancer.

Methods

Trial Design

An open-label randomized controlled trial (RCT) will be carried out, in which patients are randomized to one of two groups at a 1:1 ratio: (1) conventional care with foot reflexology (40 patients) and (2) conventional care without foot reflexology (40 patients). Randomization is stratified on the type of cancer (digestive system or lung) and the presence or absence of metastases. The sponsor is the Hospices Civils de Lyon. The principal investigator is PJS. To design this trial, we used the CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments [27].

Eligibility Criteria of Participants

Eligibility requirements for this study are the following: patients aged ≥18 years; patients with lung cancer (eg, non–small cell lung carcinomas, small cell lung cancer, mesothelioma) or digestive system cancer (eg, colorectal cancer, pancreatic cancer, liver cancer); patients on platinum-based chemotherapy with or without radiation therapy concomitant (eg, digestive system cancer: FOLFOX, FOLFIRINOX, GEMOX, LV5FU2-CDDP; lung cancer: cisplatin-vinorelbine, pemetrexed-cisplatin, pemetrexed-carboplatin, carboplatin-paclitaxel); World Health Organization performance status ≤2; patients affiliated to the national social security system or equivalent; patients able to complete the questionnaires (comprehension of oral and written French language); and patients who provide written informed consent. The exclusion criteria are phlebitis; vena cava syndrome; weight loss >5% in the 3 months before inclusion date; uncontrolled pain; patients receiving morphine or morphine

derivatives; brain metastases; patients receiving foot reflexology outside the study; patients under guardianship or curatorship or who have been deprived of their rights. All data will be collected from outpatients and inpatients.

Description of Processes, Interventions, and Comparisons

The patients randomized to the intervention group will benefit from a foot reflexology session (30 minutes) at each chemotherapy session for four cycles. The reflexology sessions will be given during chemotherapy infusion every 2 or 3 weeks, depending on the chemotherapy protocol. The sessions will be administered by two qualified reflexologists (they were trained at the French school École des Techniques en Réflexologie).

In a meta-analysis study, Lee et al [28] determined that the optimal comparator is a control group with conventional care without foot reflexology or massage therapy.

Foot reflexology is CAM, based on the principle of acupressure, that helps the body restore homeostasis. It is a holistic approach that allows one to understand the body as a whole. Each part of the body is represented by a zone or reflex point on the foot. The reflexologist stimulates each reflex zone using specific thumb and finger techniques on the patient's feet. Depending on the objective, the zones on the feet are stimulated using different types of pressure. During a session focused on the treatment of CINV, the reflexologist mainly stimulates the reflex points related to the digestive system, the lymphatic system, and kidneys to help the body eliminate toxins. The reflexology chart used in this clinical study is based on the one proposed by Eunice Ingham [29].

The reflex zones of the whole body are also found on the hands. During the first reflexology session, the reflexologist shows the patient the appropriate zones on the hands to relieve nausea. The patient will be able to stimulate these reflex points between each cycle if necessary (self-practice at home). Adherence of participants to reflexology is assessed with a diary. They have been instructed to use a diary every day between each cycle of chemotherapy to note episodes of nausea and vomiting. They also note if they took at least one antiemetic drug (on-demand treatment). If the patient uses self-massage, they note whether it has been effective.

The protocol of intervention was standardized by the reflexologists involved in this study. Over the course of the session, relaxation movements were incorporated after each stimulated reflex point. To calm nausea and vomiting, the reflexologist stimulated the upper and lower digestive reflex points, as well as smooth muscle reflex points (lymphatic system; kidneys and bladder; lungs; and thyroid and parathyroid). Encouraging deep relaxation to target anxiety involved the stimulation of the diencephalon reflex points, scapular belt reflex points, reflex points of the diaphragm, and reflex points of the spine.

Enrolment, Screening, and Allocation

Participants will be enrolled by physicians at the Lyon Sud Hospital Centre thoracic and hepatogastroenterology departments. Eligible participants who wish to participate in the study are asked to sign a written informed consent form. The randomization procedure is performed by the Interactive Web Response System (IWRS) via ClinSight software (Ennov Clinical, version 7.5.710, Ennov Group). Participants are allocated to the intervention group (with foot reflexology) or to the control group (without foot reflexology) before starting their treatment. Clinical research assistants generate the random allocation sequence and assign participants to the intervention.

Primary Objective

The primary objective is to assess the benefits of foot reflexology on CINV (from platinum-based chemotherapy) in patients with lung or digestive system cancer.

Secondary Objectives

The secondary objectives are to assess the benefits of foot reflexology in terms of overall quality of life, anxiety, and self-esteem.

Evaluation Criteria

Primary Outcome

The primary outcome is the relative change in the severity of nausea and vomiting, as assessed with a visual analogue scale (VAS). The patient is asked to mark their current nausea level on the horizontal line with anchor statements on the left (a happy face, no nausea=0 mm) and on the right (a very sick green face, paroxysm of nausea or vomiting=100 mm). Unlike vomiting, which is measurable by the number of episodes per day, nausea is a subjective experience. For that reason, we will use a VAS to evaluate the severity of nausea in patients [30]. For patients in the intervention group, this measurement will be done when the patient arrives at the outpatient or inpatient department and after the foot reflexology session, during the second cycle of chemotherapy. For patients in the control group, this measurement will be done when the patient arrives at the outpatient or inpatient department and before leaving the hospital, during the second cycle of chemotherapy. The assessment is performed by a nurse or clinical research assistant.

All patients will continue to receive standard antiemetic drugs (eg, 5-hydroxytryptamine 3 receptor antagonists, dexamethasone, and neurokinin-1 inhibitor receptor antagonists). According to chemotherapy protocols, oral antiemetic agents are included, and patients are instructed to complete the course.

Secondary Outcomes

Nausea and Vomiting

The benefits of foot reflexology on CINV will also be assessed with the diary completed every day by patients between the first and fourth cycle of chemotherapy. Every day, the patient assesses the frequency of nausea and vomiting, recording each episode of nausea and emesis, and assessing the intensity of nausea and vomiting when it is at its highest with a Likert scale (response modalities: "Very low," "Low," "Low Moderate," "Severe," "Very severe," "Unbearable").

Quality of Life

The benefits of foot reflexology on quality of life will be assessed by the relative change in the overall European

Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) score [31]. The patient is asked to complete EORTC QLQ-C30 at the baseline and end of the study (fourth cycle of chemotherapy).

Anxiety

The benefits of foot reflexology on anxiety will be assessed by the relative change in the overall Hospital and Anxiety Depression Scale (HADS) score [32]. The patient is asked to complete HADS at the baseline and end of the study (fourth cycle of chemotherapy).

Self-Esteem

The benefits of foot reflexology on the level of self-esteem will be assessed at the end-of-study visit using the Body Image Questionnaire (BIQ) [33], which measures body image at a given time. The analysis of the BIQ takes into account the level of self-esteem assessed at the baseline using the Rosenberg scale [34].

Adverse Events

All adverse events are collected during this study and the assessment of causality with foot reflexology is at the physician's discretion.

Sample Size

In a study reported by Billhult et al [35], the mean improvement for CINV (measured using a VAS) was 49.5% in the placebo group, and 73.5% in the massage group (with a common standard deviation of 32.2%). Assuming these same hypotheses, for a two-sided risk of 5%, it is necessary to include 40 patients per group to demonstrate a statistically significant difference between the two groups with a power of 90%.

Type of Statistical Analysis Used

Study data are entered into a password-protected Excel spreadsheet (version 14.0, Microsoft Corp) accessible only to the project manager. Quantitative data will be described for the entire population, using the following descriptive statistics: the number, the number of missing values, the mean, the standard deviation, the median, the interquartile range, and the range. Qualitative variables will be summarized for the entire population using the following descriptive statistics: the frequency and percentage for each category of the variable and the missing values (missing values will be counted but are not included in the denominator of the calculation of frequencies).

For the primary endpoint, comparison of the relative change in the VAS between the two groups will be performed using a linear model adjusted on the type of cancer (digestive system or lung) and the presence of metastases (randomization stratification factors). This model allows the estimation of the difference in mean relative variation of VAS between the two groups, adjusted on potential confounding factors, with a 95% confidence interval. The VAS score may be transformed satisfy the assumptions of the linear model. If the assumptions of the model cannot be verified, the comparison between the two groups will be done using the van Elteren test. Specific estimates of the difference in relative VAS variation between the groups will be provided for both types of cancer, and by metastatic status.

The comparison of the frequency of episodes of CINV between chemotherapy cycles between the two groups will be performed using a mixed effects Poisson model, integrating the number of intercycle days as offset. The model will consider the intervention group and stratification criteria as fixed effects, and will incorporate one random intercept per patient.

The proportion of chemotherapy cycles in which the patient took at least one antiemetic drug will be compared between the two groups using a mixed effect logistic regression model. The model will consider the intervention arm and stratification criteria as fixed effects, and will incorporate one random intercept per patient.

The comparison of quality of life and anxiety between the two groups will be done using a Wilcoxon test.

The comparison of self-image between the two groups will be done using a linear model adjusted on the baseline self-esteem evaluated with the Rosenberg scale. A possible transformation of the BIQ score will performed to satisfy the assumptions of the linear model.

The analysis will be performed according to the intention-to-treat principle, considering all patients that completed the endpoint evaluation in the group that was allocated to them by the randomization. The time point for the primary endpoint has been defined to minimize the risk of missing data.

For the primary endpoint, a secondary analysis will be performed per protocol, including patients with the endpoint assessment, and for whom the strategy allocated during randomization was fully implemented (ie, patients allocated to the foot reflexology group that did not receive four sessions of foot reflexology will be excluded from the analysis).

Regulatory and Ethical Considerations

This study was approved by the regional ethics committee (Île de France X CPP) on April 3, 2018 (No. ID RCB 2018-A00571-54). This study complies with the Reference Methodology (MR-001) developed by the French Data Protection Commission (Commission Nationale de l'Informatique et des Libertés), amended in October 2010, relating to the processing of personal data in clinical trials. This study follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [36].

Patients provide written informed consent that is dated and signed by the patient and the investigating physician. Patients in the control group will receive foot reflexology sessions at the end of their participation (two 30-minute sessions).

This study takes place in a university hospital. Each caregiver and investigator involved ensures optimal patient management. The project manager ensures communication and a close link between the caregivers, investigators, reflexologist, sponsor, and patients.

Results

This study was approved by the regional ethics committee (Île de France X CPP) on April 3, 2018 (No. ID RCB 2018-A00571-54). Enrollment started in June 2018. Data analysis will be performed during the second quarter of 2020 and results will be published in the last quarter of 2020.

Discussion

According to a European survey reported by Molassiotis et al [1], 35.9% of patients with cancer use CAMs, and after a diagnosis of cancer the use of CAMs increases by at least 30%. For varied reasons, some patients do not inform caregivers or health care professionals that they use CAMs [37,38]; however, certain CAMs could have potential interactions with conventional cancer treatments [39,40]. In parallel, oncologists lack adequate information about the safety and efficacy of CAMs to confidently inform their patients [41-43] and they have requested more rigorous evaluation [42,43]. Moreover, the World Health Organization's Traditional Medicine Strategy emphasizes the importance of thorough evaluation; the objectives of this strategic approach are to inform policy; determine safety, efficacy, and quality; increase access; and promote the rational use of traditional medicine [44].

This RCT (Clinicaltrials.gov identifier: NCT03508180), which began in June 2018, assesses the benefits of foot reflexology. The expected results are a decrease in CINV and anxiety, as well as an improvement in quality of life and self-esteem. This will also allow the investigation of any potential difference in benefit between patients with lung cancer and patients with digestive system cancer, and patients with different stages of cancer (metastatic and nonmetastatic). The results will be available in the last quarter of 2020.

This study does have limitations. First, the results may not be representative of all cancers; patient recruitment was only done at one cancer center. Even if conventional treatments are similar within the various private and public health care centers in France, a larger multicenter study would ensure that the results are generalizable.

In conclusion, the current management of patients with cancer involves treatment with conventional medicine while offering supportive oncological care. If the results of this study are significant, foot reflexology may be a promising complement to conventional antiemetic drugs.

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Authors' Contributions

All authors contributed to the conception or delivery of the trial. AMR is the trial manager and drafted the manuscript. AMS and VP provided senior trial management input and supported the drafting of the manuscript. AMS and AMR contributed to the methodology of the study. AMR and PJS support the daily delivery of the trial by collecting and managing the data. CR is responsible for intervention delivery (foot reflexology). FS provides statistical expertise and input and supported the sample size calculation and study design. AMR, MC, and PJS are the chief investigators and maintain overall oversight and responsibility for the trial delivery. MP provides psychosocial expertise and supported the intervention development and study design. All authors have agreed to be personally accountable for their own contributions. All authors read and approved the final manuscript.

Conflicts of Interest

Fabien Subtil is funded by the sponsor (Hospices Civils de Lyon) for this study. Charlotte Rentler is funded by the APICIL Foundation for this study. The other authors declare that they have no competing interests.

Multimedia Appendix 1
Ethical committee 04/03/2018.
[PDF File (Adobe PDF File), 278 KB - resprot_v9i7e17232_app1.pdf]

References

1. Molassiotis A, Fernández-Ortega P, Pud D, Ozden G, Scott JA, Panteli V, et al. Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncol 2005 Apr;16(4):655-663 [FREE Full text] [doi: 10.1093/annonc/mdi110] [Medline: 15699021]
2. Keene MR, Heslop IM, Sabesan SS, Glass BD. Complementary and alternative medicine use in cancer: A systematic review. Complement Ther Clin Pract 2019 May;35:33-47. [doi: 10.1016/j.ctcp.2019.01.004] [Medline: 31003679]
3. Tran V, Riveros C, Péan C, Czarnobroda A, Ravaud P. Patients' perspective on how to improve the care of people with chronic conditions in France: a citizen science study within the ComPaRe e-cohort. BMJ Qual Saf 2019 Nov;28(11):875-886 [FREE Full text] [doi: 10.1136/bmjqs-2018-008593] [Medline: 31015376]
4. Rossi E, Vita A, Baccetti S, Di Stefano M, Voller F, Zanobini A. Complementary and alternative medicine for cancer patients: results of the EPAAC survey on integrative oncology centres in Europe. Support Care Cancer 2015 Jun;23(6):1795-1806. [doi: 10.1007/s00520-014-2517-4] [Medline: 25471177]
5. Ernst E, Posadzki P, Lee MS. Reflexology: an update of a systematic review of randomised clinical trials. Maturitas 2011 Feb;68(2):116-120. [doi: 10.1016/j.maturitas.2010.10.011] [Medline: 21111551]
6. Hodgson H. Does reflexology impact on cancer patients' quality of life? Nurs Stand 2000;14(31):33-38. [doi: 10.7748/ns2000.04.14.31.33.c2817] [Medline: 11973949]
7. Stephenson NLN, Swanson M, Dalton J, Keefe FJ, Engelke M. Partner-delivered reflexology: effects on cancer pain and anxiety. Oncol Nurs Forum 2007 Jan;34(1):127-132. [doi: 10.1188/07.ONF.127-132] [Medline: 17562639]
8. Tsay SL, Chen HL, Chen SC, Lin HR, Lin KC. Effects of reflexotherapy on acute postoperative pain and anxiety among patients with digestive cancer. Cancer Nurs 2008;31(2):109-115. [doi: 10.1097/01.NCC.0000305694.74754.7b] [Medline: 18490886]
9. Yang J. [The effects of foot reflexology on nausea, vomiting and fatigue of breast cancer patients undergoing chemotherapy]. Taehan Kanho Hakhoe Chi 2005 Feb;35(1):177-185. [doi: 10.4040/jkan.2005.35.1.177] [Medline: 15778569]
10. Özdelikara A, Tan M. The Effect of Reflexology on Chemotherapy-induced Nausea, Vomiting, and Fatigue in Breast Cancer Patients. Asia Pac J Oncol Nurs 2017;4(3):241-249 [FREE Full text] [doi: 10.4103/apjon.apjon_15_17] [Medline: 28695171]
11. Jovenin N, Eche-Gass A, Chèze S, Launay-Vacher V, Mayeur D, Rey J, Groupe de travail du référentiel Association francophone pour les soins oncologiques de support (AFSOS) sur les nausées-vomissements induits par les traitements anti-cancéreux. [Antineoplastic drug induced nausea and vomiting: What is the clinical practice in 2018? An update of AFSOS clinical guidelines]. Bull Cancer 2019 May;106(5):497-509. [doi: 10.1016/j.bulcan.2019.02.002] [Medline: 30922554]
12. Hilarius DL, Kloeg PH, van der Wall E, van den Heuvel JJG, Gundy CM, Aaronson NK. Chemotherapy-induced nausea and vomiting in daily clinical practice: a community hospital-based study. Support Care Cancer 2012 Jan;20(1):107-117 [FREE Full text] [doi: 10.1007/s00520-010-1073-9] [Medline: 21258948]
13. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 2006 Sep 20;24(27):4472-4478. [doi: 10.1200/JCO.2006.05.6382] [Medline: 16983116]
14. Thibault V, Leguelinel-Blache G, Obled S, Loriot V, Phouttasang V, Wolf P, et al. [Chemotherapy for colorectal cancer: Pragmatic assessment of prescription changes and relative dose intensity]. Bull Cancer 2017 Sep;104(9):714-720. [doi: 10.1016/j.bulcan.2017.04.006] [Medline: 28578823]
15. Aspinall SL, Good CB, Zhao X, Cunningham FE, Heron BB, Geraci M, et al. Adjuvant chemotherapy for stage III colon cancer: relative dose intensity and survival among veterans. BMC Cancer 2015 Feb 18;15:62 [FREE Full text] [doi: 10.1186/s12885-015-1038-y] [Medline: 25884851]
16. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, participants of the MASCC/ESMO Consensus Conference Copenhagen 2015. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016 Sep;27(suppl 5):v119-v133. [doi: 10.1093/annonc/mdw270] [Medline: 27664248]
17. Razvi Y, Chan S, McFarlane T, McKenzie E, Zaki P, DeAngelis C, et al. ASCO, NCCN, MASCC/ESMO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients. Support Care Cancer 2019 Jan;27(1):87-95. [doi: 10.1007/s00520-018-4464-y] [Medline: 30284039]
18. Grunberg S, Clark-Snow RA, Koeller J. Chemotherapy-induced nausea and vomiting: contemporary approaches to optimal management. Proceedings from a symposium at the 2008 Multinational Association of Supportive Care in Cancer (MASCC) Annual Meeting. Support Care Cancer 2010 Mar;18 Suppl 1:S1-10. [doi: 10.1007/s00520-009-0807-z] [Medline: 20084406]
19. Vidall C, Sharma S, Amlani B. Patient-practitioner perception gap in treatment-induced nausea and vomiting. Br J Nurs 2016 Sep 08;25(16):S4-S11. [doi: 10.12968/bjon.2016.25.S4] [Medline: 27615540]
20. Morin S, Leurs I, Bousquet M, Scotté F. [Perceptual gap between oncologists/oncology nurses and patients in the management and impact of chemotherapy/radiotherapy-induced nausea and vomiting: French results of the GAP survey]. Bull Cancer 2016 May;103(5):469-477. [doi: 10.1016/j.bulcan.2016.02.011] [Medline: 27015797]

21. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 Sep 12 [FREE Full text] [doi: 10.3322/caac.21492] [Medline: 30207593]
22. Souquet PJ, Mennecier B, Duruisseaux M, Tissot C. Cancers Bronchiques à Petites Cellules. Référentiels Auvergne Rhône-Alpes en oncologie thoracique. 2019. URL: https://ressources-aura.fr/wp-content/uploads/2018/12/CPC_2019_VDEF.pdf [accessed 2020-06-11]
23. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017 Jul 01;28(suppl_4):iv1-iv21 [FREE Full text] [doi: 10.1093/annonc/mdx222] [Medline: 28881918]
24. Wu Y, Planchard D, Lu S, Sun H, Yamamoto N, Kim D, et al. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. Ann Oncol 2019 Feb 01;30(2):171-210 [FREE Full text] [doi: 10.1093/annonc/mdy554] [Medline: 30596843]
25. Société Nationale Française de Gastro-Entérologie. Thesaurus National de Cancerologie Digestive. URL: https://www.snfge.org/tncd [accessed 2020-06-11]
26. Baraniskin A, Van Laethem J, Wyrwicz L, Guller U, Wasan HS, Matysiak-Budnik T, et al. Clinical relevance of molecular diagnostics in gastrointestinal (GI) cancer: European Society of Digestive Oncology (ESDO) expert discussion and recommendations from the 17th European Society for Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer, Barcelona. Eur J Cancer 2017 Nov;86:305-317. [doi: 10.1016/j.ejca.2017.09.021] [Medline: 29065378]
27. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, CONSORT NPT Group. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Ann Intern Med 2017 Jul 04;167(1):40-47. [doi: 10.7326/M17-0046] [Medline: 28630973]
28. Lee SH, Kim JY, Yeo S, Kim SH, Lim S. Meta-Analysis of Massage Therapy on Cancer Pain. Integr Cancer Ther 2015 Jul;14(4):297-304. [doi: 10.1177/1534735415572885] [Medline: 25784669]
29. Byers D. Better Health With Foot Reflexology: The Original Ingham Method Including Hand Reflexology. New York City, NY: Ingham Pub; 1983.
30. Lee KA, Kieckhefer GM. Measuring human responses using visual analogue scales. West J Nurs Res 1989 Feb;11(1):128-132. [doi: 10.1177/019394598901100111] [Medline: 2728416]
31. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993 Mar 03;85(5):365-376. [doi: 10.1093/jnci/85.5.365] [Medline: 8433390]
32. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
33. Bruchon-Schweitzer M. Dimensionality of body perception and personality. Percept Mot Skills 1979 Jun;48(3 Pt 1):840-842. [doi: 10.2466/pms.1979.48.3.840] [Medline: 482036]
34. Vallieres EF, Vallerand RJ. Traduction et Validation Canadienne-Française de L'échelle de L'estime de Soi de Rosenberg. International Journal of Psychology 1990 Jan;25(2):305-316. [doi: 10.1080/00207599008247865]
35. Billhult A, Bergbom I, Stener-Victorin E. Massage relieves nausea in women with breast cancer who are undergoing chemotherapy. J Altern Complement Med 2007;13(1):53-57. [doi: 10.1089/acm.2006.6049] [Medline: 17309378]
36. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 5;158(3):200-207. [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
37. Buckner CA, Lafrenie RM, Dénommée JA, Caswell JM, Want DA. Complementary and alternative medicine use in patients before and after a cancer diagnosis. Curr Oncol 2018 Dec;25(4):e275-e281 [FREE Full text] [doi: 10.3747/co.25.3884] [Medline: 30111972]
38. Rossanaly Vasram R, Zysman M, Ribeiro Baptista B, Ederle C, Nguyen-Thi PL, Clement-Duchene C, et al. [Complementary and alternative medicine use by lung cancer patients]. Rev Pneumol Clin 2017 Sep;73(4):172-179. [doi: 10.1016/j.pneumo.2017.04.002] [Medline: 28756003]
39. Bozza C, Agostinetto E, Gerratana L, Puglisi F. [Complementary and alternative medicine in oncology]. Recenti Prog Med 2015 Dec;106(12):601-607. [doi: 10.1701/2094.22648] [Medline: 26780069]
40. Stub T, Quandt SA, Arcury TA, Sandberg JC, Kristoffersen AE, Musial F, et al. Perception of risk and communication among conventional and complementary health care providers involving cancer patients' use of complementary therapies: a literature review. BMC Complement Altern Med 2016 Sep 08;16:353 [FREE Full text] [doi: 10.1186/s12906-016-1326-3] [Medline: 27609097]
41. Bourgeault IL. Physicians' attitudes toward patients' use of alternative cancer therapies. CMAJ 1996 Dec 15;155(12):1679-1685 [FREE Full text] [Medline: 8976333]
42. McCall MC, Ward A, Heneghan C. Yoga in adult cancer: a pilot survey of attitudes and beliefs among oncologists. Curr Oncol 2015 Feb;22(1):13-19 [FREE Full text] [doi: 10.3747/co.22.2129] [Medline: 25684984]

43. Yang G, Lee R, Zhang H, Gu W, Yang P, Ling C. National survey of China's oncologists' knowledge, attitudes, and clinical practice patterns on complementary and alternative medicine. Oncotarget 2017 Feb 21;8(8):13440-13449 [FREE Full text] [doi: 10.18632/oncotarget.14560] [Medline: 28088780]
44. World Health Organization. WHO Traditional Medicine Strategy: 2014-2023. Geneva: World Health Organization; 2013:1-76.

Abbreviations

BIQ: Body Image Questionnaire
CAMs: complementary and alternative medicines
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
HADS: Hospital and Anxiety Depression Scale
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analogue scale

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Protocol

Guideline Recommendations for Oral Care After Acquired Brain Injury: Protocol for a Systematic Review

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Abstract

Background: Oral care is important to prevent buccal and systemic infections after an acquired brain injury (ABI). Despite recent advancements in the development of ABI clinical practice guidelines, recommendations for specific clinical processes and actions to attain adequate oral care often lack information.

Objective: This systematic review will (1) identify relevant ABI clinical practice guidelines and (2) appraise the oral care recommendations existing in the selected guidelines.

Methods: A search strategy was developed based on a recent systematic review of clinical practice guidelines for ABI. The protocol includes a search of MEDLINE, EMBASE, and DynaMed Plus databases, as well as organizational and best-practice websites and reference lists of accepted guidelines. Search terms will include medical subject headings and user-defined terms. Guideline appraisal will involve the Appraisal of Guidelines for Research and Evaluation II ratings, followed by a descriptive synopsis for oral care recommendations according to the National Health and Medical Research Council evidence levels.

Results: This project started in April 2019, when we developed the search strategy. The preliminary search of databases and websites yielded 863 and 787 citations, respectively, for a total of 1650 citations. Data collection will start in August 2020 and we expect to begin disseminating the results in May 2021.

Conclusions: Nursing staff may not have detailed recommendations on how to provide oral care for neurologically impaired patients. The findings of this review will explore the evidence for oral care in existing guidelines and improve outcomes for patients with ABI. We expect to provide adequate orientations to clinicians, inform policy and guidelines for best practices, and contribute to future directions for research in the ABI realm.

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KEYWORDS

practice guideline; evidence-based recommendations; brain injuries; oral health; oral hygiene; systematic review

Introduction

Poor oral health may lead to colonization by various microorganisms, causing buccal and respiratory infections [1-5]. Pneumonia, a life-threatening respiratory infection, is a common cause of death after vascular acquired brain injury (ABI) [6] and can be prevented through effective oral hygiene [7-9]. Good oral health is important to preserve one's overall health and well-being [10]. To maintain good oral health, evidence-based oral care practices are essential.

Managing oral care after an acquired brain injury is challenging. The damage that occurs to the brain due to traumatic or nontraumatic causes can lead to physical, behavioral, emotional, and cognitive impairments [11]. For instance, stroke—a nontraumatic, common cause of ABI—leaves one-third of survivors with long-term impairments [12], which may prevent them from managing their oral care. As a result, many are partially or totally reliant on caregivers to maintain their oral hygiene [13]. Nursing staff and family members are usually the ones who provide oral hygiene to care-dependent neurologically impaired survivors [14].

However, clinical barriers may restrict the delivery of high-quality oral care. Insufficient oral care knowledge and training are reported as some of the obstacles for nursing staff to perform adequate care [15,16]. Consequently, some professionals feel unprepared [17,18] and prioritize other care activities in the neurosciences context [19,20]. In addition, due to an overwhelming work routine in hospitals and long-term care facilities [21-23], nurses sometimes delegate oral care tasks to the least qualified members of the care team [18].

There is little direction from evidence-based literature regarding oral care provision [18,24,25], which results in great variability of practice across the care continuum [26]. Notwithstanding, there have been recent advancements in the development of clinical practice guidelines for ABI, yet they lack specific clinical instructions and processes for adequate and safe oral care provision [27-29]. A comprehensive understanding of existing oral care recommendations in ABI guidelines is badly needed.

The objectives of our proposed systematic review are to (1) update and extend the appraisal of ABI guidelines conducted in a recent systematic review [30], and (2) review and appraise existing oral care recommendations in included guidelines. Since guidelines should ideally be updated every 2 to 3 years [31] and the recent systematic review included ABI guidelines up to 2017 [30], we expect to identify new documents from our updated search. The reasons for extending the search are to help identify literature on oral health across the continuum of care (now including acute settings) and across ABI severity ranges (now including mild ABI). All oral care recommendations will be extracted from the included guidelines and rated according to their levels of evidence. This review will therefore provide a synthesis of best practices for health care professionals, which we anticipate will inform guidelines and practice standards. In addition, our results will provide insight and direction for future research.

Methods

Scope of the Protocol

This protocol is adapted from a recent systematic review of clinical practice guidelines for ABI [30]. Our review seeks to synthesize guidelines relevant to a broader range of settings and severities beyond this previous review. Therefore, our search strategy was expanded to include additional relevant information for the acute setting and for mild ABI. Protocol amendments, if necessary, will be incorporated in future publications, with details such as date, description, and rationale of each amendment.

Eligibility Criteria

Eligible guidelines will include acute and rehabilitation (inpatient and community rehabilitation) settings and pertain to mild to severe ABI. For the purpose of the current protocol, ABI refers to any damage to the brain that occurs after birth and is not related to a congenital or a degenerative disease [11]. Therefore, causes will include traumatic injury, seizures, tumors, infectious diseases, events in which the brain has been deprived of oxygen, and toxic exposure, such as substance abuse [11].

We will search guidelines published from January 1, 2006, onwards, following the methods of the recent systematic review [30]. Eligible guidelines will be guidelines published in English, particularly those produced under the support of (1) a health professional association or society, (2) a public or private organization, (3) a health care organization or plan, or (4) a government agency [32]. Further, included clinical practice guidelines must contain recommendations, strategies, or information to orient health care professional decisions. Eligible guidelines must have more than 1 component of post-ABI recommendations pertaining to adult patients [27]. In case of incomplete information, we will contact authors of particular guidelines for elaboration or clarification.

Information Sources and Search Strategy

The protocol combines multiple information sources, including databases as well as organizations and professional websites. Our search will involve MEDLINE, EMBASE, and DynaMed Plus databases. We have developed the search terms for MEDLINE, as seen in Textbox 1, using medical subject headings and user-defined terms. We will apply corresponding terms to the other 2 databases. Subsequently, we will search for organizational and best-practice websites for additional published guidelines.

Textbox 1. MEDLINE search strategy.

1. exp Craniocerebral Trauma/
2. exp Stroke/
3. exp Anoxia/
4. exp Hypoxia, Brain/
5. ((brain or head or intracran* or cerebr* or cerebellar or brainstem or vertebrobasilar) adj3 (injur* or infarc* or isch?em* or thrombo* or apoplexy or emboli* or h?emorrhag* or h?ematoma* or aneursym* or anoxi* or hypoxi*)).ab,ti.
6. (encephaliti* or mening*).ab,ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. rehabilitation.fs.
9. exp Rehabilitation/
10. exp Rehabilitation Centers/
11. rehabilitat*.ab,ti.
12. subacute care/
13. short term.ab,ti.
14. acute.ab,ti.
15. (hyperacute or hyper-acute).ab,ti.
16. ((short or urgent or emergency or acute) adj3 (term or care or stay)).ab,ti.
17. ((subacute or sub-acute) adj3 (care or stay)).ab,ti.
18. ((subacute or sub-acute or hyperacute or hyper-acute) adj3 (care or stay)).ab,ti.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp guideline/
21. Guideline$.ti.
22. (guideline or practice guideline).pt.
23. 20 or 21 or 22
24. 7 and 19 and 23

Protocol Guidelines

The design of this systematic review follows the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [33] and PRISMA-Protocols [34,35] guidelines.

Study Records

Data Management and Collection

Two independent reviewers (NG-J and M-FP) will use the web-based software Covidence (Veritas Health Innovation Ltd) [36] and the RevMan (Cochrane) software [37] to support and streamline the production of this systematic review. In addition, they will use Excel (Microsoft Corp) spreadsheets to collect, organize, and document excluded and included abstracts and articles.

Selection Process

A 2-stage process will be used to select included guidelines and extract recommendations. The first stage involves 2 independent reviewers (NG-J and M-FP) reviewing the abstracts of papers that refer to guidelines to identify the guidelines that may be eligible. In the second stage, the same reviewers will evaluate the guidelines in the full articles. These guidelines will be independently reviewed to select those that meet the inclusion criteria. The reviewers will use hierarchical coding criteria to evaluate abstracts and full articles, as shown in Textbox 2. For each stage, they will resolve discrepancies by consensus and, if needed, a third reviewer (HF) will review the documents and contribute to a final consensus decision.

Textbox 2. Hierarchical coding criteria for abstracts and full articles.

Abstracts

Hierarchical abstract coding (exclude if):

- The abstract is not in English
- The abstract clearly relates only an opinion, review, or commentary
- The abstract clearly does not involve a practice guideline or pinnacle practice information
- The abstract exclusively includes pediatric population
- The abstract does not relate to the acquired brain injury population
- The abstract clearly involves a duplicate publication to an accepted abstract

Otherwise, ACCEPT

Full Articles

Hierarchical full article coding (exclude if):

- The article is not in English
- The article clearly relates only an opinion, review, or commentary
- The article clearly does not involve a practice guideline or pinnacle practice information
- The guideline pertains to an adult sample (from a clinical context), even if there is mention of pediatric samples
- The guideline does not relate to the acquired brain injury population
- The guideline clearly involves overlap of information that is present in a more recent guideline

Otherwise, ACCEPT

Data Extraction, Appraisal of Guidelines and Recommendations, and Quality Assessment

Based on our objectives and research questions, data extraction will include the following information: (1) publication specifics (eg, country, organization, and date), (2) setting (eg, acute, rehabilitation, or community), (3) ABI population, (4) target health care professionals, and (5) categories of recommendations.

Two independent authors (LJ and NL) will first evaluate the selected clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an international tool used to assess the quality and reporting of practice guidelines [38]. These authors will rate domains of methodological quality for each guideline according to AGREE II. When there is disagreement for a given rating, a third reviewer (TH) will also appraise the guideline with AGREE II.

Subsequently, reviewers NG-J and M-FP will independently evaluate guidelines containing oral care recommendations by using the National Health and Medical Research Council (NHMRC) instrument [39]. This tool allows the assessment and comparison of the levels of evidence and includes grades for the recommendations from the included guidelines. A third reviewer (HF) will resolve disagreements by appraising the recommendations in the same manner. Once the reviewers reach consensus, the 2 initial reviewers (NG-J and M-FP) will provide a descriptive synopsis of the levels of evidence for the oral care recommendations [39]. The risk of bias assessment within and across guidelines and recommendations is included in the Rigour of Development domain of AGREE II and the Evidence Base domain of the NHMRC. Because both tools include risk of bias elements in the quality appraisal, overall quality ratings for the guidelines and recommendations will reflect such information.

Strategy for Data Synthesis

We will use the AGREE II grades to synthesize the assessed guidelines data, and we will unify the levels of evidence and grades for oral care recommendations according to NHMRC levels to allow comparison and permit description of the evidence. We will retain all identified guidelines and describe their quality and level of evidence. A systematic narrative synthesis will be provided using textual description and tables to summarize and explain the scope, context, and consistency of the clinical practice guideline recommendations. The oral care recommendations will be compared across guidelines to identify similarities and discrepancies. Our systematic review will synthesize data from the guidelines based on quality rankings and levels of evidence for recommendations.

Results

This project started in April 2019, when we developed the search strategy. The preliminary search of databases and websites yielded 863 and 787 citations, respectively, for a total of 1650. Data collection will start in August 2020 and we expect to begin disseminating the results in May 2021.

Discussion

Principal Findings

Even though good oral care prevents buccal and systemic infections after ABI [40], oral care recommendations are not

always present in ABI guidelines [27-29]. The provision of oral care can reduce respiratory pathogens in saliva from dental plaque accumulation [41] and residual food or liquid in the oral cavity [42]. Research demonstrates that good oral hygiene decreases pneumonia rates [7] and thereby helps reduce mortality [9], morbidity, and length of hospitalization [6]. In stroke survivors, for instance, pneumonia is responsible for up to 28% of deaths [43].

However, achieving the means to provide good oral care to neurologically impaired survivors is complex due to physical [44-47], behavioral [48-50], emotional [11], and cognitive impairments [51-53]. Therefore, nursing staff need specific and attainable evidence-based recommendations. Currently, these professionals unfortunately often lack adequate training [14-17], sufficient time [20-22], or satisfactory directions [12,23,24] to provide high-quality oral care, especially in the context of dysphagia [54].

ABI guidelines worldwide endorse oral care for recovery and rehabilitation [27,51-56]. The prevention of pneumonia, notably in patients with dysphagia, is the main reason for recommending oral hygiene [27,40,55,57-59]. However, better functional outcomes, patient comfort, prevention of dental complications, good nutrition, and even prevention of sepsis are also related to mouth care after ABI [28,40,55,57].

Expected Outcomes

The primary outcomes of this review will include methodological quality of guidelines and levels of evidence for oral care recommendations. We will apply priority rankings to the outcomes to inform health care professionals about highest-quality guidelines and recommendations for oral care, providing direction for future guidelines. The secondary outcome involves developing a best-practice protocol if the evidence is sufficient. There is a great need for a high-quality, process-oriented protocol for provision of oral care in neurologically impaired patients. Such a document could help orient health care professionals in their practice and provide direction for implementation research.

The results of this systematic review will be compared to the full guidelines, and differences between guidelines and recommendations will be explained. Findings may lead to the development of an oral care program that not only delivers safety within the hospital (prevention of complications) but helps clinicians identify opportunities for patients with ABI to independently manage their oral care, improving the long-term outcomes of this population.

Conclusion

This systematic review will examine the methodological quality of existing recommendations for oral care of patients with ABI. Identifying and appraising the recommendations will support knowledge translation for evidence-based practice across the continuum of care. In addition, it will provide direction for improving future guidelines, developing clinical protocols, and addressing research gaps.

Conflicts of Interest

None declared.

References

1. Dai R, Lam OL, Lo EC, Li LS, Wen Y, McGrath C. A systematic review and meta-analysis of clinical, microbiological, and behavioural aspects of oral health among patients with stroke. Journal of Dentistry 2015 Feb;43(2):171-180. [doi: 10.1016/j.jdent.2014.06.005]
2. Corsalini M, Rapone B, Grassi F, Venere DD. A study on oral rehabilitation in stroke patients: analysis of a group of 33 patients. Gerodontology 2010 Sep;27(3):178-182. [doi: 10.1111/j.1741-2358.2009.00322.x] [Medline: 20735492]
3. Yoshida M, Murakami T, Yoshimura O, Akagawa Y. The evaluation of oral health in stroke patients. Gerodontology 2012 Jun;29(2):e489-e493. [doi: 10.1111/j.1741-2358.2011.00505.x] [Medline: 21692834]
4. Anil S, Vellappally S, Hashem M, Preethanath RS, Patil S, Samaranayake LP. Xerostomia in geriatric patients: a burgeoning global concern. J Invest Clin Dent 2014 Sep 01;7(1):5-12. [doi: 10.1111/jicd.12120]
5. Prendergast V, Hinkle JL. Oral Care Assessment Tools and Interventions After Stroke. Stroke 2018 Apr;49(4):e153-e156. [doi: 10.1161/strokeaha.117.017045]
6. Hannawi Y, Hannawi B, Rao CPV, Suarez JI, Bershad EM. Stroke-Associated Pneumonia: Major Advances and Obstacles. Cerebrovasc Dis 2013;35(5):430-443. [doi: 10.1159/000350199]
7. Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ 2007 Mar 26;334(7599):889. [doi: 10.1136/bmj.39136.528160.be]
8. Fields LB. Oral Care Intervention to Reduce Incidence of Ventilator-Associated Pneumonia in the Neurologic Intensive Care Unit. Journal of Neuroscience Nursing 2008;40(5):291-298. [doi: 10.1097/01376517-200810000-00007]
9. Sjogren P, Nilsson E, Forsell M, Johansson O. A Systematic Review of the Preventive Effect of Oral Hygiene on Hospitals and Nursing Homes: Effect Estimates and Methodological Quality of Randomized Controlled Trials. Journal of American Geriatrics Society 2008;56(11):2124-2130. [doi: 10.1111/j.1532-5415.2008.01926.x]
10. Glick M, Williams DM, Kleinman DV, Vujicic M, Watt RG, Weyant RJ. A new definition for oral health developed by the FDI World Dental Federation opens the door to a universal definition of oral health. Journal of Public Health Dentistry 2017 Mar 09;77(1):3-5. [doi: 10.1111/jphd.12213]

11. Brain Injury Canada. 2019. Acquired Brain Injury (ABI) - The Basics URL: https://www.braininjurycanada.ca/acquired-brain-injury/ [accessed 2019-07-16]
12. World Health Organization. 2018. Global Burden of Stroke URL: http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf?ua=1 [accessed 2019-06-15]
13. Brady M, Furlanetto D, Hunter R, Lewis S, Milne V. Staff-led interventions for improving oral hygiene in patients following stroke. Cochrane Database Syst Rev 2006 Oct 18(4):CD003864. [doi: 10.1002/14651858.CD003864.pub2] [Medline: 17054189]
14. Cohn JL, Fulton JS. Nursing Staff Perspectives on Oral Care for Neuroscience Patients. Journal of Neuroscience Nursing 2006;38(1):22-30. [doi: 10.1097/01376517-200602000-00006]
15. Kwok C, McIntyre A, Janzen S, Mays R, Teasell R. Oral care post stroke: a scoping review. J Oral Rehabil 2014 Sep 22;42(1):65-74. [doi: 10.1111/joor.12229]
16. Yu P, Fu Q, Shi J, Tao W, Pang H, Chen X, et al. Effects of Different Levels of Caregiver Training on Oral Hygiene After Stroke. J Am Geriatr Soc 2016 Jun 20;64(6):1335-1340. [doi: 10.1111/jgs.14143]
17. Kothari M, Pillai RS, Kothari SF, Spin-Neto R, Kumar A, Nielsen JF. Oral health status in patients with acquired brain injury: a systematic review. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 2017 Feb;123(2):205-219.e7. [doi: 10.1016/j.oooo.2016.10.024]
18. Lyons M, Smith C, Boaden E, Brady MC, Brocklehurst P, Dickinson H, et al. Oral care after stroke: Where are we now? European Stroke Journal 2018 May 08;3(4):347-354. [doi: 10.1177/2396987318775206]
19. Wårdh I, Hallberg L, Berggren U, Andersson L, Sörensen S. Oral health care - a low priority in nursing. Scand J Caring Sci 2000;14(2):137-142. [Medline: 12035277]
20. Dickinson H. Maintaining oral health after stroke. Nursing Standard 2012 Aug 08;26(49):35-39. [doi: 10.7748/ns2012.08.26.49.35.c9233]
21. Yoon M, Steele C. Health care professionals' perspectives on oral care for long-term care residents: nursing staff, speech-language pathologists and dental hygienists. Gerodontology 2012 Jun;29(2):e525-e535. [doi: 10.1111/j.1741-2358.2011.00513.x] [Medline: 22462684]
22. Coker E, Ploeg J, Kaasalainen S. The Effect of Programs to Improve Oral Hygiene Outcomes for Older Residents in Long-Term Care: A Systematic Review. Research in Gerontological Nursing 2014 Jan 21;7(2):87-100. [doi: 10.3928/19404921-20140110-01]
23. Odgaard L, Kothari M. Survey of oral nursing care attitudes, knowledge and practices in a neurorehabilitation setting. Journal of Oral Rehabilitation 2019 Apr 21;46(8):730-737. [doi: 10.1111/joor.12799]
24. Talbot A, Brady M, Furlanetto DL, Frenkel H, Williams BO. Oral care and stroke units. Gerodontology 2005 Jun;22(2):77-83. [doi: 10.1111/j.1741-2358.2005.00049.x]
25. Horne M, McCracken G, Walls A, Tyrrell PJ, Smith CJ. Organisation, practice and experiences of mouth hygiene in stroke unit care: a mixed-methods study. J Clin Nurs 2014 Aug 19;24(5-6):728-738. [doi: 10.1111/jocn.12665]
26. Cutler C, Davis N. Improving oral care in patients receiving mechanical ventilation. Am J Crit Care 2005 Sep;14(5):389-394. [Medline: 16120890]
27. Hebert D, Lindsay MP, McIntyre A, Kirton A, Rumney PG, Bagg S, et al. Canadian stroke best practice recommendations: Stroke rehabilitation practice guidelines, update 2015. International Journal of Stroke 2016 Apr 14;11(4):459-484. [doi: 10.1177/1747493016643553]
28. Management of Stroke Rehabilitation Working Group. VA/DOD Clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev 2010;47(9):1-43 [FREE Full text] [Medline: 21213454]
29. Stroke Foundation of New Zealand, New Zealand Guidelines Group. Stroke Foundation of New Zealand. 2010. Clinical Guidelines for Stroke Management 2010 URL: https://www.stroke.org.nz/resources/NZClinicalGuidelinesStrokeManagement2010ActiveContents.pdf [accessed 2019-06-02]
30. Jolliffe L, Lannin NA, Cadilhac DA, Hoffmann T. Systematic review of clinical practice guidelines to identify recommendations for rehabilitation after stroke and other acquired brain injuries. BMJ Open 2018 Feb 28;8(2):e018791. [doi: 10.1136/bmjopen-2017-018791]
31. Vernooij RW, Sanabria AJ, Solà I, Alonso-Coello P, Martínez García L. Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. Implementation Sci 2014 Jan 2;9(1):3. [doi: 10.1186/1748-5908-9-3]
32. Physioterapy Evidence Database. 2019. Criteria for inclusion of evidence-based clinical practice guidelines URL: https://www.pedro.org.au/english/downloads/criteria/ [accessed 2019-07-20]
33. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology 2009 Oct;62(10):e1-e34. [doi: 10.1016/j.jclinepi.2009.06.006]
34. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 1;4(1). [doi: 10.1186/2046-4053-4-1]
35. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;349(jan02 1):g7647-g7647. [doi: 10.1136/bmj.g7647]

36. Covidence Systematic Review Software. Melbourne: Veritas Health Innovation; 2015. URL: https://www.covidence.org/home [accessed 2019-07-05]
37. Review Manager (RevMan). Copenhagen: The Cochrane Collaboration; 2014. URL: https://community.cochrane.org/help/tools-and-software/revman-5 [accessed 2019-07-05]
38. AGREE Next Steps Consortium. 2017. The AGREE II instrument URL: http://www.agreetrust.org [accessed 2018-05-20]
39. National Health and Medical Research Council. 2009. NHMRC levels of evidence and grades for recommendations for developers of guidelines URL: http://citeseerx.ist.psu.edu/viewdoc/download;jsessionid=AEFFDA62A5245D6D07F060B56789ED5A?doi=10.1.1.177.4984&rep=rep1&type=pdf [accessed 2019-05-20]
40. Intercollegiate Stroke Working Party. 2016. National clinical guideline for stroke Internet URL: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx [accessed 2019-02-20]
41. Yoon MN, Steele CM. The Oral Care Imperative. Topics in Geriatric Rehabilitation 2007;23(3):280-288. [doi: 10.1097/01.tgr.0000284771.24711.6a]
42. Cohen DL, Roffe C, Beavan J, Blackett B, Fairfield CA, Hamdy S, et al. Post-stroke dysphagia: A review and design considerations for future trials. International Journal of Stroke 2016 Mar 22;11(4):399-411. [doi: 10.1177/1747493016639057]
43. Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D. Post-stroke infection: A systematic review and meta-analysis. BMC Neurology 2011;11:110. [doi: 10.1186/1471-2377-11-110]
44. Pow E, Leung K, Wong M, Li L, McMillan A. A longitudinal study of the oral health condition of elderly stroke survivors on hospital discharge into the community. Int Dent J 2005 Oct;55(5):319-324. [doi: 10.1111/j.1875-595x.2005.tb00330.x] [Medline: 16245468]
45. Zhu HW, McMillan AS, McGrath C, Li LSW, Samaranayake LP. Oral carriage of yeasts and coliforms in stroke sufferers: a prospective longitudinal study. Oral Diseases 2008;14(1):60-66. [doi: 10.1111/j.1601-0825.2006.01347.x]
46. Ajwani S, Jayanti S, Burkolter N, Anderson C, Bhole S, Itaoui R, et al. Integrated oral health care for stroke patients - a scoping review. J Clin Nurs 2016 Dec 07;26(7-8):891-901. [doi: 10.1111/jocn.13520]
47. Hunter RV, Clarkson JE, Fraser HW, MacWalter RS. A preliminary investigation into tooth care, dental attendance and oral health related quality of life in adult stroke survivors in Tayside, Scotland. Gerodontology 2006 Sep;23(3):140-148. [doi: 10.1111/j.1741-2358.2006.00125.x]
48. Nijboer T, van de Port I, Schepers V, Post M, Visser-Meily A. Predicting Functional Outcome after Stroke: The Influence of Neglect on Basic Activities in Daily Living. Front. Hum. Neurosci 2013;7:182. [doi: 10.3389/fnhum.2013.00182]
49. Crosby GA, Munshi S, Karat AS, Worthington E, Lincoln NB. Fatigue after stroke: frequency and effect on daily life. Disability and Rehabilitation 2011 Oct 07;34(8):633-637. [doi: 10.3109/09638288.2011.613517]
50. Lerdal A, Gay CL. Acute-Phase Fatigue Predicts Limitations with Activities of Daily Living 18 Months after First-Ever Stroke. Journal of Stroke and Cerebrovascular Diseases 2017 Mar;26(3):523-531. [doi: 10.1016/j.jstrokecerebrovasdis.2016.11.130]
51. Naorungroj S, Slade G, Beck J, Mosley T, Gottesman R, Alonso A, et al. Cognitive Decline and Oral Health in Middle-aged Adults in the ARIC Study. J Dent Res 2013 Jul 19;92(9):795-801. [doi: 10.1177/0022034513497960]
52. Mlinac ME, Feng MC. Assessment of Activities of Daily Living, Self-Care, and Independence. Arch Clin Neuropsychol 2016 Jul 29;31(6):506-516. [doi: 10.1093/arclin/acw049]
53. Foltyn P. Ageing, dementia and oral health. Aust Dent J 2015 Mar 11;60(Suppl 1):86-94. [doi: 10.1111/adj.12287]
54. Stein J, Harvey R, Macko R, Winstein C, Zorowitz R. Stroke recovery & rehabilitation. New York: Demos Medical Publishing; 2009.
55. Stroke Foundation of Australia. 2017. Clinical Guidelines for Stroke Management 2017 URL: https://informme.org.au/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017 [accessed 2019-07-08]
56. Scottish Intercollegiate Guidelines Network. 2010. Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning, SIGN 118 URL: https://www.sign.ac.uk/sign-118-management-of-patients-with-stroke-rehabilitation,-prevention-and-management-of-complicati.html [accessed 2019-03-02]
57. Scottish Intercollegiate Guidelines Network. 2010. Management of patients with stroke: identification and management of dysphagia - a national guideline, SIGN 119 URL: https://www.sign.ac.uk/sign-119-management-of-patients-with-stroke-identification-and-management-of-dysphagia.html [accessed 2019-02-15]
58. National Clinical Guideline Centre. 2013. Stroke Rehabilitation: Long term rehabilitation after stroke - Clinical guideline 162 URL: https://www.ncbi.nlm.nih.gov/books/NBK247494/pdf/Bookshelf_NBK247494.pdf [accessed 2019-08-07]
59. Boulanger J, Lindsay M, Gubitz G, Smith E, Stotts G, Foley N, et al. Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. International Journal of Stroke 2018;13(9):949-984. [doi: 10.1177/1747493018786616]

Abbreviations

ABI: acquired brain injury

AGREE II: Appraisal of Guidelines for Research and Evaluation II
NHMRC: National Health and Medical Research Council
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

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Protocol

Developing a Taxonomy of Communication Techniques and Aids Used By Healthcare Providers During Patient Consultations: Protocol for a Systematic Review

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Abstract

Background: Currently, there is no available standardized taxonomy of defined communication techniques and aids used by healthcare providers during patient consultations. It is challenging to identify communication techniques that contribute to effective healthcare provider and patient consultations and to replicate communication interventions in research.

Objective: The aim of this paper is to describe a protocol for the development and pilot of a taxonomy of communication techniques and aids used by healthcare providers during patient consultations.

Methods: A systematic review will be completed to identify eligible studies. Extracted techniques and aids will be organized into a preliminary taxonomy by a multidisciplinary team. The preliminary taxonomy will be piloted by two groups: research assistants trained in taxonomy application and healthcare providers and healthcare professional students not trained in taxonomy use. The pilot will use custom developed video footage of health provider and patient interactions. Interrater validity and interview feedback will be used to inform a Delphi panel of multidisciplinary healthcare providers and patient experts when they convene to finalize the preliminary taxonomy.

Results: This study was funded in November 2017 by the Monash University Interdisciplinary Research Seed Funding Scheme. Data collection commenced in March 2018, and data analysis is in progress. We expect the results to be published in 2021.

Conclusions: This is the first known attempt to develop a defined and standardized taxonomy of communication techniques and aids used by healthcare providers in patient consultations. The findings will be used to inform future research by providing a detailed taxonomy of healthcare providers' communication techniques and standardized definitions.

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KEYWORDS

communication; patient-provider communication, patient education, taxonomy

Introduction

Successful communication of information is fundamental to effective therapeutic relationships between healthcare providers [HCP] and patients [1]. However, there is limited understanding of how to measure communication effectiveness during this interaction. An estimated 40%-80% of healthcare information communicated to patients during consultation has been reported to be forgotten immediately, and almost half of the information retained by patients is incorrect [2-4]. Additionally, the amount of information provided by HCPs may be insufficient as patients want more information than they are provided [5]. Further, HCPs have been shown to overestimate the volume of information they provide to patients [6].

HCPs use a range of interpersonal communication techniques, strategies, and aids to convey information to patients in medical consultations. In the healthcare context, the content of interpersonal communication generally falls into the categories of socio-emotional communication, diagnostic communication and problem solving, and the provision of counseling and education [7].

The content of HCP and patient consultations has been classified in The Decision Identification and Classification Taxonomy for Use in Medicine (DICTUM) by Ofstad et al [8]. The DICTUM taxonomy outlines ten categories of physician decisions, comprising of gathering additional information, evaluating test results, defining problem, drug-related, therapeutic, procedure-related, legal and insurance-related, contact related, advice and precaution, treatment goal, and deferment. Each category is defined, and specific actions are outlined. For example, in the category of 'Physician Statement,' decision items include 'Drug refund' and 'Sick leave' [8].

There is no widely accepted complete classification system or taxonomy of the communication techniques used by HCPs to transmit this content. Consequently, there is a common use of terms to describe communication techniques that are not defined clearly and may vary in definitional intent between studies. For example, "attentive listening" or "active listening" is insufficiently defined in the literature, and when a definition is provided, it is often inconsistent [9-16]. The lack of consistent definitions for communication techniques described in the literature creates limitations in the development of interventions, fidelity, study replication, and translation to teaching and practice.

There is a clear need to develop a taxonomy of communication techniques. A taxonomy is a conceptually or empirically derived grouping of objects of interest [17]. Standardized definitions for communication techniques will ensure educational consistency across disciplines and jurisdictions, enable researchers to describe interventions under investigation accurately, identify elements that contribute to overall communication effectiveness, and allow reliable translation of research into clinical practice. Such a taxonomy may be used similarly as the Behaviour Change Technique Taxonomy V1 [18], which has transformed the design and reporting of behavioral change interventions and been cited over 2000 times in the 6 years since its publication.

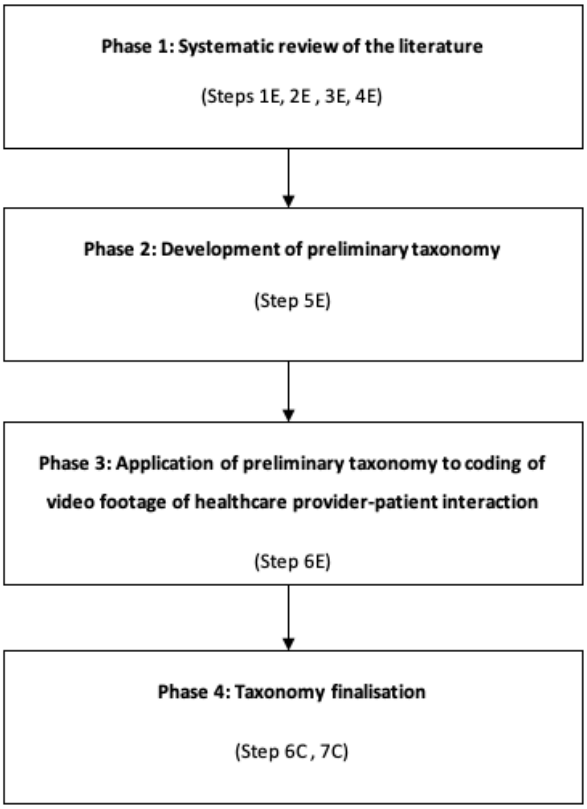
This protocol describes our method for developing a taxonomy of communication techniques and aids used by HCPs in healthcare consultations with patients.

Methods

We will adapt the taxonomy development method described by Nickerson et al [19], drawing on the 'empirical-to-conceptual' approach for phases one to three. The 'conceptual-to-empirical' approach will be used for phase four. Our four-phase process is outlined in Figure 1.

We refer to the equivalent step in Nickerson et al's seven-step model in parenthesis [19]. The letter 'E' indicates the use of the 'empirical-to-conceptual' method and 'C' indicates the 'conceptual-to-empirical' method.

Figure 1. Phases of taxonomy development.



Phase 1: Systematic Literature Review

In this phase, we identify the range of communication techniques and aids described in the health communication literature and synthesize a definition for each approach.

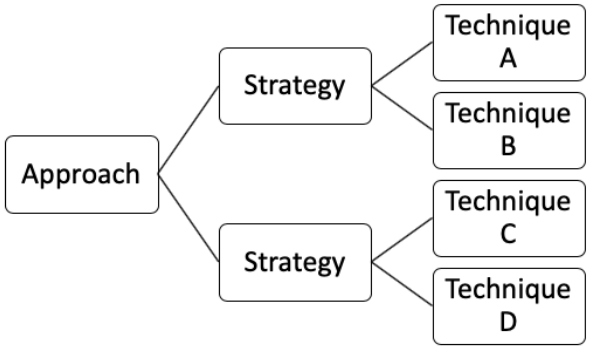
We developed a set of operational definitions to describe different concepts and measurement units in planning for this phase (Table 1). We consider this to be a necessary step given the diversity and inconsistency in terms used in this field.

Figure 2 illustrates the hierarchical relationship between our operational definitions of communication approaches, strategies, and techniques.

Table 1. Operational definitions.

Term	Operational definition
Patient	Any recipient of health or care services
Healthcare provider	A person who provides preventive, curative, promotional or rehabilitation health care
Caregiver	A family member or paid helper who regularly supports the patient
Communication technique	A single, basic unit of communication method that cannot be broken down into smaller units (eg, nodding)
Communication strategy	A specific combination of communication techniques drawn together to achieve a particular purpose (eg, attentive listening)
Communication approach	A specific combination of communication strategies or models of communication drawn together to achieve a particular purpose or that have a particular effect (eg, patient-centered care)
Communication aid	Visual and audio items that can be used independently of or in conjunction with verbal language to convey information (ie, photos, drawings, illustrations, models, props, graphs, videos or audio recordings)
Written communication aid	Information presented in written form (eg, report, letter, leaflet)

Figure 2. The hierarchical relationship between our operational definitions of communication approaches, strategies, and techniques.



Method for Systematic Review

This systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [20]. The protocol has been registered with PROSPERO (Reference/ID No CRD42018095262). We will record our searching and screening process using the bibliographic data management system Covidence.

Research Questions

Our systematic review will address the following research question:

What contemporary communication techniques and aids are used by healthcare providers in consultations with patients, as described in the literature?

Study Eligibility

The scope of this review will include studies describing interpersonal communication techniques and aids used by HCPs in healthcare consultations with patients.

We will limit the time-span for our search to papers published within the last 10 years to ensure that terms being used to describe techniques being examined are contemporary. Papers providing information only about specific communication approaches (eg, patient-centered care) will be excluded given the volume of hits identified in preliminary searching. Our focus will initially develop the lower levels of the communication technique hierarchy.

The search will exclude several interactions considered out-of-scope for project feasibility: those between HCPs, those involving interpreters or other third parties (eg, family members), and those involving patients who have additional communication needs:

- Third parties (eg, interpreters or family members)
- Doctor-doctor or nurse-nurse interactions
- Profound communication disabilities (eg, aphasia)
- Specialized technological aids (eg, iPads)
- Non-interpersonal health communication (ie, awareness campaigns or radio)
- Communication approaches (eg, patient-centered approach)
- Specialized fields (eg, palliative care)

We anticipate further work may be needed to expand our taxonomy to cover these interactions in the future. The following describes the methods that will be employed in each project phase.

Search Strategy for Identification of Relevant Studies

The following terms and Boolean operators will be used when undertaking our search:

"communication style" OR "communication technique*" OR "communication aid" OR "non-verbal communication" OR "verbal communication" OR "communication strateg*" OR "communication repair" OR "communication training" OR "conversation analysis" AND medical OR health OR consultation OR rehabilitation

Information Sources

The following databases of published literature will be searched: PubMed, Ovid Medline, CINAHL, Psychinfo, EMBASE, ERIC, Web of Science, and Linguistics and Language Behavior Abstracts.

Screening of Abstracts

Two research assistants will independently screen all titles and abstracts for eligibility against the inclusion criteria. Specifically, titles and abstracts will be included if they contain mention of communication techniques or aids used by HCPs in healthcare consultations with patients. Next, the research assistants will independently screen papers at the full-text level for the inclusion criteria. Exclusion reasons will be noted.

Data from eligible studies will be extracted independently by two reviewers using a predesigned data extraction form. The initial 10% of studies will be extracted by both reviewers to identify discrepancies in extraction methods. Where the extracted data differ between assessors, the discrepancy will be resolved by consensus. During the extraction stage, we will categorize the data into broad categories of verbal communication, non-verbal communication, and communication aids.

The data extraction document will contain the following:

- Type of technique/aid: verbal, non-verbal, aid
- Name of communication technique/aid
- Definition of communication technique/aid (if provided)
- Example of communication technique/aid (if provided)
- Additional references: References to an original paper describing a technique or its definition

Risk of Bias

We do not plan to undertake an assessment of the risk of bias for this review to the aim is related to the identification of communication techniques, strategies, and aids used by HCPs. We are not seeking to gather information about the effectiveness of outcomes, as this will not add to the development of the taxonomy.

Analysis

Descriptive content analysis will be employed, such that each description of a communication technique or aid identified will be coded. Reviewers will then create an operational definition for each code describing a communication technique that seeks to be mutually exclusive from other communication technique codes and describe the smallest "building block" likely to be feasibly useful for describing a communication technique. An exemplar definition of each code will also be added to the operational definition, where one is identified from the reviewed literature. Communication strategies will be coded, but will also be broken down into their subcomponent communication techniques. These techniques, if not already coded, will be added to the pool of communication technique codes.

Phase 2: Development of Preliminary Taxonomy

In this phase, the aim is to create a thematic structure for taxonomy elements. A multidisciplinary panel will participate in a workshop to develop the prototype taxonomy.

The objectives of the workshop will be to:

1. Collectively review and agree upon definitions of techniques and strategies identified.
2. Allocate specific techniques and aids into categories.
3. Discuss categorizations and reach consensus on taxonomy structure.
4. Identify concerns and discrepancies that will need to be addressed /resolved when finalizing the taxonomy structure in phase 4.

Participants

The investigative team will be comprised of professionals from medical, allied health, and applied linguistics fields and patient experts.

Procedure

Each communication technique and aid in the data set will be presented to the panel with a label (eg, open-ended question), a synthesized definition, and an example.

These will be presented as individual paper cards. Participants will manually arrange all items into broader categories of type (ie, non-verbal, verbal, aid) and function (eg, information gathering, rapport building, etc). The participants will discuss the allocation of each item and identify discrepancies. The taxonomy structure achieved through discussion and consensus will form the prototype taxonomy.

Analysis

An additional research team member independent of those present at the workshop will then review the thematic areas constructed, operational definitions, and exemplars provided for face validity. Suggestions for modification of the structure will be discussed iteratively within the investigative team.

Phase 3: Application of Preliminary Taxonomy to Coding of Video Footage of Provider-Patient Interaction

We will pilot a practical application of the prototype taxonomy to determine whether the taxonomy and the definitions created can be feasibly and reliably applied to code actual interactions between HCPs and patients. We aim to examine the inter-rater reliability of the application of the taxonomy and the definitions contained within it as a coding framework for recording the use of specific communication techniques used during interactions between HCPs and patients.

We are interested in two contexts:

Context A: The inter-rater reliability likely to be observed if two researchers trained in the application of the taxonomy were seeking to apply the entire taxonomy to recorded communications between HCPs and a patient.

Context B: The inter-rater reliability likely to be observed if HCPs untrained in the use of the taxonomy and students were to apply a restricted section of the taxonomy (while having access to code definitions and examples) to recorded communications between HCPs and patients. This context aims to determine if the operational definitions and examples provided intuitively make sense and give sufficient explanation to allow restricted application without additional training requirements.

Participants

Context A: Two members of the investigative team will review the video materials.

Context B: We will recruit 12 health professionals and 12 HCPs students. The health professionals and students untrained in the use of the taxonomy will be drawn from a range of disciplines. The student participants will be enrolled in a health professional degree program at Monash University.

Development of Video Footage

We will custom develop simulated interactions between HCPs and patients for video-recording. We will script these videos purposefully such that the maximum frequency across all of the videos of any one communication technique is no higher than 80% and no lower than 20%. Scripting will ensure variability in the frequency of presentation for each particular technique being assessed for coding reliability. Each video will be approximately one minute in length. A total of ten videos will be developed. The taxonomy will be segmented into sections (eg, expressing empathy), and each video segment will demonstrate a set of codes.

Procedure

Context A: The videos will be developed by two research team members (TH, VS). The script for each video with notations for when each communication strategy and technique will be employed will serve as the gold standard. Two investigators independent of these research team members who developed

the video will be provided with training on the application of the full taxonomy. They will apply coding of the video footage across the full taxonomy. Each code selected will be timestamped. The two investigators coding the video footage will be able to stop, pause, and rewind the video footage as often as needed until they are satisfied that they have completed the coding for the entirety of the taxonomy. The time taken to complete this task for each investigator for each video will be recorded. Investigators coding the video footage will then be interviewed to identify the sections of the taxonomy they found difficult to apply, and sections of the video footage to which they found it more or less difficult to apply the taxonomy.

Context B: The HCP and HCP student participants untrained in the use of the taxonomy will receive a section of codes from the provisional taxonomy. The provisional taxonomy will have been divided into sections based on the categories developed in Phase 2. Four sections of the provisional taxonomy will be purposively selected from the total number for use in this part of the investigation. Each selected section will be provided to a participant using a permuted block randomization, such that 3 students and 3 health professionals are provided with each of the 4 selected sections of the taxonomy. All participants will access the video footage and coding forms on an online portal. They will attempt to apply the code of the video footage across their allocated section of the provisional taxonomy.

Each code selected will be timestamped. Participants will be able to stop, pause, and rewind the video footage as many times as they prefer until they are satisfied that they have completed the coding for their section of the taxonomy. The time taken to complete this task for each participant for each video will be recorded. Participants coding the video footage will be asked open-ended questions to identify the codes they found difficult to apply, and sections of the video footage to which they found it more or less difficult to apply the taxonomy. All participants will complete a debrief task to provide written feedback regarding the feasibility of the taxonomy use and whether the video footage is self-evident.

Analysis

Context A: We will examine the agreement between raters by reporting the proportion of communication code items within the prototype taxonomy for which there was agreement within each video, and by reporting Kappa coefficients. For this, each item within the prototype taxonomy will be considered a dichotomous unit of measurement coded as being present within the video or not present. Pairwise comparisons will be made between each investigator rater, and between these raters and the gold standard rating inherent within the script used to develop each video.

Context B: A similar approach will be used for context B; however, a Kappa coefficient for multiple raters will be used. Kappa coefficients will be reported separately for each section of the prototype taxonomy and the health professional vs student HCP participant groups.

The verbal and written feedback obtained from both contexts' participants will be subject to content analysis with specific items being identified as problematic and reasons behind this being used in the subsequent Delphi panel phase (phase 4) of this research. Additionally, the mean (SD) duration of time taken to complete taxonomy coding for both contexts will be calculated.

Phase 4: Taxonomy Finalization Workshop

The prototype taxonomy will be revised and finalized by a face-to-face multidisciplinary Delphi panel using the results of the pilot application of the prototype taxonomy to the coding of video scenarios (phase 3). The panel will be comprised of healthcare professionals who are independent of the investigative team, come from a range of disciplines, and patient experts. The panel will be asked to consider the evidence from phases 1, 2, and 3 and consider whether changes to the prototype taxonomy are needed. Each suggested change will then be voted on anonymously by the Delphi panel with reasons for supporting or not supporting the change being written down and read out after the vote by a panel facilitator. Upon hearing these reasons and the results of the first round of voting being read out, participants will be provided with another opportunity to vote on the proposed change and provide reasons why a change was or was not supported. This process will repeat until a consensus is achieved (ie, a change is unanimously endorsed or not endorsed), or a change in the voting is not achieved in two consecutive rounds. In this circumstance, a majority decision will be used to shape the taxonomy; however, a note will be made that the particular change was not universally supported. This process will be repeated for each suggested change until the definitive model of the taxonomy is reached.

Results

This study was funded in November 2017 by the Monash University Interdisciplinary Research Seed Funding Scheme. Data collection commenced in March 2018, and data analysis is in progress. We expect to publish the results in 2021.

Discussion

Our systematic review of the literature and developed taxonomy will provide a detailed and defined classification of verbal and non-verbal communication techniques and aids available for HCPs to use with patients in healthcare consultations. We anticipate that this review will be of interest to HCPs, researchers, quality improvement departments at hospitals, clinics, and universities, and policymakers. The findings will be used to inform future research by providing a detailed taxonomy of HCPs' communication techniques and standardized definitions.

The importance of this work will manifest across a range of areas. First, it will provide a framework and tools for researchers to measure and understand the impact of different communication techniques on patient outcomes. Second, it will provide a framework on which HCP educators may structure their training programs. Third, it will help promote health literacy in patients, which is held as an area where improved communication by HCPs could promote improved health outcomes. Health literacy is defined as the "degree to which individuals have the capacity to obtain, process, and understand

basic health information and services needed to make appropriate health decisions" [21]. It has previously been reported by the World Health Organization that low health literacy "significantly drain[s] human and financial resources in the health system" [22]. Future research that directly builds on this taxonomy could investigate the frequency of use of different communication techniques in a range of contexts and for the taxonomy to be adapted to different international settings. Subsequently, additional blue-sky research could identify communication techniques that maximize patient understanding in a range of contexts such as prescribing and health service availability, which may ultimately improve patient health outcomes and minimize adverse outcomes from patient care.

Three study limitations have been identified. First, our search to identify communication techniques and aids is focussed on the published literature. There may be communication techniques being promoted by HCPs and those who train them that have not been described in the published literature, and yet may still be relevant. Second, the team driving this research is based entirely within the Australian context. It is possible that understanding and application of communication techniques applied in this context may be different from that in other countries. Similarly, differences in cultural norms and patterns of behavior may influence how the investigative team interprets the data arising from literature from other countries and cultures. Also, the Delphi panel recruited for the refinement and finalization stages of the taxonomy will be derived from the Australian context. Future work will be needed to investigate the adaptation of the final model of the taxonomy to other countries and contexts. Finally, the scope of this work excludes communication approaches and techniques used with patients who have profound communication impairments. Again, further work is needed to annex communication approaches, strategies, and techniques to our final model of the taxonomy to support its broader application and benefit.

Conclusion

To our knowledge, this is the first attempt to create a detailed taxonomy of healthcare consultation communication techniques and aids. The development of this taxonomy can support communication trial design in the future. The availability of this tool will aid researchers to describe better communication techniques and aids used in trials and cohort studies that are founded on communication.

Conflicts of Interest

None declared.

References

1. Hill S. The Knowledgeable Patient: Communication and Participation in Health. In: Melbourne: Wiley. ISBN. Australia: BMJ Books; 2011:9781444337174.
2. Brega A, Barnard J, Mabachi N, Weiss B, DeWalt D, Brach C, West, DR. AHRQ Health Literacy Universal Precautions Toolkit, Second Edition. Agency for Healthcare Research and Quality. URL: https://www.ahrq.gov/health-literacy/quality-resources/tools/literacy-toolkit/healthlittoolkit2.html [accessed 2019-06-13]
3. McGuire LC. Remembering what the doctor said: organization and adults' memory for medical information. Exp Aging Res 1996 Sep 27;22(4):403-428. [doi: 10.1080/03610739608254020] [Medline: 8968711]
4. Yuncken J, Williams CM, Stolwyk R, Haines TP. People with diabetes foot complications do not recall their foot education: a cohort study. J Foot Ankle Res 2018 Apr 6;11(1):12 [FREE Full text] [doi: 10.1186/s13047-018-0255-4] [Medline: 29636823]
5. Kinnersley P, Edwards A, Hood K, Ryan R, Prout H, Cadbury N, et al. Interventions before consultations to help patients address their information needs by encouraging question asking: systematic review. BMJ 2008 Jul 16;337:a485 [FREE Full text] [doi: 10.1136/bmj.a485] [Medline: 18632672]
6. Kessels RPC. Patients' Memory for Medical Information. J R Soc Med 2017 Nov 23;96(5):219-222. [doi: 10.1177/014107680309600504]
7. de Negri B, DiPrete BL, Hernández OJ, Roter D. Improving interpersonal communication between health care providers and clients. Quality Assurance Methodology Refinement Series. Bethesda: USAID 2009 [FREE Full text]
8. Ofstad EH, Frich JC, Schei E, Frankel RM, Gulbrandsen P. What is a medical decision? A taxonomy based on physician statements in hospital encounters: a qualitative study. BMJ Open 2016 Feb 11;6(2):e010098 [FREE Full text] [doi: 10.1136/bmjopen-2015-010098] [Medline: 26868946]
9. Delacruz N, Reed S, Splinter A, Brown A, Flowers S, Verbeck N, et al. Take the HEAT: A pilot study on improving communication with angry families. Patient Educ Couns 2017 Jun;100(6):1235-1239. [doi: 10.1016/j.pec.2016.12.012] [Medline: 28089310]
10. Hamelin N, Nikolis A, Armano J, Harris P, Brutus J. Evaluation of factors influencing confidence and trust in the patient-physician relationship: a survey of patient in a hand clinic. Chir Main 2012 Apr;31(2):83-90. [doi: 10.1016/j.main.2012.01.005] [Medline: 22365321]
11. Paternotte E, van Dulmen S, Bank L, Seeleman C, Scherpbier A, Scheele F. Intercultural communication through the eyes of patients: experiences and preferences. Int J Med Educ 2017 May 16;8:170-175 [FREE Full text] [doi: 10.5116/ijme.591b.19f9] [Medline: 28535143]

12. Giroldi E, Veldhuijzen W, Dijkman A, Rozestraten M, Muris J, van der Vleuten C, et al. How to gather information from talkative patients in a respectful and efficient manner: a qualitative study of GPs' communication strategies. Fam Pract 2016 Feb 23;33(1):100-106. [doi: 10.1093/fampra/cmv094] [Medline: 26601673]
13. Denham CR, Dingman J, Foley ME, Ford D, Martins B, O'Regan P, et al. Are You Listening…Are You Really Listening? Journal of Patient Safety 2008;4(3):148-161. [doi: 10.1097/pts.0b013e318184db52]
14. Slatore CG, Cecere LM, Reinke LF, Ganzini L, Udris EM, Moss BR, et al. Patient-clinician communication: associations with important health outcomes among veterans with COPD. Chest 2010 Sep;138(3):628-634 [FREE Full text] [doi: 10.1378/chest.09-2328] [Medline: 20299633]
15. Fassaert T, van Dulmen S, Schellevis F, van der Jagt L, Bensing J. Raising positive expectations helps patients with minor ailments: a cross-sectional study. BMC Fam Pract 2008 Jun 30;9(1):38 [FREE Full text] [doi: 10.1186/1471-2296-9-38] [Medline: 18590520]
16. Dalonges DA, Fried JL. Creating Immediacy Using Verbal and Nonverbal Methods. J Dent Hyg 2016 Aug;90(4):221-225. [Medline: 27551142]
17. Nickerson RC, Varshney U, Muntermann J. A method for taxonomy development and its application in information systems. European Journal of Information Systems 2017 Dec 19;22(3):336-359. [doi: 10.1057/ejis.2012.26]
18. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug 20;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
19. Nickerson RC, Varshney U, Muntermann J. A method for taxonomy development and its application in information systems. European Journal of Information Systems 2017 Dec 19;22(3):336-359. [doi: 10.1057/ejis.2012.26]
20. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;350(jan02 1):g7647-g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
21. Institute of Medicine. Health literacy: A prescription to end confusion. Washington, DC: National Academies Press; 2004.
22. World HO. Health Literacy: the Solid Facts. Copenhagen: WHO 2013 [FREE Full text]

Abbreviations

HCP: healthcare providers

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Protocol

Prevalence of Mental Disorders, Cognitive Impairment, and Dementia Among Older Adults in Egypt: Protocol for a Systematic Review

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Abstract

Background: In Egypt, the population of older adults is rapidly growing. The last census in 2017 indicated that older adults numbered 94.8 million, which is a 2.56% increase from the 2006 census. There is growing evidence that the older population is at greater risk for some forms of mental disorders such as depression, dementia, and many more.

Objective: This study aims to review the current evidence regarding the prevalence of mental disorders among older adults in Egypt. This will be achieved by estimating the current prevalence of mental disorders and identifying any sociodemographic correlations with mental disorders.

Methods: An electronic search of 5 key databases (MEDLINE, PsycINFO, EMBASE, AMED, and PubMed) from their date of inception was conducted. In addition, scans of reference lists and searches of key journals, citations, and relevant internet resources were conducted. Studies were included if they were published in English, point prevalence studies, conducted with older Egyptians aged ≥60 years, and conducted using a validated diagnostic tool to ascertain mental disorders. Studies that did not meet any of these criteria were excluded.

Results: This systematic review started in November 2018. The literature search of the 5 databases revealed 343 papers. After screening titles and abstracts, scanning citations and reference lists, and searching internet sources, a total of 38 full-text articles were accessed, of which 16 studies met the eligibility criteria and were included. We are currently in the process of data extraction and synthesis.

Conclusions: This research will help bring the scale of mental disorders among older adults in Egypt to the forefront. This may help ensure evidence-based initiatives are established and that priority is given to resource allocation for geriatric mental health in Egypt.

Trial Registration: PROSPERO International Prospective Register of Systematic Review CRD42018114831; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=114831

International Registered Report Identifier (IRRID): DERR1-10.2196/14637

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KEYWORDS

mental disorders; cognitive impairment; dementia; older adults; Egypt; prevalence; socio-demographic factors; systematic review; protocol

Introduction

Egypt, like most developing countries, is facing a rising trend in mental disorders, with neuro-psychiatric disorders alone accounting for 19.8% of the burden of disability [1]. Egypt is central to the Arab world, an advantage that is supported by its geographical location, which spans from the northeastern part of Africa to the southwest region of Asia [2,3]. For instance, approximately 70% of the mental health professionals in Arab countries are Egyptians [4,5].

The 2006 census showed that the elderly population (≥60 years old) represents 7.2% of the total Egyptian population [6]. At the last census in 2017, adults ≥60 years old numbered 94.8 million, which is a 2.56% increase from the 2006 census [7]. The definition of old age varies in different countries and across various research studies, where it ranges from 55 years to 75 years. Old age in Egypt is believed to begin at 60 years, which is the age of retirement [8]. However, there have been proposals to change the retirement age from 60 years to 65 years, which might take effect by 2027 [9].

The older adult population in Egypt is mostly affected by noncommunicable diseases such as mental disorders [10]. Interestingly, mental disorders have always been recognized in Egypt; in fact, over 5 millennia ago, mental disorders were viewed as a physical ailment of the heart or uterus [11]. Moreover, one of the first three mental hospitals in the world was built in Cairo, Egypt [12]. There are 15 state psychiatric hospitals in Egypt, and nearly all medical schools in Egypt have a psychiatric department offering diploma, masters, and/or PhD degrees [2,12]. Currently, there are training programs for psychiatrists, psychiatric nurses, psychologists, and social workers; however, it is estimated that the psychiatrist to population ratio is 1:70,000 [2,13].

There are 3 main types of service providers in Egypt: public, private, and nongovernmental organizations [13]. Mental health services provided by the public sector are free; however, individuals who can afford private care would rather opt for this option due to the stigma associated with mental disorders and high quality of care offered [12]. Nongovernmental organizations are mostly outpatient services that usually have a sociopolitical or religious affiliation that influences the manner in which care and support are provided.

Mental disorders in Egypt have a strong cultural and religious influence. This is perhaps attributed to the strong family support, which is feasible among extended families. Thus, values, norms and beliefs about mental disorders are passed down from generation to generation. Several speculations have been held about the causes of mental disorders [3,12]. Some opinions about the causes include a personality weakness, laziness, exposure to a sudden fright, possession of evil spirits, use of magic, trauma to the head, heredity, emotional trauma, being looked at by evil eyes, and many more [12,14].

Mental disorder in Egypt is stigmatizing, and families are afraid of societal attitudes and discrimination, which often results in delays in seeking treatment [12,15]. In addition, views about mental disorders being genetic further heightens the discrimination and makes families hide this illness from others, thereby preventing shame, ridicule, and insult to the individual and the family as a whole [12].

A national survey of adults aged 18-64 years in 5 regions estimated the prevalence of mental disorders to be 16.93%, of which mood disorders, anxiety disorders, and multiple disorders were the most commonly identified [16]. Furthermore, a systematic review that focused on the prevalence of dementia in Egypt among individuals aged ≥50 years estimated a 2.01%-5.07% prevalence [17].

Currently, there are no registered studies that have investigated all mental disorders among the older adult population aged ≥60 years using the International Classification of Disease code 10, chapter 5 (F code) for mental and behavioral disorders in a single study. Some studies have estimated the prevalence of some mental disorders such as anxiety, depression, mixed anxiety and depressive disorders, mild cognitive impairment, or dementia [18-22].

Meanwhile, the profile of psychiatric presentation in Egypt reveals that individuals also present with obsessive-compulsive disorder, personality disorder, psychosis, schizophrenia, catatonia, substance misuse, suicide, and parasuicide [2,3]. However, little is being reported about the prevalence of these mental disorders among older adults. It is presumed that the cultural beliefs about an association between these mental disorders and moral failure, compounded by religious beliefs, further account for the significant under-presentation in mental health clinics [3,12]. Thus, there is little or no report of these illnesses among emerging studies.

Generally, it is reported that sociodemographic factors such as gender, educational status, employment status, and living arrangement strongly correlate with mental disorders in Egypt. It has been reported that being female, being unemployed, having little or no education, and living alone are associated with mental disorders among older adults (≥60 years) [18-22].

The needs of the older adult population in Egypt have long been ignored [2]. Moreover, Loza [13] pointed out that mental health received late recognition within health sector reform. Thus, the necessary development and financing were not initially a priority. Therefore, it can be inferred that mental disorders among older adults in Egypt have received very little attention. This systematic review will help identify all forms of mental disorders reported among older adults aged ≥60 years. Furthermore, it will estimate the current prevalence of these mental disorders and then identify the sociodemographic factors that correlate with mental health problems.

Methods

Reporting and Quality Assessment

This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist and is documented on the PROSPERO database (PROSPERO registration number: CRD42018114831).

PRISMA has been chosen to facilitate transparent reporting of this systematic review. We acknowledge that PRISMA has

some shortcomings, such as not being able to gauge the quality of included papers [23]. This is the reason we are conducting a quality assessment of the included papers. We are using the Newcastle-Ottawa scale adapted for cross-sectional studies to assess the quality of the included studies. In addition, we are clearly reporting this protocol to allow others to judge and easily replicate this review [23].

Data Sources and Searches

A search was conducted in 5 databases: MEDLINE, PsycINFO, EMBASE, AMED, and PubMed. Databases were searched from their date of inception in order to compare the trend of mental disorders over the years. Both medical subject headings and free-text words (searches of titles and abstract) were carried out in the electronic databases. Searches included terms relating to or describing mental health disorders, cognitive impairment, dementia, prevalence, older adult, and Egypt. Boolean operators, truncation, and combinations of AND, OR, and ADJ were used when necessary. A sample of combined search terms in an electronic database is shown in Textbox 1.

In addition, we searched the reference lists of all studies that met the inclusion criteria and relevant systematic reviews for any potential eligible studies. We also searched key journals, citations, and relevant internet resources to ensure this review contains all possible studies and to ascertain that studies not indexed in the 5 chosen databases are included in this review. We contacted authors if additional information was required.

Textbox 1. Sample of combined search terms used in an electronic database.

EMBASE

(((“MENTAL DISEASE”/ OR (mental ADJ1 (disorder* OR disease* OR illness*)).ti,ab OR (Psychiatr* ADJ (disorder* OR disease* OR illness*)).ti,ab OR DEMENTIA/ OR “COGNITIVE DEFECT”/ OR (“cognitive impairment*” OR “cognitive defect*” OR “cognitive dysfunction”).ti,ab OR (dementia).ti,ab OR PSYCHIATRY/) AND ((elder* OR “old* adult*” OR geriatric* OR “old* person” OR “old* people” OR “old* age” OR “age* people” OR “aging people” OR “age* person” OR “aging person” OR “old* patient*” OR psychogeriatric* OR “aging patient*” OR “age* patient*”).ti,ab OR AGED/ OR GERIATRICS/)) AND (EPIDEMIOLOGY/ OR “CROSS-SECTIONAL STUDY”/ OR “HEALTH SURVEY”/ OR (survey* OR epidemiolog* OR cross-sectional OR prevalence*).ti,ab)) AND ((Egypt*).ti,ab OR EGYPT/)

Inclusion and Exclusion Criteria

Studies conducted in any setting such as hospitals (both inpatients and outpatients), residential homes, household surveys, and others within Egypt were included in this review. Studies were included if they were published in English, point prevalence studies, conducted with older Egyptians aged ≥60 years, and conducted with a validated diagnostic tool to ascertain mental disorders. Validation of diagnostic tools and prevalence rate is based on self-reported declaration of the original authors of the included papers. Studies that did not meet any of the criteria were excluded. It should be noted that point prevalence is used as recommended by Streiner et al [24].

Data Extraction

Two review authors (OO and GT) independently screened the studies retrieved from all sources to identify those that potentially met the inclusion criteria. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility. If there was any disagreement between the two authors, this was resolved through discussion and, if necessary, with a third member (NS) for mediation. A piloted data extraction sheet was used to extract data from the included studies. Extracted information included author’s name, year of publication, study setting(s), city, duration of the study, demographics, number of participants, method of recruitment, diagnostic test used, mental disorders studied, prevalence of mental disorders, and existence of comorbidities, current medication, and smoking status.

Quality Assessment

The Herzog modification of the Newcastle-Ottawa scale adapted for cross-sectional studies was used to assess the quality of the included studies. The scale assesses 3 main domains: selection, comparability, and outcomes. Each study could attain a maximum of 10 points. Studies with 0-4 points were classed as unsatisfactory, 5-6 points as satisfactory, 7-8 points as good, and 9-10 points as very good. Two review authors (OO and GT) assessed the risk of bias, and any disagreements were resolved by discussion and, if necessary, with a third member (NS) for mediation.

Data Analysis and Synthesis

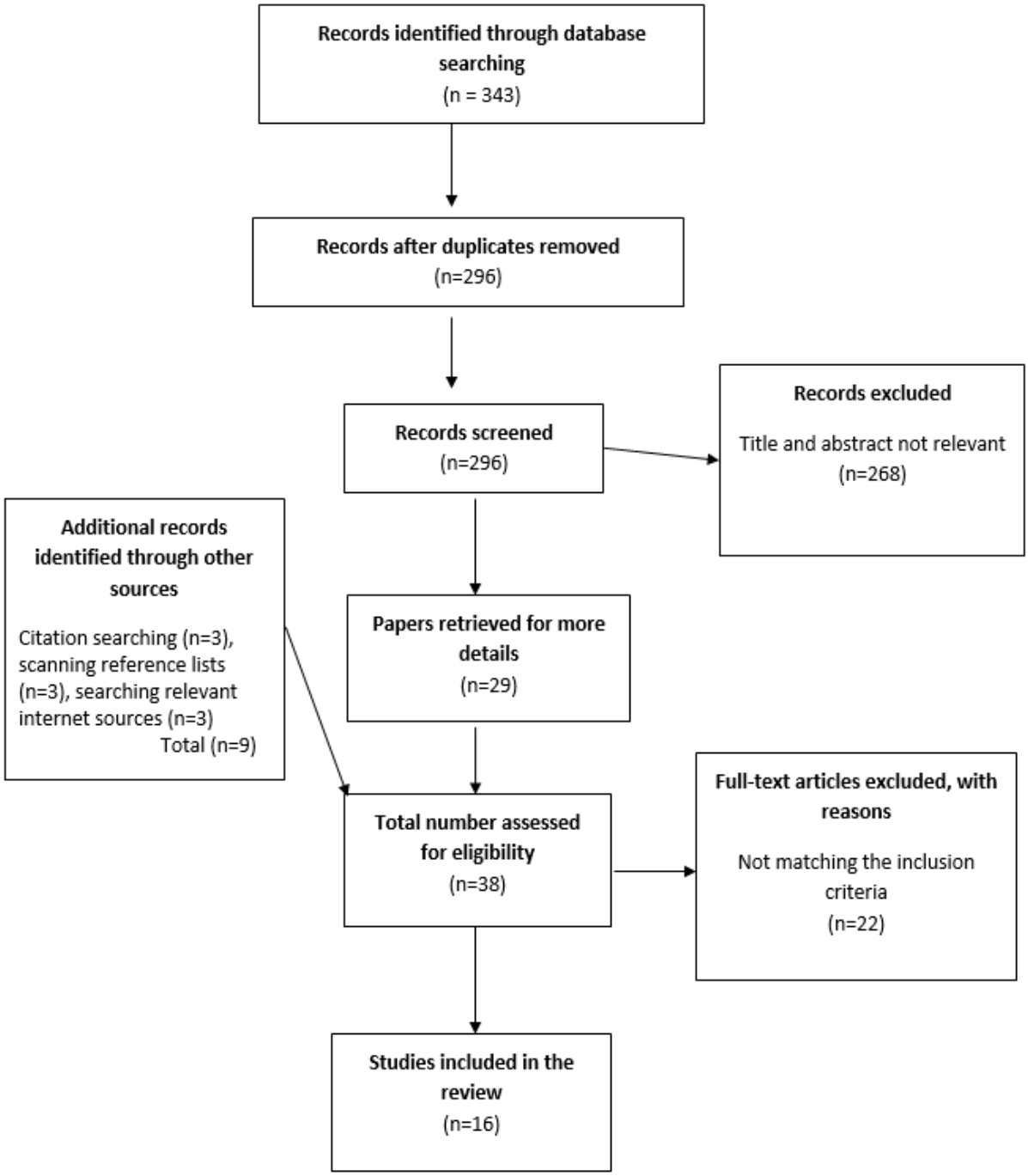
A descriptive tabular summary of included studies was documented, categorizing details based on study setting(s), city, duration of the study, demographics, number of participants, method of recruitment, diagnostic test used, mental disorders studied, and prevalence of mental disorders. The quality or risk of bias of the included studies was also evaluated.

Preliminary synthesis of the sample and population as well as demographic information (such as age, gender, education, employment, residency, marital status, and living arrangement) was carried out. Furthermore, the correlation between mental disorders and sociodemographic details within and between studies will be explored. In addition, the robustness of the synthesis will be assessed based on the methodological quality of the studies. A narrative synthesis of the findings of included studies will be provided. This is because we anticipate that the included studies will be methodologically diverse.

Results

This systematic review started on November 1, 2018. The search has been completed. The literature search of the 5 databases revealed 343 papers. After screening titles and abstracts, scanning the citations and reference lists, and searching internet sources, a total of 38 full-text articles were accessed, of which 16 studies met the eligibility criteria and were included. Figure 1 provides the details of the search outcome.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow illustrating the search outcomes.



All identified studies carried out point prevalence studies ranging from a period of 3 months to 2 years with adults aged ≥60 years. We are currently in the process of data extraction and synthesis. The findings of this review may help bring the scale of mental disorders among older adults in Egypt to the forefront, which may result in evidence-based initiatives being established as well as prioritized resource allocation for geriatric mental health in Egypt. The results of this systematic review will be published in a peer-reviewed journal.

Discussion

This systematic review identified 16 studies matching the eligibility criteria. This study is conducted as the initial step of a longitudinal study on mental disorders among the older adult population in Egypt. The paucity of existing studies highlights the need for further research.

This review will help identify mental disorders among older adults. It will also describe any associations between mental disorders and sociodemographic status. The findings may help bring the impact of mental health problems among older adults in Egypt to the forefront for policy makers, service providers, and researchers.

There might be a need to develop a uniformed approach to the demographic and social determinants of mental disorders in older adults in Egypt and similar countries. This research could

also serve as a guide when developing interventions and prioritizing resource allocation for mental health in Egypt.

Regarding potential limitations, it is anticipated that some potentially relevant studies may not be included due to selecting studies only published in English.

Authors' Contributions

OO was responsible for writing the protocol. OO, GT, and NS were involved in the conceptualization of the study. OO and GT designed the search strategy. OO was responsible for the literature search. OO, GT, and NS will be responsible for study selection, data extraction, and quality assurance. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Hermez J, Khattabi H, Sabry A, Riedner G, Hajjeh R. Achieving the Sustainable Development Goal 3: challenges in HIV testing in the Eastern Mediterranean Region (Editorial). East Mediterr Health J 2017 Dec 14;23(10):647-648 [FREE Full text] [doi: 10.26719/2017.23.10.647] [Medline: 30378672]
2. Okasha A. Focus on psychiatry in Egypt. Br J Psychiatry 2018 Jan 02;185(3):266-272. [doi: 10.1192/bjp.185.3.266]
3. Gadelkarim W, El-Maraghy M, Sule A. Impact of religion and culture on mental disorders among Egyptians. Int. psychiatry 2018 Jan 02;10(2):48-50. [doi: 10.1192/s1749367600003787]
4. Ahmed R, Gielen U. Psychology in the Arab Countries. Cairo: Menoufia University Press 1998.
5. King D. Egyptian Psychology: Subjective ImpressionsSurvey Results. Paper presented at the American Psychological Association Convention, Anaheim, CA 1983.
6. Egypt in figures 2015. Central Agency for Public Mobilization and Statistics CAPMAS. 2015. URL: http://www.msrintranet.capmas.gov.eg/pdf/EgyptinFigures2015/EgyptinFigures/Tables/PDF/1-%20/pop.pdf [accessed 2019-03-18]
7. Sayed H. Egypt's Demographic opportunity: preliminary assessment based on 2017 census. United Nations Population Fund 2018.
8. Mostafa M. The old people in Egypt, Case Study (Ismailia Governorate). Cairo, Egypt: Central Agency for Public Mobilization and Statistics; 2013 Apr 23. URL: https://www.statistics.gov.hk/wsc/CPS201-P5-S.pdf [accessed 2019-03-29]
9. Egypt. Pension & Development Network. URL: http://www.pensiondevelopment.org [accessed 2019-03-26]
10. El-Sherbiny NA, Younis A, Masoud M. A comprehensive assessment of the physical, nutritional, and psychological health status of the elderly populace in the Fayoum Governorate (Egypt). Arch Gerontol Geriatr 2016 Sep;66:119-126. [doi: 10.1016/j.archger.2016.06.001] [Medline: 27315050]
11. Okasha A. History of mental health in the Arab world. In: Okasha A, Maj M, editors. Images in Psychiatry: An Arab Perspective. Geneva, Switzerland: World Psychiatric Association; 2001:1-20.
12. Endrawes G, O'Brien L, Wilkes L. Mental illness and Egyptian families. Int J Ment Health Nurs 2007 Jun;16(3):178-187. [doi: 10.1111/j.1447-0349.2007.00465.x]
13. Loza N. Integrating Egyptian mental health services into primary care: the policy maker's perspective. Int. psychiatry 2018 Jan 02;7(1):5-6. [doi: 10.1192/s1749367600000904]
14. Okasha A, el Akabawi AS, Snyder KS, Wilson AK, Youssef I, el Dawla AS. Expressed emotion, perceived criticism, and relapse in depression: a replication in an Egyptian community. Am J Psychiatry 1994 Jul;151(7):1001-1005. [doi: 10.1176/ajp.151.7.1001] [Medline: 8010354]
15. Kelly LS, Mckenna HP. Victimization of people with enduring mental illness in the community. J Psychiatr Ment Health Nurs 1997 Jun;4(3):185-191. [doi: 10.1046/j.1365-2850.1997.00054.x]
16. Ghanem M, Gadallah M, Meky F, Mourad S, El Kholy G. National survey of Prevalence of Mental Disorders in Egypt: preliminary survey. East Mediterr Health J 2009 Jan 01;15(1):65-75. [doi: 10.26719/2009.15.1.65]
17. Elshahidi M, Elhadidi M, Sharaqi A, Mostafa A, Elzhery M. Prevalence of dementia in Egypt: a systematic review. NDT 2017 Mar;Volume 13:715-720. [doi: 10.2147/ndt.s127605]
18. Aly H, Hamed A, Mohammed N. Depression among the elderly population in sohag governorate. SMJ 2018 Feb 8;39(2):185-190. [doi: 10.15537/smj.2018.2.21353]
19. Eissa AM, Hassan GA, Azam H, Sadek HA, El Awam I. Sociodemographic correlates of depression and anxiety disorders among physically ill elderly patients. Middle East Current Psychiatry 2013;20(2):73-79. [doi: 10.1097/01.xme.0000427044.15345.7b]
20. Amer M, Mousa S, Khater M, Wahab WA. Prevalence of mild cognitive impairment among older adults living in Mansoura city, Egypt. Middle East Current Psychiatry 2012;19(1):3-7. [doi: 10.1097/01.xme.0000407821.18381.3c]
21. Farrag AF, Farwiz HM, Khedr EH, Mahfouz RM, Omran SM. Prevalence of Alzheimer's Disease and Other Dementing Disorders: Assiut-Upper Egypt Study. Dement Geriatr Cogn Disord 1998 Oct 23;9(6):323-328. [doi: 10.1159/000017084]

22. Khedr E, Fawi G, Abbas MAA, Mohammed TA, El-Fetoh NA, Al Attar G, et al. Prevalence of Mild Cognitive Impairment and Dementia among the Elderly Population of Qena Governorate, Upper Egypt: A Community-Based Study. JAD 2015 Mar 03;45(1):117-126. [doi: 10.3233/jad-142655]
23. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009 Jul 21;339(jul21 1):b2700-b2700 [FREE Full text] [doi: 10.1136/bmj.b2700] [Medline: 19622552]
24. Streiner DL, Patten SB, Anthony JC, Cairney J. Has 'lifetime prevalence' reached the end of its life? An examination of the concept. Int. J. Methods Psychiatr. Res 2010 Jan 05;18(4):221-228. [doi: 10.1002/mpr.296]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Protocol

Cannabis and Illicit Drug Use During Neurodevelopment and the Associated Structural, Functional and Cognitive Outcomes: Protocol for a Systematic Review

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Abstract

Background: High rates of cannabis and illicit drug use are experienced by young people during the final stages of neurodevelopment (aged 15-24 years), a period characterized by high neuroplasticity. Frequent drug use during this time may interfere with neurophysiological and neuropsychological development pathways, potentially leading to ongoing unfavorable neuroadaptations. The dose-response relationship between illicit drug use, exposure, and individual neurodevelopmental variation is unknown but salient with global shifts in the legal landscape and increasingly liberal attitudes and perceptions of the harm caused by cannabis and illicit drugs.

Objective: This systematic review aims to synthesize longitudinal studies that investigate the effects of illicit drug use on structural, functional, and cognitive brain domains in individuals under the neural age of adulthood (25 years). This protocol outlines prospective methods that will facilitate an exhaustive review of the literature exploring pre- and post-drug use brain abnormalities arising during neurodevelopment.

Methods: Five electronic databases (Medline, Embase, PsycINFO, ProQuest Central, and Web of Science) will be systematically searched between 1990 and 2019. The search terms will be a combination of MeSH (Medical Subject Headings), with keywords adapted to each database. Study reporting will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and if relevant, study quality will be assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Eligible studies are those that sampled youth exposed to cannabis or illicit drugs and employed neurophysiological or neuropsychological assessment techniques. Studies will be excluded if participants had been clinically diagnosed with any psychiatric, neurological, or pharmacological condition.

Results: This is an ongoing review. As of February 2020, papers are in full-text screening, with results predicted to be complete by July 2020.

Conclusions: Integrating data collected on the three brain domains will enable an assessment of the links between structural, functional, and cognitive brain health across individuals and may support the early detection and prevention of neurodevelopmental harm.

Trial Registration: PROSPERO CRD42020151442; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=151442

International Registered Report Identifier (IRRID): PRR1-10.2196/18349

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KEYWORDS

cannabis; illicit drugs; neurodevelopment; longitudinal review; protocol; neurology; review

Introduction

Illicit drug use and associated harms are highest among young people aged 15-24 years [1]. Globally, the onset of illicit drug use spikes around 15 years of age, a stage of high neuroplasticity, and rates climb throughout emerging adulthood (18-24 years) before dropping at approximately 25 years—after neuromaturation [2,3]. It comes as no surprise that illicit drug use during neurodevelopment is widespread; a quarter (24%) of adolescents (12-17 years) and over half (57%) of emerging adults report illicit drug use in the United States [4]. Moreover, from adolescence to emerging adulthood, lifetime methylenedioxymethamphetamine (MDMA; ecstasy) use surges from 0.8% up to 10.5% and cocaine use rises from 0.7% to 11.4% [4]. Although single-time drug use carries a small increase in morbidity and mortality, it may be the patterns of use and stage of neurodevelopment, that most influences the risk of neuronal aberrations and dependence [5]. Cannabis is the most commonly consumed illicit drug worldwide, with 5.6% of the world's adolescent population reporting recent use, nearly one fifth (18%) of Europeans (15-24 years) reporting past-year use [6], and 10% of young Canadians reporting daily or almost daily use [7]. In Australia, around 41% of young people (14-24 years) have used an illicit drug in the past year, representing 90% of all national illicit drug users [8]. Despite risky patterns of use and the potential for ongoing harm, there is limited research investigating the ongoing impact of illicit drug use on the developing brain.

Adolescence and emerging adulthood represent a period of protracted neurobiological development marked by structural and functional remodeling, contributing to improved cognitive performance [9,10]. Structural integration occurs throughout the brain into early adulthood, with processes such as synaptic pruning (removal of unneeded neural connections), myelination (insulation and strengthening of neural messaging), and synaptogenesis (new neural connections), occurring predominantly in the prefrontal cortex [11]. These structural advances provide the underpinning of encephalization, which is the age-related transfer of function from the primitive, autonomic systems such as the hindbrain (pons, cerebellum, and medulla oblongata) and subcortical midbrain (limbic system), to the sophisticated cognitive systems of the forebrain (cerebral cortex, including the prefrontal cortex) [12,13]. Structural and functional maturation in cortical regions of the brain, specifically in the prefrontal cortex, precipitate improved cognition functioning [14], however, occur over a nonlinear trajectory. For example, neural projections between the prefrontal cortex and subcortical limbic system oscillate between regressive and progressive changes. Although development across structural, functional, and cognitive domains are inextricably linked, they are asynchronous, so one does not indicate the presence of another. Therefore, interpreting single brain outcomes during neurodevelopment is limited, particularly if assessed during a single data instance. Triangulating neurophysiological and neuropsychological studies may help to account for different trajectories of neurodevelopment and establish a more wholistic view of brain health.

The neurotoxic impact of illicit drugs on the developing brain has been studied extensively; however, a clear relationship between exposure (drug class[es] and patterns of use) and neurological sequelae is yet to be established. Sustained use of most drugs, such as cannabis inhalants, opiates, psychostimulants, and ecstasy, tends to be associated with executive dysfunction such as declines in working memory, verbal fluency, learning, and attention [15-18] and structural and functional abnormalities in the frontal cortex and limbic system [19-22]. However, the precise and quantifiable impact of different drug classes is less clear. A recent review of neuroimaging publications involving adolescent drug use showed that most focus on alcohol, only 45% focus on cannabis, less than 2% assess ecstasy/meth and inhalants, and 7% address polydrug use [23]. Untangling the impact of illicit substance use, including the difference between regular low dose use and infrequent high dose use, is challenging in part due to the limited investigation in this area [24,25]. Studies measuring the brain's capacity to recover after abstinence are mixed [26,27], with some confirming cognitive deficits are present in the weeks after drug use [28,29], others claiming full recovery [30], and others showing persistent structural and functional changes months and years after abstinence [29,31]. Longitudinal study designs are required to discern the impact of complex patterns of illicit drug use and determine which classes carry additional risk of ongoing harm.

The age of drug use onset and corresponding stage of brain development may mediate neurophysiological and neuropsychological vulnerability to harm [32,33]. Many studies have shown a difference in harm between adolescents and adults [25], and some researchers hypothesize the brain is more protected against harm after 16 or 17 years of age [34,35]. Adding to the complexity are sex-based neurobiological factors that may subject females to higher risk than males [36-38]. Unfortunately, sex-based differences are not well understood, in part due to the underrepresentation of females in neuroimaging studies. Pressingly, the gender gap between male and female use may be closing [39-41] and could be accompanied by an increase in the number of young females presenting with neurodevelopmental aberrations. Longitudinal studies that help to untangle the relationship between pre-existing neural differences and trajectories of neurodevelopment will help elucidate individual vulnerability to harm.

Several narrative reviews have synthesized the evidence of the long-term impact of illicit drug use on the developing brain [42,43]; however, there are limited systematic reviews that can provide a complete view of the evidence. The systematic reviews are highly skewed towards cannabis use [44-46] and tend to provide insight into a single brain outcome [47]. Very few reviews harness structural, functional, and cognitive data [23,48-50], and only one incorporates findings on more than

one drug [51]. Most importantly, very few reviews assess the longitudinal harms of drugs [25,52,53] and instead rely on cross-sectional data, which provide a limited assessment of change over neurodevelopment. Of these reviews, one did not include neuroimaging data [54], and the remaining three included only one brain domain [25,52,53]. To our knowledge, there has been no systematic review of longitudinal studies measuring the long-term impacts of a broad range of common illicit drugs, with findings encompassing both neurobiological and neuropsychological outcomes. To understand the neurological health burden of illicit drugs for young people and to inform policy and future prevention programs, a systematic review of the longitudinal studies assessing the impact of illicit drug use on structural, functional, and cognitive brain domains in young people will be conducted. Specifically, the main objectives of this review include:

1. Investigate pre-existing neurodevelopmental risk factors associated with increased cannabis and illicit drug use and related harm for young people (<25 years).
2. Assess the residual, dose-dependent effects of cannabis and illicit drugs on the function, structure, and cognitive profile of the developing brain (<25 years).
3. Determine to what extent cannabis and illicit drug use during neurodevelopment (<25 years) predict sustained structural, functional, and cognitive brain changes.

Methods

This systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020151442) and was written per the Preferred Reporting Items for Systematic Review (PRISMA) guidelines [55] as provided (see Multimedia Appendix 1).

Population Characteristics

Studies that target young people aged 10-25 years who have any lifetime exposure to cannabis or another illicit drug will be included. We will exclude studies in which the average age of participants is older than 25years.

Eligibility Criteria

The proposed systematic review will include published studies that focus on young people aged 10-25 years who have used cannabis or an illicit drug; report on empirical, longitudinal data, where the same measurement has been employed over multiple time points; and where the measurements include test batteries assessing structural, functional or neuropsychological brain domains. Studies will include a sample with exposure to cannabis, illicit drugs, or both, where exposure involves at least single time use. Studies must compare participants who meet the criteria for cannabis or illicit drug exposure with a comparison group with less exposure. Eligible studies published after January 1990 in the English language will be included.

Participants who have been clinically diagnosed with psychiatric or neurological conditions will be excluded from the review to prevent confounding results. As this review focuses on brain changes over time, we will exclude cross-sectional studies.

Search Strategy

Aided by a research librarian, five electronic databases will be systematically searched: Medline (Ovid), Embase (Elsevier), PsycINFO (OvidSP), ProQuest Central, and Web of Science, using Medical Subject Headings (MeSH). Search terms will be developed individually for each database, and specific terms for each search group are defined in the additional search strategy file (see Multimedia Appendix 2 for strategy and Multimedia Appendix 3 for an example search of Medline). The search will be limited to peer-reviewed studies of human subjects published in the English language, between 1990 and 2019, given the improvement in brain scanning techniques during this time. Researchers will manually review the reference lists of eligible papers to detect further relevant papers and will cross-reference other recent systematic reviews to discover additional studies. All papers identified in the search strategy will be exported into a bibliographic database for deduplication and screening and uploaded to the Covidence online software program for screening.

Data Extraction and Screening

All titles and abstracts from the returned searches will be screened by one reviewer based on the eligibility criteria, and a random sample of 25% will be screened again by a second reviewer, with any disagreement resolved by a consensus. Similarly, full-text copies will be screened twice according to the eligibility criteria by two independent reviewers with any disagreement resolved by a consensus. Data extraction will be supported by an extraction template, which will first be piloted to ensure it adequately captures trial data. The following data will be extracted from all included full-text articles:

- Study information (author, year, title, location);
- Study characteristics (study design, imaging/test technique);
- Sample characteristics (sample size, gender and age distribution);
- Drug exposure characteristics (drug type/s, age of initiation, route of administration, frequency, quantity, abstinence period, and assessment method);
- Data characteristics (exclusion criteria, number of measurement occasions, brain region);
- The statistical approach used to investigate change over time; and
- Key results.

Where necessary, the corresponding author of the included studies will be contacted via email to obtain any relevant data not presented in the published paper. In the case of study attrition bias, authors will be contacted to request additional data to be incorporated into the review.

Outcomes

The primary outcomes of interest will be the residual and long-term differences in neurobiological (structural and functional) and neuropsychological (cognitive) brain domains between the active and control group. The neuroanatomical development trajectories of particular interest include global and local gray matter measures (volume, density, and thickness); integrity of white matter microstructure and fiber connectivity (including directional organization, myelination, axonal packing)

[56]; and receptor distribution. Global and local function, as understood through cortical activation, will be measured by blood flow and blood oxygenation level-dependent oxygen consumption [57]. Finally, cognitive performance, will be measured through neuropsychological tasks assessing attention and concentration, decision-making and risk-taking, inhibition and impulsivity, episodic and working memory, verbal fluency, planning, IQ and general executive functioning. Where possible, outcomes will be deconstructed into male and female results.

Strategy for Data Synthesis

We anticipate a high degree of heterogeneity among study design and participant characteristics, and will, therefore, conduct a narrative synthesis on all available data. If it is appropriate to combine studies, meta-analysis will be conducted using Review Manager software (Cochrane). Synthesis of the included study data will be structured according to technique type, and differences between the control and exposed groups will be compared. Pre-existing cognitive, structural, and functional features will be accounted for through standardization. If possible, a subanalysis of gender-based differences will be conducted.

Risk of Bias and Quality Assessment

Reviewers will independently assess the risk of bias by adapting Cochrane Collaboration's tool for assessing the risk of bias in trials [58]. The tool will be used to assess the extent to which biases may impact study results, such as selection bias, attrition bias, reporting bias, performance bias, and detection bias. Other relevant biases will be considered where appropriate. A third reviewer will resolve any discrepancies that may arise. Reviewers will assign scores to the six domains, and the total risk of bias will be provided for each study, with higher scores indicating a lower risk of bias.

The overall quality of the body of evidence will be determined using the Grades of Recommendation, Assessment, Development, and Evaluation approach [59]. Study quality will be graded as high (further research is unlikely to change our confidence in the effect), moderate (further research is likely to have an impact on our confidence in the effect and may change the estimate), low (further research is likely to have an impact on our confidence in the effect), and very low (uncertain about the effect estimate). The included studies will start with a high-quality rating and move downwards based on scoring, and observational studies will begin on a low-quality rating and move upwards.

Results

This paper describes an ongoing review. As of February 2020, papers are in full-text screening, with results predicted to be complete by July 2020.

Discussion

Accumulating research assessing the impact of illicit drug use on the developing brain underscores the need for a systematic review to assist clinicians, educators, and public health advisors in evidence-based practice. The significant consequences of illicit drug use, such as an increase in the likelihood of developing a drug use disorder or a persisting mental deficit, may be preventable [37,60]. The shifting legal landscape and subsequent liberalization of attitudes and perception of the harm of drugs make quantifying their precise neurological impact critically important. Synthesizing a current view of the evidence of illicit drug use and brain development may support the early detection and prevention of neurodevelopmental harm.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 158 KB - resprot_v9i7e18349_app1.pdf]

Multimedia Appendix 2
Example MeSH (Medical Subject Headings) from search strategy.
[PDF File (Adobe PDF File), 17 KB - resprot_v9i7e18349_app2.pdf]

Multimedia Appendix 3
Example of search strategy in Medline/Ovid.
[PDF File (Adobe PDF File), 28 KB - resprot_v9i7e18349_app3.pdf]

References

1. Bosch OG, Esposito F, Dornbierer D, von Rotz R, Kraehenmann R, Staempfli P, et al. Prohedonic properties of gamma-hydroxybutyrate are associated with changes in limbic resting-state functional connectivity. Hum Psychopharmacol Clin Exp 2018 Nov 13;33(6):e2679. [doi: 10.1002/hup.2679] [Medline: 30426556]
2. Degenhardt L, Chiu W, Sampson N, Kessler RC, Anthony JC, Angermeyer M, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med 2008 Jul 01;5(7):e141 [FREE Full text] [doi: 10.1371/journal.pmed.0050141] [Medline: 18597549]
3. Johnson SB, Blum RW, Giedd JN. Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. J Adolesc Health 2009 Sep;45(3):216-221 [FREE Full text] [doi: 10.1016/j.jadohealth.2009.05.016] [Medline: 19699416]
4. Results from the 2018 National Survey on Drug Use and Health: Detailed tables. Substance Abuse and Mental Health Services Administration. Rockville,: MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2019. URL: https://www.samhsa.gov/data/ [accessed 2019-12-01]
5. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. The Lancet 2013 Nov;382(9904):1564-1574. [doi: 10.1016/s0140-6736(13)61530-5]
6. European Monitoring Centre for Drugs and Drug Addiction. Prevention of Addictive Behaviours. European Drug Report: Trends and developments. Luxembourg: Publications Office of the European Union; 2015. URL: https://www.emcdda.europa.eu [accessed 2019-12-01]
7. Michelle R. National Cannabis Survey 2nd quarter. Statistics Canada. 2019. URL: https://www.statcan.gc.ca [accessed 2019-12-01]
8. Roger W, Peter B, Esperanza VT. The Household, Income and Labour Dynamics in Australia Survey: Selected Findings from Waves 1 to 17. University of Melbourne. 2019. URL: https://melbourneinstitute.unimelb.edu.au [accessed 2019-12-01]
9. Giedd J. Structural magnetic resonance imaging of the adolescent brain. Annals of the New York Academy of Sciences 2004;1021:77-85. [doi: 10.1196/annals.1308.009] [Medline: 15251877]
10. Sowell ER. Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children. Journal of Neuroscience 2004 Sep 22;24(38):8223-8231. [doi: 10.1523/jneurosci.1798-04.2004]
11. Durston S, Hulshoff Pol HE, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H. Anatomical MRI of the developing human brain: what have we learned? J Am Acad Child Adolesc Psychiatry 2001 Sep;40(9):1012-1020. [doi: 10.1097/00004583-200109000-00009] [Medline: 11556624]
12. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. Brain 1991 Oct;114 (Pt 5)(5):2037-2049. [doi: 10.1093/brain/114.5.2037] [Medline: 1933232]
13. Giedd J, Castellanos F, Kozuch P, Casey B, Kaysen D, King A, et al. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Biological Psychiatry 1994 May;35(9):713. [doi: 10.1016/0006-3223(94)91008-1]
14. Gaillard WD, Hertz-Pannier L, Mott SH, Barnett AS, LeBihan D, Theodore WH. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. Neurology 2000 Jan 11;54(1):180-185. [doi: 10.1212/wnl.54.1.180] [Medline: 10636145]
15. Ornstein T, Iddon J, Baldacchino A, Sahakian B, London M, Everitt B, et al. Profiles of Cognitive Dysfunction in Chronic Amphetamine and Heroin Abusers. Neuropsychopharmacology 2000;23(2):113-126. [doi: 10.1016/S0893-133X(00)00097-X]
16. Bolla KI, McCann UD, Ricaurte GA. Memory impairment in abstinent MDMA ("Ecstasy") users. Neurology 1998 Dec 01;51(6):1532-1537. [doi: 10.1212/wnl.51.6.1532] [Medline: 9855498]
17. Zakzanis KK, Young DA. Memory impairment in abstinent MDMA ("Ecstasy") users: a longitudinal investigation. Neurology 2001 Apr 10;56(7):966-969. [doi: 10.1212/wnl.56.7.966] [Medline: 11294938]
18. Yücel M, Lubman D. Neurocognitive and neuroimaging evidence of behavioural dysregulation in human drug addiction: implications for diagnosis, treatment and prevention. Drug Alcohol Rev 2007 Jan;26(1):33-39. [doi: 10.1080/09595230601036978] [Medline: 17364834]
19. Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain Morphological Changes and Early Marijuana Use. Journal of Addictive Diseases 2010 Feb 02;19(1):1-22. [doi: 10.1300/j069v19n01_01]
20. Churchwell JC, Lopez-Larson M, Yurgelun-Todd DA. Altered frontal cortical volume and decision making in adolescent cannabis users. Front Psychol 2010;1:225 [FREE Full text] [doi: 10.3389/fpsyg.2010.00225] [Medline: 21833280]
21. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, et al. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Research: Neuroimaging 1996 May;67(1):29-38. [doi: 10.1016/0925-4927(96)02817-x]
22. Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, et al. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology (Berl) 2007 Oct 9;194(2):173-183 [FREE Full text] [doi: 10.1007/s00213-007-0823-y] [Medline: 17558500]
23. Silveri MM, Dager AD, Cohen-Gilbert JE, Sneider JT. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. Neurosci Biobehav Rev 2016 Nov;70:244-259 [FREE Full text] [doi: 10.1016/j.neubiorev.2016.06.042] [Medline: 27377691]

24. Conway KP, Vullo GC, Nichter B, Wang J, Compton WM, Iannotti RJ, et al. Prevalence and patterns of polysubstance use in a nationally representative sample of 10th graders in the United States. J Adolesc Health 2013 Jun;52(6):716-723 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.12.006] [Medline: 23465320]
25. Blest-Hopley G, Giampietro V, Bhattacharyya S. Residual effects of cannabis use in adolescent and adult brains - A meta-analysis of fMRI studies. Neurosci Biobehav Rev 2018 May;88:26-41. [doi: 10.1016/j.neubiorev.2018.03.008] [Medline: 29535069]
26. Meier MH, Schriber RA, Beardslee J, Hanson J, Pardini D. Associations between adolescent cannabis use frequency and adult brain structure: A prospective study of boys followed to adulthood. Drug Alcohol Depend 2019 Sep 01;202:191-199. [doi: 10.1016/j.drugalcdep.2019.05.012] [Medline: 31357120]
27. Yücel M, Lubman DI, Solowij N, Brewer WJ. Understanding drug addiction: a neuropsychological perspective. Aust N Z J Psychiatry 2007 Dec 26;41(12):957-968. [doi: 10.1080/00048670701689444] [Medline: 17999268]
28. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Marijuana Treatment Project Research Group. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 2002 Mar 06;287(9):1123-1131. [doi: 10.1001/jama.287.9.1123] [Medline: 11879109]
29. Bolla K, Brown K, Eldreth D, Tate K, Cadet J. Dose-related neurocognitive effects of marijuana use. Neurology 2002 Nov 12;59(9):1337-1343. [doi: 10.1212/01.wnl.0000031422.66442.49] [Medline: 12427880]
30. Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001 Oct 01;58(10):909-915. [doi: 10.1001/archpsyc.58.10.909] [Medline: 11576028]
31. Solowij N. Cannabis and cognitive functioning. Cambridge University Press 2006. [doi: 10.1017/cbo9780511526824] [Medline: 22135433]
32. Cheetham A, Allen NB, Whittle S, Simmons JG, Yücel M, Lubman DI. Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. Biol Psychiatry 2012 Apr 15;71(8):684-692. [doi: 10.1016/j.biopsych.2011.10.029] [Medline: 22129756]
33. Filbey FM, Aslan S, Calhoun VD, Spence JS, Damaraju E, Caprihan A, et al. Long-term effects of marijuana use on the brain. Proc Natl Acad Sci U S A 2014 Nov 25;111(47):16913-16918 [FREE Full text] [doi: 10.1073/pnas.1415297111] [Medline: 25385625]
34. Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug and Alcohol Dependence 2003 Apr;69(3):303-310. [doi: 10.1016/s0376-8716(02)00334-4]
35. Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, et al. Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology (Berl) 1999 Mar 4;142(3):295-301. [doi: 10.1007/s002130050892] [Medline: 10208322]
36. Reneman L, Booij J, de Bruin K, Reitsma JB, de Wolff FA, Gunning WB, et al. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. The Lancet 2001 Dec;358(9296):1864-1869. [doi: 10.1016/s0140-6736(01)06888-x]
37. Johnston L, Miech R, O'Malley P, Bachman J, Schulenberg J, Patrick M. Monitoring the Future national survey results on drug use, 1975-2017: Overview, key findings on adolescent drug use. In: Ann Arbor: Institute for Social Research The University of Michigan. Michigan: The University of Michigan; 2018.
38. Bava S, Tapert SF. Adolescent brain development and the risk for alcohol and other drug problems. Neuropsychol Rev 2010 Dec 19;20(4):398-413 [FREE Full text] [doi: 10.1007/s11065-010-9146-6] [Medline: 20953990]
39. Wilkins R, Lab I, Butterworth P, Vera-Toscano E. The Household, Income and Labour Dynamics in Australia (HILDA) Survey: Selected Findings from Waves 1 to 17. Melbourne Institute: Applied Economic & Social Research.: University of Melbourne; 2019. URL: https://melbourneinstitute.unimelb.edu.au [accessed 2019-12-01]
40. Results from the 2018 National Survey on Drug Use and Health: Detailed tables. Substance Abuse and Mental Health Services Administration. Rockville: MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2019. URL: https://www.samhsa.gov/data/ [accessed 2019-11-01]
41. Slade T, Chapman C, Swift W, Keyes K, Tonks Z, Teesson M. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. BMJ Open 2016 Oct 24;6(10):e011827 [FREE Full text] [doi: 10.1136/bmjopen-2016-011827] [Medline: 27797998]
42. Lubman DI, Yücel M, Hall WD. Substance use and the adolescent brain: a toxic combination? J Psychopharmacol 2007 Nov 02;21(8):792-794. [doi: 10.1177/0269881107078309] [Medline: 17984159]
43. Squeglia L, Jacobus J, Tapert S. The influence of substance use on adolescent brain development. Clin EEG Neurosci 2009 Jan;40(1):31-38 [FREE Full text] [doi: 10.1177/155005940904000110] [Medline: 19278130]
44. Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Exp Clin Psychopharmacol 2012 Oct;20(5):420-429. [doi: 10.1037/a0029117] [Medline: 22731735]
45. Ganzer F, Bröning S, Kraft S, Sack P, Thomasius R. Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. Neuropsychol Rev 2016 Jun 28;26(2):186-222. [doi: 10.1007/s11065-016-9316-2] [Medline: 27125202]

46. Scott JC, Slomiak ST, Jones JD, Rosen AFG, Moore TM, Gur RC. Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Psychiatry 2018 Jun 01;75(6):585-595 [FREE Full text] [doi: 10.1001/jamapsychiatry.2018.0335] [Medline: 29710074]
47. Baker ST, Yücel M, Fornito A, Allen NB, Lubman DI. A systematic review of diffusion weighted MRI studies of white matter microstructure in adolescent substance users. Neurosci Biobehav Rev 2013 Sep;37(8):1713-1723. [doi: 10.1016/j.neubiorev.2013.06.015] [Medline: 23845745]
48. Lisdahl KM, Gilbart ER, Wright NE, Shollenbarger S. Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. Front Psychiatry 2013;4:53 [FREE Full text] [doi: 10.3389/fpsyt.2013.00053] [Medline: 23847550]
49. Ganzer F, Bröning S, Kraft S, Sack P, Thomasius R. Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. Neuropsychol Rev 2016 Jun 28;26(2):186-222. [doi: 10.1007/s11065-016-9316-2] [Medline: 27125202]
50. Martín-Santos R, Fagundo AB, Crippa JA, Atakan Z, Bhattacharyya S, Allen P, et al. Neuroimaging in cannabis use: a systematic review of the literature. Psychol. Med 2009 Jul 23;40(3):383-398. [doi: 10.1017/s0033291709990729]
51. Silveri MM, Dager AD, Cohen-Gilbert JE, Sneider JT. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. Neurosci Biobehav Rev 2016 Nov;70:244-259 [FREE Full text] [doi: 10.1016/j.neubiorev.2016.06.042] [Medline: 27377691]
52. Gorey C, Kuhns L, Smaragdi E, Kroon E, Cousijn J. Age-related differences in the impact of cannabis use on the brain and cognition: a systematic review. Eur Arch Psychiatry Clin Neurosci 2019 Mar 24;269(1):37-58 [FREE Full text] [doi: 10.1007/s00406-019-00981-7] [Medline: 30680487]
53. Blest-Hopley G, Giampietro V, Bhattacharyya S. Regular cannabis use is associated with altered activation of central executive and default mode networks even after prolonged abstinence in adolescent users: Results from a complementary meta-analysis. Neurosci Biobehav Rev 2019 Jan;96:45-55 [FREE Full text] [doi: 10.1016/j.neubiorev.2018.10.026] [Medline: 30395923]
54. Macleod J, Oakes R, Copello A, Crome I, Egger M, Hickman M, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. The Lancet 2004 May;363(9421):1579-1588. [doi: 10.1016/s0140-6736(04)16200-4]
55. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4(1):1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
56. Mills K, Lalonde F, Clasen L, Giedd J, Blakemore SJ. Developmental changes in the structure of the social brain in late childhood and adolescence. Social cognitive and affective neuroscience. Social Cognitive and Affective Neuroscience 2012;9(1):123-131. [doi: 10.1093/scan/nss113] [Medline: PMC3871734]
57. Burnett S, Sebastian C, Cohen Kadosh K, Blakemore S. The social brain in adolescence: evidence from functional magnetic resonance imaging and behavioural studies. Neurosci Biobehav Rev 2011 Aug;35(8):1654-1664 [FREE Full text] [doi: 10.1016/j.neubiorev.2010.10.011] [Medline: 21036192]
58. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343(oct18 2):d5928-d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]
59. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 24;336(7650):924-926. [doi: 10.1136/bmj.39489.470347.ad]
60. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999 Oct;2(10):861-863. [doi: 10.1038/13158] [Medline: 10491603]

Abbreviations

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation
MDMA: methylenedioxymethamphetamine
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Patient Portal Functionalities and Uptake: Systematic Review Protocol

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Abstract

Background: Patient portals are digital health tools adopted by health care organizations. The portals are generally connected to the electronic health record of the health care organization and offer patients functionalities such as access to the medical record, ability to order repeat prescriptions, make appointments, or message the health care provider. Patient portals may be beneficial for both patients and the health care system. Patient portals can widely differ from one context to another due to the differences in the portal functionalities and capabilities and it is anticipated that outcomes associated with the functionalities also differ. Current systematic reviews report outcomes associated with patient portal uptake but do not explicitly specify the patient portal functionalities.

Objective: The aim of this systematic review is to synthesize the evidence on health and health care quality outcomes associated with patient portal use among adult (18 years or older) patients. The review research questions are as follows: What kind of health outcomes do tethered patient portals and patient portal functionalities contribute to in adult patients (18 years or older)? and What kind of health care quality outcomes, including health care utilization outcomes, do tethered patient portals and patient portal functionalities contribute to in adult patients (18 years or older)?

Methods: The systematic review will be conducted by searching the MEDLINE, EMBASE, and Scopus databases for relevant literature. The review inclusion criteria will be studies about adult patients (18 years or older), studies only about tethered patient portals, and studies with or without a comparator. We will report patient portal–associated health and health care quality outcomes based on the patient portal functionalities. All quantitative primary study types will be included. Risk of bias of included studies will be assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials and the National Heart, Lung, and Blood Institute's quality assessment tools. Data will be synthesized using narrative synthesis and will be reported according to the patient portal functionalities, country, disease, and health care system model.

Results: Searches will be conducted in September 2019, and the review is anticipated to be completed by the end of June 2020.

Conclusions: This systematic review will provide an overview of health and health care quality outcomes associated with patient portal use among adult patients, providing detailed information about the functionalities of the portals and their associations with the outcomes. The review could potentially help patient portal evaluation studies by providing insights into outcomes associated with the different functionalities of patient portals.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42019141131; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=141131

International Registered Report Identifier (IRRID): PRR1-10.2196/14975

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KEYWORDS

personal health record; patient portal; electronic health records; online access; patient records; systematic review

Introduction

Technology is affecting all aspects of health care systems. With the introduction of electronic health records (EHRs), patients are now able to access their medical records through patient portals, or personal health records (PHRs). Tethered patient portals or PHRs are connected to the EHR operated by the health care provider or organization and typically contain information about patient's health records such as allergies, immunizations, medication, and upcoming appointments [1]. Some patient portals can also include information such as genetic data, preventative or customized medical advice [1], or offer functionalities such as ordering repeat prescriptions, messaging health care providers, and sharing health care record [2].

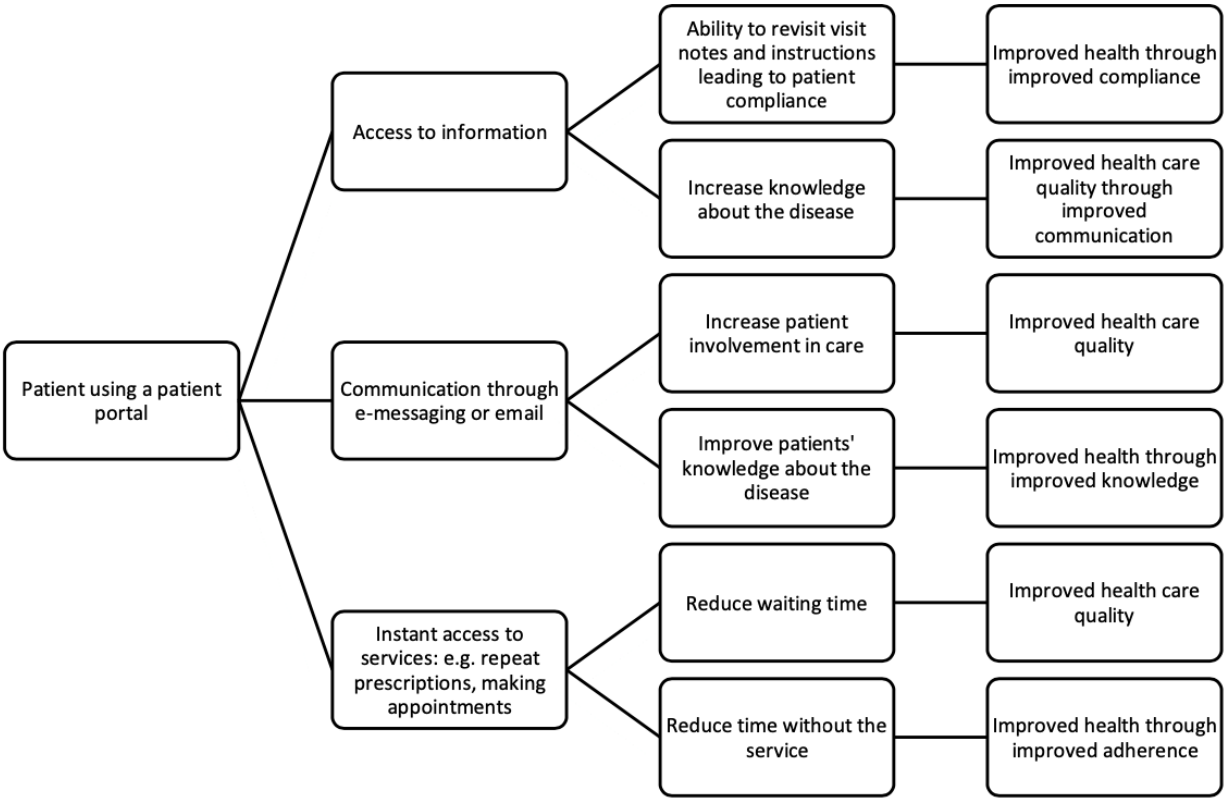
Patient portals are generally offered through the primary care providers, but can also be offered in hospital care, or during acute care [3]. The technology provides some benefits to patients and the health care system. For the health care system, portals may contribute to reducing phone call and visits [4], reducing emergency department visits [5], reducing hospital readmissions, improving the quality and efficiency of the health care system [6,7], and reducing health care service utilization in the long run and improving adherence to medical appointments [8]. For the patient, the use of patient portal may contribute to assisting in medical decision making [9], improving health care outcomes [6,10], improving adherence [11], improving patient- or person-centered care [4], improving patient satisfaction and increasing patient safety [12], and improving disease management and prevention [6,7]. In addition, patient portal functionalities such as viewing medical record may improve the relationship between patients and their providers [13]. Patient portals also make it possible to connect different emerging technologies such as wearable devices and mobile health (mHealth) technologies and collect the information in the patient record [14].

Although patient portals are associated with benefits to patients' health and to the health care system, there are no definitive explanations about how they contribute to improved outcomes. A theoretical framework depicting how a patient portal access could improve health and health care quality experience is illustrated in Figure 1 using findings of qualitative studies. The benefits are often explained through the use of specific functionalities of the portal. For example, patients' access to the health record with visit notes gives them ability to revisit their notes, which in turn improves their compliance with the care plan set out by the doctor [15,16] and also increases their confidence [17,18]. At the same time, access to the health record or test results gives the patients the chance to instantly and continuously review their record, increasing their knowledge about their condition [15] and improving their communication with the health care provider through increased ability to discuss their health care condition [15,16,18]. Other functionalities of patient portals such as e-messaging or secure messaging and patient education can improve patients' involvement in their care [15] and their knowledge about their disease [19], respectively. Patients' ability to refill medication through the portal allows them to efficiently refill medication, reducing the time they spend without medication, and as a consequence may improve their adherence and compliance with medication regime [17,20].

When reviewing patient portal studies it is important to consider possible sources of bias. Patient portal studies are often subject to bias due to the complex mechanisms involved between technology use and outcomes. Uptake usually varies between patients and often only registration on the portal is accounted for in studies. For example, while a meta-analysis reported a mean adoption rate of 51% (95% CI 42%-62%) from 40 studies about patient portals [21], a patient portal for laboratory results viewing with additional functionality of e-messaging received only 8.91% views out of the 208,635 tests released through the portal [22]. Second, registration or access to the portal does not guarantee use of the portal. A study among 301 patients with asthma reported that patients rarely used the patient portal on a regular basis and only about one-half used the portal in general [23]. In addition, studies cannot possibly take into account all of the interventions/factors other than the patient portal that may contribute to the patient outcomes [23].

Health care systems around the world are adopting patient portals [11,24,25]. In England, the National Health Service (NHS) made patient portals universally available in all general practices since 2015 [26]. The outcomes of the introduction of patient portals in England are yet to be examined, but before any outcomes can be expected, there needs to be an uptake of the technology by patients. Most published systematic reviews about patient portals focused on health outcome [11,24,25], patient experience outcomes such as patient engagement [27] or patient satisfaction [12], facilitators and barriers of use [21], and impact on quality [7]. However, most of these systematic reviews are now outdated due to the increased number of studies about patient portals in the last 1-2 years. Some reviews focused on patient portal adoption by a patient subgroup such as patients with diabetes [6,10], or cancer [2]. One meta-analysis reported patient portal adoption stratified by study setting (controlled versus real-world) but did not report patient portal functionalities of the included studies [21].

Figure 1. Theoretical framework of how patient portal use could lead to improved health and health care quality.



Although a number of published systematic reviews about patient portals are available, there are currently no reviews, that we know of, that focus on patient portal functionalities. When describing the outcomes, contextual factors such as the health care setting, patient type, and the functionalities of the patient portal should be considered as much as possible. Research reporting patient portal outcomes can provide valuable evidence if the context and the patient portal functionalities are clearly described and specified [6], because the context could contribute to the success of the technology. In addition, because patient portal adoption can generally be higher among patients with chronic diseases [28], the literature focused on studying the patient portal mostly by patient subpopulations such as those with diabetes or hypertension [17]. It is, therefore, essential to report user characteristics and contextual factors when considering patient portals.

There are a number of systematic review protocols of ongoing reviews about patient portals. Ammenwerth et al. [29] are planning to report patient portal outcomes based on the functionalities of the portal in which they will compare patient portals with access to the EHR alone with portals that have additional functionalities. However, the review will only include randomized controlled trials and cluster randomized controlled trials. Other upcoming reviews are examining patient portal user *expectations* [30]. An upcoming review by Petrovskaya et al. [31] plans to report patient and health care outcomes as a result of using patient portals among others; however, this will be an umbrella review and will only include other systematic reviews. Some other upcoming reviews will only focus on specific diseases such as diabetes, multiple sclerosis, and lower limb arthroplasty [32], or on one functionality of the patient portals (ie, having access to the medical record) [33], or will report only specific health care outcomes such as *no-show appointments* and *emergency visits* [34].

The aim of this systematic review is to synthesize the evidence on health and health care quality outcomes associated with patient portal use among adult (18 years or older) patients.

The review research questions are as follows:

- What kind of health outcomes do tethered patient portals and patient portal functionalities contribute to in adult patients (18 years or older)?
- What kind of health care quality outcomes, including health care utilization outcomes, do tethered patient portals and patient portal functionalities contribute to in adult patients (18 years or older)?

All research questions will be stratified by country, disease type, and health care system model.

Methods

Guidelines and Study Registration

This section will outline the methods of the systematic review using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [35] (Multimedia Appendix 1). This protocol is registered in PROSPERO, International Prospective Register of Systematic Reviews (registration number: CRD42019141131).

Inclusion Criteria

The review inclusion criteria with reference to participants, interventions, comparators, and outcomes (PICOS) framework [36] are reported in Table 1.

Table 1. Inclusion criteria for the systematic review using the participants, interventions, comparators, and outcomes (PICOS) framework.

Characteristics	Criteria
Population	• All adult patient(s) (18 years or older).
Intervention	• Tethered patient portals only (patient portals that are connected to the patient's electronic medical record). Patient portals functionalities could include, but are not limited to functionalities for viewing the medical record, making appointments or ordering repeat prescriptions, communicating with the health care providers. Patient portals will be included as long as they are connected to the electronic health care record despite the functionalities they offer. The patient portal could be based in any health care setting including primary care, secondary care, or specialist care.
Comparator	• Usual care, other intervention, or no comparator.
Outcomes	Primary outcomes: • Changes in patient health outcome measures associated with portal use. • Changes in health care quality outcomes including health care utilization.
Study types	• Only quantitative study design will be included.

Exclusion Criteria

- PHRs or patient portals that are not connected to the EHR.
- The review will exclude patient portals that are designed only to deliver patient education or counselling.
- Qualitative studies.

Information Sources and Search Strategy

The databases that will be searched include (1) MEDLINE (through Ovid), (2) EMBASE (through Ovid), and (3) Scopus. The search will have no restrictions or limits. The base search strategy was developed in the MEDLINE database (Multimedia Appendix 2) through multiple discussions with a medical librarian. The strategy will be modified and adjusted for each database according to the relevant keywords and subject headings in each database. Further studies will be identified through checking the references of eligible studies.

Study Records and Selection

We will use the Zotero (Roy Rosenzweig Center for History and New Media, USA) reference management software for removing duplicates and managing records. Studies will be scanned through the reading of the titles and abstracts in the first instance. Study title and abstracts will be assessed against the inclusion and exclusion criteria and studies that are clearly irrelevant will be excluded. Relevant studies and studies that did not provide enough detail in the abstract to judge their eligibility will then be assessed through full-text reading. Two members of the research team will independently perform title, abstract, and full-text screenings of the studies and discuss any discrepancies with a third reviewer. The study selection process will be recorded in a PRISMA flow diagram [35].

Data Extraction

Data extraction will be performed independently by two reviewers. A data extraction form was formulated to collect relevant data from the identified studies (Multimedia Appendix 3). The information collected in the data abstraction form will include (1) the last name of the author(s) and year of publication; (2) country of patient portal; (3) patient portal functionalities (the types of functionalities will not be defined prior to the review to avoid limiting the types that could be included. However, the functionalities, could include, but are not limited to functionalities mentioned in Figure 1, including accessing information through the portal, e-messaging, repeat prescription ordering, or appointment booking); (4) study type (controlled or real world); (5) patient characteristics, such as age group and sex; (6) any other patient characteristics specified in the study (such as patients with diabetes); (7) context-related factors (if any), such as type of health care setting (primary care or secondary care, or private or public health care); and (8) outcomes (health outcomes and health care quality outcomes will be recorded separately). Health outcomes could include any changes in disease indicators such as changes in blood pressure, plasma glucose concentration (hemoglobin A1c), or cholesterol levels. Health care quality outcomes could include any indicators of health care quality such as health care utilization rates, mortality rates, or disease-specific quality indicators. Study type is important because a previous meta-analysis found significant differences in adoption rates between controlled settings and real-world settings with patients being 10.8 times more likely to adopt the portals in controlled settings when compared with real-world settings (95% CI 3.2-36.3) [21].

Quality Appraisal

The risk of bias of randomized controlled trials will be assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [37]. Observational, cross-sectional, and quasi-experimental studies will be assessed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for each study design [38]. The NHLBI tool helps assess the "internal validity of studies" and identify possible sources of bias [39]. The tool can be used to rate studies as good, fair, or poor in terms of risk of bias. Risk of bias assessment will be performed independently by two reviewers using the criteria from each of the risk of bias assessment tools

depending on the type of study (Tables 1 and 2 in Multimedia Appendix 4). Summaries of risk of bias assessments will be presented as a table or a graph or in both formats for each study design. Results of the risk of bias assessment will be taken into account when interpreting findings from the studies; however, these results will not likely be used to exclude studies based on the risk of bias. These results will instead further help assess the confidence in outcomes concluded from the included studies.

Data Analysis and Synthesis

It is anticipated that performing a meta-analysis will be unlikely due to the heterogeneity of studies. Studies are likely to vary in terms of the methods used to collect and analyze the data, and in the outcomes reported. Alternatively, a narrative synthesis method will be used following guidelines suggested by Popay et al. [40] and the Cochrane Consumers and Communication Review Group (data synthesis and analysis document) [41]. The analysis will start by exploring the differences between and within the studies and identifying patterns in study outcomes. The relationship between studies, and gaps in the study findings will also be addressed in the synthesis.

Results

This systematic review is ongoing. The software searches started in September 2019. Data abstraction and data synthesis are expected to be completed by the end of June 2020. The review is anticipated to be completed by the end of June 2020. We are planning to disseminate the forthcoming systematic review in a peer-reviewed journal.

Discussion

Principal Study Findings

This systematic review will provide a comprehensive overview of the patient portal literature. To make it easy to compare between studies examining patient portals, we will categorize results by patient portal functionalities, disease, country, and health care system model. In the discussion section of the completed review, we will discuss implications from the studies, researcher assumptions, quality of the data, strengths and limitations of the review, and areas for future research.

Comparison With Previous Work

A common theme in current systematic reviews is the high heterogeneity between studies evaluating or assessing patient portals as well as the high heterogeneity between the functionalities offered by each portal [10]. Certain patient portal functionalities can have a higher association with improved health outcomes than others [6]. To control for the differences between the different portals, we will compare outcomes associated with portals based on the patient portal functionalities taking into account the disease or condition for which the portals are used for whenever possible. The outcomes of this review will inform a population-level analysis of patient portal use stratified by patient portal functionality, disease, country, and health care system model.

Limitations

It is a possibility that studies with low patient portal uptake do not report or publish their study findings. One way to deal with publication bias is by including both published and unpublished literature such as gray literature [42]. However, due to time constraints this review will only include published and peer-reviewed studies which subjects this review also to publication bias. The review will omit qualitative studies due to the drastic differences in methods and reporting of the results. However, this does not indicate that qualitative studies are not important to understand the outcomes related to patient portals. A systematic review focusing on qualitative studies reporting patient portal outcomes will help to further understand the mechanisms involved between patient portal use and health outcomes and can complement the findings of the forthcoming review.

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Authors' Contributions

AA, GG, FG, and CC initiated the review design. SA and RHJ participated in the study design. AA drafted the manuscript. All authors read and approved the final manuscript. AA is the guarantor.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P 2015 Checklist.
[DOCX File , 20 KB - resprot_v9i7e14975_app1.docx]

Multimedia Appendix 2

Sample search strategy.
[DOCX File , 13 KB - resprot_v9i7e14975_app2.docx]

Multimedia Appendix 3
Sample data extraction form.
[DOCX File , 13 KB - resprot_v9i7e14975_app3.docx]

Multimedia Appendix 4
Sample risk of bias assessment forms.
[DOCX File , 16 KB - resprot_v9i7e14975_app4.docx]

References

1. Roehrs A, da CCA, Righi RDR, de OKSF. Personal Health Records: A Systematic Literature Review. J Med Internet Res 2017 Jan 06;19(1):e13 [FREE Full text] [doi: 10.2196/jmir.5876] [Medline: 28062391]
2. Aljabri D, Dumitrascu A, Burton MC, White L, Khan M, Xirasagar S, et al. Patient portal adoption and use by hospitalized cancer patients: a retrospective study of its impact on adverse events, utilization, and patient satisfaction. BMC Med Inform Decis Mak 2018 Jul 27;18(1):70 [FREE Full text] [doi: 10.1186/s12911-018-0644-4] [Medline: 30053809]
3. Sadasivaiah S, Lyles CR, Kiyoi S, Wong P, Ratanawongsa N. Disparities in Patient-Reported Interest in Web-Based Patient Portals: Survey at an Urban Academic Safety-Net Hospital. J Med Internet Res 2019 Mar 26;21(3):e11421 [FREE Full text] [doi: 10.2196/11421] [Medline: 30912747]
4. Rigby M, Georgiou A, Hyppönen H, Ammenwerth E, de KN, Magrabi F, et al. Patient Portals as a Means of Information and Communication Technology Support to Patient- Centric Care Coordination - the Missing Evidence and the Challenges of Evaluation. A joint contribution of IMIA WG EVAL and EFMI WG EVAL. Yearb Med Inform 2015 Aug 13;10(1):148-159 [FREE Full text] [doi: 10.15265/IY-2015-007] [Medline: 26123909]
5. Tsai R, Bell EJ, Woo H, Baldwin K, Pfeffer MA. How Patients Use a Patient Portal: An Institutional Case Study of Demographics and Usage Patterns. Appl Clin Inform 2019 Jan;10(1):96-102 [FREE Full text] [doi: 10.1055/s-0038-1677528] [Medline: 30727003]
6. Coughlin SS, Williams LB, Hatzigeorgiou C. A systematic review of studies of web portals for patients with diabetes mellitus. Mhealth 2017;3:23 [FREE Full text] [doi: 10.21037/mhealth.2017.05.05] [Medline: 28736732]
7. Kruse CS, Bolton K, Freriks G. The effect of patient portals on quality outcomes and its implications to meaningful use: a systematic review. J Med Internet Res 2015;17(2):e44 [FREE Full text] [doi: 10.2196/jmir.3171] [Medline: 25669240]
8. Zhong X, Liang M, Sanchez R, Yu M, Budd PR, Sprague JL, et al. On the effect of electronic patient portal on primary care utilization and appointment adherence. BMC Med Inform Decis Mak 2018 Dec 16;18(1):84 [FREE Full text] [doi: 10.1186/s12911-018-0669-8] [Medline: 30326876]
9. Jordan SR, Brungardt A, Phimphasone-Brady P, Lum HD. Patient Perspectives on Advance Care Planning via a Patient Portal. Am J Hosp Palliat Care 2019 Feb 25:1049909119832820. [doi: 10.1177/1049909119832820] [Medline: 30803245]
10. Sun R, Korytkowski MT, Sereika SM, Saul MI, Li D, Burke LE. Patient Portal Use in Diabetes Management: Literature Review. JMIR Diabetes 2018 Nov 06;3(4):e11199 [FREE Full text] [doi: 10.2196/11199] [Medline: 30401665]
11. Elers P, Nelson F. Improving healthcare through digital connection? Findings from a qualitative study about patient portals in New Zealand. Aust J Prim Health 2018 Nov;24(5):404-408. [doi: 10.1071/PY17116] [Medline: 30149829]
12. Mold F, de LS, Sheikh A, Majeed A, Wyatt JC, Quinn T, et al. Patients' online access to their electronic health records and linked online services: a systematic review in primary care. Br J Gen Pract 2015 Mar;65(632):e141-e151 [FREE Full text] [doi: 10.3399/bjgp15X683941] [Medline: 25733435]
13. Legler A, Price M, Parikh M, Nebeker JR, Ward MC, Wedemeyer L, et al. Effect on VA Patient Satisfaction of Provider's Use of an Integrated Viewer of Multiple Electronic Health Records. J Gen Intern Med 2019 Jan;34(1):132-136. [doi: 10.1007/s11606-018-4708-z] [Medline: 30338474]
14. Paglialonga A, Patel AA, Pinto E, Mugambi D, Keshavjee K. The healthcare system perspective in mHealth. In: Andreoni G, Perego P, Frumento E, editors. mHealth Current and Future Applications. Cham: Springer International Publishing; 2019:127-142.
15. McAlearney AS, Sieck CJ, Gaughan A, Fareed N, Volney J, Huerta TR. Patients' Perceptions of Portal Use Across Care Settings: Qualitative Study. J Med Internet Res 2019 Jun 06;21(6):e13126 [FREE Full text] [doi: 10.2196/13126] [Medline: 31172960]
16. Dalal AK, Dykes P, Samal L, McNally K, Mlaver E, Yoon CS, et al. Potential of an Electronic Health Record-Integrated Patient Portal for Improving Care Plan Concordance during Acute Care. Appl Clin Inform 2019 May;10(3):358-366. [doi: 10.1055/s-0039-1688831] [Medline: 31141830]
17. Casillas A, Perez-Aguilar G, Abhat A, Gutierrez G, Olmos-Ochoa TT, Mendez C, et al. Su salud a la mano (your health at hand): patient perceptions about a bilingual patient portal in the Los Angeles safety net. J Am Med Inform Assoc 2019 Dec 01;26(12):1525-1535. [doi: 10.1093/jamia/ocz115] [Medline: 31373362]

18. Reed ME, Huang J, Millman A, Graetz I, Hsu J, Brand R, et al. Portal Use Among Patients With Chronic Conditions: Patient-reported Care Experiences. Med Care 2019 Oct;57(10):809-814. [doi: 10.1097/MLR.0000000000001178] [Medline: 31415340]
19. Truong TM, Lipschultz E, Danahey K, Schierer E, Ratain MJ, O'Donnell PH. Assessment of Patient Knowledge and Perceptions of Pharmacogenomics Before and After Using a Mock Results Patient Web Portal. Clin Transl Sci 2019 Sep 06. [doi: 10.1111/cts.12681] [Medline: 31490020]
20. Hawkes JE, Mittal M, Davis M, Brixner D. Impact of Online Prescription Management Systems on Biologic Treatment Initiation. Adv Ther 2019 Aug;36(8):2021-2033 [FREE Full text] [doi: 10.1007/s12325-019-01000-w] [Medline: 31168763]
21. Fraccaro P, Vigo M, Balatsoukas P, Buchan IE, Peek N, van DVSN. Patient Portal Adoption Rates: A Systematic Literature Review and Meta-Analysis. Stud Health Technol Inform 2017;245:79-83. [Medline: 29295056]
22. Foster B, Krasowski MD. The Use of an Electronic Health Record Patient Portal to Access Diagnostic Test Results by Emergency Patients at an Academic Medical Center: Retrospective Study. J Med Internet Res 2019 Jun 28;21(6):e13791 [FREE Full text] [doi: 10.2196/13791] [Medline: 31254335]
23. Apter AJ, Bryant-Stephens T, Perez L, Morales KH, Howell JT, Mullen AN, et al. Patient Portal Usage and Outcomes Among Adult Patients with Uncontrolled Asthma. J Allergy Clin Immunol Pract 2020 Mar;8(3):965-970.e4. [doi: 10.1016/j.jaip.2019.09.034] [Medline: 31622684]
24. de LS, Ross P, Shifrin M, Hercigonja-Szekeres M, Seroussi B. A comparison of approaches to providing patients access to summary care records across old and new europe: an exploration of facilitators and barriers to implementation. Stud Health Technol Inform 2013;192:397-401. [Medline: 23920584]
25. Ammenwerth E, Schnell-Inderst P, Hoerbst A. The impact of electronic patient portals on patient care: a systematic review of controlled trials. J Med Internet Res 2012;14(6):e162 [FREE Full text] [doi: 10.2196/jmir.2238] [Medline: 23183044]
26. NHS England. About GP Online Services. 2019. URL: https://www.england.nhs.uk/gp-online-services/about-the-prog/ [accessed 2019-04-04] [WebCite Cache ID 77NjwBRUG]
27. Irizarry T, DeVito DA, Curran CR. Patient Portals and Patient Engagement: A State of the Science Review. J Med Internet Res 2015;17(6):e148 [FREE Full text] [doi: 10.2196/jmir.4255] [Medline: 26104044]
28. Turner K, Hong Y, Yadav S, Huo J, Mainous AG. Patient portal utilization: before and after stage 2 electronic health record meaningful use. J Am Med Inform Assoc 2019 Oct 01;26(10):960-967. [doi: 10.1093/jamia/ocz030] [Medline: 30947331]
29. Ammenwerth E, Lannig S, Hörbst A, Muller G, Schnell-Inderst P. Adult patient access to electronic health records. Cochrane Database Syst Rev 2017;2017(6):CD012707. [doi: 10.1002/14651858.CD012707]
30. Riippa I, Linna M, Rönkkö I, Kröger V. Use of an electronic patient portal among the chronically ill: an observational study. J Med Internet Res 2014 Dec 08;16(12):e275 [FREE Full text] [doi: 10.2196/jmir.3722] [Medline: 25488754]
31. Petrovskaya O, Lau F, Antonio M. Synthesizing and translating evidence on patient portals: a protocol for an umbrella review with stakeholder engagement. PROSPERO 2018 CRD42018096657. 2018. URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=96657 [accessed 2019-04-25]
32. Bulbul A, Parkinson A, Desborough J, Smith J. A systematic review of patient attitudes towards the use of patient portals for the management of type 1 diabetes, multiple sclerosis and lower limb arthroplasty. PROSPERO 2019 CRD42019120942. 2019. URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=120942 [accessed 2019-04-25]
33. Tapuria A, Porat T, Kalra D, D'souza G, Curcin V. The impact of promoting patient access to their electronic health care record: a systematic review. PROSPERO 2019 CRD42019117426. 2019. URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=117426 [accessed 2019-04-25]
34. Avdagovska M, Olson K, Gramlich L, Vohra S, Ballermann M, Paul P. The impact of personal health records portals on no-show appointments and emergency room visits: a realist review protocol. PROSPERO 2017 CRD42017065027. 2017. URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=65027 [accessed 2019-04-25]
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 Jul 21;6(7):e1000097 [FREE Full text] [doi: 10.1371/journal.pmed.1000097] [Medline: 19621072]
36. Centre for Reviews and Dissemination. CRD's Guidance for Undertaking Reviews in Health Care. England: Centre for Reviews and Dissemination, University of York; 2009. URL: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf [accessed 2020-07-05]
37. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928 [FREE Full text] [Medline: 22008217]
38. National Heart, Lung, and Blood Institute (NHLBI). Study Quality Assessment Tools. Bethesda, MD: US Department of Health & Human Services; 2018. URL: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [accessed 2020-07-05]
39. National Heart, Lung, and Blood Institute (NHLBI). Background: Development and Use of Study Quality Assessment Tools. Bethesda, MD: US Department of Health & Human Services; 2018. URL: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [accessed 2020-07-04]

40. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews: A Product from the ESRC Methods Programme. 2006 Jan 20. URL: https://www.lancaster.ac.uk/shm/research/nssr/research/dissemination/publications/NS_Synthesis_Guidance_v1.pdf [accessed 2020-07-05]
41. Ryan R, Cochrane Consumers Communication Review Group. Cochrane Consumers and Communication Review Group: Data Synthesis and Analysis. 2013 Jun 20. URL: https://www.lancaster.ac.uk/shm/research/nssr/research/dissemination/publications/NS_Synthesis_Guidance_v1.pdf [accessed 2020-07-05]
42. Song F, Hooper, Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? OAJCT 2013 Jul;2013:71-81. [doi: 10.2147/OAJCT.S34419]

Abbreviations

EHR: electronic health record
NHLBI: National Heart, Lung, and Blood Institute
NHS: National Health Service
PHR: personal health record
PICOS: participants, interventions, comparators, and outcomes
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Original Paper

A Remotely Delivered, Peer-Led Physical Activity Intervention for Younger Breast Cancer Survivors (Pink Body Spirit): Protocol for a Feasibility Study and Mixed Methods Process Evaluation

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Abstract

Background: Younger breast cancer survivors consistently report a greater impact of their cancer experience on quality of life compared with older survivors, including higher rates of body image disturbances, sexual dysfunction, and fatigue. One potential strategy to improve quality of life is through physical activity, but this has been understudied in younger breast cancer survivors, who often decrease their activity during and after cancer treatment.

Objective: The aim of this study is to explore the feasibility and acceptability of a technology-based, remotely delivered, peer-led physical activity intervention for younger breast cancer survivors. We will also assess the preliminary impact of the intervention on changes in physical activity and multiple aspects of quality of life.

Methods: This study is a community-academic partnership between University of California, San Diego and Haus of Volta, a nonprofit organization that promotes positive self-image in younger breast cancer survivors. This ongoing pilot study aims to recruit 30 younger breast cancer survivors across the United States (<55 years old, >6 months post primary cancer treatment, self-report <60 min of moderate-to-vigorous-intensity physical activity [MVPA]) into a 3-month peer-delivered, fully remote exercise program. Participants will complete 6 biweekly video chat sessions with a trained peer mentor, a fellow younger breast cancer survivor. Participants will receive a Fitbit Charge 3; weekly feedback on Fitbit data from their peer mentor; and access to a private, in-app Fitbit Community to provide and receive support from other participants and all peer mentors. At baseline, 3 months, and 6 months, participants will complete quality of life questionnaires, and MVPA will be measured using the ActiGraph accelerometer. Feasibility and acceptability will be explored through a mixed methods approach (ie, quantitative questionnaires and qualitative interviews). Intervention delivery and adaptations by peer mentors will be tracked through peer mentor self-evaluations and reflections, review of video-recorded mentoring sessions, and monthly templated reflections by the research team.

Results: Recruitment began in September 2019. As of February 2020, the physical activity intervention is ongoing. Final measures are expected to occur in summer 2020.

Conclusions: This study explores the potential for physical activity to improve sexual function, body image, and fatigue, key quality of life issues in younger breast cancer survivors. Using peer mentors extends our reach into the young survivor community. The detailed process evaluation of intervention delivery and adaptations by mentors could inform a future hybrid-effectiveness implementation trial. Finally, remote delivery with commercially available technology could promote broader dissemination.

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KEYWORDS

physical activity; cancer survivors; peer mentors; quality of life; pilot study; breast cancer; fitness trackers; mobile phone

Introduction

Background

Although women diagnosed with breast cancer at less than 50 years of age comprise fewer than 10% of all breast cancer survivors [1], they have lower survival rates than older survivors and experience unique health and psychosocial issues [2]. Younger age at diagnosis is a risk factor for more advanced disease, and younger women often undergo more aggressive treatment regimens [3]. Younger cancer survivors consistently report a higher impact of their cancer experience on quality of life compared with older survivors [4]. This is likely due to a combination of more aggressive treatments and being diagnosed at a time when they are in the midst of forming relationships, starting and raising families and/or caring for aging parents, and establishing a career and work-life balance [5-9]. Cancer-related physical and psychosocial changes can impact productivity at home and work, even after treatment concludes [10-12]. Key psychosocial concerns in this population include body image disturbances because of physical changes (eg, hair loss, weight gain, and surgical scars), sexual functioning, and fatigue [4,5,13-17]. To date, few evidence-based interventions have been identified for younger breast cancer survivors to improve these aspects of quality of life.

In older breast cancer survivors, physical activity reduces the risk of cancer recurrence and mortality [18-21]. Physical activity has also been shown to decrease fatigue and may ameliorate some of the most troubling problems of younger survivors, such as poor body image and sexual dysfunction [22-24]. Younger breast cancer survivors often reduce their activity levels during and after treatment [25] and are less likely to be active than similar-aged women without cancer [26]. Few physical activity interventions have been tested in younger cancer survivors [27-29], although younger survivors would be best served by interventions designed or adapted to target their specific needs. General barriers to exercise such as scheduling and lack of time may be particularly relevant for younger cancer survivors due to a combination of persistent side effects from aggressive treatment regimens and the many competing demands of this life stage [8]. In addition, given young survivors' higher rates of depressive symptoms and fatigue, they may be more likely than older survivors to experience psychological barriers to activity (eg, low motivation and emotional distress) [8]. Taken together, these factors make it difficult for younger cancer survivors to start and maintain an exercise routine.

Intervention modalities that do not require in-person attendance and can be accessed anytime and anywhere, such as remotely delivered, technology-based physical activity interventions using wearable trackers and mobile phones, may help younger breast cancer survivors overcome barriers to exercising. Commercially available wearable activity trackers and their companion mobile apps (such as the Fitbit and Fitbit app) can facilitate numerous theory-based techniques shown to be associated with increasing exercise in cancer survivors, including self-monitoring, goal setting, and performance feedback on several activity-related metrics, including the number of steps taken, minutes of moderate-to-vigorous-intensity physical activity (MVPA), and continuous heart rate tracking [30-38]. Several studies using wearable trackers have demonstrated their efficacy, particularly when combined with traditional counseling, for increasing physical activity in the general population [39] and in older breast cancer survivors [40,41]. However, these trackers have not been tested with younger cancer survivors.

Adding peer support features to technology-based exercise interventions may enhance their effectiveness [42] and may be appealing to younger cancer survivors [7,43,44]. A mixed methods study of breast cancer survivors' preferences for social support features within technology-supported, remotely delivered physical activity interventions revealed that survivors were highly interested in using technology-supported message boards to post questions, give and receive feedback, and share ideas with other survivors [42]. Similarly, survivors believed that sharing their exercise on a progress board or within a private community would help formalize goals, create a sense of accountability, and facilitate an understanding of their achievements relative to their peers [42]—behavioral theory–supported behavior change techniques [31]. Previous exercise intervention studies in young cancer survivors that have included online forums through study websites [27,29] or Facebook [28] have reported low engagement with the forums, perhaps due to lack of moderation [27] or moderation by a researcher [28,29]. Moderation of web- or app-based message boards by other younger cancer survivors could further enhance intervention effectiveness by increasing the likelihood that participants will engage with theory-based strategies designed to promote behavior change [42]. Further research is needed to determine feasible and acceptable strategies for increasing physical activity, and potential benefits for quality of life, among the understudied population of younger breast cancer survivors.

Community-Academic Partnership

This project is a community-academic partnership between University of California, San Diego (UC San Diego) and Haus of Volta, a nonprofit organization based in Murrieta, California, that works with younger breast cancer survivors to promote positive body image and positive outlook on life after cancer. Coauthor SN is the founder and Chief Executive Officer of Haus of Volta, and SN and SJH are coprincipal investigators (PIs) of this project. The overall goal of this community-academic

partnership is to develop an intervention that has the potential for dissemination and use by Haus of Volta. The project was developed using a community-based participatory research approach, which emphasizes the equal partnership and active involvement of community members and researchers in all aspects of the research process [45,46]. The initial research questions were developed based on SN's personal experience with breast cancer and her outreach in the young survivor community. The physical activity intervention being tested in this pilot study is based on a 3-month theory- and technology-based intervention that successfully increased MVPA in older breast cancer survivors, delivered by a research interventionist in an academic comprehensive cancer center setting [47]. SN served as a primary resource in the design of the pilot intervention. As part of the development of the grant proposal, 5 members of the Haus of Volta Community Advisory Board field-tested the pilot intervention components and worked with the UC San Diego research team to make modifications to meet the needs of young breast cancer survivors, thereby enhancing the cultural sensitivity and relevance of the intervention to this population. These modifications included 100% remote delivery and the addition of the Pink Body Spirit Fitbit Community and the intervention toolbox (see the *3-Month Physical Activity Intervention* section). SN and the Haus of Volta Community Advisory Board reviewed the quality of life questionnaires (see the *Measures* section) to confirm that the questions were worded in ways that would address the issues and concerns young breast cancer survivors face. Any modifications to methods over the course of the project will be documented and collectively decided upon by Haus of Volta and UC San Diego. Haus of Volta will contribute to the interpretation and dissemination of the mixed methods findings.

Study Objectives

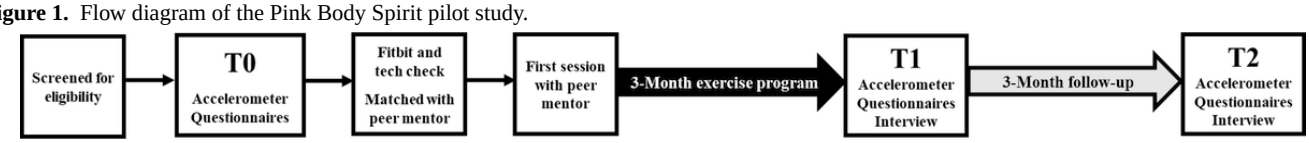
This study will conduct a single-arm, pre-post pilot trial of Pink Body Spirit, a 3-month remotely delivered, peer-led physical activity intervention, in 30 younger breast cancer survivors. This community-academic partnership project has 3 aims: (1) explore the feasibility and acceptability of the pilot study methods using a parallel mixed methods approach (postintervention quantitative surveys and qualitative interviews), (2) assess the preliminary impact of the intervention on physical activity and quality of life, and (3) use a multimethod approach to explore the process of intervention delivery and adaptations by peer mentors. The overall goal is to develop an intervention that can be disseminated and used by Haus of Volta. This protocol paper reports on the rationale, methodology, and outcome measures of this ongoing community-academic partnership project.

Methods

Study Design and Overview

Thirty younger breast cancer survivors (diagnosed when aged under 50 years and currently aged under 55 years, completed active treatment [ie, surgery, chemotherapy, and/or radiation], and self-reporting <60 min of MVPA per week) will be enrolled into a 3-month physical activity program, Pink Body Spirit. The Pink Body Spirit program is based on an intervention that was successful at increasing physical activity in older survivors delivered by a research interventionist in an academic comprehensive cancer center setting [40,47]. The Pink Body Spirit program will use peer mentors, motivational interviewing, and technology (Fitbit and Fitbit Community) to support behavior change. Five younger breast cancer survivors (diagnosed when aged under 50 years and currently aged under 55 years) have been trained as peer mentors to deliver the program to fellow younger survivors. To help address common barriers to exercise among young cancer survivors, the program is fully remote [8,48]. Participants will complete 6 video chat or phone sessions with their peer mentor biweekly and interact with their peer mentor and other participants through a private Fitbit Community at least weekly. To promote accountability, participants will be informed that their peer mentor will be able to see the physical activity data collected by the Fitbit. Between scheduled sessions, peer mentors will use real-time Fitbit data to identify participants in need of additional support to increase their exercise. At baseline (T0), 3 months (postintervention; T1), and 6 months (follow-up; T2), participants will complete quality of life questionnaires, and MVPA will be measured using the ActiGraph accelerometer. At T1 and T2, participants will also complete quantitative satisfaction questionnaires and qualitative interviews. Using a mixed methods approach (see *Mixed Methods Evaluation* section), findings from quantitative questionnaires and qualitative interviews will be triangulated to explore feasibility, acceptability, and satisfaction with the pilot study methods. Feasibility will be assessed through recruitment and retention metrics and adherence to intervention components (completion of intervention sessions, wearing the Fitbit, and posting in the Fitbit Community). A multimethod process evaluation will explore how the intervention was delivered and adaptations needed or made by peer mentors. Participants will be enrolled on a rolling basis, and intervention process data collected throughout the study will be used iteratively to provide feedback to peer mentors and adapt the program to meet the needs of the target population. The UC San Diego Institutional Review Board approved this study. Figure 1 shows the study flow diagram.

Figure 1. Flow diagram of the Pink Body Spirit pilot study.



Participants

Recruitment

Nationwide recruitment is being led by co-PI and younger breast cancer survivor SN. Recruitment will primarily occur through social media postings in groups tailored toward younger breast cancer survivors across the United States, including the Young Survival Coalition. Social media recruitment strategies have proven successful in recruiting young cancer survivors into research studies [49]. SN also gives presentations at many community events throughout Southern California and will use these community connections to support recruitment. Breast cancer oncologists and patient navigators at UC San Diego Moores Cancer Center have been asked to provide information to any patients who appear to meet the study criteria.

Eligible women must meet the following inclusion criteria: (1) breast cancer survivor diagnosed when aged between 18 and 49 years and currently aged between 18 and 54 years; (2) completed active treatment (specifically surgery, chemotherapy, and/or radiotherapy) at least six months before enrollment; (3) sedentary, defined as self-reporting less than 60 min of MVPA each week; (4) accessible by phone or video chat; and (5) have a Fitbit-compatible cellphone, tablet, or laptop with internet. Exclusion criteria include the following: (1) self-reported medical condition that could make it potentially unsafe to be in an unsupervised physical activity intervention as determined by the Physical Activity Readiness Questionnaire or self-reported peripheral neuropathy that interferes with ambulation, (2) currently pregnant, (3) inability to commit to a 3-month intervention schedule, or (4) prisoner.

Phone Screening

Women will be directed from the recruitment methods to call or email the study office to be phone screened for eligibility. Screener questions will include date of diagnosis, date when treatment was completed, self-reported activity, willingness to comply with study procedures, and access to and comfort with technology. The Physical Activity Readiness Questionnaire (PAR-Q) will be used to assess the risk of complications resulting from physical activity, including potential heart, joint, or bone problems [50]. Women who endorse any of the PAR-Q items will not be eligible for the trial. We will also ask about self-reported neuropathy and lymphedema that could make it difficult for a participant to exercise safely on their own. If eligibility is unclear after phone screening, the study physician (coauthor HIS) will review the data to determine if study enrollment is appropriate.

Informed Consent

Interested and eligible women will be provided additional information about the study and have any questions answered by the research staff. Potential participants will then be emailed a link to a web-based consent form through REDCap, a secure research database hosted on UC San Diego servers.

Pink Body Spirit Peer Mentors

The Pink Body Spirit peer mentors are women who were diagnosed with breast cancer when they were less than 50 years old and have completed all active treatments for breast cancer (ie, surgery, chemotherapy, and/or radiation). The peer mentors were selected by co-PI SN and are being paid for their time by the grant funding this project. Peer mentors were trained by LSW and SJH in fall 2018 and spring 2019. All trainings were recorded for future use. Trainings included the following: Research Ethics, Privacy, and Data Safety; Exercising Safely and Adverse Events; Intervention Protocol and Delivery; and Motivational Interviewing (details provided below).

Research Ethics, Privacy, and Data Safety

All peer mentors completed the mandatory UC San Diego Collaborative Institutional Training Initiative (CITI) and Health Insurance Portability And Accountability (HIPAA) web-based trainings. An additional web-based Zoom training led by LSW applied key components covered in the CITI and HIPAA trainings to issues that are specifically relevant to this study.

Exercising Safely and Adverse Events

This web-based Zoom training led by LSW and SJH focused on exercising safely after breast cancer. Mock scenarios specifically relevant to this project were reviewed as a group to ensure that the mentors had gained the necessary knowledge of American College of Sports Medicine recommendations for cancer survivors [51] and how to help participants set safe and appropriate exercise goals. They were also trained on the study protocol to respond to and report adverse events. During biweekly mentoring sessions, peer mentors will ask participants if there have been any adverse events. Peer mentors were trained to encourage participants to seek medical attention and stop physical activity if necessary.

Intervention Protocol and Delivery

LSW worked with a peer mentor to create training videos of mock video chat mentoring sessions. The videos were distributed to all peer mentors along with a detailed script for the first mentoring session and the follow-up sessions. Peer mentors practiced the mentoring sessions with each other and individuals unfamiliar with the study. Before gaining approval to mentor study participants, peer mentors completed 2 mock sessions with LSW over Zoom video chat to demonstrate proficiency of the protocol content, logistics, and safety information. The approval process also included the verification of proper tracking of the mock sessions in the REDCap database.

Motivational Interviewing

Peer mentors were trained in motivational interviewing techniques for communicating with others, effective in supporting behavior change [52]. Motivational interviewing is a collaborative, goal-oriented method of communication with particular attention to the language of change. It is designed to strengthen an individual's motivation for and movement toward a specific goal by eliciting and exploring the person's own arguments for change. Peer mentors completed a standardized, publicly available, introductory course on motivational interviewing (10 hours [53]). The web-based training course, which could be completed anytime and anywhere, introduced peer mentors to the general principles of motivational interviewing (express empathy, develop discrepancy, roll with resistance, and support self-efficacy) and provided an overview of critical skills (open-ended questions, affirmations, reflective

listening, and summaries). Following the web-based introductory training, peer mentors completed a study-specific in-person course on motivational interviewing led by co-PI and clinical psychologist SJH (4 hours). The in-person training focused on using motivational interviewing skills specifically to increase physical activity within the study protocol. During this training, peer mentors practiced mock visits with each other, and SJH and LSW provided real-time feedback on their use of motivational interviewing skills. Of note, the study team and 3 peer mentors based in Southern California elected to conduct this training in person, but 2 peer mentors were trained entirely remotely. The in-person training was recorded, and peer mentors who were trained remotely practiced mock visits with each other and LSW over Zoom video chat in preparation for final approval by LSW.

3-Month Physical Activity Intervention (Pink Body Spirit)

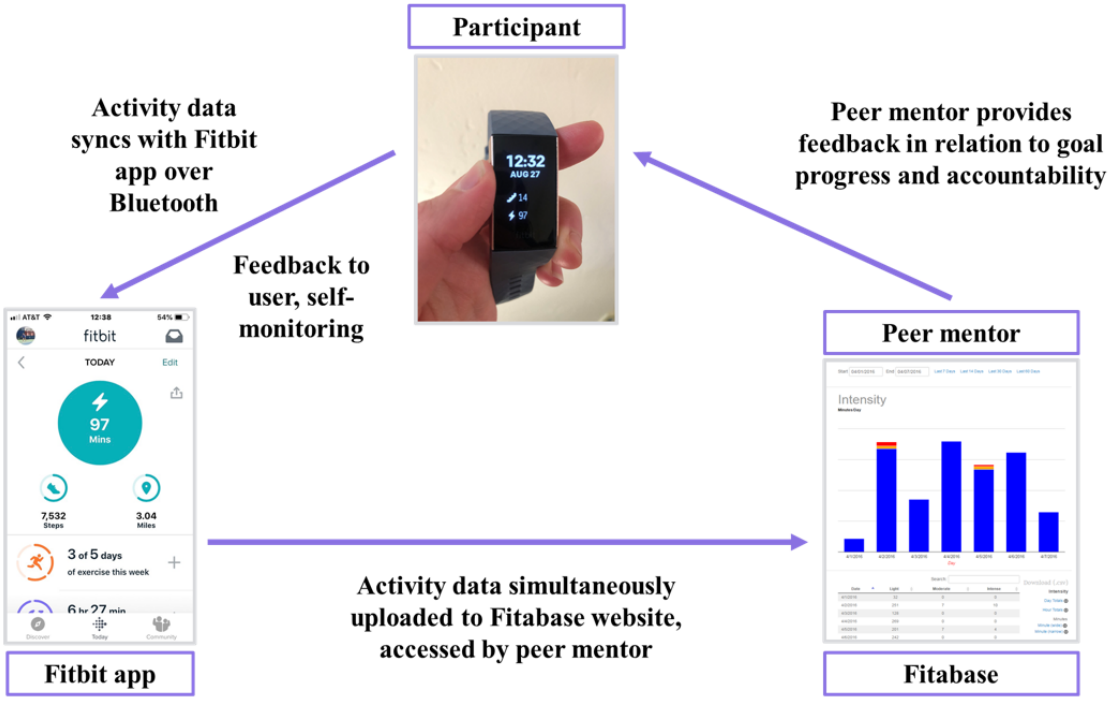
Technology Support Session and Peer Mentor Matching

The Pink Body Spirit intervention will begin after participants have completed the T0 measures. Participants will be mailed a Fitbit Charge 3 and will be matched with a peer mentor based on mutual schedule availability. Participants will then complete a brief technology support session via Zoom video conferencing with research staff. During this 15-min session, research staff will help participants set up their Fitbit and test the Zoom video conferencing in preparation for the peer mentoring sessions. Proactive technical support from research staff will allow peer mentors to focus on goal setting and behavior change strategies.

Peer Mentoring Sessions

Participants will meet with their peer mentor 6 times over the course of the 3-month intervention. After completing the technology support session, participants will have an initial 45-min phone or video meeting (based on preference and capability) with their peer mentor. Initial meeting topics will include the following: (1) self-monitoring with the Fitbit; (2) in-app, private Fitbit Community; (3) goal setting; and (4) scheduling 5 biweekly follow-up sessions. The Pink Body Spirit intervention is guided by Control Theory [54] and Social Cognitive Theory [55]. Participants will learn how to self-monitor their physical activity using the Fitbit (see Fitbit details mentioned later; Figure 2). To promote self-efficacy, women will be encouraged to set specific, step-wise goals [39,47]. To increase self-efficacy and promote intention formation, peer mentors will use motivational interviewing techniques during the mentoring sessions. Participants will set a starting goal and a specific action plan to meet that goal. Goal setting will focus on safe and gradual increases in activity over time to meet the American College of Sports Medicine's [51] and the American Cancer Society's [56] guidelines for cancer survivors of engaging in at least 150 min of MVPA per week. To increase behavioral capability, peer mentors will teach participants how to use the Fitbit to monitor heart rate to determine moderate intensity and how to customize the display of their Fitbit app such that active minutes are displayed as the primary activity goal. A total of 5 follow-up video or phone sessions (approximately 20 min) will be scheduled biweekly over the 3-month program to check on progress, revise goals, and provide support. To promote accountability, participants will be informed that their peer mentor will be able to see the activity data collected by the Fitbit. Fitbit data will support performance feedback and goal review during biweekly follow-up sessions. To promote social support, improve rapport, and enhance continuity, participants will remain with their same peer mentor for the entire 3-month program.

Figure 2. Visual depiction of how Fitbits will be used to support increasing physical activity in the Pink Body Spirit pilot study.



Peer mentors will meet with LSW and SJH biweekly (1 hour) over Zoom video conferencing to gain support in delivering the intervention through discussion of how intervention sessions are going, problem solving for difficult participants, and practicing of skills. The use of the REDCap database, the Fitbit Community, safety, and adverse events will also be discussed. All intervention sessions will be video recorded. A random 50% of initial goal-setting sessions and a random 20% sample of follow-up sessions will be reviewed by the research staff. Review of the session recordings will serve a dual purpose: (1) to examine the use of motivational interviewing techniques and the safety of session content, which will be used to support peer mentors during biweekly supervision meetings, and (2) to examine adaptations from the study protocol. LSW will provide feedback to mentors based on the review of session recordings and information from participant qualitative interviews that are analyzed throughout the intervention using a rapid approach.

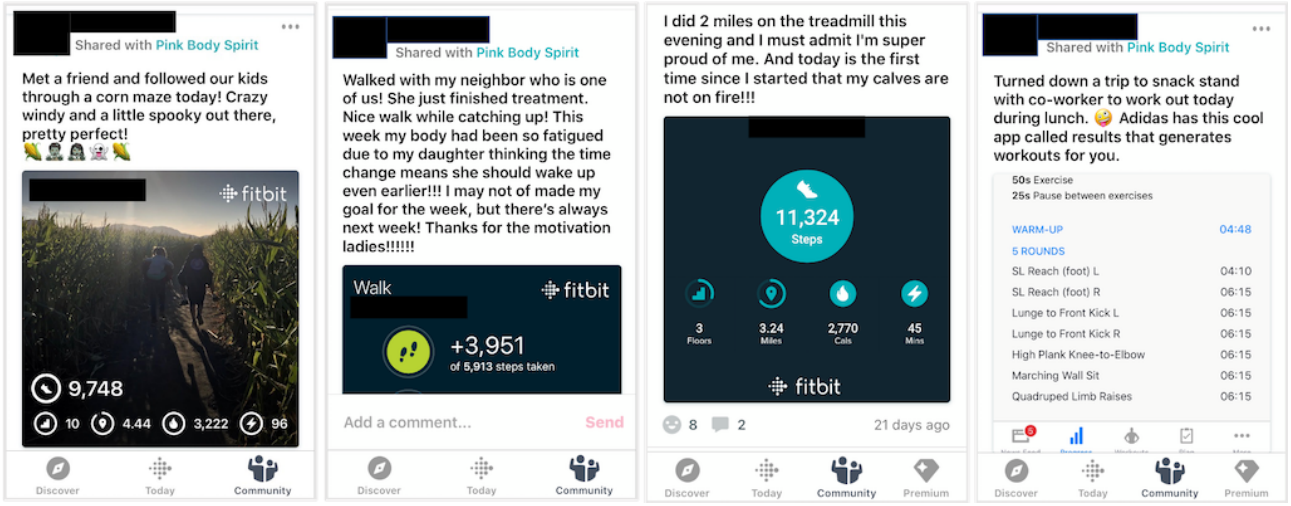
Fitbit and Associated Apps

Participants will receive a Fitbit Charge 3 (Fitbit, Inc.), an accelerometer-based activity monitor that provides real-time feedback on several activity-related metrics, including the number of steps taken, minutes of MVPA, and continuous heart rate tracking. The Fitbit was selected owing to its relatively low cost and ubiquity in the consumer wearables marketplace and in research studies. It is water resistant up to 50 m, has a battery life of approximately 1 week, and has 15 exercise modes to set goals and track statistics for activities as varied as swimming, yoga, and strength training. The Fitbit wirelessly uploads to the Fitbit website and smartphone app (Android, Apple, or Windows) that provide graphical visualizations of daily activity patterns. Participants will be instructed to wear their Fitbit daily and sync the tracker with the mobile app at least once per week so that their peer mentor can view their data in Fitabase (Small Steps Lab). Fitabase is a password-protected, web-based database program that collects physical activity and heart rate data from the Fitbit cloud. Through Fitabase, peer mentors can see graphs of daily light, moderate, and vigorous activity; date of last Fitbit sync; and Fitbit battery level for each of their mentees. Peer mentors will use the Fitbit data to support their scheduled follow-up sessions by identifying days with low activity where activity could be added and days with high activity to reinforce what is working well. Peer mentors will also be asked to check each of their participants' Fitbit data through the Fitabase website at least weekly. Peer mentors will be trained to use Fitabase to identify general trends in activity and provide feedback to participants through email, text, or private Fitbit messages between biweekly mentoring sessions. Peer mentors will be provided with sample messages and encouraged to reach out to participants when (1) they decrease activity or do not meet their weekly goal, (2) they exceed their weekly goal, or (3) they have not worn or synced their Fitbit. This method of proactively reaching out to participants between scheduled sessions was highly successful and extremely liked in our previous study. Figure 2 illustrates how Fitbits will be used in the Pink Body Spirit intervention.

Fitbit Community

Participants will join a private Community group within the Fitbit mobile app where they can communicate with each other, see the activity Leaderboard (ie, activity levels of other participants), and gain support from all peer mentors. The Fitbit Community targets several theoretical constructs including social support; rewards and recognition (by other participants and mentors); and opportunities, barriers, and problem solving (through collective sharing of challenges, solutions, and resources). During the initial mentoring session, peer mentors will demonstrate how to access and post in the Fitbit Community. Step-by-step instructions for accessing and posting in the Fitbit Community will also be included with the Fitbit when mailed to participants. Participants will be asked to read and post in the in-app, private Fitbit Community at least once a week. To overcome the limitations of past studies in young cancer survivors that observed low engagement with online forums, the Fitbit Community will be moderated by peer mentors. Peer mentors will provide support to all participants through the Fitbit Community by checking it at least once a week and responding or posting as appropriate. Peer mentors will also reinforce participation in the Fitbit Community during biweekly mentoring sessions. Figure 3 shows example Fitbit Community posts.

Figure 3. Sample posts from the private, in-app Pink Body Spirit Fitbit Community (note: app screenshots have been redacted to maintain confidentiality).



Toolbox

Peer mentors will be encouraged to individualize the intervention through the use of a *toolbox* of exercise-related strategies and materials to help participants overcome barriers and achieve their unique exercise goals. Peer mentors will be able to spend up to US $40 on each participant to provide them with toolbox items such as fitness apps (free or paid), exercise materials for home-based workouts (eg, resistance bands, stability ball, or jump rope), and information about free workouts or exercise groups. Peer mentors can offer toolbox resources any time after the first session, and they must be linked with the participant's individual exercise goal and action plan. Development of the toolbox was guided by the Haus of Volta Community Advisory Board's field testing. The flexible, individualized toolbox approach has been a key component of numerous successful lifestyle interventions [57,58].

Postintervention Follow-Up Period (Months 4 to 6)

The postintervention follow-up period in months 4 to 6 will focus on exploring the extent to which participants continue to engage with their mentors and different aspects of the Pink Body Spirit program beyond the initial 3-month intervention. There will be no scheduled contacts or video chat sessions with peer mentors during the follow-up period, but participants will still be encouraged to continue wearing and syncing their Fitbit to track their activity and participate in the Pink Body Spirit Fitbit Community. Peer mentors will be advised that they are not expected to check activity data on Fitabase once a mentee has entered the follow-up period. Although there are no planned sessions, some contacts may still occur. If a peer mentor chooses to communicate with a mentee during the follow-up period, it will be tracked in the REDCap database (date of support, mode [eg, email, Fitbit message, text, call, or Zoom video chat], and general reason for support).

Measurement

Baseline Assessment (T0)

Participants will be emailed a link to a battery of web-based questionnaires consisting of quality of life measures, theoretical constructs for physical activity change, and self-reported muscle strengthening, stretching, and flexibility exercises. Participants will self-report demographics, general medical history, menstrual and reproductive history, and cancer history. Self-reported general medical history will include all current conditions and medications prescribed by a health care provider and dietary and nutritional supplements. Self-reported menstrual and reproductive history will include any history of hysterectomy and/or oopherectomy, age at first menstrual period, last menstrual period, and/or reason(s) period has stopped. Self-reported cancer history will include date of diagnosis, stage at diagnosis, type of surgery, date of surgery, cancer treatments (radiation, chemotherapy, and/or hormonal therapy, history and current), infusions for human epidermal growth factor receptor 2-positive breast cancer (eg, Herceptin, history and current), and lymphedema (history and current).

Once the questionnaires have been completed, participants will be mailed an ActiGraph GT3X+ accelerometer, a device that objectively measures activity, and instructed to wear it on the hip for the next 7 days during waking hours (for at least 12 hours per day). Two compliance reminders will be placed over the 7-day wear period. Once the ActiGraph has been worn for 7 days for at least 12 hours per day, participants will return it to the study office using a prepaid envelope. Upon receipt, ActiGraph data will be screened for sufficient wear time. If participants have not worn the device for at least 10 hours over 5 days or 50 hours over 4 days, they will be mailed another device and asked to rewear it. Participants will receive US $20 for completing the T0 measures. All T0 measures will be completed, and sufficient wear time will be verified before being matched with a peer mentor to begin the exercise program.

Postintervention Assessment (T1)

Three months after completing the first intervention session with their peer mentor, participants will repeat the web-based questionnaires completed at T0 and complete a 3-month quantitative satisfaction questionnaire. They will again be mailed an ActiGraph and asked to wear it for 7 days. The same wear and mail-back instructions and compliance protocol described above will be used. After returning the ActiGraph, participants will complete a 3-month qualitative interview. Participants will receive US $20 for completing the ActiGraph and questionnaire and US $10 for the individual interview.

Follow-Up Assessment (T2)

Six months after completing the first intervention session with their peer mentor, participants will repeat the web-based questionnaires completed at T0 and complete a 6-month quantitative satisfaction questionnaire. They will again be mailed an ActiGraph and asked to wear it for 7 days. The same wear and mail-back instructions and compliance protocol described above will be used. After returning the ActiGraph, participants will complete a 6-month qualitative interview. Participants will receive US $20 for completing the ActiGraph and questionnaire and US $10 for the individual interview.

Measures and Outcomes

Feasibility and Acceptability

Recruitment and Retention

We will report recruitment and retention using a Consolidated Standards of Reporting Trials diagram. We will track those who contact the study office via phone or email. Specifically, we will track the number of women who contact the study office, referral source for each (eg, social media, community event, UC San Diego patient navigator), number of women phone screened, number of eligible participants, and number of participants enrolled in the study. We will compare the yield from different recruitment approaches and assess if any eligibility criteria have excluded a disproportionate number of otherwise eligible women.

Adherence

Adherence to the intervention will utilize several metrics: completion of intervention sessions, wearing the Fitbit, and posting in the Fitbit Community. Adherent will be defined as completing 2 out of 3 of the following activities: completing >75% of the sessions, wearing the Fitbit on >75% of the days,

or posting in the Fitbit Community at least once per week for >75% of the weeks.

Mixed Methods Evaluation

A parallel mixed methods approach will be used to explore the feasibility, acceptability, and satisfaction of the Pink Body Spirit intervention from the participants' perspectives. Quantitative satisfaction questionnaires will be used to gain breadth of understanding, and qualitative interviews will add depth of understanding [59].

Quantitative Satisfaction Questionnaire (Postintervention and Follow-Up)

Questionnaires will build off questions used to evaluate the previous intervention in older breast cancer survivors upon which the Pink Body Spirit program is based [41]. Topics will include overall ratings of the program, the extent to which the program provided motivation to start and continue exercising, and the likelihood of recommending the program to other younger survivors. A series of items using Likert-scale response options will assess self-reported frequency of use, satisfaction with, and helpfulness of each intervention component. Participants will be asked to rate different features of the Fitbit tracker, the Fitbit app, and the Fitbit Community. There will be a *did not use* option for each feature assessed. Participants will also be asked to rate their satisfaction with the number, length, and content of peer mentoring sessions as well as the Zoom video conferencing format. Open-ended questions will ask participants to describe their favorite and least favorite aspects of the program and provide suggestions for how to improve Pink Body Spirit. Additional topics for the T2 questionnaire will include continued use of intervention components, including the Fitbit, Fitbit Community, and toolbox items, after the 3-month intervention has formally concluded; the extent to which participants continue to communicate with peer mentors; and participants' interest in being trained to serve as a peer mentor in a future study or program. To assess general attitudes toward Pink Body Spirit, we will use items from 2 validated, Likert-type measures of feasibility and acceptability [60]. Questionnaires will be piloted internally with the research and peer mentor teams before use.

Qualitative Interviews

At T1 and T2, individual, semistructured interviews will be conducted via Zoom video conferencing. Each interview will last approximately 45 min. Interviews will be video recorded and uploaded to the UC San Diego server. Interviews will explore topics such as overall perceptions of the intervention and specific components (eg, peer mentors and Fitbit), barriers and facilitators to behavior change, perceived health benefits (particularly in the targeted domains of body image, sexual functioning, and fatigue), the remote delivery format, and ways to improve the Pink Body Spirit program for other young breast cancer survivors. Semistructured interviews are proposed to keep the interview prioritized and targeted, but also allow for the flexibility to use additional probes to clarify responses and add depth to participants' answers. Interview questions will be asked in a flexible order, and wording may be adapted to maximize each participant's understanding. The interview guide will be piloted internally with the research team and with younger breast cancer survivors not involved in the study before administration. For consistency, LSW will conduct all interviews with the participants.

Physical Activity

ActiGraph GT3X+

The ActiGraph GT3X+ (ActiGraph, LLC) will be used to measure changes in minutes of MVPA from T0 to T1 and T1 to T2. This is the gold standard measure of free-living physical activity that provides blinded data collection. For 7 days around each measurement time point, participants will wear the ActiGraph GT3X+, a research grade, hip-worn accelerometer that measures movement and intensity of activity and that has been validated against heart rate telemetry and total energy expenditure. Physical activity data are not shown to the wearer. The GT3X+ provides second-by-second estimates of activity that can be categorized into minutes spent in sedentary, light, moderate, and vigorous activity using calibration thresholds. Sufficient wear time will be defined as 5 days with ≥600 min of wear time or 3000 min (50 hours) across 4 days. Time spent in sedentary behavior and light, moderate, and vigorous activity will be derived using Freedson cut-points [61].

Fitbit Charge 3

Data from the Fitbit Charge 3 will be used to calculate daily adherence to wearing the Fitbit throughout the intervention and to support peer mentoring. Participants will be asked to wear the Fitbit for as many hours per day as possible. Fitbit data will be wirelessly uploaded to the user's personal Fitbit account and downloaded by our research team through Fitabase (Small Steps Labs), a web-based database program that collects physical activity and heart rate from the Fitbit cloud. Fitabase allows each participant's Fitbit data to be batch downloaded at the 1-min level. Fitbit uses a proprietary algorithm to classify each minute as sedentary, light, moderate, or vigorous activity. Nonwear time will be determined based on the lack of heart rate or activity (steps or intensity) at any given minute [62]. Daily adherence to wearing the Fitbit will be defined as >5 min of wear [62]. A 5 min threshold for a valid Fitbit wear day will be used to avoid recording days where the Fitbit had simply been picked up and moved from one place to another, while simultaneously avoiding excluding days where the participant had purposefully worn the Fitbit. Fitbit data will not be used to measure changes in physical activity as participants cannot be blinded to the data collected.

Quality of Life

Body Image

Body image will be measured using the Body Image Scale (BIS), a 10-item scale developed for cancer survivors that measures perceptions of body disturbance related to cancer and its treatment [63]. Each item is rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). Higher scores indicate poorer body image. The BIS has shown high reliability (Cronbach α=.93), good clinical validity, and sensitivity to changes in psychosocial and physical activity interventions in older breast cancer survivors [63,64].

Sexual Function

Sexual function will be assessed using the Female Sexual Function Index (FSFI). The FSFI comprises 19 items assessing 6 domains of sexual functioning over the past 4 weeks: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items) [65]. The FSFI has been shown to be highly acceptable to breast cancer survivors and has good internal consistency (Cronbach α=.83-.96); test-retest reliability (r=0.74-0.86); and convergent, divergent, and discriminant validity [66]. The FSFI has been responsive to change in exercise intervention trials [67,68].

Fatigue

Fatigue will be assessed through the Patient-Reported Outcomes Measurement Information System Cancer Fatigue v1.0 measure [69]. The computer adaptive testing form will be used; participants will only complete 4-10 items out of the entire question bank. Higher scores indicate higher levels of fatigue. This instrument has shown responsiveness to change over time in prospective [69,70] and intervention [71] studies in cancer survivors.

Process Evaluation of Peer Mentor Adaptations and Delivery

A multimethod approach will be used to explore the process of intervention delivery and adaptations made by peer mentors. These data will help us describe and understand barriers and facilitators to delivery, identify delivery strategies for use in a future study, and refine how to use delivery methods being tested in this study to maximize the potential for success in future studies. Data collection will occur during and after intervention delivery, and data from all sources will be used iteratively to improve intervention delivery by peer mentors. The data sources for this evaluation will include the following:

1. Peer mentor session feedback: After each mentoring session, peer mentors will electronically record their confidence and preparedness for delivering the session in REDCap. Questions were developed in partnership with a peer mentor and have been pilot tested and refined with the other peer mentors during mock training sessions. Questions will ask about the extent to which peer mentors used motivational interviewing skills during their session; the helpfulness of the motivational interviewing training in preparing them for the session; their confidence during the session; and general notes and reflections about the session, including any explicit adaptations made.
2. Zoom peer mentoring sessions will be recorded by peer mentors and uploaded to the UC San Diego server. As described above, a random 50% of initial goal-setting sessions and a random 20% sample of the follow-up sessions will be reviewed by LSW to support peer mentor supervision and safety and appropriateness of exercise goals set. A template will be used to guide the exploration of adaptations from the protocol, barriers and facilitators to intervention delivery, and other aspects of the intervention process.
3. LSW will write monthly reflections to document adaptations and process outcomes. Templated reflections will be based on discussions and interactions with multiple stakeholders (peer mentors, research team, and any informal feedback from participants). The reflections will help document key activities, events, and changes occurring over the course of the study.

Statistical Analysis

Feasibility and Acceptability

We will explore how adherence varies between the 3 measures (completion of intervention sessions, wearing the Fitbit, and posting in the Fitbit Community) using descriptive statistics.

Postintervention and Follow-Up Quantitative Satisfaction Questionnaires

Descriptive statistics will be used to analyze the questionnaire responses. Responses will be reported as percentages or as mean (SD) as applicable. Open-ended responses will be coded using a standardized process. All open-ended questions and responses will be reviewed by 2 team members. Each response will be assigned at least one code, and codes will be nested into categories. Multiple coders and team consensus will be used to enhance the validity of the coding process and ensure that responses are accurately sorted into representative codes and categories.

Postintervention and Follow-Up Qualitative Interviews

Individual interviews will be video recorded and transcribed. A rapid assessment approach will be used to analyze qualitative interviews. The rapid assessment process is defined as "intensive, team-based, qualitative inquiry using triangulation, iterative data analysis, and additional data collection to quickly develop a *preliminary understanding* of a situation from the insider's perspective" [72]. This method will allow us to feed data from participants back into the ongoing study to improve it. Data that could be fed back may include ways in which peer mentors could be more effective, tools that could be added to the toolbox, and barriers and facilitators that can be feasibly addressed to improve the intervention for other participants. In addition, the project timeline is relatively condensed, so a rapid approach, whereby qualitative analyses are conducted over the course of the intervention, may be more feasible than conducting all qualitative analyses after data collection has ended. Although traditional, in-depth qualitative analyses may be more constructivist, exploratory, and inductive, rapid analysis takes a more positivist approach that is explanatory and deductively oriented [73]. Coding will occur on a monthly basis. A team-based approach will be used to maximize the dependability and validity of the analyses and preliminary findings. As this is a minimally interpretive approach, individuals with limited qualitative training can participate [73]. The project will employ the five rapid analysis steps outlined by Dr Alison Hamilton [73].

Mixed Methods Interpretation

The quantitative surveys and qualitative interviews will be analyzed, and results will be reported separately. We will triangulate the quantitative and qualitative results to explore feasibility, acceptability, and satisfaction with the pilot study methods. The 2 sets of results (QUAN + QUAL) will be

synthesized in the interpretation. The co-PI SN and Haus of Volta will contribute to interpretation.

Preliminary Intervention Impacts on Physical Activity and Quality of Life

Descriptive statistics (mean [SD] and n [%] where applicable) will be calculated for each variable of interest at T0, T1, and T2. Separate paired *t* tests will assess changes in each variable of interest from T0 to T1 and T1 to T2. The level of significance will be set at α=.05. From the means and SDs, Cohen *d* will be calculated to determine the effect size. These data will allow us to estimate the sample size needed to detect clinically significant intervention effects at an α of .05 and power of 0.80, should the program be tested in a larger efficacy trial.

Multimethod Process Evaluation of Intervention Delivery and Peer Mentor Adaptations

All findings will be triangulated to deepen our exploration of the intervention delivery process and adaptations made by peer mentors throughout the study. Peer mentor field notes will be downloaded from REDCap and reviewed by LSW. She will record memos throughout her review and will prepare a separate summary of the field notes for each of the 5 peer mentors. At the end of the study, the 5 summaries will be synthesized in a single narrative summary. LSW will follow up with peer mentors directly if any of the field notes require further clarification. Video recordings of sessions will be reviewed using a template checklist of predetermined variables. Data from each category of the template (eg, adaptations, barriers to intervention delivery, and facilitators to intervention delivery) will be transferred to a matrix. At the end of the study, LSW will develop a narrative summary for each category. Templated reflections will also be synthesized in a narrative summary at the end of the project.

Results

Recruitment began in September 2019. As of February 2020, the physical activity intervention is ongoing. Final measures are expected to occur in summer 2020, with mixed methods data analysis and results available in winter 2021.

Discussion

Overview

This project leverages the complementary community-academic research expertise of Haus of Volta and UC San Diego to develop and deliver a novel intervention. Using a community-based participatory research approach, the UC San Diego research team worked closely with SN and Haus of Volta to adapt an evidence-based physical activity program to meet the needs of younger breast cancer survivors. This study will uniquely assess the potential for physical activity to improve body image and sexual function, key issues for younger breast cancer survivors that contribute to poor quality of life. Remote delivery using commercially available technology increases the potential for sustainability and dissemination.

Limitations

Study limitations will be addressed whenever possible. One potential limitation is peer mentor drop out or turn over. Peer mentor selection, hiring, and caseloads will be determined by SN. If a peer mentor needs to discontinue mentoring before the end of the study, we will attempt to learn about their experience serving as a peer mentor. Valuable information will still be gained about the feasibility and acceptability of the program. Moreover, the small sample size may limit the generalizability of the findings, and the small group of younger women who choose to participate in this trial may not be representative of all younger breast cancer survivors. However, we will make the best use of our small study sample by using multiple qualitative and quantitative methods to take an in-depth look at the feasibility and acceptability of the Pink Body Spirit intervention and adaptations made by mentors in delivering the program. Exploring feasibility and acceptability using a mixed methods approach will help examine different facets of the intervention experience and provide a more complete picture of participants' perspectives. In addition, using mixed methods will provide greater assurance about the validity of the research questions and the amount of data collected to answer these questions.

Future Directions

There are several potential future directions after the completion of this pilot trial. If the intervention shows preliminary benefit for physical activity and/or quality of life, the investigators may choose to test the program in an adequately powered efficacy trial based on effect sizes from this pilot study. Alternatively, the detailed process evaluation of program delivery and adaptations made by the peer mentors could inform a future hybrid-effectiveness implementation trial. A hybrid trial would facilitate a formal evaluation of the implementation process. Another possible outcome is that Haus of Volta will bring the Pink Body Spirit program directly into the community. Through this project, we aim to increase the skills of younger breast cancer survivors so that they can better support each other in making healthy lifestyle choices and improving well-being, in line with Haus of Volta's mission to promote positive self-image and health in younger breast cancer survivors. We elected to use a publicly available web-based training program for the majority of the motivational interviewing skills training and recorded the in-person training to support fully remote training of 2 peer mentors. The length of the training was not a barrier to engaging peer mentors and supported the development of introductory-level skills. Furthermore, all study-specific web-based Zoom trainings (eg, research ethics, exercising safely after breast cancer, and supporting safe exercise goal setting) were recorded for future use. The extensive peer mentor trainings have provided leadership skills to the peer mentors not only to deliver the intervention as part of this research study but also to continue serving as advisers to younger breast cancer survivors in various capacities after the study ends. Engaging Haus of Volta in interpretation of the results will enhance self-efficacy for conducting research and understanding and disseminating results. Part of the goal of reviewing and interpreting the results as a community-research partnership is to develop ways to empower and support the younger breast cancer survivor community to continue the physical activity

program and peer mentoring in an ongoing manner. Haus of Volta could use pilot findings to apply for more funding to sustain the program. Pilot study results will be summarized in lay language for use by Haus of Volta and partnering organizations and for dissemination in survivor-centered settings, further increasing the impact and outreach in the younger breast cancer survivor community.

Conclusions

The proposed study represents a novel contribution to the literature by providing rich information on ways to promote increasing physical activity and potential benefits to quality of life for younger breast cancer survivors. This project benefits from the combined knowledge of the community regarding the challenges faced by young breast cancer survivors and the research team's expertise in conducting physical activity interventions and mixed methods evaluations. As smartphone ownership is reported by the majority of Americans and is increasing across all race/ethnicity, income, and age groups [74], this technology-supported, peer-delivered intervention has the potential for broad reach in geographically diverse, younger breast cancer survivors.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
California Breast Cancer Research Program grant review.
[PDF File (Adobe PDF File), 177 KB - resprot_v9i7e18420_app1.pdf]

References

1. Miller K, Nogueira L, Mariotto A, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019 Sep;69(5):363-385 [FREE Full text] [doi: 10.3322/caac.21565] [Medline: 31184787]
2. Ademuyiwa F, Cyr A, Ivanovich J, Thomas M. Managing breast cancer in younger women: challenges and solutions. Breast Cancer (Dove Med Press) 2016;8:1-12 [FREE Full text] [doi: 10.2147/BCTT.S68848] [Medline: 26730210]
3. Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Adolescents and young adults with breast cancer have more aggressive disease and treatment than patients in their forties. Ann Surg Oncol 2019 Nov;26(12):3920-3930. [doi: 10.1245/s10434-019-07653-9] [Medline: 31376035]
4. van Leeuwen M, Husson O, Alberti P, Arraras JI, Chinot OL, Costantini A, EORTC QLG. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health Qual Life Outcomes 2018 Jun 4;16(1):114 [FREE Full text] [doi: 10.1186/s12955-018-0920-0] [Medline: 29866185]
5. Pinto A. Sexuality and breast cancer: prime time for young patients. J Thorac Dis 2013 Jun;5(Suppl 1):S81-S86 [FREE Full text] [doi: 10.3978/j.issn.2072-1439.2013.05.23] [Medline: 23819031]
6. Ventura EE, Ganz PA, Bower JE, Abascal L, Petersen L, Stanton AL, et al. Barriers to physical activity and healthy eating in young breast cancer survivors: modifiable risk factors and associations with body mass index. Breast Cancer Res Treat 2013 Nov;142(2):423-433 [FREE Full text] [doi: 10.1007/s10549-013-2749-x] [Medline: 24177756]
7. Rabin C, Simpson N, Morrow K, Pinto B. Intervention format and delivery preferences among young adult cancer survivors. Int J Behav Med 2013 Jun;20(2):304-310. [doi: 10.1007/s12529-012-9227-4] [Medline: 22328444]
8. Rabin C. Barriers to increasing physical activity among young adult cancer survivors. J Adolesc Young Adult Oncol 2017 Jun;6(2):372-376. [doi: 10.1089/jayao.2016.0056] [Medline: 27893307]
9. Ottenbacher AJ, Day RS, Taylor WC, Sharma SV, Sloane R, Snyder DC, et al. Exercise among breast and prostate cancer survivors--what are their barriers? J Cancer Surviv 2011 Dec;5(4):413-419 [FREE Full text] [doi: 10.1007/s11764-011-0184-8] [Medline: 21598023]
10. Parsons HM, Harlan LC, Lynch CF, Hamilton AS, Wu X, Kato I, et al. Impact of cancer on work and education among adolescent and young adult cancer survivors. J Clin Oncol 2012 Jul 1;30(19):2393-2400 [FREE Full text] [doi: 10.1200/JCO.2011.39.6333] [Medline: 22614977]
11. Stone DS, Ganz PA, Pavlish C, Robbins WA. Young adult cancer survivors and work: a systematic review. J Cancer Surviv 2017 Dec;11(6):765-781 [FREE Full text] [doi: 10.1007/s11764-017-0614-3] [Medline: 28478587]
12. Vetsch J, Wakefield CE, McGill BC, Cohn RJ, Ellis SJ, Stefanic N, et al. Educational and vocational goal disruption in adolescent and young adult cancer survivors. Psychooncology 2018 Feb;27(2):532-538. [doi: 10.1002/pon.4525] [Medline: 28778113]
13. Avis NE, Crawford S, Manuel J. Quality of life among younger women with breast cancer. J Clin Oncol 2005 May 20;23(15):3322-3330. [doi: 10.1200/JCO.2005.05.130] [Medline: 15908646]

14. Ruddy KJ, Greaney ML, Sprunck-Harrild K, Meyer ME, Emmons KM, Partridge AH. Young women with breast cancer: a focus group study of unmet needs. J Adolesc Young Adult Oncol 2013 Dec 1;2(4):153-160 [FREE Full text] [doi: 10.1089/jayao.2013.0014] [Medline: 24380034]
15. Hungr C, Sanchez-Varela V, Bober SL. Self-image and sexuality issues among young women with breast cancer: practical recommendations. Rev Invest Clin 2017;69(2):114-122 [FREE Full text] [doi: 10.24875/ric.17002200] [Medline: 28453509]
16. Leinert E, Singer S, Janni W, Harbeck N, Weissenbacher T, Rack B, et al. The impact of age on quality of life in breast cancer patients receiving adjuvant chemotherapy: a comparative analysis from the prospective multicenter randomized Adebar trial. Clin Breast Cancer 2017 Apr;17(2):100-106. [doi: 10.1016/j.clbc.2016.10.008] [Medline: 27884722]
17. Rosenberg SM, Tamimi RM, Gelber S, Ruddy KJ, Kereakoglow S, Borges VF, et al. Body image in recently diagnosed young women with early breast cancer. Psychooncology 2013 Aug;22(8):1849-1855 [FREE Full text] [doi: 10.1002/pon.3221] [Medline: 23132765]
18. Sheppard VB, Hicks J, Makambi K, Hurtado-de-Mendoza A, Demark-Wahnefried W, Adams-Campbell L. The feasibility and acceptability of a diet and exercise trial in overweight and obese black breast cancer survivors: the stepping STONE study. Contemp Clin Trials 2016 Jan;46:106-113 [FREE Full text] [doi: 10.1016/j.cct.2015.12.005] [Medline: 26655430]
19. Rock CL, Flatt SW, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, et al. Results of the exercise and nutrition to enhance recovery and good health for you (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. J Clin Oncol 2015 Oct 1;33(28):3169-3176 [FREE Full text] [doi: 10.1200/JCO.2015.61.1095] [Medline: 26282657]
20. Chen X, Lu W, Zheng W, Gu K, Matthews CE, Chen Z, et al. Exercise after diagnosis of breast cancer in association with survival. Cancer Prev Res (Phila) 2011 Sep;4(9):1409-1418 [FREE Full text] [doi: 10.1158/1940-6207.CAPR-10-0355] [Medline: 21795422]
21. Schmid D, Leitzmann M. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol 2014 Jul;25(7):1293-1311 [FREE Full text] [doi: 10.1093/annonc/mdu012] [Medline: 24644304]
22. Mishra S, Scherer R, Geigle P, Berlanstein DR, Topaloglu O, Gotay CC, et al. Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev 2012 Aug 15(8):CD007566. [doi: 10.1002/14651858.CD007566.pub2] [Medline: 22895961]
23. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. Ann Behav Med 2011 Feb;41(1):32-47 [FREE Full text] [doi: 10.1007/s12160-010-9225-1] [Medline: 20931309]
24. Speck RM, Gross CR, Hormes JM, Ahmed RL, Lytle LA, Hwang W, et al. Changes in the body image and relationship scale following a one-year strength training trial for breast cancer survivors with or at risk for lymphedema. Breast Cancer Res Treat 2010 Jun;121(2):421-430. [doi: 10.1007/s10549-009-0550-7] [Medline: 19771507]
25. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst 2012 Mar 7;104(5):386-405. [doi: 10.1093/jnci/djr541] [Medline: 22271773]
26. National Cancer Institute, Bethesda MD. Cancer Trends Progress Report. 2020 Mar. URL: https://progressreport.cancer.gov/ [accessed 2020-06-08]
27. Rabin C, Dunsiger S, Ness KK, Marcus BH. Internet-based physical activity intervention targeting young adult cancer survivors. J Adolesc Young Adult Oncol 2011 Dec;1(4):188-194 [FREE Full text] [doi: 10.1089/jayao.2011.0040] [Medline: 23610737]
28. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. J Cancer Surviv 2013 Sep;7(3):355-368 [FREE Full text] [doi: 10.1007/s11764-013-0279-5] [Medline: 23532799]
29. Rabin C, Pinto B, Fava J. Randomized trial of a physical activity and meditation intervention for young adult cancer survivors. J Adolesc Young Adult Oncol 2016 Mar;5(1):41-47. [doi: 10.1089/jayao.2015.0033] [Medline: 26812450]
30. Bluethmann SM, Vernon SW, Gabriel KP, Murphy CC, Bartholomew LK. Taking the next step: a systematic review and meta-analysis of physical activity and behavior change interventions in recent post-treatment breast cancer survivors. Breast Cancer Res Treat 2015 Jan;149(2):331-342 [FREE Full text] [doi: 10.1007/s10549-014-3255-5] [Medline: 25555831]
31. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychol Health 2011 Nov;26(11):1479-1498. [doi: 10.1080/08870446.2010.540664] [Medline: 21678185]
32. Bluethmann SM, Bartholomew LK, Murphy CC, Vernon SW. Use of theory in behavior change interventions. Health Educ Behav 2017 Apr;44(2):245-253 [FREE Full text] [doi: 10.1177/1090198116647712] [Medline: 27226430]
33. Sullivan AN, Lachman ME. Behavior change with fitness technology in sedentary adults: a review of the evidence for increasing physical activity. Front Public Health 2016;4:289 [FREE Full text] [doi: 10.3389/fpubh.2016.00289] [Medline: 28123997]

34. Mercer K, Li M, Giangregorio L, Burns C, Grindrod K. Behavior change techniques present in wearable activity trackers: a critical analysis. JMIR Mhealth Uhealth 2016 Apr 27;4(2):e40 [FREE Full text] [doi: 10.2196/mhealth.4461] [Medline: 27122452]
35. Lyons EJ, Lewis ZH, Mayrsohn BG, Rowland JL. Behavior change techniques implemented in electronic lifestyle activity monitors: a systematic content analysis. J Med Internet Res 2014 Aug 15;16(8):e192 [FREE Full text] [doi: 10.2196/jmir.3469] [Medline: 25131661]
36. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. Health Psychol 2009 Nov;28(6):690-701. [doi: 10.1037/a0016136] [Medline: 19916637]
37. Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. Int J Behav Nutr Phys Act 2017 Mar 28;14(1):42 [FREE Full text] [doi: 10.1186/s12966-017-0494-y] [Medline: 28351367]
38. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
39. Hartman SJ, Nelson SH, Cadmus-Bertram LA, Patterson RE, Parker BA, Pierce JP. Technology- and phone-based weight loss intervention: pilot RCT in women at elevated breast cancer risk. Am J Prev Med 2016 Nov;51(5):714-721 [FREE Full text] [doi: 10.1016/j.amepre.2016.06.024] [Medline: 27593420]
40. Hartman SJ, Nelson SH, Myers E, Natarajan L, Sears DD, Palmer BW, et al. Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: the memory & motion study. Cancer 2018 Jan 1;124(1):192-202 [FREE Full text] [doi: 10.1002/cncr.30987] [Medline: 28926676]
41. Hartman SJ, Nelson SH, Weiner LS. Patterns of FitBit use and activity levels throughout a physical activity intervention: exploratory analysis from a randomized controlled trial. JMIR Mhealth Uhealth 2018 Feb 5;6(2):e29 [FREE Full text] [doi: 10.2196/mhealth.8503] [Medline: 29402761]
42. Lloyd G, Hoffman S, Welch W, Blanch-Hartigan D, Gavin KL, Cottrell A, et al. Breast cancer survivors' preferences for social support features in technology-supported physical activity interventions: findings from a mixed methods evaluation. Transl Behav Med 2020 May 20;10(2):423-434. [doi: 10.1093/tbm/iby112] [Medline: 30445595]
43. Robertson MC, Tsai E, Lyons EJ, Srinivasan S, Swartz MC, Baum ML, et al. Mobile health physical activity intervention preferences in cancer survivors: a qualitative study. JMIR Mhealth Uhealth 2017 Jan 24;5(1):e3 [FREE Full text] [doi: 10.2196/mhealth.6970] [Medline: 28119278]
44. Abrol E, Groszmann M, Pitman A, Hough R, Taylor RM, Aref-Adib G. Exploring the digital technology preferences of teenagers and young adults (TYA) with cancer and survivors: a cross-sectional service evaluation questionnaire. J Cancer Surviv 2017 Dec;11(6):670-682 [FREE Full text] [doi: 10.1007/s11764-017-0618-z] [Medline: 28634734]
45. Israel BA, Schulz AJ, Parker EA, Becker AB. Review of community-based research: assessing partnership approaches to improve public health. Annu Rev Public Health 1998;19:173-202. [doi: 10.1146/annurev.publhealth.19.1.173] [Medline: 9611617]
46. Israel BA, Coombe CM, Cheezum RR, Schulz AJ, McGranaghan RJ, Lichtenstein R, et al. Community-based participatory research: a capacity-building approach for policy advocacy aimed at eliminating health disparities. Am J Public Health 2010 Nov;100(11):2094-2102. [doi: 10.2105/AJPH.2009.170506] [Medline: 20864728]
47. Hartman SJ, Natarajan L, Palmer BW, Parker B, Patterson RE, Sears DD. Impact of increasing physical activity on cognitive functioning in breast cancer survivors: rationale and study design of memory & motion. Contemp Clin Trials 2015 Nov;45(Pt B):371-376 [FREE Full text] [doi: 10.1016/j.cct.2015.09.021] [Medline: 26427563]
48. Wu YP, Yi J, McClellan J, Kim J, Tian T, Grahmann B, et al. Barriers and facilitators of healthy diet and exercise among adolescent and young adult cancer survivors: implications for behavioral interventions. J Adolesc Young Adult Oncol 2015 Dec;4(4):184-191 [FREE Full text] [doi: 10.1089/jayao.2015.0028] [Medline: 26697268]
49. Gorman JR, Roberts SC, Dominick SA, Malcarne VL, Dietz AC, Su HI. A diversified recruitment approach incorporating social media leads to research participation among young adult-aged female cancer survivors. J Adolesc Young Adult Oncol 2014 Jun 1;3(2):59-65 [FREE Full text] [doi: 10.1089/jayao.2013.0031] [Medline: 24940529]
50. Thomas S, Reading J, Shephard RJ. Revision of the physical activity readiness questionnaire (PAR-Q). Can J Sport Sci 1992 Dec;17(4):338-345. [Medline: 1330274]
51. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. J Support Oncol 2012;10(5):171-177 [FREE Full text] [doi: 10.1016/j.suponc.2012.02.001] [Medline: 22579268]
52. Martins RK, McNeil DW. Review of motivational interviewing in promoting health behaviors. Clin Psychol Rev 2009 Jun;29(4):283-293. [doi: 10.1016/j.cpr.2009.02.001] [Medline: 19328605]
53. Motivational Interviewing Step by Step. Pychotherapy.net Academy. URL: https://academy.psychotherapy.net/store/jhDjd9Xc [accessed 2020-06-08]
54. Carver CS, Scheier MF. Control theory: a useful conceptual framework for personality–social, clinical, and health psychology. Psychol Bull 1982;92(1):111-135. [doi: 10.1037/0033-2909.92.1.111]
55. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice Hall; 1986.

56. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62(4):243-274 [FREE Full text] [doi: 10.3322/caac.21142] [Medline: 22539238]
57. Diabetes Prevention Program (DPP) Research Group. The diabetes prevention program (DPP): description of lifestyle intervention. Diabetes Care 2002 Dec;25(12):2165-2171 [FREE Full text] [doi: 10.2337/diacare.25.12.2165] [Medline: 12453955]
58. Look AHEAD Research Group, Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, et al. The look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity (Silver Spring) 2006 May;14(5):737-752 [FREE Full text] [doi: 10.1038/oby.2006.84] [Medline: 16855180]
59. Creswell J. In: Plano W, Clark VL, editors. Designing and Conducting Mixed Methods Research. Third Edition. Thousand Oaks, CA: SAGE Publications; 2018.
60. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
61. Freedson PS, Melanson E, Sirard J. Calibration of the computer science and applications inc accelerometer. Med Sci Sports Exerc 1998 May;30(5):777-781. [doi: 10.1097/00005768-199805000-00021] [Medline: 9588623]
62. Nelson SH, Weiner LS, Natarajan L, Parker BA, Patterson RE, Hartman SJ. Continuous, objective measurement of physical activity during chemotherapy for breast cancer: the activity in treatment pilot study. Transl Behav Med 2019 May 29:- epub ahead of print. [doi: 10.1093/tbm/ibz079] [Medline: 31141593]
63. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. Eur J Cancer 2001 Jan;37(2):189-197. [doi: 10.1016/s0959-8049(00)00353-1] [Medline: 11166145]
64. Lewis-Smith H, Diedrichs PC, Rumsey N, Harcourt D. Efficacy of psychosocial and physical activity-based interventions to improve body image among women treated for breast cancer: a systematic review. Psychooncology 2018 Dec;27(12):2687-2699. [doi: 10.1002/pon.4870] [Medline: 30161285]
65. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26(2):191-208. [doi: 10.1080/009262300278597] [Medline: 10782451]
66. Bartula I, Sherman KA. The female sexual functioning index (FSFI): evaluation of acceptability, reliability, and validity in women with breast cancer. Support Care Cancer 2015 Sep;23(9):2633-2641. [doi: 10.1007/s00520-015-2623-y] [Medline: 25669965]
67. Halis F, Yildirim P, Kocaaslan R, Cecen K, Gokce A. Pilates for better sex: changes in sexual functioning in healthy Turkish women after pilates exercise. J Sex Marital Ther 2016 May 18;42(4):302-308. [doi: 10.1080/0092623X.2015.1033576] [Medline: 25826474]
68. Lorenz TA, Meston CM. Exercise improves sexual function in women taking antidepressants: results from a randomized crossover trial. Depress Anxiety 2014 Mar;31(3):188-195 [FREE Full text] [doi: 10.1002/da.22208] [Medline: 24754044]
69. Cella D, Lai J, Jensen SE, Christodoulou C, Junghaenel DU, Reeve BB, et al. PROMIS fatigue item bank had clinical validity across diverse chronic conditions. J Clin Epidemiol 2016 May;73:128-134 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.08.037] [Medline: 26939927]
70. Jensen RE, Moinpour CM, Potosky AL, Lobo T, Hahn EA, Hays RD, et al. Responsiveness of 8 patient-reported outcomes measurement information system (PROMIS) measures in a large, community-based cancer study cohort. Cancer 2017 Jan 1;123(2):327-335 [FREE Full text] [doi: 10.1002/cncr.30354] [Medline: 27696377]
71. Rogers LQ, Vicari S, Trammell R, Hopkins-Price P, Fogleman A, Spenner A, et al. Biobehavioral factors mediate exercise effects on fatigue in breast cancer survivors. Med Sci Sports Exerc 2014 Jun;46(6):1077-1088 [FREE Full text] [doi: 10.1249/MSS.0000000000000210] [Medline: 24212124]
72. Beebe J. Rapid Assessment Process: An Introduction. Lanham, MD: AltaMira Press; 2001.
73. Hamilton A. Qualitative Methods in Rapid Turn-Around Health Services Research. VA's Health Services Research and Development Service. 2013. URL: https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=780 [accessed 2020-06-08]
74. Mobile Fact Sheet. Pew Research Center. 2019. URL: https://www.pewinternet.org/fact-sheet/mobile/ [accessed 2019-06-12]

Abbreviations

BIS: Body Image Scale
CITI: Collaborative Institutional Training Initiative
FSFI: Female Sexual Function Index
HIPAA: Health Insurance Portability And Accountability
MVPA: moderate-to-vigorous-intensity physical activity
PAR-Q: Physical Activity Readiness Questionnaire
PI: principal investigator

T0: baseline
T1: postintervention
T2: follow-up
UC San Diego: University of California, San Diego

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Original Paper

Feasibility of a Mobile Health App for Routine Outcome Monitoring and Feedback in Mutual Support Groups Coordinated by SMART Recovery Australia: Protocol for a Pilot Study

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Abstract

Background: Despite the importance and popularity of mutual support groups, there have been no systematic attempts to implement and evaluate routine outcome monitoring (ROM) in these settings. Unlike other mutual support groups for addiction, trained facilitators lead all Self-Management and Recovery Training (SMART Recovery) groups, thereby providing an opportunity to implement ROM as a routine component of SMART Recovery groups.

Objective: This study protocol aims to describe a stage 1 pilot study designed to explore the feasibility and acceptability of a novel, purpose-built mobile health (mHealth) ROM and feedback app (Smart Track) in SMART Recovery groups coordinated by SMART Recovery Australia (SRAU) The secondary objectives are to describe Smart Track usage patterns, explore psychometric properties of the ROM items (ie, internal reliability and convergent and divergent validity), and provide preliminary evidence for participant reported outcomes (such as alcohol and other drug use, self-reported recovery, and mental health).

Methods: Participants (n=100) from the SMART Recovery groups across New South Wales, Australia, will be recruited to a nonrandomized, prospective, single-arm trial of the Smart Track app. There are 4 modes of data collection: (1) ROM data collected from group participants via the Smart Track app, (2) data analytics summarizing user interactions with Smart Track, (3) quantitative interview and survey data of group participants (baseline, 2-week follow-up, and 2-month follow-up), and (4) qualitative interviews

with group participants (n=20) and facilitators (n=10). Feasibility and acceptability (primary objectives) will be analyzed using descriptive statistics, a cost analysis, and a qualitative evaluation.

Results: At the time of submission, 13 sites (25 groups per week) had agreed to be involved. Funding was awarded on August 14, 2017, and ethics approval was granted on April 26, 2018 (HREC/18/WGONG/34; 2018/099). Enrollment is due to commence in July 2019. Data collection is due to be finalized in October 2019.

Conclusions: To the best of our knowledge, this study is the first to use ROM and tailored feedback within a mutual support group setting for addictive behaviors. Our study design will provide an opportunity to identify the acceptability of a novel mHealth ROM and feedback app within this setting and provide detailed information on what factors promote or hinder ROM usage within this context. This project aims to offer a new tool, should Smart Track prove feasible and acceptable, that service providers, policy makers, and researchers could use in the future to understand the impact of SMART Recovery groups.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12619000686101; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377336.

International Registered Report Identifier (IRRID): PRR1-10.2196/15113

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KEYWORDS

SMART Recovery; mutual support group; mutual aid; routine outcome monitoring; treatment progress feedback; mHealth; addiction; mobile phone

Introduction

Background

Using standardized outcome measures to regularly monitor client progress in alcohol and other drug (AOD) settings is an important mechanism for monitoring the effectiveness of service provision [1-3]. Routine outcome monitoring (ROM) provides clinicians with timely feedback about client progress and allows clinicians to tailor treatment to the individual needs of clients and guide treatment decisions [4]. This may be of particular importance when a client is *not on track* (ie, not improving in line with clinical norms [4]). ROM has been specifically recommended for use in AOD treatment settings as the provision of tailored feedback to clients has been found to improve treatment outcomes across a range of AOD treatment settings (eg, acute, community, veterans) [3,5,6]. Evidence also supports clinician use of ROM and tailored feedback to enhance outcomes and/or prevent further deterioration for those clients identified as *not on track* early in addiction and/or mental health treatment [7,8].

Despite the importance of ROM and tailored feedback, ongoing variability in the implementation, sustainability, and use of ROM data has been noted [9]. The time associated with the completion, scoring, interpretation, and feedback of outcome assessments represents a key barrier to systematic implementation [6,9]. Using a digital platform to administer ROM and feedback may help address these concerns. Mobile health (mHealth) [10] apps can provide quick, easy, interactive, and engaging platforms for tracking and accessing information about health and health-related behaviors [11]. Evidence from the United Kingdom suggests that almost 60% of individuals who access AOD treatment own a smartphone [12]. This figure is likely higher in Australia as it is the leading global adopter of smartphones (88% ownership [13]). Given the ubiquity of smartphones, smartphone apps have the added benefit of engaging individuals in real time, in their natural environment, and offering moment-to-moment support as needed [14]. Moreover, a key benefit highlighted in a recent systematic review of mHealth apps is their ability to provide timely, individualized feedback [15]. Accordingly, an opportunity exists to utilize mHealth to enhance engagement, streamline administration, and put the client at the center of the ROM and feedback process.

To date, much of the literature on ROM and feedback has focused on the provision and use of feedback by clinicians [16,17]. Improving client involvement in the feedback process represents an important clinical and research priority [18]. It is not only consistent with the principles of recovery-oriented service provision and strengths-based care [19] but is also therapeutically useful. Within mental health settings, the benefits of providing clients with outcome feedback include improved client insight; enhanced knowledge, skill, and confidence to effectively self-manage their condition(s); and greater satisfaction, engagement, and involvement in treatment [16]. Evidence from related approaches (eg, *therapeutic assessment* [20]) has also shown that providing clients with assessment feedback during psychotherapy promotes client self-verification, self-discovery, and self-enhancement [18]. Moreover, delivering feedback directly to the client seems to further enhance the positive impact of ROM on treatment outcome(s), particularly among group-based treatment settings [6]. Therefore, to meet this important need of putting the client at the center of the ROM and feedback process, during the first phase of this study, we developed a purpose-built mHealth app.

Mutual Support Groups

Mutual support refers to the reciprocal provision of social, emotional, and informational support by group members undergoing recovery from addiction [21]. Mutual support groups are widely available [22], commonly accessed [23], and play an extremely important role in the treatment of AOD use disorders [2,24]. Two approaches recommended by clinical guidelines include 12-step models (eg, Alcoholics Anonymous) and Self-Management and Recovery Training (*SMART Recovery* [2,24]). Although the 12-step models are traditionally the most

well-known and accessed models for mutual support [22], other approaches (eg, SMART Recovery) are gaining momentum. For example, SMART Recovery Australia has seen an almost 40% increase in groups over the last 4 years, with over 300 groups currently running nationwide [25]. Although accumulating evidence points to the benefit of participating in mutual support groups [26,27], much of the research is derived from the 12-step models. In light of the growth of SMART Recovery groups, expanding the evidence base beyond the 12-step models is a priority. A major limitation in developing a strong evidence base is the lack of outcome data evaluating service delivery. Accordingly, the purpose-built mHealth app developed during the first phase of the study provides a mechanism for not only improving service provision but also providing unique insights into the outcome(s) demonstrated by SMART Recovery participants.

Although many AOD services provided by public health and nongovernment organizations are contracted to monitor client outcomes routinely [28], we are unaware of any research describing the use of ROM in mutual support groups for addictive behaviors. As a trained facilitator leads all SMART Recovery groups, a unique opportunity exists to work with SMART Recovery facilitators to embed ROM and tailored feedback as a standard component of the groups. Investigating the use of ROM and feedback within a mutual support setting helps address the need for improved participant involvement in the assessment and feedback process [18], in addition to building a platform for improving the evidence base for SMART Recovery, a clinical and research priority [27].

This Study

In this paper, we detail the study protocol for a nonrandomized, prospective, single-arm pilot study, with a concurrent cost evaluation and nested qualitative evaluation designed to explore the feasibility and acceptability of a novel mHealth ROM and feedback app (*Smart Track*) in SMART Recovery groups coordinated by SRAU. The secondary objectives are to describe Smart Track usage patterns, psychometric properties of the ROM items, and participant-reported outcomes.

Methods

Approval, Registration, and Reporting

This study was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District (ISLHD) Health and Medical Human Research Ethics Committee (HREC; 2018/099; HREC/18/WGONG/34). The trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000686101). Any amendments will be submitted to the ISLHD HREC before implementation, as per HREC guidelines. Any important protocol modifications will be reported in the outcomes paper. To enhance the quality, completeness, and transparency of the proposed study, this study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials [29] and the Consolidated Standards of Reporting Trials-eHealth checklist [30] (Multimedia Appendix 1).

Participants

Eligibility

Participants must be at least 18 years of age, currently participating in one or more SMART Recovery groups located within New South Wales (NSW), have a current email address or be willing to obtain an email address, and be able to comprehend English at a level sufficient to complete study requirements.

Participants will be eligible irrespective of their self-reported computer and/or smartphone literacy. No restrictions will be placed on concomitant care, including the frequency or duration of SMART Recovery group participation or participation in other forms of AOD treatment. Participants will only be excluded if they are unable or unwilling to provide informed consent. Exclusion criteria were kept to a minimum to ensure that the study sample is representative of people attending SMART Recovery groups.

Smartphone Ownership

Although we expect that most participants will own a smartphone [12,13], potential participants do not need to own a smartphone to participate. The research team will provide tablets to study sites (locations where regular SMART Recovery groups are held) so that participants can use the tablet before and/or after attending a group to complete the ROM questions and receive feedback.

Study Setting

Potential participants will be sourced from the SMART Recovery groups held in NSW, Australia. A full list of study sites will be reported in the outcomes paper. SMART Recovery groups are held in the community as well as in inpatient, outpatient, and clinical health organizations, including private, public, and not-for-profit mental health, AOD, and general health services. Online SMART Recovery groups are also available. A detailed description of the SMART Recovery groups has been provided elsewhere [31]. Briefly, SMART Recovery focuses on self-empowerment and utilizes evidence-based techniques (eg, cognitive behavioral therapy and motivational interviewing) [32]. To ensure that our sample adequately reflects SMART Recovery participants, study sites with established SMART Recovery groups were selected to reflect a range of geographical locations and service providers. At the time of manuscript submission, 147 groups were conducted throughout the NSW.

Enrollment

Group facilitators will use a script to introduce the study to potential participants and invite expressions of interest. The following strategies will be adopted to maximize adequate enrollment. Group facilitators will be asked to check in with participants regarding the completion and/or return of expression of interest forms (across a maximum of 3 meetings). A member of the research team will also visit SMART Recovery groups throughout the recruitment period to directly provide group members with information about the study and collect the expression of interest forms. Depending on accrual, the study may also be advertised (eg, online, local media,

flyers/pamphlets, and study website) to extend participant recruitment beyond this study's sites.

Informed Consent

A member of the research team (AKB) will collect informed consent from all study participants (written or verbal according to the participant's preference). A copy of consent (audio recording and/or signed consent form) will be retained for all study participants and securely stored according to the HREC–approved methods.

Overview of the mHealth Routine Outcome Monitoring and Feedback App (Smart Track)

The Smart Track app was designed for participants attending SMART Recovery groups. ROM items are intended for weekly completion. However, it is up to the individual to decide whether, when, and how they engage with Smart Track. Given the low-risk, low-burden nature of this study, there are no contingencies for discontinuing access to the Smart Track app. Owing to app store regulations, Smart Track will not be restricted to study participants. It will be freely available for download through Android and iPhone Operating System stores (only data from those who provide consent will be included in the study).

Publications detailing the methods and findings from the qualitative work [33] and app development process (including theoretical foundations) will be reported separately. To provide context, a brief summary is presented here. The Smart Track app was developed during the first phase of this study using participatory design workshops and an iterative development process informed by the (1) consideration of existing ROM tools, (2) qualitative feedback [33] and usability testing sessions with SMART Recovery participants and facilitators, (3) clinical and research expertise from the members of the expert advisory and steering committees, and (4) technological and creative expertise of the development team employed to work on this study (GHO, Sydney) [34].

The functionality of Smart Track was initially tested with 3 members of the research team. Several bugs were identified and fixed before the amended beta version was released to a convenience sample (n=40) for further testing. This convenience sample of beta testers included members of the expert advisory committee, steering committee, SMART Recovery board members, and SMART Recovery facilitators. Further refinements were made in line with the feedback received (bug fixes, minor amendments to functionality, and content).

Smart Track Routine Outcome Monitoring Domains and Items

Consistent with clinical guidelines [3,35] and informed by recommendations arising from systematic reviews evaluating ROM in both mental health [18] and addiction [6] settings, we sought to create a tool that provided multidimensional assessment and feedback. Utilizing an iterative process, we generated a list of candidate outcomes (group attendance; goal setting and attainment; values; self-efficacy; quality of life; self-care; mental health; quantity, frequency, and impact of addictive behavior(s); social support; financial stability; optimism; and frequency, strength, and duration of urges). Corresponding assessment items and/or instruments were then identified to measure these domains. Where possible, validated free-to-access measurement instruments were selected from the published literature. Some changes to the structure, wording, and/or response format were required to improve the clarity and appropriateness of some items. The final item set included in the tool is detailed in Multimedia Appendix 2 [36-47] as a function of the target domain and assessment frequency.

Smart Track Tailored Feedback

The same iterative process was used to inform the content, format, and frequency of the Smart Track feedback. On the basis of the participants' responses to individual ROM items and/or subscale scores, tailored visual cues (eg, colors and arrows) are used to provide a *snapshot* of progress within each domain (eg, current score range and/or direction of progress). Participants can also select one or more domains to receive further detailed feedback (written and visual).

The written feedback comprises encouraging statements, self-reflection questions, and/or self-management suggestions. As health messages are more effective when they are tailored to the individual [48] and tailored feedback is central to both popularity [49] and effectiveness [14] of mHealth apps for alcohol use, written feedback and visual cues are tailored. Visual feedback comprises a graph illustrating the participant's progress over time (with the option of viewing data for the week, month, and year). Guided by the literature highlighting the utility of providing feedback according to the level of observed progress (eg, *on-track* or *off-track* [16]) and informed by previous *stop-light*–style ROM feedback systems (see the study by Kendrick et al [7] for a review), written feedback and visual cues are tailored according to three pathways, based on whether individual domain scores suggest (1) a *good* score range or improvement (green), (2) an *ok* score range or stability (yellow), or (3) a *less good* score range or deterioration (red). The chosen logic allows feedback content and visual cues to be tailored such that all progress is encouraged and reinforced, with a specific focus on (1) maintaining change (green), (2) highlighting additional change(s) that may be of benefit (yellow), or (3) troubleshooting difficulties and/or seeking support (red).

Additional Features of Smart Track

Inconsistent engagement (client and/or clinician) has long been identified as a challenge to both ROM and feedback [50] and, more broadly, the mHealth literature [51]. Therefore, in addition to the core ROM and feedback functionality, several additional features (Table 1) have been included. Aside from the hints, tips, and motivational statements (which automatically feature once per day that the app is used), it is up to the individual as to how frequently they access various features.

Table 1. Additional Smart Track features.

Feature	Description
Customizable support(s) and personal motivation(s)	Participants have the option of tailoring the app content by uploading key contact number(s), support services and/or personal motivation(s) for change (photo, audio, video, and/or written)
Resources	Information about self-management strategies (including SMART[a] Recovery resources) and motivational stories from people with lived experience of addictive behavior(s)
Hints, tips, and motivational statements	A self-management tip, motivational statement, or inspirational quote will be included as pop-up content. These brief messages comprise direct and adapted quotes from the transcripts of the qualitative interviews
Journal	There is a free text box on each feedback page to allow participants to reflect on their progress and/or the tailored feedback provided
Interactive urge log	In addition to tracking the number, frequency, and strength of urges, when the participant reports an urge, this interactive tool prompts the participants to manage their urges, log triggers, and reflect on how to maintain and/or improve effective urge self-management

[a]SMART: Self-Management and Recovery Training.

Implementation Strategies

The app contains an in-built *walk through* to orient new users to the features of the app. We also intend to develop a brief tutorial to assist participants with app download and set up. Consistent with the recommendations for improving ROM uptake [9], SMART Recovery facilitators at each study site will assume the role of *local champions* of Smart Track. The research team will work with the facilitators to orient them to the app so that they are confident in responding to the participants' questions about ROM completion and troubleshooting any difficulties that may arise. Participants and facilitators may also contact the research team directly for support. SMART Recovery facilitators will also prompt, encourage, and support study participants to regularly complete the ROM questions before and/or attending a SMART Recovery group.

In-app push notifications will also be used to prompt participants to complete the ROM items. In-app notifications (red marker) will also be used to highlight section(s) that require participants' attention (eg, outstanding 7-day plan).

Data Collection Procedures

The participant timeline is outlined in Figure 1, and the corresponding schedule of participant assessments is summarized in Table 2. There are 4 main modes of data collection in this study: (1) participant-completed ROM data collected via Smart Track (Multimedia Appendix 1), (2) broader app-generated data analytics summarizing interactions with Smart Track, (3) quantitative baseline and follow-up assessments with study participants, and (4) qualitative interviews with study participants and group facilitators.

Baseline and follow-up assessments will primarily be conducted over the telephone by a member of the research team (a trained clinical psychologist). To promote follow-up, appointments will be scheduled at a time convenient to the participants, with options to accommodate participants' preferences for video link, face-to-face, and/or self-report (where feasible). Telephone, text, letter, and/or facilitator prompting will be utilized (as needed) to remind the participants of upcoming and/or missed appointments.

Figure 1. Participant flow chart. SMART: Self-Management and Recovery Training.

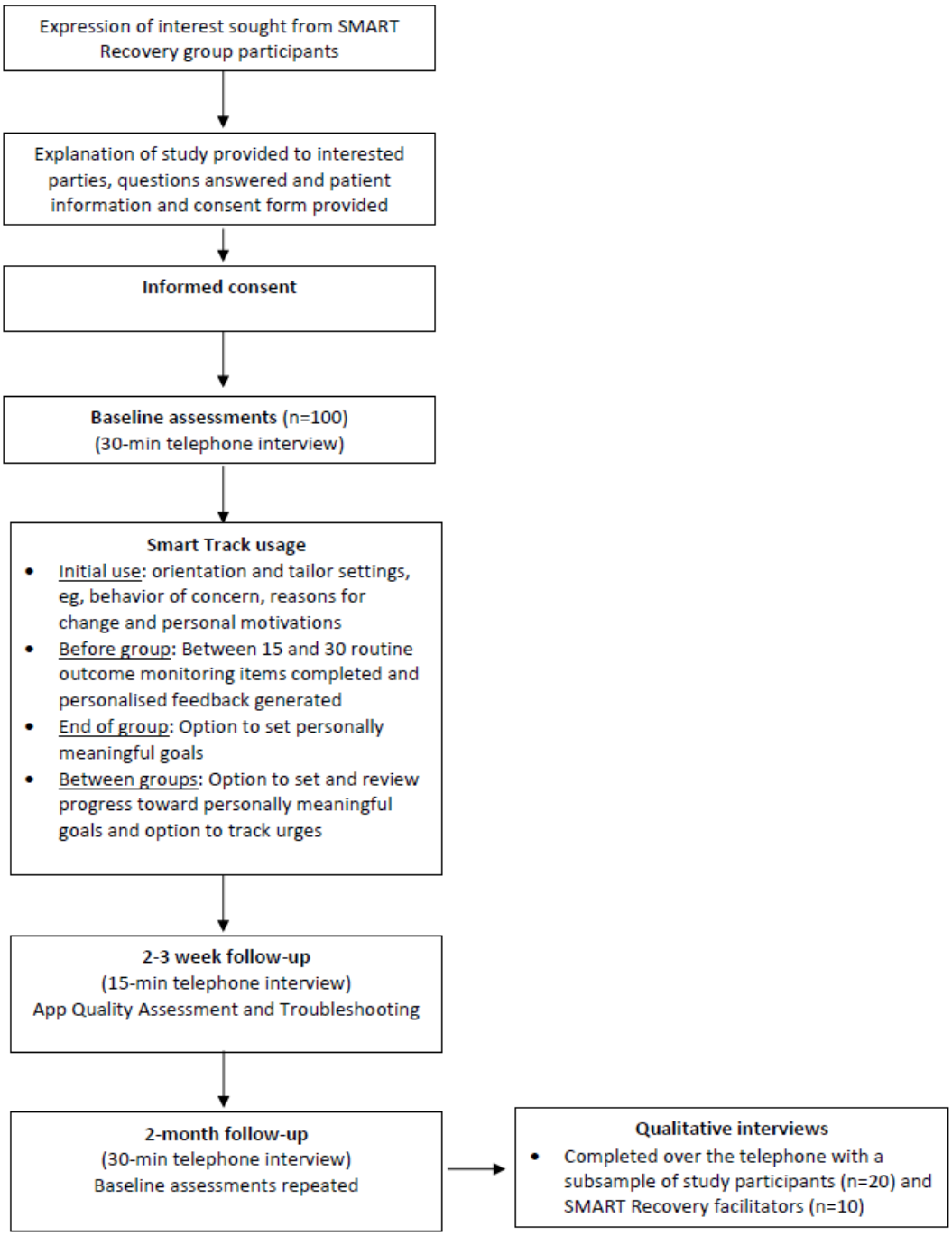

Table 2. Schedule of data collection.

Data collection method/instrument	Baseline	Daily	Weekly	2-week follow-up	2-month follow-up
SMART[a] Recovery participants					
Smart Track app					
Data analytics		✓			
ROM items[b]			✓		
Telephone interview					
Demographics	✓				✓
Network of Alcohol and other Drug Agencies Client Outcome Management System					
Severity of Dependence Scale	✓				✓
Drug and alcohol use	✓				✓
Kessler 10+ scale	✓				✓
The World Health Organization Quality of Life–8	✓				✓
New South Wales minimum data set items (living arrangements and income)	✓				✓
BTOM-C[c] items on arrests	✓				✓
BTOM-C items on risky drug using practices	✓				✓
Substance Use Recovery Evaluator	✓				✓
Client Services Receipt Inventory	✓				✓
Mobile App Rating Scale–user version				✓	
Digital Working Alliance Inventory				✓	✓
Qualitative interview (n=20)					✓
SMART Recovery facilitators					
Demographics					✓
Mobile App Rating Scale–user version					✓
Qualitative interview (n=10)					✓

[a]SMART: Self-Management and Recovery Training.

[b]See Multimedia Appendix 2 for a detailed description of routine outcome monitoring items as a function of assessment domain and frequency of administration.

[c]BTOM-C: Brief Treatment Outcome Measure-Concise.

Data Handling and Storage

Initially, the ROM data entered by participants into Smart Track will be stored locally on the participants' phones. When the participants connect to the internet, ROM data will be transmitted to a secure mobile and web app development platform (managed by SRAU), before transmitting to a secure server hosted by the University of Wollongong.

The participants' responses to the baseline and follow-up research assessment instruments will be entered at the time of interview directly into REDCap, a secure web application for building and managing online surveys and databases. Further information about data management, monitoring, and dissemination is provided in Multimedia Appendix 3.

Key Measures and Assessment Instruments

Primary Objectives: Feasibility and Acceptability

Mobile App Data Analytics

Mobile app data analytics will be captured daily throughout the study period using a mobile and web app development platform. Mobile app data analytics provide insight into how and when participants interact with an app (including participants' interactions with the on-site tablets provided by the research team). In this study, analytics will be used to inform both feasibility (primary objective) and to describe usage patterns (secondary objective).

Qualitative Feedback

A qualitative evaluation (described under *Nested Qualitative Evaluation*) will be conducted 2 months postbaseline to collect detailed feedback from study participants and facilitators regarding their experience of and satisfaction with Smart Track.

App Quality Assessment

The Mobile App Rating Scale (MARS) [52] is designed to assess the quality of mHealth apps. The original version of this rating tool is designed to be completed by researchers, professionals, and/or clinicians [52]. The Mobile Application Rating Scale–User Version (uMARS [53]) is a simplified, end-user version. A total of 16 items are used to assess app quality across 4 domains (engagement, functionality, aesthetics, and information quality). Items are rated on a scale from 1 to 5 (1=*inadequate* and 5=*excellent*). Means are calculated for each quality domain and summed to produce an overall app quality mean score. Each instrument also contains 4 additional items to assess *subjective quality* and a further 6 items to assess the perceived impact of the app. Both the MARS [52] and uMARS [53] have excellent internal consistency and sound test-retest reliability.

The Digital Working Alliance Inventory (D-WAI) [54] is a brief, simple scale designed to assess therapeutic alliances within the context of app usage. It was recently developed to address the need for improved assessment of working alliances when evaluating the quality of digital health apps [54]. The D-WAI comprises 6 items and is derived from the short form of the Working Alliance Inventory [55], a commonly implemented and validated index of working alliances [56-58].

Cost Analysis

Health Services and Medication: Usage and Cost

An adapted version of the Client Service Receipt Inventory (CSRI)—*generic* UK mental health [59] will be used to assess health services and medication usage. The content of this inventory has been updated to reflect key sources of mental health expenditure in Australia [60]. These data will allow us to explore clinical and treatment characteristics that may be associated with app usage and will provide some insight into costing.

Time and Resource Utilization

Time and resource utilization will be captured in Microsoft Excel using a *cost capture template* [61-63]. This template will be used by the research team to maintain a record of cost data associated with the conduct of the study and the development and implementation of Smart Track. Only costs required to develop and implement the Smart Track app will be included in the cost analysis.

Secondary Objectives

Usage Patterns, Psychometric Properties, and Participant-Reported Outcomes

Secondary objectives will be informed by (1) participant-entered (and missing) data for Smart Track ROM items (detailed in Multimedia Appendix 2), (2) app-generated data analytics, and (3) the following data (eg sociodemographic characteristics; drug and alcohol use; health and social functioning; and recovery) collected by the research team at baseline and follow-up assessments.

Demographic Characteristics

Collection of sociodemographic characteristics (referral source, date of birth, gender, marital status, indigenous status, education/training, accommodation, and income) will be guided by items from the CSRI [59] and/or NSW minimum data set (MDS) for drug and alcohol treatment services [64].

The Network of Alcohol and other Drug Agencies (NADA) Client Outcome Management System (COMS) was developed by NADA to address the need for greater consistency in how outcomes are assessed across the drug and alcohol treatment sector [46]. We have chosen to use the COMS in this study to ensure that our data are directly comparable with the broader drug and alcohol treatment sectors. The COMS comprises a battery of items designed to assess 4 key domains: (1) drug and alcohol use, (2) psychological health, (3) health and social functioning, and (4) blood-borne virus (BBV) risk. The instruments used to assess each domain are outlined below. The COMS will be administered in full at baseline and at 2-month follow-up. A subset of items (Multimedia Appendix 2) will also be administered via Smart Track.

Client Outcome Management System: Drug and Alcohol Use

Severity of Dependence Scale

The Severity of Dependence Scale [65] is a 5-item screening measure of the psychological aspects of dependence that takes less than 1 min to complete. The items assess feelings of impaired control over drug taking, together with preoccupations and anxieties about drug taking. Participants will be asked to respond based on the substance that was causing them the greatest concern (1) over the preceding 2 months and (2) when they began attending SMART Recovery. The items are rated on a 4-point Likert scale, and total scores range from 0 to 15. Higher scores indicate a higher level of dependence. It is widely validated for use across a range of drug types, including heroin, cannabis, cocaine, amphetamine, and benzodiazepines [65-67].

Substance Use

Alcohol and tobacco use is measured by assessing both frequency (number of days) and quantity used during the preceding 4 weeks. Furthermore, 2 separate measurements for alcohol are included: number of days the person drank alcohol (and average number of drinks per day) and number of days of heavier drinking than usual (and average number of drinks on those days). For benzodiazepines and any illicit drugs, only the number of days of use is assessed.

Client Outcome Management System: Psychological Health

The Kessler 10 scale (K10) [68] is a widely used self-report measure of psychological distress. It comprises 10 questions that assess the level of nervousness, agitation, psychological fatigue, and depression in the past 4 weeks [68]. Each item is scored from 1 to 5, from *none of the time* to *all of the time*. Scores are then totaled, resulting in a K10 score between 10 and 50, with higher scores indicating greater distress [69]. The Kessler 10+ scale includes 4 additional questions to provide a context for interpretation (number of days where work, study, and/or management of daily activities were stopped and/or reduced because of these feelings; number of times professional help was sought; and perceived contribution of physical health

problems to reported distress) [46]. The K10 has been successfully used in a range of populations, including a range of different Australian settings [69] and specifically with users of AOD in Australian settings [70].

Client Outcome Management System: Health and Social Functioning

World Health Organization Quality of Life Scale–8

The World Health Organization Quality of Life–8 [71] questions (also known as the EUROHIS QoL-8) is a very brief adaptation of the WHOQOL-100 and the WHOQOLBREF. Each item is scored from 1 (eg, not at all/very poor/very dissatisfied) to 5 (eg, completely/very good/very satisfied). Items are totaled (range 8-40), with higher scores reflecting greater perceived quality of life over the preceding 2 weeks. Domain scores can also be calculated for overall perception of the quality of life, overall perception of health, physical quality of life, psychological quality of life, satisfaction with social relationships, and satisfaction with the environment. It has been used and validated across a range of populations and settings [45,71], including AOD [72] and mental health [73].

New South Wales Minimum Data Set Items

To provide a differing and more objective assessment of the changes in the perceived quality of life [46], the COMS also includes two items on living arrangements ("Who do you live with?" and "Usual accommodation?") and 1 item on income status ("What is your main source of income?") taken from the NSW MDS [64]. Each item is answered by selecting one option from the response categories provided.

Two items on crime from the Brief Treatment Outcome Measure–Concise (BTOM-C) [47] are also included. These items were developed by the NSW Ministry of Health and assess the number of times the individual has been arrested in the last 2 months and how many arrests were for offenses committed in the preceding 2 months.

Client Outcome Management System: Blood-Borne Virus Risk

The BBV exposure risk-taking domain of the COMS comprises 4 items from the BTOM-C [47] on injecting drug use and overdose. These items are part of the validated BTOM measurement tool developed by NSW Health [47]. They are designed to measure changes and outcomes in relation to injecting and other risky drug use practices.

Client Perspectives of Recovery

The Substance Use Recovery Evaluator (SURE) [43] is designed to measure recovery from drug and alcohol dependence. It was developed in close consultation with people in recovery and comprises 21 items across 5 domains (drinking and drug use, self-care, relationships, material resources, and outlook on life). Items are summed to generate domain scores and an overall recovery score, with higher scores indicating greater progress toward recovery. Evidence supports face and content validity, acceptability, and usability for people in recovery [43]. We have selected the SURE as it is the first patient-reported outcome measure to provide a multidomain assessment of recovery, as defined by adults with experience of addiction [19]. Holistic assessment across a range of domains is consistent with both service user needs [74] and recovery-oriented service provision [19], thereby increasing the relevance of our findings to both service users and service providers. The SURE will be administered in full at baseline and at 2-month follow-up, with items also administered via Smart Track.

Nested Qualitative Evaluation

Qualitative interviews will be conducted 2 months postbaseline to explore the experience and opinions of participants with diverse engagement with Smart Track. Participants will be purposively sampled according to their baseline characteristics, pattern of Smart Track usage, and responses to the 2-month follow-up assessment. Specifically, we wish to explore the experience and opinions of 2 groups of SMART Recovery participants: (1) those who attended SMART groups regularly and completed the ROM regularly (n=10) and (2) those who attended SMART groups regularly and did not complete the ROM regularly (n=10). A qualitative researcher independent from the research team will use a topic guide to ask additional open-ended questions to the selection of participants (n=20) until the nominated sample size in both groups is reached. The research team will monitor recruitment to ensure that there is an adequate distribution of gender, main behavior of concern, geographical location, and group setting. Two corresponding groups of SMART Recovery facilitators (n=5 for each group) will also be recruited, namely (1) one group with members who regularly used Smart Track and (2) another group with members who did not regularly use Smart Track.

All interviews will be audio-recorded. A professional transcriber working under a confidentiality agreement will transcribe the recordings. The transcripts will be checked against the recordings for accuracy and deidentified (by removal of identifying information).

Study Outcomes

Primary and secondary endpoints are presented in Tables 3 and 4, respectively.

Table 3. Primary endpoints.

Primary objective	Primary endpoint
To explore the feasibility of using Smart Track as part of SMART[a] Recovery groups for the purposes of ROM[b] and tailored feedback	• Proportion of eligible participants who consent to the study • Proportion of missing data for each of the ROM items/instruments at each week of administration, across the 2-month period of Smart Track usage • Costs associated with developing Smart Track and maintaining the app until the completion of data collection • Participant engagement with Smart Track, as indexed by data analytics captured daily across the data collection period
To explore the acceptability of using Smart Track as part of SMART Recovery groups for the purposes of ROM and tailored feedback	• Detailed qualitative feedback from SMART Recovery group members and facilitators to explore their experience of and satisfaction with Smart Track (2-month follow-up) • Quality ratings as assessed by participant and facilitator ratings of the user version of the Mobile App Rating Scale (2-week follow-up) and Mobile App Rating Scale (2-month follow-up), respectively • Digital therapeutic alliance ratings as assessed by participant ratings of the Digital Working Alliance Inventory (2-week and 2-month follow-up)

[a]SMART: Self-Management and Recovery Training.

[b]ROM: routine outcome monitoring.

Table 4. Secondary endpoints.

Secondary objective	Secondary endpoints
To explore how participants engage with the app and describe usage patterns	• Demographic, clinical, and treatment factors (as measured by Client Service Receipt Inventory, COMS[a], and SURE[b] at baseline and 2-month follow-up) associated with (in)completion of Smart Track ROM[c] items • Data analytics captured daily across the data collection period
To provide preliminary evidence for the psychometric properties of the ROM items administered by Smart Track	• Internal reliability and convergent and divergent validity of COMS and SURE items administered by Smart Track (relative to the complete versions administered at baseline and 2-month follow-up)
To provide preliminary evidence for participant-reported outcomes in behaviors of concern, recovery, and mental health	Participant-reported progress across the 2-month period of app usage in the following: • Addictive behaviors (COMS [41] and item adapted from the Screener for Substance and Behavioral Addictions [42]) • Addiction recovery (SURE [43]) • Mental health (Kessler [44,68])

[a]COMS: Client Outcome Management System.

[b]SURE: Substance Use Recovery Evaluator.

[c]ROM: routine outcome monitoring.

Participant Reimbursement

Consistent with the Australian guidelines for acknowledging the time and value of consumer participation [75], participants will be offered modest reimbursement for any time, travel, and inconvenience associated with participation in the study assessments (supermarket voucher to the value of AUD $19.60 for baseline and 2-month follow-up assessments; AUD $1=US $0.65).

Statistical Analysis

Primary Objectives

Given the primary objectives of exploring feasibility and acceptability, outcome data will primarily utilize descriptive statistics (eg, summarizing the recruitment rate, proportion of missing data, data analytics, MARS and uMARS quality ratings, and D-WAI alliance ratings). Descriptive statistics will be supplemented by the following cost and qualitative analyses.

Cost Analysis

A cost analysis will be conducted with the assistance of the health economics unit at the Hunter Medical Research Institute, Australia. The analysis will adopt a health provider perspective; it will measure and report the cost associated with developing and maintaining Smart Track. This is policy-relevant information as it estimates the resources required to translate the model of care to another location. Cost modeling will be conducted to report the direct costs of the additional resources required to develop and maintain Smart Track. The perspective adopted will be limited in the base case analysis to that of the health provider. Costs and resource use will be prospectively collected for the duration of the feasibility study and will be valued using a combination of hospital data from NSW Health, Medicare Benefits Schedule tariffs, and market rates.

Downstream cost savings associated with hospitalization will also be explored.

Qualitative Evaluation

Qualitative data will be examined to inform the acceptability of Smart Track by exploring the participants' and facilitators' experiences of the perceived usefulness of ROM and any reason(s) for nonadherence. The analysis will proceed in 2 ways. First, we will identify key concepts and experiences to inform future development and/or refinement of Smart Track content, features, and/or procedures. Second, if there is sufficient data, an inductive approach [76] will be used to shed light on the ways in which individuals understand themselves and their actions (such as in the SMART Recovery group). The methodology also allows for individual beliefs and experiences to be positioned within broader social, service, and policy contexts, including factors such as drug treatment policy and service availability and social attitudes toward drugs and people who use them [77].

Secondary Objectives

App Engagement and Usage Patterns

A detailed exploration of the relationship between app usage (as indexed by frequency of ROM completion, number of missing items, and time to disengagement) and participant characteristics (demographic, clinical, and treatment variables) will be explored using linear regression. Furthermore, we intend to explore the ROM data graphically to see (1) whether it is likely to characterize particular patterns of usage and (2) whether these patterns appear to be influenced by various participant characteristics. Potential patterns that emerge during this exploratory phase will be followed up using latent trajectory analysis. This will clarify whether app use increases, decreases, or has some other pattern over time. Descriptive statistics will also be used to summarize app-generated data analytics.

Preliminary Psychometrics of Smart Track ROM Items

Preliminary psychometrics for Smart Track items will be explored via sensitivity to change, internal consistency, test-retest reliability, convergent validity, and exploratory factor analysis. Internal consistency of Smart Track ROM items will be evaluated using Cronbach alpha coefficient. Pearson correlation analysis will be used to examine the test-retest reliability of ROM scores for the first and second completion of each item set. Convergent validity will be examined using Pearson correlation analysis to explore the associations of initial ROM scores with the standardized measures (COMS and SURE) administered at baseline. Sensitivity to change will be examined via effect sizes, reliable change index (RCI), and growth curve modeling. As appropriate, internal consistency, test-retest reliability, concurrent validity, and RCI will be further examined as a function of age group, gender, and primary behavior of concern.

Effect sizes will be estimated for participants' average ROM change scores between the first and last sessions. To explore the minimum reliable amount of change in scores (while accounting for measurement error [78]), we will calculate RCI between participants' first and last ROM scores. The Jacobson and Traux criteria [78] will be applied to describe the proportion of participants who improved, did not change, or deteriorated. RCIs will also be calculated for the standardized measures administered at baseline and follow-up to allow comparisons with the ROM items. Growth curve modeling will be used to estimate the average rates of change in ROM scores across the 2-month period of ROM usage.

Method of Dealing With Missing Data

Descriptive analyses will use all available data. Inferential analyses (eg, linear regression and growth curve modeling) will use multiple imputation (with chained regression equations) as the primary method of dealing with missing data. The number of imputed data sets will depend on the fraction of missing data, but the stability of results will be assessed over a range of imputation numbers.

Participant Outcomes

Participants' responses to the COMS and SURE (as captured via interview and ROM items across the 2-month data collection period) will be summarized using descriptive statistics.

Power

We aim to recruit participants from 13 sites that conduct a combined total of 25 groups per week. Assuming an average of 6 eligible participants per group per week and a target sample size of 100 participants, we anticipate recruitment to take between 4 and 6 weeks (for an estimated recruitment rate between 11% and 17%). A sample of this size will enable the estimation of the recruitment rate and 95% CI, with a margin of error of no more than 7%.

Results

At the time of submission, 13 sites (25 groups per week) had agreed to be involved. Funding was awarded on August 14, 2017 and ethics approval was granted on April 26, 2018 (HREC/18/WGONG/34; 2018/099). Enrollment is due to commence in July 2019. Data collection is due to be finalized in October 2019.

Discussion

Principal Findings

Integrating ROM and tailored feedback into SMART Recovery groups is an important step toward improving client care [5,6,79]. Given the dearth of published research specifically examining the effectiveness of SMART Recovery [27], ROM provides the opportunity to establish an evidence base for SMART Recovery. Improved engagement with ROM and feedback requires innovative solutions [9]. To overcome the current limitations [9,18,80], in this project, we have harnessed technology to develop a fee-free mHealth app that provides interactive, client-centered, multidimensional progress monitoring. Written and visual feedback is generated automatically and is available almost instantly. Consistent with the need to improve the quality of mHealth solutions [81], Smart Track is grounded in theory, informed by an in-depth understanding of the needs and opinions of SMART Recovery

participants and facilitators, and will undergo methodologically rigorous evaluation.

Conclusions

To the best of our knowledge, this study will be the first to use ROM and tailored feedback within a mutual support group setting. Our study design will provide an opportunity to identify the acceptance of a novel mHealth ROM and feedback app within this setting and provide detailed information on the factors that help to promote or hinder the use of ROM within this context. The study will provide important contextual information to inform the development of future intervention studies focused on the effectiveness of adding ROM plus feedback to SMART Recovery. Further, should Smart Track prove feasible and acceptable, this project offers a new tool that service providers, policy makers and researchers could one day use to understand the impact of SMART Recovery.

Acknowledgments

We gratefully acknowledge the creative and technical expertise of GHO (Customer Experience Agency, Sydney). Ryan Chao (Executive Creative Director) provided overall creative direction and lead the user experience design. James Legge (Executive Strategy Director) led the strategy and facilitated our workshops. Marcos Martini (BBA Technical Lead) was responsible for overall development of the App across iOS and Android. Sharon Peng (UX/UI designer) designed the user experience, user interface and conducted the usability tests. Phoebe Calcutt (Project Manager) managed the overall delivery of the App. We also wish to acknowledge the time and expert insights from the members of our steering committee and the valuable support and contributions made by SMART Recovery participants and facilitators to the development of Smart Track and the conduct of this research. Funding for this research was provided by the NSW Ministry of Health under the NSW Health Alcohol and Other Drugs Early Intervention Innovation Grant Scheme. The funding body did not directly contribute to the design, conduct, analysis, write-up and submission of this research for publication and does not have ultimate authority over any of these activities.

Conflicts of Interest

RM is the executive director of SMART Recovery Australia. AA is employed by SMART Recovery as the national program manager and trainer. PK, FD, ALB, AS, LH, VM, BL, AKB, JK, and AA volunteer as members of the SMART Recovery Australia research advisory committee. The potential and/or perceived conflict of interest is negligible. The role of study investigators on the research advisory committee and/or as an employee of SMART Recovery is freely available on the SMART Recovery Australia website (and study participants can be directed to this information as required). Furthermore, the team responsible for informing the study design and overseeing the conduct of the study and data analysis also comprises researchers, clinicians, and statisticians independent from SMART Recovery. An independent qualitative researcher will collect and analyze qualitative data, and an independent statistical team will conduct the quantitative and economic analyses. No financial conflicts of interest exist. Author contributions [82], and the composition of the expert advisory and steering committees are described in Multimedia Appendix 4.

Multimedia Appendix 1
Study reporting and registration.
[PDF File (Adobe PDF File), 1361 KB - resprot_v9i7e15113_app1.pdf]

Multimedia Appendix 2
Content and administration of routine outcome monitoring items.
[DOCX File , 27 KB - resprot_v9i7e15113_app2.docx]

Multimedia Appendix 3
Data management, monitoring and dissemination.
[DOCX File , 23 KB - resprot_v9i7e15113_app3.docx]

Multimedia Appendix 4
Roles and responsibilities.
[DOCX File , 23 KB - resprot_v9i7e15113_app4.docx]

Multimedia Appendix 5
Peer Review Summary by NSW Health.
[PDF File (Adobe PDF File), 284 KB - resprot_v9i7e15113_app5.pdf]

References

1. Burgess P, Pirkis J, Coombs T. Routine outcome measurement in Australia. Int Rev Psychiatry 2015;27(4):264-275. [doi: 10.3109/09540261.2014.977234] [Medline: 25768326]
2. The National Institute for Health and Care Excellence. Drug Use Disorders in Adults URL: https://www.nice.org.uk/guidance/qs23 [accessed 2020-05-18]
3. The National Institute for Health and Care Excellence. 2011. Alcohol-use Disorders: Diagnosis, Assessment and Management of Harmful Drinking (High-Risk Drinking) and Alcohol Dependence URL: https://www.nice.org.uk/guidance/cg115 [accessed 2020-05-26]
4. Lambert MJ, Harmon C, Slade K, Whipple JL, Hawkins EJ. Providing feedback to psychotherapists on their patients' progress: clinical results and practice suggestions. J Clin Psychol 2005 Feb;61(2):165-174. [doi: 10.1002/jclp.20113] [Medline: 15609358]
5. Goodman JD, McKay JR, DePhilippis D. Progress monitoring in mental health and addiction treatment: a means of improving care. Prof Psychol Res Pr 2013 Aug;44(4):231-246. [doi: 10.1037/a0032605]
6. Carlier IV, Eeden WA. Routine outcome monitoring in mental health care and particularly in addiction treatment: evidence-based clinical and research recommendations. J Addict Res Ther 2017;8(4):-. [doi: 10.4172/2155-6105.1000332]
7. Kendrick T, El-Gohary M, Stuart B, Gilbody S, Churchill R, Aiken L, et al. Routine use of patient reported outcome measures (PROMs) for improving treatment of common mental health disorders in adults. Cochrane Database Syst Rev 2016 Jul 13;7:CD011119 [FREE Full text] [doi: 10.1002/14651858.CD011119.pub2] [Medline: 27409972]
8. Shimokawa K, Lambert MJ, Smart DW. Enhancing treatment outcome of patients at risk of treatment failure: meta-analytic and mega-analytic review of a psychotherapy quality assurance system. J Consult Clin Psychol 2010 Jun;78(3):298-311. [doi: 10.1037/a0019247] [Medline: 20515206]
9. Boswell JF, Kraus DR, Miller SD, Lambert MJ. Implementing routine outcome monitoring in clinical practice: benefits, challenges, and solutions. Psychother Res 2015;25(1):6-19. [doi: 10.1080/10503307.2013.817696] [Medline: 23885809]
10. Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, WHO mHealth Technical Evidence Review Group. Guidelines for reporting of health interventions using mobile phones: mobile health (mhealth) evidence reporting and assessment (mERA) checklist. Br Med J 2016 Mar 17;352:i1174. [doi: 10.1136/bmj.i1174] [Medline: 26988021]
11. Boudreaux ED, Waring ME, Hayes RB, Sadasivam RS, Mullen S, Pagoto S. Evaluating and selecting mobile health apps: strategies for healthcare providers and healthcare organizations. Transl Behav Med 2014 Dec;4(4):363-371 [FREE Full text] [doi: 10.1007/s13142-014-0293-9] [Medline: 25584085]
12. Milward J, Day E, Wadsworth E, Strang J, Lynskey M. Mobile phone ownership, usage and readiness to use by patients in drug treatment. Drug Alcohol Depend 2015 Jan 1;146:111-115. [doi: 10.1016/j.drugalcdep.2014.11.001] [Medline: 25468818]
13. Drumm JW, Morne S, Davey M. Deloitte US. 2017. Smart Everything, Everywhere: Mobile Consumer Survey 2017 - The Australian Cut URL: https://www2.deloitte.com/au/mobile-consumer-survey [accessed 2020-05-26]
14. Garnett C, Crane D, West R, Brown J, Michie S. Identification of behavior change techniques and engagement strategies to design a smartphone app to reduce alcohol consumption using a formal consensus method. JMIR Mhealth Uhealth 2015 Jun 29;3(2):e73 [FREE Full text] [doi: 10.2196/mhealth.3895] [Medline: 26123578]
15. Han M, Lee E. Effectiveness of mobile health application use to improve health behavior changes: a systematic review of randomized controlled trials. Healthc Inform Res 2018 Jul;24(3):207-226 [FREE Full text] [doi: 10.4258/hir.2018.24.3.207] [Medline: 30109154]
16. Gondek D, Edbrooke-Childs J, Fink E, Deighton J, Wolpert M. Feedback from outcome measures and treatment effectiveness, treatment efficiency, and collaborative practice: a systematic review. Adm Policy Ment Health 2016 May;43(3):325-343 [FREE Full text] [doi: 10.1007/s10488-015-0710-5] [Medline: 26744316]
17. Davidson K, Perry A, Bell L. Would continuous feedback of patient's clinical outcomes to practitioners improve NHS psychological therapy services? Critical analysis and assessment of quality of existing studies. Psychol Psychother 2015 Mar;88(1):21-37. [doi: 10.1111/papt.12032] [Medline: 24850588]
18. Carlier I, Meuldijk D, van Vliet IM, van Fenema E, van der Wee NJ, Zitman F. Routine outcome monitoring and feedback on physical or mental health status: evidence and theory. J Eval Clin Pract 2012 Feb;18(1):104-110. [doi: 10.1111/j.1365-2753.2010.01543.x] [Medline: 20846319]
19. NSW Mental Health Commission. 2014. Living Well: A Strategic Plan for Mental Health in NSW 2014-2024 URL: https://nswmentalhealthcommission.com.au/resources/living-well-strategic-plan-for-mental-health-in-nsw-2014-2024 [accessed 2020-05-18]
20. Finn SE, Tonsager ME. Therapeutic effects of providing MMPI-2 test feedback to college students awaiting therapy. Psychol Assess 1992;4(3):278-287. [doi: 10.1037/1040-3590.4.3.278]
21. Public Health England. 2015. Improving Mutual Aid Engagement: A Professional Development Resource URL: http://webarchive.nationalarchives.gov.uk/20170807160728/http://www.nta.nhs.uk/r-Evidence%20and%20Guidance.aspx [accessed 2020-05-18]
22. Kelly J, Yeterian J. The role of mutual-help groups in extending the framework of treatment. Alcohol Res Health 2011;33(4):350-355 [FREE Full text] [Medline: 23580019]

23. Kaskutas LA, Borkman TJ, Laudet A, Ritter LA, Witbrodt J, Subbaraman MS, et al. Elements that define recovery: the experiential perspective. J Stud Alcohol Drugs 2014 Nov;75(6):999-1010 [FREE Full text] [doi: 10.15288/jsad.2014.75.999] [Medline: 25343658]
24. The National Institute for Health and Care Excellence. 2011. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking (High-Risk Drinking) and Alcohol Dependence URL: https://www.nice.org.uk/guidance/cg115 [accessed 2020-05-18]
25. SMART Recovery Australia. 2019. Our Reach URL: https://smartrecoveryaustralia.com.au/training-register-for-training/ [accessed 2020-05-18]
26. Ferri M, Amato L, Davoli M. Alcoholics anonymous and other 12-step programmes for alcohol dependence. Cochrane Database Syst Rev 2006 Jul 19(3):CD005032. [doi: 10.1002/14651858.CD005032.pub2] [Medline: 16856072]
27. Beck AK, Forbes E, Baker AL, Kelly PJ, Deane FP, Shakeshaft A, et al. Systematic review of SMART recovery: outcomes, process variables, and implications for research. Psychol Addict Behav 2017 Feb;31(1):1-20. [doi: 10.1037/adb0000237] [Medline: 28165272]
28. Kelly PJ, Robinson LD, Baker AL, Deane FP, McKetin R, Hudson S, et al. Polysubstance use in treatment seekers who inject amphetamine: drug use profiles, injecting practices and quality of life. Addict Behav 2017 Aug;71:25-30. [doi: 10.1016/j.addbeh.2017.02.006] [Medline: 28242532]
29. Chan A, Tetzlaff J, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Br Med J 2013 Jan 8;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
30. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of web-based and mobile health interventions. J Med Internet Res 2011 Dec 31;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
31. Kelly PJ, Raftery D, Deane FP, Baker AL, Hunt D, Shakeshaft A. From both sides: participant and facilitator perceptions of SMART recovery groups. Drug Alcohol Rev 2017 May;36(3):325-332. [doi: 10.1111/dar.12416] [Medline: 27246699]
32. Horvath AT, Yeterian J. SMART recovery: self-empowering, science-based addiction recovery support. J Groups Addict Recover 2012 Apr;7(2-4):102-117. [doi: 10.1080/1556035X.2012.705651]
33. Gray RM, Kelly PJ, Beck AK, Baker AL, Deane FP, Neale J, et al. A qualitative exploration of SMART recovery meetings in Australia and the role of a digital platform to support routine outcome monitoring. Addict Behav 2020 Feb;101:106144. [doi: 10.1016/j.addbeh.2019.106144] [Medline: 31648139]
34. GHO Sydney. URL: http://www.ghosydney.com [accessed 2020-05-26]
35. The National Institute for Health and Care Excellence. 2008. Drug Misuse: Psychosocial Interventions URL: https://www.nice.org.uk/guidance/cg51/evidence/drug-misuse-psychosocial-interventions-full-guideline-pdf-195261805 [accessed 2020-05-18]
36. SMART Recovery Australia. 2015. SMART Recovery Facilitator Training Manual: Practical Information and Tools to Help You Facilitate a SMART Recovery Group URL: http://www.anzctr.org.au/Steps11and12/377336-(Uploaded-17-04-2019-09-10-15)-Study-related%20document.docx [accessed 2020-05-26]
37. SMART Recovery Australia. 2016. SMART Recovery Australia Participants' Manual: Tools and Strategies to Help You Manage Addictive Behaviours URL: http://www.anzctr.org.au/Steps11and12/377336-(Uploaded-17-04-2019-09-10-15)-Study-related%20document.docx [accessed 2020-05-26]
38. Wilson KG, Sandoz EK, Kitchens J, Roberts M. The valued living questionnaire: defining and measuring valued action within a behavioral framework. Psychol Rec 2017 Jun 30;60(2):249-272. [doi: 10.1007/bf03395706]
39. Miller W, Rollnick S. Motivational Interviewing: Preparing People to Change Addictive Behavior. Third Edition. New York, USA: Guildford Press; 2013.
40. Nikolaos KF. Assessment of homework completion. In: Kazantzis N, Deane FP, Ronan KR, L'Abate L, editors. Using Homework Assignments in Cognitive Behavior Therapy. New York, USA: Routledge Taylor & Francis Group; 2005:50-60.
41. NADA. 2009. NGO Drug and Alcohol and Mental Health Information Management Project: Determining the Treatment Outcomes Data Collection Set URL: https://www.nada.org.au/wp-content/uploads/2018/06/determining_the_data_collection_set_dec09.pdf [accessed 2020-05-15]
42. Schluter MG, Hodgins DC, Wolfe J, Wild TC. Can one simple questionnaire assess substance-related and behavioural addiction problems? Results of a proposed new screener for community epidemiology. Addiction 2018 Aug;113(8):1528-1537. [doi: 10.1111/add.14166] [Medline: 29357188]
43. Neale J, Vitoratou S, Finch E, Lennon P, Mitcheson L, Panebianco D, et al. Development and validation of 'sure': a patient reported outcome measure (PROM) for recovery from drug and alcohol dependence. Drug Alcohol Depend 2016 Aug 1;165:159-167 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.06.006] [Medline: 27344196]
44. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 2002 Aug;32(6):959-976. [doi: 10.1017/s0033291702006074] [Medline: 12214795]

45. da Rocha NS, Power MJ, Bushnell DM, Fleck MP. The EUROHIS-QOL 8-item index: comparative psychometric properties to its parent WHOQOL-BREF. Value Health 2012 May;15(3):449-457 [FREE Full text] [doi: 10.1016/j.jval.2011.11.035] [Medline: 22583455]
46. Network of Alcohol & Other Drugs Agencies. 2012. Using the Client Outcomes Management System (COMS) URL: https://www.nada.org.au/wp-content/uploads/2019/03/Technical-Report_COMS-Data-Report-2013-Final.pdf [accessed 2020-05-26]
47. Lawrinson P, Copeland J, Indig D. National Drug and Alcohol Research Centre (NDARC). 2003. The Brief Treatment Outcome Measure: Opioid Maintenance Pharmacotherapy (BTOM) Manual URL: https://ndarc.med.unsw.edu.au/resource/brief-treatment-outcome-measure-opioid-maintenance-pharmacotherapy-btom-manual [accessed 2020-05-26]
48. Noar SM, Benac CN, Harris MS. Does tailoring matter? Meta-analytic review of tailored print health behavior change interventions. Psychol Bull 2007 Jul;133(4):673-693. [doi: 10.1037/0033-2909.133.4.673] [Medline: 17592961]
49. Hoeppner BB, Schick MR, Kelly LM, Hoeppner SS, Bergman B, Kelly JF. There is an app for that - or is there? A content analysis of publicly available smartphone apps for managing alcohol use. J Subst Abuse Treat 2017 Nov;82:67-73. [doi: 10.1016/j.jsat.2017.09.006] [Medline: 29021117]
50. Duncan EA, Murray J. The barriers and facilitators to routine outcome measurement by allied health professionals in practice: a systematic review. BMC Health Serv Res 2012 May 22;12:96 [FREE Full text] [doi: 10.1186/1472-6963-12-96] [Medline: 22506982]
51. Berrouiguet S, Baca-García E, Brandt S, Walter M, Courtet P. Fundamentals for future mobile-health (mhealth): a systematic review of mobile phone and web-based text messaging in mental health. J Med Internet Res 2016 Jun 10;18(6):e135 [FREE Full text] [doi: 10.2196/jmir.5066] [Medline: 27287668]
52. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. JMIR Mhealth Uhealth 2015 Mar 11;3(1):e27 [FREE Full text] [doi: 10.2196/mhealth.3422] [Medline: 25760773]
53. Stoyanov SR, Hides L, Kavanagh DJ, Wilson H. Development and validation of the user version of the mobile application rating scale (uMARS). JMIR Mhealth Uhealth 2016 Jun 10;4(2):e72 [FREE Full text] [doi: 10.2196/mhealth.5849] [Medline: 27287964]
54. Henson P, Wisniewski H, Hollis C, Keshavan M, Torous J. Digital mental health apps and the therapeutic alliance: initial review. BJPsych Open 2019 Jan;5(1):e15 [FREE Full text] [doi: 10.1192/bjo.2018.86] [Medline: 30762511]
55. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the working alliance inventory. Psychother Res 2006 Jan;16(1):12-25. [doi: 10.1080/10503300500352500]
56. Munder T, Wilmers F, Leonhart R, Linster HW, Barth J. Working alliance inventory-short revised (WAI-SR): psychometric properties in outpatients and inpatients. Clin Psychol Psychother 2010;17(3):231-239. [doi: 10.1002/cpp.658] [Medline: 20013760]
57. Falkenström F, Hatcher RL, Holmqvist R. Confirmatory factor analysis of the patient version of the working alliance inventory--short form revised. Assessment 2015 Oct;22(5):581-593. [doi: 10.1177/1073191114552472] [Medline: 25271007]
58. Smits D, Luyckx K, Smits D, Stinckens N, Claes L. Structural characteristics and external correlates of the working alliance inventory-short form. Psychol Assess 2015 Jun;27(2):545-551. [doi: 10.1037/pas0000066] [Medline: 25642928]
59. Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft G, Brewin CR, Wing J, editors. Measuring Mental Health Needs. London, UK: Gaskell/Royal College of Psychiatrists; 1992.
60. Medibank Private Health Insurance. 2013. The Case for Mental Health Reform in Australia: A Review of Expenditure and System Design URL: https://www.medibank.com.au/Client/Documents/Pdfs/The_Case_for_Mental_Health_Reform_in_Australia.pdf [accessed 2020-05-26]
61. Major G, Ling R, Searles A, Niddrie F, Kelly A, Holliday E, et al. The costs of confronting osteoporosis: cost study of an Australian fracture liaison service. JBMR Plus 2019 Jan;3(1):56-63 [FREE Full text] [doi: 10.1002/jbm4.10046] [Medline: 30680364]
62. Ling R, Rush A, Carter C, Carpenter J, Watson PH, Byrne JA, et al. An Australian biobank certification scheme: a study of economic costs to participating biobanks. Biopreserv Biobank 2018 Feb;16(1):53-58. [doi: 10.1089/bio.2017.0095] [Medline: 29215912]
63. Yoong SL, Grady A, Wiggers J, Flood V, Rissel C, Finch M, et al. A randomised controlled trial of an online menu planning intervention to improve childcare service adherence to dietary guidelines: a study protocol. BMJ Open 2017 Sep 11;7(9):e017498 [FREE Full text] [doi: 10.1136/bmjopen-2017-017498] [Medline: 28893755]
64. NSW Health - NSW Government. 2015. Nsw Minimum Data Set (MDS) for Drug and Alcohol Treatment Services URL: https://www.health.nsw.gov.au/aod/Pages/minimum-data-set.aspx [accessed 2020-05-26]
65. Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, et al. The severity of dependence scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 1995 May;90(5):607-614. [doi: 10.1046/j.1360-0443.1995.9056072.x] [Medline: 7795497]
66. Hides L, Dawe S, Young R, Kavanagh D. The reliability and validity of the severity of dependence scale for detecting cannabis dependence in psychosis. Addiction 2007 Jan;102(1):35-40. [doi: 10.1111/j.1360-0443.2006.01669.x] [Medline: 17207121]

67. Kaye S, Darke S. Determining a diagnostic cut-off on the severity of dependence scale (SDS) for cocaine dependence. Addiction 2002 Jun;97(6):727-731. [doi: 10.1046/j.1360-0443.2002.00121.x] [Medline: 12084142]
68. Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry 2003 Feb;60(2):184-189. [doi: 10.1001/archpsyc.60.2.184] [Medline: 12578436]
69. Andrews G, Slade T. Interpreting scores on the Kessler psychological distress scale (K10). Aust N Z J Public Health 2001 Dec;25(6):494-497. [doi: 10.1111/j.1467-842x.2001.tb00310.x] [Medline: 11824981]
70. Hides L, Lubman DI, Devlin H, Cotton S, Aitken C, Gibbie T, et al. Reliability and validity of the Kessler 10 and patient health questionnaire among injecting drug users. Aust N Z J Psychiatry 2007 Feb;41(2):166-168. [doi: 10.1080/00048670601109949] [Medline: 17464695]
71. Schmidt S, Mühlan H, Power M. The EUROHIS-QOL 8-item index: psychometric results of a cross-cultural field study. Eur J Public Health 2006 Aug;16(4):420-428. [doi: 10.1093/eurpub/cki155] [Medline: 16141303]
72. Schmidt S, Power M, Bullinger M, Nosikov A. The conceptual relationship between health indicators and quality of life: results from the cross-cultural analysis of the EUROHIS field study. Clin Psychol Psychother 2005 Jan;12(1):28-49. [doi: 10.1002/cpp.432]
73. Schmidt S, Power M. Cross-cultural analyses of determinants of quality of life and mental health: results from the Eurohis study. Soc Indic Res 2006 May;77(1):95-138 [FREE Full text] [doi: 10.1007/s11205-005-5555-y]
74. Neale J, Tompkins C, Wheeler C, Finch E, Marsden J, Mitcheson L, et al. 'You're all going to hate the word 'recovery' by the end of this': service users' views of measuring addiction recovery. Drugs 2014 Aug 4;22(1):26-34. [doi: 10.3109/09687637.2014.947564]
75. Health Issues Centre. 2015. Paying and Reimbursing Consumers: Position Statement URL: https://www.healthissuescentre.org.au [accessed 2020-05-15]
76. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
77. Kellehear A. The Unobtrusive Researcher: A Guide to Methods. Sydney, Australia: Allen & Unwin; 1993.
78. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991 Feb;59(1):12-19. [doi: 10.1037//0022-006x.59.1.12] [Medline: 2002127]
79. Lambert MJ, Whipple JL, Kleinstäuber M. Collecting and delivering progress feedback: a meta-analysis of routine outcome monitoring. Psychotherapy (Chic) 2018 Dec;55(4):520-537. [doi: 10.1037/pst0000167] [Medline: 30335463]
80. Jensen-Doss A, Haimes EM, Smith AM, Lyon AR, Lewis CC, Stanick CF, et al. Monitoring treatment progress and providing feedback is viewed favorably but rarely used in practice. Adm Policy Ment Health 2018 Jan;45(1):48-61 [FREE Full text] [doi: 10.1007/s10488-016-0763-0] [Medline: 27631610]
81. Michie S, Yardley L, West R, Patrick K, Greaves F. Developing and evaluating digital interventions to promote behavior change in health and health care: recommendations resulting from an international workshop. J Med Internet Res 2017 Jun 29;19(6):e232 [FREE Full text] [doi: 10.2196/jmir.7126] [Medline: 28663162]
82. International Committe of Medical Journal Editors. 2019. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals URL: http://www.icmje.org/icmje-recommendations.pdf [accessed 2020-05-18]

Abbreviations

AOD: alcohol and other drug
BBV: blood-borne virus
BTOM-C: Brief Treatment Outcome Measure-Concise
COMS: Client Outcome Management System
CSRI: Client Service Receipt Inventory
D-WAI: Digital Working Alliance Inventory
HREC: Human Research Ethics Committee
ISLHD: Illawarra Shoalhaven Local Health District
K10: Kessler 10 scale
MARS: Mobile App Rating Scale
MDS: minimum data set
mHealth: mobile health
NADA: Network of Alcohol and other Drug Agencies
NSW: New South Wales
RCI: reliable change index
ROM: routine outcome monitoring
SMART: Self-management And Recovery Training
SURE: Substance Use Recovery Evaluator
uMARS: Mobile Application Rating Scale–User Version

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Protocol

Development of an Intervention to Support the Reproductive Health of Cambodian Women Who Seek Medical Abortion: Research Protocol

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Abstract

Background: In Cambodia, abortion has been legally permitted on request during the first trimester of pregnancy since 1997. However, although there has been an increase in the percentage of women having induced abortion and medical abortion, there has also been a decrease in the percentage of women who say they received help from a health worker with their abortion. These data point toward the *demedicalization* of abortion, and although medical abortion has been shown to be safe, there are concerns about safety, given the variety of available products and counseling provided. These concerns are particularly relevant for female factory workers, who typically come from rural areas where access to good health care and information about reproductive health care is limited.

Objective: This study aims to understand the reproductive health needs of female Cambodian garment factory workers after medical abortion from a multidisciplinary and mixed-methods perspective, focusing on how they seek and share medical abortion- and health-related information; how they use their mobile phones for this and other purposes; what cultural challenges exist around reproductive health; and how they might be magnified or mitigated by mobile phones, linguistic challenges around health care, and mobile phone use. The main purpose of this study is to combine multidisciplinary methods, theories, and expertise to gain new, culturally grounded insights into family planning and medical abortion in Cambodia, but the findings could help inform the development of a relevant intervention to support comprehensive postabortion care.

Methods: The methods proposed are interviews and participant observation among factory workers, health providers, and mobile phone providers; a linguistic analysis of relevant data (interview transcripts, web-based sources, and other fieldwork materials); and digital methods to understand what kind of information about medical abortion exists on the web in Cambodia and how it is accessed by the targeted population.

Results: The data collection part of the project will end on December 31, 2020. The team conducted 67 semistructured interviews with female factory workers, women who sought a medical abortion, health providers, and mobile phone providers; participant observation with factory workers and health providers; and an analysis of YouTube and Facebook to understand what kind of information is available, who creates it, and how it is used. The team is currently performing data analysis, and the findings are clustered around (1) the use of mobile phones and digital resources for health-related and medical abortion-related information, (2) the experience of medical abortion care, and (3) the development of an intervention through edutainment videos.

Conclusions: The project highlights both the widely untapped potential of using digital platforms (especially YouTube and Facebook) to distribute accurate information on medical abortion and the challenges in providing individual information via mobile phones while respecting individuals' privacy.

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KEYWORDS

reproductive health; abortion; Cambodia; mHealth; mobile phone

Introduction

In Cambodia, abortion has been legally available on request during the first trimester of pregnancy since 1997 [1,2]. Drugs used in medical abortion containing mifepristone and misoprostol were approved in 2010 and made available in a restricted number of health facilities [2,3]. Although nationwide surveys report an increase in the percentage of women having induced abortion and medical abortion, they also report a decrease in the percentage of women who say they received help from a health worker with their abortion. These data point toward the *demedicalization* of abortion, a phenomenon that is being observed globally, as evidenced by the increased use of medical abortion pills at home with limited contact with trained health care professionals [4]. Although medical abortion has been shown to be safe and up to 98% effective for early pregnancy terminations, there are concerns about safety, given the variety of available products and counseling provided [5]. Further research on this topic is needed.

The Cambodian garment industry accounts for a significant proportion of formal employment of the female labor force and is an important contributor to Cambodia's economy. As of 2015, there were 837 garment factories in Cambodia, providing formal employment to approximately 700,000 garment factory workers, of which approximately 85% are women, most of whom are of reproductive age [6,7]. It has been estimated that one-fourth of all Cambodian women between 18 and 29 years are working in garment factories. Typically, these women come from rural areas where access to high-quality information about reproductive health is limited. Furthermore, it is also likely that migrating to urban areas puts women in a disadvantaged position as they are no longer able to receive family or community support and are more vulnerable to sexual exploitation, often resulting in unwanted pregnancies and sexually transmitted infections [6].

Marie Stopes International Cambodia (MSIC) is part of the Marie Stopes International (MSI) global partnership. MSIC has been delivering high-quality sexual and reproductive health services in Cambodia since 1998, covering seven provinces. MSIC provides family planning, contraception, safe abortion, and postabortion care within the legal framework of Cambodia. In addition, MSIC operates a contact center that serves as a link between MSIC and the general public for all the services that MSIC provides and for general information about sexual and reproductive health, including family planning, safe abortion, postabortion care, and other sexual and reproductive health issues. MSIC has strong relationships with garment factories having undertaken 2 relevant projects in recent years: Partnering to Save Lives (PSL) and Worker Health. PSL is a project funded by the Australian Department of Foreign Affairs and Trade and is a collaboration between MSIC, CARE Cambodia, and Save the Children that started in 2013. PSL conducted a baseline survey of the knowledge, attitudes, and practices of garment factory workers in 2014 and 2016, which provides background information about our research participants in terms of mobile phone ownership, awareness of abortion services, and contraception options [7]. Worker health is a project funded by the United States Agency for International Development and a collaboration between MSIC and the Population Council to increase the access of garment factory workers to and utilization of health services, particularly high-quality reproductive health and voluntary family planning services. Their systematic review of garment sector health interventions showed that there was limited use of mobile health services [6].

This project, a collaboration between the London School of Hygiene and Tropical Medicine (LSHTM), the School of Oriental and African Studies (SOAS) University of London, King's College London, and MSIC, funded by the United Kingdom Arts and Humanities Research Council (AHRC), aims to complement previous and ongoing projects but focuses particularly on support for reproductive health after medical abortion and health-seeking behaviors in general. Understanding the reproductive health needs of female Cambodian garment factory workers after medical abortion, together with understanding how they seek and share information and how they use mobile phones, could help inform the development of a relevant intervention to support comprehensive postabortion care. To do so, however, it is necessary to understand (1) how they use mobile phones and how they fit within offline practices of information sharing; (2) the cultural challenges around reproductive health and how they might be magnified or mitigated by mobile phones; and (3) the linguistic challenges around mobile phone use, for example, language input, or oral versus written practices.

Women seeking medical abortion from clinics such as MSI are routinely offered a follow-up appointment, but many will not attend unless they have a problem. For those seeking medical abortion from informal clinics and pharmacies, very little is known about outcomes such as follow-up rates, use of contraception, repeat abortion, and complications (such as uterine rupture or incomplete abortion), and observational studies report that women are often given little information on how to use medications and postabortion family planning [2]. Against this background, mobile phone communication is a potential way to maintain communication with women after they have obtained medical abortion drugs from a health care

provider by overcoming distance and access barriers and potentially providing new modes of interaction, such as synchronous and asynchronous voice communications through instant messaging apps. There is an emerging body of evidence supporting the feasibility, acceptability, and efficacy of digital interventions for behavior change [8,9]. However, as smartphones become increasingly common in low- and middle-income countries, a new generation of digital health apps is being developed without considering the populations they target from a sociocultural and linguistic perspective. This is the gap that the collaboration between LSHTM, SOAS, and Marie Stopes International addresses: bringing health care, sociocultural, linguistic, and local expertise together to understand how mobile phones, existing communication patterns, and health care interventions can come together in a way that is cost- and time-effective for the providers and fit into the cultural patterns of language, information exchange, and social interactions of the targeted population.

This study aims to conduct a joint research project using qualitative methods from a multidisciplinary perspective to, first, study health information gathering and sharing among factory workers and reproductive health issues after medical abortion in Cambodia from medical, cultural, and information-sharing practice perspectives; and second, design a pilot intervention delivered by mobile phone to support the reproductive health of women who work in factories around Phnom Penh.

Methods

Methodological Approach

This study will focus on the following populations: first, women working in selected garment factories around Phnom Penh; second, private health care providers near selected garment factories; and third, women working in garment factories seeking medical abortion from private providers near garment factories. Women working in garment factories will be selected if they are willing to be interviewed and observed at work and in their living quarters, own or do not own a mobile phone, are using contraception or have used medical abortion pills or not, and are 18 years and older. Garment factories will be selected if they are located near Phnom Penh and have an existing relationship with MSIC. Private providers will be selected based on whether they are a pharmacy or small private clinic, are located near Phnom Penh, are selling medical abortion pills (not limited to registered products), the manager and at least one worker is willing to participate, and are employing workers aged 18 years or older. Women seeking medical abortion from private providers will be invited to participate in the study based on if they (1) are using medical abortion pills, purchased from study pharmacies during the study period; (2) purchased medication by themselves; (3) had access to a mobile phone and were willing to be followed up by phone with questions about their abortion periodically after taking the first drug; (4) are 18 years and older; (5) if their gestational age is less than 9 weeks (calculated from the last menstrual period), have a confirmed pregnancy (self-reported); and (6) are willing and able to give informed consent.

The research project in Cambodia will draw on qualitative methods from public health and the humanities/social sciences. One of the goals will be to use more ethnographic perspectives within the context of the intervention mapping (IM) approach commonly used to develop health behavior change interventions. Ethnographic work will be employed to reach a holistic picture of the environment in which the women live and work, without focusing exclusively or necessarily on reproductive health care. Ethnographic work will take place at the very beginning of the project as an exercise in idea generation and contextualization for the subsequent phase, IM. IM is a well-established methodology for conducting interdisciplinary intervention development and is flexible enough to be adapted to different cultural settings [10]. It will allow the research partnership to build on the IM approach recently used by LSHTM colleagues (Ona McCarthy/CF) to develop an intervention to support contraception use in Palestine, Bolivia, and Tajikistan [11] as well as qualitative methods used by the SOAS researchers, methods that require constant refining of research questions [12], and user-centered design principles [13]. IM is a cumulative process that often necessitates moving back and forth through the following steps: (1) needs assessment, (2) specifying behavior change resulting from the intervention, (3) designing the intervention, (4) producing and refining the intervention content, (5) planning intervention implementation, and (6) planning intervention evaluation. This project will focus on steps 1-4 and will bring a cultural and sociological perspective to these phases. The methodological collaboration will focus, in particular, on the needs assessment and intervention design phases. A key aspect of the partnership will be to explore and discuss findings in relation to the theories and perspectives of each of the disciplines contributing to it. The following research activities are planned, with activities 1 to 3 focusing on IM step 1: (1) participant observation and interviews regarding the current behaviors of women in health information gathering and sharing, (2) interviews with private providers and garment factory infirmary workers in the vicinity of garment factories that provide or refer for medical abortion, (3) interviews with women seeking medical abortion from private providers, (4) specifying behavior change to result from the intervention, (5) designing the intervention, and (6) producing and refining intervention content.

Activity 1: Participant Observation and Interviews Regarding Women's Current Behaviors in Health Information Gathering and Sharing

The objectives of activity 1 are to understand how women look for and share information related to health care, in particular, abortion and postabortion services, in their everyday life; to understand the local context, in terms of resources, access, and geography, and to generate ideas for activity 2. Field research will begin with observations, *hanging out*, and semistructured interviews among female factory workers in the targeted neighborhood. To gain a holistic understanding of *needs* beyond specific health care–related ones and thus discover what kind of information channels they use, and who they trust, the team will try to recruit a larger pool of participants than those who will participate in activity 2 (eg, 25-50 participants). Researchers will conduct participant observation in key places such as

garment factories with links to MSIC (eg, during lunch breaks and before and after work), garment factory infirmaries, pharmacies, and other places where young women meet in their leisure time. Locations and potential participants will be identified with the help of the project's Cambodian staff according to the criteria discussed earlier. Fieldwork will be carried out by the main principal investigators (PIs) and UK-based students with Khmer language skills and by a Cambodian research assistant to ensure that it is done in a culturally sensitive manner.

A possible plan for this initial fieldwork is as follows. The researchers will live in a guesthouse in the area to experience the environment and familiarize themselves with life in the neighborhood (eg, mapping out health care–related resources, including restaurants, shops, and other points of congregation; experiencing life inside and outside the factories and where women live; etc). On the first day, they will go to the factories that have agreed to participate in the project and be introduced to the staff and potential research participants (Multimedia Appendix 1). The first week will be spent *hanging out* at both the factory and outside, befriending different potential participants, having meals with them, and, if they agree, joining them for activities outside the factory or to visit their living quarters. The researchers will explain the purpose of their research and ask for permission to take photos and record conversations if appropriate (Multimedia Appendix 2). Alongside participant observation and hanging out with women, researchers will conduct participant observation in local pharmacies and a clinic. With the consent of the participants, the researchers will follow a nurse or an administrative person for a day to see who they interact with; what kind of questions they ask; and how they use computers, phones, and mobile phones. When there are close interactions with the clinic's patients, our role and project will be explained, and researchers will stay only with the patient's consent. Similarly, participant observation in a private provider will include one of the researchers spending a few hours over different days in the pharmacy, observing the flux of people, and how they interact with providers to ask for health care–related information. Halfway through this first period of fieldwork, the researchers will identify among their contacts key informants to interview. The interviews will start with a general overview of informants' use of mobile phones and then focus on health care needs and information-seeking tactics (Multimedia Appendix 3). If and when appropriate, researchers will also ask interviewees to show (rather than only describe) how they look for health-related information on their mobile phones. This phase will be followed by virtual observation of websites and specific social network pages mentioned by interviewees [14]. If invited, the researchers will also follow interviewees on social media or *friend* them on instant messaging programs or social networks. Due to privacy concerns, no material or direct quotes from these specific sources will be used in a way that could make the research participants identifiable. For example, if screenshots are captured, they will be transcribed, stripped of any identifying element, and then translated. The translation will not be used verbatim in any publication or public presentation. If quotes or images or screenshots are shown or published, they will be a composite of source material (ethical procedures are given in the *Ethical Considerations and Research Governance* section. The field site will remain the same for the duration of the project, and the UK-based and/or Cambodia-based researchers might go back at regular intervals to conduct follow-up observations and interviews.

Following feedback from reviewers from a medical background, who asked for clarifications about observation and interaction-based research methods that are common in the social sciences but interpreted differently in the medical sciences, the PIs added a clarification on how they were planning to conduct fieldwork. This is added here to the original research protocol, as it highlights that one of the challenges of conducting multidisciplinary research is that different disciplines interpret differently what on the surface are the same methods (eg, interviews and participant observation). The specific feedback asked for a detailed form for guiding observations and questioned the idea of *hanging out* and *befriending participants on social media* as potentially deceptive forms of research.

There is no specific form for guiding or recording observations. As is common in ethnographic research [15], each field researcher has a personal way of keeping a field diary, which ranges from taking notes on paper or her mobile phone during the day (or simply memorizing specific moments), then writing them up in a diary form in the evening, to taking photos of events or places that seem important, to sketching, and making voice memos. The point to stress is that the researchers are not entering the field with preconceived ideas about what is important and should be noticed and what is not. Activity 1 is ethnographic, so it is aimed at gathering a holistic picture of the environment in which the women work and live, their relationships, and the places they visit. The interviews will be semistructured, not structured (characterized by a fixed set of questions), to allow interviewers to follow up on the interviewees' responses and discover themes that cannot be planned beforehand. The goal is to touch on the themes described in the protocol but in as open a way as possible, so that the researchers can follow the lead of the women rather than vice versa. In other words, instead of asking, "how do you use your mobile phone to look for health-related information," which implies that the interviewee *has* used her mobile phone to look for health-related information, the interviewer would follow up on the interviewee's description of her daily life to find out more about both mobile phone use and health-related information.

Researchers' questions and follow-up questions will not stray outside the broad headings outlined in the topic guides, but researchers will let interviewees lead the interview and talk about any topic they would like to discuss. A relationship of mutual trust between researchers and research participants is an essential element of good ethnographic research, and it is what leads to findings of what really matters to research participants, rather than what researchers think matters**.** Similarly, the researchers will not ask to follow factory workers on social media but will accept any invitation to *friend* that is offered them, asking specifically if anonymized data can be used for data analysis. The researchers are not looking for specific information about specific individuals or screenshots of specific conversations, but there might be important and

useful information about how people communicate and engage on social media that would not be otherwise accessible. Thus, the data gathered from engagement in social media will be used for internal analysis. If a screenshot is deemed a particularly useful visual support of points we discover, the researchers might ask for permission from the person or group in the conversation to use it, appropriately anonymized, in presentations and publications. Befriending research participants on social media is by now a fairly standard research method in digital anthropology [16], and the participants are always free to defriend the researcher if they do not want to be involved with them any longer. Research participants who use social media are typically very fluent in the etiquette of friending, defriending, and managing different identities and different social circles on the web. In general, in ethnographic research, there are no findings without a relationship of trust, which is built through time and interactions. This can potentially create ethical dilemmas regarding friendships that can arise between researchers and research participants [17], but they are not about the researcher disguising or lying about her role, and they are part of the constant negotiation of being in the field, carrying out research in naturalistic rather than laboratory settings. The researchers follow the recommendations from the Association of Internet Researchers Ethics Working Committee in 2012 that highlight that "ethical decision-making is best approached through the application of practical judgment attentive to the specific context" [18].

Activity 2: Interviews With Private Providers and Garment Factory Infirmary Workers in the Vicinity of Garment Factories That Provide or Refer to Medical Abortion

The objectives of activity 2 are to understand the perspective of health care providers, such as private providers and garment factory infirmary staff, to find and share health care information, and to conduct a needs assessment. Semistructured interviews will be conducted with the staff of private providers (including pharmacies) and garment factory infirmaries where participant observation has been previously conducted to understand their perspective on how women find, share, and act on health care–related and abortion-related information. Researchers aim to interview a wide variety of stakeholders in the process as much as possible (approximately 10-20 participants), not only health care providers such as physicians and nurses but also administrative and support staff. The interviews will focus on their direct experience of being asked about health care–related and abortion-related information in person and via other means (eg, by phone) as well as their observations on the topic. Interviewers will ask questions about the characteristics of providers and staff, including age, sex, education level, and the number of years worked, their current medical abortion, and emergency contraception sales. When possible, interviewers will attempt to ground their responses using specific artifacts such as web pages, mobile phones, and anything else that suggests itself as a potential productive avenue of inquiry from the preceding participant observation and interviews. Private provider managers will be approached by a research assistant who will explain the study and inform them of the tasks that will be required by participating staff. If private provider managers consent to participate, they will be asked to sign an informed consent form. All workers at the participating provider will then be approached and asked for informed consent to participate in the study (the *Ethical Considerations and Research Governance* section provides further details).

Activity 3: Interviews With Women Seeking Medical Abortion Services From Private Providers

The objectives of activity 3 are to increase the understanding of the local context, reasons for abortion, postabortion care issues, and mobile phone use; to increase the understanding about the feasibility of recruitment of women seeking medical abortion from pharmacies to phone (digital health) follow-up support and research studies; and to seek views on possible intervention(s). An exploratory qualitative study of approximately 10 to 20 semistructured interviews and follow-up with women seeking medical abortion will be conducted by a member of the research team. Participants will be recruited by working together with private providers. The *Ethical Considerations and Research Governance* section provides more details on the recruitment and consent procedures. Participants will be offered an initial face-to-face interview at the location of their choice, but because of potential privacy and confidentiality issues, the interviews will be conducted by phone if they prefer. Ideally, a short initial interview will be conducted at the time when the woman attends the private provider. If the participant consents, additional short interviews will be undertaken at 2 and 4 weeks to learn more about the women's experience over the initial postabortion period. These interviews will also be conducted at the location of the participants' choice, either face-to-face or by phone. Interviews will be recorded and transcribed if possible and with consent. In addition, there may be additional communication by mobile phone between the participants and Cambodian researchers. This could take the form of the researcher asking, "how are you?" or "if you have any problems, please call me." No messages will contain terms related to abortion, contraception, or MSI. The aim of this communication is to document further any postabortion care issues and provide support where appropriate. Phone communications will be anonymized and documented.

Activity 4: Specifying Behavior Change Resulting From the Intervention

The objective of activity 4 is to analyze and discuss the findings of activities 1 to 3 to specify behavior changes resulting from the intervention. The study population will be described in terms of sociodemographic characteristics using descriptive statistics. With the interviewees' permission, interviews will be recorded and transcribed and then translated into English, and a thematic analysis undertaken. A coding frame will be developed iteratively to analyze the first few transcripts and will then be used to code all transcripts. The findings from activities 1 to 3 will be summarized and synthesized and discussed in research seminars with a range of stakeholders in Cambodia and the United Kingdom to specify potential behavior changes resulting from the intervention. The goal is to create a map of different types of communication patterns and personas that correspond to each behavior. Personas are frequently used in

human-computer interaction research [19] and are an example of the type of methodological cross-pollination the project aims to create.

Activity 5: Designing the Intervention

Activity 5 aims to seek views on possible interventions; to co-design a potential intervention with input from garment factory workers, medical abortion clients, pharmacists, MSIC research and marketing team, call center, and external organizations as required; and to develop specific message content, tone, and style. This activity builds on outputs from activity 4. The intervention components will be developed based on up-to-date empirical evidence and in collaboration with service users and providers. For the intervention design, the investigators will choose theory-informed behavior change methods to include in the intervention and deciding how to deliver them, as common in IM mapping approaches, but drawing from theories in the health field and cultural/information studies, to find the best fit with local circumstances, language, and effective interventions for supporting reproductive health after medical abortion. Although focus groups can be useful for generating ideas among participants for intervention development, this could be challenging for our target population of factory workers seeking medical abortion from private pharmacies in terms of logistics and privacy concerns.

It is anticipated that service users and health care providers will be recruited to participate in this part of the study in the same way as with activities 2 and 3. The researchers plan to undertake approximately 10 to 20 interviews with service users and providers. The study team will provide participants with information regarding the aim of the study and obtain consent as per activities 2 and 3. The researcher will elicit participants' preferences for the intervention and seek comments from them on any preliminary messages/content developed, specifically asking about the acceptability, comprehensibility, and appropriateness of the messages/content developed and suggestions for improvement. According to the feedback received, messages will be retained, discarded, or modified, and retested, if necessary. If it is felt that an intervention delivered by a mobile phone is feasible, the research team will simultaneously evaluate digital health communication software options to deliver the intervention (eg, voice or instant messaging) with an appropriate design and level of technology with or without creative content providers. The researchers will ensure that any intervention content is consistent with the Cambodian Ministry of Health guidance.

Activity 6: Producing and Refining Intervention Content

The objectives of activity 6 are to further seek service users' views on acceptability, comprehensibility, and appropriateness of the messages developed and suggestions for improvement. In particular, the aims are to evaluate the reliability of technology, comprehensibility, and acceptability of message content; to produce and refine the intervention content; and to describe and publish potential intervention(s) to be evaluated. This will build further on activity 6 by testing actual messages with participants. The intervention will be tested and modified with input from approximately 10 to 20 clients identified by the study team. It is anticipated that service users and health care providers will be recruited to participate in this part of the study in the same way as with activities 2 and 3. Information for participants and consent forms will be adapted accordingly. If a digital health intervention is developed, participants will be sent intervention content to their mobile phones. The researchers will seek comments regarding the messages and suggestions regarding how messages could be improved via a subsequent phone call. The participants' responses will inform the final modifications to the intervention.

Ethical Considerations and Research Governance

Ethical considerations, including informed consent procedures, measures to protect confidentiality, and potential risks and benefits to participants, are considered by participant type, as follows. For all participants, the PIs will be responsible for the overall informed consent procedures for the project. CS undertook the Introduction to Good Clinical Practice course in May 2012 and has experience in recruiting women seeking abortion services for the Mobile Technology for Improved Family Planning study in Cambodia. EO has experience in undertaking ethnographic research with garment factory workers in China and completed the Ethics in Social and Behavioral Sciences course at SOAS in January 2016. They will ensure that all researchers working on the project comply with the consent procedures outlined in the protocol. All study participants (provider managers, providers, and medical abortion clients) will be informed about the purpose of the study and the potential risks and benefits relating to their participation in the study. Participants will be 18 years and older and interviewed or engaged by researchers based in the United Kingdom and Cambodia. All the study participants have the right to choose to partake in the study or refuse to participate. Study staff will be instructed to record all refusals and to attest to obtaining informed consent from the study participants. Further details of the consent procedures are described according to the type of research participant.

In Cambodian abortion law, under certain circumstances, parental consent for an abortion is required if the woman is less than 18 years of age. Therefore, conducting research on unintended pregnancy potentially raises issues that require additional safeguards beyond the scope of the design of this research project. For example, women may feel uncomfortable to consent to participate and give honest answers if they are younger than 18 years. The researchers accept the limitation that the findings of the study will not be generalizable to women younger than 18 years. In practice, the PIs do not feel that it is appropriate to ask for proof of age. They will ask women how old they are as part of the provision of information and consent to participate in the project. If they report that they are less than 18 years of age, they will be informed that they will not be able to participate in this research project. However, they will be offered contact information for the MSI call center or the nearest clinic if they have issues that they want to discuss further.

Taking adequate steps to protect the identity of all participants is a significant assurance, given the ethical implications that arise from the sensitive nature of the research. Protecting the

privacy and confidentiality of participants will also be necessary to overcome concerns that may otherwise prevent individuals from participating in the study. In terms of data collection, data collectors (including providers and research assistants) will be trained to respect and understand how to safeguard participant confidentiality and data protection. Study participants will not be identified by name or by any other potentially identifying information (such as pharmacy name or location) in any report or publication resulting from study data. Material from web-based sources (eg, chat transcripts, photos, etc) will be gathered only with the consent of the research participants. To mitigate the risks to participants' privacy, researchers will anonymize the source as much as possible of the material that is gathered (eg, deleting the original sound files as soon as the interview is transcribed and deleting information that might make the interviewee recognizable from the transcript itself). The potential benefits outweigh the risks: digital platforms are increasingly used to search, exchange, and circulate information, including health care information, but because of the semiclosed nature of many of these platforms, very little is publicly known about the details of how this happens.

In terms of data storage, participants' contact information and names will be stored separately from questionnaires/transcripts on contact information sheets, which will link to the questionnaire and interview data using a unique personal ID for each participant. Contact information and informed consent documents will be stored in a locked cabinet in a locked room in the MSIC office. All the data forms/questionnaires will be kept under the custody of authorized personnel in locked cabinets. Data entry software, accessible only by study investigators, will be password protected, and full database access (also password protected) will be restricted. Data will be stored for 5 years after the project and then will be deleted. Photos will be downloaded daily from digital cameras or phones onto the computer of the researcher who has taken them. They will be subsequently deleted from the digital device and saved only in the computer on a password-protected folder. The photos will be labeled in a way to preserve people's privacy as much as possible, for example, through the use of pseudonyms and by deleting or anonymizing with photo editing software photos that might reveal personal data (eg, screenshots of mobile phones where the phone number is visible). As with other materials gathered, participants' contact information and names will be stored separately from questionnaires/transcripts on contact information sheets, which will link to the questionnaire and interview data using a unique personal ID for each participant. Images will be analyzed through qualitative analysis software, which will be password protected and accessible only by the study investigators. Images will be used in presentations and publications if the research participants consent. All images that are not used for those purposes will be deleted 5 years after the project, as per the data management plan. The risk of loss of confidentiality may occur if any of these procedures are inadvertently breached. All possible efforts will be made to prevent this from happening.

Further Details of Factory Workers

Activity 1 is based on qualitative ethnographic methods. The research participants will be contacted through the factory, with which there will be a memorandum of understanding. The researchers will do their utmost to avoid any factory worker feeling pressured to participate in the research project. The first phase of the activity will be observational, and the researchers will spend time in the factory to become familiar with the environment and with potential research participants. This will give potential research participants the chance to become acquainted with the researchers and to ask questions about the research in an informal and group environment. To widen the group of participants, the researchers will also rely on personal contacts of the Cambodia-based researchers and on the networks they will create once in the field, informing potential participants of the research project and the consent procedure in the same manner as in the factory. The researchers do not foresee more than the minimal risk associated with this phase of the research. Due to this and to minimize any concern about possible breaches of confidentiality, they would like approval to use oral as well as voluntary written consent. Owing to historical and cultural reasons, requiring participants who are not well educated and are from poorer backgrounds to sign written documentation, such as consent forms, can heighten their perception of the risks should confidentiality be breached. In addition, in Cambodia, signed documents may be seen as political documents rather than statements of legal facts or contracts designed to protect the research participant. The informed consent process for activity 1 will go as follows. At the beginning of the observation process, the researchers will introduce themselves and their research and tell participants that they would like to spend time informally with them. They will make it clear that participants can leave at any time or refuse any request to chat. If researchers take photos or do recordings where individuals can be identified, they will ask for permission to do so and explain how they will use such material. The researchers will anonymize any such materials as appropriate as soon as possible. For example, if they take photos of mobile phone usage, they will download the photos to their computers and blackout or photoshop information that might make the participants recognizable, such as phone numbers, avatars, and other personal information. Before the first interview, researchers will verbally review the points detailed in the consent form (Multimedia Appendix 2) and ask for verbal permission to conduct the interview. If audiotaping or photographing, they will also verbally review the points detailed in the audio consent form and in the photo consent form (Multimedia Appendix 2). If permission is given, the researchers will ask participants if they are willing to sign a written consent form (Multimedia Appendix 2). If the participant declines to sign the written consent forms but gives verbal permission, the researcher will offer the interviewee a copy of the written consent forms for her records, complete the oral consent form (Multimedia Appendix 2), and proceed with the interview. If written permission is given, the researcher will give the interviewee a copy for her records and archive the signed consent form. The oral form is the written form read by a native speaker and recorded as a sound file, which is then distributed to potential participants (through mobile phone Bluetooth, most likely) who have the time to listen, maybe with trusted friends, to the description of the research project and think about it before accepting to participate. The sound file will also remain with them if they want to hear it again. This

ensures that they have the time to process information about the project and can provide informed consent without having to rely on written forms. This is aligned with research that suggests that alternatives to written consent are preferable among certain populations, especially in developing countries [20-22]. In ethnographic research, there is no expectation of independently witnessed consent—in fact, in the case of interviews, that might be considered a breach of the privacy of the interviewee. If the interviewee agrees for the interview to be recorded, then she will be asked to repeat this agreement on tape. Again, it is important to stress that the level of risk for activities 1 and 2 is rather different and that the process for informed consent outlined for activity 1 is aligned with the expectations and conventions of ethnographic fieldwork [23].

As previously mentioned, the researchers foresee minimal risks for the research participants in this phase. Possible risks include the participants being disappointed to be befriended by researchers and then lose touch with them. To mitigate this risk, researchers involved in this phase will accept any offer to stay in touch with the participants on social media and remain friends on the web until the participants desire so. The previous experience of PIs who have worked together shows that most research participants are not particularly interested in remaining in touch with researchers but those who can often become involved informally in the research as key informants and *sounding boards* for researchers' ideas. This could be a way to involve research participants in the project in an active way, as grassroot researchers rather than only a source of information for the researchers, and make the project more grounded in the local reality. A second possible risk is that those who participate in the research might be seen with suspicion by coworkers and other people in their environment. The researchers believe that their approach is built to mitigate these risks as much as possible, as they will enter the field site with the approval of the factory management and spend a few days just observing the environment and chatting informally to a large number of people. Once potential research participants are identified, they will discreetly be asked if they are interested in being interviewed, and the place and time of the interview will be decided by them. Finally, as with all research, there is a risk of breach of confidentiality despite the procedures in place to preserve it. Disclosure of participants' responses outside of the research would be highly unlikely to put them at risk or to be damaging to their health, financial standing, employability, or reputation.

Payments will only be made to compensate for travel expenses and refreshments but not to represent an inducement to participate. The researchers expect interviews to take place near the factory and to be paying directly for snacks and refreshments, rather than to reimburse research participants for it. If travel expenses need to be reimbursed, the researcher will follow the guidelines set out in section *Further Details for Women Seeking Abortion Services*.

Further Details of Private Provider Workers

Each provider or factory infirmary manager and worker will be asked to give their informed consent to participate by signing a consent form. Providers will have as much time as they need to consider and ask questions. If some workers of a private provider do not want to participate, but the manager agrees to participate, the provider will be included, but nonparticipating staff members will not be expected to approach clients about the study. If the manager does not consent for the provider to participate, no other providers will be approached in that private provider.

These are some potential risks associated with research with private providers. Participating private providers may provide medical abortion medications without prescription. The research study will undertake a no harm approach to the situation by informing participating providers about local regulations on dispensing medical abortion drugs, but participating providers who continue to provide medical abortion drug without a prescription will not be reported to the authorities unless the study team encounters situations that may pose significant risk to study participants (eg, sales of misoprostol to women with known gestational age >12 weeks or sales of products that cannot be used to induce an abortion). In such cases, the provider will be visited by a member of the MSIC team, who will explain the risk this poses to the women affected and to the providers' own business. The clinical team member will explain that if this practice continues, the program may be compelled to alert authorities about the risk. The details of participating private providers and workers will be kept confidential. Reports will not reveal the identity of participating private providers or individual providers. There is a risk of breach of confidentiality resulting in the identity of participating providers being revealed and potentially revealing illegal practices (eg, off-label sales). An initial consultation with selected providers will take place before providers are formally approached to assess the acceptability of the research procedures and the intervention.

Further Details for Women Seeking Abortion Services

The following recruitment and consent procedure for women seeking medical abortion is adapted from studies recently, given ethical approval to evaluate interventions to increase call center support for pharmacy-provided medical abortion being conducted by MSI in Zambia and Bangladesh. The recruitment of study participants will be as follows. Preliminary inquiries with private providers in the vicinity of garment factories suggest that the number of women seeking medical abortion can vary from a few per week to >30 per week. As it is common for there to be several private providers in the vicinity of a factory, it should be feasible to have a research assistant present in the nearby area to work with providers to recruit participants. Recruitment of study participants will involve private provider workers being trained to recruit clients into the study working together with the research team, and a memorandum of understanding will be developed and agreed by both parties. The details of this recruitment procedure are described in the following paragraph. Consenting private providers will be expected to ask clients seeking medical abortion whether they are willing to participate in the study during enrollment periods. Providers will be trained through an in-person visit to inform clients purchasing medical abortion pills about the study using a standardized script, to provide interested clients purchasing medical abortion pills (regardless of indication) with a study leaflet, to introduce interested clients to a member of the

research team to hear more about the study or obtain their phone number for a research team member to call them back, and to explain that speaking to a member of the research team does not constitute enrollment and the client can just hear more about the study and then decide not to take part. To increase the understanding of the generalizability of the study and recruitment of women seeking medical abortion from providers, it is necessary to keep a record about the number of clients who purchase medical abortion pills and who agree or do not agree to take part and are not informed of the study (eg, clients who visit when the participating provider is busy or not present). The record will not contain the words medical abortion or directly refer to the names of the drugs being sold to reduce the social and business risks to providers of keeping the form in the premises.

The following payments to private provider procedures are adapted from studies recently, given ethical approval to evaluate interventions to increase call center support for pharmacy medical abortion being conducted by MSI in Zambia and Bangladesh. Consenting private providers will be expected to ask medical abortion clients whether they are willing to participate in the study during the study enrollment period. The estimate is that it will take a maximum of 10 min to inform a client about this study, time that could be spent focusing on their business. Providers are also expected to remain committed to the study over the study period, so their role in data collection needs to be reflected in the reimbursement for taking part. Each participating private provider will be compensated for the time spent recruiting clients with payments of US $25 per week. In addition, a similar payment will be considered for the use of a private room in which to conduct interviews. To ensure that providers are not under pressure to ask clients to participate in the study against their will, the reimbursement will not depend on recruitment performance. It will be explained that if none of their clients are interested in participating, this will not affect their relationship with MSIC or the amount of money they receive from the study. As a result, providers have the option to participate, take the incentive, and do not inform any customers about the study.

Providers will be asked to keep track of the number of clients requesting medical abortion at their facility. They will be asked to record the number of clients who are informed of the study and who are interested in or decline to participate. The tally sheet will not include the word abortion, and the names of the drugs sold will be coded to avoid the providers facing any social or business risks because of stigma around medical abortion. Providers will be asked to store these data in a confidential area. The tally sheet will not have any information about individual purchasers or providers.

The recruitment and interview steps are as follows. Women seeking medical abortion services from participating private providers will be invited to hear more about the study and participate in it on the day they purchase the pills. The standard medical abortion procedures are as follows. First, the client attends a private provider requesting medical abortion. Next, the provider will carry out the medical abortion provision as per their standard practices with regard to any counseling on medical abortion or any eligibility assessments they typically conduct. The research procedures are as follows. For all clients who choose medical abortion, after the client has purchased the product to initiate medical abortion, they will be introduced to the study by the provider and invited to learn more about the study. Providers will introduce clients to the study using a standard script and ask whether they would be interested in speaking to somebody from the research team, who will give them more information about the study. It will be explained that speaking to somebody from the research team does not constitute enrollment and will not affect any aspect of service provision. Loss of confidentiality is deemed a potential risk to the study participants. It is possible that women accessed medical abortion without informing their close family or friends. It is likely that the woman has kept her medical abortion pill use secret from people she lives with or is close to. Several specific measures will be taken to protect the confidentiality and anonymity of medical abortion purchasers. Providers will be trained to introduce the medical abortion pill purchaser to the study in a confidential manner (eg, to ask the purchaser to move to a quiet location to introduce the study and to avoid using the word abortion when speaking to clients about the study, particularly if there are other clients in the location). If a member of the research team is present, the provider will introduce the women to a member of the research team. If a member of the research team is not present, then the provider will ask for the woman's phone number and explain that somebody from the research team will call them. In this case, the woman will be asked what phone number they would like to be called on and whether they have any preference regarding the time of day for the call and any other preferences regarding the return call. These details will be recorded in a recruitment log. The woman will be asked whether there is any risk of someone else answering the phone and whether it is acceptable to ask for her by name and say that the researchers are calling about a market research survey. Research assistants will be told to ensure that women are in a private place where they cannot be overheard before starting the interview. Female research assistants will be used wherever possible to prevent potential suspicion of infidelity resulting from long phone calls with study participants. Either in person or by phone, the research assistant will provide information about the study. Study respondents will be asked whether they would like to have more time to think about whether they want to participate. Respondents will be given up to 48 hours to think about whether they would like to participate and will be given the option of receiving a call back from the research assistant or calling back the research assistant themselves. If the respondent provided informed consent, the research assistant will then conduct a baseline interview and arrange a time for a day 14 interview. The interviews will be conducted by phone or at a place of the interviewee's choice (eg, their home, MSI clinic, or provider location), according to their preference. On day 14, women will be recontacted at the agreed time for a second interview by phone. If the woman does not pick up, the research assistant will make up to 3 additional attempts to get through. The research assistant will be trained to confirm the woman's identity and have a cover story about who they are and reason for calling to ensure that women's privacy is protected. Research assistants will be women to reduce the risk of suspicion of infidelity. At the end of the interview, a

follow-up interview date and time will be arranged for a final interview on day 30. On day 30, women will be contacted at the agreed time for a follow-up interview. The same phone procedures will be used as in the day 14 interview. The proposed recruitment steps for this study differ from those undertaken for the MSI study in Zambia, whereby women were asked by the pharmacist to send an SMS text message with a unique code word to the study team and subsequently called back by the study team to receive more information on the study. This project does not propose to either ask women to send an SMS text message with a code word because previous research has shown that the use of SMS text messaging is less common in Cambodia because of literacy and phones not supporting the Khmer script, and private providers have stated that this recruitment method will be too complex. Furthermore, this study differs from the Zambia study in that a research assistant will be based on the location during the recruitment period.

There are some potential risks associated with conducting research with women seeking medical abortion. Some questions asked to women as part of the research are sensitive and risk discomfort or distress. The clients will be reminded during the consent procedure and each interview that they are free to leave the interview at any time or skip any questions they do not want to answer. If a client is experiencing health problems during either interview, they will be referred to a Marie Stopes Cambodia clinic or the call center for medical counseling. Potential harm, such as intimate partner violence, could result as a result of messages sent by the research team intended for the participant being read or listened to by a third party. To mitigate this, explicit consent to send SMS text messages or voice messages will be sought, in addition to consent for face-to-face and phone interviews. Initial messages will not mention any terms related to abortion, contraception, or MSI and take the form of the researcher asking, “how are you?” or “if you have any problems, please call me.” The nature of subsequent messages to be tested will be informed by the needs assessment during activities 1 to 3. Any intervention content that is tested will be followed up with a phone call to obtain feedback. The research team will ask whether it is likely that the messages could have been accessed by a third party and about any harm that may have resulted from this. Participants will be offered referral information if required at the end of each interview, in case they have further questions about sexual and reproductive health, and to address the fact that they might be asked sensitive questions about intimate partner violence during the study. All participants, regardless of whether they disclose an experience of violence or not, will be offered information of organizations providing support to women who have experienced domestic violence. Interviewers will be familiar with these organizations and will be able to provide further information to participants if needed. The participant will be told that she can call the study number if she needs further information in the next 6 months and, after her final interview, will be told she can contact the MSIC call center for referral information at any time. Participants in the study will be women who are self-administering medical abortion pills, and there are medical risks of taking medical abortion medications without adequate counseling or information. However, this is a risk that women in Cambodia face every day regardless of their participation in this study, and this study aims to find ways to reduce this risk for women across the country.

Payments to participants will only be made to compensate for travel expenses, refreshments, and mobile phone costs (SMS text messages and phone calls) but not to represent an inducement to participate. Thus, those participating in interviews will be given US $3-$4 to compensate for travel and a snack *if* they have to travel to meet the research team but not if they do not have to travel. This rate is derived from MSIC experience and is consistent with compensation for reasonable costs incurred by acceptors in a donor-funded voluntary surgical contraception program that is not considered an incentive. The breakdown of the US $4 payment is as follows: (1) cost of transportation (round trip) is US $2, US $1 per client for refreshments during the procedure (this covers the cost of a basic rice/meat meal) and a US $1 contribution to a phone card (if the participant has incurred phone/SMS text messaging costs).

Results

The project was funded by the UK-based AHRC and Medical Research Council (MRC) as part of their joint AHRC-MRC Global Public Health Global Challenge Research Fund Partnership Awards. The project began on October 1, 2018, and will end on December 31, 2020. Ethical approval was obtained from the LSHTM (April 4, 2018, LSHTM Ethics Ref: 14646), from MSI (April 5, 2018, MSI protocol number: 003-18), and by the Cambodian Ministry of Health (April 27, 2018, approval number: 094NECHR). The team conducted 67 semistructured interviews with female factory workers, women who sought medical abortion, health providers, and mobile phone providers; participant observation with factory workers and health providers; and an analysis of YouTube and Facebook to understand what kind of information is available, who creates it, and how it is used. The team is currently conducting data analysis, and findings are clustered around (1) the use of mobile phones and digital resources for health-related and medical abortion -related information, (2) the experience of medical abortion care, and (3) the development of an intervention through edutainment videos. The results from the project are expected to be published between 2020 and 2021.

Discussion

In summary, this study aims to conduct a joint research project using qualitative methods from a multidisciplinary perspective to study health information gathering and sharing among factory workers and reproductive health issues after medical abortion in Cambodia from medical, cultural, and information-sharing practice perspectives and to design a pilot intervention delivered by mobile phones to support the reproductive health of women who work in factories around Phnom Penh. To our knowledge, this is the first study of this kind. Potential limitations are that many researchers are not based in Cambodia. However, the resulting cross-cultural interactions may result in additional insights that might otherwise not have been obtained.

We plan to disseminate findings to 3 audiences. First, academics, through academic publications and conference participation;

second, practitioners, through workshops and training, one half-day workshop in each country for academics and practitioners, organized halfway through the project as a way to present early findings and get feedback from experts. The workshop in Cambodia will be organized with local partners; and third, research participants. A working hypothesis is that peer-to-peer communication is an effective way to engage women in postabortion care. If fieldwork confirms this, a training workshop for women in the target population (eg, garment factory workers) who are interested in becoming peer-to-peer counselors and for health care staff will be organized to train them further in health communication and on the best practices that emerged from the field.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Information for Participants.
[DOCX File , 26 KB - resprot_v9i7e17779_app1.docx]

Multimedia Appendix 2
Consent Forms.
[DOCX File , 20 KB - resprot_v9i7e17779_app2.docx]

Multimedia Appendix 3
Topic Guides.
[DOCX File , 18 KB - resprot_v9i7e17779_app3.docx]

References

1. Hemmings J, Rolfe B. Abortion in Cambodia. Options. 2008 Jul. URL: https://options.co.uk/ [accessed 2019-06-01]
2. Petitet PH, Ith L, Cockroft M, Delvaux T. Towards safe abortion access: an exploratory study of medical abortion in Cambodia. Reprod Health Matters 2015 Feb;22(44 Suppl 1):47-55 [FREE Full text] [doi: 10.1016/S0968-8080(14)43826-6] [Medline: 25702068]
3. Fetters T, Vonthanak S, Picardo C, Rathavy T. Abortion-related complications in Cambodia. BJOG 2008 Jul;115(8):957-68; discussion 968 [FREE Full text] [doi: 10.1111/j.1471-0528.2008.01765.x] [Medline: 18651879]
4. Scott RH, Filippi V, Moore AM, Acharya R, Bankole A, Calvert C, et al. Setting the research agenda for induced abortion in Africa and Asia. Int J Gynaecol Obstet 2018 Aug;142(2):241-247. [doi: 10.1002/ijgo.12525] [Medline: 29745418]
5. Harvey P. Medical abortion: the hidden revolution. J Fam Plann Reprod Health Care 2015 Jul;41(3):193-196 [FREE Full text] [doi: 10.1136/jfprhc-2014-100990] [Medline: 26106105]
6. Heng M, Bajracharya A. Garment Sector Health Interventions in Cambodia: A Comprehensive Review. The Evidence Project. 2017 Apr 17. URL: http://evidenceproject.popcouncil.org/ [accessed 2019-06-01]
7. Sopheab H. Reproductive, Maternal and Neonatal Health Knowledge, Attitudes and Practices among Female Garment Factory Workers in Phnom Penh and Kandal Provinces. Partnering to Save Lives (PSL). 2014 Aug 1. URL: https://www.care-cambodia.org/psl [accessed 2019-06-01]
8. Zhao J, Freeman B, Li M. Can mobile phone apps influence people's health behavior change? An evidence review. J Med Internet Res 2016 Oct 31;18(11):e287 [FREE Full text] [doi: 10.2196/jmir.5692] [Medline: 27806926]
9. Payne HE, Lister C, West JH, Bernhardt JM. Behavioral functionality of mobile apps in health interventions: a systematic review of the literature. JMIR Mhealth Uhealth 2015 Feb 26;3(1):e20 [FREE Full text] [doi: 10.2196/mhealth.3335] [Medline: 25803705]
10. Bartholomew L, Markham C, Ruiter R, Fernandez M, Kok G, Parcel G. Planning Health Promotion Programs: An Intervention Mapping Approach. San Francisco, California, United States: Jossey-Bass; 2016.
11. McCarthy O. An Intervention Delivered by App Instant Messaging to Increase Use of Effective Contraception Among Young Women in Bolivia. ClinicalTrials. 2016. URL: https://clinicaltrials.gov/ct2/show/NCT02905526 [accessed 2016-10-10]
12. Creswell JW, Miller DL. Determining validity in qualitative inquiry. Theory Pract 2000 Aug;39(3):124-130. [doi: 10.1207/s15430421tip3903_2]
13. Abras C, Maloney-Krichmar D, Preece J. User-centered design. In: Encyclopedia of Human Computer Interaction. Thousand Oaks, CA: Sage Publications; 2004.
14. Hargittai E, Sandvig C. Digital Research Confidential: The Secrets of Studying Behavior Online. New York, USA: MIT Press; 2015.
15. Emerson R, Fretz E, Shaw L. Writing Ethnographic Fieldnotes. In: Writing Ethnographic Fieldnotes. Chicago, USA: University of Chicago Press; 2001.

16. Miller D. Why We Post. DERC - Digital Ethnography Research Centre. 2015. URL: https://digital-ethnography.com/why-we-post/ [accessed 2020-02-07]
17. Thorne B. 'You still takin' notes?' fieldwork and problems of informed consent. Soc Prob 1980 Feb;27(3):284-297. [doi: 10.2307/800247]
18. Ethical Decision-Making and Internet Research: Recommendations from the AoIR Ethics Working Committee (Version 2.0). Association of Internet Researchers. 2012. URL: https://aoir.org/reports/ethics2.pdf [accessed 2019-06-04]
19. Pruitt J, Grudin J. Personas: Practice and Theory. In: Proceedings of the 2003 Conference on Designing for User Experiences. 2003 Presented at: DUX'03; June 1-3, 2003; San Francisco, California. [doi: 10.1145/997078.997089]
20. Benitez O, Devaux D, Dausset J. Audiovisual documentation of oral consent: a new method of informed consent for illiterate populations. Lancet 2002 Apr 20;359(9315):1406-1407. [doi: 10.1016/S0140-6736(02)08361-7] [Medline: 11978341]
21. Fitzgerald DW, Marotte C, Verdier RI, Johnson WD, Pape JW. Comprehension during informed consent in a less-developed country. Lancet 2002 Oct 26;360(9342):1301-1302. [doi: 10.1016/S0140-6736(02)11338-9] [Medline: 12414207]
22. Bhutta Z. Beyond informed consent. Bull World Health Organ 2004 Oct;82:7. [Medline: 15643799]
23. Lofland J, Lofland L. Handbook of Ethnography. London, UK: Sage Publications; 2001.

Abbreviations

AHRC: Arts and Humanities Research Council
IM: intervention mapping
LSHTM: London School of Hygiene and Tropical Medicine
MRC: Medical Research Council
MSI: Marie Stopes International
MSIC: Marie Stopes International Cambodia
PI: principal investigator
PSL: Partnering to Save Lives
SOAS: School of Oriental and African Studies

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Protocol

Prospective Study Evaluating a Pain Assessment Tool in a Postoperative Environment: Protocol for Algorithm Testing and Enhancement

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Abstract

Background: Assessment of pain is critical to its optimal treatment. There is a high demand for accurate objective pain assessment for effectively optimizing pain management interventions. However, pain is a multivalent, dynamic, and ambiguous phenomenon that is difficult to quantify, particularly when the patient's ability to communicate is limited. The criterion standard of pain intensity assessment is self-reporting. However, this unidimensional model is disparaged for its oversimplification and limited applicability in several vulnerable patient populations. Researchers have attempted to develop objective pain assessment tools through analysis of physiological pain indicators, such as electrocardiography, electromyography, photoplethysmography, and electrodermal activity. However, pain assessment by using only these signals can be unreliable, as various other factors alter these vital signs and the adaptation of vital signs to pain stimulation varies from person to person. Objective pain assessment using behavioral signs such as facial expressions has recently gained attention.

Objective: Our objective is to further the development and research of a pain assessment tool for use with patients who are likely experiencing mild to moderate pain. We will collect observational data through wearable technologies, measuring facial electromyography, electrocardiography, photoplethysmography, and electrodermal activity.

Methods: This protocol focuses on the second phase of a larger study of multimodal signal acquisition through facial muscle electrical activity, cardiac electrical activity, and electrodermal activity as indicators of pain and for building predictive models. We used state-of-the-art standard sensors to measure bioelectrical electromyographic signals and changes in heart rate, respiratory rate, and oxygen saturation. Based on the results, we further developed the pain assessment tool and reconstituted it with modern wearable sensors, devices, and algorithms. In this second phase, we will test the smart pain assessment tool in communicative patients after elective surgery in the recovery room.

Results: Our human research protections application for institutional review board review was approved for this part of the study. We expect to have the pain assessment tool developed and available for further research in early 2021. Preliminary results will be ready for publication during fall 2020.

Conclusions: This study will help to further the development of and research on an objective pain assessment tool for monitoring patients likely experiencing mild to moderate pain.

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KEYWORDS

pain measurement; pain, postoperative; acute pain; health monitoring; wearable electronic devices; machine learning; multimodal biosignals

Introduction

Background

Pain is the most common reason for patients to seek medical care and is associated with many illnesses [1]. There is a high demand for tools to assess patients' pain in the clinical context. Tools are needed especially when the patient's own opinion is difficult to obtain. Assessment of pain is particularly difficult when the ability of a patient to communicate is limited (eg, during critical illness, in infants and preverbal toddlers, or in patients under sedation or anesthesia, with intellectual disabilities, and at the end of life) [2]. How pain is assessed and managed at the bedside is widely variable, and the prevalent practices remain suboptimal [3]. Inadequately treated pain has major physiological, psychological, economic, and social ramifications for patients, their families, and society [4]. Undertreatment of pain could result in many adverse effects and other complications and may evolve into chronic pain syndromes. It could also cause delayed discharge or prolonged recovery, which may incur higher health care costs and more patient suffering [5]. Overtreatment of pain, on the other hand, may result in unintended adverse consequences such as acute respiratory complications or in long-term complications such as opioid addiction. These issues are particularly pronounced for noncommunicative patients who are unable to articulate their experience of pain [6].

Automated and continuous pain intensity assessment for poorly communicating patients can enable timely treatment, reduce the monitoring burden on clinicians, and contribute to optimizing the use of analgesics and managing side effects and complications [7]. As pain intensity is difficult to quantify [8], the criterion standard of pain assessment is self-reporting using tools such as a visual analog scale (VAS) and numeric rating scale (NRS) [9]. These tools are rife with deficits, which are even more pronounced in vulnerable patient populations [6,10].

State-of-the-art automatic and objective pain intensity assessment techniques described in the literature use physiological data, obtained by monitoring the changes in patients' physiological data, such as electromyography (EMG), electrocardiography (ECG), photoplethysmography (PPG), and electrodermal activity (EDA), to identify autonomic nervous system reactions to pain. One of the most well-known pain indicators is facial muscle activity. The facial nerve controls voluntary and involuntary activity of the facial muscles. The involuntary control of facial muscles is both protective and emotional, signaling the experience of pain. Other objective pain assessment tools include the surgical pleth index (formerly the surgical stress index), based on analysis of the PPG waveform and heart rate. Similarly, analysis of skin conductance has been used as a surrogate for pain in clinical situations [11].

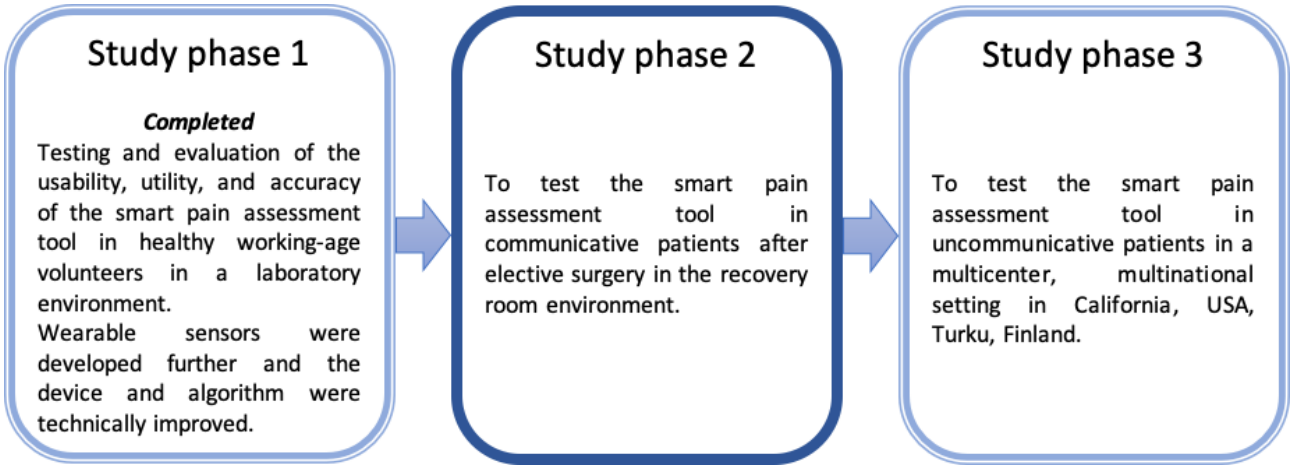
Objective

Wearable technology is a promising paradigm to integrate several technologies and communication solutions [12,13]. The aim of this research project is to develop an automatic and versatile pain assessment tool algorithm for detection and assessment of pain in a reliable and objective way in noncommunicative patients. The final objective of the research project is to develop a smart pain assessment tool to detect and assess pain employing behavioral and physiological indicators for a wide range of users and patients, from infants to elderly people, who are unable to communicate normally.

The main research project consists of 3 study phases, which Figure 1 describes. Phase 1 of the research project focused on developing pain assessment techniques in voluntary healthy adults. In phase 1, the usability, utility, and accuracy of the new pain assessment tool were evaluated and tested in 30 healthy working-age volunteers. We used state-of-the-art standard sensors to measure bioelectrical EMG signals, as well as changes in heart rate, respiratory rate, oxygen saturation, and galvanic skin response. Based on the results, the pain assessment tool was further developed and reconstituted with modern wearable sensors, device, and algorithm.

Phase 2, described in this paper, involves the further development of and research on a pain assessment tool in patients likely experiencing mild to moderate pain. In phase 3, we will conduct a trial to assess the effectiveness of the whole platform in uncommunicative patients at 2 sites, both of which will have both intervention and control groups. In the intervention and control patients, continuous pain intensity assessments will be collected by the sensors embedded in a facial patch worn by all study patients.

Figure 1. Study design for the development of a pain assessment tool.



Methods

Study Design

This protocol focuses on the second phase of a larger prospective observational data collection study to collect training data from patients likely experiencing mild to moderate pain (institutional review board [IRB] approval from Human Research Protections HS# 2017-3747). Figure 1 describes all study phases of the pain assessment tool.

The IRB approved the recruitment of 30 participants selected from the Acute Pain Service patient list at University of California, Irvine Medical Center (UCIMC) in Irvine, CA, USA. The Acute Pain Service unit at UCIMC serves over 100 participants weekly, enabling the lead physician to recruit patients for this study. We will collect primary demographic data from each patient, including height, weight, body mass index, and sex.

Approximately 30 minutes of continuous biosignals (EMG, ECG, and EDA) data will be collected from the participants. We will separate this 30-minute period into 2 parts: control (baseline pain) and experimental. Each part will consist of 2 to 3 challenge intervals in an attempt to capture pain perception before, during, and after a stimulus, with appropriate rest periods to make the statistical analysis more powerful.

In the control part, we will use a transcutaneous electrical nerve stimulation (TENS) unit [14] to obtain the patient's baseline pain level by placing the TENS on the participant's forearm and consistently prompting for NRS pain scores. We believe it is prudent to provide some level of baseline assessment above the patient's existing postsurgical pain to attempt to find a baseline of pain for comparison among participants. Therefore, we are using TENS as a means of standardizing the patient threshold for experiencing pain and as a way to keep the data consistent with the previous phase of the study conducted on healthy volunteers.

In the experimental part, patients will be engaged with soft activities (eg, walking, coughing, sitting, lifting legs) that may cause a pain sensation. The participant's experience of pain will be recorded using NRS. The NRS for pain is a unidimensional measure of pain intensity and a segmented numeric version of the VAS, in which a respondent points to a number (integers from 0 to 10) on the NRS that best represents the intensity of their pain [15]. The usual format is a horizontal bar or line. Similar to the pain VAS, the NRS is anchored by terms describing pain intensity extremes [16]. We expect to find solutions from multiple parameters that are robust in response to different acute pain cases or study designs. All protected health information will be redacted prior to data analysis.

Participants

The prospective study will be conducted at UCIMC. The primary study population will comprise adults ranging in age from 18 to 89 years. The maximum number of patients to be asked for their consent and data collection, including withdrawals, is 30. We expect 20 to complete the study.

Eligibility Criteria

Participants who are enrolled on this UCIMC protocol must meet the following criteria: (1) are aged 18 years or older, (2) will be consulted by the APS, (3) have the ability to communicate, (4) have provided written informed consent, and (5) have healthy, intact facial skin. Participants will be excluded if they have (1) any diagnosed condition affecting cognitive functions (eg, dementia, psychosis), (2) hand deformities that prevent the sensor from being placed, (3) any diagnosed condition affecting the central nervous system, or facial nerves or muscles, or (4) significant facial hair growth in the area where the sensors will be attached.

We must consider the natural variation in caseload (such as trauma and elective procedures) specific to both of our institutions' regions, coupled with the fact that the recovery period is different for each patient. All candidates considered for enrollment universally will be experiencing postoperative pain during their hospitalization, and all will be receiving analgesic treatment. The study team ensures that patient safety will not be compromised while maintaining regulatory compliance, and future studies will be aimed at multicenter studies with a larger, diverse sample size to support generalizability.

Recruitment

After IRB approval, we will screen the medical records at UCIMC, to which APS has access, to determine patient

eligibility using the protocol inclusion and exclusion criteria. The anesthesiologist will approach their patients directly about study participation at the University of California Irvine Douglas Hospital, Orange, CA, USA. The study procedure will be continued if patients show interest and are suitable for the study (according to the inclusion and exclusion criteria). The study physician will explain the study in detail, providing both oral and written information. If a patient decides not to participate in the study, the study will be discontinued for this patient. If the patient is still willing to participate, the study participant enrollment log will be updated accordingly. During the study, participants' experience of pain intensity will be recorded using the NRS.

Informed Consent

Eligible patients will be given a consent form to consider until the following day, when the study physician will follow up regarding their participation. We encourage all participants to discuss study participation with their family and friends before consenting. Patients will be enrolled in the study only after one of the investigators has reviewed the consent form with each patient, ensuring that the patient has understood the study, has answered all questions, and has provided written informed consent. Patients are also informed about their right to withdraw from the study at any time, that their participation is voluntary, and that withdrawal would not affect their patient care.

Clinical Trials

iHURT

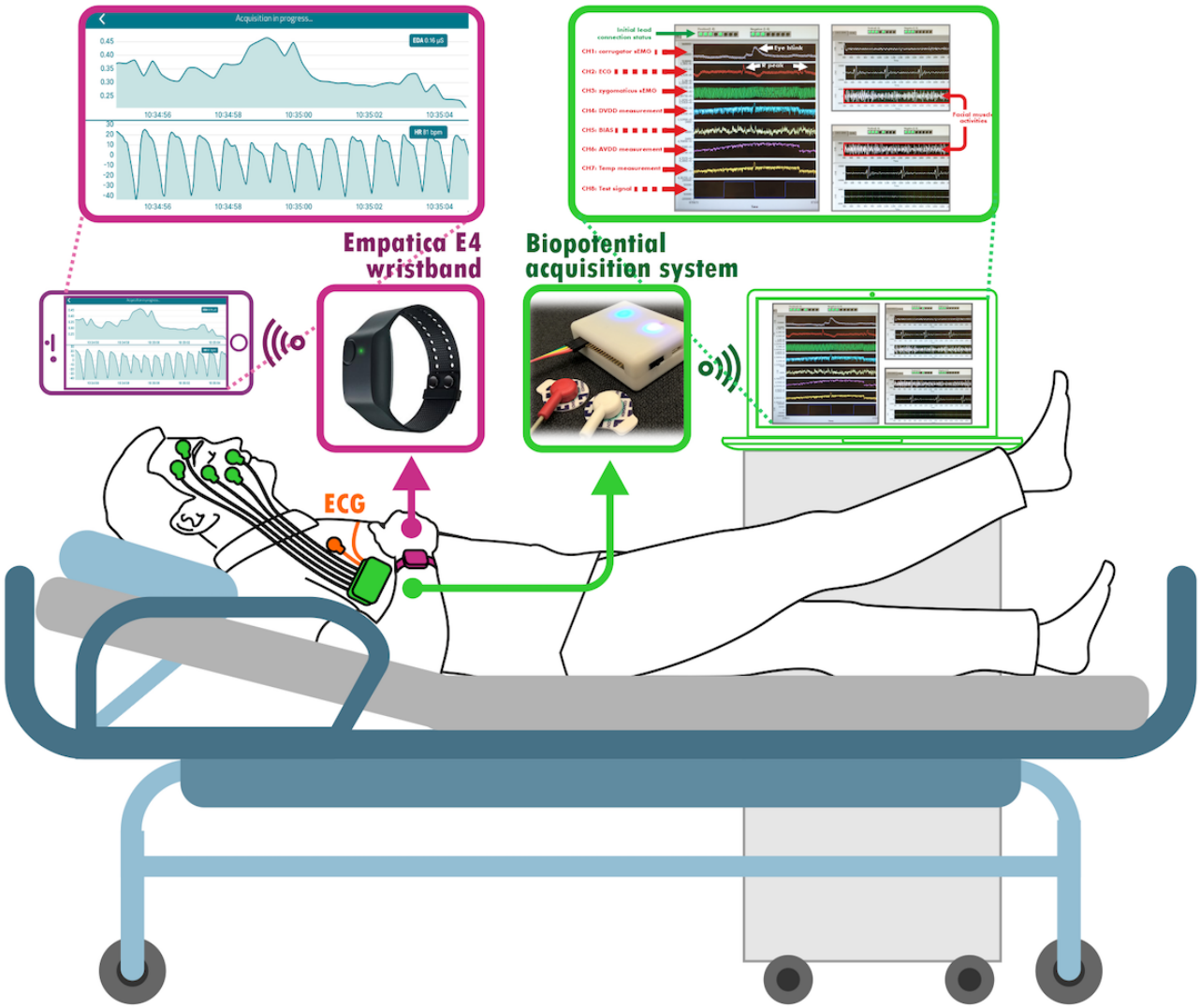
iHURT is a system that tracks changes in the activity of facial muscles (ie, changes in facial expressions) developed at the University of Turku, Finland. It simultaneously uses physiological signs such as heart rate, heart rate variability, respiratory rate, and EDA as adjuvant measures as we attempt to develop an algorithm for pain assessment in hospitalized patients. The technology used in this study to capture the aforementioned signals includes the following components.

Eight-Channel Biopotential Acquisition System for EMG and ECG Recording

EMG and ECG are both biopotential signals captured from the skin surface. We developed the system used to collect them in our previous work [14]. The system includes commercially available electrodes (eg, in 24-mm diameter), electrode-to-device lead wires, an ADS1299-based portable device, and computer software (LabVIEW version 14.0f2, National Instruments) receiving streaming data from the portable device. The small analog potentials sensed from the skin surface are amplified (maximum gain: 24) and digitized, and the raw data of each channel at the rate of 500 samples per second are sent to the computer software through Bluetooth. The software visualizes the waveforms and saves the raw data into files.

The device is configured to work in single-ended mode, called a monopolar electrode configuration, where the potential in each channel is measured between the electrode on the target site and the common reference electrode. The common reference electrode is placed on a neutral bony area behind the ear. For this reason, 2 channels are used to collect the lead I ECG, as Figure 2 illustrates. One channel measures the potential between the ECG on the right arm and the reference, and the other channel measures the potential between the ECG on the left arm and the reference. A further 5 channels are for facial EMG measurement, which monitor the activities of 5 facial muscles: frontalis, corrugator supercilii, orbicularis oculi, levator labii superioris, and zygomaticus major. The electrode placement follows the EMG research guidelines [15].

Figure 2. Setup of the biopotential acquisition system on the patient. ECG: electrocardiogram.



Empatica E4 Wristband for EDA and PPG Recording

As a sensitive and convenient measure of indexing changes in sympathetic arousal associated with emotion, cognition, and attention, EDA has been widely used in psychological studies [16] and in some commercial devices. As a noninvasive and low-cost measure of monitoring changes in blood volume, PPG has been widely used in health studies.

To monitor EDA and PPG, we use the commercially available Empatica E4 (Empatica Inc, Boston, MA, USA) wristband. The wristband will permit participants to maneuver more easily, as it will not impede their movements and will reduce the time of each patient encounter because it is considerably easier to position on the patient. The wristband has an internal memory that can record up to 36 hours of data and allows for wireless data transmission. The E4 wristband is rechargeable, with a charging time of less than 2 hours. It includes an EDA sensor, which measures the constantly fluctuating changes in certain electrical properties of the skin. This device can also noninvasively monitor blood volume pulse PPG in real time through green and red light-emitting diodes.

TENS Device

The TENS device is a US Food and Drug Administration (FDA)–cleared Class II over-the-counter HealthmateForever YK15AB (HealthmateForever, Lenexa, KS, USA) electrotherapy device. The TENS unit works by delivering small electrical impulses through electrodes that have adhesive pads to attach them to a person's skin.

Data Collection

For patients who have consented to participate, a study team member will explain what will happen in the next 30 minutes, how to report their pain level, and what the NRS is. The team member will demonstrate how the TENS unit works on themselves with separate electrodes and explain that it is not harmful. Then, the following components will be placed on the participant: (1) the 8 leads of the EMG and ECG, (2) the Empatica E4 sensor, and (3) the TENS unit on the contralateral arm.

The biopotential acquisition device will be connected to the study analyst's laptop and the Empatica E4 will be connected to the study analyst's iPhone, both over Bluetooth. Data recording will begin after the study participant, clinical researcher, and study analyst are ready. The start of the

recording period will be marked on the computer. Data from the sensors will be collected for a maximum period of 30 minutes. In addition, patients will be asked to complete the following parts of the procedure.

First, in the control part, after the study equipment is placed on the participant, a member of the study team will turn on the TENS device while the patient is sitting. Patients will be asked to slowly increase the TENS unit level on the contralateral arm to the highest tolerable level for them, rest for at least 10 seconds, and then decrease it to level 0, including an additional rest between TENS challenges. At each point the study team member will ask for the NRS pain score. During this period, the other devices will be simultaneously collecting physiological data.

Second, during the experimental part, as the patient is resting in the transition between the control and experimental part, the TENS unit will be disconnected. Then, patients will be engaged with soft activities (eg, walking, coughing, sitting, lifting legs) that may cause a pain sensation wearing the noninvasive devices connected excluding the TENS device. At each point (before, during, and after activity performance), the study team member will ask for the NRS pain score. During this period, the other devices will be simultaneously collecting physiological data.

Each part will consist of 2 to 3 challenge intervals in an attempt to capture pain perception using NRS before, during, and after a stimulus with appropriate rest periods to make the statistical analysis more powerful. During this period, the other devices will be simultaneously collecting physiological data.

Software for Data Display and Storage

We will use data acquisition software (LabVIEW version 14.0f2) to capture data from the device and sensors. As mentioned above, 2 devices will transmit data wirelessly through Bluetooth and 1 via a serial wired USB. The computer with Bluetooth USB adapters receives data from these sensor nodes. We developed a LabVIEW program in Windows for real-time waveform plotting, marking time stamps, and saving the raw data along with the time stamps. The waveform plotting function ensures checking of data validity during measurement. Raw data will be saved for offline processing and analysis.

Algorithm for Pain Data Analysis

The pain intensity assessment algorithm will be developed after the data collection phase, including basic signal preprocessing and a machine learning algorithm. The designed algorithm will be built based on the preliminary algorithm from phase 1 of the study and will be verified and compared between the 2 databases.

Statistical Analysis

Sample Size Calculation

Figure 3 illustrates how multidimensional data obtained during phase 1 of the study can be processed and reduced to 2 dimensions for visualization by principal component analysis [17] to demonstrate different pain levels.

Figure 3. Principal component (pc) analysis of different pain levels showing all tests.

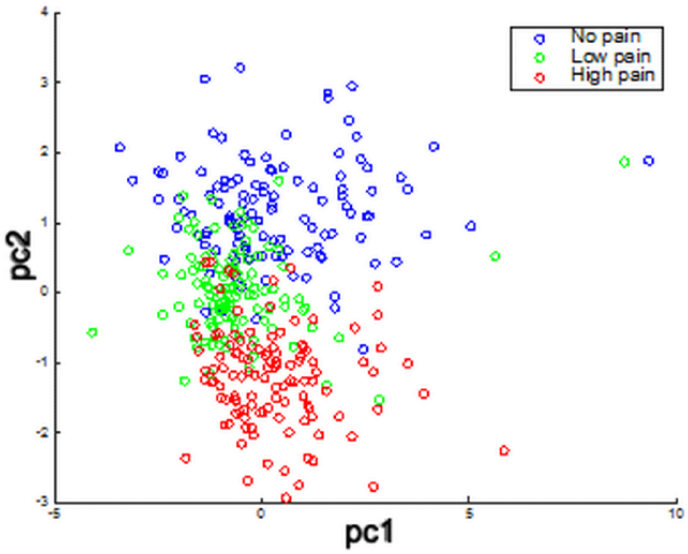
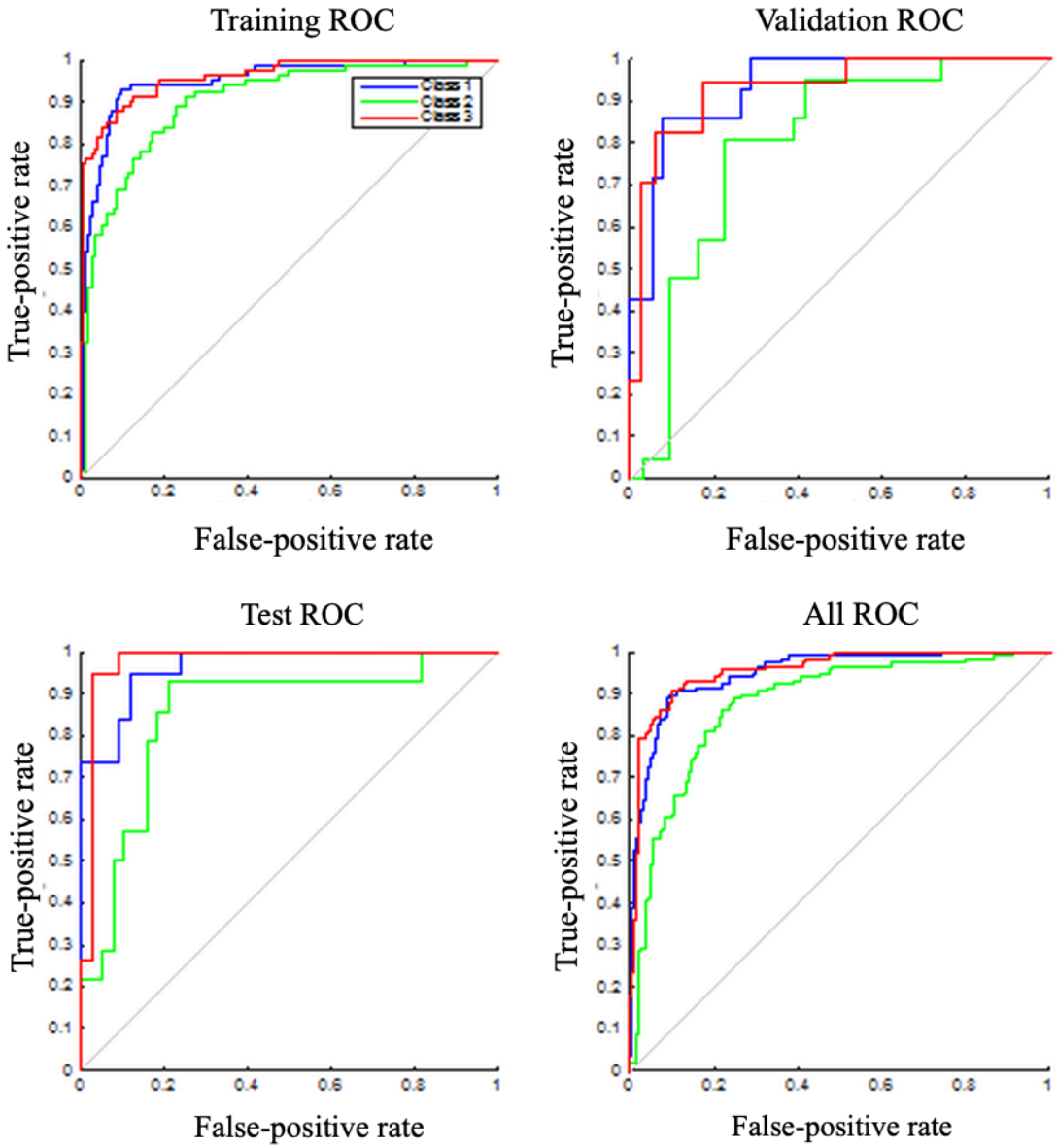


Figure 4 shows receiver operating characteristic curves of multidimensional data classification with an artificial neural network [18]. The results are consistent with the data visualization in Figure 3, where moderate to severe pain (shown in red) can be differentiated from no-pain samples (shown in blue). Jiang et al [19] previously published a comprehensive machine learning analysis of the phase 1 data. Our phase 1 results showed 76.7% accuracy when we used leave-1-participant-out cross-validation, showing that the data can be generalized. We also explored solutions for remote pain assessment in phase 1. We designed and implemented an electronic health system consisting of biosignal measurement and a wireless transmission device, online data processing in the cloud, and a remote data presentation webpage for the caregiver [19].

Figure 4. Receiver operating characteristic (ROC) curves of training, validation, and test datasets.



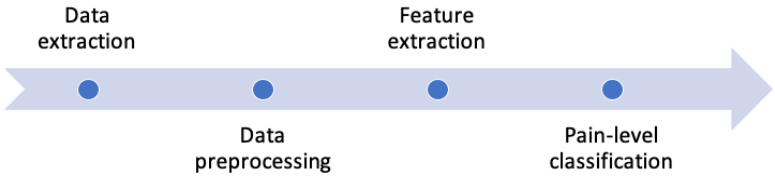
For phase 2, we will attempt to further improve the accuracy of the electronic health system and identify proper personalization methods based on the demographic data, the profile of the patient when admitted to hospital, and the biosignals collected from the patient. For the prospective study, we will recruit patients who meet the inclusion criteria. We will take into account the attrition rate and will have a maximum enrollment of 30 participants. We calculated this sample size taking into account the receiver operating characteristic analyses from the previous phase results [19,20].

Planned Analysis

We will design a multimodal software tool for signal processing, data fusion, and machine learning for pain assessment and classification based on the processing flow developed from study phase 1.

The analysis of pain can be broken down into the following stages: data preprocessing, filtering, feature extraction, and classification (Figure 5). Different modalities collected from patients such as EMG, ECG, and EDA signals are labelled with the patient's self-reported pain level. Once we extract these raw signals, we will use their corresponding timestamps to help synchronize the data and better understand the changes in physiological signs when pain is induced.

Figure 5. Block diagram of planned analysis.



The next step is to digitally filter out the noise produced during data collection. Noise can be caused by multiple sources. For example, motion artifacts, baseline wander, and power channels are all common sources of noise in a clinical setting. The low- and high-frequency noise is digitally filtered using a Butterworth filter and the necessary frequencies are allowed to pass through using a bandpass filter.

For optimal classification performance, we will extract features from multiple signal domains and approaches, for example, statistical features and entropy extracted from the signal time domain and the frequency domain [20]. We will further optimize the extracted multiple features in combination to reach a balance between classification performance and computation complexity. These features are receptive to changes in pain stimuli and therefore are good factors in determining an individual's pain levels.

Finally, once we obtain these features and their corresponding pain labels, we can use machine learning techniques to train models based on these data. Furthermore, we will automatically classify and predict the pain levels of any future patients using this existing model.

Outcome Variables

The final outcome of phase 2 is the prediction of patients' pain levels based on metrics such as accuracy, sensitivity, specificity, and the area under curve with respect to patients' self-reported NRS as the reference standard.

Results

We have started implementing the protocol, and we are in the process of data collection. We expect to complete the analyses in early fall 2020 and then publish them. The dataset will be available for further research in early 2021.

Discussion

Contributions

This is, to our knowledge, the first protocol for collecting physiological signals from patients with postoperative pain for the development of an automatic pain assessment tool. Existing databases have targeted several types of pain, for example, chronic pain [21], neonatal pain [22], shoulder pain [23], or experimental acute pain [24-26], but not postoperative pain. The proposed methods and database will fill the gaps in developing and testing automatic pain assessment tools for clinical acute pain.

The proposed data collection protocol is for multimodal development, similar to some of the aforementioned databases [21,24-26]. However, it includes a variety of signal sources for development not included in existing databases, covering more than indices for autonomic nervous activities such as ECG, EDA, and PPG and nonverbal pain behaviors such as facial expressions and body postures. Thus, the proposed method could provide additional information by merging prior knowledge for each signal (eg, [27,28]) with new types of data.

Strengths

Although the data collection focuses on postoperative pain, we included a controllable experimental pain stimulus, which was induced separate from the movement inductions. The benefit of this design is twofold. First, the physiological responses to each stimulation can be compared with each other in terms of similarity and difference within the database. Second, this design connects this study to previous studies using experimental pain stimulation only, where pain threshold (the stimulus intensity at which pain begins to be felt) and pain tolerance (the maximum pain intensity a person is able to tolerate) were mainly used as pain self-reports.

Limitations

The main limitation is the presence of noise (or incorrect labels), making machine learning difficult. Although a certain level of noise has been shown to be positive in order to obtain a more tolerant and robust algorithm, given the real day-to-day data, the noise ratio must be low so that this does not interfere with machine learning. In our case, noise comes mainly from the cognitive difference in pain levels and motion artifacts. These artifacts can be from several sources, such as the movement of the electrodes on the face while the patient is talking.

Another limitation of this protocol is that some physiological parameter changes (eg, elevated heart rate) can result from a compound reaction to both pain stimulus and the motion itself. However, these two factors cannot be separated within the same patient, that is, moving without causing any pain. One solution could be recruiting healthy controls to make the same motions and to observe the physiological parameter response difference from postoperative patients.

Conclusion

This study will help to further the development of and research on an objective and self-aware pain assessment tool for monitoring patients in clinical settings using both behavioral and physiological indicators. The resultant solution will be an automatic, user-centered, and versatile pain assessment system, based on the internet of things.

Acknowledgments

This research was supported by the Academy of Finland project Personalized Pain Assessment System based on IoT 313488. We acknowledge Arman Anzanpour for sensor development in the first phase of the study and graphic design.

Conflicts of Interest

None declared.

References

1. Tompkins DA, Hobelmann JG, Compton P. Providing chronic pain management in the "Fifth Vital Sign" Era: Historical and treatment perspectives on a modern-day medical dilemma. Drug Alcohol Depend 2017 Apr 01;173 Suppl 1:S11-S21 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.12.002] [Medline: 28363315]
2. Breivik H, Borchgrevink P, Allen S, Rosseland L, Romundstad L, Hals EKB, et al. Assessment of pain. Br J Anaesth 2008 Jul;101(1):17-24 [FREE Full text] [doi: 10.1093/bja/aen103] [Medline: 18487245]
3. Gregory J, McGowan L. An examination of the prevalence of acute pain for hospitalised adult patients: a systematic review. J Clin Nurs 2016 Mar 18;25(5-6):583-598. [doi: 10.1111/jocn.13094] [Medline: 26778249]
4. Arif-Rahu M, Grap MJ. Facial expression and pain in the critically ill non-communicative patient: state of science review. Intensive Crit Care Nurs 2010 Dec;26(6):343-352 [FREE Full text] [doi: 10.1016/j.iccn.2010.08.007] [Medline: 21051234]
5. Stites M. Observational pain scales in critically ill adults. Crit Care Nurse 2013 Jun;33(3):68-78. [doi: 10.4037/ccn2013804] [Medline: 23727853]
6. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013 Jan;41(1):263-306. [doi: 10.1097/CCM.0b013e3182783b72] [Medline: 23269131]
7. Payen J, Bosson J, Chanques G, Mantz J, Labarere J, DOLOREA Investigators. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post Hoc analysis of the DOLOREA study. Anesthesiology 2009 Dec;111(6):1308-1316. [doi: 10.1097/ALN.0b013e3181c0d4f0] [Medline: 19934877]
8. Raffaeli W, Arnaudo E. Pain as a disease: an overview. J Pain Res 2017;10:2003-2008 [FREE Full text] [doi: 10.2147/JPR.S138864] [Medline: 28860855]
9. Thong ISK, Jensen MP, Miró J, Tan G. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure? Scand J Pain 2018 Jan 26;18(1):99-107. [doi: 10.1515/sjpain-2018-0012] [Medline: 29794282]
10. Herr K, Coyne PJ, McCaffery M, Manworren R, Merkel S. Pain assessment in the patient unable to self-report: position statement with clinical practice recommendations. Pain Manag Nurs 2011 Dec;12(4):230-250. [doi: 10.1016/j.pmn.2011.10.002] [Medline: 22117755]
11. Ledowski T, Ang B, Schmarbeck T, Rhodes J. Monitoring of sympathetic tone to assess postoperative pain: skin conductance vs surgical stress index. Anaesthesia 2009 Jul;64(7):727-731 [FREE Full text] [doi: 10.1111/j.1365-2044.2008.05834.x] [Medline: 19183409]
12. Shi Y, Ding G, Wang H, Eduardo Roman H, Lu S. The fog computing service for healthcare. : IEEE; 2015 Presented at: International Symposium on Future Information and Communication Technologies for Ubiquitous HealthCare (Ubi-HealthTech); May 28-30, 2015; Beijing, China. [doi: 10.1109/Ubi-HealthTech.2015.7203325]
13. Kasaeyan Naeini E, Shahhosseini S, Subramanian A, Yin T, Rahmani AM, Dutt N. An edge-assisted and smart system for real-time pain monitoring. : IEEE; 2019 Presented at: IEEE/ACM International Conference on Connected Health: Applications, Systems and Engineering Technologies (CHASE); Sep 25-27, 2019; Arlington, VA, USA p. 47-52. [doi: 10.1109/chase48038.2019.00023]
14. Sarker VK, Jiang M, Gia TN, Anzanpour A, Rahmani AM, Liljeberg P. Portable multipurpose bio-signal acquisition and wireless streaming device for wearables. : IEEE; 2017 Presented at: IEEE Sensors Applications Symposium (SAS); Mar 13-15, 2017; Glassboro, NJ, USA p. 1-6. [doi: 10.1109/sas.2017.7894053]
15. Fridlund AJ, Cacioppo JT. Guidelines for human electromyographic research. Psychophysiology 1986 Sep;23(5):567-589. [doi: 10.1111/j.1469-8986.1986.tb00676.x] [Medline: 3809364]
16. Critchley HD. Electrodermal responses: what happens in the brain. Neuroscientist 2002 Apr;8(2):132-142. [doi: 10.1177/107385840200800209] [Medline: 11954558]
17. Jolliffe IT. Principal component analysis. In: Wiley StatsRef: Statistics Reference Online. Atlanta, GA: American Cancer Society; Sep 29, 2014.
18. Bishop CM. Neural Networks for Pattern Recognition. Birmingham, UK: Oxford University Press; 1995.
19. Jiang M, Gia TN, Anzanpour A, Rahmani A, Westerlund T, Salantera S, et al. IoT-based remote facial expression monitoring system with sEMG signal. 2016 Presented at: IEEE Sensors Applications Symposium (SAS); Apr 20-22, 2016; Catania, Italy. [doi: 10.1109/SAS.2016.7479847]
20. Jiang M, Rahmani AM, Westerlund T, Liljeberg P, Tenhunen H. Facial expression recognition with sEMG method. 2015 Presented at: IEEE International Conference on Computer and Information Technology; Ubiquitous Computing and

Communications; Dependable, Autonomic and Secure Computing; Pervasive Intelligence and Computing; Oct 26-28, 2015; Liverpool, UK. [doi: 10.1109/CIT/IUCC/DASC/PICOM.2015.148]
21. Aung MSH, Kaltwang S, Romera-Paredes B, Martinez B, Singh A, Cella M, et al. The automatic detection of chronic pain-related expression: requirements, challenges and the multimodal EmoPain dataset. IEEE Trans on Affect Comput 2016 Oct 1;7(4):435-451. [doi: 10.1109/taffc.2015.2462830]
22. Brahnam S, Nanni L, Sexton R. Introduction to neonatal facial pain detection using common and advanced face classification techniques. In: Advanced Computational Intelligence Paradigms in Healthcare. Berlin, Germany: Springer; 2007:225-253.
23. Lucey P, Cohn JF, Prkachin KM, Solomon PE, Matthews I. Painful data: The UNBC-McMaster shoulder pain expression archive database. 2011 Presented at: IEEE Face and Gesture; Mar 21-25, 2011; Santa Barbara, CA, USA. [doi: 10.1109/FG.2011.5771462]
24. Jiang M, Mieronkoski R, Syrjälä E, Anzanpour A, Terävä V, Rahmani AM, et al. Acute pain intensity monitoring with the classification of multiple physiological parameters. J Clin Monit Comput 2018 Jun 26;33(3):493-507. [doi: 10.1007/s10877-018-0174-8]
25. Walter S, Gruss S, Ehleiter H, Tan J, Traue H, Crawcour S. The biovid heat pain database data for the advancement and systematic validation of an automated pain recognition system. : IEEE; 2013 Presented at: IEEE International Conference on Cybernetics (CYBCO); Jun 13-15, 2013; Lausanne, Switzerland. [doi: 10.1109/cybconf.2013.6617456]
26. Gruss S, Geiger M, Werner P, Wilhelm O, Traue HC, Al-Hamadi A, et al. Multi-modal signals for analyzing pain responses to thermal and electrical stimuli. J Vis Exp 2019 Apr 05(146). [doi: 10.3791/59057] [Medline: 31009005]
27. Ye J, Lee K, Chou Y, Sie H, Huang R, Chuang C. Assessing pain intensity using photoplethysmography signals in chronic myofascial pain syndrome. Pain Pract 2018 Mar 23;18(3):296-304. [doi: 10.1111/papr.12601] [Medline: 28502104]
28. Syrjala E, Jiang M, Pahikkala T, Salantera S, Liljeberg P. Skin conductance response to gradual-increasing experimental pain. 2019 Presented at: 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 23-27 Jul, 2019; Berlin, Germany p. 3482-3485. [doi: 10.1109/embc.2019.8857776]

Abbreviations

ECG: electrocardiography
EDA: electrodermal activity
EMG: electromyography
IRB: institutional review board
NRS: numeric rating scale
PPG: photoplethysmography
TENS: transcutaneous electrical nerve stimulation
UCIMC: University of California, Irvine Medical Center
VAS: visual analog scale

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Protocol

Effectiveness of Using Mental Health Mobile Apps as Digital Antidepressants for Reducing Anxiety and Depression: Protocol for a Multiple Baseline Across-Individuals Design

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Abstract

Background: The use of mental health mobile apps to treat anxiety and depression is widespread and growing. Several reviews have found that most of these apps do not have published evidence for their effectiveness, and existing research has primarily been undertaken by individuals and institutions that have an association with the app being tested. Another reason for the lack of research is that the execution of the traditional randomized controlled trial is time prohibitive in this profit-driven industry. Consequently, there have been calls for different methodologies to be considered. One such methodology is the single-case design, of which, to the best of our knowledge, no peer-reviewed published example with mental health apps for anxiety and/or depression could be located.

Objective: The aim of this study is to examine the effectiveness of 5 apps (*Destressify*, *MoodMission*, *Smiling Mind*, *MindShift*, and *SuperBetter*) in reducing symptoms of anxiety and/or depression. These apps were selected because they are publicly available, free to download, and have published evidence of efficacy.

Methods: A multiple baseline across-individuals design will be employed. A total of 50 participants will be recruited (10 for each app) who will provide baseline data for 20 days. The sequential introduction of an intervention phase will commence once baseline readings have indicated stability in the measures of participants' mental health and will proceed for 10 weeks. Postintervention measurements will continue for a further 20 days. Participants will be required to provide daily subjective units of distress (SUDS) ratings via SMS text messages and will complete other measures at 5 different time points, including at 6-month follow-up. SUDS data will be examined via a time series analysis across the experimental phases. Individual analyses of outcome measures will be conducted to detect clinically significant changes in symptoms using the statistical approach proposed by Jacobson and Truax. Participants will rate their app on several domains at the end of the intervention.

Results: Participant recruitment commenced in January 2020. The postintervention phase will be completed by June 2020. Data analysis will commence after this. A write-up for publication is expected to be completed after the follow-up phase is finalized in January 2021.

Conclusions: If the apps prove to be effective as hypothesized, this will provide collateral evidence of their efficacy. It could also provide the benefits of (1) improved access to mental health services for people in rural areas, lower socioeconomic groups, and children and adolescents and (2) improved capacity to enhance face-to-face therapy through digital homework tasks that can be shared instantly with a therapist. It is also anticipated that this methodology could be used for other mental health apps to bolster the independent evidence base for this mode of treatment.

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KEYWORDS

mHealth; eHealth; mobile apps; mobile phone; anxiety; depression; single-case study

Introduction

Background

Mobile health apps for smartphones and tablet devices have become a lucrative business, with worldwide expenditure estimated to be over US $92 billion [1]. Apps are increasingly being used to monitor, assess, and improve mental health. There are now more than 10,000 publicly available mental health–specific apps [2]. Most of these apps lack published evidence for their effectiveness, making it difficult for clinicians and consumers to know which app is the most appropriate [3]. Currently, choices are made using reviews and ratings available in app stores [4], but these can produce unreliable results [5].

Although effective treatments for anxiety and depression exist, many people do not access these for various reasons [6]. However, with ownership of smartphones being at 70% of the global population and rising [7], mental health apps potentially offer a partial solution to limitations in service availability and acceptability.

Previous Research

Published reviews have found that mental health apps can be effective for reducing anxiety [8] and depression [9] with an overall effect size of small to moderate [10]. Within this research, there are some notable shortcomings, including substantial heterogeneity across studies. For example, there have been differences in dosage [11,12] duration of interventions [13,14] and the absence of long-term follow-up data [15].

Another limitation of previous research is that most of it has been carried out by individuals who have developed the app, who have stood to gain financially from its sales, and/or who were otherwise associated with it [3]. For instance, a recent review of app stores found that only 1.02% of mental health apps offering therapeutic treatment for anxiety and/or depression had been evaluated using *independent* research [3]. Furthermore, in a meta-analysis of 9 studies on apps targeting anxiety [8] and in another meta-analysis of 18 studies on apps targeting depression [9], none involved independent research or replication (note that some studies were included in both meta-analyses).

A possible reason for the lack of research on apps is the time factor for large-scale experimental designs. Specifically, randomized controlled trials (RCTs) that demonstrate the efficacy of an intervention by measuring and comparing the outcomes of matched treatment and control groups are often lengthy to conduct. This is a barrier to achieving results in a time frame that is acceptable to the profit-driven app market. In the time it takes to complete an RCT, the app being studied may have been updated or disappeared from the market altogether as newer apps with enhanced features emerge in its place. Furthermore, RCTs are not necessarily the most appropriate study design for every situation, with another limitation of RCTs being lower ecological validity [16].

Single-Case Designs

Single-case research designs address the issue of ecological validity by testing the effectiveness of an intervention for individuals (ie, performance under real-world conditions). However, single-case designs can also control for threats to internal validity and thus test for the efficacy of a treatment. Such designs go beyond a study with a sample of one participant and involve continuous and repeated measurements, random assignment, sequential introduction of the treatment, and specific data analysis and statistics [17]. Robust results in clinical psychology and behavioral science can be demonstrated when benefits are shown in 3 to 5 cases [18-20]. A single-case design is also safer than an RCT for vulnerable participants because their well-being is monitored by gathering and analyzing data more frequently during the study, and treatment can be altered if there is a clinically significant decline in status [21,22]. For mental health apps, single-case designs are a viable alternative for accelerating the evidence base [23,24].

Objectives and Aims

The main objective of this study is to use a single-case design to examine the effectiveness of 5 mental health apps that purport to have efficacy for reducing symptoms of anxiety and/or depression.

This study seeks to answer the following research questions: (1) Do the apps in this study provide clinically significant improvements in symptoms of anxiety and/or depression? (2) What individual characteristics of participants influence the results in this regard? and (3) What individual characteristics of the apps influence the results?

The only hypothesis to be tested in this study is based on question 1:

- Hypothesis 1: the use of apps will produce improvements in mental health and well-being in line with the 3-phase model of psychotherapy outcomes [25].

The Howard et al [25] model proposed that the outcome of any psychotherapeutic intervention will involve progressive reductions in subjective distress, then symptomatology, and, finally, an increase in overall life functioning.

Methods

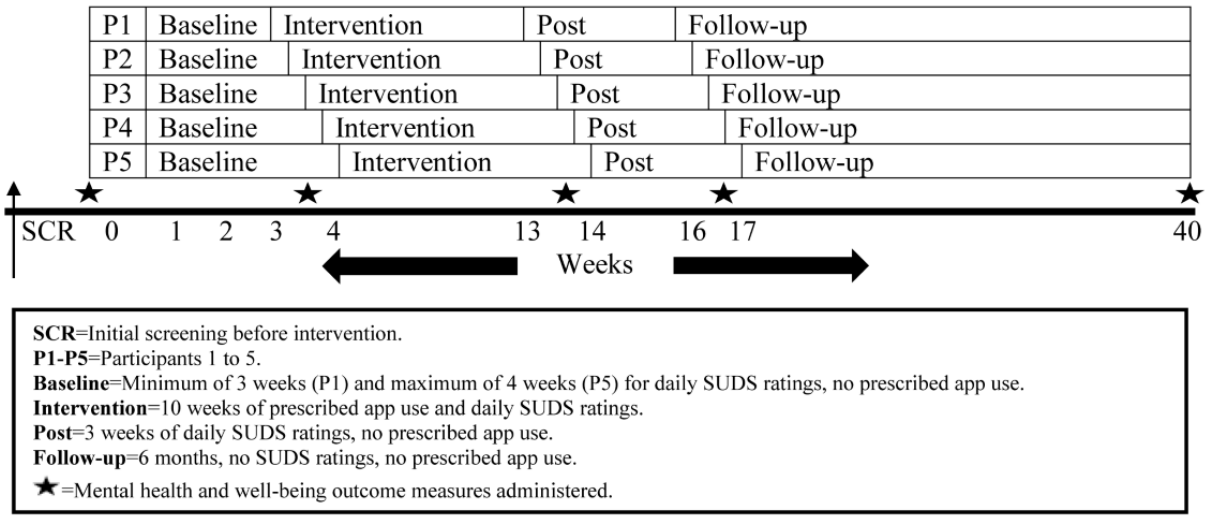
Study Design

This study is registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR), which is a primary registry in the World Health Organization Registry Network (registration number: ACTRN12619001302145p).

A multiple baseline across-individuals design will be employed. Multiple baseline designs in mental health intervention studies are those where a baseline period of stability of symptoms is established before the intervention is introduced. In this way, each participant acts as their own control, and internal validity is demonstrated when there is no change in symptoms until after the treatment is introduced [18]. In the design to be used in this study, all participants commence the baseline period at the same time but start the treatment at different times after a minimum number of daily data readings (at least 20) have been received. This sequential commencement approach further strengthens the internal validity by reducing the likelihood of history, maturation, or other extraneous factors explaining any observed

emotional or behavioral change that occurs simultaneously with the introduction of the treatment. The multiple data recordings allow for the use of analytical techniques such as a time series analysis [20,26] and will involve participants reporting ratings of subjective units of distress (SUDS) via SMS text messaging using a 10-point scale. In this design, 4 or more baselines are recommended [18,20], and these will follow the pattern shown in Figure 1.

Figure 1. Overview of the proposed study design.



This research will use a *prescribed dosage* approach, as if the app was a *digital antidepressant*: one 10-min *dose* of app use per day for 5 days per week. The 10-week intervention period creates equivalence with one 50-min session per week for 10 weeks, which is the annual maximum number of psychology sessions rebated under Australia's Medicare system [27]. The rationale for a minimum 3-week postintervention period (to demonstrate the stability of the treatment effect) is similar to that described earlier, namely, that 20 daily SUDS ratings are needed for a valid data analysis. The justification for using the 5 chosen apps are as follows: (1) each has some evidence of efficacy published in a peer-reviewed journal, (2) all have publicly available free versions, and (3) all can fit the *prescribed dosage* approach. The chosen apps use 3 popular evidence-based frameworks employed across mental health settings for treating anxiety and/or depression: cognitive behavioral therapy (CBT), mindfulness, and positive psychology. Finally, the rationale for using 10 participants per app is that, even accounting for a 50% to 60% attrition rate [28], approximately 3 to 5 participants per app will provide enough data for a valid statistical analysis using time series conventions. As previously noted, this number of replications in a single-case design with similarly presenting individuals can produce robust and generalizable findings if the results are comparable in each case [18-20].

Recruitment

Commencing in January 2020, participants will be recruited throughout Australia by advertising the proposed study to nongovernment organizations that run programs for clients with mental illness (eg, the Benevolent Society), contacting associations of mental health professionals that may alert their members to the proposed study (eg, Australian Psychological Society), and contacting support groups and other organizations in the mental health sector (eg, Mental Health Victoria), requesting they advertise the proposed study on their various social media platforms. The advertisement is shown in Multimedia Appendix 1. Recruitment will cease once 50 participants are recruited. Owing to the nature of the proposed study design, new participants cannot commence after the study has started because the multiple baseline design requires participants to begin at the same time and then have specifically staggered phase commencements after that. Figure 1 demonstrates this process.

All 50 participants (10 for each app) will be randomized to an app and their position in the single-case design (ie, P1 to P10) using the web-based random number generator, *Research Randomizer* [29]. The full inclusion and exclusion criteria are presented in Textboxes 1 and 2, respectively. A financial reimbursement will be offered to participants of Aus $0.50 (US $0.33) per daily SUDS rating sent via a text message. The researchers acknowledge that financial payments have the potential to interfere with ecological validity, because a person in the community would not normally be paid for using a mental health app, and intrinsic motivation, because people could potentially use the app for the benefit of financial remuneration rather than for the value of improving their mental health. However, the low amount of remuneration being offered of approximately Aus $45.00 (US $29.41) on average is not considered payment for participation in the proposed study but rather reimbursement of personal expenses incurred while taking part in the proposed study. Given that the effectiveness of mental health apps has the potential to benefit those from low socioeconomic groups, being reimbursed for providing in excess of 80 text messages will alleviate reasons that a potential participant of lower socioeconomic background could provide

for being out of pocket for the cost of sending text messages from their mobile phone. Therefore, it is envisaged that prospective participants will more likely have motivation to improve their mental health beyond receiving financial remuneration. In addition, this financial incentive will not be advertised, and participants will only learn about this when they provide consent when completing the demographics questionnaire.

Textbox 1. Study eligibility: inclusion criteria.

Inclusion criteria:

- 18 years of age or older
- Ability to read English
- Have access to a smartphone or tablet device capable of connecting to the internet and downloading the required app and sending and receiving SMS text messages
- Agreeable to providing daily subjective units of distress ratings via SMS text messages and to completing self-report measures at 5 different time points (including 6-month follow-up)
- Mild-to-moderate anxiety and/or depression, diagnosed by a qualified health professional and confirmed by the researchers (all of whom are clinical psychologists) after screening. Screening involves analyzing the participants' scores on the first completed set of outcome measures: the Depression Anxiety Stress Scale-21 short-form version and the Outcome Questionnaire-45 second edition version. For more information on these, see the *Mental Health and Well-Being* subsection.

Textbox 2. Study eligibility: exclusion and removal criteria.

Exclusion criteria:

- Severe anxiety and/or depression, as indicated by the initial outcome measures and in any responses to specific questions in the demographics questionnaire
- History of psychosis or other complex mental health presentation as deemed by the researchers to be unsuitable for participation in this research. There will be a question in the demographics questionnaire that asks participants for their complete mental health diagnoses
- Current suicidal ideation, as indicated by a participant's responses on the initial outcome measures

Removal criteria:

- Not providing any subjective units of distress rating for a 2-week period
- Not providing a minimum of 20 subjective units of distress ratings in the baseline and postintervention phases or a minimum of 40 subjective units of distress ratings in the intervention phase
- Not completing outcome measures either preintervention or postintervention
- Clinically significant/unsafe decline in mental health as indicated by subjective units of distress ratings or outcome measures or in the judgment of researchers
- Suicidal ideation

Materials

Participants will supply their own smartphones and/or tablet devices. In total, 5 different apps will be used: (1) *Destressify* [30,31], (2) *MoodMission* [32-35], (3) *Smiling Mind* [36,37], (4) *MindShift* [15,38], and (5) *SuperBetter* [39,40].

All the apps are supported by published research demonstrating statistically significant efficacy for the treatment of anxiety and/or depression. Each app has an accompanying website with further information and an accessible privacy policy. Detailed information about each app and its accompanying research is provided in Multimedia Appendix 2.

Measures

A number of measures of participants' experiences and outcomes will be used, as described in the following sections.

Biographic and Demographic Features

The demographics questionnaire has been developed by the researchers to obtain information that will be examined to ascertain if any patterns in the outcome data are related to aspects of an individual's demographic profile. Areas covered include mental health literacy [41], motivation to change [42], chronicity of anxiety and/or depression [43], and technology proficiency, all of which may influence results. Multimedia Appendix 3 contains the complete demographics questionnaire and all other measures used in this research.

Mental Health and Well-Being

A 3-phase model of psychotherapy outcomes [25] is applied.

1. Subjective well-being: SUDS ratings—participants rating their well-being in response to the question, "How do you feel today?," with 0 indicating no distress and 10 indicating worst distress [44].

2. Symptoms: the Depression Anxiety Stress Scale-21 short-form version (DASS-21) [45]. Participants rate their experience of symptoms of depression, anxiety, and stress over the previous week on a 4-point scale, ranging from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time). Items in each subscale are summed to provide scores for symptoms of depression and anxiety, with higher scores indicating greater severity of symptomatology. The total scores for depression and anxiety subscales are multiplied by 2 to interpret the norms [46,47]. Severity ratings for the depression subscale are 0-9 (normal), 10-13 (mild), 14-20 (moderate), 21-27 (severe), and ≥28 (extremely severe). Norms for the anxiety subscale were set as 0-7 (normal), 8-9 (mild), 10-14 (moderate), 15-19 (severe), and 20+ (extremely severe). The DASS-21 has been shown to demonstrate sound psychometric properties and validity [48].
3. Life functioning: the Outcome Questionnaire-45 second edition version (OQ-45.2) [49] is a 45-item self-report scale that measures overall interpersonal relationships and social role functioning in adults aged 18 years and older [50]. An index for overall life functioning is calculated [51]. Participants rate their feelings over the previous week on a 5-point scale, ranging from 0 (never) to 4 (always). The scale consists of both positive and negative items that are reverse-scored; higher scores indicate greater symptoms of distress and difficulties in interpersonal relations. A total score of ≥63 is indicative of clinically significant symptoms, with the subscale cutoffs for clinical significance being 35 for symptom distress, 14 for interpersonal relations, and 11 for social role [51]. The OQ-45.2 has demonstrated high internal consistency (α=.90) and test-retest reliability of *r*=.84 over a minimum 3-week period [52]. The OQ-45.2 has also shown good construct and concurrent validity in a community sample when using the total score as opposed to interpreting the 3 individual subscales [53].

Experience of App Usage

The Mobile Application Rating Scale-user version (uMARS) [54] is a 20-item questionnaire that records an individual's rating on the quality of a mobile app. It contains multiple-choice and Likert-type responses and a free text field allowing users to provide a qualitative description of any aspect of the app or their experience of using the app that they wish to comment on. The uMARS contains 5 subscales: engagement, functionality, aesthetics, information quality, and a subjective quality appraisal. It has been found to have excellent internal consistency (α=.90) and good test-retest reliability [54].

Procedure

Figures 1 and 2 illustrate the phases of this research. Recruitment commenced in January 2020.

Figure 2. Flowchart of study and participant involvement.

Phase 1 (Prebaseline)

Web-based links to the information sheet for participants and consent form, the demographics questionnaire, and the mental health and well-being outcome measures (DASS-21 and OQ-45.2) are sent by email and SMS text messages and completed digitally by participants using the Qualtrics survey platform [55] and the OQ-Analyst platform [56]. Participants are screened for suitability to be in the proposed study by having their outcome measure and demographics questionnaire responses analyzed for evidence of severe anxiety and/or depression, suicidal ideation, or the presence of other severe mental illnesses such as psychosis. If researchers require further information from any participant, the participant will be contacted to clarify any queries or concerns. If a participant is deemed inappropriate for the proposed study, she/he will be directed by the researchers toward more appropriate forms of care.

Phase 2 (Baseline)

Accepted participants provide daily SUDS ratings for a minimum of 20 days or until a stable baseline profile of current psychological distress is achieved. At the end of this phase, the mental health and well-being outcome measures (DASS-21 and OQ-45.2) are completed.

Phase 3 (Intervention)

Participants are provided with generic instructions for all apps, links to both the Apple App Store and Google Play Store for their app, and specific instructions on how to use their app once it is downloaded (Multimedia Appendix 2). In addition, website links to information on the type of evidence-based framework their app uses and emergency contact information in the event of a mental health crisis are provided. Participants continue to supply daily SUDS ratings for the minimum 10-week intervention. Data analysis will be ongoing throughout this phase and will be used to assist in determining whether any participant's mental health is significantly deteriorating. If a participant provides a SUDS rating of 10 for 2 consecutive days, they will be contacted for a check on their welfare. Similarly, if a participant's SUDS ratings are above 8 for 5 consecutive days, they will also be contacted for a check on their welfare. We have chosen these cutoff values because the information provided to participants about the SUDS indicates that 8 is equal to their perception of feeling *very distressed* and 10 is equal to their perception of feeling the *worst distress*. The SUDS does not have a universal categorization label for each point on the scale, in addition to the number. Instead, it was designed to allow flexibility in an individual's self-assessment [57] and labeling can vary from study to study. The mental health and well-being outcome measures (DASS-21 and OQ-45.2) and uMARS are completed at the end of this phase. If a participant's responses on the outcome measures reveal a clinically significant decline in mental health compared with their responses at the beginning of the intervention, which places them in a severe category of mental illness, she/he will be contacted for a check on their welfare. In all cases, if a participant is categorized as being inappropriate for continuation in the proposed study, she/he will be directed toward more appropriate forms of care.

Phase 4 (Postintervention)

Participants provide SUDS ratings for at least 20 days following the completion of their official intervention period. Once a minimum of 20 SUDS ratings have been received, they will complete another DASS-21 and OQ-45.2. Participants are given information on all the apps so that they may explore the others if they wish.

Phase 5 (Follow-Up)

Participants are followed up at 6 months, where they will be asked to complete the mental health and well-being outcome measures (DASS-21 and OQ-45.2).

Expected Time Frames

The daily SUDS text messages will take a few seconds to reply to; app use will be a minimum of 10 min per day, 5 days per week for 10 weeks; the mental health and well-being outcome measures (DASS-21 and OQ-45.2) are expected to take less than 10 min each to complete on 5 different occasions; and the demographics questionnaire completed in phase 1 and the uMARS questionnaire completed in phase 3 are expected to take 15 min each.

The proposed study will run for approximately 40 weeks. Data analysis will be completed by approximately December 2020. A write-up for publication is expected to be completed by January 2021.

Data Analysis

Descriptive Statistics and Qualitative Accounts

Descriptive statistics will be used to compare individuals and augment other analytical techniques. The data obtained from the uMARS will be used to assist in gaining an enhanced understanding of participant attitudes toward their app. Depending on the amount of qualitative information provided by participants, it will be converted via a *content analysis* [58] and will be coded into networks that hierarchically classify, identify, and summarize key themes. Data obtained from the uMARS will be plotted, as explained in the Visual Inspection subsection.

Time Series Analysis

A process for conducting time series analyses for psychological research was described by Borckardt et al [59] using the *R* statistical software package. In the proposed study, the commencement of the intervention will be the predictor in a regression model that uses data before and after this point to determine if there has been a statistically significant impact on subjective distress, as measured by SUDS ratings. A minimum of 20 data points are required in each phase [20,26]. The *R* statistical package will use conventions of autoregressive integrative moving average (ARIMA) modeling to account for autocorrelated data [60] when building the model.

The time series analyses [59] will evaluate statistically significant changes across the phases of the proposed study. Overall level and trends across time will be considered, and if necessary, adjustments will be made for irregular variation effects. An *irregular factor* is similar to the error terms used in many statistical models, such as generalized linear modeling. The methods of making such adjustments differ depending on the nature of the collected data but may include the augmented Dickey-Fuller test, Durbin-Watson test and/or the Ljung-Box test as part of an ARIMA model.

Clinical Significance and Statistical Reliability

Meaningful or clinically significant changes occur when an individual is in the dysfunctional (clinical) range at the commencement of treatment and in the functional (nonclinical) range at the end of treatment [61,62]. The clinical significance index (CSI) indicates whether individuals have made meaningful improvements to their emotional health and moved from being clinically dysfunctional to functional [63]. The reliable change index (RCI) verifies the statistical significance of any change in an individual's score from pre- to postintervention [62]. This approach is particularly useful for single-case designs because it allows researchers to focus on individual functioning [64] and to adjust treatment if necessary. Jacobson and Truax [62]

developed a classification system to describe the change in a participant's mental health in a study's conclusion: *recovered*=clinically significant and statistically reliable; *improved*=not clinically significant, but statistically reliable; *unchanged*=not clinically significant or statistically reliable; and *deteriorated*=clinically significant and/or statistically reliable in a worsening direction.

To determine the CSI, a cutoff point between the scores obtained by the functional and dysfunctional populations on a particular measure is identified [61,62]. Scores on either side of this point are statistically more likely to indicate whether an individual is functional or dysfunctional [61,62]. Normative data are required for both functional and dysfunctional populations for the measures being used. The CSI is based on the following formula [62]:

where 1 represents the nonclinical population and 2 represents the clinical population.

The RCI is a function of a measure's standard deviation and reliability [61]. It measures an individual's change in self-reported score from pretreatment to follow-up for statistical reliability. If an individual's change exceeds 1.96 times the SE, the change is statistically reliable at $P<.05$ because it is unlikely to occur more than 5% of the time as a result of measure discrepancy or chance [61]. The RCI is calculated as follows [62]:

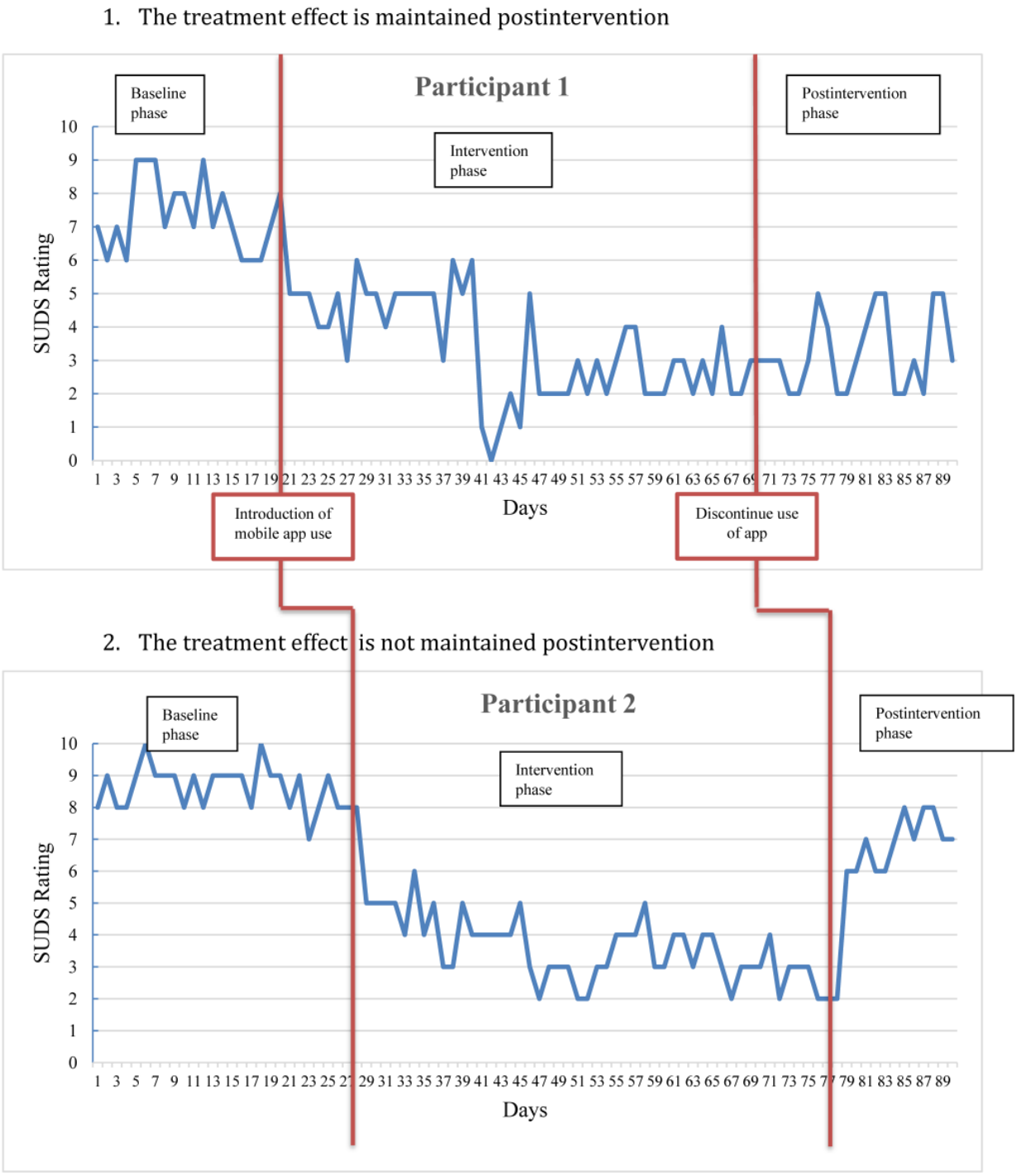
where $S_{diff}=\sqrt{2}(S_E)^2$ and $S_E=SD$ of both groups$\times(\sqrt{1}-$test-retest reliability).

Clinical significance will be calculated based on participants' scores on the mental health and well-being outcome measures (DASS-21 and OQ-45.2) across the various phases using the framework suggested by Jacobson and Truax [62]. Using the OQ-Analyst platform, clinical significance will be compared with statistical significance and visual inspection.

Visual Inspection

Visual inspection of plotted data allows for a personal judgment about the effect of an intervention and can often produce more meaningful information than approaches involving the calculation of statistical significance [20]. In this study, visual inspection will be possible using up to 112 data points of SUDS ratings, as illustrated in Figure 3. Data obtained from the uMARS will be plotted against participant ratings from the mental health and well-being outcome measures (DASS-21 and OQ-45.2) and SUDS data and inspected for any observed relationships.

Figure 3. Example of how participant data may be affected and graphed using a multiple baseline across-individuals design.



Data Management

Management and storage of data will occur in line with the Management and Storage of Research Data and Materials Policy of the University of New England [65]. Specifically, all nondigital materials will be scanned and digitally stored indefinitely with all other digital information pertaining to this research on the University of New England research data cloud storage facility. Digital information will be password protected and accessible only to appropriate research staff.

Data Exclusion

Data will be excluded from time series and visual analyses if a participant fails to provide a minimum of 20 SUDS ratings in phase 1 (baseline) and/or phase 4 (postintervention) and 40 SUDS ratings in phase 3 (intervention). Data will be excluded from CSI and RCI analyses if a participant fails to complete baseline and/or postintervention mental health and well-being outcome measures (DASS-21 and OQ-45.2). Owing to the nature of the proposed study design, participants who dropout because they did not provide the required minimum data cannot be replaced by new participants once the baseline phase has commenced.

Ethics Approval

Ethics approval was granted by the University of New England Human Research Ethics Committee on November 1, 2019 (approval number: HE19-186). This research will be conducted under the guidelines of the National Statement on Ethical Conduct in Human Research by the Australian National Health and Research Council [66]. Any changes to procedures outlined in this protocol will be forwarded to the University of New England Human Research Ethics Committee for approval before implementation. Such changes will also be acknowledged on the trial registration at the ANZCTR.

Results

Reporting of results will follow the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth [67] guidelines. The Procedure section provides the estimated timelines.

Discussion

Principal Findings

Information about and descriptions of the previous research on each app are provided in Multimedia Appendix 2. Previous research on mental health apps is lacking, and there are other issues impacting this research. The methodologies employed in the studies based on the apps used in the proposed study are heterogeneous, and this is in keeping with other previous research on other mental health apps [3]. The studies here had varying attrition rates (the *Destressify* research [30] reported 19.9%; *MoodMission* [34], 54.8%; *Smiling Mind* [36], 17.7%; *MindShift* [15], 46.7%; and *SuperBetter* [39], 73.9%), but the varying intervention times and methodologies may have contributed to these attrition rates. Some studies were conducted by researchers who either developed the app or had an otherwise pre-existing association with the app being tested (in the case of *MoodMission* and *SuperBetter*). Other studies had participants with varying degrees of severity of anxiety and depression at commencement that were measured with varying outcome instruments (*Destressify*, *MoodMission*, and *Smiling Mind* did not specify the participants' mental health status in their inclusion criteria; *MindShift* had participants with moderate-to-high levels of anxiety, as indicated by their ratings on at least one scale of the Patient Health Questionnaire; and *SuperBetter* had participants who scored higher than 16 on the Center for Epidemiological Studies Depression Scale). Nevertheless, all studies were published in peer-reviewed journals and authored by individuals who have associations with legitimate academic institutions and mental health organizations. Therefore, we hypothesize that our results will reveal the apps to be effective for reducing symptoms of anxiety and depression, as reflected in the previous research.

Potential Added Value for Clinicians and Consumers

This study is unique with respect to any published study of mental health apps that could be located. This independent research, using a single-case methodology, allows for an in-depth examination of personal factors that may impact the effectiveness of these apps. It will therefore add value to existing studies on these specific apps. However, it is also anticipated that this research will be automated to the point where the design can be used to examine larger samples with the rigor of an RCT experimental design, thereby having a positive impact on increasing future research at a faster rate. It also provides an opportunity for evidence-based mental health treatment to reach those who are not already receiving it.

If mental health apps have demonstrated effectiveness, they could be incorporated by clinicians into face-to-face therapy to enhance the experience of consumers. For example, some apps allow users to complete homework tasks set by their therapist or to make thought diary entries that can be shared digitally with their therapist. Other information such as physiological readings and user-entered information such as SUDS ratings can also be sent digitally to clinicians to gain a more accurate reading of their client's emotional health between sessions [68].

There are potential benefits for health systems and mental health consumers if apps can gain increased legitimacy for their ability to effectively manage anxiety and depression. These include the following: more economical for low socioeconomic groups to obtain mental health treatment compared with face-to-face services [69], improved access for those in rural areas where there may be limited treatment options [70], reduced stigma [71] because of anonymous assistance, access for children and adolescents who are already large consumers of smartphones and the internet [72], and it is simply a preferred way to receive mental health information for some [73]. Therefore, it is important to increase research on the efficacy and effectiveness of mental health apps using appropriate and scientifically validated methodologies in addition to RCTs, as the widely considered gold standard of RCTs may not be the most appropriate for analyzing mental health apps [23,74].

This study will examine a number of mental health apps that differ in several ways: (1) having different theoretical frameworks (*MoodMission* and *MindShift* use CBT, *Destressify* and *Smiling Mind* use mindfulness, and *SuperBetter* uses positive psychology), (2) being developed by different teams in different countries (*Destressify* was developed in the United States by individuals with an interest in mindfulness meditation, *MoodMission* was developed in Australia by a team of psychologists and researchers at Monash University, *Smiling Mind* was set up as a not-for-profit organization in Australia by mental health and meditation experts, *MindShift* was developed in Canada by a not-for-profit mental health organization, and *SuperBetter* was developed in the United States by a game designer and mental health researchers from Stanford University and the University of Pennsylvania), and (3) containing different aesthetic qualities and types of activities with different aims (*Destressify* focuses on reducing stress, *MoodMission* focuses on providing short activities designed to help an individual in response to how they are feeling at that time, *Smiling Mind* focuses on teaching mindfulness skills in a structured format using guided meditation, *MindShift* focuses on reducing anxiety by using a number of different interventions such as graded exposure and using a thought journal, and *SuperBetter* is very colorful with a playful tone that may appeal to individuals who like video games). Multimedia Appendix 2 provides further information about each app. Having a diversity of apps is

important because there may be differences in the way consumers react to different aspects of an app. It is known that face-to-face therapy outcomes can be influenced by client-therapist rapport [75], client motivation [42], and chronicity/history of mental illness [43]. Therefore, there may be different aspects of a mental health app that contribute to its effectiveness, such as gamification, aesthetics, usability/interface [76], and evidence-based framework.

In sum, the reasons mentioned earlier support the need for a vigorous research agenda on the effectiveness of mental health apps, and this study methodology can assist in realizing this.

Limitations and Strengths

This study has some limitations. First, it may not be possible to generalize the findings if the outcomes for participants with the same condition differ in significant ways. Second, there is no certainty that participants will provide daily SUDS ratings for 16 weeks, despite the minimal effort involved. Third, with many brands of smartphones using different versions of software, there is a risk that the technology between phone and app may not be compatible for some participants.

This study also has several strengths. By using questionnaires that consider subject distress, symptoms, and life functioning at different time points, the design allows for a comprehensive approach toward the impact of the apps. The use of the DASS-21 and OQ-45.2 questionnaires at multiple time points will allow an examination of issues such as suicidality, dysfunctional coping activities (such as excessive alcohol consumption), physical health, and sleep disturbance. The single-case design will also provide in-depth information about individual responses and offers a way that clinicians may be able to contribute to the evaluation process (see the Conclusions section). Finally, there is the ambitious goal of offering a future methodology that could be applied to larger RCTs via a highly digitized procedure.

Conclusions

The evidence base for mental health apps that offer treatments for anxiety and depression is currently low. This study may assist in improving this situation in several ways. First, it may allow more clinicians to participate in the research process. Marshall et al [74] have outlined a proposal to establish a centralized database where clinicians and researchers contribute information and data on the effectiveness of mental health apps by using a standardized protocol that forms the basis of this research. Such a repository of information on mental health apps would mean an ever-increasing knowledge base that clinicians, researchers, government authorities, and academic institutions could refer to. Although there are existing websites that offer professional reviews with useful insights into mental health apps (eg, *PsyberGuide* [77], *Head To Health* [78], *Reachout Australia* [79], *Health Navigator* [80], and the *NHS App Library* [81]), these are based on professionals' perspectives and not systematic and scientific observations. The results of increased research, such as that outlined in the proposed study, have the potential to add valuable empirical data to such websites to reinforce the reviews posted there.

If a collaborative scientific methodology was used by clinicians and researchers to rate the effectiveness of mental health apps, this would also potentially allow more transparent categorization of mental health apps in the various app stores [74]. Currently, reliance on app stores leads to potential confusion for consumers as ratings and reviews may be unreliable or even fake [5]. Using the methodology in this study is one way that, if willing, the app stores could *certify* mental health apps as having reached an acceptable level of independently verified effectiveness [3]. This would allow consumers to more clearly identify apps validated by scientific research.

Finally, given the large number of consumers who own a smartphone globally [82], if more people are able to use efficacious mental health apps on their phones, it could potentially free up scarce face-to-face services in communities struggling to meet the demand for interventions to address mild-to-moderate mental health problems.

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Authors' Contributions

JM wrote the manuscript drafts. DD provided substantial reviews, and WB provided proofreading and editing. DD and WB supervised the overall research project. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Poster used to attract participants.
[PDF File (Adobe PDF File), 310 KB - resprot_v9i7e17159_app1.pdf]

Multimedia Appendix 2
Information about the apps used in the present study.
[PDF File (Adobe PDF File), 3500 KB - resprot_v9i7e17159_app2.pdf]

Multimedia Appendix 3
Forms and measures used in the present study.
[PDF File (Adobe PDF File), 4209 KB - resprot_v9i7e17159_app3.pdf]

References

1. Newzoo: The Destination for Games Market Insights. 2018. Global Mobile Market Report URL: https://newzoo.com/solutions/standard/market-forecasts/global-mobile-market-report/ [accessed 2019-09-15]
2. Torous J, Firth J, Huckvale K, Larsen ME, Cosco TD, Carney R, et al. The emerging imperative for a consensus approach toward the rating and clinical recommendation of mental health apps. J Nerv Ment Dis 2018 Aug;206(8):662-666. [doi: 10.1097/NMD.0000000000000864] [Medline: 30020203]
3. Marshall JM, Dunstan DA, Bartik W. The digital psychiatrist: in search of evidence-based apps for anxiety and depression. Front Psychiatry 2019;10:831 [FREE Full text] [doi: 10.3389/fpsyt.2019.00831] [Medline: 31803083]
4. Huang H, Bashir M. Users' adoption of mental health apps: examining the impact of information cues. JMIR Mhealth Uhealth 2017 Jun 28;5(6):e83 [FREE Full text] [doi: 10.2196/mhealth.6827] [Medline: 28659256]
5. Xie Z, Zhu S. AppWatcher: Unveiling the Underground Market of Trading Mobile App Reviews. In: Proceedings of the 8th ACM Conference on Security & Privacy in Wireless and Mobile Networks. 2015 Presented at: WiSec'15; June 22-26, 2015; New York, USA. [doi: 10.1145/2766498.2766510]
6. Gunter RW, Whittal ML. Dissemination of cognitive-behavioral treatments for anxiety disorders: overcoming barriers and improving patient access. Clin Psychol Rev 2010 Mar;30(2):194-202. [doi: 10.1016/j.cpr.2009.11.001] [Medline: 19942331]
7. Barboutov K, Furuskar A, Inam R. Ericsson. Stockholm: Niklas Heuveldop; 2017. Ericsson Mobility Report URL: https://www.ericsson.com/assets/local/mobility-report/documents/2017/ericsson-mobility-report-june-2017.pdf [accessed 2020-05-21]
8. Firth J, Torous J, Nicholas J, Carney R, Rosenbaum S, Sarris J. Can smartphone mental health interventions reduce symptoms of anxiety? A meta-analysis of randomized controlled trials. J Affect Disord 2017 Aug 15;218:15-22 [FREE Full text] [doi: 10.1016/j.jad.2017.04.046] [Medline: 28456072]
9. Firth J, Torous J, Nicholas J, Carney R, Pratap A, Rosenbaum S, et al. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. World Psychiatry 2017 Oct;16(3):287-298 [FREE Full text] [doi: 10.1002/wps.20472] [Medline: 28941113]
10. Lai J, Jury A. Te Pou o te Whakaaro Nui. Auckland: Te Pou o te Whakaaro Nui; 2018. Effectiveness of e-mental health approaches: Rapid review URL: https://www.tepou.co.nz/uploads/files/resource-assets/E-therapy%20report%20FINAL%20July%202018.pdf [accessed 2020-05-21]
11. Firth J, Torous J, Carney R, Newby J, Cosco TD, Christensen H, et al. Digital technologies in the treatment of anxiety: recent innovations and future directions. Curr Psychiatry Rep 2018 May 19;20(6):44 [FREE Full text] [doi: 10.1007/s11920-018-0910-2] [Medline: 29779065]
12. Fleming T, Bavin L, Lucassen M, Stasiak K, Hopkins S, Merry S. Beyond the trial: systematic review of real-world uptake and engagement with digital self-help interventions for depression, low mood, or anxiety. J Med Internet Res 2018 Jun 6;20(6):e199 [FREE Full text] [doi: 10.2196/jmir.9275] [Medline: 29875089]
13. Howells A, Ivtzan I, Eiroa-Orosa FJ. Putting the 'app' in happiness: a randomised controlled trial of a smartphone-based mindfulness intervention to enhance wellbeing. J Happiness Stud 2014 Oct 29;17(1):163-185. [doi: 10.1007/s10902-014-9589-1]
14. Boisseau CL, Schwartzman CM, Lawton J, Mancebo MC. App-guided exposure and response prevention for obsessive compulsive disorder: an open pilot trial. Cogn Behav Ther 2017 Nov;46(6):447-458. [doi: 10.1080/16506073.2017.1321683] [Medline: 28565937]
15. Paul AM, Fleming CJ. Anxiety management on campus: an evaluation of a mobile health intervention. J Technol Behav Sci 2018 Sep 19;4(1):58-61. [doi: 10.1007/s41347-018-0074-2]
16. Watson B, Procter S, Cochrana W. Using randomised controlled trials (RCTs) to test service interventions: issues of standardisation, selection and generalisability. Nurse Res 2004;11(3):28-42. [doi: 10.7748/nr2004.04.11.3.28.c6203] [Medline: 15065482]
17. Krasny-Pacini A, Evans J. Single-case experimental designs to assess intervention effectiveness in rehabilitation: a practical guide. Ann Phys Rehabil Med 2018 May;61(3):164-179 [FREE Full text] [doi: 10.1016/j.rehab.2017.12.002] [Medline: 29253607]
18. Barlow D, Nock M, Hersen M. Single Case Experimental Designs. Second Edition. Boston, UK: Pearson; 2009.

19. Horner RH, Carr EG, Halle J, McGee G, Odom S, Wolery M. The use of single-subject research to identify evidence-based practice in special education. Except Child 2016 Jul 24;71(2):165-179 [FREE Full text] [doi: 10.1177/001440290507100203] [Medline: 22973420]
20. Kazdin A. Research Design in Clinical Psychology. Volume 5. Boston, UK: Pearson; 2017.
21. Machalicek W, Horner RH. Special issue on advances in single-case research design and analysis. Dev Neurorehabil 2018 May;21(4):209-211. [doi: 10.1080/17518423.2018.1468600] [Medline: 29799298]
22. Bentley KH, Kleiman EM, Elliott G, Huffman JC, Nock MK. Real-time monitoring technology in single-case experimental design research: opportunities and challenges. Behav Res Ther 2019 Jun;117:87-96. [doi: 10.1016/j.brat.2018.11.017] [Medline: 30579623]
23. Clough BA, Casey LM. Smart designs for smart technologies: research challenges and emerging solutions for scientist-practitioners within e-mental health. Prof Psychol Res Pr 2015 Dec;46(6):429-436. [doi: 10.1037/pro0000053]
24. Mehrotra S, Tripathi R. Recent developments in the use of smartphone interventions for mental health. Curr Opin Psychiatry 2018 Sep;31(5):379-388. [doi: 10.1097/YCO.0000000000000439] [Medline: 29985179]
25. Howard KI, Lueger RJ, Maling MS, Martinovich Z. A phase model of psychotherapy outcome: causal mediation of change. J Consult Clin Psychol 1993 Aug;61(4):678-685. [doi: 10.1037//0022-006x.61.4.678] [Medline: 8370864]
26. Jebb AT, Tay L, Wang W, Huang Q. Time series analysis for psychological research: examining and forecasting change. Front Psychol 2015;6:727 [FREE Full text] [doi: 10.3389/fpsyg.2015.00727] [Medline: 26106341]
27. Australian Government Department of Health. 2019. Medicare Benefits Schedule - Item 80110 URL: http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=80110 [accessed 2019-10-15]
28. Hochheimer CJ, Sabo RT, Krist AH, Day T, Cyrus J, Woolf SH. Methods for evaluating respondent attrition in web-based surveys. J Med Internet Res 2016 Nov 22;18(11):e301 [FREE Full text] [doi: 10.2196/jmir.6342] [Medline: 27876687]
29. Urbaniak G, Plous S. Research Randomizer. 2019. URL: https://www.randomizer.org/ [accessed 2019-10-14]
30. Lee RA, Jung ME. Evaluation of an mhealth app (DeStressify) on university students' mental health: pilot trial. JMIR Ment Health 2018 Jan 23;5(1):e2 [FREE Full text] [doi: 10.2196/mental.8324] [Medline: 29362209]
31. DeStressify. 2015. URL: https://www.destressify.com/ [accessed 2019-10-10]
32. Bakker D, Kazantzis N, Rickwood D, Rickard N. Development and pilot evaluation of smartphone-delivered cognitive behavior therapy strategies for mood- and anxiety-related problems: MoodMission. Behav Cogn Psychother 2018 Nov;25(4):496-514 [FREE Full text] [doi: 10.1016/j.cbpra.2018.07.002]
33. MoodMission: Change The Way You Feel. 2019. URL: http://moodmission.com/ [accessed 2019-10-10]
34. Bakker D, Kazantzis N, Rickwood D, Rickard N. A randomized controlled trial of three smartphone apps for enhancing public mental health. Behav Res Ther 2018 Oct;109:75-83. [doi: 10.1016/j.brat.2018.08.003] [Medline: 30125790]
35. Bakker D, Rickard N. Engagement in mobile phone app for self-monitoring of emotional wellbeing predicts changes in mental health: MoodPrism. J Affect Disord 2018 Feb;227:432-442. [doi: 10.1016/j.jad.2017.11.016] [Medline: 29154165]
36. Flett JA, Hayne H, Riordan BC, Thompson LM, Conner TS. Mobile mindfulness meditation: a randomised controlled trial of the effect of two popular apps on mental health. Mindfulness 2019 Oct 31;10(5):863-876. [doi: 10.1007/s12671-018-1050-9]
37. Smiling Mind: Help Shape Our Future. 2019. URL: https://www.smilingmind.com.au/ [accessed 2019-10-10]
38. Anxiety Canada. 2019. MindShift CBT URL: https://anxietycanada.com/resources/mindshift-cbt/ [accessed 2019-10-10]
39. Roepke AM, Jaffee SR, Riffle OM, McGonigal J, Broome R, Maxwell B. Randomized controlled trial of SuperBetter, a smartphone-based/internet-based self-help tool to reduce depressive symptoms. Games Health J 2015 Jun;4(3):235-246. [doi: 10.1089/g4h.2014.0046] [Medline: 26182069]
40. SuperBetter: Everyone Has Heroic Potential. 2019. URL: https://www.superbetter.com [accessed 2019-10-10]
41. Jorm AF. Mental health literacy: empowering the community to take action for better mental health. Am Psychol 2012 Apr;67(3):231-243. [doi: 10.1037/a0025957] [Medline: 22040221]
42. Addis M, Jacobson N. A closer look at the treatment rationale and homework compliance in cognitive-behavioral therapy for depression. Cognit Ther Res 2000;24:313-326. [doi: 10.1023/A:1005563304265]
43. Hamilton KE, Dobson KS. Cognitive therapy of depression: pretreatment patient predictors of outcome. Clin Psychol Rev 2002 Jul;22(6):875-893. [doi: 10.1016/s0272-7358(02)00106-x] [Medline: 12214329]
44. Wolpe J, Lazarus A. Behavior therapy techniques: A guide to the treatment of neuroses. Elmsford, NY: Pergamon Press; 1966:A.
45. Henry JD, Crawford JR. The short-form version of the depression anxiety stress scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005 Jun;44(Pt 2):227-239. [doi: 10.1348/014466505X29657] [Medline: 16004657]
46. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the Beck depression and anxiety inventories. Behav Res Ther 1995 Mar;33(3):335-343. [doi: 10.1016/0005-7967(94)00075-u] [Medline: 7726811]
47. Antony MM, Bieling PJ, Cox BJ, Enns MW, Swinson RP. Psychometric properties of the 42-item and 21-item versions of the depression anxiety stress scales in clinical groups and a community sample. Psychol Assess 1998 Jun;10(2):176-181. [doi: 10.1037/1040-3590.10.2.176]

48. Osman A, Wong JL, Bagge CL, Freedenthal S, Gutierrez PM, Lozano G. The depression anxiety stress scales-21 (DASS-21): further examination of dimensions, scale reliability, and correlates. J Clin Psychol 2012 Dec;68(12):1322-1338. [doi: 10.1002/jclp.21908] [Medline: 22930477]
49. Boswell DL, White JK, Sims WD, Harrist RS, Romans JS. Reliability and validity of the outcome questionnaire-45.2. Psychol Rep 2013 Jun;112(3):689-693. [doi: 10.2466/02.08.PR0.112.3.689-693] [Medline: 24245064]
50. Beckstead DJ, Hatch AL, Lambert MJ, Eggett DL, Goates MK, Vermeersch DA. Clinical significance of the outcome questionnaire (OQ-45.2). Behav Anal 2003;4(1):86-97. [doi: 10.1037/h0100015]
51. Lambert M, Finch A. The outcome questionnaire. In: Maruish ME, editor. The Use of Psychological Testing for Treatment Planning and Outcomes Assessment. Second Edition. Hillsdale, NJ: Erlbaum Behavioral Science; 1999:831-870.
52. Lambert MJ. Helping clinicians to use and learn from research-based systems: the OQ-analyst. Psychotherapy (Chic) 2012 Jun;49(2):109-114. [doi: 10.1037/a0027110] [Medline: 22642518]
53. Mueller R, Lambert M, Burlingame G. Construct validity of the outcome questionnaire: a confirmatory factor analysis. J Pers Assess 1998 Apr;70(2):248-262. [doi: 10.1207/s15327752jpa7002_5]
54. Stoyanov SR, Hides L, Kavanagh DJ, Wilson H. Development and validation of the user version of the mobile application rating scale (uMARS). JMIR Mhealth Uhealth 2016 Jun 10;4(2):e72 [FREE Full text] [doi: 10.2196/mhealth.5849] [Medline: 27287964]
55. Qualtrics. 2019. Make Every Interaction a Great Experience URL: https://www.qualtrics.com/au/ [accessed 2019-10-16]
56. OQ-Analyst. 2019. URL: http://www.oqmeasures.com/oq-analyst-3/ [accessed 2019-10-16]
57. Wolpe J. The Practice of Behavior Therapy. New York, USA: Pergamon Press; 1969.
58. Krippendorff K. Content Analysis: An Introduction to Its Methodology. Third Edition. Thousand Oaks, CA: Sage Publications; 2013.
59. Borckardt JJ, Nash MR, Murphy MD, Moore M, Shaw D, O'Neil P. Clinical practice as natural laboratory for psychotherapy research: a guide to case-based time-series analysis. Am Psychol 2008;63(2):77-95. [doi: 10.1037/0003-066X.63.2.77] [Medline: 18284277]
60. Houle TT. Statistical analyses for single-case experimental designs. In: Barlow DH, Nock MK, Hersen M, editors. Single Case Experimental Designs: Strategies for Studying Behavior for Change. Boston, UK: Pearson Education; 2009.
61. Evans C, Margison F, Barkham M. The contribution of reliable and clinically significant change methods to evidence-based mental health. Evid-Based Ment Health 1998 Aug 1;1(3):70-72. [doi: 10.1136/ebmh.1.3.70] [Medline: 28850992]
62. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991 Feb;59(1):12-19. [doi: 10.1037//0022-006x.59.1.12] [Medline: 2002127]
63. Jacobson NS, Roberts LJ, Berns SB, McGlinchey JB. Methods for defining and determining the clinical significance of treatment effects: description, application, and alternatives. J Consult Clin Psychol 1999 Jun;67(3):300-307. [doi: 10.1037//0022-006x.67.3.300] [Medline: 10369050]
64. Kazdin AE. The meanings and measurement of clinical significance. J Consult Clin Psychol 1999 Jun;67(3):332-339. [doi: 10.1037//0022-006x.67.3.332] [Medline: 10369053]
65. Policies - University of New England (UNE). 2019. Management and Storage of Research Data and Materials Policy URL: https://policies.une.edu.au/view.current.php?id=00208 [accessed 2019-10-13]
66. The National Health and Medical Research Council. 2018. The National Statement on Ethical Conduct in Human Research URL: https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 [accessed 2019-10-13]
67. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of web-based and mobile health interventions. J Med Internet Res 2011 Dec 31;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
68. Beiwinkel T, Kindermann S, Maier A, Kerl C, Moock J, Barbian G, et al. Using smartphones to monitor bipolar disorder symptoms: a pilot study. JMIR Ment Health 2016 Jan 6;3(1):e2 [FREE Full text] [doi: 10.2196/mental.4560] [Medline: 26740354]
69. Jones E, Lebrun-Harris LA, Sripipatana A, Ngo-Metzger Q. Access to mental health services among patients at health centers and factors associated with unmet needs. J Health Care Poor Underserved 2014 Feb;25(1):425-436. [doi: 10.1353/hpu.2014.0056] [Medline: 24509036]
70. Sakai C, Mackie TI, Shetgiri R, Franzen S, Partap A, Flores G, et al. Mental health beliefs and barriers to accessing mental health services in youth aging out of foster care. Acad Pediatr 2014;14(6):565-573. [doi: 10.1016/j.acap.2014.07.003] [Medline: 25439155]
71. Bowers H, Manion I, Papadopoulos D, Gauvreau E. Stigma in school‐based mental health: perceptions of young people and service providers. Child Adolesc Ment Health 2012 Jun 19;18(3):165-170. [doi: 10.1111/j.1475-3588.2012.00673.x] [Medline: 24843434]
72. Holloway D, Green L, Livingstone S. Edith Cowan University Research Online Institutional Repository. London, UK: The EU Kids Online Network; 2013. Zero to eight: Young children and their Internet use URL: https://ro.ecu.edu.au/cgi/viewcontent.cgi?referer=&httpsredir=1&article=1930&context=ecuworks2013 [accessed 2020-05-21]

73. Wang K, Varma DS, Prosperi M. A systematic review of the effectiveness of mobile apps for monitoring and management of mental health symptoms or disorders. J Psychiatr Res 2018 Dec;107:73-78. [doi: 10.1016/j.jpsychires.2018.10.006] [Medline: 30347316]
74. Marshall JM, Dunstan DA, Bartik W. Smartphone psychology: new approaches towards safe and efficacious mobile mental health apps. Prof Psychol Res Pr 2019 Dec 2:- epub ahead of print. [doi: 10.1037/pro0000278]
75. Tang TZ, DeRubeis RJ. Sudden gains and critical sessions in cognitive-behavioral therapy for depression. J Consult Clin Psychol 1999 Dec;67(6):894-904. [doi: 10.1037//0022-006x.67.6.894] [Medline: 10596511]
76. Rickard N, Arjmand H, Bakker D, Seabrook E. Development of a mobile phone app to support self-monitoring of emotional well-being: a mental health digital innovation. JMIR Ment Health 2016 Nov 23;3(4):e49 [FREE Full text] [doi: 10.2196/mental.6202] [Medline: 27881358]
77. PsyberGuide. 2019. URL: https://psyberguide.org/ [accessed 2019-10-07]
78. Head to Health. 2019. URL: https://headtohealth.gov.au [accessed 2019-10-07]
79. ReachOut. 2019. Tools and Apps URL: https://au.reachout.com/tools-and-apps [accessed 2019-10-07]
80. Health Navigator NZ. 2019. App Library URL: https://www.healthnavigator.org.nz/apps/ [accessed 2019-10-07]
81. United Kingdom National Health Service. 2019. Mental Health Apps URL: https://www.nhs.uk/apps-library/category/mental-health/ [accessed 2019-10-07]
82. Statista. Statista. New York: Statista; 2019. Number of smartphone users worldwide from 2016 to 2021 (in billions) URL: https://www.statista.com/statistics/330695/number-of-smartphone-users-worldwide/ [accessed 2020-05-21]

Abbreviations

ANZCTR: Australian and New Zealand Clinical Trials Registry
ARIMA: autoregressive integrative moving average
CBT: cognitive behavioral therapy
CSI: clinical significance index
DASS-21: Depression Anxiety Stress Scale-21 short-form version
OQ-45.2: Outcome Questionnaire-45 second edition version
RCI: reliable change index
RCT: randomized controlled trial
SUDS: subjective units of distress
uMARS: user version of the Mobile Application Rating Scale

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Protocol

Adherence Tracking With Smart Watches for Shoulder Physiotherapy in Rotator Cuff Pathology: Protocol for a Longitudinal Cohort Study

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Abstract

Background: Physiotherapy is essential for the successful rehabilitation of common shoulder injuries and following shoulder surgery. Patients may receive some training and supervision for shoulder physiotherapy through private pay or private insurance, but they are typically responsible for performing most of their physiotherapy independently at home. It is unknown how often patients perform their home exercises and if these exercises are performed correctly without supervision. There are no established tools for measuring this. It is, therefore, unclear if the full benefit of shoulder physiotherapy treatments is being realized.

Objective: The proposed research will (1) validate a smartwatch and machine learning (ML) approach for evaluating adherence to shoulder exercise participation and technique in a clinical patient population with rotator cuff pathology; (2) quantify the rate of home physiotherapy adherence, determine the effects of adherence on recovery, and identify barriers to successful adherence; and (3) develop and pilot test an ethically conscious adherence-driven rehabilitation program that individualizes patient care based on their capacity to effectively participate in their home physiotherapy.

Methods: This research will be conducted in 2 phases. The first phase is a prospective longitudinal cohort study, involving 120 patients undergoing physiotherapy for rotator cuff pathology. Patients will be issued a smartwatch that will record 9-axis inertial sensor data while they perform physiotherapy exercises both in the clinic and in the home setting. The data collected in the clinic under supervision will be used to train and validate our ML algorithms that classify shoulder physiotherapy exercise. The validated algorithms will then be used to assess home physiotherapy adherence from the inertial data collected at home. Validated outcome measures, including the Disabilities of the Arm, Shoulder, and Hand questionnaire; Numeric Pain Rating Scale; range of motion; shoulder strength; and work status, will be collected pretreatment, monthly through treatment, and at a final follow-up of 12 months. We will then relate improvement in patient outcomes to measured physiotherapy adherence and patient baseline variables in univariate and multivariate analyses. The second phase of this research will involve the evaluation of a novel rehabilitation program in a cohort of 20 patients. The program will promote patient physiotherapy engagement via the developed technology and support adherence-driven care decisions.

Results: As of December 2019, 71 patients were screened for enrollment in the noninterventional validation phase of this study; 65 patients met the inclusion and exclusion criteria. Of these, 46 patients consented and 19 declined to participate in the study. Only 2 patients de-enrolled from the study and data collection is ongoing for the remaining 44.

Conclusions: This study will provide new and important insights into shoulder physiotherapy adherence, the relationship between adherence and recovery, barriers to better adherence, and methods for addressing them.

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KEYWORDS

rehabilitation; treatment adherence and compliance; wearable electronic devices; machine learning; rotator cuff

Introduction

Overview

Rotator cuff pathology is the most common cause of shoulder pain and disability [1,2], and it is associated with significant utilization of health care resources [3] and societal and economic costs [1]. Exercise-based physiotherapy is the established first-line treatment for this condition [4-6] and is also a critical element of rehabilitation following rotator cuff surgery [7,8]. Adherence to prescribed physiotherapy is essential for successful rehabilitation in both conservatively and operatively managed patients [9,10]. However, adherence to physiotherapy is often poor [9,11], particularly in the home setting [9,12,13] and in worker populations [10]. Currently, there are no established methods to effectively and objectively measure adherence to home shoulder physiotherapy [12,14]. Thus, the rate and quality of participation with home shoulder therapy and the relationship between adherence and recovery are unknown.

We have developed the Smart Physiotherapy Activity Recognition System (SPARS), a novel solution for measuring adherence to home shoulder physiotherapy from inertial sensor data recorded on a smart watch using state-of-the-art machine learning (ML) techniques [15]. SPARS was shown to classify exercises for participation monitoring with high (99.99%) accuracy in 20 healthy adults.

The proposed study will further develop and validate our technology to assess home shoulder physiotherapy adherence to both participation and technique in a population with rotator cuff pathology. We will measure the rate of adherence, establish the relationship between adherence and recovery, and explore possible patient factors predictive of poor home physiotherapy adherence. In addition, we will examine ethical and related policy issues associated with the deployment of this technology, specifically investigating patient privacy, individual rights, clinical decision making, health resource allocation, and policy in the setting of artificial intelligence–based surveillance of patient self-management strategies. Guided by ethical analysis and a user-centered design process, we will develop and pilot test a conscientious rehabilitation program with individualized adherence-driven patient care.

Rotator Cuff Pathology

Shoulder pain and dysfunction are among the most common musculoskeletal health problems and can affect 16% to 21% of the adult population with increasing incidence in advancing age [16-18]. Shoulder pain and dysfunction have an impact on the performance of essential activities of daily living (eg, dressing, hygiene, eating, and work) and result in substantial utilization of health care resources [3]. Rotator cuff pathology is the most common cause of shoulder pain and disability [1,2], accounting for up to 60% of all shoulder conditions [19]. Rotator cuff pathology is also a common cause of disability and employee time loss in the workplace and is associated with a high rate of claims and large societal and economic costs [1]. In the Ontario worker population, the shoulder is the second most frequent site of injury (after lower back) for high-impact claims [20].

Physiotherapy and nonnarcotic analgesia are the first-line treatment for symptomatic rotator cuff pathology [21]. Numerous studies and systematic reviews have concluded that many patients undergoing nonoperative rehabilitation for rotator cuff pathology achieve significant and durable improvements in shoulder pain and function [4,5,19,22-33]. The effectiveness of rehabilitation depends on the physiotherapy protocol that is used. Holmgren et al [34] demonstrated that a specific exercise protocol supervised by physiotherapists was superior to a self-directed range of motion exercises performed at home. Østerås et al [35] demonstrated a dose-response to rotator cuff rehabilitation, with high-dose (greater frequency and intensity) exercise training producing greater benefits than low-dose training.

Clinical trials have not demonstrated a clear benefit of surgical intervention over physiotherapy for the initial treatment of degenerative rotator cuff tears [22,23,36-38]. Current clinical practice guidelines, therefore, recommend that surgical management of rotator cuff pathology should be reserved for some selected cases (acute full-thickness traumatic tears in young patients) and when nonoperative modalities have failed to achieve the desired improvement in the function or symptoms after 6 to 12 weeks [24,39]. Postoperative rehabilitation with exercise-based physiotherapy is considered an essential component in the surgical management of rotator cuff pathology [7,8].

Home Physiotherapy for Rotator Cuff Pathology

There is little comparative data on the relative effectiveness of supervised physiotherapy versus home-based exercise for rotator cuff pathology [3,24]. Although several trials have sought to address this question [34,40-42], all were of low sample size and adherence to the prescribed physiotherapy was not measured. The efficacy (or lack thereof) of a self-management strategy can only be determined if it is adhered to, which

requires measurement of adherence. These studies also used different exercise regimens for their study groups, with the group in supervised therapy receiving a more extensive, specific, and individualized exercise regimen. To our knowledge, no study has directly compared the supervised and independent performance of the same rotator cuff rehabilitation protocol or sought to determine the optimal balance between supervised and independent exercise in hybrid programs. Despite these limitations, the efficacy of independent exercise for rotator cuff rehabilitation is supported by many studies with good outcomes that made extensive use of home exercise in their rehabilitation protocol [3,7,8].

Adherence to Rehabilitation

Adherence is defined as the extent to which the patient follows medical instructions [43]. There is a general assumption that, where a treatment program is efficacious, adherence to the program improves outcome. Patient adherence to a prescribed physiotherapy has been shown to be an important predictor for the successful management of musculoskeletal disorders [9]. However, adherence to standard exercise protocols is often poor with estimates of non or partial nonadherence varying between 50% and 70% [9,11], with worse adherence for home exercise protocols [9].

In the context of physiotherapy and rehabilitation, the concept of adherence is multidimensional [44]. It includes behaviors such as attending clinical appointments, actively participating in physiotherapist-supervised rehabilitation activities, carrying out home exercise and rehabilitation activities, avoiding potentially harmful and contraindicated activities, and wearing protective or therapeutic devices [44]. Physiotherapy clinic attendance is readily measured, and the Sport Injury Rehabilitation Adherence Scale [44] has been used for evaluating in-clinic adherence. The correct use of protective devices has been measured by observations at clinical follow-up [10] and with temperature sensors [45-47].

Measuring adherence to home physiotherapy exercises remains an open problem [48]. Adherence to this component of a rehabilitation program is particularly vital as this activity calls for the greatest level of independent patient engagement in the rehabilitation process. Adherence diaries, in which patients log their independent exercises, is the recommended and most widely used measure of adherence to home exercise [48]. However, adherence diaries have significant limitations. The validity and reliability of the adherence diary have not been established, and poor patient acceptability results in low rates of diary completion [48]. Furthermore, the written diary has no means to establish if the prescribed exercises have been performed correctly. The proposed study will validate a novel method for measuring participation and technique adherence to home shoulder physiotherapy exercises.

Adherence to Rotator Cuff Rehabilitation

Several studies on patients with rotator cuff pathology have measured rehabilitation adherence variables, including clinic attendance, adherence to postoperative restrictions, and home physiotherapy participation during rotator cuff rehabilitation [4,10,13,26,49-51]. Nonadherence (eg, to protective device use and clinic attendance) is more prevalent in workers' compensation patients (52%) than nonworkers (4%) [10]. There is also a relationship between adherence and improved clinical outcomes in the nonoperative [50] and operative management [10,51] of rotator cuff pathology.

Unfortunately, adherence to home rotator cuff exercises has only been measured with adherence diaries [4,26,50] or in response to directed questioning [51]. The completion rates for the adherence diaries varied from 60% to 75% [4,26,50]. Furthermore, the validity of a patient's self-reported adherence is questionable as a research instrument [52]. Therefore, the rate and effect of adherence to home rotator cuff exercise participation and technique remain unknown. The proposed study will address this knowledge gap in a cohort of 120 patients with rotator cuff pathology.

Are Home Shoulder Physiotherapy Exercises Performed Correctly?

Patients with rotator cuff pathology have abnormal shoulder kinematics [53,54]. Due to the weakness of the rotator cuff, these patients develop a functional instability, where shoulder motion reduces the available supraspinatus muscle outlet, causing impingement [55]. There is a known relationship between altered shoulder kinematics, pain, and rotator cuff tear size [56]. It is believed that the altered kinematics and impingement exacerbate the condition, contributing to ongoing deterioration of the rotator cuff [54,55]. Restoration of normal shoulder kinematics, in particular muscular control of the scapula, is a focus of physiotherapy for rotator cuff pathology [19,57], and there are some data that contribute to improved patient outcomes [58]. An important role of the physiotherapist in rotator cuff rehabilitation is to supervise the process of kinematic retraining, ensuring that appropriate muscle recruitment and motion patterns are developed and maintained during exercise [59]. No study has determined whether the motion patterns trained during supervised therapy sessions are maintained in the home setting or independent exercise. The proposed study seeks to establish if there are kinematic differences between supervised and home rotator cuff rehabilitation exercises and determine if there is a relationship between exercise technique and shoulder recovery.

Factors Affecting Adherence

The barriers to adherence to supervised outpatient physiotherapy clinics have been summarized in a systematic review by Jack et al [12] in 2010. There was strong evidence to suggest that low baseline levels of physical activity; low in-treatment adherence to exercise; low self-efficacy, depression, and anxiety; helplessness; poor social support; greater perceived number of barriers to exercise; and increased pain during exercise are all significant barriers to physiotherapy adherence. The majority of studies reviewed measured adherence only in terms of clinic appointments. Several studies [60-64] investigated the barriers to adherence to unsupervised home exercise programs. However, these studies suffered from the limitations of the existing adherence diary instrument outlined previously (poor objectivity, poor compliance with the diary, and inability to measure technique adherence). The barriers to unsupervised home

physiotherapy, therefore, remain uncertain; they will be explored in the proposed study.

Potential Technologies for Measuring Adherence to Home Shoulder Physiotherapy

Several technologies have been developed and pilot tested to provide more objective and complete assessments of adherence to home physiotherapy [13,15,65-72], but none have been validated in a clinical population. The common premise underlying a technical solution to adherence monitoring is using sensors to record patient home physiotherapy and have a computer algorithm classify activity type and potentially evaluate the technique. Various sensors have been investigated for this application, including video and depth sensors [65-68], strain sensors mounted on elastic bands [13], and inertial sensors [15,69-72].

Inertial sensors include accelerometers, gyroscopes, and magnetometers. These sensors are combined in small, inexpensive integrated circuit packages called inertial measurement units (IMUs). IMUs are found in smartphones, smart watches, and GPS devices, and they enable ongoing navigation with loss of GPS signals (eg, indoors). Advances in the capability of these sensors have enabled their use in demanding clinical applications, such as upper extremity motion tracking [73], clinical shoulder evaluation [74-77], kinematic analysis [78-82], and shoulder physiotherapy adherence evaluation [15,69,70].

Inertial sensors are, in our opinion, an ideal method for measuring adherence to home shoulder physiotherapy. These sensors are already integrated into robust, accessible devices, such as smart watches, facilitating low-cost deployment. Such wearable devices are unobtrusive and easy to use anywhere, unlike solutions based on video capture. Finally, they are highly accurate for this task [15] and can theoretically be used to measure adherence to any exercise involving motion.

Several studies have investigated the potential for shoulder physiotherapy adherence evaluation using inertial sensors in the laboratory setting. McGirr et al [69] used a 3-axis gyroscope to classify 3 shoulder exercises performed with an elastic band and were able to classify activity type, but with relatively low accuracy (86%-91%). Pan et al [70] used classical ML techniques to classify 5 different shoulder exercises from multiple synchronized inertial sensors mounted on the chest, upper arm, and wrist, achieving classification accuracy of 96.9% in the laboratory setting. Our pilot study used state-of-the-art deep learning algorithms to classify 7 evidence-based physiotherapy exercises from a single wrist-worn IMU in a commercial smart watch with an accuracy of 99.99% [15].

Deep learning is a class of ML algorithms for training deep hierarchical models, such as artificial neural networks (ANNs), which are ML models partly inspired by biological neural networks found in animal brains [83]. Recent advances in deep learning and computer performance have together spurred revolutionary developments in the capabilities of modern artificial intelligence systems [84]. In our pilot work, we demonstrated that deep learning significantly outperforms classical ML algorithms for inertial exercise classification [15].

Unlike classical ML models, neural networks can also benefit from transfer learning [85], which facilitates network retraining and updating in various contexts, such as adding a new exercise class or patient to the training dataset. Although significant computational resources are required for training ANNs, trained ANNs can be compact and deployable with modest computer hardware [86]. The ML models we developed in our pilot work were designed for deployment and real-time operation on a smart watch, having only 300,000 parameters. This aspect of the SPARS design permits a highly reliable edge-computing system architecture, where end-user apps are always responsive and function independent of internet connectivity or cloud computing infrastructure.

Ethical and Policy Issues Related to Measuring Adherence to Patient Self-Management Strategies

There are a number of ethical and policy issues raised by the proposed project that will be examined in detail, concurrent with the clinical validation of the SPARS technology. Building on our past work addressing the challenges of introducing innovative digital health technologies [87], this analysis will inform the design and use of SPARS in the delivery of adherence-driven care. Drawing on the critical bioethics of Hedgecoe [88], we will examine the actual lived experiences and policy realities that are implicated in SPARS deployment and program development. However, we can anticipate, based on the bioethics literature, that issues at the intersection of ethics and policy will be raised in 3 distinct areas.

First, the act of surveillance introduces a number of ethical challenges. One is that surveillance stands to influence the behavior of participants, despite the conflicting evidence on the ways in which the proposed *Hawthorne effect* might occur [89]. Beyond a simple form of data collection, however, the collection of ubiquitous data about movements could have a number of unanticipated consequences [90]. A potential effect is to enhance the frequency or quality with which exercises are performed, but others include the distrust of the technology and health care providers who ultimately observe the data. Where participants might feel coerced into completing a form of physical activity, especially in cases where workplace injuries are involved, resistance might be substantial [91]. These are ethically important challenges that need to be addressed throughout this program and will dictate what data are collected, how they are controlled, and how and to whom the analysis results are presented.

Second, the surveillance and related project data promise to generate insights about which types of patients engage in exercises with the greatest fidelity. Findings related to patient profiles of those who engage and those who do not could be used in a variety of ways, including reallocating resources to those who stand to benefit from high engagement or enhanced behavioral change programs for those who do not engage. Generally, these questions of resource allocation relate to the priority-setting process for rehabilitation programs [92] and require detailed analysis to inform policy.

Third, the algorithms being deployed in this study are developed by individuals with particular views of the world. The types of data being used to train the algorithms, assumptions about the

functioning of the technology, and beliefs about appropriate outputs are all shaped by the education, race, gender, and other social realities of the people writing the computer code. These points relate to bias that could potentially be built into the algorithm itself and the fairness of its outputs [93].

Each of these points will form a substantive focus on the ethical and policy analyses that are part of this study.

Specific Research Aims

The specific research aims, and related objectives and hypotheses for this study are detailed below.

Aim 1: Develop and Validate the Smart Physiotherapy Activity Recognition System For Evaluating Shoulder Physiotherapy Adherence

Objectives

The related objectives are as follows:

1. Inertial sensor data are collected during supervised physiotherapy for 120 patients with rotator cuff pathology over full treatment duration (up to 5 months).
2. Technical failures preventing supervised data collection are less than 5%.
3. The SPARS artificial intelligence is trained to classify physiotherapy exercise type and technique with classification accuracy exceeding 90% and 80%, respectively.

Aim 2: Measure the Rate of Adherence to Home Shoulder Physiotherapy, the Relationship Between Adherence and Recovery, and Identify Barriers to Home Physiotherapy Adherence

Objectives

The related objectives are as follows:

1. Inertial sensor data are collected during home physiotherapy for 120 patients with rotator cuff pathology over full treatment duration (up to 5 months).
2. Technical failures preventing home data collection are less than 5%.
3. Clinical outcomes: return to work status, shoulder range of motion, rotator cuff strength, and patient-reported outcomes of pain and disability are collected pretreatment, monthly through treatment (up to 5 months), and at 12-months final follow-up. The final follow-up exceeds 85%.
4. A total of 23 potentially significant predictors of home physiotherapy adherence (identified in Methods: Barriers to Adherence) are collected for all study participants at the time of recruitment.

Hypotheses

The related hypotheses are as follows:

1. Exercise technique adherence is better for supervised sessions than at home ($P<.05$).
2. There will be a statistically significant association ($P<.05$) between home physiotherapy exercise participation and technique adherence and the identified clinical outcomes.

Aim 3: Develop and Pilot Test a Conscientious Smart Physiotherapy Activity Recognition System–Powered Shoulder Rehabilitation Program That Provides Individualized Adherence-Driven Patient Care in Accordance With Ethical Innovation and User-Centered Design Practices

Objectives

The related objectives are as follows:

1. Conduct and analyze qualitative interviews with stakeholders and end users to identify functional needs and different perspectives on ethical commitments and challenges related to individual experiences, privacy, clinical decision making, health resource allocation, and policy.
2. Develop novel shoulder rehabilitation strategies within the Working Condition Program, leveraging validated SPARS adherence analytics to conscientiously guide physiotherapy treatment as per the ethical, policy, and user-centered design analysis.
3. Pilot test the rehabilitation program in 20 patients. Conduct postimplementation qualitative interviews to re-examine ethical, policy, and design issues.

Hypotheses

The methodology to be drawn upon for the service design process and qualitative evaluation is fundamentally inductive and user-driven. Therefore, it would not be appropriate to articulate specific hypotheses to drive our data collection. We have outlined several ethical and policy issues that we will address, but we will approach the participants in ways that encourage them to describe the experiences and issues most pertinent to their own viewpoints. In so doing, we will remain open to all insights that emerge from design activities and qualitative interviews.

Methods

Smart Physiotherapy Activity Recognition System Technical Development and Clinical Validation Study (Aims 1 and 2)

We will further develop SPARS to evaluate the physiotherapy exercise technique and validate the SPARS exercise type and technique evaluations in a clinical population undergoing physiotherapy treatment for rotator cuff pathology. The relationship between adherence and recovery and barriers to home physiotherapy adherence will also be determined in this clinical validation study.

Population

We will conduct a prospective longitudinal cohort study of 120 patients who have been referred to Sunnybrook Health Sciences Centre for the management of rotator cuff pathology. The inclusion criteria will be as follows: (1) age ≥18 years; (2) diagnosis of unilateral rotator cuff tendinosis, shoulder impingement syndrome, or degenerative or traumatic rotator cuff tear; (3) planned conservative or operative management; and (4) capacity to participate in home shoulder physiotherapy.

Exclusion criteria will be as follows: (1) upper extremity neurologic deficit; (2) bilateral symptomatic rotator cuff pathology; and (3) failed surgical management of rotator cuff pathology.

Inertial Data Collection

Each study subject will be provided with a smart watch to be worn on their affected extremity when performing the prescribed physiotherapy exercise. The smart watch must be worn for all physiotherapy exercise sessions conducted over the duration of treatment, up to a maximum of 5 months. This includes all supervised physiotherapy sessions at the Holland Centre and any physiotherapy exercise sessions conducted by the patient independently (home exercises). No alteration to the prescribed physiotherapy will be undertaken during this clinical validation study.

The smart watches purchased for this study will have a 9-axis IMU (3-axis accelerometer, 3-axis gyroscope, and 3-axis magnetometer). The inertial sensors will be sampled at 50 Hz and recorded to the internal memory storage on the smart watch. The inertial data will be encrypted using the Rivest–Shamir–Adleman public-key cryptosystem. The smart watch will permit up to 150 hours of sensor data recording to its 4 GB internal memory. The sensor data will be retrieved and removed from the smart watch when the patient attends supervised physiotherapy at the Holland Centre (2 times per week).

Inertial Data Labeling

The researchers will attend a supervised physiotherapy session for each patient once every 2 weeks to record exercise type and technique labels synchronously with inertial data collection, based on the input from the treating physiotherapist. The technique will be labeled as a binary variable, indicating if the treating physiotherapist was satisfied that the exercise was performed correctly (as intended). The treating physiotherapist will also make a record of prescribed home exercises and exercise type and technique evaluations at each supervised physiotherapy session.

Supervised Physiotherapy Video Recording

Color video recordings of supervised physiotherapy sessions will be made during 30 supervised inertial data collections. The videos will be used for the reliability analysis of the exercise type and technique labels assigned by the treating physiotherapist, and 2 blinded physiotherapists will review and reclassify the video data independently.

Home Physiotherapy Adherence Diaries

Patients will log their home physiotherapy activities in an adherence diary for 2 weeks, during the strengthening phase of their rehabilitation. Validation of the SPARS adherence measurement will include a comparison with these data.

Clinical and Return to Work Outcomes Data

Validated clinical outcomes will be collected to measure the relationship between home physiotherapy adherence and patient recovery. The following validated clinical outcome measures will be collected (1) pretreatment; (2) monthly through treatment; and (3) at 12-months final follow-up (items 1-3 only); these items are routinely collected by the Sunnybrook's Working Conditions Program (WCP):

1. Work status (full-time, part-time, off-work, modified, or regular duties)
2. Numeric Pain Rating Scale (NPRS)
3. Disabilities of the Arm, Shoulder, and Hand (DASH) scores
4. Rotator cuff strength testing using manual muscle testing
5. Shoulder active range of motion measured with a goniometer.

The NPRS is valid and reliable for clinical practice [94,95]. The DASH has proven reliability, validity, and responsiveness in patients with shoulder problems [96-98]. Manual muscle testing and range of motion measurement using a goniometer are standard accepted methods for rotator cuff strength testing and shoulder range motion evaluation in the clinical setting [99], with established validity and reliability [100-104].

Barriers to Adherence

The following potentially significant adherence predictors [12,105-110] will be collected for each patient at recruitment: age, sex, body mass index, dominant side involvement, symptom duration, mechanism of injury (traumatic or degenerative), rotator cuff tear thickness and size, type of operative procedures, comorbidity (cumulative illness rating scale [111]), smoking status, alcohol intake, opioid intake, cannabinoid intake, the baseline level of physical activity, education, marital status, job demands, socioeconomic status (current income), perceived social support (Enhancing Recovery in Coronary Heart Disease Social Support Inventory [112]), patient self-efficacy (2-item Pain Self-Efficacy Questionnaire [113]), Patient Expectation Questionnaire [114], and Hospital Anxiety and Depression Scale [115].

Data Management, Monitoring, and Reporting

The data for this project consist of the following (1) inertial sensor data; (2) video data; (3) clinical outcome scores; (4) adherence predictor variables; and (5) adherence diaries. Items 2-4 include personal information. Video data will be anonymized with face deidentification and audio removal. Data items will be linked with a subject identification number and stored on secure servers at Sunnybrook Research Institute, behind institutional firewalls, with restricted physical access. The database will be encrypted, and access will be limited to researchers carrying out activities related to the proposed study. Continuous data redundancy and versioning will mitigate the risk of large data loss.

When a patient attends supervised physiotherapy at the Holland Centre, their smart watch inertial data are uploaded to Google Cloud Storage. The retrieved data are immediately verified by a software tool that checks and reports the proper functioning of the sensors and correct watch usage to the researchers, ensuring that anomalies are detected promptly. Our research engineer will administer the study database, review the incoming data, and update the research team during monthly project meetings.

Smart Physiotherapy Activity Recognition System-Home Physiotherapy Participation Adherence

The ML algorithms underlying SPARS will be trained in a supervised learning framework to classify (recognize) different activities from the characteristic time series of inertial signals they produce in the smart watch inertial sensors. A detailed description of our implementation and its evaluation are presented in our previous pilot study [15] and our open-source software package for ML time series (seglearn) [116]. Briefly, sensor data are segmented into fixed-length windows (2-4 sec in length) that are learned by a deep convolutional recurrent neural network (CRNN) classifier. Once trained, the classifier can be used to reconstruct a record of activities from the recorded inertial sensor data.

The ML algorithms underlying SPARS will be trained and validated using the labeled inertial sensor data collected during supervised physiotherapy sessions. The trained SPARS algorithms will then generate a record of exercises performed from inertial sensor data collected during unsupervised home sessions and supervised sessions during which synchronous data labeling was not performed. Comparing the quantity and frequency of home exercises measured by SPARS with the prescribed exercises will serve as our measure of participation adherence. Participation adherence will be measured as a percentage of the prescribed activity over each 2-week interval of treatment.

Smart Physiotherapy Activity Recognition System-Home Physiotherapy Technique Adherence

A second supervised learning algorithm will be trained, validated, and optimized to classify the exercise technique from the labeled inertial sensor data collected during the supervised physiotherapy sessions. We anticipate that a CRNN architecture similar to the exercise type classifier will likely be suitable. The validated technique classifier will be used to evaluate the technique adherence from the inertial data collected during unsupervised home sessions.

Anticipated challenges with the proposed supervised learning approach to technique evaluation include class imbalance and recovery-related changes in exercise performance. It is anticipated that many more correct technique training examples may be available for some exercises and that an exercise may be performed incorrectly in ways not observed during the supervised sessions, leading to class imbalance. It is also anticipated that through recovery, the expectation for technique and performance of an exercise may change over time, creating a moving target for the technique classifier. The challenge of class imbalance may be mitigated using several potential approaches including (1) random over and undersampling [117]; (2) cost-sensitive learning [117]; (3) semisupervised learning [118]; (4) anomaly detection [119,120]; and (5) synthetic data augmentation [121]. The challenge of recovery-related performance changes may be mitigated by providing our technique classifier metadata related to the classification task (eg, treatment week, pathology, and surgery) [116], implementing patient-specific ML models using transfer learning, and periodically retraining the ML models through recovery.

Smart Physiotherapy Activity Recognition System–Powered Rehabilitation Program Development and Pilot Testing (Aim 3)

We will examine functional needs and ethical and related policy issues associated with the deployment of SPARS to design, implement, and pilot test novel rehabilitation strategies that provide individualized adherence-driven patient care in accordance with ethical innovation and user-centered design practices.

Examination of User Needs, Ethical Issues, and Policy Issues

We will complete qualitative interviews with patients, health care providers (primary care physicians, orthopedic surgeons, and physiotherapists), and policy-level stakeholders at the WCP, Workplace Safety and Insurance Board (WSIB), and the Ontario Ministry of Health and Long Term Care to examine different perspectives on individual experiences, ethical commitments, and challenges that arise, ranging from individual worker anxieties to allocation decision making regarding the distribution of limited resources to promote rehabilitation. The methodology will follow Yin's [122] embedded single-case study methodology, wherein there is a single overarching case with 2 embedded units of analysis. The overarching case is the project, which includes the effort to generate and validate the SPARS technology, to co-design a program relying on that technology and to provide indications of acceptability and impact. The 2 embedded units of analysis will be (1) policy issues raised by SPARS technology and (2) the effort to co-design the rehabilitation program. The analysis will be open-ended, with no propositions guiding qualitative data collection, such that analysis can be as inductive as possible [122]. However, analytic insights will draw on the work of Hedgecoe [88,123] to gain insight into the appropriate balance between individual experiences and health system mandates, promoting a careful and critical analysis of the ethical issues outlined earlier.

Adherence-Driven Rehabilitation Program Design and Implementation

Adherence-driven rehabilitation and clinical management strategies will be codeveloped by our health sciences, bioengineering, and social sciences and humanities researchers and our principal Knowledge Translation User organization—leveraging input from the qualitative ethical and policy analysis—and our integrated knowledge translation activities. The design efforts will inform individual and program decision making on critical issues such as to whom and how the adherence analysis is presented and how adherence analysis should inform clinical decisions, physiotherapy treatment, resource allocation, and allied health provider engagement and support. Administration, clinician and patient user-interface, and workflow requirements will be confirmed through a user-centered design process detailed (subsequently) in our integrated knowledge translation strategy. The developed clinical process model and needs assessment will inform SPARS implementation from data collection to the presented analysis.

Pilot Test

The rehabilitation program will be pilot tested in 20 patients in the third year of research. The validated SPARS will provide the ability to monitor patient adherence to their prescribed home shoulder physiotherapy, allowing the treating physiotherapists and physicians to incorporate this information into their clinical decision making in accordance with the parameters of the program design. Baseline adherence predictors, inertial data, and clinical outcomes will be captured and stored as specified for the clinical validation study. Qualitative interviews will be conducted with patients, physicians, and stakeholders involved in the pilot program, for examination and analysis of postimplementation perspectives and challenges in accordance with Yin's case study methodology [122]. Clinical end points and program cost-efficacy will be assessed in comparison with the matched historical controls involved in the validation study.

Data Analysis

Sample Size

The proposed sample size of 120 for clinical validation yields a power of 80% to detect weak correlations (R>0.25) between physiotherapy adherence and clinical outcomes, accepting a 5% alpha error. Sample size feasibility was confirmed by the WCP, anticipating a recruitment rate of 70%. The pilot study sample size (20) was used to detect implementation challenges with an incidence rate greater than 15% at a 95% confidence level [124] (not statistically significant differences in clinical or economic outcomes).

Construct Validity

The construct validity of the SPARS adherence measures will be evaluated using cross-validated exercise type and technique classification performance metrics (accuracy, precision, recall, and f1-score) from the labeled inertial data. The cross-validated metrics will be assessed for 3 different fold splitting strategies: (1) by-subject; (2) by-session; and (3) within-session. Respectively, these estimate SPARS performance for (1) new subjects (with no training data); (2) new sessions for subjects with prior training data; and (3) new exercise repetitions within a session from which training data were acquired. The by-session cross-validation most closely approximates the use case in the proposed study and will benchmark SPARS performance against our stated measurable objectives.

Concurrent Validity

Concurrent validity of SPARS will be established with (1) patient home exercise adherence diaries; and (2) physiotherapist exercise logs recorded in the absence of the researchers. The number and type of exercises measured by SPARS will be evaluated against both the adherence diaries and physiotherapist logs. The evaluations of the SPARS technique will be compared with the physiotherapist logs. Systematic bias between measurement methods will be evaluated using a paired sample t test and Bland-Altman plots [125]. Reproducibility will be evaluated using an intraclass correlation with a 2-way random-effects model for absolute agreement interclass correlation coefficient (2,1) [126].

Criterion Validity

Changes in clinical outcomes will be evaluated as a function of SPARS adherence measures using univariate linear regression analysis, with management subgroup (conservative or operative) and population subgroup (worker or patient) as moderators. This analysis will examine both the concurrent and predictive effects of home physiotherapy adherence on clinical outcomes.

Inter-Rater Reliability

The inter-rater reliability of the exercise type and technique (human-assigned) labels will be evaluated using Fleiss kappa from the independent ratings of the treating physiotherapist recorded at the time of data collection and 2 research physiotherapists following a video review.

Univariable and Multivariable Analyses

The relationship between adherence (dependent variable) and individual baseline adherence predictor variables and environment (home or clinic) will be examined using parametric univariable statistical analyses, linear regression for continuous predictors, and 2-sample t tests and analysis of variance for binary and multiclass categorical predictors. A multivariable analysis will be conducted to model adherence from statistically significant predictors (maximum 12) and evaluate their relative importance.

Algorithmic Fairness

Equalized odds and equal opportunity fairness metrics [127] will be calculated for adherence classifiers on selected subgroups (sex and workers' compensation status). Fairness-aware classifier training with prejudice regularization [128] will be considered if needed to produce fair results.

Economic End Point

The incremental cost-effectiveness ratio of the pilot program will be assessed by comparing patient health care resource utilization and return to work with matched historical controls [129].

Results

Approvals and Funding

This study was approved by the institutional research ethics board at the Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada, on December 21, 2018. The project was successfully funded by the following 2 grant programs:

1. WSIB of Ontario Research Grants Program: January 1, 2019, to December 31, 2021.
2. Collaborative Health Research Project Special call: Artificial Intelligence, Health, and Society; Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council; and Social Sciences and Humanities Research Council: April 1, 2019, to March 31, 2022.

Timeline

The study timeline is shown in Figure 1. All activities are occurring on track as scheduled. Data collection will be

completed by July 2021 and April 2022 for the clinical validation and implementation stages of the project, respectively.

Recruitment

Patient recruitment began in July 2019. As of December 2019, 71 patients were screened for enrollment, of whom 65 patients met the inclusion and exclusion criteria. Of these, 46 patients consented and 19 declined to participate in the study. Of those recruited, 9 have worker's compensation claims and 37 do not. Figure 2 shows the recruitment status and patient flow of the ongoing study.

Data Collection App Details

Data collection is being performed using a custom Android Wear app and the Huawei Watch 2 smart watch. We are collecting 9-axis inertial sensor data and heart rate data during supervised and independent physiotherapy exercises. The sensor data are collected on the smart watch and uploaded to Google Cloud Storage servers. Labeling of the supervised activities is performed in a separate Android app running on an Android tablet (Samsung Tab A) and operated by our research team.

Figure 1. Study timeline. SPARS: Smart Physiotherapy Activity Recognition System.

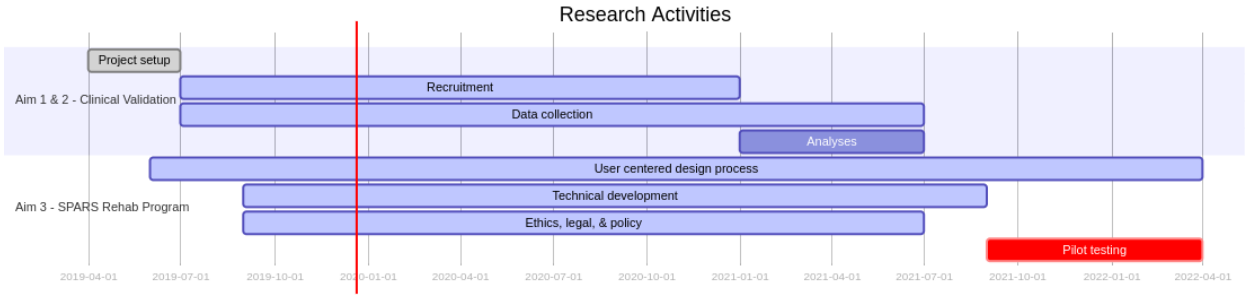
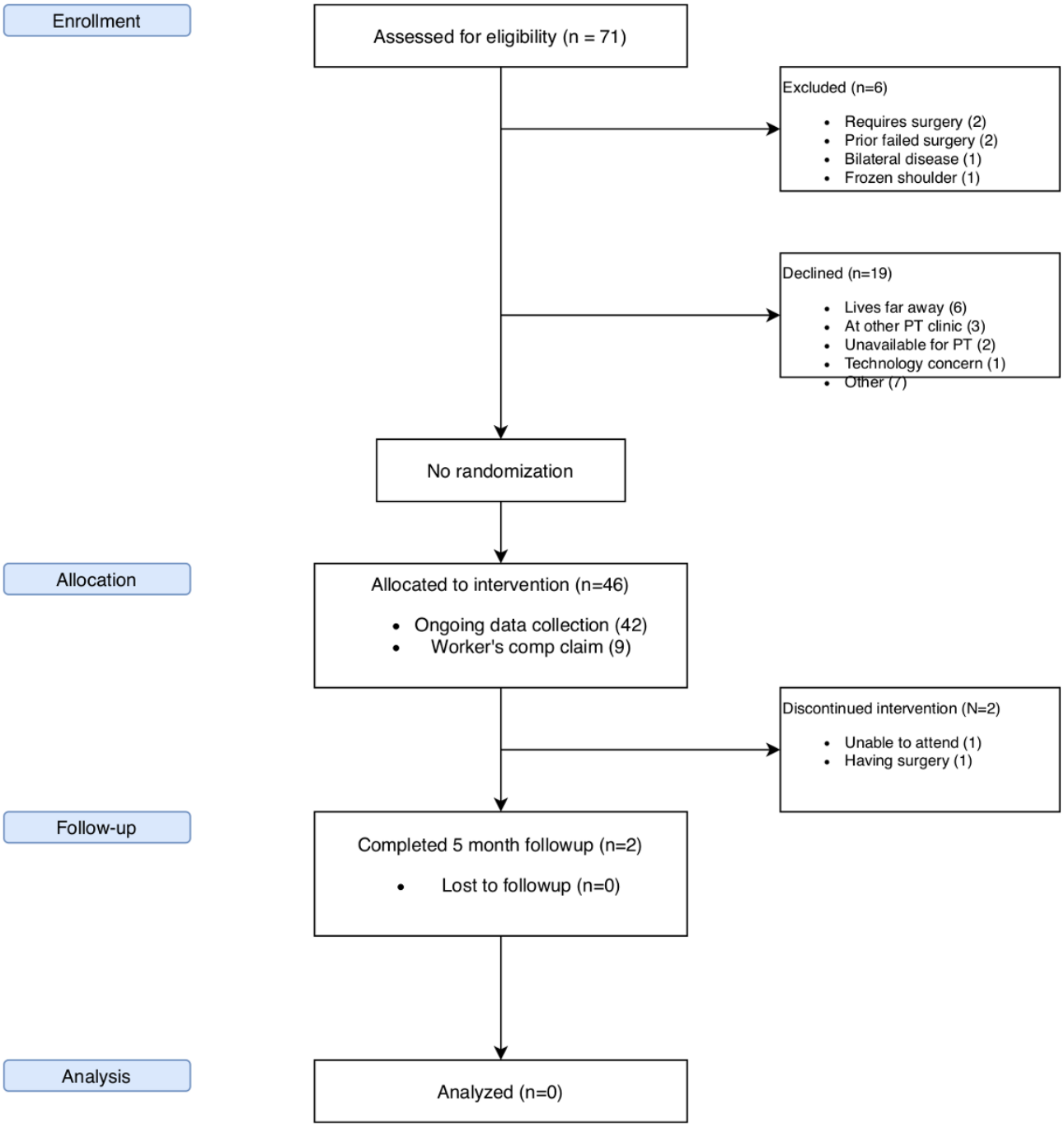


Figure 2. Recruitment and patient flow as of December 2019.



Discussion

Principal Findings

Exercise-based physiotherapy is considered essential in the management of rotator cuff pathology, both as a first-line treatment [4-6] and for postoperative rehabilitation [7,8]. The current paradigm for the delivery of physiotherapy services involves in-person patient assessments and training for prescribed exercise activities, but it requires the patients to perform majority of their exercises independently at home. There is a body of literature that indicates patients often struggle to fully engage in their prescribed activities [9,11], suggesting that many may not receive the full benefit of this important treatment.

A significant barrier to better understanding the impact of this problem on physiotherapy outcomes has been the challenge of accurately assessing adherence to physiotherapy participation in the home setting. This limitation precludes accurate and objective measurement of the administered physiotherapy dose for protocols that include an independent home component.

This manuscript describes a research protocol by which a smart watch and ML approach will be validated for tracking exercise-based shoulder physiotherapy in a cohort of patients with rotator cuff pathology. The validated instrument will also be used in a noninterventional fashion to assess the rate of adherence in the study population, the relationship between adherence and recovery, and patient factors related to physiotherapy adherence. As a final phase of this project, we

will pilot an adherence-driven rehabilitation program where real-time measurement of physiotherapy adherence is utilized to promote better patient engagement in their home program.

A smart watch was selected as the platform for physiotherapy adherence tracking chiefly for patient comfort during exercise and ease of use. A significant proportion of the rotator cuff pathology demographic is elderly [16,17] and many have low technology literacy. The smart watch platform we have developed only requires that a patient put on their watch before physiotherapy exercise and that they ensure it is charged before doing so. This is in contrast to other systems that either require multiple sensors to be strapped to various points on the body [70] or a computer vision approach that requires some setup in the exercise environment to obtain and maintain an appropriate field of view [65]. In our setup, raw inertial data are processed using a modern deep learning approach, which we have shown previously to significantly outperform classical algorithms utilizing an engineered feature representation [15]. Although the deep learning approach requires significantly more computing resources for training, the inference time is comparable with classical models and feasible for evaluation either as a cloud service or directly on a patient's mobile device [15].

There are a number of limitations to the proposed study. In the validation phase of this research, the act of measuring physiotherapy adherence may impact patients' likelihood of adherence, even in a double-blinded noninterventional fashion, as proposed. Therefore, the assessed adherence rate in the study population may not be generalizable to populations that receive no tracking at all. A further limitation is that the ML algorithms validated in the clinic context will generalize well to the home setting. This risk will be mitigated by assessing algorithm generalization across multiple clinic sessions and to new patients (subject stratification). We assume that if that algorithm generalizes in both these cases, generalization to the home setting is also likely. As we also assess the criterion validity for adherence tracking, a positive relationship between adherence and recovery, if detected, it would serve as further evidence for the validity of algorithm construct.

Despite the efforts we have invested in developing a simple, accurate, and robust method for tracking shoulder physiotherapy, tracking errors will inevitably occur and result in imperfect adherence measurement. These errors could be secondary to software glitches, poor algorithm generalization, accidental or intentional misuse or disuse, hardware failure, and others. Therefore, the adherence estimates that we calculate for each patient will be subject to these errors, which may be random or biased to certain study subjects. To mitigate and assess these effects, we will collect survey data from each patient on their use of the smart watches and ask each patient to manually complete a 2-week adherence diary so that we can compare the measured adherence with patient self-report.

A limitation of the final interventional phase of this study is the pilot sample size (N=20) and the absence of a true control group. Although we can compare the interventional cohort with historical controls in the validation cohort, a better comparison would be with a control group with no tracking at all as per the current standard of care. Ultimately, a larger randomized controlled trial (RCT) would be required to adequately assess the effect of an adherence-driven rehabilitation program on recovery. The pilot study we conduct is primarily powered to detect implementation challenges, refine the system design, and estimate the effect size as required preliminaries to funding and carrying out a larger multicenter RCT.

Conclusions

This protocol paper describes a peer-reviewed, grant-funded study to validate a smart watch and ML approach to assess patient adherence to exercise-based shoulder physiotherapy in a population with rotator cuff pathology. This study will provide new and important insights into shoulder physiotherapy adherence, the relationship between adherence and recovery, barriers to better adherence, and methods for addressing them. The ultimate goal of this work is to improve physiotherapy delivery and outcomes for patients with musculoskeletal injuries and disorders.

Conflicts of Interest

DB is a cofounder and holds equity in Halterix Corporation, a digital physiotherapy company. DB was involved in the development of the software apps being used to carry out this research. MH, SM, and CW hold equity in Halterix Corporation, a digital physiotherapy company. Otherwise, the authors do not have any personal financial interests related to the subject matter discussed in this manuscript.

Multimedia Appendix 1
Peer review reports from Collaborative Health Research Projects - NSERC Partnered.
[PDF File (Adobe PDF File), 434 KB - resprot_v9i7e17841_app1.pdf]

References

1. Kemp KA, Sheps DM, Luciak-Corea C, Styles-Tripp F, Buckingham J, Beaupre LA. Systematic review of rotator cuff tears in workers' compensation patients. Occup Med (Lond) 2011 Dec;61(8):556-562. [doi: 10.1093/occmed/kqr068] [Medline: 22016341]
2. Morris AC, Singh JA, Bickel C, Ponce BA. Exercise therapy following surgical rotator cuff repair. Cochrane Database Syst Rev 2015(2):CD011531. [doi: 10.1002/14651858.CD011531]

3. Page MJ, Green S, McBain B, Surace SJ, Deitch J, Lyttle N, et al. Manual therapy and exercise for rotator cuff disease. Cochrane Database Syst Rev 2016 Jun 10(6):CD012224. [doi: 10.1002/14651858.CD012224] [Medline: 27283590]
4. Kuhn JE, Dunn WR, Sanders R, An Q, Baumgarten KM, Bishop JY, MOON Shoulder Group. Effectiveness of physical therapy in treating atraumatic full-thickness rotator cuff tears: a multicenter prospective cohort study. J Shoulder Elbow Surg 2013 Oct;22(10):1371-1379 [FREE Full text] [doi: 10.1016/j.jse.2013.01.026] [Medline: 23540577]
5. Desmeules F, Boudreault J, Dionne CE, Frémont P, Lowry V, MacDermid JC, et al. Efficacy of exercise therapy in workers with rotator cuff tendinopathy: a systematic review. J Occup Health 2016 Sep 30;58(5):389-403 [FREE Full text] [doi: 10.1539/joh.15-0103-RA] [Medline: 27488037]
6. Steuri R, Sattelmayer M, Elsig S, Kolly C, Tal A, Taeymans J, et al. Effectiveness of conservative interventions including exercise, manual therapy and medical management in adults with shoulder impingement: a systematic review and meta-analysis of RCTs. Br J Sports Med 2017 Sep;51(18):1340-1347 [FREE Full text] [doi: 10.1136/bjsports-2016-096515] [Medline: 28630217]
7. Littlewood C, Bateman M, Clark D, Selfe J, Watkinson D, Walton M, et al. Rehabilitation following rotator cuff repair: a systematic review. Shoulder Elbow 2015 Apr;7(2):115-124 [FREE Full text] [doi: 10.1177/1758573214567702] [Medline: 27582966]
8. Thomson S, Jukes C, Lewis J. Rehabilitation following surgical repair of the rotator cuff: a systematic review. Physiotherapy 2016 Mar;102(1):20-28. [doi: 10.1016/j.physio.2015.08.003] [Medline: 26510584]
9. Holden MA, Haywood KL, Potia TA, Gee M, McLean S. Recommendations for exercise adherence measures in musculoskeletal settings: a systematic review and consensus meeting (protocol). Syst Rev 2014 Feb 10;3:10 [FREE Full text] [doi: 10.1186/2046-4053-3-10] [Medline: 24512976]
10. Cuff DJ, Pupello DR. Prospective evaluation of postoperative compliance and outcomes after rotator cuff repair in patients with and without workers' compensation claims. J Shoulder Elbow Surg 2012 Dec;21(12):1728-1733. [doi: 10.1016/j.jse.2012.03.002] [Medline: 22652063]
11. Peek K, Sanson-Fisher R, Mackenzie L, Carey M. Interventions to aid patient adherence to physiotherapist prescribed self-management strategies: a systematic review. Physiotherapy 2016 Jun;102(2):127-135. [doi: 10.1016/j.physio.2015.10.003] [Medline: 26821954]
12. Jack K, McLean SM, Moffett JK, Gardiner E. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. Man Ther 2010 Jun;15(3):220-228 [FREE Full text] [doi: 10.1016/j.math.2009.12.004] [Medline: 20163979]
13. Faber M, Andersen MH, Sevel C, Thorborg K, Bandholm T, Rathleff M. The majority are not performing home-exercises correctly two weeks after their initial instruction-an assessor-blinded study. PeerJ 2015;3:e1102 [FREE Full text] [doi: 10.7717/peerj.1102] [Medline: 26244112]
14. Bollen JC, Dean SG, Siegert RJ, Howe TE, Goodwin VA. A systematic review of measures of self-reported adherence to unsupervised home-based rehabilitation exercise programmes, and their psychometric properties. BMJ Open 2014 Jun 27;4(6):e005044 [FREE Full text] [doi: 10.1136/bmjopen-2014-005044] [Medline: 24972606]
15. Burns DM, Leung N, Hardisty M, Whyne CM, Henry P, McLachlin S. Shoulder physiotherapy exercise recognition: machine learning the inertial signals from a smartwatch. Physiol Meas 2018 Jul 23;39(7):075007. [doi: 10.1088/1361-6579/aacfd9] [Medline: 29952759]
16. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain 2003 Mar;102(1-2):167-178. [doi: 10.1016/s0304-3959(02)00372-x] [Medline: 12620608]
17. Luime JJ, Koes BW, Hendriksen IJ, Burdorf A, Verhagen AP, Miedema HS, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. Scand J Rheumatol 2004;33(2):73-81. [doi: 10.1080/03009740310004667] [Medline: 15163107]
18. Minagawa H, Yamamoto N, Abe H, Fukuda M, Seki N, Kikuchi K, et al. Prevalence of symptomatic and asymptomatic rotator cuff tears in the general population: from mass-screening in one village. J Orthop 2013;10(1):8-12 [FREE Full text] [doi: 10.1016/j.jor.2013.01.008] [Medline: 24403741]
19. Kuhn JE. Current concepts: rotator cuff pathology in athletes--a source of pain or adaptive pathology? Curr Sports Med Rep 2013;12(5):311-315. [doi: 10.1249/JSR.0000000000000000] [Medline: 24030304]
20. By the Numbers: WSIB Statistical Report. Workplace Safety and Insurance Board. 2016. URL: https://www.wsib.ca/en/numbers-wsib-statistical-report [accessed 2020-06-04]
21. Beaudreuil J, Dhénain M, Coudane H, Mlika-Cabanne N. Clinical practice guidelines for the surgical management of rotator cuff tears in adults. Orthop Traumatol Surg Res 2010 Apr;96(2):175-179 [FREE Full text] [doi: 10.1016/j.otsr.2010.02.002] [Medline: 20464793]
22. Ketola S, Lehtinen J, Arnala I, Nissinen M, Westenius H, Sintonen H, et al. Does arthroscopic acromioplasty provide any additional value in the treatment of shoulder impingement syndrome?: a two-year randomised controlled trial. J Bone Joint Surg Br 2009 Oct;91(10):1326-1334. [doi: 10.1302/0301-620X.91B10.22094] [Medline: 19794168]
23. Haahr JP, Østergaard S, Dalsgaard J, Norup K, Frost P, Lausen S, et al. Exercises versus arthroscopic decompression in patients with subacromial impingement: a randomised, controlled study in 90 cases with a one year follow up. Ann Rheum Dis 2005 May;64(5):760-764 [FREE Full text] [doi: 10.1136/ard.2004.021188] [Medline: 15834056]

24. Kuhn JE. Exercise in the treatment of rotator cuff impingement: a systematic review and a synthesized evidence-based rehabilitation protocol. J Shoulder Elbow Surg 2009;18(1):138-160. [doi: 10.1016/j.jse.2008.06.004] [Medline: 18835532]
25. Ainsworth R, Lewis JS. Exercise therapy for the conservative management of full thickness tears of the rotator cuff: a systematic review. Br J Sports Med 2007 Apr;41(4):200-210 [FREE Full text] [doi: 10.1136/bjsm.2006.032524] [Medline: 17264144]
26. Bang MD, Deyle GD. Comparison of supervised exercise with and without manual physical therapy for patients with shoulder impingement syndrome. J Orthop Sports Phys Ther 2000 Mar;30(3):126-137. [doi: 10.2519/jospt.2000.30.3.126] [Medline: 10721508]
27. McClure PW, Bialker J, Neff N, Williams G, Karduna A. Shoulder function and 3-dimensional kinematics in people with shoulder impingement syndrome before and after a 6-week exercise program. Phys Ther 2004 Sep;84(9):832-848. [Medline: 15330696]
28. Senbursa G, Baltaci G, Atay A. Comparison of conservative treatment with and without manual physical therapy for patients with shoulder impingement syndrome: a prospective, randomized clinical trial. Knee Surg Sports Traumatol Arthrosc 2007 Jul;15(7):915-921. [doi: 10.1007/s00167-007-0288-x] [Medline: 17333123]
29. Michener LA, McClure PW, Sennett BJ. American shoulder and elbow surgeons standardized shoulder assessment form, patient self-report section: reliability, validity, and responsiveness. J Shoulder Elbow Surg 2002;11(6):587-594. [doi: 10.1067/mse.2002.127096] [Medline: 12469084]
30. Grant HJ, Arthur A, Pichora DR. Evaluation of interventions for rotator cuff pathology: a systematic review. J Hand Ther 2004;17(2):274-299. [doi: 10.1197/j.jht.2004.02.013] [Medline: 15162111]
31. Green S, Buchbinder R, Hetrick S. Physiotherapy interventions for shoulder pain. Cochrane Database Syst Rev 2003(2):CD004258. [doi: 10.1002/14651858.CD004258] [Medline: 12804509]
32. Brudvig TJ, Kulkarni H, Shah S. The effect of therapeutic exercise and mobilization on patients with shoulder dysfunction : a systematic review with meta-analysis. J Orthop Sports Phys Ther 2011 Oct;41(10):734-748. [doi: 10.2519/jospt.2011.3440] [Medline: 21891875]
33. Marinko LN, Chacko JM, Dalton D, Chacko CC. The effectiveness of therapeutic exercise for painful shoulder conditions: a meta-analysis. J Shoulder Elbow Surg 2011 Dec;20(8):1351-1359. [doi: 10.1016/j.jse.2011.05.013] [Medline: 21889366]
34. Holmgren T, Oberg B, Sjöberg I, Johansson K. Supervised strengthening exercises versus home-based movement exercises after arthroscopic acromioplasty: a randomized clinical trial. J Rehabil Med 2012 Jan;44(1):12-18 [FREE Full text] [doi: 10.2340/16501977-0889] [Medline: 22124602]
35. Osterås H, Torstensen TA. The dose-response effect of medical exercise therapy on impairment in patients with unilateral longstanding subacromial pain. Open Orthop J 2010 Jan 5;4:1-6 [FREE Full text] [doi: 10.2174/1874325001004010001] [Medline: 20148093]
36. Moosmayer S, Lund G, Seljom US, Haldorsen B, Svege IC, Hennig T, et al. Tendon repair compared with physiotherapy in the treatment of rotator cuff tears: a randomized controlled study in 103 cases with a five-year follow-up. J Bone Joint Surg Am 2014 Sep 17;96(18):1504-1514. [doi: 10.2106/JBJS.M.01393] [Medline: 25232074]
37. Kukkonen J, Joukainen A, Lehtinen J, Mattila KT, Tuominen EK, Kauko T, et al. Treatment of nontraumatic rotator cuff tears: a randomized controlled trial with two years of clinical and imaging follow-up. J Bone Joint Surg Am 2015 Nov 4;97(21):1729-1737. [doi: 10.2106/JBJS.N.01051] [Medline: 26537160]
38. Heerspink FO, van Raay JJ, Koorevaar RC, van Eerden PJ, Westerbeek RE, van 't Riet E, et al. Comparing surgical repair with conservative treatment for degenerative rotator cuff tears: a randomized controlled trial. J Shoulder Elbow Surg 2015 Aug;24(8):1274-1281. [doi: 10.1016/j.jse.2015.05.040] [Medline: 26189808]
39. Martin S, Martin T. Management of Rotator Cuff Tears. UpToDate. URL: https://www.uptodate.com/contents/management-of-rotator-cuff-tears [accessed 2018-05-02]
40. Walther M, Werner A, Stahlschmidt T, Woelfel R, Gohlke F. The subacromial impingement syndrome of the shoulder treated by conventional physiotherapy, self-training, and a shoulder brace: results of a prospective, randomized study. J Shoulder Elbow Surg 2004;13(4):417-423. [doi: 10.1016/j.jse.2004.02.002] [Medline: 15220882]
41. Werner A, Walther M, Ilg A, Stahlschmidt T, Gohlke F. [Self-training versus conventional physiotherapy in subacromial impingement syndrome]. Z Orthop Ihre Grenzgeb 2002;140(4):375-380. [doi: 10.1055/s-2002-33394] [Medline: 12183784]
42. Hayes K, Ginn KA, Walton JR, Szomor ZL, Murrell GA. A randomised clinical trial evaluating the efficacy of physiotherapy after rotator cuff repair. Aust J Physiother 2004;50(2):77-83 [FREE Full text] [doi: 10.1016/s0004-9514(14)60099-4] [Medline: 15151491]
43. de Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nur 2016 Jun 22;2(4):323. [doi: 10.1016/s1474-5151(03)00091-4]
44. Kolt GS, Brewer BW, Pizzari T, Schoo AM, Garrett N. The sport injury rehabilitation adherence scale: a reliable scale for use in clinical physiotherapy. Physiotherapy 2007 Mar;93(1):17-22. [doi: 10.1016/j.physio.2006.07.002]
45. Rahman T, Borkhuu B, Littleton AG, Sample W, Moran E, Campbell S, et al. Electronic monitoring of scoliosis brace wear compliance. J Child Orthop 2010 Aug;4(4):343-347 [FREE Full text] [doi: 10.1007/s11832-010-0266-6] [Medline: 21804897]

46. Sangiorgio SN, Ho NC, Morgan RD, Ebramzadeh E, Zionts LE. The objective measurement of brace-use adherence in the treatment of idiopathic clubfoot. J Bone Joint Surg Am 2016 Oct 5;98(19):1598-1605. [doi: 10.2106/JBJS.16.00170] [Medline: 27707845]
47. Prospective Sensor Controlled Compliance Analysis of Shoulder Abduction Splint After Rotator Cuff Repair (SENSABDUKT). ClinicalTrials. 2017. URL: https://clinicaltrials.gov/ct2/show/NCT03054753 [accessed 2018-05-03]
48. Frost R, Levati S, McClurg D, Brady M, Williams B. What adherence measures should be used in trials of home-based rehabilitation interventions? A systematic review of the validity, reliability, and acceptability of measures. Arch Phys Med Rehabil 2017 Jun;98(6):1241-56.e45. [doi: 10.1016/j.apmr.2016.08.482] [Medline: 27702555]
49. Conroy DE, Hayes KW. The effect of joint mobilization as a component of comprehensive treatment for primary shoulder impingement syndrome. J Orthop Sports Phys Ther 1998 Jul;28(1):3-14. [doi: 10.2519/jospt.1998.28.1.3] [Medline: 9653685]
50. Ludewig PM, Borstad JD. Effects of a home exercise programme on shoulder pain and functional status in construction workers. Occup Environ Med 2003 Nov;60(11):841-849 [FREE Full text] [doi: 10.1136/oem.60.11.841] [Medline: 14573714]
51. Ahmad S, Haber M, Bokor DJ. The influence of intraoperative factors and postoperative rehabilitation compliance on the integrity of the rotator cuff after arthroscopic repair. J Shoulder Elbow Surg 2015 Feb;24(2):229-235. [doi: 10.1016/j.jse.2014.06.050] [Medline: 25240808]
52. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient compliance with paper and electronic diaries. Control Clin Trials 2003 Apr;24(2):182-199. [doi: 10.1016/s0197-2456(02)00320-3] [Medline: 12689739]
53. Ludewig PM, Cook TM. Alterations in shoulder kinematics and associated muscle activity in people with symptoms of shoulder impingement. Phys Ther 2000 Mar;80(3):276-291. [Medline: 10696154]
54. Ludewig PM, Reynolds JF. The association of scapular kinematics and glenohumeral joint pathologies. J Orthop Sports Phys Ther 2009 Feb;39(2):90-104 [FREE Full text] [doi: 10.2519/jospt.2009.2808] [Medline: 19194022]
55. Page P. Shoulder muscle imbalance and subacromial impingement syndrome in overhead athletes. Int J Sports Phys Ther 2011 Mar;6(1):51-58 [FREE Full text] [Medline: 21655457]
56. Scibek JS, Carpenter JE, Hughes RE. Rotator cuff tear pain and tear size and scapulohumeral rhythm. J Athl Train 2009;44(2):148-159 [FREE Full text] [doi: 10.4085/1062-6050-44.2.148] [Medline: 19295959]
57. Dewhurst A. An exploration of evidence-based exercises for shoulder impingement syndrome. Int Musculoskelet Med 2013 Jul 18;32(3):111-116. [doi: 10.1179/175361410x12652805808476]
58. Baumer TG, Chan D, Mende V, Dischler J, Zauel R, van Holsbeeck M, et al. Effects of rotator cuff pathology and physical therapy on in vivo shoulder motion and clinical outcomes in patients with a symptomatic full-thickness rotator cuff tear. Orthop J Sports Med 2016 Sep;4(9):2325967116666506 [FREE Full text] [doi: 10.1177/2325967116666506] [Medline: 27734020]
59. van der Meijden OA, Westgard P, Chandler Z, Gaskill TR, Kokmeyer D, Millett PJ. Rehabilitation after arthroscopic rotator cuff repair: current concepts review and evidence-based guidelines. Int J Sports Phys Ther 2012 Apr;7(2):197-218 [FREE Full text] [Medline: 22530194]
60. Chen CY, Neufeld PS, Feely CA, Skinner CS. Factors influencing compliance with home exercise programs among patients with upper-extremity impairment. Am J Occup Ther 1999;53(2):171-180. [doi: 10.5014/ajot.53.2.171] [Medline: 10200840]
61. Sluijs EM, Kok GJ, van der Zee J. Correlates of exercise compliance in physical therapy. Phys Ther 1993 Nov;73(11):771-82; discussion 783. [doi: 10.1093/ptj/73.11.771] [Medline: 8234458]
62. Brewer BW, Cornelius AE, van Raalte JL, Tennen H, Armeli S. Predictors of adherence to home rehabilitation exercises following anterior cruciate ligament reconstruction. Rehabil Psychol 2013 Feb;58(1):64-72 [FREE Full text] [doi: 10.1037/a0031297] [Medline: 23438001]
63. Schoo A, Morris ME, Bui QM. Predictors of home exercise adherence in older people with osteoarthritis. Physiotherapy Canada 2005 Jul;57(3):179-187 [FREE Full text] [doi: 10.3138/ptc.57.3.179]
64. Stenström CH, Arge B, Sundbom A. Home exercise and compliance in inflammatory rheumatic diseases--a prospective clinical trial. J Rheumatol 1997 Mar;24(3):470-476. [Medline: 9058651]
65. Zhao W, Feng H, Lun R, Epsy DD, Reinthal MA. A Kinect-based Rehabilitation Exercise Monitoring and Guidance System. In: 5th International Conference on Software Engineering and Service Science. 2014 Presented at: ICSESS'14; June 27-29, 2014; Beijing, China URL: https://ieeexplore.ieee.org/document/6933678 [doi: 10.1109/ICSESS.2014.6933678]
66. Tousignant M, Boissy P, Corriveau H, Moffet H. In home telerehabilitation for older adults after discharge from an acute hospital or rehabilitation unit: a proof-of-concept study and costs estimation. Disabil Rehabil Assist Technol 2006 Sep;1(4):209-216. [doi: 10.1080/17483100600776965] [Medline: 19260168]
67. Anton S, Anton F. Monitoring Rehabilitation Exercises Using MS Kinect. In: E-Health and Bioengineering Conference. 2015 Presented at: EHB'15; November 19-21, 2015; Iasi, Romania URL: https://ieeexplore.ieee.org/document/7391463 [doi: 10.1109/EHB.2015.7391463]
68. Lauzé M, Martel DD, Agnoux A, Sirois M, Émond M, Daoust R, et al. Feasibility, acceptability and effects of a home-based exercise program using a gerontechnology on physical capacities after a minor injury in community-living older adults: a pilot study. J Nutr Health Aging 2018;22(1):16-25. [doi: 10.1007/s12603-017-0938-8] [Medline: 29300417]

69. McGirr K, Harring SI, Kennedy TS, Pedersen MF, Hirata RP, Thorborg K, et al. An elastic exercise band mounted with a bandcizer can differentiate between commonly prescribed home exercises for the shoulder. Int J Sports Phys Ther 2015 Jun;10(3):332-340 [FREE Full text] [Medline: 26075148]
70. Pan J, Chung H, Huang J. Intelligent shoulder joint home-based self-rehabilitation monitoring system. Int J Smart Home 2013 Sep 30;7(5):395-404. [doi: 10.14257/ijsh.2013.7.5.38]
71. Yurtman A, Barshan B. Automated evaluation of physical therapy exercises using multi-template dynamic time warping on wearable sensor signals. Comput Methods Programs Biomed 2014 Nov;117(2):189-207. [doi: 10.1016/j.cmpb.2014.07.003] [Medline: 25168775]
72. Taylor PE, Almeida GJ, Kanade T, Hodgins JK. Classifying human motion quality for knee osteoarthritis using accelerometers. Conf Proc IEEE Eng Med Biol Soc 2010;2010:339-343. [doi: 10.1109/IEMBS.2010.5627665] [Medline: 21096970]
73. Shen S, Wang H, Roy CR. I am a Smartwatch and I can Track my User's Arm. In: Proceedings of the 14th Annual International Conference on Mobile Systems, Applications, and Services. 2016 Presented at: MobiSys'16; June 25-30, 2016; Singapore. [doi: 10.1145/2906388.2906407]
74. de Baets L, van der Straaten R, Matheve T, Timmermans A. Shoulder assessment according to the international classification of functioning by means of inertial sensor technologies: a systematic review. Gait Posture 2017 Sep;57:278-294. [doi: 10.1016/j.gaitpost.2017.06.025] [Medline: 28683420]
75. Körver RJ, Heyligers IC, Samijo SK, Grimm B. Inertia based functional scoring of the shoulder in clinical practice. Physiol Meas 2014 Feb;35(2):167-176. [doi: 10.1088/0967-3334/35/2/167] [Medline: 24398361]
76. Pichonnaz C, Lécureux E, Bassin J, Duc C, Farron A, Aminian K, et al. Enhancing clinically-relevant shoulder function assessment using only essential movements. Physiol Meas 2015 Mar;36(3):547-560. [doi: 10.1088/0967-3334/36/3/547] [Medline: 25690269]
77. Werner BC, Holzgrefe RE, Griffin JW, Lyons ML, Cosgrove CT, Hart JM, et al. Validation of an innovative method of shoulder range-of-motion measurement using a smartphone clinometer application. J Shoulder Elbow Surg 2014 Nov;23(11):e275-e282. [doi: 10.1016/j.jse.2014.02.030] [Medline: 24925699]
78. Crabolu M, Pani D, Raffo L, Conti M, Crivelli P, Cereatti A. In vivo estimation of the shoulder joint center of rotation using magneto-inertial sensors: MRI-based accuracy and repeatability assessment. Biomed Eng Online 2017 Mar 21;16(1):34 [FREE Full text] [doi: 10.1186/s12938-017-0324-0] [Medline: 28320423]
79. Picerno P, Viero V, Donati M, Triossi T, Tancredi V, Melchiorri G. Ambulatory assessment of shoulder abduction strength curve using a single wearable inertial sensor. J Rehabil Res Dev 2015;52(2):171-180 [FREE Full text] [doi: 10.1682/JRRD.2014.06.0146] [Medline: 26230401]
80. Roldán-Jiménez C, Cuesta-Vargas AI. Age-related changes analyzing shoulder kinematics by means of inertial sensors. Clin Biomech (Bristol, Avon) 2016 Aug;37:70-76. [doi: 10.1016/j.clinbiomech.2016.06.004] [Medline: 27362972]
81. Roldán-Jiménez C, Cuesta-Vargas AI. Studying upper-limb kinematics using inertial sensors: a cross-sectional study. BMC Res Notes 2015 Oct 3;8:532 [FREE Full text] [doi: 10.1186/s13104-015-1517-x] [Medline: 26433573]
82. Rose M, Curtze C, O'Sullivan J, El-Gohary M, Crawford D, Friess D, et al. Wearable inertial sensors allow for quantitative assessment of shoulder and elbow kinematics in a cadaveric knee arthroscopy model. Arthroscopy 2017 Dec;33(12):2110-2116. [doi: 10.1016/j.arthro.2017.06.042] [Medline: 28866347]
83. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature 2015 May 28;521(7553):436-444. [doi: 10.1038/nature14539] [Medline: 26017442]
84. Wang H, Raj B. On the origin of deep learning. ArXiv 2017 Feb 24:- epub ahead of print(1702.07800) [FREE Full text]
85. Yosinski J, Clune J, Bengio Y, Lipson H. How transferable are features in deep neural networks? ArXiv 2014 Nov 06:- epub ahead of print(1411.1792) [FREE Full text]
86. Zhang X, Wu X, Luo D. Real-Time Activity Recognition on Smartphones Using Deep Neural Networks. In: Proceedings of the IEEE 12th International Conference on Ubiquitous Intelligence and Computing. 2015 Presented at: UIC-ATC-ScalCom'15; August 10-14, 2015; Beijing, China. [doi: 10.1109/uic-atc-scalcom-cbdcom-iop.2015.224]
87. Shaw J, Agarwal P, Desveaux L, Palma DC, Stamenova V, Jamieson T, et al. Beyond. NPJ Digit Med 2018;1:48 [FREE Full text] [doi: 10.1038/s41746-018-0059-8] [Medline: 31304327]
88. Hedgecoe A. Bioethics and the reinforcement of socio-technical expectations. Soc Stud Sci 2010 Apr;40(2):163-186. [doi: 10.1177/0306312709349781] [Medline: 20527320]
89. Paradis E, Sutkin G. Beyond a good story: from Hawthorne effect to reactivity in health professions education research. Med Educ 2017 Jan;51(1):31-39. [doi: 10.1111/medu.13122] [Medline: 27580703]
90. Fairchild AL, Bayer R. Public health. Ethics and the conduct of public health surveillance. Science 2004 Jan 30;303(5658):631-632. [doi: 10.1126/science.1094038] [Medline: 14752148]
91. Tarasuk V, Eakin JM. The problem of legitimacy in the experience of work-related back injury. Qual Health Res 2016 Jul;5(2):204-221. [doi: 10.1177/104973239500500205]
92. Gibson JL, Martin DK, Singer PA. Setting priorities in health care organizations: criteria, processes, and parameters of success. BMC Health Serv Res 2004 Sep 8;4(1):25 [FREE Full text] [doi: 10.1186/1472-6963-4-25] [Medline: 15355544]

93. Amodei D, Olah C, Steinhardt J, Christiano P, Schulman J, Mané D. Concrete problems in AI safety. ArXiv 2016 Jun 21:- epub ahead of print(1606.06565) [FREE Full text]
94. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs 2005 Aug;14(7):798-804. [doi: 10.1111/j.1365-2702.2005.01121.x] [Medline: 16000093]
95. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain 2011 Oct;152(10):2399-2404. [doi: 10.1016/j.pain.2011.07.005] [Medline: 21856077]
96. Beaton DE, Katz JN, Fossel AH, Wright JG, Tarasuk V, Bombardier C. Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. J Hand Ther 2001;14(2):128-146. [Medline: 11382253]
97. Staples MP, Forbes A, Green S, Buchbinder R. Shoulder-specific disability measures showed acceptable construct validity and responsiveness. J Clin Epidemiol 2010 Feb;63(2):163-170. [doi: 10.1016/j.jclinepi.2009.03.023] [Medline: 19683414]
98. Roy J, MacDermid JC, Woodhouse LJ. Measuring shoulder function: a systematic review of four questionnaires. Arthritis Rheum 2009 May 15;61(5):623-632 [FREE Full text] [doi: 10.1002/art.24396] [Medline: 19405008]
99. Jain NB, Wilcox RB, Katz JN, Higgins LD. Clinical examination of the rotator cuff. PM R 2013 Jan;5(1):45-56 [FREE Full text] [doi: 10.1016/j.pmrj.2012.08.019] [Medline: 23332909]
100. Brookham RL, McLean L, Dickerson CR. Construct validity of muscle force tests of the rotator cuff muscles: an electromyographic investigation. Phys Ther 2010 Apr;90(4):572-580. [doi: 10.2522/ptj.20090024] [Medline: 20133443]
101. Kelly BT, Kadrmas WR, Speer KP. The manual muscle examination for rotator cuff strength. An electromyographic investigation. Am J Sports Med 1996;24(5):581-588. [doi: 10.1177/036354659602400504] [Medline: 8883676]
102. Hayes K, Walton JR, Szomor ZL, Murrell GA. Reliability of 3 methods for assessing shoulder strength. J Shoulder Elbow Surg 2002;11(1):33-39. [doi: 10.1067/mse.2002.119852] [Medline: 11845146]
103. Mullaney MJ, McHugh MP, Johnson CP, Tyler TF. Reliability of shoulder range of motion comparing a goniometer to a digital level. Physiother Theory Pract 2010 Jul;26(5):327-333. [doi: 10.3109/09593980903094230] [Medline: 20557263]
104. Kolber MJ, Hanney WJ. The reliability and concurrent validity of shoulder mobility measurements using a digital inclinometer and goniometer: a technical report. Int J Sports Phys Ther 2012 Jun;7(3):306-313 [FREE Full text] [Medline: 22666645]
105. Chester R, Shepstone L, Daniell H, Sweeting D, Lewis J, Jerosch-Herold C. Predicting response to physiotherapy treatment for musculoskeletal shoulder pain: a systematic review. BMC Musculoskelet Disord 2013 Jul 8;14:203 [FREE Full text] [doi: 10.1186/1471-2474-14-203] [Medline: 23834747]
106. Chester R, Jerosch-Herold C, Lewis J, Shepstone L. Psychological factors are associated with the outcome of physiotherapy for people with shoulder pain: a multicentre longitudinal cohort study. Br J Sports Med 2018 Feb;52(4):269-275 [FREE Full text] [doi: 10.1136/bjsports-2016-096084] [Medline: 27445360]
107. Bassett S. The assessment of patient adherence to physiotherapy rehabilitation. N Z J Physiotherapy 2003;31(2):60-66 [FREE Full text]
108. Jin J, Sklar GE, Oh VM, Li SC. Factors affecting therapeutic compliance: a review from the patient's perspective. Ther Clin Risk Manag 2008 Feb;4(1):269-286 [FREE Full text] [doi: 10.2147/tcrm.s1458] [Medline: 18728716]
109. Raman J, Walton D, MacDermid JC, Athwal GS. Predictors of outcomes after rotator cuff repair-a meta-analysis. J Hand Ther 2017;30(3):276-292. [doi: 10.1016/j.jht.2016.11.002] [Medline: 28237073]
110. Razmjou H, Boljanovic D, Lincoln S, Holtby R, Gallay S, Henry P, et al. Outcome of expedited rotator cuff surgery in injured workers: determinants of successful recovery. Orthop J Sports Med 2017 May;5(5):2325967117705319 [FREE Full text] [doi: 10.1177/2325967117705319] [Medline: 28589156]
111. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. A critical review of available methods. J Clin Epidemiol 2003 Mar;56(3):221-229. [doi: 10.1016/s0895-4356(02)00585-1] [Medline: 12725876]
112. Mitchell PH, Powell L, Blumenthal J, Norten J, Ironson G, Pitula CR, et al. A short social support measure for patients recovering from myocardial infarction: the ENRICHD social support inventory. J Cardiopulm Rehabil 2003;23(6):398-403. [doi: 10.1097/00008483-200311000-00001] [Medline: 14646785]
113. Nicholas MK, McGuire BE, Asghari A. A 2-item short form of the pain self-efficacy questionnaire: development and psychometric evaluation of PSEQ-2. J Pain 2015 Feb;16(2):153-163. [doi: 10.1016/j.jpain.2014.11.002] [Medline: 25463701]
114. Razmjou H, Lincoln S, Axelrod T, Holtby R. Factors contributing to failure of rotator cuff surgery in persons with work-related injuries. Physiother Can 2008;60(2):125-133 [FREE Full text] [doi: 10.3138/physio.60.2.125] [Medline: 20145776]
115. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
116. Burns D, Whyne C. Seglearn: a python package for learning sequences and time series. J Mach Learn Res 2018;19(83):1-7 [FREE Full text] [doi: 10.1007/978-1-4842-2823-4_3]
117. He H, Garcia E. Learning from imbalanced data. IEEE Trans Knowl Data Eng 2009 Sep;21(9):1263-1284. [doi: 10.1109/TKDE.2008.239]
118. Zeng M, Yu T, Wang X, Nguyen L, Mengshoel O, Lane I. Semi-supervised convolutional neural networks for human activity recognition. Arxiv 2017:- epub ahead of print(1801.07827) [FREE Full text] [doi: 10.1109/BigData.2017.8257967]

119. Chalapathy R, Menon A, Chawla S. Anomaly detection using one-class neural networks. ArXiv 2018 Feb 18:- epub ahead of print [FREE Full text]
120. Zhang M, Wu J, Lin H, Yuan P, Song Y. The application of one-class classifier based on CNN in image defect detection. Procedia Comput Sci 2017;114:341-348. [doi: 10.1016/j.procs.2017.09.040]
121. Young A, Ling M, Arvind D. IMUSim: A Simulation Environment for Inertial Sensing Algorithm Design and Evaluation. In: Proceedings of the 10th ACM/IEEE International Conference on Information Processing in Sensor Networks. 2011 Presented at: ACM-IEEE'11; April 12-14, 2011; Chicago, IL, USA URL: https://ieeexplore.ieee.org/document/5779038
122. Yin R. Case Study Research: Design and Methods. Fourth Edition. Thousand Oaks, CA: Sage Publications; 2008.
123. Hedgecoe AM. Critical bioethics: beyond the social science critique of applied ethics. Bioethics 2004 Apr;18(2):120-143. [doi: 10.1111/j.1467-8519.2004.00385.x] [Medline: 15146853]
124. Viechtbauer W, Smits L, Kotz D, Budé L, Spigt M, Serroyen J, et al. A simple formula for the calculation of sample size in pilot studies. J Clin Epidemiol 2015 Nov;68(11):1375-1379. [doi: 10.1016/j.jclinepi.2015.04.014] [Medline: 26146089]
125. Watson P, Petrie A. Method agreement analysis: a review of correct methodology. Theriogenology 2010 Jun;73(9):1167-1179 [FREE Full text] [doi: 10.1016/j.theriogenology.2010.01.003] [Medline: 20138353]
126. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016 Jun;15(2):155-163 [FREE Full text] [doi: 10.1016/j.jcm.2016.02.012] [Medline: 27330520]
127. Hardt M, Price E. Equality of opportunity in supervised learning. Arxiv 2016 epub ahead of print(1610.02413) [FREE Full text]
128. Kamishima T, Akaho S, Asoh H, Sakuma J. Fairness-Aware Classifier with Prejudice Remover Regularizer. In: Joint European Conference on Machine Learning and Knowledge Discovery in Databases. 2012 Presented at: ECML PKDD'12; September 23-27, 2012; Bristol, United Kingdom. [doi: 10.1007/978-3-642-33486-3_3]
129. Cook J, Drummond M, Heyse JF. Economic endpoints in clinical trials. Stat Methods Med Res 2004 Apr;13(2):157-176. [doi: 10.1191/0962280204sm359ra] [Medline: 15068259]

Abbreviations

ANN: artificial neural networks
CRNN: convolutional recurrent neural network
DASH: Disabilities of the Arm, Shoulder, and Hand
IMU: inertial measurement unit
ML: machine learning
NPRS: Numeric Pain Rating Scale
RCT: randomized controlled trial
SPARS: Smart Physiotherapy Activity Recognition System
WCP: Working Conditions Program
WSIB: Workplace Safety and Insurance Board

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Protocol

Deep Learning Frameworks for Rapid Gram Stain Image Data Interpretation: Protocol for a Retrospective Data Analysis

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Abstract

Background: In recent years, remarkable progress has been made in deep learning technology and successful use cases have been introduced in the medical domain. However, not many studies have considered high-performance computing to fully appreciate the capability of deep learning technology.

Objective: This paper aims to design a solution to accelerate an automated Gram stain image interpretation by means of a deep learning framework without additional hardware resources.

Methods: We will apply and evaluate 3 methodologies, namely fine-tuning, an integer arithmetic–only framework, and hyperparameter tuning.

Results: The choice of pretrained models and the ideal setting for layer tuning and hyperparameter tuning will be determined. These results will provide an empirical yet reproducible guideline for those who consider a rapid deep learning solution for Gram stain image interpretation. The results are planned to be announced in the first quarter of 2021.

Conclusions: Making a balanced decision between modeling performance and computational performance is the key for a successful deep learning solution. Otherwise, highly accurate but slow deep learning solutions can add value to routine care.

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KEYWORDS

high performance computing; rapid Gram stain classification; image data analysis; deep learning; convolutional neural network

Introduction

In recent years, remarkable progress has been made in deep learning due to the emergence of big data processing technology. Deep learning is a family of machine learning that consists of multiple neurons in multiple layers. A neuron is a mathematical function with weights and biases, known as parameters. It receives real numbers from the neurons in the previous layer, generates another real number, and transmits it to the neurons in the next layer. The parameters for each of these neurons are optimally determined by a backpropagation algorithm, such as stochastic gradient descent, that looks for the minimum of a function. This contributes to the success of deep learning of image data compared with conventional techniques because it is able to learn the intrinsic data features without handcrafted feature engineering.

Gram stain is a laboratory procedure for the rapid classification and identification of microbial pathogens. Unlike other microbiology processes that can be fully automated [1], the

interpretation of Gram stain images still relies on human users, such as a physician or trained medical technical assistant. Although Gram stain seems like a medical image analysis problem, to the best of our knowledge, only 1 research paper [2] has used the deep learning method to automate the Gram stain analysis. One of the challenges is that microbial pathogens, particularly gram-negative organisms, and the background material, such as bloodstains, look highly similar on a slide. Furthermore, in cases of a low density of bacteria in a clinical sample, the manual search by microscopy is tedious and will only examine a fraction of the microscope slide, and thus may be error-prone.

Smith et al [2] achieved 94.9% classification accuracy out of 468 Gram-stained slides from positive blood cultures. The respective sensitivities and specificities were 98.4% and 75.0% for gram-positive cocci in chains and pairs, 93.2% and 97.2% for gram-positive cocci in clusters, and 96.3% and 98.1% for Gram-negative rods. The authors reused the pretrained model called Inception-v3 [3] and retrained the last layer with their image data (100,213 image crops of 146×146 pixels for training and testing) instead of constructing an end-to-end model from the scratch. This approach is called transfer learning [4] because it reuses precomputed model parameters. The major advantage of transfer learning is that it is able to reduce computational costs for the model training.

Despite the high accuracy achieved by Smith et al, there are still many open questions to be addressed. With regard to modeling, transfer learning could be improved with fine-tuning [5] instead of modifying only the last layer. Fine-tuning is a type of transfer learning that allows one to adjust the ratio of retraining layers. This is highly relevant to Gram stain classification because Inception-v3 was constructed with ImageNet [6], which contains 1.2 million nature images and 1000 image classes, such as dogs and cats, that are unrelated to Gram stain images. Therefore, increasing the number of unfrozen (retraining) layers (ie, decreasing the number of freezing layers) with Gram stain images is anticipated to yield better results. With respect to computational performance, it takes about 9 minutes to classify a whole-slide image of 28,032×28,032 pixels with a computer consisting of Intel Core i7 (Intel Corp) with 32 GB of RAM and a Nvidia GTX 1070 graphics processing unit (GPU). The turnaround time for multiple samples encountered in the medical laboratory would not provide timely decision-making, although this solution can run the job 24/7.

This study aims to design a rapid deep learning solution for Gram stain interpretation without acquiring hardware resources, and it provides the optimal proportion for the fine-tuning. The hypothesis and the study design to evaluate the hypothesis will be explained in the following section.

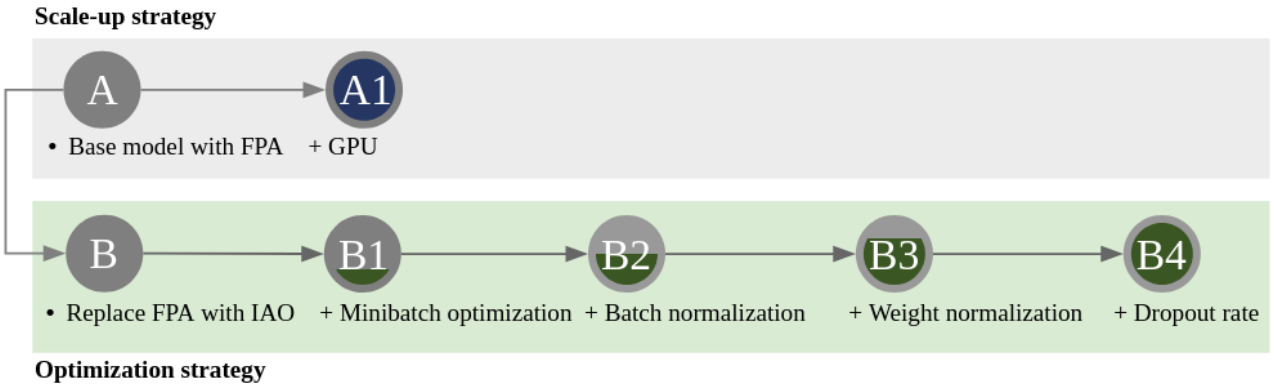
Methods

This section addresses the hypothesis, study design, data collection and description, study population, statistical considerations for nonbiased model construction and evaluation, and tools in detail.

Study Design

This study does not investigate a clinical hypothesis but performs an empirical evaluation of a deep learning framework for Gram stain image interpretation. The hypothesis to be tested is that the optimization of a deep learning framework will perform better than a scale-up strategy with a single GPU. In order to test this hypothesis, two strategies will be examined, as shown in Figure 1. The scale-up strategy stacks up more computer capabilities (model A, highlighted in blue). On the other hand, the optimization strategy tunes the granular configuration of a deep learning framework (model B, depicted in green).

Figure 1. Two strategies will be compared. The lineage of model A is the implementation of the scale-up strategy (highlighted in blue). On the other hand, the lineage of model B is the implementation of the optimization strategy (depicted in green). Model A is the base model with FPA framework, while model B replaces the floating-point arithmetic with IAO. Each model is built on top of a predecessor model. For instance, model A1 is empowered with a single GPU and model B1 is empowered with the optimal minibatch size. FPA: floating-point arithmetic. GPU: graphics processing unit. IAO: integer arithmetic only.



In order to avoid model bias, 4 pretrained models (Mobilenet [7] with versions 1 and 2, and Inception [3] with versions 3 and 4) will be evaluated. Mobilenet and Inception were originally trained with ImageNet [6], which contains 1.2 million nature images and 1000 classes. Therefore, it is necessary to retrain them on the new data set, as described in the "Data Collection" section, because Gram stain interpretation is barely linked to the original task. The method that retrains a pretrained model without changing network architecture is called fine-tuning. Fine-tuning is a specific transfer learning technique that modifies

more layers than the last layer, also known as the fully connected layer, and their corresponding weights and biases. The optimal proportion of the fine-tuning will be empirically determined in this study. Concretely, 10 implementations will be evaluated, with the proportions of frozen layer to unfrozen layer (retraining layer) at 9:1, 8:2, ongoing up to 0:10 (from the shallow strategy to the deep strategy). The computational performance will be measured by time to achieve the target accuracy metric [8] of 95%.

Once the base model is implemented with Tensorflow [9] (Google Corp) as described above, model A will be accelerated with 2 approaches. Model A1 is the scale-up implementation built on top of model A with a single GPU. In contrast, model B is a mutated model of model A because it replaces floating-point arithmetic with an integer arithmetic–only deep learning framework called Tensorflow Lite [10]. Model B1 aims to detect the optimal batch size for Gram stain classification. Model B2 and B3 activate batch normalization and weight normalization. Normalization penalizes large input numbers and weights. Finally, model B4 prunes the model network by adjusting the dropout rate, which speeds up the execution time. These hyperparameters—batch size, batch normalization, weight normalization, and dropout rate—are chosen based on the findings from previous studies [11-14]. The specification of the hyperparameter space is defined in Table 1. The boundary is chosen to be wide to account for many possible combinations of the hyperparameters.

Table 1. Specification of the hyperparameter space for the model B family. Minibatch size and dropout rate are quantified to avoid an exhaustive search.

Model	Hyperparameter	Original value range	Quantified values
B1	Minibatch size	{1-infinity}	{32, 64, 128, 256, 512}
B2	Batch normalization	{on, off}	{on, off}
B3	Weight normalization	{on, off}	{on, off}
B4	Dropout rate	{0-1}	{0, 0.1, 0.2, 0.3, 0.4, 0.5}

The objective of this study is to understand the relation between computation time and each hyperparameter, not to create a hyperparameter optimization [15] that searches for a global minimum or the local minima of hyperparameters.

Data Collection

This study will use 8728 Gram stain images from between 2015 and 2018 for modeling and images generated in 2019 for testing. Data are archived in a workstation at the Institute for Clinical Chemistry at the Medical Faculty Mannheim of Heidelberg University, Germany. Sample images and labels are shown in Figure 2. The sizes of the cropped images vary from 800×600 pixels to 1920×1080 pixels. Note that the image is not a whole-slide image, but a crop of the interests—the microorganisms and the slide background.

Figure 2. A sample image of Gram stain data. The image label does not have a link to personal information.

The label data corresponding to the image are stored in a central database for reporting purposes and extracted for this study. Each image is associated with 2 labels: (1) Gram stain class (ie, either gram-positive or gram-negative) and (2) a class for the genus. The genus label includes 5 of the most frequently encountered germs: (1) *Staphylococcus*, (2) *Escherichia*, (3) *Streptococcus*, (4) *Enterococcus*, and (5) others, for the rest of the germs that are rarely presented. This setting prevents a potential risk of identifying a patient with an extremely rare microorganism. Of the 8728 images, 446 images (5.11%) are associated with multiple classes. These images with multiple class labels are excluded because object recognition, that is, bacterial differentiation, is beyond the scope of this study.

Study Population

The population for this study is a group of sepsis patients, whose blood samples contain at least one harmful bacterium, such as *Staphylococcus*, *Escherichia*, or *Streptococcus*. This study does not recruit control and treatment groups. However, a set of gram-positive images would be regarded as one group, while gram-negative images would be regarded as a comparison group for this study. This is a retrospective data analysis reusing an archived image data set, as described in the "Data Collection" section.

Statistical Analysis

This section will address and describe the 3 underlying statistical considerations towards a solid study design: (1) the class balancing strategy for the input data set, (2) the proper split ratio for training and evaluation, and (3) the metric for the model evaluation.

Class Balancing

Imbalanced input data sets are a common limiting factor that degrades model quality. Chawla et al [16] systematically proved that data augmentation can improve the imbalanced class problem and demonstrated the benefits. In the classification of bone lesions from x-ray images, Gupta et al [17] mitigated the small number of positive samples by using data augmentation. In the given image data available for this study, gram-positive results are twice as frequent as gram-negative results. In order to balance the class proportion, this study will apply the data augmentation technique, which enriches the data set by cropping, rotating, zooming, and flipping the given images.

Split Ratio

The data set will be split into a training set, a hold-out development set, and a test set. The hold-out development set is different from the test set, as the development set will only be used for tuning the model parameters in order to not bias classification. The training set for deep learning algorithms is increased to 99% of the entire data set when there are more than a million data points. However, this study will follow best practice in machine learning, in which the splitting ratio is 60%, 20%, and 20% [18], because the available data points for this study are 8728 images.

Cross-validation is not used in this study for model validation. Cross-validation estimates the performance of the model statistically, but it is not the chosen method for evaluating a deep learning model. For instance, a 10-fold cross-validation creates a model with 9 folds and tests the model with the hold-out data (1 fold) 10 times. When we evaluate the model with 100 whole-slide (28,032×28,032 pixels) images, each round will take at least 900 minutes with a workstation powered by Intel Core i7 with 32 GB of RAM and a Nvidia GTX 1070 GPU, which is the same hardware setting and the same image size used in the study by Smith et al [2]. For the 10-fold cross-validation, it would take more than 6 days to evaluate 1 model, which is beyond the capacity of the workstation.

Metric for Evaluation

Despite considerable efforts that have been devoted to deep learning research, not many studies consider the computational efficiency, but focus solely on model evaluation. In order to provide more insightful information, this study will evaluate models with the classical metrics, such as accuracy, confusion matrix, and area under curve, as well as the training and testing times of models, to achieve the target accuracy proposed by the Stanford Data Analytics for What's Next project team [8].

Apparatus

This study will use Tensorflow [9] (floating-point arithmetic framework) and Tensorflow Lite [10] for deep learning solutions. Both of these frameworks are open source tools developed by the Google Brain team, and they are able to accelerate deep learning calculation by using multicore central processing units (CPUs) and GPUs. With regard to a model-debugging tool, TensorBoard will be used to graphically track all execution history.

All solutions will be developed and deployed in the data center at the Heinrich-Lanz-Center for Digital Health. The hardware configuration for this study is one Intel Xeon Silver 4110 CPU (Intel Corp), one Tesla V100 PCIe 32 GB GPU (Nvidia Corp), and 189 GB memory. The server is virtualized by Docker technology (Docker Inc) [19] for reproducible research.

Results

This study will provide an empirical guideline on how to accelerate a high-performance deep learning model without losing predictive power. Concretely, 2 results will be highlighted: (1) the performance improvement of an integer arithmetic–only deep learning framework for Gram stain image classification and (2) the optimal setting of fine-tuning and hyperparameters for 4 pretrained models (Mobilenet version 1 and 2 and Inception version 3 and 4). All models and the code for training and evaluation will be freely accessible in a public repository for reproducible research.

As of October 2019, this study has been approved by the institutional review board of Medical Faculty Mannheim of Heidelberg University, and the image data for the retrospective data analysis are available. The results are planned to be announced in the first quarter of 2021.

Discussion

Limitations

Distributed computing across multiple machines will not be covered in this study. Although it is the usual method to process big data, it is not always the most efficient choice to process the data. According to Boden et al [20], distributed systems are surprisingly inefficient in training machine learning models compared with a single workstation. The size of the input data for this study is 25 GB and it fits into the capacity of a standalone workstation. In future work, we would like to study Apache Spark [20], which enables distributed machine learning model training when the data do not fit into the memory of a single computer.

This study does not aim to propose novel neural network architecture, which requires many days of GPU processing time with state-of-the-art computational infrastructure that is not available within the scope of this project. Also, designing an outperforming architecture for image classification is a saturated topic, as many researchers have devoted their endeavors to this problem in the last decade. Nevertheless, for those who are interested in this topic, Elsken et al published a state-of-the-art review paper [21] that provides an overview of existing works and categorizes them into 3 dimensions.

Risk of Project Failure

An insufficient amount of image data could lead to an underpowered deep learning solution. The proper input data size is still an open question in the computer vision community. The answer is, “it depends.” It depends on the number of classes, image size, image quality, and complexity of the problem. For instance, classifying a black image versus a white image demands fewer input data compared with classifying a gram-positive image versus a gram-negative image.

In medical data analysis, power analysis is widely applied for determining the minimum sample size required. Unfortunately, power analysis is not applicable to unstructured data such as images. A rule of thumb for a good input size is 1000 images per class [21], which was the basis of an object recognition competition that was part of the Pascal Visual Object Classes challenge [22]. This study is anticipated to have low failure, since about 5800 gram-positive labeled images and 2700 gram-negative images are available for modeling.

Data Protection Considerations

Although this study does not use any personal information for data analysis, the name of the input data consists of a unique identifier for the experiment. This experiment identifier harbors a remote risk of linking back to personal information in the database. In the interest of data protection, this identifier is anonymized and securely stored at the Heinrich-Lanz-Center for Digital Health , which is protected by the hospital network firewalls. Unlike data pseudonymization, which transforms the identifier, data anonymization is an irreversible technique that removes the identifier permanently. The anonymized data will be archived for reproducibility.

The study will comply with the latest version of the Declaration of Helsinki [23] and Professional Code for Physicians in Germany. Patient names and other personal data are subject to the legal requirements concerning confidential medical communication. They comply with European Directive 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, the EU General Data Protection Regulation and the German Federal Data Protection Act, and the State Data Protection Act Baden-Württemberg.

Conflicts of Interest

None declared.

References

1. Bourbeau PP, Ledeboer NA. Automation in clinical microbiology. J Clin Microbiol 2013 Jun;51(6):1658-1665 [FREE Full text] [doi: 10.1128/JCM.00301-13] [Medline: 23515547]
2. Smith KP, Kang AD, Kirby JE. Automated Interpretation of Blood Culture Gram Stains by Use of a Deep Convolutional Neural Network. J Clin Microbiol 2018 Mar;56(3) [FREE Full text] [doi: 10.1128/JCM.01521-17] [Medline: 29187563]
3. Szegedy C, Liu W, Jia Y, Sermanet P, Reed S, Anguelov D, Erhan D, Vanhoucke V, Rabinovich A. Going Deeper With Convolutions. 2015 Presented at: Conference on Computer Vision and Pattern Recognition; Jun 7-12, 2015; Boston URL: https://www.cv-foundation.org/openaccess/content_cvpr_2015/html/Szegedy_Going_Deeper_With_2015_CVPR_paper.html [doi: 10.1109/cvpr.2015.7298594]
4. Shin HC, Roth HR, Gao M, Lu L, Xu Z, Nogues I, et al. Deep Convolutional Neural Networks for Computer-Aided Detection: CNN Architectures, Dataset Characteristics and Transfer Learning. IEEE Trans Med Imaging 2016 May;35(5):1285-1298 [FREE Full text] [doi: 10.1109/TMI.2016.2528162] [Medline: 26886976]
5. Tajbakhsh N, Shin JY, Gurudu SR, Hurst RT, Kendall CB, Gotway MB. Convolutional Neural Networks for Medical Image Analysis: Full Training or Fine Tuning? IEEE Trans Med Imaging 2016 May;35(5):1299-1312 [FREE Full text] [doi: 10.1109/TMI.2016.2535302] [Medline: 26978662]
6. Russakovsky O, Deng J, Su H, Krause J, Satheesh S, Ma S, et al. ImageNet Large Scale Visual Recognition Challenge. Int J Comput Vis 2015 Apr 11;115(3):211-252. [doi: 10.1007/s11263-015-0816-y]

7. Howard A, Zhu M, Chen B, Kalenichenko D, Wang W, Weyand T, et al. MobileNets: Efficient Convolutional Neural Networks for Mobile Vision Applications. arXiv. 2017 Apr 16. URL: https://arxiv.org/pdf/1704.04861.pdf [accessed 2020-06-17]
8. Coleman C, Narayanan D, Kang D, Zhao T, Zhang J, Nardi L, et al. DAWNBench: An End-to-End Deep Learning Benchmark and Competition. In: SysML Conference. 2018 Presented at: SysML Conference; February 15-16, 2018; Stanford, CA.
9. Abadi M, Barham P, Chen J, Chen Z, Davis A, Dean J, Devin M, Ghemawat S, Irving G, Isard M, Kudlur M, Levenberg J, Monga R, Moore S, Murray DG, Steiner B, Tucker P, Vasudevan V, Warden P, Wicke M, Yu Y, Zheng X. TensorFlow: A System for Large-Scale Machine Learning. 2016 Presented at: 12th USENIX Symposium on Operating Systems Design and Implementation; November 2-4, 2016; Savannah, GA, USA URL: https://www.usenix.org/conference/osdi16/technical-sessions/presentation/abadi
10. TensorFlow Lite. TensorFlow. URL: https://www.tensorflow.org/lite [accessed 2020-06-17]
11. Ioffe S, Szegedy C. Batch Normalization: Accelerating Deep Network Training by Reducing Internal Covariate Shift. 2015 Presented at: International Conference on Machine Learning; July 7-9, 2015; Lille, France URL: https://arxiv.org/pdf/1502.03167.pdf
12. Goyal P, Dollár P, Girshick R, Noordhuis P, Wesolowski L, Kyrola A, et al. Accurate, Large Minibatch SGD: Training ImageNet in 1 Hour. arXiv. URL: https://arxiv.org/pdf/1706.02677.pdf [accessed 2020-06-16]
13. Salimans T, Kingma D. Weight Normalization: A Simple Reparameterization to Accelerate Training of Deep Neural Networks. 2016 Jun 3 Presented at: Neural Information Processing Systems (NIPS); December 5-10, 2016; Barcelona, Spain URL: http://arxiv.org/abs/1602.07868
14. Wen W, Wu C, Wang Y, Chen Y, Li H. Learning Structured Sparsity in Deep Neural Networks. 2016 Oct 18 Presented at: Neural Information Processing Systems (NIPS); December 5-10, 2016; Barcelona SPAIN URL: http://arxiv.org/abs/1608.03665
15. Bergstra J, Bardenet R, Bengio Y, Kégl B. Algorithms for Hyper-Parameter Optimization. 2011 Presented at: Neural Information Processing Systems (NIPS); December 12-17, 2011; Granada, Spain URL: http://papers.nips.cc/paper/4443-algorithms-for-hyper-parameter-optimization.pdf
16. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE: Synthetic Minority Over-sampling Technique. JAIR 2002 Jun 01;16:321-357. [doi: 10.1613/jair.953]
17. Gupta A, Venkatesh S, Chopra S, Ledig C. Generative Image Translation for Data Augmentation of Bone Lesion Pathology. 2019 Feb 6 Presented at: International Conference on Medical Imaging with Deep Learning (MIDL); July 8-10, 2019; London, United Kingdom URL: http://arxiv.org/abs/1902.02248
18. Ng A. Improving deep neural networks: Hyperparameter tuning, regularization and optimization. Coursera. URL: https://www.coursera.org/learn/deep-neural-network [accessed 2020-06-20]
19. Boettiger C. An introduction to Docker for reproducible research. SIGOPS Oper Syst Rev 2015 Jan 20;49(1):71-79 [FREE Full text] [doi: 10.1145/2723872.2723882]
20. Boden C, Rabl T, Markl V. Distributed Machine Learning-but at what COST? 2017 Presented at: Neural Information Processing Systems (NIPS); December 4-9, 2017; Long Beach, CA, USA.
21. Hinton G, Srivastava N, Krizhevsky A, Sutskever I, Salakhutdinov R. Improving neural networks by preventing co-adaptation of feature detectors. arXiv. 2012 Jul 3. URL: https://arxiv.org/pdf/1207.0580.pdf [accessed 2020-06-19]
22. Everingham M, Eslami SMA, Van Gool L, Williams CKI, Winn J, Zisserman A. The Pascal Visual Object Classes Challenge: A Retrospective. Int J Comput Vis 2014 Jun 25;111(1):98-136. [doi: 10.1007/s11263-014-0733-5]
23. World Medical Association.. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ 2001;79(4):373-374 [FREE Full text] [Medline: 11357217]

Abbreviations

CPU: central processing unit
GPU: graphics processing unit

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Protocol

Premature or Small for Gestational Age Discrimination: International Multicenter Trial Protocol for Classification of the Low-Birth-Weight Newborn Through the Optical Properties of the Skin

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Abstract

Background: A low birth weight is an independent risk factor for adverse infant outcomes and a predictor of chronic disease in adulthood. In these situations, differentiating between prematurity and small for gestational age (SGA) or simultaneous conditions is essential to ensuring adequate care. Such diagnoses, however, depend on reliable pregnancy dating, which can be challenging in developing countries. A new medical optoelectronic device was developed to estimate gestational age (GA) at birth based on newborn skin reflection.

Objective: This study will aim to evaluate the device's ability to detect prematurity or SGA, or both conditions simultaneously as well as predict short-term pulmonary complications in a cohort of low-birth-weight newborns.

Methods: This study protocol was designed for a multicenter cohort including referral hospitals in Brazil and Mozambique. Newborns weighing 500-2500 g will be eligible for inclusion with the best GA available, considering the limited resources of low-income countries. Comparator-GA is based on reliable last menstrual period dating or ultrasound assessment before 24 weeks' gestation. Estimated GA at birth (Test-GA) will be calculated by applying a novel optoelectronic device to the newborn's skin over the sole. The average difference between Test-GA and Comparator-GA will be analyzed, as will the percentage of newborns who are correctly diagnosed as preterm or SGA. In addition, in a nested case–control study, the accuracy of skin reflection in the prediction of prematurity-related respiratory problems will be evaluated. The estimated required sample size is 298 newborns.

Results: Teams of health professionals were trained, and standard operating procedures were developed following the good practice guidelines for the clinical investigation of medical devices for human participants. The first recruitment started in March 2019 in Brazil. Data collection is planned to end in December 2020, and the results should be available in March 2021.

Conclusions: The results of this clinical study have the potential to validate a new device to easily assess postnatal GA, supporting SGA identification when pregnancy dating is unreliable or unknown.

Trial Registration: ReBec: RBR-33rnjf; http://www.ensaiosclinicos.gov.br/rg/RBR-33rnjf/

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KEYWORDS

prematurity; fetal growth restriction; childbirth; skin physiological phenomena; photomedicine; equipment and supplies

Introduction

Background

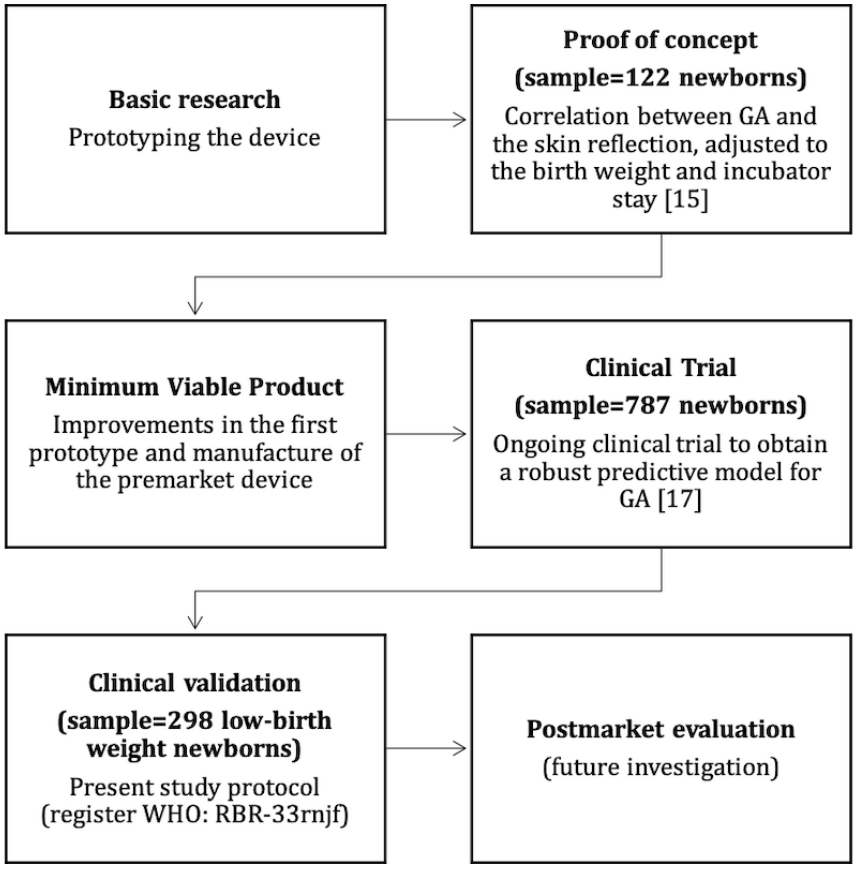
Low birth weight is associated with short- and long-term mortality and morbidity and is a predictor of chronic diseases in adulthood [1,2]. Small for gestational age (SGA) refers to a newborn with birth weight below the tenth percentile for gestational age (GA) and sex according to the expected standard growth curve [2]. Distinguishing between prematurity and SGA or both conditions in low-birth-weight newborns is critical to ensuring appropriate provision of care and has the potential to save lives [3,4]. Treatment of prematurity usually involves respiratory support and the administration of exogenous surfactant, to increase alveolar surface tension. Besides, most SGA newborns may have suffered from chronic intrauterine hypoxia due to placental oxygen delivery failure, and thus require specific support [5]. The diagnoses of prematurity and SGA depend heavily on a reliable GA estimation [6]. Although easy access to early obstetric ultrasonography has overcome many of the uncertainties related to pregnancy dating based on a woman's recollection of her last menstrual period [6,7], this practice is not widely available in low- and middle-income countries [8]. Pregnancy dating based on the last menstrual period is affected by memory recall, confusion caused by early pregnancy bleeding interpreted as menstruation, irregular menses, the effect of hormonal contraception and intrauterine devices, maternal chronic disease, and poor nutrition [9,10]. Apart from this, unequal access to technological solutions in health care challenges the agenda of sustainable development goals [11] and contributes to increased neonatal morbidity and mortality. The availability of an affordable and low-maintenance device that can accurately evaluate GA at birth has the potential to rationalize management decisions and avoid unnecessary interventions and their related costs, essential aspects of health care systems [12].

Prior Work

The optical properties of the skin's interaction with light can be evaluated by devices that emit and receive photons [13]. Variations in light scattering through the skin are believed to be associated with changes in skin thickness, the concentration of chromophores, and light wavelength [14]. A novel technology was developed to estimate GA at birth (Test-GA) by analyzing the photobiological properties of the newborn's skin in combination with clinical variables [15]. This noninvasive and nonionizing technology features a probe containing light emitters and receivers that is brought in contact with the skin over the sole. A mathematical algorithm provides an estimated GA within seconds, combining the skin reflection with clinical adjusters, such as birth weight and incubator stay [15].

The timeline of the new medical device development involves sequential steps [16], represented in Figure 1. The prototype of the device previously evaluated 115 newborns at 24-41 weeks' gestation with promising results [15]. After insights from this first clinical experiment published in 2017, the technology received improvements to mitigate external influences in the test, such as humidity, ambient light, and to ease the user handling. The current version is a small device, about the size of a pen, with an automated ability to measure skin reflection. To reduce examiner influence, the device now warns about errors of measurement. Clinical variables are presented in a digital screen immediately after the newborn skin assessment. Since February 2019, a clinical trial is taking place in 5 Brazilian hospitals to advance the GA prediction modeling, using a sample of 787 newborns [17]. The planned date of last enrollment is July 2020.

Figure 1. The development timeline of the preemie-test device. GA: gestational age.



Present Protocol of Research

This protocol gathers data from Brazil and Mozambique referral centers. This step represents the clinical validation of the prediction model established in the preceding clinical trials. It aims to validate an optimized version of the device in low-resource birth settings, using a data set obtained in different populations, before introducing it in the market. The analysis relies on real-world antenatal GA estimations obtained during pregnancy in which first-trimester ultrasound may not always be available or reliable. The primary hypothesis of this study is that photobiological properties of the skin measured by the device, and adjusted by clinical variables, will allow the accurate prediction of GA (Test-GA) in low-birth-weight newborns.

The primary objective of this study is to validate the preemie test statistical model for GA estimation at birth and its accuracy to detect prematurity in low-birth-weight newborns. The secondary objective is to evaluate whether there is an association between skin reflection and the occurrence of early respiratory complications.

Methods

Study Design

This protocol describes a multicenter prospective cohort study that aims to evaluate the ability of the preemie test device to estimate GA of low-birth-weight newborns. A nested case–control study will evaluate the relationship between the optical properties of the skin and newborn respiratory complications related to prematurity.

Study Settings, Ethics, and Dissemination

The study will be performed in the following hospitals: Hospital das Clínicas, Universidade Federal de Minas Gerais, and Hospital Sofia Feldman in Brazil; and in the Hospital Central de Maputo and Eduardo Mondlane University in Mozambique, all of which are referral centers for high-risk pregnancies and neonatal care. The University Research Council in Brazil acts as the coordinating center of this multicenter cooperation. Each local ethics review board will independently approve the study protocol. The ethical approval number is CAAE 91134218.4.0000.5149 in Brazil, and IRB00002657 in Mozambique. Parents will be asked to sign an informed consent form on behalf of the newborns as recommended by the Regulatory Bodies for Good Clinical Research Practice. The parents will retain the right to discontinue study participation at all times. The protocol of this clinical study is registered in the International Clinical Trials Registry Platform (RBR-33rnjf).

Data Sharing Statement

The authors intend to share the minimal anonymized data set necessary to replicate the study findings. Unidentified data and study-related documents will be accessible online to the researchers and regulatory agencies. The corresponding author will provide data access under reasonable request.

Patient and Public Involvement

A flyer with information on the relevance, aims, and procedures of this investigation will be distributed to parents of the newborns. Results will be disseminated through scientific publications, congress participation, and on the project website

(http://skinage.medicina.ufmg.br). All participants will be volunteers and will not receive any compensation or advantages.

Eligibility Criteria and Participant Timeline

A sequential enrollment of newborns will follow the inclusion of participants based on eligibility criteria until the sample size is achieved. The inclusion criteria are liveborn infants weighing 500-2499 g with GA information obtained using a qualified last menstrual period or obstetric ultrasound <24 weeks' gestation (Comparator-GA). Exclusion criteria are structural skin alterations or conditions that modify the skin, such as anhydramnios, hydrops, congenital skin diseases, and chorioamnionitis.

Table 1 illustrates the schedule of enrollment, test application, and endpoint measurement. The skin assessment will occur during the first 24 hours of age. The newborns will be followed up for 72 hours until discharge, held in hospital (for treatment-related purposes), or death, whichever occurs first, considered the study exit. The newborns will continue to receive standard assistance after the study follow-up according to settings, resources, and local staff definitions, whether during hospital admission or at hospital discharge or re-admission.

Table 1. Participant timeline of the study.

Study procedures	Before Test-GA	Test-GA, ≤24 hours old	72 hours old: discharged, held in hospital, or death
Enrollment 1: Prospective cohort study[a,b]	X		
Informed consent	X		
Taking of obstetric history	X		
Intervention: Test-GA		X	
Comparator: Best estimation of GA available		X	
Enrollment 2: Nested case–control study[c]			X
Assessments and analysis[d]			X

[a]Inclusion criteria are liveborn, Comparator-GA (reliable last menstrual period [18] or ultrasound assessment at <24 weeks' gestation [8]), birth weight (500-2499 g), and ≤24 hours old.

[b]Exclusion criteria are malformation with structural skin alterations and skin modifiers (eg, anhydramnios, hydrops, congenital skin diseases, chorioamnionitis).

[c]To determine eligibility criteria for paired allocation according to birth weight range to either the case group (TTN or RDS) or the control group (without TTN, RDS, tachypnea due to other reasons, or bloodstream infection).

[d]Neonatal outcomes including respiratory complications due to prematurity, neonatal intensive care unit admission, or ventilatory support

GA: gestational age; RDS: respiratory distress syndrome; TTN: transitory tachypnea of the newborn.

Within the study cohort, a secondary nested case–control study will include newborns with the following inclusion criteria: (1) for the case group, respiratory distress syndrome or transitory tachypnea of the newborn; (2) for the control group, newborns will be randomly selected with no respiratory diseases or manifestations by other conditions, paired by birth weight range: <1000 g, 1000-1499 g, or 1500-2499 g.

Intervention

The assessment with the device will occur as soon as possible after birth according to the detailed protocol of the skin assessment available online [19]. The device provides automatic data acquisition with minimum operator influence and stores values in an electronic database. No values will be displayed on the device screen, thereby blinding the users to the results obtained at the time of acquisition. Characteristics of the components, wavelength of the light emitter, and external acquisition for the metering process categorized the safety level of this medical device as Class II (noninvasive and medium risk) according to the regulatory agency in Brazil. The prototype unit of measurement and process of GA estimation are patented (Nos BR1020170235688 and CTIT-PN862, respectively) [20].

Training, Roles, and Monitoring

Teams of health professionals were trained and standard operating procedures were developed following the good practice guidelines for the clinical investigation of medical devices for human participants according to the International Organization for Standardization 14155:2011 [21] and the regulatory health agency's recommendations for the approval of medical devices [22]. The training occurred in September 2018 in Brazilian hospitals and in July 2019 in the Hospital Central de Maputo, Mozambique. Data collection and monitoring have been happening since then. All participating centers were visited by the study coordinator to qualify the clinical investigators for training in Good Clinical Research Practice, with attention paid to the requirements for validation of medical devices and the completion of at least 30 simulated examinations. Local research coordinators contributed to development of the study protocol and will supervise the data collection and record confidentiality.

Data Definition and Collection

Comparator-GA is calculated by obstetric data obtained at the time of enrollment. The requirements for establishing the best GA calculation (assessed by interviewing the mother) are based on the following:

- reliable last menstrual period dating, including certainty about last menstrual dating, regular menstrual cycles, no

contraceptives within 3 months of conception, and no abortion or delivery 2 months prior to conception [18]; OR
- ultrasound <24 weeks' gestation, considered reference for low-income countries as recommended by the World Health Organization (WHO) [8], even if the clinical information on last menstrual period is absent.

For data curation, pregnancy dating based on ultrasonography reports will be adjusted to Intergrowth 21 standards. Fetal crown–rump length [23] as well as femur length and head circumference will be used to recalculate GA [24]. When both ultrasound and reliable last menstrual period dating are available, correction will depend on whether there are discrepancies in excess of 5, 7, 10, or 14 days according to the identified GA at first assessment as recommended in ACOG Committee Opinion guideline number 700 (May 2017) [6].

Test-GA will be determined by statistical analysis according to signals stored in the device's processor and clinical data. For this, the GA modeling prediction is based on the result of another ongoing clinical trial (registration number RBR-3f5bm5). This study is taking place at 5 Brazilian centers with the analysis of the skin reflection and clinical data of 787 newborns, with 24-42 weeks of gestation, using strict rules of the crown–rump length ultrasound measurement for pregnancy dating [17]. We expect to establish the prediction model toward the end of the RBR-3f5bm5 clinical trial in September 2020.

Birth weight is the first measurement performed by the local staff during the first 24 hours of life. A digital scale for standardizing weighing is already present in all settings.

A double system of clinical data collection was implemented. Trained researchers will fill out paper-based formularies and an electronic interface. Original ultrasound and clinical information reports of the antenatal care will be scanned. A double-check data conference will adjust typos comparing original paper–based documents with the electronic clinical records before the statistical analysis. The system has been designed to avoid inconsistencies in typing data according to preset constraints of expected information. Recordkeeping and server backup will be performed according to informatics best practices. To guarantee anonymity, patient identification will only be accessible by the collaborating center coordinators. The data entry form is available in Multimedia Appendix 1.

Study Outcomes

Primary Outcomes

The primary endpoints will be differences between the Test-GA and Comparator-GA estimates and proportion of correct preterm newborn detections by the Test-GA at <37 weeks' gestation with a 1-week margin of error.

Secondary Outcomes

The secondary endpoint will be the proportion of correctly identified SGA newborns under the tenth percentile of GA according to Intergrowth 21 standards [25]. For this endpoint, the proportion of SGA newborns detected by the Test-GA will be compared with that detected by the Comparator-GA.

Others secondary endpoints in the case–control nested study will be the capacity of the Test-GA results to predict the following neonatal complications:

- Respiratory distress syndrome based on clinical and radiological findings and respiratory outcomes [26,27].
- Transitory tachypnea of the newborn based on clinical findings and respiratory outcomes [26].
- Ventilatory support due to pulmonary immaturity.
- Neonatal intensive care unit admission for pulmonary immaturity.

Sample Size

The sample size calculation is estimated based on the primary endpoint. Previous studies reported that Test-GA has 90%-100% accuracy at identifying premature newborns [28]. Using the inferior value of the confidence interval, an overall sample size of 298 newborns, including premature and term, is required for a robust evaluation of the device's accuracy as recommended by Flahault et al [29].

Statistical Analysis

To assess differences between the Test-GA and Comparator-GA estimates, average difference (with standard deviations), intraclass correlation coefficient, paired *t*-testing, and Bland–Altman scatter plots [30] will be used. To evaluate the accuracy of Test-GA in identifying preterm and SGA neonates, sensitivity, specificity (with 95% confidence intervals), and receiver operating characteristic curves and other discriminant analysis techniques will be calculated. The relationship between the measurement of the newborn's skin reflectance and newborn's respiratory complications due to immaturity will be evaluated using receiver operating characteristic curves, association tests, and risk ratios. The significance level for hypothesis tests will be 5%, together with 95% confidence intervals.

Results

The study began in November 2018 with the training of health professionals in the different participating centers. Then, standard operating procedures were developed following the good practice guidelines for the clinical investigation of medical devices for human participants. The first recruitment started in March 2019 in Brazil. Data collection is planned to end in December 2020, and the results should be available in March 2021.

Discussion

Strengths and Limitations

The novel device is expected to contribute to the risk evaluation of the newborn, adding clinical value anywhere a child is born without GA information, with focus on scenarios with a limited access to high-cost technology. GA is a trigger information in birth scenario for making decisions on the best delivery of care [6-8]. Actions for the preterm birth morbidity and mortality mitigation face the faith that GA estimate is a trivial task [31]. This study will provide evidence of the accuracy of an original method for GA calculation at birth that will be useful in settings

where GA is not routinely assessed by ultrasound during pregnancy [8]. Last menstrual period dating will be estimated by interview [18] and clinical document scanning to overcome the issue of absent ultrasound dating and memory recall inaccuracies. WHO recognizes 4-As medical devices as essential to the reliable functioning of health systems. For this proposal, the framework of development gathers Available, Accessible, Appropriate, and Affordable health technologies [32]. Effective and low-cost medical devices might be a contribution to mitigating the gap between well-equipped care settings and the needy ones for the reduction of preventable newborn deaths [8,33]. The emergent technology we test in this clinical study (ie, light scan to determine skin age) is included in the WHO compendium of innovative health technologies for low-resource settings due to the potential to improve health systems in these settings [33].

Regarding the step for a new technology validation, previous reports suggested alternative approaches for postnatal GA prediction, as well as for forecasting respiratory morbidity related to preterm birth prognosis. Using some elements of the newborn screening of congenital diseases associated with birth weight, a predicting mathematical model estimated the GA with high accuracy [34]. The accuracy analyses were useful to evaluate the performance of quantitative ultrasound texture assessment in order to predict neonatal respiratory morbidity [35].

This study will also evaluate an additional step beyond the prematurity identification based on the GA, the capacity of the technology to identify immediate respiratory complications due to immaturity in the newborn. The lung maturity of a newborn is related to a deficiency of surfactant, a phospholipid essential for alveolar stability, which is affected by the chronology of gestation and factors such as maternal disease [36]. This hypothesis is based on the synchronous development of fetal organs and tissues during gestation. We expect limitations in respiratory outcome evaluations, from the chest X-ray pattern and the improvement after surfactant therapy, as these resources are not always available in low-income settings. However, we believe that GA assessed by the new device could also help to identify those newborns who need respiratory support in the target population.

The results of this clinical study have the potential to validate a new device to easily assess postnatal GA, supporting SGA identification when pregnancy dating is unreliable or unknown. The quality of information about the chronology of pregnancy at birth is critical for the detection of premature and SGA newborns, differentiating small and sick infants from those who are small but healthy [6].

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Authors' Contributions

All authors contributed to the design of the study protocol. ZR and RR prepared the manuscript with regular inputs from RG, GV, JG, ST, and NM. RRS and DA-D-C made substantial contributions to study design, planned data collection, and prepared the team for good clinical practices. EC, JG, and ZR designed the database and data management systems, and the data analysis plan for the study.

Conflicts of Interest

Authors declare a patent deposit on behalf of the Universidade Federal de Minas Gerais and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil, http://www.fapemig.br/en/. The inventors were ZR and RG: BR1020170235688 (CTIT-PN862).

Multimedia Appendix 1
Data entry form.
[DOCX File , 1289 KB - resprot_v9i7e16477_app1.docx]

References

1. Castanys-Muñoz E, Kennedy K, Castañeda-Gutiérrez E, Forsyth S, Godfrey KM, Koletzko B, et al. Systematic review indicates postnatal growth in term infants born small-for-gestational-age being associated with later neurocognitive and

metabolic outcomes. Acta Paediatr 2017 Aug;106(8):1230-1238 [FREE Full text] [doi: 10.1111/apa.13868] [Medline: 28382722]
2. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 2004 Aug;191(2):481-487. [doi: 10.1016/j.ajog.2004.01.036] [Medline: 15343225]
3. Howson CP, Kinney MV, McDougall L, Lawn JE. Born Too Soon: Preterm birth matters. Reprod Health 2013 Nov 15;10:S1 (2013). [doi: 10.1186/1742-4755-10-s1-s1]
4. Figueras F, Savchev S, Triunfo S, Crovetto F, Gratacos E. An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome. Ultrasound Obstet Gynecol 2015 Jan 27;45(3):279-285. [doi: 10.1002/uog.14714]
5. Bhutta Z, Giuliani F, Haroon A, Knight H, Albernaz E, Batra M, et al. Standardisation of neonatal clinical practice. BJOG 2013 Jul 11;120:56-63. [doi: 10.1111/1471-0528.12312]
6. Committee Opinion No 700: Methods for Estimating the Due Date. Committee Opinion No 700: Methods for Estimating the Due Date. Obstet Gynecol 2017 May;129(5):e150-e154. [doi: 10.1097/aog.0000000000002046]
7. Lee AC, Panchal P, Folger L, Whelan H, Whelan R, Rosner B, et al. Diagnostic Accuracy of Neonatal Assessment for Gestational Age Determination: A Systematic Review. Pediatrics 2017 Dec;140(6):e20171423. [doi: 10.1542/peds.2017-1423] [Medline: 29150458]
8. Lee AC, Blencowe H, Lawn JE. Small babies, big numbers: global estimates of preterm birth. The Lancet Global Health 2019 Jan;7(1):e2-e3. [doi: 10.1016/S2214-109X(18)30484-4]
9. Wilcox AJ, Weinberg CR, Baird DD. Timing of Sexual Intercourse in Relation to Ovulation — Effects on the Probability of Conception, Survival of the Pregnancy, and Sex of the Baby. N Engl J Med 1995 Dec 07;333(23):1517-1521. [doi: 10.1056/nejm199512073332301]
10. Hoffman CS, Messer LC, Mendola P, Savitz DA, Herring AH, Hartmann KE. Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester. Paediatr Perinat Epidemiol 2008 Nov;22(6):587-596. [doi: 10.1111/j.1365-3016.2008.00965.x] [Medline: 19000297]
11. Gostin LO, Friedman EA. The Sustainable Development Goals: One-Health in the World's Development Agenda. JAMA 2015;314(24):2621-2622. [doi: 10.1001/jama.2015.16281] [Medline: 26660329]
12. World Health Organization. Regulatory system strengthening for medical products. World Health Assembly, 67. 2014. URL: https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_32-en.pdf [accessed 2020-06-09]
13. Anderson RR, Parrish JA. The optics of human skin. J Invest Dermatol 1981 Jul;77(1):13-19 [FREE Full text] [doi: 10.1111/1523-1747.ep12479191] [Medline: 7252245]
14. Lock-Andersen J, Therkildsen P, de Fine Olivarius F, Gniadecka M, Dahlstrøm K, Poulsen T, et al. Epidermal thickness, skin pigmentation and constitutive photosensitivity. Photodermatol Photoimmunol Photomed 1997 Aug;13(4):153-158. [doi: 10.1111/j.1600-0781.1997.tb00220.x] [Medline: 9453085]
15. Reis ZSN, Vitral GLN, de Souza IMF, Rego MAS, Guimaraes RN. Newborn skin reflection: Proof of concept for a new approach for predicting gestational age at birth. A cross-sectional study. PLoS One 2017;12(9):e0184734 [FREE Full text] [doi: 10.1371/journal.pone.0184734] [Medline: 28931040]
16. Medina LA, Kremer GEO, Wysk RA. Supporting medical device development: a standard product design process model. Journal of Engineering Design 2013 Feb;24(2):83-119. [doi: 10.1080/09544828.2012.676635]
17. Reis ZSN, Guimarães RN, Rego MAS, Maia de Castro Romanelli R, Gaspar JDS, Vitral GLN, et al. Prematurity detection evaluating interaction between the skin of the newborn and light: protocol for the preemie-test multicentre clinical trial in Brazilian hospitals to validate a new medical device. BMJ Open 2019 Mar 05;9(3):e027442. [doi: 10.1136/bmjopen-2018-027442]
18. Nguyen TH, Larsen T, Engholm G, Møller H. Increased adverse pregnancy outcomes with unreliable last menstruation. Obstet Gynecol 2000 Jun;95(6 Pt 1):867-873. [doi: 10.1016/s0029-7844(99)00639-0] [Medline: 10831983]
19. Reis Z, Vitral GLN, Guimarães RN, Aguiar RAPL, Romanelli RMC. The Preemie-Test for the Assessment of the Newborn Skin Maturity. URL: https://www.protocols.io/view/the-preemie-test-for-the-assessment-of-the-newborn-7ynhpve [accessed 2020-06-11]
20. Reis ZSN, Guimarães RN. Dispositivo para determinação da idade gestacional, processos e usos.: Brazil Patent Appl. BR1020160256020; 2016. URL: https://globaldossier.uspto.gov/#/result/publication/BR/102017023568/1
21. International Organization for Standardization. Clinical Investigation of Medical Devices for Human Subjects: Good Clinical Practice (ISO 14155:2011). 2011. URL: https://www.iso.org/standard/45557.html [accessed 2020-06-09]
22. Agência Nacional de Vigilância Sanitária, Ministério da Saúde. Resolução - RDC Nº 10, DE 9 DE Março DE 2010. 2015. URL: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0010_09_03_2010.html [accessed 2020-06-09]
23. Papageorghiou AT, Kennedy SH, Salomon LJ, Ohuma EO, Cheikh IL, Barros FC, International FetalNewborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown-rump length in the first trimester of pregnancy. Ultrasound Obstet Gynecol 2014 Dec;44(6):641-648 [FREE Full text] [doi: 10.1002/uog.13448] [Medline: 25044000]

24. Papageorghiou AT, Kemp B, Stones W, Ohuma EO, Kennedy SH, Purwar M, International FetalNewborn Growth Consortium for the 21st Century (INTERGROWTH-21st). Ultrasound-based gestational-age estimation in late pregnancy. Ultrasound Obstet Gynecol 2016 Dec;48(6):719-726 [FREE Full text] [doi: 10.1002/uog.15894] [Medline: 26924421]
25. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Ismail LC, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. The Lancet 2014 Sep;384(9946):869-879. [doi: 10.1016/S0140-6736(14)61490-2]
26. Liszewski MC, Stanescu AL, Phillips GS, Lee EY. Respiratory Distress in Neonates. Radiologic Clinics of North America 2017 Jul;55(4):629-644. [doi: 10.1016/j.rcl.2017.02.006]
27. Reuter S, Moser C, Baack M. Respiratory Distress in the Newborn. Pediatrics in Review 2014 Oct 01;35(10):417-429. [doi: 10.1542/pir.35-10-417]
28. Reis Z, Guimara˜es RN. Gestational age estimate using novel approaches based on the properties of the neonatal. Int J Gynecol Obstet 2018 Oct 11;143(53):158-542 [FREE Full text] [doi: 10.1002/ijgo.12582]
29. Flahault A, Cadilhac M, Thomas G. Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of Clinical Epidemiology 2005 Aug;58(8):859-862. [doi: 10.1016/j.jclinepi.2004.12.009]
30. Altman DG, Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. The Statistician 1983 Sep;32(3):307-317 [FREE Full text] [doi: 10.2307/2987937]
31. Reis ZSN, Gaspar JDS, Vitral GLN, Abrantes VB, de-Souza IMF, Moreira MTS, et al. Quality of Pregnancy Dating and Obstetric Interventions During Labor: Retrospective Database Analysis. JMIR Pediatr Parent 2020 Apr 15;3(1):e14109 [FREE Full text] [doi: 10.2196/14109] [Medline: 32293572]
32. World Health Organization. Medical Devices: Managing The Mismatch: An Outcome Of The Priority Medical Devices Project. Geneva: World Health Organization; 2010. URL: https://apps.who.int/iris/handle/10665/44407 [accessed 2020-06-09]
33. World Health Organization. WHO Compendium of Innovative Health Technologies for Low-Resource Settings, 2016-2017. Geneva: World Health Organization; 2018. URL: http://apps.who.int/iris [accessed 2020-06-09]
34. Wilson K, Hawken S, Murphy MSQ, Atkinson KM, Potter BK, Sprague A, et al. Postnatal Prediction of Gestational Age Using Newborn Fetal Hemoglobin Levels. EBioMedicine 2017 Feb;15:203-209 [FREE Full text] [doi: 10.1016/j.ebiom.2016.11.032] [Medline: 27939425]
35. Palacio M, Bonet-Carne E, Cobo T, Perez-Moreno A, Sabrià J, Richter J, Fetal Lung Texture Team. Prediction of neonatal respiratory morbidity by quantitative ultrasound lung texture analysis: a multicenter study. Am J Obstet Gynecol 2017 Aug;217(2):196.e1-196.e14 [FREE Full text] [doi: 10.1016/j.ajog.2017.03.016] [Medline: 28342715]
36. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000(2):CD000511. [doi: 10.1002/14651858.CD000511] [Medline: 10796380]

Abbreviations

GA: gestational age
RDS: respiratory distress syndrome
SGA: small for gestational age
TTN: transitory tachypnea of the newborn
WHO: World Health Organization

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Protocol

Internet-Delivered Cognitive Behavioral Therapy for Problematic Alcohol Use in a Workplace Setting: Protocol for Quantitative and Qualitative Evaluation of Feasibility and Outcomes

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Abstract

Background: Internet-based cognitive behavioral therapy (ICBT) for mental health issues has been successfully implemented in routine health care settings, and research indicates that ICBT can also be applied to decrease problematic alcohol use in workplace settings. However, studies investigating the feasibility of implementing ICBT in a workplace setting have been lacking.

Objective: The current study aims to investigate the feasibility of delivering ICBT for problematic alcohol use within an employee assistance program (EAP).

Methods: The study has a quantitative naturalistic design, quantitively comparing ICBT and face-to-face treatment, and allowing for qualitative interviews with employees and employers. Recruitment of participants follows a five-session in-person psychological assessment at an EAP regarding an employee's presumed problematic alcohol consumption. All assessed employees referred to ICBT or face-to-face treatment will be offered participation in the study. Interviews will be held with employees and their employer representatives following ICBT to elucidate both stakeholders' experience and perception of ICBT and its context. Outcome comparisons between ICBT and face-to-face treatment will be assessed quantitatively using a Reliable Change Index and analysis of variance. Thematic analysis and Grounded Theory will be used to analyze the interview material.

Results: The study is set to begin in April 2020 and to end in September 2021. The aim is to recruit up to 150 participants to the quantitative part of the study and 45 participants (15 employees and 30 employer representatives) to the qualitative part of the study.

Conclusions: The current study will provide knowledge that is lacking and urgently needed on how to implement ICBT for problematic alcohol use in a workplace setting.

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KEYWORDS

workplace setting; ICBT; alcohol; protocol; mental health; feasibility; CBT; cognitive behavioral therapy; intervention; workplace

Introduction

Problematic alcohol use causes harm both to the individual and to significant others, as well as generates considerable societal costs [1]. Alcohol consumption has declined in high-income countries, in parallel with substantial increases in lower-middle-income countries, although the overall prevalence of problematic alcohol use is still worryingly high [2]. In Sweden, 20% of men and 13% of women are considered hazardous drinkers [3]. Costs to society due to alcohol have been estimated to exceed one percent of the gross national product in high- and middle-income countries [1]. About half of all societal alcohol-related costs comprise loss of production at the workplace due to factors such as absence and reduced work capacity. Other common consequences of problematic alcohol use among employees are accidents, injuries, and increased healthcare costs [4-6]. The many negative consequences of hazardous alcohol use among employees are often presented as arguments for employers to implement alcohol prevention measures, capitalizing on the potential of the workplace to serve as a platform for primary, secondary, and tertiary prevention [7], since only one-fifth of individuals with alcohol use disorder seek treatment for their problems [8]. In Sweden, employment covers over two-thirds of the population between the ages of 15 and 74 [9]. Given that adults spend a large proportion of the day at the workplace, exposure to preventive interventions can be maximized [6]. To this end, employee assistance programs (EAP) have been developed to provide early and easily accessible help for employees [7].

Internet interventions in the form of internet-delivered cognitive behavior therapy (ICBT) have been studied for more than 20 years, and research shows that, for mood and anxiety disorders, they are often as effective as face-to-face psychotherapy [10]. Although some of these interventions have been developed as public health interventions, accessible to the general public, many have been developed as clinical alternatives to regular psychotherapy, and there are now several examples of clinics offering therapist-guided ICBT as an integrated part of routine health care [11]. Although there are fewer studies on ICBT for problematic alcohol use compared to ICBT for mood and anxiety disorders, the literature suggests that ICBT is also beneficial for this population [12]. A recent individual patient data meta-analysis demonstrated that internet interventions for problematic alcohol use are effective in reducing alcohol consumption, with guided interventions being more effective than unguided ones [13]. Studies on internet interventions for problematic alcohol use have mainly been conducted in general population samples [14], although there are successful examples of internet interventions conducted in clinical settings [15]. Further, a handful of studies have been conducted in workplace settings; for example, a six-week internet intervention specifically tailored to employees resulted in significant reductions in weekly standard units regardless of whether the employee received guidance from a psychologist or not [16], while a fully self-guided internet intervention with 62 modules, showed significant reductions over time in alcohol consumption. However, there were no significant differences in comparison to a self-help booklet [17]. Although these studies suggest that ICBT can be successfully used in a workplace setting, there are, to our knowledge, no studies on the feasibility of ICBT for employees at a site that provides EAP. Offering ICBT at sites using EAP has several advantages compared to face-to-face CBT. Since ICBT is available online anytime, the employee does not need to leave the workplace to receive treatment, thus reducing travel time and expenses associated with face-to-face treatment. If production loss due to treatment is cut, the employer might be more prone to pay for treatment and help the employee, particularly in smaller businesses and those not affiliated with an EAP provider [18]. Studies on the feasibility of ICBT at sites providing EAP, from both quantitative and qualitative perspectives, are needed in order to promote a greater understanding of how internet interventions might be provided in this context, possibly increasing the likelihood of successful dissemination of internet interventions in workplace settings in Sweden and elsewhere. Also, introducing ICBT at an EAP has several advantages compared to face-to-face treatment: lesser absenteeism from work due to reduced travel, less attrition from the more easily accessed treatment, and the employer might be more prone to cover treatment costs since cutting travel time means less production loss.

Objectives

This study aims to investigate the feasibility of providing ICBT for employees with problematic alcohol use at Alna Sweden, a provider of EAP in Sweden. In order to determine feasibility, both quantitative and qualitative approaches will be used. The quantitative aspect of the study concerns evaluating ICBT in comparison with face-to-face treatment. The following research questions will be addressed:

1. What changes in alcohol consumption and mental health occur over time among employees who receive ICBT or face-to-face treatment for problematic alcohol use?
2. In what way do alcohol and mental health outcomes differ between employees exposed to ICBT as compared to face-to-face treatment?

The following research questions will be investigated in qualitative interviews among those receiving ICBT:

1. The employee perspective:
   a. What does the employee perceive as positive or negative about receiving ICBT for problematic alcohol use?
   b. Does the employee experience any specific influence of the workplace setting on receiving ICBT; if so, how is it expressed?
2. The employer perspective:
   a. How does the employer perceive possible effects of ICBT on employee functioning in the workplace during and after treatment?
   b. To what extent does the employer perceive ICBT as a feasible intervention for problematic alcohol use in the workplace setting?

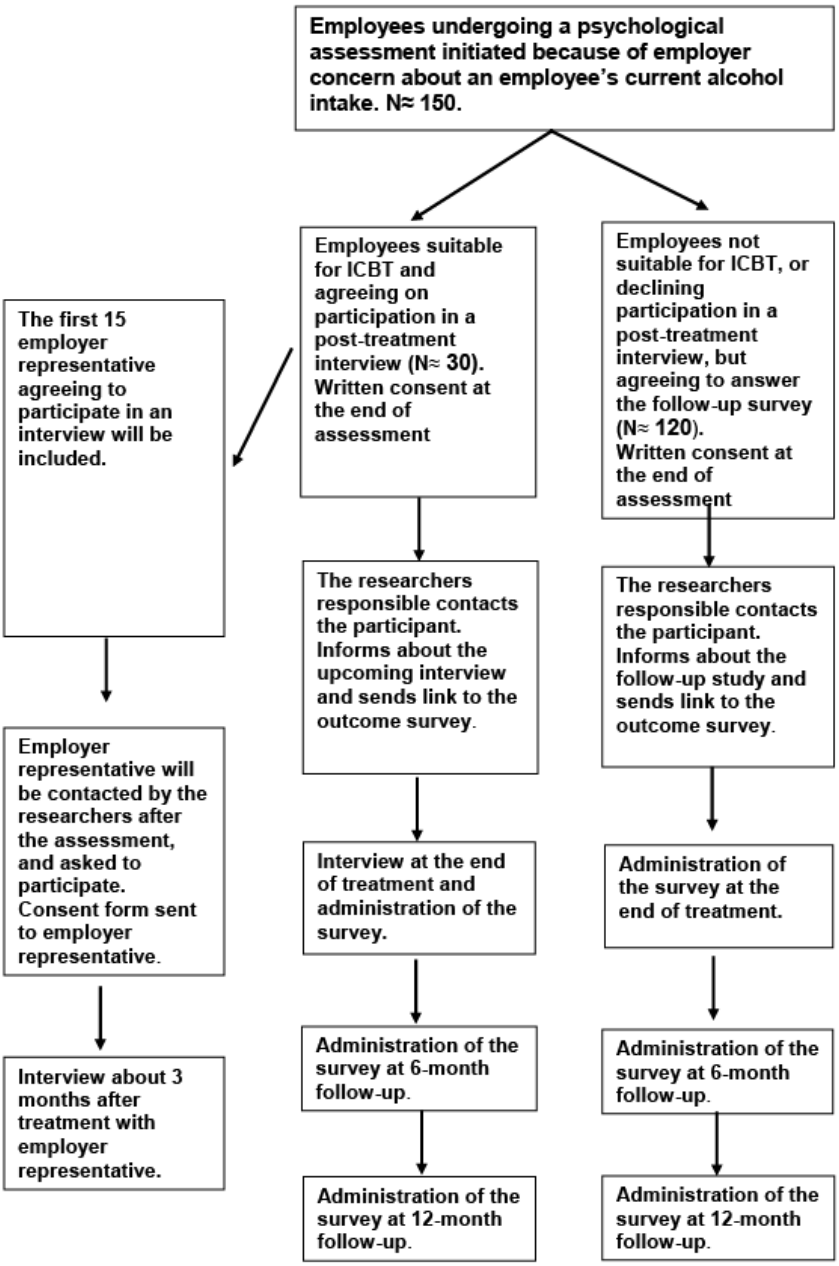
Methods

Overview

In the current research project, employees who undergo an assessment at Alna Sweden and who are referred to psychotherapy for problematic alcohol use will be offered participation in the quantitative naturalistic study. Those who are recommended ICBT will also be offered participation in a qualitative study (see Figure 1 for an overview).

During the study, Alna will offer ICBT administered by treatment providers (psychologists and psychotherapists) working for Alna. The providers will receive training in ICBT delivery before the start of the study.

Figure 1. Flowchart for recruitment procedure.



Treatment Setting

Alna Sweden is an organization that was founded in 1961 by the central trade unions and employers' organizations. The Alna EAP offers prevention, assessment, and treatment of alcohol and drug use problems among employees at organizations and companies all over Sweden. Alna conducts around 150 employee assessments per year. Usually, these assessments are initiated based on employer concern about an employee's current alcohol or drug use. The Alna assessment, which is carried out by licensed psychologists, consists of a comprehensive mapping of the employee's current problems and resources as well as an assessment of the employee's treatment needs. In the majority of cases, the assessment leads to recommendations for further treatment, usually in the form of 10-15 sessions of face-to-face CBT based on relapse prevention [19]. In the vast majority of cases, the employer chooses to follow the recommendation for referral to treatment and also finances the treatment. With Sweden being a sparsely populated country, employees who receive treatment often live at great geographical distances from

the nearest Alna Sweden treatment provider, resulting in significant workplace absenteeism in the form of travel time, aside from any absenteeism due to the actual session time.

Recruitment Procedure

Recruitment will take place following the Alna assessment of employee needs. The assessment begins with a session where the employee participates together with an employer representative (usually the manager or personnel from human resources). The focus of this initial session is on the employee's alcohol consumption, which has, in some way, affected work performance. The employee then undergoes a comprehensive psychological assessment over 3-4 subsequent sessions, which, in addition to alcohol consumption and other addictive behaviors, also covers mental and physical health, social relations, economic aspects, and motivation for change. Blood samples are taken in parallel to the psychological assessment.

Naturalistic Study

Towards the end of the assessment, all employees referred for psychological treatment (both face-to-face and ICBT) will be invited to participate in the study by the Alna assessment psychologist. If the employee consents, the appropriate treatment (face-to-face or ICBT) will be proposed for the employer. If the employer approves the cost, the employee will be referred to the chosen treatment, and written informed consent will be obtained at the last assessment. The participants will then be contacted by the researchers and be asked to respond to an online survey, accessed via an e-mail link.

Qualitative Study

In cases where the treatment provider considers ICBT a suitable for the employee, it will be presented as a treatment alternative requiring participation in post-treatment interviews. After that, the procedure is the same as in the naturalistic study. Hence, if the employer agrees to cover the cost for ICBT, and informed consent is collected, the participants will be contacted by the researchers and be asked to respond to the online survey, accessed via an e-mail link. The participants in the qualitative study will also receive information about the interview. These participants will be included in the naturalistic (responding to the survey) and the qualitative study (participating in the interviews). Up to 30 participants will be recruited for the qualitative study.

Eligibility

Inclusion Criteria

All employees who have undergone the Alna assessment and have been referred to face-to-face treatment or ICBT are eligible to participate in the naturalistic study. Those who have been referred to ICBT are also eligible for inclusion in the qualitative study. ICBT will only be available to employees agreeing to participate in the qualitative study. All employers with employees who have been referred to ICBT will be offered participation in the part of the qualitative study that concerns employers.

Exclusion Criteria

For the naturalistic study, exclusion criteria are drug use (information collected during the assessment) and suicidality (information collected during assessment and treatment).

Study Design

Naturalistic Study

All employees undergoing an Alna assessment and who are referred to psychological treatment, either regular face-to-face or ICBT, will be offered participation in the naturalistic study. Informed written consent will be provided at the final assessment session. Those who agree to participate will be provided a link to an online survey for pre-treatment measurement. A follow-up evaluation will take place immediately after completion of treatment (face-to-face psychotherapy or ICBT) and after another six and 12 months. Data collected at the start of the Alna assessment will be included retroactively, to allow evaluation of possible behavior changes during the assessment. Every employee that is offered treatment at Alna will be asked to participate in the study. Since Alna carries out approximately 150 assessments per year, the goal is to recruit all of the assessed employees. The recruitment process will go on for a year and a half if needed.

Qualitative Interview Study

In the qualitative study, employees referred to ICBT and their employers will be asked to participate in interviews, the former targeting the employee's experiences of ICBT and the later targeting employer perceptions. A total of 45 participants will be recruited, with up to 30 employees and up to 15 employer representatives. Semi-structured interviews will take place within two months following treatment conclusion. Interview guides will be based on the research objectives presented. A panel of researchers with a background in addiction and/or internet-delivered treatment will be asked to review the interview guides to ensure that the relevant areas are covered. The employees and employer representatives who agree to participate in the study will receive the interview questions in advance to be able to reflect on the topics included, thus, increasing the possibility of describing their experiences of treatment accurately. The interviews will mainly be conducted via telephone or video meetings since participants are recruited from all over Sweden, but may also be carried out face-to-face. All of the interviews will be recorded and transcribed verbatim.

Platform and Login Procedure for the Internet-Delivered Treatment

The web-based treatment platform that will be used to deliver ICBT will require a secure, two-factor identification bank-issued national e-identification login. This identification process ensures that the right person receives the treatment and that unauthorized persons cannot access the treatment or stored data.

Outcome Measures

Online Survey Questionnaires

Timeline Followback

A seven-day Timeline Followback questionnaire (TLFB) [20,21] will be used to measure preceding week alcohol consumption, as measured in standard units. TLFB can be used during different measures of time, eg, one or two weeks. The user has to specify how much alcohol he/she has consumed each day during the specified period.

Alcohol Use Disorders Identification Test

The Alcohol Use Disorders Identification Test (AUDIT) will be used to measure problematic alcohol use [22]. AUDIT has 10 items. The minimum score is 0, and the maximum score is 40. Eight of the questions have an item response range from 0 to 4, ranging from "Never" to "Almost every day." Two questions have an item response in three steps (0, 2, and 4), ranging from "Never" to "Almost every day." The instrument has a one-factor solution.

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 is a nine-item instrument that measures depression, including a final item measuring suicidal thoughts. The instrument has excellent internal consistency (Cronbach α=.89) and good test-retest correlation (.84) [23]. The instrument has a single-factor solution. The minimum score is 0, and the maximum is 27 points [23]. Item responses range from 0 ("Not at all") to 3 ("Nearly every day").

Generalized Anxiety Disorder-7

The Generalized Anxiety Disorder-7 is a short instrument designed to measure anxiety. Its internal consistency is excellent (Cronbach α=.92), and it has good test-retest reliability (intraclass correlation .83) [24]. The questionnaire contains seven questions and has a single-factor solution. It is a self-report measure, with a minimum score of 0 and a maximum score of 21 points, with an item range of 0 ("Not at all") to 3 ("Nearly every day") [24].

The World Health Organization-Five Well-Being Index

The World Health Organization-Five Well-Being Index is an internationally validated instrument focused on well-being, consisting of five items. Good internal consistency was observed in a Swedish general population sample (Cronbach α=.83). The minimum score is 0, and the maximum score is 15 [25]. Item responses range from 0 ("All of the time") to 3 ("Never").

Blood Samples

Blood samples for two alcohol markers, carbohydrate-deficient transferrin (CDT) and Phosphatidylethanol (B-PEth), will be taken at the start of the assessment and then once a month during treatment. B-PEth and CDT are indicators of alcohol intake. Both markers can detect low levels of alcohol intake. The diagnostic sensitivity was 99% for B-PEth, and for CDT, the sensitivity varied based on intake from 40% for low intake to 90% for very high intake. Specificity is very high for PEth (99%) and is lower for CDT [26].

Internet-Delivered Treatment

The ICBT program to be used in this study has been evaluated in previous studies in problematic alcohol use [27,28]. It is based on CBT and relapse prevention and includes 13 modules, each consisting of text and a worksheet with practical exercises. The program also includes an alcohol diary. In the current study, the program will be used together with guidance from a psychologist/psychotherapist both through written platform messages and via three video sessions. For details about treatment content, see [27].

Ethical Considerations

As with all psychological treatment, there is a small risk that participants in internet-delivered treatment deteriorate [29]. As an additional safety measure, employees participating in ICBT will respond to questions on suicidal ideation every week and will be monitored weekly for alcohol consumption and mood changes. Among those receiving ICBT, the therapist and employee will meet via weekly video sessions three times during treatment. If a participant deteriorates during ICBT, Alna will offer support face-to-face and via telephone and, if necessary, alternative treatment, and the employer will be informed, consistent with Alna's standard procedure. During the interviews, the participants will have the opportunity to reflect and reason about their process, which can create awareness of their treatment and perhaps lead to further positive effects of the treatment, which can, in turn, promote healthier behaviors and promote overall well-being.

Another ethical issue is data security. All databases containing personal data will be encrypted to minimize the risk of a breach. In addition, all the servers where data is stored will be encrypted and require a one-time password to be made available for analysis. Furthermore, data will be handled according to the European Union General Data Protection Regulation. All recorded interviews and associated transcripts will be stored on Stockholm University's encrypted database. The audio files will not contain identifying information (name, workplace, etc). Also, no names or social security numbers will be used in the online survey tool and database (Qualtrics) where self-assessment forms are completed; research participants will identify themselves with a code assigned to them by the researchers.

The issues stated above were addressed in an ethical application to the Swedish Ethical Review authority, which approved (Ref. 2019-04183).

Planned Analysis

Since the study has a mixed methods design, both quantitative and qualitative methods will be applied.

Quantitative Analysis

The quantitative data will be analyzed by using the Reliable Change Index, identifying clinically significant change on an individual level [30]. The significance level to calculate the Reliable Change Index was set at $P<.05$. Analysis of variance or generalized estimating equations will be used to analyze outcome data. Within- and between-group effect sizes also will be calculated.

Qualitative Analysis

The interviews will be carried out by the first and second authors. Interview length will vary between 45-60 minutes and will be transcribed ad verbatim. The participants will not be allowed to double-check and confirm the answers given in the interview. The main reason for this is that the participants will receive the questions before the interview and will thus be able to prepare answers. The interviews will be analyzed by using thematic analysis [31] and Grounded Theory [32,33]. Both the first and second authors will code the data. The transcripts from the employees and the employer representatives will be analyzed using inductive thematic analysis. The six steps proposed will be used in the analytic endeavor covering helping and hindering factors [31]. Grounded Theory will be applied to describe the process of attending ICBT in a workplace setting [34]. The coders will have an ongoing discussion about when saturation of the model is met. The focus will be to build a model mirroring the process that the different participants underwent during treatment.

Attrition Management

Employees who do not complete ICBT will be included in both the quantitative and qualitative analyses to ensure a robust analysis of the outcomes of the treatments. Also, face-to-face non-completers will be included in the analysis. Comparisons between baseline characteristics of the attrition group and treatment completers will be reported. If an employee participating in the qualitative part of the project declines to participate in the interview, an additional participant will be recruited.

Results

The results from this study will yield an understanding of ICBT in a workplace setting and of whether it could be helpful for employees; an understanding of the employer representative will also be gained.

Recruitment started in April 2020 and is expected to continue until September 2021. Manuscripts for publication will be drafted after that, one focusing on the quantitative outcomes and three focusing on the qualitative analyses. Quantitative results are expected to be submitted at the end of 2021, and the qualitative data will be submitted for publication in spring 2022.

Discussion

The workplace offers unique opportunities to reach people with problematic alcohol use. Internet-delivered treatment offered within the context of an EAP has several advantages over face-to-face treatment that could stand to benefit both employees (ie, reduced travel time and travel expenses, increased anonymity) and employers (ie, lower production loss). However, proper scientific evaluations are critical before this form of treatment can be meaningfully implemented into such organizations on a broader scale.

Strengths and Limitations

There are several strengths to the current project. First, although there are a handful of studies conducted on internet-delivered treatment in the workplace [16,17], this is the first study on internet-delivered treatment conducted within the context of an EAP. The current study will, therefore, have important implications for EAPs and similar organizations that are interested in implementing internet-delivered treatment, possibly as an alternative to face-to-face treatment. Further, this is also, to our knowledge, the first study to investigate the internet-delivered treatment of problematic alcohol use using a “mixed methods” approach, ie, applying both quantitative and qualitative methods. Thus, the quantitative evaluations of the treatment will be complemented with qualitative interviews, providing insight into the diversity of experiences and viewpoints among employees and employers involved in the internet-delivered treatment. Finally, outcomes of internet-delivered and face-to-face treatment will be compared in terms of drinking and overall mental health.

Some study limitations are apparent a priori. The quantitative study is a naturalistic one, and the results will indicate possible trends in results, but without the possibility of assessing causality. Also, the qualitative study will consist of a convenience sample from the quantitative cohort, possibly resulting in a biased selection. However, some of the helping and hindering factors associated with delivering ICBT in a workplace context can serve as a starting point for future studies and serve as a foundation for future implementation. Also, the participants might exaggerate treatment gains and positive aspects of the treatment since it is financed by their employer. Special attention will be focused on this aspect during the interviews. Attrition can be a problem in any study investigating treatment effects and is especially common in internet interventions. However, non-completers will be included in the analysis to ensure that attrition is taken into account when reporting outcomes. Another limitation to be taken into account is the probable effect of the assessment procedure. As the Alna assessment with its five separate sessions is quite comprehensive, a positive change in the employee’s consumption, mood, and other symptoms is expected to occur even before the start of treatment. As mentioned, a pre-assessment data collection point has been included to allow evaluation of the impact that the assessment might have.

Authors' Contributions

DF is the author of the study protocol. KS is a co-author of the study protocol and the project’s principal investigator. AHB and CS are co-authors, and CS and AHB developed the internet-delivered treatment modules. All authors actively participated in the design of the study and in shaping the final version of the protocol.

Conflicts of Interest

Author AHB is a co-owner of a company, TeleCoach AB, aiming to disseminate digital interventions. The company is not currently active. The study is funded by AFA Insurance, grant number 180008, and by The Swedish Retail Monopoly (Systembolaget) Research Council, grant number FO 2019-0025. Author AHB was supported in this current work by the Swedish Research Council (grant no. K2012-61P-22131-01-6). The development and evaluation of the ICBT intervention offered in this study were initially funded by an earlier AFA Insurance grant to author AHB, grant no. 110248. The funding bodies had no role in study design, data collection, analysis, data interpretation, or writing manuscripts.

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The remaining authors declare no conflict of interest.

References

1. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The Lancet 2009 Jun;373(9682):2223-2233. [doi: 10.1016/s0140-6736(09)60746-7]
2. Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. The Lancet 2019 Jun;393(10190):2493-2502. [doi: 10.1016/s0140-6736(18)32744-2]
3. Folkhälsomyndigheten. Folkhälsan i Sverige årsrapport 2018. Folkhälsomyndigheten 2018;Retrieved from Östersund [FREE Full text]
4. Ames GM, Grube JW, Moore RS. The relationship of drinking and hangovers to workplace problems: an empirical study. J. Stud. Alcohol 1997 Jan;58(1):37-47. [doi: 10.15288/jsa.1997.58.37]
5. Mangione TW, Howland J, Amick B, Cote J, Lee M, Bell N, et al. Employee drinking practices and work performance. J. Stud. Alcohol 1999 Mar;60(2):261-270. [doi: 10.15288/jsa.1999.60.261]
6. Pidd K. , Berry, J. G., Harrison, J. E., Roche, A. M., Driscoll, T. R., & Newson, R. S. Alcohol and work: Australian Institute of Health and Welfare. Canberra: Media and Publishing Unit; 2006:A.
7. Levy Merrick ES, Volpe-Vartanian J, Horgan CM, McCann B. Alcohol & Drug Abuse: Revisiting Employee Assistance Programs and Substance Use Problems in the Workplace: Key Issues and a Research Agenda. PS 2007 Oct;58(10):1262-1264. [doi: 10.1176/ps.2007.58.10.1262]
8. Rehm J, Allamani A, Elekes Z, Jakubczyk A, Manthey J, Probst C, et al. Alcohol dependence and treatment utilization in Europe – a representative cross-sectional study in primary care. BMC Fam Pract 2015 Jul 29;16(1). [doi: 10.1186/s12875-015-0308-8]
9. Labour Force Survey. Statistics Sweden. 2018. URL: https://www.scb.se/en/finding-statistics/statistics-by-subject-area/labour-market/labour-force-surveys/labour-force-surveys-lfs/ [accessed 2020-03-01]
10. Andersson G, Titov N, Dear BF, Rozental A, Carlbring P. Internet‐delivered psychological treatments: from innovation to implementation. World Psychiatry 2019 Jan 02;18(1):20-28. [doi: 10.1002/wps.20610]
11. Titov N, Dear B, Nielssen O, Staples L, Hadjistavropoulos H, Nugent M, et al. ICBT in routine care: A descriptive analysis of successful clinics in five countries. Internet Interv 2018 Sep;13:108-115 [FREE Full text] [doi: 10.1016/j.invent.2018.07.006] [Medline: 30206525]
12. Hadjistavropoulos HD, Mehta S, Wilhelms A, Keough MT, Sundström C. A systematic review of internet-delivered cognitive behavior therapy for alcohol misuse: study characteristics, program content and outcomes. Cognitive Behaviour Therapy 2019 Oct 10:1-20. [doi: 10.1080/16506073.2019.1663258]
13. Riper H, Hoogendoorn A, Cuijpers P, Karyotaki E, Boumparis N, Mira A, et al. Effectiveness and treatment moderators of internet interventions for adult problem drinking: An individual patient data meta-analysis of 19 randomised controlled trials. PLoS Med 2018 Dec 18;15(12):e1002714. [doi: 10.1371/journal.pmed.1002714]
14. Sundström C, Blankers M, Khadjesari Z. Computer-Based Interventions for Problematic Alcohol Use: a Review of Systematic Reviews. Int J Behav Med 2017 Oct;24(5):646-658 [FREE Full text] [doi: 10.1007/s12529-016-9601-8] [Medline: 27757844]
15. Kiluk BD, Nich C, Buck MB, Devore KA, Frankforter TL, LaPaglia DM, et al. Randomized Clinical Trial of Computerized and Clinician-Delivered CBT in Comparison With Standard Outpatient Treatment for Substance Use Disorders: Primary Within-Treatment and Follow-Up Outcomes. Am J Psychiatry 2018 Sep 01;175(9):853-863 [FREE Full text] [doi: 10.1176/appi.ajp.2018.17090978] [Medline: 29792052]
16. Boß L, Lehr D, Schaub MP, Paz Castro R, Riper H, Berking M, et al. Efficacy of a web-based intervention with and without guidance for employees with risky drinking: results of a three-arm randomized controlled trial. Addiction 2017 Dec 04;113(4):635-646 [FREE Full text] [doi: 10.1111/add.14085]

17. Brendryen H, Johansen A, Duckert F, Nesvåg S. A Pilot Randomized Controlled Trial of an Internet-Based Alcohol Intervention in a Workplace Setting. Int J Behav Med 2017 Oct;24(5):768-777. [doi: 10.1007/s12529-017-9665-0] [Medline: 28755326]
18. Berman A, Nielsen C, Ahlström J, Sundström C, Forsström D, Sundqvist K. Employer attitudes towards providing internet treatment to employees with problematic alcohol use. Manuscript in preparation 2021.
19. Marlatt GA, George WH. Relapse Prevention: Introduction and Overview of the Model. British journal of addiction 1984 Sep;79(3):261-273. [doi: 10.1111/j.1360-0443.1984.tb00274.x]
20. Hoeppner BB, Stout RL, Jackson KM, Barnett NP. How good is fine-grained Timeline Follow-back data? Comparing 30-day TLFB and repeated 7-day TLFB alcohol consumption reports on the person and daily level. Addictive Behaviors 2010 Dec;35(12):1138-1143. [doi: 10.1016/j.addbeh.2010.08.013]
21. Sobell L, Sobell MB. Timeline follow-back. In: Measuring alcohol consumption. New York: Springer; 1992:41-72.
22. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test (AUDIT) Manual: Guidelines for Use in Primary Care. Department of Mental Health and Substance Dependence. World Health Organization / Department of Mental Health and Substance Dependence. 2001. URL: https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=FF60C8E9D5BEECC63E56EB08FD875F09?sequence=1
23. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Intern Med 2001 Sep;16(9):606-613. [doi: 10.1046/j.1525-1497.2001.016009606.x]
24. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. Arch Intern Med 2006 May 22;166(10):1092. [doi: 10.1001/archinte.166.10.1092]
25. Löve J, Andersson L, Moore CD, Hensing G. Psychometric analysis of the Swedish translation of the WHO well-being index. Qual Life Res 2013 Jun 7;23(1):293-297. [doi: 10.1007/s11136-013-0447-0]
26. Aradottir S, Asanovska G, Gjerss S, Hansson P, Alling C. PHosphatidylethanol (PEth) concentrations in blood are correlated to reported alcohol intake in alcohol-dependent patients. Alcohol Alcohol 2006;41(4):431-437. [doi: 10.1093/alcalc/agl027] [Medline: 16624837]
27. Sundström C, Kraepelien M, Eék N, Fahlke C, Kaldo V, Berman AH. High-intensity therapist-guided internet-based cognitive behavior therapy for alcohol use disorder: a pilot study. BMC Psychiatry 2017 May 26;17(1). [doi: 10.1186/s12888-017-1355-6]
28. Sundström C, Eék N, Kraepelien M, Fahlke C, Gajecki M, Jakobson M, et al. High- versus low-intensity internet interventions for alcohol use disorders: results of a three-armed randomized controlled superiority trial. Addiction 2020 May;115(5):863-874. [doi: 10.1111/add.14871]
29. Rozental A, Boettcher J, Andersson G, Schmidt B, Carlbring P. Negative Effects of Internet Interventions: A Qualitative Content Analysis of Patients' Experiences with Treatments Delivered Online. Cognitive Behaviour Therapy 2015 Feb 23;44(3):223-236. [doi: 10.1080/16506073.2015.1008033]
30. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991 Feb;59(1):12-19. [doi: 10.1037//0022-006x.59.1.12] [Medline: 2002127]
31. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
32. Glaser BG, Strauss AL. Discovery of grounded theory: Strategies for qualitative research. Oxfordshire: Routledge; 2017.
33. Pidgeon N, Henwood K. Using grounded theory in psychological research. Oxfordshire: Taylor & Francis; 1997.
34. Corbin JM, Strauss A. Grounded theory research: Procedures, canons, and evaluative criteria. Qual Sociol 1990;13(1):3-21. [doi: 10.1007/bf00988593]

Abbreviations

B-PEth: Phosphatidylethanol
CBT: cognitive behavioral therapy
CDT: carbohydrate-deficient transferrin
EAP: employee assistance program
ICBT: internet-based cognitive behavioral therapy
TFLB: timeline followback

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Protocol

An Evaluation of Agreement of Breathing Rates Measured by a Novel Device, Manual Counting, and Other Techniques Used in Clinical Practice: Protocol for the Observational VENTILATE Study

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Abstract

Background: Respiratory rate (RR) is the most sensitive physiological observation to predict clinical deterioration on hospital wards, and poor clinical monitoring has been highlighted as a primary contributor to avoidable mortality. Patients in intensive care have their RR monitored continuously, but this equipment is rarely available on general hospital wards.

Objective: The primary objective is to assess the accuracy of the RespiraSense device in comparison with other methods currently used in clinical practice. The secondary objective is to assess the accuracy of the RespiraSense device in participants in different positions and when reading aloud.

Methods: A single-center, prospective observational study will investigate the agreement of the RespiraSense device as compared with other device measurements (capnography, electrocardiogram) and the current standard measurement of RR (manual counting by a trained health care professional). The different methods will be employed concurrently on the same participant as part of a single study visit.

Results: Recruitment to this study has not yet started as funding decisions are still pending. Therefore, results are not available at this stage. It is anticipated that the data required could be collected within 2 months of first recruitment to the study and data analysis completed within 6 months of the study start date.

Conclusions: The Evaluation of Agreement of Breathing Rates Measured by a Novel Device, Manual Counting, and Other Techniques Used in Clinical Practice (VENTILATE) study will provide further validation of the use of the RespiraSense device in subjects with abnormal respiratory rates.

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KEYWORDS

respiratory; monitoring; device; medical; piezoelectric; respiration; vital signs; telemetry; respiratory function tests; tachypnoea; bradypnoea

Introduction

Background

Patients admitted to acute hospitals undergo regular monitoring of their vital observations as a key component of their care. In 2007, the National Institute for Health and Clinical Excellence (NICE) produced recommendations for the measurement and recording of physiological observations [1] in response to several multicenter studies that revealed a significant lack of documentation of these observations.

Since the 1990s it has been recognized that the respiratory rate (RR) is the most sensitive physiological observation to predict cardiac arrest on hospital wards [2]. Despite this understanding, monitoring of the RR is demonstrated to be the most common vital sign to be inaccurately measured or recorded [3-5]. More recently, poor clinical monitoring has been highlighted as a primary contributor to avoidable mortality in English hospitals, implicated in 31% of preventable deaths [6].

The most commonly taught and used technique for measuring the RR is manually counting the number of breaths per minute a patient takes. A manual RR should be measured for a period of at least 1 minute, and the normal range for adults (aged 18 years and above) is 12 to 20 breaths per minute [7]. However, a recent cross-sectional study identified significant inaccuracies in the measurement of the RR among UK doctors and highlighted it as an important aspect of clinical care that is currently being poorly performed [8]. Manual counting among other clinical staff in routine practice has also been observed to be inaccurate, possibly due to the approach of counting breaths for 15 seconds and then multiplying by 4 to get breaths per minute, thus introducing error. This leads to somewhat of a self-fulfilling prophecy where expected inaccuracies in the measurement of the RR reduce the confidence of clinical staff at all levels in the usefulness of a reportedly abnormal RR [9].

Patients in intensive care are able to have their RR monitored accurately and continuously by capnography [10]. This type of monitoring can be invasive as it usually requires endotracheal intubation, and patients in other hospital areas do not usually need such an invasive intervention nor is the nursing staff likely to have access to such equipment. However, a systematic review has identified that the existing evidence for routine continuous noninvasive respiratory monitoring on general hospital wards is still inconclusive, and studies are lacking in methodological quality [11]. It recommends that future research should focus on technology explicitly suitable for general hospital wards and explore tailored alarm and treatment algorithms. The first step in such research is to explore the level of agreement between any new technology and current methods of establishing RR.

The significance of the accuracy of the RR recording cannot be overestimated [8,9]; it plays an important role in many clinical assessment systems, including the assessment of acute asthma and systemic inflammatory response syndrome and in the calculation of early warning scores [8]. This score alerts staff to any clinical deterioration and depending on the severity of the score, prompts a review from nursing or clinical staff.

The adoption of these scores has subsequently led to the development of multiple track and trigger information technology systems to allow early detection of patient deterioration [1]. Current systems rely on the manual assessment of the RR by a health care provider (HCP) and entry of data onto a live database in order for it to be processed. At Portsmouth Hospitals NHS Trust (PHT), the Vitalpac (System C) mobile clinical software system is used to record observations and calculates an early warning score (National Early Warning Score [NEWS]) depending on the degree of deviation from the normal range, with the total score proportionate to the overall level of risk (Table 1).

The RespiraSense device (PMD Solutions Ltd) was developed to improve the detection of changes in the RR in order to alert staff to out-of-range values that may be clinically significant. In a 48-patient investigation, data were collected to evaluate the difference in RR measurements between the developed RespiraSense device, electrocardiogram (ECG), and direct nursing observations [12]. A clinically relevant agreement between all RR measurements by the 3 different methods was demonstrated. However, few abnormal values were recorded in this investigation, and further research is required to ensure that the device works well to accurately measure the RR at values both higher and lower than the normal range.

Table 1. Escalation protocol for the deteriorating patient [8].

Vital sign	Score						
	3	2	1	0	1	2	3
Pulse	≤40	—	41-50	51-90	91-110	111-130	≥131 Unrecordable due to patient condition
Temperature (°C)	≤35	—	35.1-36	36.1-38	38.1-39	≥39	Unrecordable due to patient condition
BP[a] systolic (mm Hg)	≤90	91-100	101-110	111-219	—	—	≥220 Unrecordable due to patient condition
Respiratory rate (bpm)	≤8	—	9-11	12-20	—	21-24	≥25 or Unrecordable due to patient condition
AVPU[b]	—	—	—	Alert	—	—	Voice pain unresponsive[c]
SaO_2[d]	≤91	92-93	94-95	≥96 or Unrecordable because patient refused, equipment unavailable, other reason	—	—	Unrecordable due to patient condition
Inspired O_2	—	—	—	Air	—	Any supplemental O_2[e]	—

[a]BP: blood pressure.

[b]AVPU: alert, verbal, pain, unresponsive.

[c]If AVPU is V or C due to patient sedation, it will be charted as S and score 0 rather than 3.

[d]SaO_2: oxygen saturation.

[e]Note that "any supplemental O_2" applies to any supplemental oxygen the patient is receiving. It does not apply to patients who are on masks through which only air is being supplied (air delivery possible through tracheostomy, bilevel positive airway pressure or continuous positive airway pressure, for example).

Objectives

This research aims to assess the accuracy of the RespiraSense device in comparison with other methods (capnography, ECG) and standard care (manual RR monitoring) in healthy participants across a range of predetermined RRs. The information from this study will contribute to the evidence base on RespiraSense to enable its use in clinical practice.

This investigation will supplement the following research that has been conducted in demonstrating the efficacy and/or accuracy of RespiraSense in a clinical setting:

- "Evaluation of a continuous monitoring device in capturing respiratory rate compared to industry standard and gold standard" (Bangor, study reference PMD-CS-007)
- "Can respiratory rate predict the risk of deterioration of septic patients?" (Denmark, study reference PMD-CS-006ii)
- "A quality assurance study of respiratory rate measurements on obese patients with a novel monitoring technology" (Portsmouth, study reference PMD-CS-011)

The primary objective is to assess the agreement of the RespiraSense device with alternative methods of RR counting in healthy participants. Secondary objectives are to (1) explore whether the position of the participant has any effect on the agreement between the RespiraSense device readings and alternative methods of RR counting, (2) explore whether the agreement of the RespiraSense device and alternative RR methods alters when a participant is reading aloud, and (3) establish agreement between manual counting of the RR and retrospective adjudication of video. The exploratory objective is to record any dermatological effects of the device.

Methods

Patient Selection

Selection criteria for the study are shown in Textbox 1.

Textbox 1. Selection criteria.

Inclusion

- Male or female
- Aged ≥18 to 60 years
- Able and willing to provide written informed consent

Exclusion

- Any significant medical condition that may be worsened by the effect of slow or fast breathing
- Significant hearing impairment
- Skin unsuitable for device following assessment of skin fragility
- Unable to access left side of abdominal wall to attach device
- Neuromuscular disease and irregular chest wall movements
- Allergy to medical-grade skin adhesive
- Pregnant women during second and third trimester

Recruitment

Participants will be recruited from the population of staff and students currently working or on placement at PHT. Flyers advertising the study will be posted in communal areas where these groups are likely to congregate (eg, doctors' mess, ward break rooms). These flyers will contain contact details for the research team and advise those who are interested in taking part in the study to contact the research team.

Potential participants will be contacted by telephone and sent a participant information sheet (PIS). Participants who then wish to take part in the study will be invited to a screening visit. During this visit, the study will be explained, all questions answered, and participant will be screened against the inclusion and exclusion criteria. Additionally, the participant will be asked to breathe at a rate of 30 breaths per minute to assess their comfort while performing a study procedure. Those who are unable to maintain a rate of 30 breaths per minute for 2 minutes will be excluded from the study. Following this screening visit, the participant will be followed up with a telephone call to confirm that they are still willing to take part in the study.

Study Design

The study is a single-center, prospective observational study to investigate the agreement of the RespiraSense device compared with (1) other device measurements (capnography, ECG) and (2) the current standard measurement of RR (manual counting by a trained HCP). The different methods will be employed concurrently on the same participant as part of a single study visit.

Once participants have provided consent, the following baseline data will be collected:

- Demographics (age, sex)
- Height, weight (to calculate body mass index)
- Skin assessment at RespiraSense device attachment site (color, texture, uniformity of appearance, integrity). It will also be confirmed that the skin has no discoloration or rash, epidermal loss, blistering, edema, tears, maceration or folliculitis
- Oxygen saturation and pulse oximetry

Participants will be asked to wear a hospital gown and be positioned on an examination couch in the simulation suite. The RespiraSense device, a nasal cannula, and an ECG will be attached and a video recorder positioned to ensure the viewers of the video experience the same image as the HCP performing manual RR monitoring.

A computer-based metronome will be used to produce a repetitive tone at a set rate, which is played to each participant via headphones. The metronome has been produced for the study by the study sponsor team using Microsoft Visual Basic. The metronome rates will be generated using a random number generator program, and the order of the different rates will vary with each participant to ensure the rates are random. The participants will be asked to begin to inspire when each tone is heard and will be given a 20-second warm-up period during which time they will regulate their breathing pattern to match the rate of the tone they hear. Each participant will be asked to breathe at one value from each of the following categories for 2 minutes:

- ≤8 breaths per minute
- 9 to 11 breaths per minute
- 12 to 20 breaths per minute
- 21 to 24 breaths per minute
- 25 to 29 breaths per minute
- 30 to 35 breaths per minute

One rate will be randomly generated from within each of the 6 categories. Examples of potential sets are shown in Table 2.

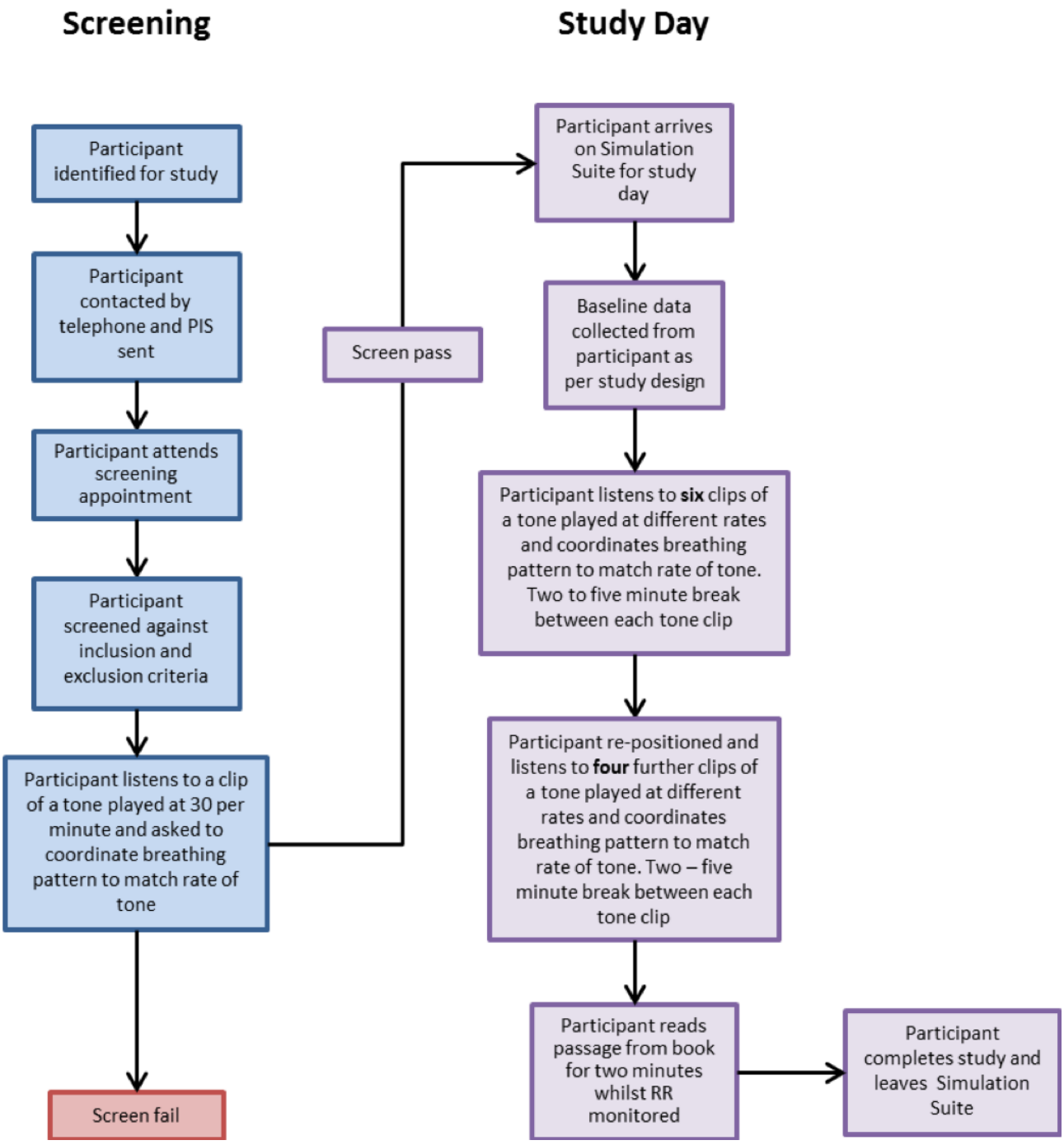
Table 2. Examples of possible sets of metronome rates to be used.

Participant	First rate	Second rate	Third rate	Fourth rate	Fifth rate	Sixth rate
Participant A	6	10	23	17	28	32
Participant B	5	14	9	22	31	26
Participant C	11	7	13	21	33	27

Each participant will be studied in the normal position (ie, sitting at 45 degrees on a couch) for 6 different metronome rates. They will then be studied in one of the three following additional positions for an additional 4 metronome rates: supine (flat on their back), left lateral decubitus (recovery) position, or sitting at 90 degrees (chair position).

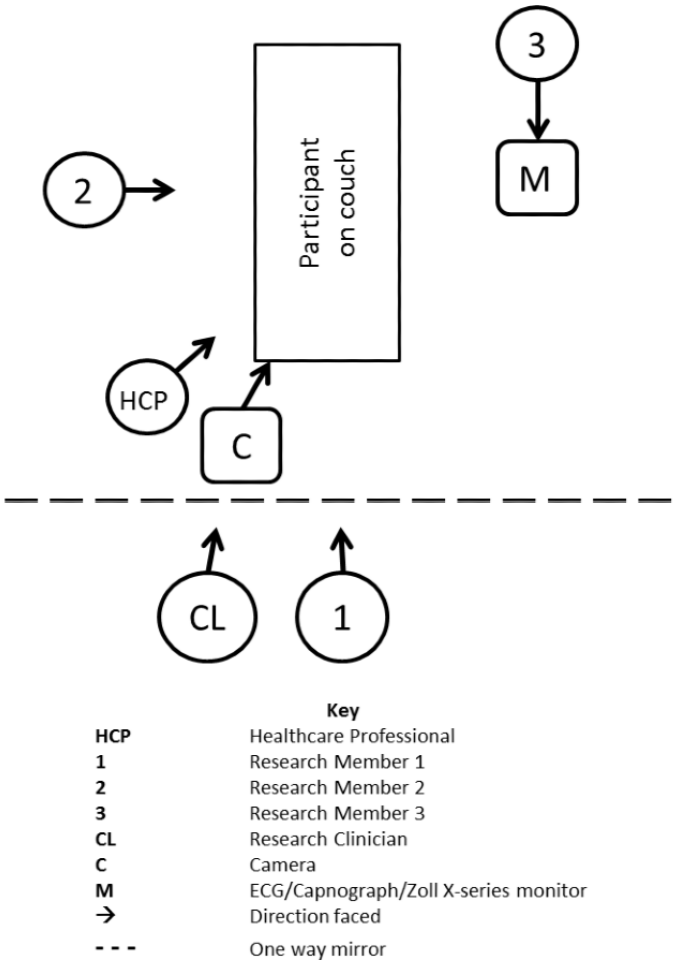
Each metronome rate will be maintained for 2 minutes with 2 to 5 minutes in between for transition (or longer if required by the participant to return to normal breathing rates). A full process flow of the requirements of each participant is shown in Figure 1.

Figure 1. Participant process flow diagram.



The research team will consist of 3 members; the layout of the study room is shown in Figure 2. Research member 1 will indicate to the participant when a new metronome rate starts. After the 20-second warm-up period, research member 1 will indicate the beginning of the 2-minute monitoring period by announcing the word Start. The HCP will start their manual counting of the participant's RR 30 seconds after the beginning of each new metronome rate; they will be informed by research member 1 when to start counting. They will be given 60 seconds to calculate the manual RR and will be informed by research member 1 when to stop counting. They will then record the RR in the case report form. The participant will continue to breathe at the specified rate for a further 30 seconds (for a total of 2 minutes) and will be informed by research member 1 when the metronome rate has finished so that they return to normal breathing.

Figure 2. Schematic of room layout.



Research member 3, blinded to the rates being played in each metronome rate, will record RR values for the continuous ECG and capnography monitoring and the X Series monitor (Zoll Medical Corp) at 60 and 120 seconds. Research member 2 will press the Start and Stop button on the RespiraSense device at the beginning and end of each 2-minute metronome rate and will record the start and stop time on the case report form.

Following the 10 metronome rates, the participant will then be asked to read a verse from a book for 2 minutes. During this time, their RR will be monitored in the same way as for the 10 metronome rates. Once the participant has finished reading aloud, the study will finish.

Throughout the study procedure, a video recording will be made using the portable Scotia Medical Observation and Training System (Scotia UK Plc), the audiovisual system installed in the simulation suite, which includes an in situ camera system (hardware and software).

Ethical Considerations

The study will not be initiated before the protocol and all study relevant material such as the informed consent forms and PIS have received approval/favorable opinion from the Health Research Authority and PHT Research and Development department. Any changes to protocol or relevant study documents will be approved by the sponsor. As RespiraSense is a CE-marked product being used within its intended purpose, regulatory approval is not necessary for this investigation.

Study Device

The RespiraSense device is based on piezoelectric technology. This technology is in the form of films that are an ultraflat laminated layer of piezo material. This material, when bent or strained, produces a small varying voltage difference. This monitor measures the motion of the chest and abdomen during respiratory effort to measure the RR directly from this motion. The stages of development of these devices are described as fully compliant devices to European Medical Device Standards.

RespiraSense is intended to act as a short-term monitoring device to assess RR over time by continuously recording, storing, and periodically transmitting RR data. It has no diagnostic function in this study.

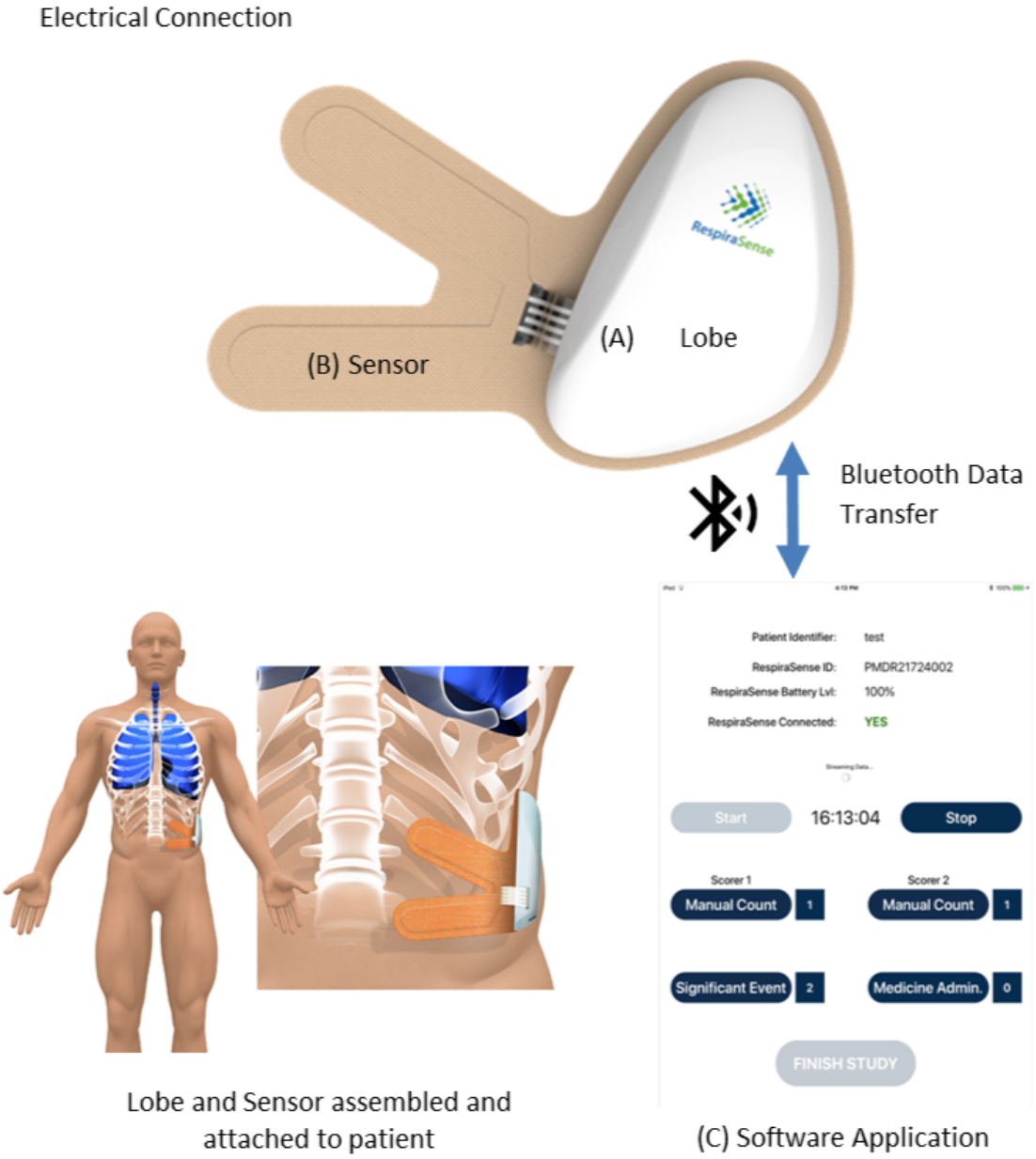
Traceability of each device's construction will be recorded in the company's Design History File. Each lobe used on a patient will be recorded in an accountability log with the patient study number. Sensors will not be retained once used and will be disposed of by the patient or the HCP.

During this investigation, the sensor will be attached to the patient's skin in the chest area using medical grade adhesive that has been tested to and complies with ISO10993 (Biological evaluation of medical devices). The RespiraSense device has the dimensions 100 mm × 55 mm × 15 mm, the sensor weighs 50 grams, and the following risks are listed:

- Class IIb medical device which conforms with IEC60601-1:A1:2012 and so no risk of electrical shock as no electrical current is passed through the body
- The device has low weight and as such is not considered to produce any skin ulcers
- The device will be adhered using medical grade tape which will minimize reaction to adhesive
- Wireless transmission of information conforms to standard Bluetooth communication protocols which are currently used in clinical settings
- Discomfort to the patient is considered minimum as the device in placed in a position where side-lying will not cause added pressure to the patient

The RespiraSense is a noninvasive, body-worn, cableless, battery-powered, respiration rate monitoring device. The system consists of 3 parts as shown in Figure 3: the lobe, sensor, and software application. This figure also shows the final assembled device attached to the patient.

Figure 3. RespiraSense device and data flow.



The system uses a specifically designed adhesive attachment accessory (sensor), which fixes the device to the patient's chest and contains piezo films that convert breathing motion into an electrical output. The lobe provides and communicates measurement values and technical information such as battery state wirelessly via Bluetooth to the software application hosted on a commercial off-the-shelf tablet computer. It can also provide basic information on activity status of the patient. The application and removal of the elements of the RespiraSense device, along with the maintenance of the device during operation, will be managed by a trained research nurse. Nasal end-tidal CO_2 monitoring will be performed using Microstream Smart CapnoLine Plus $EtCO_2$ sampling line (Zoll Medical Corp) with a disposable adult/intermediate nasal cannula. Data will be collected and automatically logged onto an SD card in the X Series monitor.

Data Transfer and Processing

Once the participant has completed the study, all data collected by the RespiraSense device will be uploaded to a secure cloud-based storage system from which it will be extracted and analyzed by the team at PMD Solutions Ltd. This data will be anonymized and linked to a specific subject ID number allocated during the study. No participant identifiable data will be transmitted to the team at PMD Solutions Ltd. The RespiraSense-calculated RRs for each participant will then be matched to the data collected by the other methods for analysis.

The study database and video recording files will be stored on secure Trust electronic file servers. The associated file name storing this data will be labeled with the title of the clinical investigation and linked to the subject ID number. This file will be saved for a minimum duration of 5 years and will be made available to national authorities upon request in writing. All digital and paper archives will conform to the requirements of the Data Protection Act (United Kingdom, 2018) which incorporates the standards laid out by the General Data Protection Regulation (European Union, 2016).

Statistical Analysis

The primary end point is the RR as measured by multiple methods. The primary objective of the analysis is to examine the agreement between the RespiraSense device and the other measurement methods for this end point. The mean difference between each pair of methods will be calculated with 95% confidence intervals. Variances will be tested for nonequality with an *F* test. The distributions of the differences will be examined with Bland-Altman plots. Limits of agreement (LoAs) and proportions of measurements outside the limits will be compared. If the differences between methods markedly increase with their mean, the analysis will be repeated with a log transformation of the measurements. A secondary analysis of agreement by participant position (45 degree sitting vs other positions) for each pair of methods will be performed using an analysis of variance.

Patient Population Size

We expect to have statistically significant data following the collection of 300 data sets (10 distinct measurements taken from 30 unique participants). This is based on statistical analysis of previous studies.

The precision of the mean and precision of the LoAs depend on the standard deviation of the differences. We use the value of 1.79 breaths per minute as the standard deviation reported in the Lee study [12] for comparison of RespiraSense and ECG and the same value for the comparison of RespiraSense with end-tidal capnography, this being regarded as more accurate than ECG. For comparison with an HCP, we use the value of 2.5 breaths per minute, also from the Lee study.

Table 3 shows the number required for different precisions of the mean difference using 95% confidence intervals. Table 4 shows the number required for different precisions of the LoA.

Table 3. Precision of mean at 95% confidence interval.

Breaths per minute	Precision of the mean	Standard error of the mean	N
1.79	1	0.51	13
1.79	0.5	0.26	50
1.79	0.4	0.2	77
1.79	0.3	0.15	137
1.79	0.25	0.13	197[a]
1.79	0.2	0.1	308
1.79	0.1	0.05	1231
2.5	1	0.51	25
2.5	0.5	0.26	97
2.5	0.4	0.2	151
2.5	0.3	0.15	267[a]
2.5	0.25	0.13	385
2.5	0.2	0.1	601
2.5	0.1	0.05	2401

[a]Precisions to be expected if 30 participants provide 10 data points each, allowing for a 10% loss of data.

Table 4. Precision of limits of agreement at 95% confidence interval.

Breaths per minute	Precision of LoA[a]	Standard error of LoA	N
1.79	1	0.51	37
1.79	0.5	0.26	148
1.79	0.4	0.2	231[b]
1.79	0.3	0.15	411
1.79	0.25	0.13	591
1.79	0.2	0.1	924
1.79	0.1	0.05	3693
2.5	1	0.51	73
2.5	0.6	0.31	201[b]
2.5	0.5	0.26	289
2.5	0.4	0.2	451
2.5	0.3	0.15	801
2.5	0.25	0.13	1153
2.5	0.2	0.1	1801
2.5	0.1	0.05	7203

[a]LoA: limits of agreement.

[b]Precisions to be expected if 30 participants provide 10 data points each, allowing for a 10% loss of data.

Feasibility Assessment

The feasibility of performing this study with data collected from participants in a single session is based on upon previous successful observational studies that have been performed by the research team at PHT. These include the Using the Inflammacheck Device to Measure the Level of Exhaled Breath Condensate Hydrogen Peroxide in Patients With Asthma and Chronic Obstructive Pulmonary Disease (EXHALE) pilot study [13] and a previous study validating the RespiraSense device in patients with a large body mass index [14].

Results

Recruitment to this study has not yet started as funding decisions are still pending. Therefore, results are not available at this

stage. It is anticipated that the data required could be collected within 2 months of first recruitment to the study and data analysis completed within 6 months of the study start date.

Discussion

Rationale for Study Design

The Evaluation of Agreement of Breathing Rates Measured by a Novel Device, Manual Counting, and Other Techniques Used in Clinical Practice (VENTILATE) study will test the accuracy of the RespiraSense device at the extremes of RR. The selection of randomized RRs from within defined categories allows these abnormal RRs to be compared with normal RRs without introducing variability in the participant or the HCP. Additionally, video recording of the study procedures allows for independent sampling and monitoring of the ability of the HCP to manually count the RR by another HCP.

We chose to use healthy volunteers without underlying cardiopulmonary disease. It was not deemed safe or appropriate to use patients exhibiting extremes of RR in an observational study of this type. It was decided that the safest way to observe the RRs of interest for the study would be for healthy volunteers to consciously breathe at a given rate.

There are multiple points of contact during the screening visit to minimize the chance that participants fail to complete the study procedures. In addition to the standard practice of providing a PIS and allowing the participant time to consider what will be required of them during the study, the participants will also experience one of the higher RRs that they will be asked to perform during the study day. We chose to do this with the aim of reducing the number of participants who are unable to complete all of the study procedures.

Although the risk of harm to study participants is low, further measures will be taken to mitigate these risks. The potential risk of feeling unwell after breathing at high or low RRs will be mitigated by allowing participants to rest for longer than scheduled or to stop the procedure entirely should they feel unable to continue. A clinician will be present throughout the study procedures and will be able to stop the study at their discretion if they feel it is not safe or would be inappropriate to continue.

Additionally, the randomization of the RRs selected will be prescreened to prevent high variability between tachypnoea and bradypnea in a short space of time. A set of rates will be randomly generated by a custom random number generator which is programmed to select a rate from within each of the categories listed in the Study Design section. Each set generated will be reviewed by a clinician involved in the study and assessed for extreme variability and overall safety. Sets that pass this screening will be saved and assigned randomly to participants at the time of the study data collection. Examples of an acceptable and unacceptable set are shown in Table 5.

Table 5. Acceptable and unacceptable respiratory rate sets.

	First rate	Second rate	Third rate	Fourth rate	Fifth rate	Sixth rate
Acceptable	6	10	23	17	28	32
Unacceptable	5	31[a]	22	14	26	9[a]

[a]Rates with extreme variability.

Another potential risk for participants using the RespiraSense device is the risk of reaction to the adhesive. This risk has two parts. The first is allergic reaction to the adhesive. This risk has been given a risk level of 2 by the PMD risk management team. A risk level of 2 indicates the risk has been reduced as low as possible. Although the severity of this potential risk is high, this occurrence has not been observed by PMD in any use of the device and has not been found in literature searches. This risk is mitigated by excluding volunteers who are allergic to medical-grade adhesive.

The second component is a mild reaction to the adhesive. This has been given a risk level of 2 by the PMD risk management team. A risk level of 2 indicates the risk has been reduced as low as possible. This risk is of low severity (mild reaction/discomfort) and moderate occurrence level. This risk is mitigated by excluding volunteers based on a skin fragility assessment. It is also possible that mild irritation that will not require medical intervention may be experienced for patients on oral steroids.

The procedures will be carried out in the simulation suite in the Learning and Development department which is located within the Resuscitation Department of PHT, and an experienced member of the resuscitation team will always be present. If a participant should become unwell as a result of the procedures, they will be withdrawn from the study and assessed by clinical team, and subsequently care will be escalated as appropriate.

The outputs of the RespiraSense sensor will not be used to assist any clinical decision, so there are no risks associated with use of the data collected with the device in this study.

Limitations

The primary limitation to this study is the awareness from all participants that they are being monitored. This may alter the behavior of the participant and subsequently influence the data collected from them, known as the Hawthorne effect. The most likely influence that is expected to be seen is a change in the method of manual RR counting performed by the HCP. There is a large degree of variability in clinical practice when counting the RR. The awareness of being observed has the potential to encourage those who would use a method involving a shorter count and multiplication to employ a full count for 60 seconds. This will reduce the accuracy of the comparison between the RespiraSense device and current clinical practice.

Conclusions

The VENTILATE study will provide further validation of the use of the RespiraSense device in subjects with abnormal

respiratory rates. It will assess the device's ability to measure abnormal RRs and compare with multiple other techniques used in various aspects of clinical practice. The results provided will help to guide the usefulness of the device in clinical practice in the future.

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Authors' Contributions

MTJ is responsible for drafting this article. EH is responsible for the study design and protocol, contributed to drafting this article, and is the proposed principal investigator. CF contributed significantly to the protocol development and study design. PM is responsible for the development of the computer-based metronome and random number generator and contributed to the protocol and study design. GS, NS, LT, EW, MW, TB, JG, DL, SB, MR, JW, and JL contributed to the protocol and study design. PB and MA are responsible for the statistical oversight of the protocol and study design. MC is responsible for the study database development and contributed to the protocol and study design. AJC contributed to the protocol and study design and is the proposed chief investigator for the study.

Conflicts of Interest

None declared.

References

1. NICE. Acutely ill patients in hospital: recognition of and response to acute illness in adults in hospital. NICE Clin Guidel 2007 Jul;50:1-107. [Medline: 21204323]
2. Fieselmann JF, Hendryx MS, Helms CM, Wakefield DS. Respiratory rate predicts cardiopulmonary arrest for internal medicine inpatients. J Gen Intern Med 1993 Jul;8(7):354-360. [Medline: 8410395]
3. Badawy J, Nguyen OK, Clark C, Halm EA, Makam AN. Is everyone really breathing 20 times a minute? Assessing epidemiology and variation in recorded respiratory rate in hospitalised adults. BMJ Qual Saf 2017 Oct;26(10):832-836 [FREE Full text] [doi: 10.1136/bmjqs-2017-006671] [Medline: 28652259]
4. Jonsson T, Jonsdottir H, Möller AD, Baldursdottir L. Nursing documentation prior to emergency admissions to the intensive care unit. Nurs Crit Care 2011;16(4):164-169. [doi: 10.1111/j.1478-5153.2011.00427.x] [Medline: 21651656]
5. Edmonds ZV, Mower WR, Lovato LM, Lomeli R. The reliability of vital sign measurements. Ann Emerg Med 2002 Mar;39(3):233-237. [Medline: 11867974]
6. Hogan H, Healey F, Neale G, Thomson R, Black N, Vincent C. Learning from preventable deaths: exploring case record reviewers' narratives using change analysis. J R Soc Med 2014 Apr 29;107(9):365-375. [doi: 10.1177/0141076814532394]
7. Moore T. Respiratory assessment in adults. Nurs Stand 2007;21(49):48-56. [doi: 10.7748/ns2007.08.21.49.48.c4605] [Medline: 17844906]
8. Philip K, Pack E, Cambiano V, Rollmann H, Weil S, O'Beirne J. The accuracy of respiratory rate assessment by doctors in a London teaching hospital: a cross-sectional study. J Clin Monit Comput 2015 Aug;29(4):455-460 [FREE Full text] [doi: 10.1007/s10877-014-9621-3] [Medline: 25273624]
9. Philip K, Richardson R, Cohen M. Staff perceptions of respiratory rate measurement in a general hospital. Br J Nurs 2013;22(10):570-574. [doi: 10.12968/bjon.2013.22.10.570] [Medline: 23752455]
10. Subbe CP, Kinsella S. Continuous monitoring of respiratory rate in emergency admissions: evaluation of the RespiraSense sensor in acute care compared to the industry standard and gold standard. Sensors (Basel) 2018 Aug 17;18(8) [FREE Full text] [doi: 10.3390/s18082700] [Medline: 30126085]
11. van Loon K, van Zaane B, Bosch EJ, Kalkman CJ, Peelen LM. Non-invasive continuous respiratory monitoring on general hospital wards: a systematic review. PLoS One 2015;10(12):e0144626 [FREE Full text] [doi: 10.1371/journal.pone.0144626] [Medline: 26658343]
12. Lee PJ. Clinical evaluation of a novel respiratory rate monitor. J Clin Monit Comput 2016 Apr;30(2):175-183. [doi: 10.1007/s10877-015-9697-4] [Medline: 25900144]
13. Neville D, Fogg C, Brown T, Jones T, Lanning E, Bassett P, et al. Using the Inflammacheck device to measure the level of exhaled breath condensate hydrogen peroxide in patients with asthma and chronic obstructive pulmonary disease (the EXHALE pilot study): protocol for a cross-sectional feasibility study. JMIR Res Protoc 2018 Jan 30;7(1):e25 [FREE Full text] [doi: 10.2196/resprot.8768] [Medline: 29382628]
14. Kinsella AL. A quality assurance study of respiratory rate measurements on obese patients with a novel monitoring technology. 2017. URL: https://clinicaltrials.gov/ct2/show/record/NCT03306537 [accessed 2019-12-23]

Abbreviations

ECG: electrocardiogram
EXHALE: Using the Inflammacheck Device to Measure the Level of Exhaled Breath Condensate Hydrogen Peroxide in Patients With Asthma and Chronic Obstructive Pulmonary Disease pilot study
HCP: health care provider
LoA: limit of agreement
NEWS: National Early Warning Score
NICE: National Institute for Clinical Excellence
PHT: Portsmouth Hospitals NHS Trust
PIS: participant information sheets
RR: respiratory rate
VENTILATE: Evaluation of Agreement of Breathing Rates Measured by a Novel Device, Manual Counting, and Other Techniques Used in Clinical Practice

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Protocol

TeleWound Practice Within the Veterans Health Administration: Protocol for a Mixed Methods Program Evaluation

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Abstract

Background: Chronic wounds, such as pressure injuries and diabetic foot ulcers, are a significant predictor of mortality. Veterans who reside in rural areas often have difficulty accessing care for their wounds. TeleWound Practice (TWP), a coordinated effort to incorporate telehealth into the provision of specialty care for patients with skin wounds, has the potential to increase access to wound care by allowing veterans to receive this care at nearby outpatient clinics or in their homes. The Veterans Health Administration (VA) is championing the rollout of the TWP, starting with regional implementation.

Objective: This paper aims to describe the protocol for a mixed-methods program evaluation to assess the implementation and outcomes of TWP in VA.

Methods: We are conducting a mixed-methods evaluation of 4 VA medical centers and their community-based outpatient clinics that are participating in the initial implementation of the TWP. Data will be collected from veterans, VA health care team members, and other key stakeholders (eg, clinical leadership). We will use qualitative methods (ie, semistructured interviews), site visits, and quantitative methods (ie, surveys, national VA administrative databases) to assess the process and reach of TWP implementation and its impact on veterans' clinical outcomes and travel burdens and costs.

Results: This program evaluation was funded in October 2019 as a Partnered Evaluation Initiative by the US Department of Veterans Affairs, Diffusion of Excellence Office, and Office of Research and Development, Health Services Research and Development Service, Quality Enhancement Research Initiative Program (PEC 19-310).

Conclusions: Evaluation of the TWP will identify barriers and solutions to TeleWound implementation in a small number of sites that can be used to inform successful rollout of the TWP nationally. Our evaluation work will inform future efforts to scale up the TWP across VA and optimize reach of the program to veterans across the nation.

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KEYWORDS

implementation; telehealth; wound care; veteran; protocol; wound; outcome

Introduction

Telehealth and Wound Care

Chronic skin wounds are a substantial health problem among veterans. Research has shown that within veteran cohorts, wounds are a more significant predictor of mortality than coronary artery disease, peripheral arterial disease, or stroke [1]. Veterans who reside in rural areas receive less specialty care services than their urban-dwelling counterparts [2,3] due to transportation-related and time-related barriers [4], indicating that there may be a gap between those who need wound care and those who receive it. As such, efforts are needed to improve access to specialty wound care services, particularly for veterans who reside in rural areas.

One strategy for improving access to care is to incorporate telehealth technologies into health care service delivery. Telehealth programs offered within the Veterans Health Administration (VA) have shown great promise in improving care delivery and outcomes among veterans. For example, receiving telehealth services has been associated with decreased health care use and inpatient length of stay; improvements in quality of life, satisfaction, and clinical outcomes; and reduced health care costs [5-8].

Specific to wound care, recent evidence supports the utility of incorporating telehealth into the delivery of wound care services, noting positive impacts such as reduced wound healing time, fewer adverse events, reduced travel costs, and enhanced ability of nursing staff to conduct comprehensive care [9-11]. The integration of telehealth and wound care may be particularly impactful within VA, where improving access to care, particularly access to specialty care services, for veterans living in rural and highly rural areas can be challenging. These challenges are due in large part to the fact that these veterans must often travel great distances to reach their nearest VA facility. Incorporating telehealth technology into wound care services provides a means to deliver care closer to (or even in) veterans' homes. Within this context, VA's TeleWound Practice (TWP) emerged.

The Origins of VA's TeleWound Practice

TWP encompasses a coordinated effort to incorporate telehealth technology into the delivery of specialty wound care services. This process can be asynchronous, such as taking a picture of a patient's wound and sending it to a wound care specialist for review, referred to as store-and-forward telehealth (SFT), or synchronous, such as real-time video visits in which the patient is either in their home or a VA community-based outpatient clinic (CBOC) and has a video visit with a wound care specialist at a main VA hospital facility using clinical video telehealth (CVT) or VA Video Connect (VVC). Compared with traditional in-person clinic visits, TWP visits may result in decreased travel burden and cost, more flexible scheduling, and a greater likelihood of seeing the provider best matched to veterans' needs. A potential advantage to the health care system is the more efficient use of scarce resources (eg, highly trained specialists). Additionally, TWP encompasses standardized care team member training and clinical documentation across the system, as well as an emphasis on interprofessional stakeholder collaboration.

Within VA, the TWP program originated at a VA medical center that serves a large number of veterans who live in rural or highly rural areas. The program was highly successful at this facility, decreasing patient travel burden related to wound care and eliciting high levels of patient satisfaction. Because of this early and encouraging success, the TWP was selected by VA for widescale rollout, beginning with regional-level implementation.

The regional implementation of TWP will leverage a multicomponent, facilitation-based implementation strategy. Components of the implementation strategy include (1) identifying a clinical champion at each facility to support local rollout of the TWP program; (2) facilitating recurring virtual meetings (akin to a learning collaborative) to engage key stakeholders, share lessons learned, and discuss strategies for overcoming barriers; and (3) deploying necessary training to staff. Through the program evaluation described here, VA national operations program offices have partnered with VA researchers to evaluate the TWP program implementation process and outcomes. Findings from this evaluation will be used to inform further rollout of the program nationally.

Objective

This protocol represents the real-world application of evidence-based implementation science principles in a large learning health care system and the collaboration between operations and researchers to conduct program evaluations in an effort to improve widescale implementation of evidence-based interventions and in turn, improve patient care.

Evaluation Aims

The proposed aims of our evaluation are to (1) evaluate the implementation process of the TWP program regional rollout, (2) assess the impact of the TWP on clinical outcomes related to wound care, and (3) assess the impact of the TWP on health care system outcomes related to wound care.

Methods

Conceptual Framework

To formulate our evaluation plan, we drew from a conceptual model frequently used in eHealth–related research and program evaluation, the Practical, Robust Implementation and Sustainability Model (PRISM) [12,13].

PRISM has 4 major domains: the intervention, the intervention recipients (eg, patients, clinical team members), the implementation and sustainability infrastructure, and the broader environment [12,13]. By using PRISM to guide our evaluation efforts, we will be able to account for the different stakeholders of the TWP, their perspectives on the intervention being implemented, and other characteristics that could influence implementation efforts.

PRISM outcome measures follow the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework [12,13]. RE-AIM evaluates implementation processes and outcomes along several dimensions, including reach,

effectiveness, adoption, implementation, and maintenance of practices and results over time [12,14-17]. Our evaluation team will use PRISM as a guide by which to frame our evaluation efforts.

Operation Partners

The TWP program evaluation will be facilitated by our partnerships with several national-level VA operations program offices. These partners include VA's Diffusion of Excellence (DOE) office, which is leading the implementation efforts, VA's National Podiatry Office, VA's National Spinal Cord Injuries and Disorders Program Office, the VA Office of Nursing Services, and the Office of Connected Care – Telehealth Services. Each office has a vested interest in the success of the TWP program and a unique role in supporting its implementation.

Design and Data Sources

Our team will use a mixed-methods assessment to achieve our evaluation aims. The evaluation plan includes a combination of site visits, semistructured interviews, surveys, and analysis of VA administrative data to evaluate the TWP implementation process and impact on outcomes from the perspective of multiple stakeholders.

Setting

The TWP program is being implemented in 4 VA medical centers that are part of 1 VA regional network (and select CBOCs, engaged at each center's discretion).

Participants

Stakeholders include facility leadership, health care team members (ie, clinic managers, telehealth staff, and providers/wound care specialists), and veterans who receive TWP care from the participating VA medical centers and their CBOCs, as appropriate.

Implementation Readiness

To prepare for the evaluation, our operations partners collected implementation readiness and preliminary process data. The preliminary process data were collected by DOE leadership at a TWP kick-off meeting hosted by the DOE and collaborating operational partners in the summer of 2019. These preliminary data were shared with the evaluation team. Kick-off meeting attendees (TWP site representatives) completed a readiness tool gauging their ability to implement TWP care.

Our evaluation team followed up with the collection of additional implementation readiness data via telephone with TWP clinical champions at each implementation site. Data collected from each site's clinical champions included when the site began providing TeleWound care, the status of equipment (eg, 3-dimensional [3D] cameras), the training of staff, and the extent of the program, including which clinics and CBOCs were involved and what types of telehealth they were providing (eg, SFT, CVT, VVC). Because the implementation timelines differed across the 4 sites, we felt it was particularly important to document the date that each of these implementation milestones was reached to ensure that we will be able to accurately track implementation progress and program outcomes moving forward. In addition, we plan to conduct periodic check-ins via telephone calls with the implementation sites to monitor implementation progress.

Planned Data Collection

Administrative Data

Data on patient-level and system-level outcomes and patient characteristics will be obtained from national VA administrative databases housed in the VA Corporate Data Warehouse (CDW). CDW data are refreshed nightly, allowing for real-time monitoring of patient-level health and utilization information. We will obtain the following patient characteristics from the CDW: demographics (age, gender, marital status, race, income), diagnosis, number of outpatient encounters, number of inpatient admissions, VA enrollment priority group, rurality of residence, and provider location and specialty. We will obtain the following utilization data on a monthly basis: number of veterans who had a TeleWound encounter, number of TeleWound encounters by clinic and location, type of telehealth visit, and visit diagnoses. To measure the impact of the TWP on patient travel cost and burden, we will assess travel costs to receive wound care. Travel costs will be estimated using the distance from veterans' homes to the VA health care facilities where they received wound care and the Internal Revenue Service standard business reimbursement rates for travel by private automobile. Distances will be estimated based on veterans' and facilities' ZIP codes [18,19]. Table 1 identifies the outcomes related to each aim of the evaluation and their corresponding data sources.

Table 1. Evaluation outcomes and data sources.

Outcome	Data source
Aim 1: stakeholder perspectives and reach of the program	
Implementation barriers and facilitators	Patient surveys/interviews, provider surveys/interviews, site visits
Patient satisfaction	Patient surveys/interviews, site visits
Provider satisfaction	Provider surveys/interviews, site visits
TWP[a] utilization: number and type of telehealth	CDW[b]
Number of providers engaged	CDW
Aim 2: clinical outcomes related to wound care	
Hospitalizations following the initial TeleWound encounter	
Within 30 days	CDW
Within 90 days	CDW
Within 12 months	CDW
Amputations following the initial TeleWound encounter	
Within 30 days	CDW
Within 90 days	CDW
Within 12 months	CDW
Aim 3: health care systems outcomes	
Mean number of miles traveled to receive wound care	CDW
Mean travel cost	CDW for ZIP codes, federal reimbursement rates

[a]TWP: TeleWound Practice.

[b]CDW: Corporate Data Warehouse.

Veteran Survey

Surveys assessing veteran experiences with and perceptions of TeleWound care will be deployed in VA fiscal year 2020-2021, no earlier than 3 months after the facilities included in our evaluation have implemented the TWP. We will identify veterans who received TeleWound care using clinic stop codes and the TeleWound workload capture code (4-Character National Code defined as WCUC) recorded in the CDW.

Survey mailing processes will follow a modified version of the principles of tailored design [20]. We will first mail veterans an introductory letter providing a brief overview of the study and invitation to participate, along with a copy of the survey, a small appreciation gift (eg, refrigerator magnet), and a postage-paid return envelope. We will send reminders and a second survey to veterans who have not responded within 6 weeks of the first mailing. A thank-you letter will also be sent upon completion of the survey.

The veteran survey will follow the dimensions of the PRISM model and interests of our operational partners. This survey will collect data on the type of TeleWound services received, veteran perceptions of TeleWound care, quality of life, wound self-management, and demographics.

Veteran Semistructured Interviews

At the end of the veteran survey, participants will be asked to indicate whether they are willing to complete a semistructured telephone interview to provide more details about their experiences receiving TeleWound care. Those who agree will be invited to participate in the interview. If possible and as appropriate, we will select respondents that represent the 4 implementation sites and that have received different types of TeleWound care (ie, SFT, CVT, VVC).

We will conduct interviews with up to 25 veterans. All interviews will be one-on-one, semistructured, about 30 to 45 minutes in duration, and audio-recorded for verbatim transcription and subsequent analysis. The semistructured interview guide will further explore the topics covered in the survey, including experiences with TeleWound care, perceptions of TeleWound care, whether they received training or engaged in other preparation activities prior to their TeleWound visits, the impact of TeleWound care on their wound self-management, and suggestions for improvement.

VA Care Team Member Survey

We will also conduct an online survey with VA care team members involved in the provision of TWP care. We will work with our operations partners and site leadership to identify appropriate providers and staff to reach out to, which could include individuals who work in a range of areas (eg, spinal cord injury, nursing, podiatry, infectious disease, endocrinology, primary care).

The survey and sampling frame list will be managed through the VA-approved Research Electronic Data Capture (REDCap) system. Eligible VA care team members will be sent an email introducing the study and inviting them to participate and the

link to the survey. To achieve an optimal response rate, an email reminder with the link to the survey will be sent 2 weeks later. A final email reminder will be sent 2 weeks after that. Email recruitment efforts will be augmented with instant messages (IMs) sent via interoffice IM.

Like the veteran surveys, care team member surveys will collect data on topics that map onto the PRISM model, as well as those identified as important by our operational partners. The topics addressed within the survey will include perceptions of and experiences with telehealth, perceptions of TeleWound training, barriers and facilitators to delivering TeleWound care, availability of equipment and other resources needed to deliver TeleWound care, suggestions for improvements, and demographics.

Key Stakeholder Semistructured Interviews

Key stakeholder interview procedures will follow those of the patient interviews detailed above. We will ask participants of the VA care team member survey to indicate whether they are willing to be contacted for a semistructured telephone interview at the end of the survey. Agreeable individuals will be invited to participate in an interview. We will also use snowball sampling to identify additional care team members and facility leadership to invite to participate, as appropriate.

We will conduct interviews with up to 20 key stakeholders. All interviews will be one-on-one, semistructured, and audio-recorded for verbatim transcription and subsequent analysis. Interviews will be approximately 30 minutes long. Semistructured interview guides will be used to ensure that comparable topics are covered across interviews.

Key stakeholder interviews will provide data to complement survey data, including information about implementation processes (including training and equipment), barriers and facilitators to TWP implementation, program reach and impact, and perceptions of the TWP and its implementation.

Site Visits

Site visits are a type of field-based data collection strategy in which one can observe, interact, and understand people and programs in their natural setting [21]. Our evaluation team will conduct site visits at 2 implementation sites (and their associated CBOCs, as appropriate). Site visits will provide us with an opportunity to observe the TWP from both the main facility and the rural CBOC sites to get a richer understanding of the process and workflow involved in using TWP. The site visit activities will be used to inform our team's interpretation of the data collected from other sources (eg, interviews, surveys, administrative data).

During the site visits, our team will conduct additional key stakeholder interviews with individuals (eg, nurse managers, telehealth clinical technicians, licensed practical nurses, wound care specialists) at the selected main facility and their CBOCs using the interview guide described above. Field notes will also be taken to record observations of the TWP at the main facility and its CBOCs in real time. Flow maps of the TeleWound process will be developed based on our observations and input from interviews.

Data Analysis

Quantitative Analyses (Survey and Administrative Data)

Survey and administrative data will be analyzed using descriptive and bivariate statistics, including means, medians, frequencies, standard deviations, chi-square tests, and Wilcoxon rank sum tests. Our evaluation team will compare the change in use of telehealth for wound care in participating sites before and after TWP implementation.

Specifically, we will compare the frequency and percentage of veterans who had wound care visits who used telehealth before and after TWP implementation using a chi-square test. Type of TeleWound care will be identified and responses will be compared across these modalities (ie, SFT, CVT, VVC). We will also look at the demographic characteristics of patients who received TeleWound care versus in-person care in a clinic to see if rural veterans were more likely to receive TeleWound services. The frequency and percentage of unique veterans with hospitalizations for wound-related complications within 30 days, 90 days, and 12 months following an initial wound encounter will be described and compared between veterans who received TeleWound care and veterans who received wound care in person. Frequency and percentage of unique veterans with amputations for wound-related complications within 30 days, 90 days, and 12 months following an initial wound encounter will also be analyzed. In addition, we will describe and compare the mean number of miles traveled to receive wound care and the mean travel costs over a 12-month period between veterans who received TeleWound care and veterans who received wound care in person. Finally, to examine uptake of TeleWound in each facility, we will identify the number of unique providers involved in TeleWound as well as the range of wounds treated (eg, pressure injuries, burns, chronic wounds). Analyses will include unadjusted and multiple regression models, which will assess the impact of the TWP on key outcomes (eg, hospitalizations, amputations, travel burden, costs).

Qualitative Analyses

Members of our evaluation team will use content analysis, including the constant comparative method, to identify and tabulate key themes emergent from the data [22]. Our coding approach will be both deductive and inductive and informed by our site visits. Coders will develop an initial code list a priori based on the components of the PRISM model, which encompasses a range of factors (as described above) that may influence the implementation of the TWP. Within the components of the model, coders will inductively develop additional codes and analyze the text for themes and patterns. Field notes recorded at the site visits will also be used to help identify these initial codes. Upon completion of deductive coding, a series of meetings will be held with members of the larger evaluation team to identify further themes as needed.

Data Triangulation

Our evaluation plan will use an explanatory sequential design, wherein quantitative data will be collected and analyzed first, followed by qualitative data. Once analyses are complete, members of our evaluation team will integrate qualitative and

quantitative data using side-by-side comparisons of the qualitative data and joint displays, which include qualitative themes and selected dimensions from the quantitative data [23].

Results

This program evaluation was funded in October 2019 as a Partnered Evaluation Initiative by the US Department of Veterans Affairs, Diffusion of Excellence Office, and Office of Research and Development, Health Services Research and Development Service, Quality Enhancement Research Initiative Program (PEC 19-310).

Discussion

Partnered Program Evaluation in a Learning Health Care System

Literature favoring the integration of telehealth into care provision continues to accumulate, suggesting that offering care virtually is effective and can improve important outcomes, such as access to health care [5,6,24-26]. Within this body of literature, evidence suggesting that delivering wound care using telehealth is feasible, improves health care outcomes, and reduces costs [27-29] is burgeoning. Using available evidence to inform health care is aligned with the goals of a large learning health care system such as VA and is illustrated by the TWP program, including the investment VA has made in establishing relationships between leadership, front-line clinical staff, and program evaluators to support its implementation.

The evaluation we describe here illustrates this strong partnership between our evaluation team and operations leadership. To date, DOE leadership has been a tremendous asset to our evaluation efforts and has also assumed responsibility for conducting the implementation of the TWP. One important aspect of implementation activities thus far, which was organized and run by the DOE, is holding regular calls with key participants from the sites and operational partners to monitor progress, identify problems, problem solve, and share solutions. Moreover, DOE leadership obtained and facilitated training on the 3D cameras, which some sites will be using to provide SFT TeleWound care. In addition, the DOE organized the TWP kick-off meeting, wherein key informants and operations partner representatives reviewed plans and shared early experiences.

Our evaluation team has also been able to leverage these operations-driven implementation activities as the foundation of our TWP evaluation. The information and experiences detailed through these important early implementation milestones have helped to inform the content of our data collection instruments and plans for timing of data collection efforts. Similarly, our early evaluation findings have and will continue to be fed back to DOE and other operations leadership, allowing them to enhance the effectiveness of their implementation plans in real time. These synergistic implementation and evaluation activities underscore the importance of partnerships between operations leadership, key stakeholders, and program evaluators to the success of program implementation and evaluation alike.

Limitations

Our evaluation team is not facilitating the implementation of the TWP program; however, we are and will continue to provide feedback to the DOE about implementation progress and barriers as our evaluation activities move forward. Because of the pragmatic nature of implementation studies, there is less control of processes and structures during an implementation project than other more controlled types of projects, but this also increases ecological validity. Our strategies for primary data collection are subject to biases, including recall bias and social desirability.

Conclusions

Regular communication between implementation sites, DOE leadership facilitating the implementation, and the evaluation team is key to tracking implementation progress, lessons learned, and barriers and facilitators to the success of the TWP. An important consideration for our evaluation work is that TWP implementation is occurring in a dynamic environment and as such, new equipment, changing staff and leadership, and varying facility and staff priorities and demands may arise during the implementation period. Changes such as these may make implementation challenging but highlight the ever-present importance of keeping the goals of TWP and the needs of veterans at the forefront of efforts to implement and evaluate activities.

The efforts to date on this project have demonstrated how critical early investments in infrastructure are to the success of TWP program implementation. The TWP program has unique needs and requirements to be addressed before the program can be implemented, and in turn, the implementation process and subsequent outcomes can be evaluated. The evaluation plans we detail will inform efforts moving forward and will be integral to the facilitation of TWP throughout VA.

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Conflicts of Interest

None declared.

References

1. Brennan MB, Hess TM, Bartle B, Cooper JM, Kang J, Huang ES, et al. Diabetic foot ulcer severity predicts mortality among veterans with type 2 diabetes. J Diabetes Complications 2017 Mar;31(3):556-561 [FREE Full text] [doi: 10.1016/j.jdiacomp.2016.11.020] [Medline: 27993523]
2. Njei B, Esserman D, Krishnan S, Ohl M, Tate JP, Hauser RG, et al. Regional and Rural-Urban Differences in the Use of Direct-acting Antiviral Agents for Hepatitis C Virus: The Veteran Birth Cohort. Med Care 2019 Apr;57(4):279-285 [FREE Full text] [doi: 10.1097/MLR.0000000000001071] [Medline: 30807449]
3. Koifman J, Hall R, Li S, Stamplecoski M, Fang J, Saltman AP, et al. The association between rural residence and stroke care and outcomes. J Neurol Sci 2016 Apr 15;363:16-20. [doi: 10.1016/j.jns.2016.02.019] [Medline: 27000213]
4. Cordasco KM, Mengeling MA, Yano EM, Washington DL. Health and Health Care Access of Rural Women Veterans: Findings From the National Survey of Women Veterans. J Rural Health 2016 Sep;32(4):397-406. [doi: 10.1111/jrh.12197] [Medline: 27466970]
5. Darkins A. Changing the location of care: management of patients with chronic conditions in Veterans Health Administration using care coordination/home telehealth. J Rehabil Res Dev 2006;43(4):vii-xii [FREE Full text] [doi: 10.1682/jrrd.2006.03.0029] [Medline: 17123179]
6. Crowley ST, Belcher J, Choudhury D, Griffin C, Pichler R, Robey B, et al. Targeting Access to Kidney Care Via Telehealth: The VA Experience. Adv Chronic Kidney Dis 2017 Jan;24(1):22-30. [doi: 10.1053/j.ackd.2016.11.005] [Medline: 28224939]
7. Chu S, Boxer R, Madison P, Kleinman L, Skolarus T, Altman L, et al. Veterans Affairs Telemedicine: Bringing Urologic Care to Remote Clinics. Urology 2015 Aug;86(2):255-260. [doi: 10.1016/j.urology.2015.04.038] [Medline: 26168998]
8. Darkins A, Kendall S, Edmonson E, Young M, Stressel P. Reduced cost and mortality using home telehealth to promote self-management of complex chronic conditions: a retrospective matched cohort study of 4,999 veteran patients. Telemed J E Health 2015 Jan;21(1):70-76. [doi: 10.1089/tmj.2014.0067] [Medline: 24841071]
9. Smith-Strøm H, Igland J, Østbye T, Tell GS, Hausken MF, Graue M, et al. The Effect of Telemedicine Follow-up Care on Diabetes-Related Foot Ulcers: A Cluster-Randomized Controlled Noninferiority Trial. Diabetes Care 2018 Jan;41(1):96-103. [doi: 10.2337/dc17-1025] [Medline: 29187423]
10. Le Goff-Pronost M, Mourgeon B, Blanchère JP, Teot L, Benateau H, Dompmartin A. Real-World Clinical Evaluation And Costs Of Telemedicine For Chronic Wound Management. Int J Technol Assess Health Care 2018 Jan;34(6):567-575. [doi: 10.1017/S0266462318000685] [Medline: 30369340]
11. Kolltveit BH, Thorne S, Graue M, Gjengedal E, Iversen MM, Kirkevold M. Telemedicine follow-up facilitates more comprehensive diabetes foot ulcer care: A qualitative study in home-based and specialist health care. J Clin Nurs 2018 Mar;27(5-6):e1134-e1145. [doi: 10.1111/jocn.14193] [Medline: 29193527]
12. Feldstein AC, Glasgow RE. A practical, robust implementation and sustainability model (PRISM) for integrating research findings into practice. Jt Comm J Qual Patient Saf 2008 Apr;34(4):228-243. [doi: 10.1016/s1553-7250(08)34030-6] [Medline: 18468362]
13. McCreight M, Rabin B, Glasgow R, Ayele RA, Leonard CA, Gilmartin HM, et al. Using the Practical, Robust Implementation and Sustainability Model (PRISM) to qualitatively assess multilevel contextual factors to help plan, implement, evaluate, and disseminate health services programs. Transl Behav Med 2019 Nov 25;9(6):1002-1011. [doi: 10.1093/tbm/ibz085] [Medline: 31170296]
14. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999 Sep;89(9):1322-1327. [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]
15. Bakken S, Ruland CM. Translating clinical informatics interventions into routine clinical care: how can the RE-AIM framework help? J Am Med Inform Assoc 2009;16(6):889-897 [FREE Full text] [doi: 10.1197/jamia.M3085] [Medline: 19717799]
16. Glasgow RE, Estabrooks PE. Pragmatic Applications of RE-AIM for Health Care Initiatives in Community and Clinical Settings. Prev Chronic Dis 2018 Jan 04;15:E02 [FREE Full text] [doi: 10.5888/pcd15.170271] [Medline: 29300695]
17. Kwan BM, McGinnes HL, Ory MG, Estabrooks PA, Waxmonsky JA, Glasgow RE. RE-AIM in the Real World: Use of the RE-AIM Framework for Program Planning and Evaluation in Clinical and Community Settings. Front Public Health 2019;7:345 [FREE Full text] [doi: 10.3389/fpubh.2019.00345] [Medline: 31824911]
18. Stroupe KT, Weaver FM, Cao L, Ippolito D, Barton BR, Burnett-Zeigler IE, et al. Cost of deep brain stimulation for the treatment of Parkinson's disease by surgical stimulation sites. Mov Disord 2014 Nov;29(13):1666-1674. [doi: 10.1002/mds.26029] [Medline: 25220042]
19. Hynes DM, Stroupe KT, Fischer MJ, Reda DJ, Manning W, Browning MM, for ESRD Cost Study Group. Comparing VA and private sector healthcare costs for end-stage renal disease. Med Care 2012 Mar;50(2):161-170. [doi: 10.1097/MLR.0b013e31822dcf15] [Medline: 21945972]

20. Dillman D, Smyth J, Christian L. Internet, Phone, Mail, and Mixed-Mode Surveys: The Tailored Design Method. 4th ed. New York, NY: John Wiley & Sons Inc; 2014.
21. Yin RK. Qualitative Research from Start to Finish. 2nd ed. New York, NY: Guilford Press; 2015.
22. Lindlof TR, Taylor BC. Qualitative Communication Research Methods. 4th Edition. Los Angeles, CA: SAGE Publications; 2017.
23. Guetterman TC, Fetters MD, Creswell JW. Integrating Quantitative and Qualitative Results in Health Science Mixed Methods Research Through Joint Displays. Ann Fam Med 2015 Nov;13(6):554-561 [FREE Full text] [doi: 10.1370/afm.1865] [Medline: 26553895]
24. Naka F, Lu J, Porto A, Villagra J, Wu ZH, Anderson D. Impact of dermatology eConsults on access to care and skin cancer screening in underserved populations: A model for teledermatology services in community health centers. J Am Acad Dermatol 2018 Feb;78(2):293-302. [doi: 10.1016/j.jaad.2017.09.017] [Medline: 29061478]
25. Speyer R, Denman D, Wilkes-Gillan S, Chen Y, Bogaardt H, Kim J, et al. Effects of telehealth by allied health professionals and nurses in rural and remote areas: A systematic review and meta-analysis. J Rehabil Med 2018 Feb 28;50(3):225-235 [FREE Full text] [doi: 10.2340/16501977-2297] [Medline: 29257195]
26. Beswick DM, Vashi A, Song Y, Pham R, Holsinger FC, Rayl JD, et al. Consultation via telemedicine and access to operative care for patients with head and neck cancer in a Veterans Health Administration population. Head Neck 2016 Jun;38(6):925-929. [doi: 10.1002/hed.24386] [Medline: 26899939]
27. Gamus A, Chodick G. Costs and Benefits of Telemedicine Compared to Face-to-Face Treatment in Patients with Lower Extremity Ulcers. Adv Wound Care (New Rochelle) 2019 Jul 01;8(7):291-297 [FREE Full text] [doi: 10.1089/wound.2018.0906] [Medline: 31737419]
28. Chanussot-Deprez C, Contreras-Ruiz J. Telemedicine in Wound Care. Advances in Skin & Wound Care 2013;26(2):78-82. [doi: 10.1097/01.asw.0000426717.59326.5f] [Medline: 23337648]
29. Zarchi K, Haugaard VB, Dufour DN, Jemec GB. Expert advice provided through telemedicine improves healing of chronic wounds: prospective cluster controlled study. J Invest Dermatol 2015 Mar;135(3):895-900 [FREE Full text] [doi: 10.1038/jid.2014.441] [Medline: 25290685]

Abbreviations

3D: 3-dimensional
CBOC: community-based outpatient clinic
CDW: Corporate Data Warehouse
CVT: clinical video telehealth
DOE: Diffusion of Excellence
IM: instant message
PRISM: Practical, Robust Implementation and Sustainability Model
RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance
SFT: store-and-forward
TWP: TeleWound Practice
VA: Veterans Health Administration
VVC: Veterans Health Administration Video Connect

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Protocol

Developing Effective Methods for Electronic Health Personalization: Protocol for Health Telescope, a Prospective Interventional Study

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Abstract

Background: Existing evaluations of the effects of mobile apps to encourage physical activity have been criticized owing to their common lack of external validity, their short duration, and their inability to explain the drivers of the observed effects. This protocol describes the setup of Health Telescope, a longitudinal panel study in which the long-term effects of mobile electronic health (eHealth) apps are investigated. By setting up Health Telescope, we aim to (1) understand more about the long-term use of eHealth apps in an externally valid setting, (2) understand the relationships between short-term and long-term outcomes of the usage of eHealth apps, and (3) test different ways in which eHealth app allocation can be personalized.

Objective: The objectives of this paper are to (1) demonstrate and motivate the validity of the many choices that we made in setting up an intensive longitudinal study, (2) provide a resource for researchers interested in using data generated by our study, and (3) act as a guideline for researchers interested in setting up their own longitudinal data collection using wearable devices. For the third objective, we explicitly discuss the General Data Protection Regulation and ethical requirements that need to be addressed.

Methods: In this 4-month study, a group of approximately 450 participants will have their daily step count measured and will be asked daily about their mood using experience sampling. Once per month, participants will receive an intervention containing a recommendation to download an app that focuses on increasing physical activity. The mechanism for assigning recommendations to participants will be personalized over time, using contextual data obtained from previous interventions.

Results: The data collection software has been developed, and all the legal and ethical checks are in place. Recruitment will start in Q4 of 2020. The initial results will be published in 2021.

Conclusions: The aim of Health Telescope is to investigate how different individuals respond to different ways of being encouraged to increase their physical activity. In this paper, we detail the setup, methods, and analysis plan that will enable us to reach this aim.

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KEYWORDS

eHealth; mHealth; personalization; longitudinal study; wearables; panel study; persuasive technology; gdpr

Introduction

Background

The World Health Organization has identified physical inactivity as the fourth leading risk factor of death worldwide [1]. Physical inactivity is defined as *the absence of sufficient bodily movement produced by skeletal muscles requiring energy expenditure*. It has been estimated that every year, over 5 million people die as a result of insufficient physical activity. Physical inactivity carries part of the burden of, among others, coronary heart disease, type 2 diabetes, breast cancer, and colon cancer, as one of the multiple causes of these diseases. Additionally, increased physical inactivity affects mental health, with research showing a positive correlation between physical inactivity and depression [2]. Research estimates that an increase of 10% in activity can save 1.3 million lives yearly [3].

In this paper, we describe the protocol of Health Telescope, a unique longitudinal study researching the effects of the personalized offering of various existing electronic health (eHealth) apps designed to motivate users to increase physical activity. In recent years, longitudinal studies have been argued to be unavoidable for research investigating behavior change, as solidifying behavior change may take months or years [4]. We took up this challenge of measuring the effects of behavior change apps over a long period of time. Furthermore, we specifically focus on the personalized offering of these apps to investigate whether personalization can improve the effectiveness of common eHealth apps. This protocol paper describes the setup, methods, materials, and analysis plan of Health Telescope to enable other researchers to understand and judge the validity of the data collected within the project. In our description, we focus strongly on the ethical and legal aspects of setting up our panel study. We hope this paper provides a useful resource for others aiming to set up longitudinal eHealth studies.

The Rise and Effects of eHealth

Mobile apps aimed at making users improve their health autonomously have been growing in number in recent years, including apps that persuade users to be more active, apps that track food intake, and apps that offer help with mental health issues. The total value of this mobile health or eHealth app market was estimated in 2018 at US $28.32 billion and is projected to reach US $102.35 billion by 2023 [5]. These apps have the potential to increase the level of control that individuals have over their health while improving general health in several ways. Among other factors, users may identify health issues earlier, autonomous use can be a lower barrier than receiving help from a professional, and new routes for preventative measures can be taken.

The number of mobile apps labeled as eHealth apps is growing tremendously, with over 1000 new apps entering top app stores every day [6]. This increase is accompanied by a growing skepticism, as research has not yet conclusively shown a positive effect on health and long-term wellbeing [7-9]. The absence of a convincing effect of eHealth apps is largely attributed to nonusage [10], which might itself be caused by distinct characteristics of eHealth services [10], social aspects of use [10], and eHealth literacy [11].

The rapid proliferation and short lifetime of apps make identifying apps that accomplish the intended behavior change effectively for a group of users a very difficult task. Properly identifying behavior change is not trivial, as can be demonstrated by a simple example as follows. Suppose an individual adopts the mindset of changing ways and being healthier, and in this process, downloads an eHealth app. After using the app for several weeks, the app is abandoned. However, over the course of months, the user does change ways. This change can, at least in part, be attributed to the earlier usage of the eHealth app. This scenario demonstrates that it is firstly difficult to determine whether an app contributes to a change in lifestyle and that it is secondly difficult to measure the outcome if the user has stopped engaging with the app.

Additionally, as has been demonstrated before in the literature [12], the effectiveness of eHealth apps to motivate healthy behaviors might, in part, be driven by a correct match between the app itself and its user (ie, a personalized app might have a larger effect). One can wonder whether currently, the apps that users download from the various app stores provide a correct match. All of the major app stores offering eHealth apps currently use a 5-star rating system to grade their apps, which is one of the factors driving the download behaviors of users. However, these ratings arguably have their issues [13,14]. While alternatives have been proposed [15], we currently do not properly understand how we can personalize the choice of eHealth apps [16]. Recently, there has been substantial interest in sequential allocation methods that combine machine learning to predict the effects of treatments for individuals based on historical data, with effective methods to balance exploring different treatments and exploiting the seemingly best treatment [17]. Effectively, these novel methods select personalized treatments as data are collected over time. This is a potentially promising approach as it allows us to reach beyond simple user ratings by using data to improve the match between a user and an app.

Health Telescope

To answer these pressing questions regarding the effects (both long-term and short-term effects) and methods for personalization of eHealth apps, we set up Health Telescope, a large-scale interventional panel study. In the current protocol paper, we highlight the choices we made in setting up this prospective study. Health Telescope is used to actively and iteratively test different approaches of personalization and, at the same time, track the longitudinal effectiveness of these personalized offerings. Health Telescope allows us to answer major open questions regarding the effectiveness of eHealth apps. First, by closely monitoring app usage, engagement, activity, and mood, we aim to obtain a better understanding of the short-term and long-term effects of eHealth apps. Second, by actively experimenting with different eHealth app encouragement schemes, we test the effects of personalizing eHealth offerings.

The importance of large-scale studies that follow individuals for a longer period has been argued in recent years [18]. To our

best knowledge, Health Telescope is the first large-scale long-term study that follows and intensively gathers activity and behavioral data from participants. With this protocol, we aim to motivate researchers to set up similar studies, as we believe research in eHealth stands to benefit from thorough long-term studies.

The Health Telescope study aims to achieve the following three objectives, labeled study objectives 1-3 (SOs 1-3):

- SO1: The study aims to measure the effect of eHealth for longer periods. To accomplish this, we choose a panel uptime of at least 4 months.
- SO2: The study aims to correlate short-term and long-term measures. To accomplish this, we combine behavioral measures with periodic surveys and analyze their relations over time.
- SO3: The study aims to test the effects of personalization in allocating health apps. To accomplish this, we set up iterative interventions and an allocation scheme that uses collected data to predict which health app is expected to lead to the highest activity increase, given a person's background information, activity, and behavior.

In this protocol description paper, we aim to accomplish the following three objectives, labeled protocol objectives 1-3 (POs 1-3):

- PO1: The paper aims to demonstrate and motivate the validity behind the setup of Health Telescope.
- PO2: The paper aims to confirm its function as a steppingstone for future researchers interested in the data generated by Health Telescope.
- PO3: The paper aims to serve as a guideline for those setting up longitudinal studies using wearable devices.

The rest of the paper is structured as follows: the Methods section and its various subsections elaborate on the research questions and describe the various aspects in setting up the panel; the Results section briefly expands on the timeline of the project; and the Discussion section goes into the advantages and disadvantages of the chosen setup and presents the conclusions.

Methods

Study Design and Aims

Health Telescope is a prospective interventional panel study (N=450) measuring activity and iteratively testing the effect of recommending distinct eHealth apps to participants, with the goal of personalization (ie, finding a relation between an individual and an app that can provide motivation to be sufficiently active). The study is designed to run a minimum of 4 months. We would like to continue to monitor participants past these 4 months to further measure the long-term effects of eHealth app usage. We plan to do so assuming the dropout rate of participants is low enough to keep a sufficiently large group for further analysis.

The study has been approved by METCBrabant, the Ethics Review Board of Tilburg University, the Netherlands, and the General Data Protection Regulation (GDPR) compliance officer of Tilburg University. Furthermore, a Data Protection Impact Assessment check was performed by the Technical University of Eindhoven and Tilburg University. We detail the approval process in the sections "Ethical Approval" and "GDPR Compliance" to aid researchers who, like us, have to go through this process (PO3).

During the study, participant data are measured, and participants receive a daily request to complete a three-question survey concerning their mood (this is detailed in the section "Health Telescope App"). The set of interventions is defined as five messages that will be sent to participants' smartphones, four of which contain a recommendation to download a specific health app (we expand upon this in the section "Interventional Apps"), and the fifth does not recommend any app. The messages recommending apps provide a brief textual summary of the app's functionalities. Every month, each participant will be allocated to one of the interventions.

The allocation of interventions is, in part, personalized. We detail our personalization logic in the section "Allocation of Interventions" below.

The participants will be recruited in Q4 of 2020 (details are provided in the section "Recruitment") and are expected to participate for a minimum of 4 months. The participant group of the panel will be made up of a diverse set of Dutch adults who are interested in using mobile health apps, recruited mainly through general practitioners (more information is provided in the "Recruitment" section). We select this wide range of users to allow the results to speak for a general audience who may download a mobile health app (which helps answer SO1 and SO3). It is relevant to mention that, to appeal to the participant group, the apps chosen to be recommended in the panel (detailed in the section "Interventional Apps") do not require a user to be in superior physical shape for use.

Data are collected through a combination of the following: a wearable device handed out to participants at the start of the study, a mobile app that tracks phone use and GPS, and survey responses measuring mood and happiness using the experience sampling method (ESM) [19].

The section "Data Collection" provides a concrete overview of the data that are collected in the study. This diverse set of data collection methods allows us to monitor eHealth app usage and its effects on various outcome measures (SO1). Furthermore, the duration of the panel allows us to examine the relationship between the long-term and short-term measures of the effects of eHealth (SO2). Finally, we will provide interventions, with an intervention constituting a recommendation to start using a selected eHealth app. These interventions will, in part, be personalized (ie, we will recommend an app that we expect to be the most effective for a given user based on the data collected thus far). This personalization allows us to evaluate the effect of personalization (SO3).

Recruitment

Inclusion Criteria

Participants are recruited via several paths. To be eligible for participation, a respondent needs to meet the following criteria:

live in the Netherlands; speak Dutch; be 18 years or older; possess an Android phone running Android 6.0 or newer that they are willing to use in the study; be sufficiently smartphone and internet literate to use the app; and intend to participate for the full duration of the study.

Note that participants are considered smartphone and internet literate when they can navigate an Android smartphone and get through the setup process, including the introduction survey, app installation, and wearable setup. To ensure participants can perform these steps, the emphasis is put on highlighting the steps in the setup process during the information sessions that participants go through before entering the panel.

We deliberately do not focus on a specific health group, such as those defined by specific choices of BMI, chronic disease, or age. This is to ensure that knowledge gained from this project can be applied to the general group of app users (the group that downloads apps like the ones tested in this project). The panel will be formed through the following channels:

- Health insurance employees (approximately 150 participants): A large health insurer in the Netherlands that helped fund the Health Telescope project has indicated they would like to give their employees the chance to enroll in the panel. Advertisements will be sent out through internal communication channels, inviting employees to attend an introductory meeting where the purpose and details of the panel will be explained.
- General practitioner visitors (approximately 300 participants): Part of the panel will consist of individuals recruited directly through general practitioners. Three general practitioner offices in Geldrop, a village in Noord-Brabant with 28,500 inhabitants, have agreed to assist in recruitment. Advertising will be done in the practices, as well as through email.

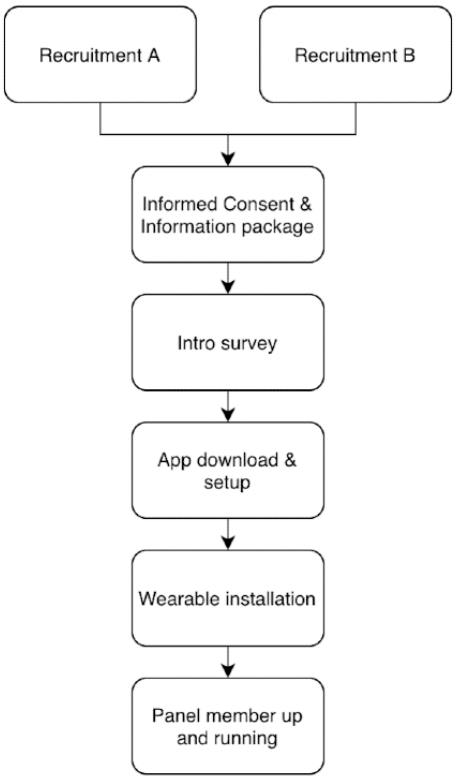
Recruitment Process and Materials

To ensure participants understand the objectives of the study and the actions they are expected to perform, we set up information sessions that potential participants need to attend before entering the panel. In these sessions, the study goals and the steps of the setup that participants need to go through (detailed in Figure 1) are explained to a group of approximately 25 respondents.

Before entering the participant group, all respondents are given the necessary introductory documents. Included in this is an informed consent document that is mandatory for participation. These documents are available elsewhere [20]. If the respondents have additional questions before deciding to participate, they are able to pose them through the project website or by directly contacting the team through email. To ensure users understand what happens to their data, there is a thorough privacy policy available elsewhere [21].

Figure 1 shows the steps potential participants go through in the recruitment process. The individual steps are further described in the section “Data Collection.”

Figure 1. Steps in the enrollment of participants. Starting with recruitment (from different sources), participants receive study information and an informed consent (IC) form and take the introduction survey before downloading and installing the app. After installing the wearable, participants are set up and enrolled in the study.



Setup for Investigating Objectives

In setting up the study, we look at how to achieve the goals of the study as presented below.

SO1: Effects of eHealth Apps

To test the effects of eHealth apps, we will create a group of participants who receive a recommendation to use one of the interventional apps and compare this to a group of users who are not given this recommendation. Specifically, we will test if there is a relevant difference in the average increase or decrease in activity for the daily steps taken in the month after a recommendation compared with the control group that does not receive this recommendation.

Additionally, measuring phone usage allows us to identify active users of health apps, allowing for comparison with a group that does not use health apps.

SO2: Correlation of Short- and Long-Term Measures

By selecting a 4-month study uptime at minimum, we can research if short-term measures (ie, activity or health app usage 1 week after the intervention) correlate with long-term measures (ie, activity a month after the intervention). To examine long-term measures further, we will attempt to monitor participants after the initial 4 months.

SO3: Personalization of App Allocation

To test the effect of the personalized allocation as described above, we will create, based on the collected data, a model that aims to predict which eHealth app is the most successful for which participant. The results of this model will be used to allocate apps (to intervene), and this will allow us to compare the effectiveness of randomly selected apps with those selected based on the prediction model.

Allocation of Interventions

During the study, participants will receive recommendations to download and use certain eHealth apps. Figure 2 shows the recruitment and dropout of participants over time. We aim to recruit 150 participants each month and expect a dropout of 20% of participants each month. We explain how these groups are used for the allocation of interventions below.

Figure 2. Panel size over time, including recruitment of participants, as well as the number of assigned participants in the treatment and control groups. We use a control ratio of 0.2 and a monthly decay rate of 0.2.

Group number	Participants	Assignment	M1	M2	M3	M4
		Treatment	120	96	77	62
1	150	Control	30	24	20	16
		Treatment		120	96	77
2	150	Control		30	24	20
		Treatment			120	96
3	150	Control			30	24
		Total treatments:	120	216	293	235
Control ratio	Decay Rate	Total control:	30	54	74	60
0.2	0.2	Total participants:	150	270	367	295

One-Month Blocks

The study is divided into blocks of 1 month. Upon entering the panel, every participant has their activity recorded and is asked about their mood for a month, without receiving an intervention. The data serve as baseline data for participant activity. Note that the recruitment is done over the course of 3 months. From the second block onwards, participants will receive interventions. Participants will receive one intervention per block. Participants who get recommended the same app for multiple months in a row, will receive a message explaining that they should keep using the app they were assigned last month.

Rollout

The recruitment for Health Telescope is planned to take 3 months, enrolling 150 participants per month. Participants recruited in later months will receive interventions based on the data already generated by the existing participants.

Treatment and Control Group Allocation

In this section, we describe which participant at what point in time will receive which treatment (ie, which eHealth app will be recommended according to which logic).

First, in each month (Figure 2), a number of participants will be allocated to the control group; for these participants, no app will be recommended that month.

Allocation to the control group is random. For each participant, there is a 20% chance to be assigned to the control group in a specific month. Control groups are individually created for every round of intervention. Note that we choose to create control groups individually per month as opposed to a fixed control group that never receives any app recommendations throughout the study, since we believe never assigning any app may negatively impact participant engagement with the panel and may lead to a higher dropout rate.

Second, in the different months of the duration of the study, different allocation schemes will be used to recommend one of the four eHealth apps included in the study. If one of the four

apps is recommended, users end up in the treatment group that specific month. We will use the following logic to allocate apps to participants: (1) In months 1 and 2, simple random allocation will be used. Thus, each app has a respective 20% chance of being selected for a participant; (2) In month 3, we will use the data collected in months 1 and 2 to create a model that aims to predict the effect of each app, for a given user, on the number of steps taken that month. We will use Bayesian additive regression tree (BART) to generate these predictions. BART is essentially a sum-of-trees model that can be used to effectively model nonlinear main and multiple-way interaction effects. Thus, it is well suited to model the interactions between the participant characteristics and the effects of the different apps. In month 3, for each new participant that is in the treatment group, the app that has the highest predicted effect will be selected. Thus, in this group of 120 participants, we will test the effects of personalizing the selected app based on the data collected previously.

Data Collection

Data collection consists of several components including data collection during the setup phase (Figure 1) and data collection during the duration of the panel (Table 1). In this section, we describe each step and its components in turn.

Table 1. Summary of data collected in Health Telescope.

Data type	Frequency	Example
Step count	Every hour, the number of steps taken during that hour is measured.	2 PM-3 PM: 739 steps
Heart rate	Heart rate is measured at 1-hour intervals.	2 PM: 73 bpm
Sleep data	The start and end times of sleep are measured daily, yielding the total sleep time.	February 23: 11:16 PM-7:12 AM
Experience sampling	Up to once per day, we ask participants brief questions using push messages.	February 23, 2 PM: I generally feel energetic: Yes I currently feel happy: Completely agree Smiley: Happy
GPS location	Every 4 hours, the GPS location is saved	2 PM: 38.8977 N, 77.0365 W
Phone usage	We measure screen time and usage of apps on participants' mobile phones. *Note: We only measure the duration of use and do not in any way measure what happens within an app.*	Chrome: 2:03 PM-2:04 PM Facebook: 2:04 PM-2:17 PM Messages: 2:23 PM-2:25 PM Mail: 2:25 PM-2:37 PM

Introduction Survey

The intake survey (Multimedia Appendix 1 [22]) consists of the following three parts: (1) a section providing demographic information on participants; (2) a section giving details on how active participants perceive to be; and (3) a section measuring the following constructs:

- Big Five Personality traits: A 50-item five-point Likert Big Five Personality traits questionnaire [23] measures conscientiousness, openness to experience, extraversion, agreeableness, and neuroticism. These traits have been found to correlate with physical activity and obesity [24].
- Need for Cognition scale: An 18-item seven-point Likert Need for Cognition questionnaire [25] measures the extent to which an individual is inclined towards effortful cognitive activities [26]. Need for Cognition has been found to moderate the responses individuals have toward different ways of being messaged [27].
- Susceptibility to Persuasion scale: A 26-item seven-point Likert Susceptibility to Persuasion questionnaire [12] separates an individual's persuadability in five constructs (reciprocity, scarcity, authority, commitment, and liking). This gives direct information on how to apply the interventions in the study.

Wearable

Wearables have increasingly been used in research to detect daily steps taken, heart rate, sleep behavior, and even skin conductance, but show large inaccuracy in most data types [28,29]. The exception to this has been steps taken [28], which shows accuracy similar to that for devices designed solely for counting steps. Among the currently available wearables, Xiaomi MiBand 2 provides accurate measurements [28] at a relatively low price point. Furthermore, the MiBand is IP-67 waterproof and has a charge time of around 3 hours for 1-month charge. Participants are not asked to wear the MiBand for any specific number of hours or specific activity, instead participants are asked to wear the band similarly to how they would if they were not in the panel. This is done to (1) minimize participant burden and (2) maintain participant autonomy. Additionally, the MiBand allows for the transmission of unprocessed data to our servers, without sending the data to the developers first. This is a feature not present on every wearable on the market but is necessary for smooth data collection. The MiBand measures the following:

- Steps: The steps taken are measured every minute by the gyroscope in the MiBand.
- Heart rate: By default, the MiBand only measures and records heart rate when users manually do so. We changed that to also sample heart rate every hour.

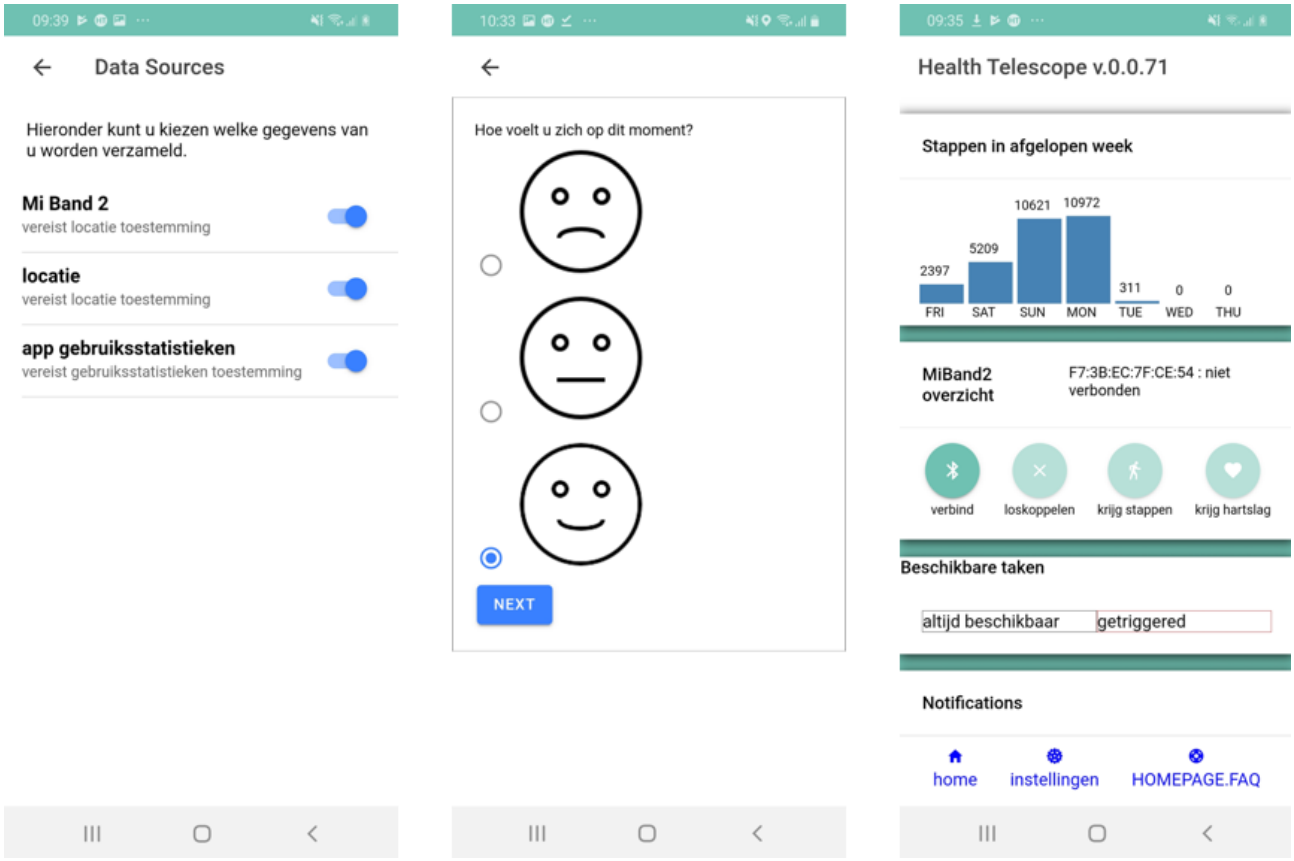
- Sleep data: The gyroscope in the MiBand combined with an information layer (using rules such as “first daily unlock”) allows us to assess sleep.

Health Telescope App

The Health Telescope app is a mobile app (screenshots of which can be seen in Figure 3) developed for the project that encompasses several goals. The app was designed to allow us to do the following:

- Communicate with participants: The app allows us to send users push messages with updates about the panel, is used to deliver interventions, and functions as a primary method of communication.
- Collect phone data: The app allows us to send the data as described in the section “Data Collection” from the users’ phones to our database.
- Record surveys: Surveys will be sent out and answered through the app.
- Manage user consent: Users can manage their accounts, including changing which data can be collected, looking into the data, and granting or revoking consent to researchers to process the data.

Figure 3. Screenshots of the Health Telescope app.



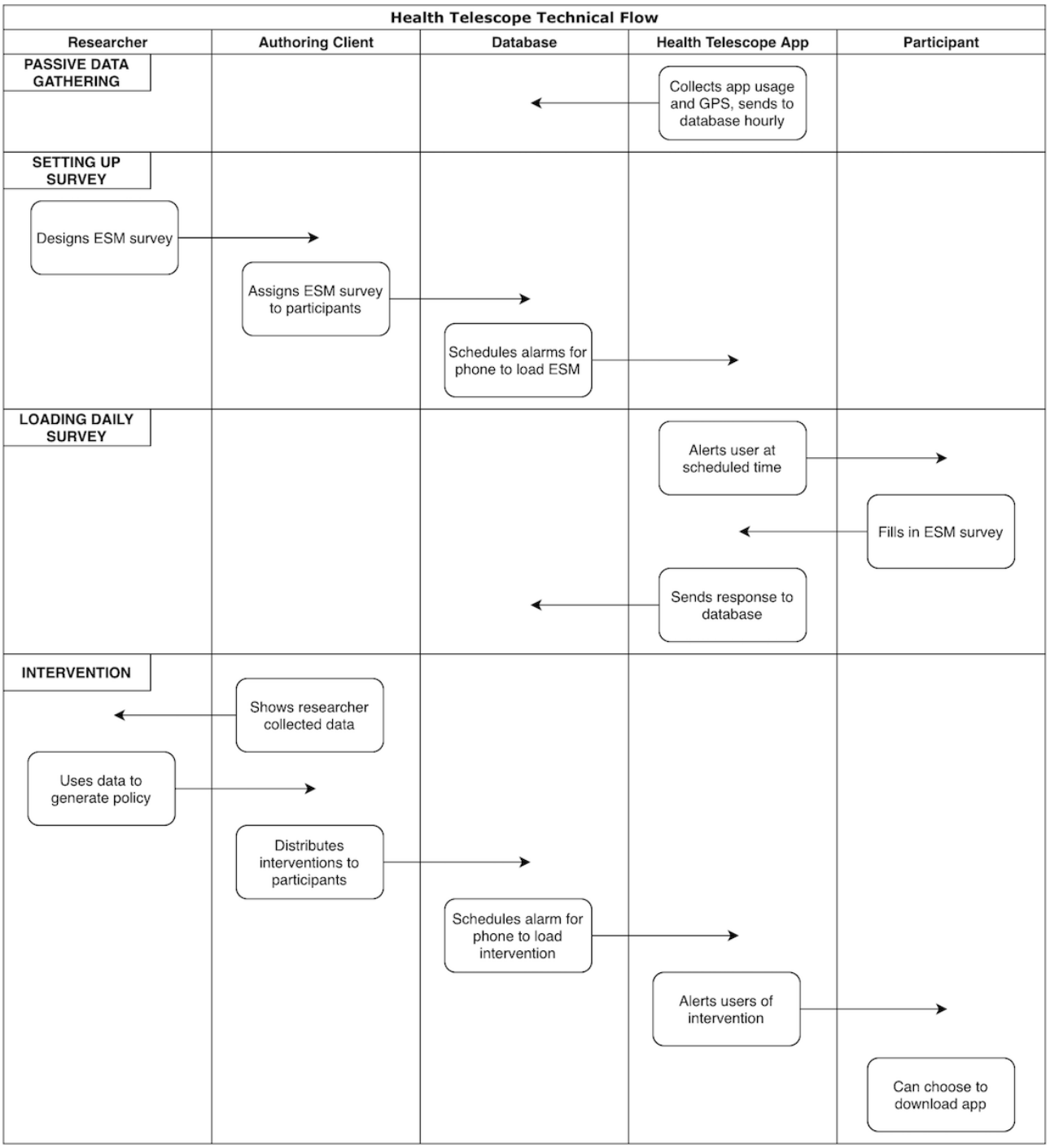
The app pairs with the wearable, recording steps, heart rate, and sleep data and displaying the first two to the user. The home screen further contains a list of the communications sent to the user. This consists of questionnaires and intervention messages. Every data type seen in Table 1 is collected and sent to the Health Telescope database every hour. The following data are collected by the app:

- GPS: Every hour, the GPS location of the participant’s phone is determined in the Health Telescope app. This location is first encrypted and then transmitted from the phone to the database. GPS tracking provides information regarding user behavior that might not be obtainable from activity data. Examples include commuting distance and capturing the difference between activity on a treadmill from that out in the world.
- Phone usage statistics: Every hour, a list of services that have been active on the participant’s phone will be sent to the database. This list contains the total time, total screen time, and total background time of app use. The data are used both for understanding the user’s behavior through the types of apps used and for measuring the use of a recommended eHealth app.
- Experience sampling: Participants will be given questionnaires daily, through the Health Telescope app. We use the ESM to periodically ask participants about their mood and happiness. The ESM has been shown to be a cost-effective way of measuring mental health [30]. The questions are designed as short and simple, as this can reduce participant burden [31]. By regularly and briefly checking up on how participants feel, we can obtain information on how activity relates to happiness, as well as investigate the effects of interventions on participants’ short- and long-term happiness. Two questionnaires are administered. The first is the two-item mood questionnaire. Mood will be assessed using a two-item mood questionnaire that splits mood into valence and activity. Each item is rated on a five-point Likert scale. Mood is deliberately chosen

as a measure over well-being or long-term happiness, as researchers from the Tilburg Experience Sampling Center recommended it, with the main merit being its quick fluctuation; in contrast, well-being and happiness often tend to mostly change over longer periods [32], providing less information on day-to-day changes in mood. The second is the three-point smiley face questionnaire. Using smiley faces as response options is a simple technique that is argued to be an elegant way of measuring hedonic levels of happiness [33]. This coincides with the goal of measuring "in-the-moment" emotions. The response options for this questionnaire are a happy, neutral, and sad smiley face.

Figure 4 shows the activities that take place during data collection. The data types and system in this figure are described in the sections "Data Collection" and "Data Management," respectively. Passive data gathering happens hourly, surveys are set up by researchers to load onto participants' phones periodically, and interventions take place monthly.

Figure 4. Visualization of the interactions in the panel infrastructure for passive data gathering, setting up surveys, loading of daily surveys, and interventions. ESM: experience sampling method.



Interventional Apps

The apps that we use for interventions are shown in Table 2. These apps were selected from a Dutch app store, the GGD App Store [34]. The *Gemeenschappelijke Gezondheidsdienst (GGD)*, the Dutch community health service, created this app store, where they test mobile apps for user-friendliness, reliability, substantiation, and privacy before being allowed on the app store. A global score, as well as a detailed verdict per category, can be seen on the website. Hence, all the apps we selected have been extensively checked. The GGD furthermore details whether the apps make use of distinct behavior change theories [35].

It is important to note that nonusage of a recommended app is important information as well. As we aim to evaluate existing eHealth apps, seeing whether they are even downloaded and used is important in its own right. As such, participants are fully allowed to not follow a recommendation if they do not believe the recommendation suits them, and participants are allowed to uninstall or stop using a recommended app at any time.

In selecting suitable apps to include in the study, we aimed to select a set of apps that are individually diverse enough to allow different user groups to find an app that might be suitable for them. This means apps should be accessible for new users who may be inexperienced with exercise and should offer content suitable for experienced users as well. Furthermore, we aimed to select apps that implement different behavior change approaches, such that we can use these approaches as one of the building blocks of our personalization approach. Ensuring that the apps used in the study are accessible and use different behavior change methods is necessary to answer the project's objectives (PO1-3).

Table 2. Details of the apps used.

App name	Ways of encouragement	Behavioral change techniques
Runtastic	This app allows users to choose a level of encouragement during workouts. Results can be shared with friends.	Feedback on behavior Social comparison
Runkeeper	This app allows for goal setting. The app sends reminders to work out. Users are rewarded with badges.	Goal setting Social incentive
Human	This app incentivizes users to move for half an hour per day. Results can be shared on Facebook.	Goal setting Social comparison
Seven	The app focuses on having daily workouts and allows users to compare their performance to peers.	Commitment Social comparison

Statistical Analysis

To be able to meet the study objectives, it is important to include sufficient participants in the study. Here, we detail in which ways the study objectives can be tested and we calculate the number of participants needed for each of these tests. Although we will conduct analyses additional to those described here to fully understand the collected data, this section aims to (1) motivate the primary analysis carried out for each study objective and (2) motivate that, given reasonable assumptions regarding the effect sizes of the selected eHealth apps, our sample size is sufficient to attain our objectives.

SO1: Effect of eHealth Usage

For each recommended app, a between samples *t* test comparing the average difference in activity between the group of participants who downloaded the recommended app (denoted as T) and the control group (denoted as C) will be carried out (Figure 2) in a given month. Using an estimated standard deviation of 2295 steps (as found in earlier work [36]) for activity, we will test for a difference in steps by about 1500 steps per day, which we deem a relevant and meaningful effect size. Using a power of 0.8 and a significance level of .05, we found that we need approximately 41 participants per app to conduct each of the different independent tests. Hence, our recruitment plan in which over 250 people are recruited should suffice to obtain a control group and four treatment groups (one for each app) that are large enough to meaningfully test the null hypothesis that, on average, eHealth usage increases monthly activity levels.

SO2: Long- and Short-Term Effects of eHealth Usage

To test whether short-term measures of physical activity meaningfully relate to long-term measures of users' mood, we will examine the correlation between these different measures at different points in time. Our setup (Figure 2) allows us to correlate activity in the first week of usage of a recommended app to mood in week 4. We test for a correlation of 0.4 or higher, which we deem a relevant and meaningful positive correlation. Using a power of 0.8 and a significance level of .05, we found that we need approximately 235 participants to reject the null hypothesis. Our recruitment plan provides within-subject data for more than 300 subjects, and hence, we collect a sufficiently large sample to reach our objective.

SO3: Personalizing the Selection of eHealth Apps

The effect of using participant data to allocate interventions will be tested by analyzing the difference in activity in different intervention groups. In Figure 2, we denote different groups of participants who are recruited in different "waves." The first two waves will allow us to collect data that we can use to create a model to predict the effectiveness of different interventions for different participants (see the section "Treatment and Control Group Allocation"). We will create a model using the data collected from 300 participants included in the first two waves of the study. Figure 2 shows the 120 interventions given in month 1 and 216 interventions in month 2, which combine to a projected data set of 336 rows to train the model. This model will be used to recommend eHealth apps in the third month, based on the best predicted change in activity for a participant;

thus, effectively, our recommendations will be personalized. To test if personalization is effective, we will again conduct a between samples *t* test, and this time, we will compare the average activity of the "personalized intervention" group (group 3, treatment in Figure 2) to the control group. Similar to the analysis provided above for SO1, we found that our 120 participants in the treatment group in month 3 will be sufficient to conduct this test.

Ethical Approval

This project has been approved by the Ethical Review Board of Tilburg University, the Netherlands. METCBrabant carried out a medical-ethical review and deemed the study to not need additional medical-ethical regulations. In this section, we will (1) detail our recruitment and information materials; (2) outline the process of ethical approval; and (3) discuss our considerations to submit for ethical approval as opposed to medical-ethical approval. We expand on the issues relating to the ethical and legal approval process, as several researchers we spoke to in this process emphasized how unique and interesting the Health Telescope is owing to the scope of the study as well as the design considerations regarding the recently changed European privacy laws. We hope that by sharing our experiences, others can more easily proceed through the required checks for similar projects.

Minimizing Participant Burden

To ensure ethical integrity, we have communicated our goals with the ethics review board of Tilburg University from the start of the project. We were guided in minimizing participant burden by making as many aspects of the study as possible voluntary in nature. To participate, it is not mandatory to wear the wearable, participate in surveys, download the interventional apps, or engage with these apps. This approach upholds academic ethical standards, and the optional engagement design also closely mimics real-world scenarios where users are not bound by rules or rewards to keep engaging with interventional apps and instead rely on their willpower and motivation. This allows close inspection of the effect that personalization has on engagement, activity, and well-being.

Ethical Versus Medical Approval

Academic research in the Netherlands needs to be reviewed and approved by an ethical review board. Additionally, the country maintains a stricter approval process when research is considered medical [37]. To belong in this category, the study needs to (1) involve *medical research* and (2) subject participants to specific actions and behavioral rules, where *medical research* is defined as "research with the goal of answering a question in the area of disease and health (etiology, pathogenesis, phenomena/symptoms, diagnosis, prevention, and result of treatment of a disease) by systematically gathering and studying data. The research aims to contribute to medical knowledge that also holds for populations outside of the direct research population."

Health Telescope falls within a grey area of these criteria. It concerns health behaviors but does not force any rules on the participants. The Health Telescope study design has been assessed by METCBrabant [38] and approved as nonmedical-ethical research. This can be attributed to the voluntary nature of every aspect of the panel. Panel members have the choice to act on any recommendation, and data collection (as detailed in the section "Data Collection") is optional for every data type.

GDPR Compliance

On April 14, 2018, the GDPR [39] was adopted. Under this legislation, every entity dealing with data within the European Union has to comply with a set of data rights aimed to give the group of users, formalized as *data subjects*, more rights over the data they produce. The Health Telescope project was designed to comply with this new regulation. Under the GDPR, data collection and storage need to be done in a way that puts data subjects in control of their data, and privacy is ensured by design. The GDPR officer of Tilburg University checked the study's alignment with the GDPR principles and approved the study. Since this law is novel, we devote special attention to the actions taken when setting up Health Telescope to comply with GDPR regulations. We discuss each identified right and subsequently detail how our study setup complies. The eight rights that data subjects have, as well as the way we implement these rights, are as follows:

1. Right to be informed: Data subjects have the right to be informed about the processing of their data, as well as any changes to the data made due to any of the other rights. We comply with this right by design, by informing participants of what data are collected and why this is useful, sharing the results from the study, and keeping an open line of communication in case any information is not clear using the Health Telescope app.
2. Right to access: Data subjects have the right to, at any time, ask whether their data are being processed for any reason and, if so, request access to their data. This right is included in Health Telescope. The way data are processed is communicated from the start of the study through the information received by participants. Additionally, participants can request access to their data at any time by sending an email to the Health Telescope team. These requests are processed within 4 weeks.
3. Right to data portability: Data subjects have the right to, at any time, transfer their data from one digital processing system to another. We incorporate this right similarly to the right to access. Participants can get a full copy of their data and can receive extracts from our server in CSV files by sending an email request.
4. Right to restrict processing: Data subjects have the right to restrict the processing of their data to the procedures they consent to. This right is included in our design in two ways. First, participants can choose whether they want data to be recorded for any data type separately, and they can change their consent on this at any time. Second, if additional research is done through Health Telescope, participants can choose to opt-in or out of this research.
5. Right to object: Data subjects have the right to object to any processing of their personal data. The combination of implementing right 2 and right 4 leads to compliance with this right. The use of communication channels combined

with participants' ability to have their data erased ensures compliance.

6. Right to rectification: Data subjects have the right to have any incorrect data of theirs that is stored be rectified by the data controller. Through the implementation of the right to access and clear communication, we aim to give participants the tools that also ensure this right is respected. If participants want any incorrect data to be rectified, it will be rectified.
7. Right to erasure: Data subjects have the right to, when data is processed with their consent as a legal basis, withdraw this consent and have all personal data deleted entirely. We include this right in our design. Participants have the ability to delete their data irreversibly.
8. Right to not be subject to automated processing: Data subjects have the right to not be subject to decisions made purely from automated processing. This includes profiling, which produces legal effects greatly affecting them. This specific right has three exceptions to it [40]. For the interventions in Health Telescope, we need to automatically process data into a set of rules. One of the exceptions to this right is informed consent. If participants are aware that their data can be used for the interventions and consent to it, we can use automated processing.

Transmission of data between devices uses HTTPS encryption, and all data are kept in encrypted storage. Servers can only be accessed after user authorization, and all server access is logged. In case of a data leak, we will follow the protocol for data leaks as defined by Tilburg University [6,39,41].

Dissemination

Publishing

The research findings following the Health Telescope study will be presented at international conferences, as well as reported in international peer-reviewed academic journals. Other longitudinal panel studies have increased the scientific output from their research by allowing additional researchers to analyze the panel data. We aim to follow this procedure. The Health Telescope team is actively open to cooperation with organizations interested in the data generated in the study. Applying for data access or cooperation will be possible through the Health Telescope website.

Data Management

The Health Telescope app and database were created by RoboticBit. The database can be accessed by researchers through an authoring client, a web interface with tools for researchers to set up surveys, distribute interventions, and manage participants. The database will be realized and managed on the network of Technical University Eindhoven. Participants can request access to their data by sending an email to the Health Telescope team. The primary researchers of the Health Telescope team will have full access to the database. Any additional researchers who would like to access the data can request extracts of the part of the data that they need.

Data Sharing

During the panel study and for a maximum of 10 years after the data collection has concluded, we aim to give researchers access to the collected data. There is a procedure to access the data based on explicit consent from participants, as the data are very sensitive.

Results

Funding for the project began in November 2017. Ethical approval was obtained in February 2019. Privacy and data handling were investigated and approved in a data protection impact assessment performed by Technical University Eindhoven in April 2019. The data collection software has been developed, and an internal pilot was held in June 2019. Another pilot was planned for Q2 of 2020 but has been postponed owing to COVID-19 quarantine measures. We currently expect to start recruitment in Q4 of 2020. Initial results will be published in 2021, and the full study will take 4 months.

Discussion

Revisiting the Objectives

The Health Telescope study aims to investigate how different individuals respond to different ways of being encouraged to increase their physical activity using eHealth apps. The study was specifically designed to allow for long-term data collection as the long-term effects of the use of eHealth apps are largely unknown. This long-term data collection allows us to satisfy our first goal (SO1) of estimating the long-term effects of eHealth interventions and allows us to passively collect enough data to accomplish the second goal (SO2) of comparing short- and long-term outcomes. Finally, our interventions allow us to test whether a personalized selection of eHealth apps improves their effectiveness (SO3). Note that we have specifically selected apps using different behavioral change techniques. This allows us to not only simply test the effect of the app but also compare how different techniques influence a person.

We hope that our thorough description of the process of setting up this panel study is able to accomplish the objectives of this paper. To accomplish the first objective (PO1), we detailed the panel setup, explaining both the process and reasoning for our decisions. We described the process of being in the panel, showed the collected data, and included the steps for data access to accomplish the second objective (PO2) and help future researchers who want to use Health Telescope data. Finally, we detailed the design, approval procedures, and plans for analysis to achieve the third objective (PO3) and guide researchers interested in setting up similar research.

Limitations

One aspect of the study that carries risk is the potential loss of data that may come with the power that Health Telescope participants have over their data. While the information supplied to participants can help them understand why the collection of data is important, their preferences toward privacy might hinder data collection. To limit this risk, we have performed a pilot assessment focused on user experience and have made some

alterations to the app based on the results of this pilot. Additionally, as recruitment is gradual, we can observe participant behavior and investigate any risks during recruitment. Another factor that is difficult to estimate is the dropout rate in the panel. While measures to minimize the consequences of dropout have been put in place, such as a plan to keep participants engaged, periodic recruitment to keep an active panel, a panel size allowing for some dropout, and an iterative study design, it is important to closely monitor dropout.

A potential confounding factor in our setup is the fact that the Health Telescope app itself provides minimal feedback regarding the activity of the participant. While this might influence the behavior of participants, not showing such feedback was deemed not feasible in pretests as participants wondered whether their MiBand was properly paired. However, given that our final comparisons are experimental and the feedback the Health Telescope app provides is the same in the treatment and control arms, we believe that this minimal feedback does not interfere with our objectives.

Panel studies are known to have several types of biases, including attrition bias of dropout, nonresponse bias, selection bias, and participation bias. These biases could distort the results if they lead to a homogeneous participant group. To limit this, recruitment is performed through multiple channels, and gradual recruitment. Close monitoring for participant group consistency can help shape the desired diverse group of participants.

Conclusions

This protocol described the setup of the Health Telescope study. Health Telescope will enable us to answer several pressing questions regarding the long-term effectiveness of eHealth apps designed to motivate users to lead an active lifestyle. Furthermore, the longitudinal nature of the study, combined with the unique ability to provide interventions over time, will allow us to study the effects of personalizing eHealth recommendations. We hope that by sharing this protocol, we can make it easier for others to (1) analyze the data resulting from the Health Telescope study, which we aim to disclose, and (2) set up their own longitudinal evaluations of the effectiveness of eHealth apps.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Introduction survey.
[DOCX File , 27 KB - resprot_v9i7e16471_app1.docx]

References

1. UN. General Assembly (66th sess. : 2011-2012). President, UN. General Assembly. High-Level Meeting of Heads of State and Government on the Prevention and Control of Non-Communicable Diseases (2011 : New York). Political Declaration of the High-Level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases : draft resolution / submitted by the President of the General Assembly. World Health Organization. 2011 Sep 16. URL: https://digitallibrary.un.org/record/710899?ln=en [accessed 2020-07-08]
2. Kamphuis MH, Geerlings MI, Tijhuis MA, Giampaoli S, Nissinen A, Grobbee DE, et al. Physical inactivity, depression, and risk of cardiovascular mortality. Med Sci Sports Exerc 2007 Oct;39(10):1693-1699. [doi: 10.1249/mss.0b013e3180f6109f] [Medline: 17909394]
3. Lee I, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012 Jul 21;380(9838):219-229 [FREE Full text] [doi: 10.1016/S0140-6736(12)61031-9] [Medline: 22818936]
4. Kamphuis MH, Geerlings MI, Tijhuis MA, Giampaoli S, Nissinen A, Grobbee DE, et al. Physical inactivity, depression, and risk of cardiovascular mortality. Med Sci Sports Exerc 2007 Oct;39(10):1693-1699 [FREE Full text] [doi: 10.1249/mss.0b013e3180f6109f] [Medline: 17909394]
5. Knowledge Sourcing Intelligence LLP. Mobile Health (mHealth) App Market - Industry Trends, Opportunities and Forecasts to 2023. Research and Markets. 2017. URL: https://www.researchandmarkets.com/reports/4435917/mobile-health-mhealth-app-market-industry [accessed 2020-07-08]
6. Android and Google Play statistics. AppBrain. 2020 Jul 08. URL: https://www.appbrain.com/stats/ [accessed 2020-07-08]
7. Helf C, Hlavacs H. Apps for life change: Critical review and solution directions. Entertainment Computing 2016 May;14:17-22. [doi: 10.1016/j.entcom.2015.07.001]
8. Enam A, Torres-Bonilla J, Eriksson H. Evidence-Based Evaluation of eHealth Interventions: Systematic Literature Review. J Med Internet Res 2018 Nov 23;20(11):e10971 [FREE Full text] [doi: 10.2196/10971] [Medline: 30470678]

9. Geraghty AW, Torres LD, Leykin Y, Pérez-Stable EJ, Muñoz RF. Understanding attrition from international Internet health interventions: a step towards global eHealth. Health Promot Int 2013 Sep;28(3):442-452 [FREE Full text] [doi: 10.1093/heapro/das029] [Medline: 22786673]
10. Hardiker NR, Grant MJ. Factors that influence public engagement with eHealth: A literature review. Int J Med Inform 2011 Jan;80(1):1-12. [doi: 10.1016/j.ijmedinf.2010.10.017] [Medline: 21112244]
11. Choi NG, Dinitto DM. The digital divide among low-income homebound older adults: Internet use patterns, eHealth literacy, and attitudes toward computer/Internet use. J Med Internet Res 2013 May 02;15(5):e93 [FREE Full text] [doi: 10.2196/jmir.2645] [Medline: 23639979]
12. Kaptein M, De Ruyter B, Markopoulos P, Aarts E. Adaptive Persuasive Systems. ACM Trans. Interact. Intell. Syst 2012 Jun;2(2):1-25. [doi: 10.1145/2209310.2209313]
13. Kuehnhausen M, Frost VS. Trusting Smartphone Apps? To install or not to install, that is the question. 2013 Presented at: IEEE International Multi-Disciplinary Conference on Cognitive Methods in Situation Awareness and Decision Support (CogSIMA); 2013; San Diego. [doi: 10.1109/cogsima.2013.6523820]
14. Girardello M, Michahelles F. AppAware: which mobile applications are hot? 2010 Presented at: The 12th International Conference on Human Computer Interaction with Mobile Devices and Services; September 7-10, 2010; Lisbon. [doi: 10.1145/1851600.1851698]
15. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. JMIR Mhealth Uhealth 2015 Mar 11;3(1):e27 [FREE Full text] [doi: 10.2196/mhealth.3422] [Medline: 25760773]
16. Orji R, Moffatt K. Persuasive technology for health and wellness: State-of-the-art and emerging trends. Health Informatics J 2018 Mar;24(1):66-91. [doi: 10.1177/1460458216650979] [Medline: 27245673]
17. Kock AB, Thyrsgaard M. Optimal sequential treatment allocation. ArXiv e-prints 2017 arXiv:1705.09952 [FREE Full text]
18. Vandelanotte C, Müller AM, Short CE, Hingle M, Nathan N, Williams SL, et al. Past, Present, and Future of eHealth and mHealth Research to Improve Physical Activity and Dietary Behaviors. J Nutr Educ Behav 2016 Mar;48(3):219-228.e1. [doi: 10.1016/j.jneb.2015.12.006] [Medline: 26965100]
19. Csikszentmihalyi M, Larson R. Validity and reliability of the experience-sampling method. In: Flow and the foundations of positive psychology. New York: Springer; 2014:35-54.
20. Health Telescope Documents. Health Telescope. URL: https://health-telescope.com/documents [accessed 2020-07-08]
21. Health Telescope Privacy Policy. Health Telescope. URL: https://health-telescope.com/your-privacy [accessed 2020-07-08]
22. Health Telescope Participation Form. Health Telescope. URL: https://health-telescope.com/participate [accessed 2020-07-08]
23. Goldberg LR. An alternative "description of personality": The Big-Five factor structure. Journal of Personality and Social Psychology 1990;59(6):1216-1229. [doi: 10.1037/0022-3514.59.6.1216]
24. Magee CA, Heaven PC. Big-Five personality factors, obesity and 2-year weight gain in Australian adults. Journal of Research in Personality 2011 Jun;45(3):332-335. [doi: 10.1016/j.jrp.2011.02.009]
25. Cacioppo JT, Petty RE. The need for cognition. Journal of Personality and Social Psychology 1982 Jan;42(1):116-131. [doi: 10.1037/0022-3514.42.1.116]
26. Cacioppo JT, Petty RE, Kao CF, Rodriguez R. Central and peripheral routes to persuasion: An individual difference perspective. Journal of Personality and Social Psychology 1986;51(5):1032-1043. [doi: 10.1037/0022-3514.51.5.1032]
27. Steward WT, Schneider TR, Pizarro J, Salovey P. Need for Cognition Moderates Responses to Framed Smoking-Cessation Messages1. J Appl Social Pyschol 2003 Dec;33(12):2439-2464. [doi: 10.1111/j.1559-1816.2003.tb02775.x]
28. El-Amrawy F, Nounou MI. Are Currently Available Wearable Devices for Activity Tracking and Heart Rate Monitoring Accurate, Precise, and Medically Beneficial? Healthc Inform Res 2015 Oct;21(4):315-320 [FREE Full text] [doi: 10.4258/hir.2015.21.4.315] [Medline: 26618039]
29. Wen D, Zhang X, Liu X, Lei J. Evaluating the Consistency of Current Mainstream Wearable Devices in Health Monitoring: A Comparison Under Free-Living Conditions. J Med Internet Res 2017 Mar 07;19(3):e68 [FREE Full text] [doi: 10.2196/jmir.6874] [Medline: 28270382]
30. Simons CJ, Drukker M, Evers S, van Mastrigt GA, Höhn P, Kramer I, et al. Economic evaluation of an experience sampling method intervention in depression compared with treatment as usual using data from a randomized controlled trial. BMC Psychiatry 2017 Dec 29;17(1):415 [FREE Full text] [doi: 10.1186/s12888-017-1577-7] [Medline: 29284448]
31. de Leeuw ED. Dropouts in Longitudinal Data. In: Encyclopedia of Statistics in Behavioral Science. Hoboken, New Jersey, United States: John Wiley & Sons; 2005.
32. Yap SC, Anusic I, Lucas RE. Does happiness change? Evidence from longitudinal studies. In: Stability of Happiness. Amsterdam: Elsevier; 2014:127-145.
33. Veenhoven R. Measures of Happiness: Which to Choose? In: Metrics of Subjective Well-Being: Limits and Improvements. New York: Springer; 2017:65-84.
34. GGD AppStore. URL: https://ggdappstore.nl [accessed 2020-07-08]
35. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]

36. Bohannon RW. Number of pedometer-assessed steps taken per day by adults: a descriptive meta-analysis. Phys Ther 2007 Dec;87(12):1642-1650. [doi: 10.2522/ptj.20060037] [Medline: 17911274]
37. Wet Medisch-wetenschappelijk onderzoek met mensen. CCMO. URL: https://www.ccmo.nl/onderzoekers/wet-en-regelgeving-voor-medisch-wetenschappelijk-onderzoek/wetten/wet-medisch-wetenschappelijk-onderzoek-met-mensen-wmo [accessed 2020-07-08]
38. METC Brabant. URL: https://metcbrabant.nl [accessed 2020-07-08]
39. EU GDPR. URL: https://eugdpr.org/ [accessed 2020-07-08]
40. GDPR: Automated individual decision-making, including profiling. GDPR. URL: https://gdpr-info.eu/art-22-gdpr/ [accessed 2020-07-08]
41. Research Data Management Regulations. Tilburg University. 2019. URL: https://www.tilburguniversity.edu/sites/default/files/download/Vertaling%20Regeling%20onderzoeksdatamanagement%20%28Jan2019%29_2.pdf [accessed 2020-07-08]

Abbreviations

BART: Bayesian additive regression tree
ESM: experience sampling method
GGD: Gemeenschappelijke Gezondheidsdienst
GDPR: General Data Protection Regulation
PO: protocol objective
SO: study objective

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Protocol

Development of a Short Instrument for Measuring Health-Related Quality of Life in Oncological Patients for Clinical Use: Protocol for an Observational Study

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Abstract

Background: Cancer patients often suffer from the physical and psychological burden of their disease and its treatment. This is frequently insufficiently identified and addressed in clinical practice. In the context of improving patient-centered care in oncological patients, patient-reported outcomes (PROs) represent an important addition to current routine care. So far, available PRO questionnaires for cancer patients are unsuitable for routine procedures due to their length and complexity.

Objective: This study aimed to develop and psychometrically test a short questionnaire to measure health-related quality of life (HrQoL) in cancer patients for use in routine care.

Methods: This observational study consists of two parts: (1) a qualitative study to develop a short questionnaire measuring HrQoL and (2) a quantitative study to psychometrically test this questionnaire in five oncological departments of a comprehensive cancer center. In part 1 of the study, semistructured interviews with 28 cancer patients, as well as five focus groups with 22 clinicians and nurses, were conducted to identify clinically relevant dimensions of HrQoL. The identified dimensions were complemented with related dimensions from empirical studies and reviewed via expert discussion. Based on this, a short instrument was developed. In part 2 of the study, the developed questionnaire was tested in cancer in- and outpatients at five participating oncological clinics using additional standardized questionnaires assessing HrQoL and other important PROs. The questionnaire was presented to more than 770 patients twice during treatment.

Results: The project started in May 2017 with recruitment for study phase I beginning in December 2017. Recruitment for study phases I and II ended in April 2018 and February 2019, respectively. After study phase II and psychometrical analyses, the newly developed questionnaire measuring the HrQoL of all cancer entities in routine care was finalized.

Conclusions: With five to six dimensions and one item per dimension, the developed questionnaire is short enough to not disrupt routine procedures during treatment and is profound enough to inform clinicians about the patient's HrQoL impairments and status.

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International Registered Report Identifier (IRRID): RR1-10.2196/17854

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KEYWORDS

patient-reported outcomes; health-related quality of life; oncology; psychometric validation; mixed methods study

Introduction

In addition to morbidity rates, the impact of health-related quality of life (HrQoL) has grown in cancer treatment [1]. Medical research shows a continual improvement in early detection and treatment of cancer [1]. Subsequently, there are more long-term survivors, though patients often suffer from the consequences of cancer and its treatment [2]. Assuming that cancer has become a chronic disease for many patients, the HrQoL of cancer patients needs further attention in routine procedures [3].

Cancer patients' role (eg, in a family or group of friends), their relationship to their spouse, and their social life can be affected by psychological impairments [4,5]. Also, the perceived existential threat to the integrity of patients can have a psychological impact [4]. As a consequence, psychosocial distress, as well as psychological comorbidities (ie, anxiety and depressive disorders) can occur or be amplified during or after treatment [6].

Symptoms of cancer are more or less distinct, depending on the cancer entity [7]. Prostate carcinoma, for example, depicts a symptom-free course for months or years in most cases [8]. On the other hand, pituitary tumors can affect the life of the person immensely [9]. Cancer patients often experience severe side effects due to their treatment such as pain, fatigue, weak immune system, indigestion, sexual dysfunction, nausea, or hair loss [10]. Correspondingly, the negative impact on the patient's HrQoL can be significant [5], which emphasizes the importance of focusing on HrQoL in clinical practice and research.

In the 1990s, HrQoL was established as an essential part of cancer treatment, and since then it has existed alongside disease-related outcomes [3]. Furthermore, HrQoL can be used to evaluate treatment in cancer patients [11]. At present, HrQoL is used as a parameter for benefit-cost analysis [12], assessing which limitations in quality of life can be endured in exchange for prolonged life. HrQoL proves to be an aspect of patient-reported outcomes (PROs) since information given by the patients themselves [12] is the best source from which state of health can be adequately assessed [11]. This highlights the importance of integrating PROs, and thus HrQoL, into patient-centered care since they have been proven to be more reliable than the clinician's assessment; they can also aid with earlier symptom identification [13]. Therefore, PROs should be implemented into clinical practice to improve screening of distress, optimize treatment, and measure quality of care [14-20].

The question that is raised is whether HrQoL impairment in a patient is taken into account in cancer treatment. Time is a scarce resource for medical staff and has to be spent carefully [21]. Although patient-centered care, including HrQoL, is eminent and part of the German National Cancer Plan [22], there is currently no sufficient resource-oriented procedure to measure, analyze, interpret, or act upon HrQoL data [23]. Even though there already exists questionnaires to measure HrQoL in oncological patients, the complexity and time-consuming nature of these assessments prevent use in clinical routine. An example of a PRO questionnaire is the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QoL-C30) [24]. It is a highly recommended tool for the measurement of HrQoL in cancer patients [25]. Since it comprises eight scales, several additional single items, and disease-specific modules, it is not practical for use during routine procedures [26]. Oncological patients are generally older and should be questioned several times over the course of treatment; therefore, a long questionnaire like the EORTC QoL-C30 depletes more capacity than available for both patients and practitioners [27]. These difficulties also occur with other instruments (eg, Functional Assessment of Cancer Therapy [Fact-G] [28], World Health Organization Quality of Life [WHOQOL] [29]) and result in insufficient integration of PRO measurements in clinical routine procedures [27].

This issue can be improved by implementing measurements that are shorter, more adaptive, and prompt action. For example, the Distress Thermometer (DT) is short, which makes it a more applicable instrument [30]. Developed by the National Comprehensive Cancer Network (NCCN), this screening tool determines the type and extent of psychosocial distress in oncological patients. Though it does not measure all aspects of HrQoL, it is often used in clinical practice to screen for need of support and shortages in a patient's HrQoL. It consists of an 11-step analogue scale from 0 to 10 to measure distress, and a list of problems. However, the NCCN-DT is only used in screening procedures [30] and misses relevant dimensions of HrQoL such as physical complaints and autonomy [31]. Including its list of problems, the NCCN-DT amounts to 36 items, which is a problematic length for a questionnaire used in routine care [27]. Due to its high feasibility [30], however, the NCCN-DT is able to function as a first step in the development of a reliable and adequate instrument in assessing HrQoL in oncological patients.

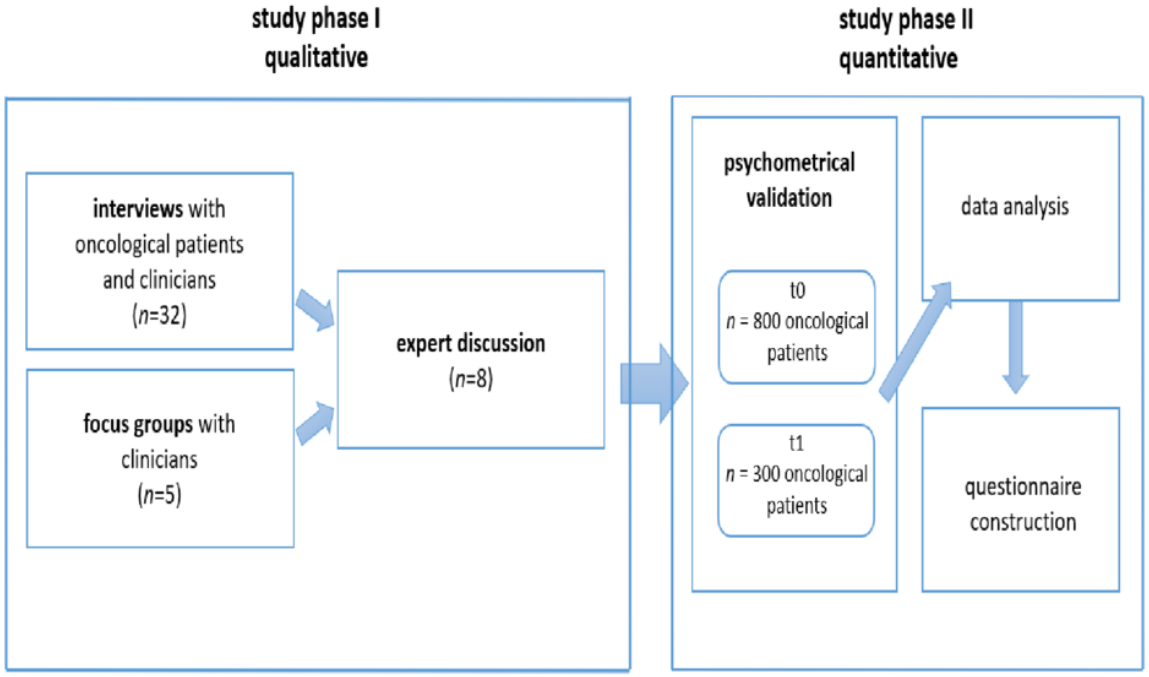
Hence, there are no suitable short instruments to measure HrQoL in oncological patients for use in clinical routine care. The present study is the first part of a larger project that ultimately targets the implementation of PROs in cancer care clinical practice at the University Medical Center Hamburg-Eppendorf. The aim of this study is to develop a psychometrically validated short instrument with six visual analogue scales with one item each, for repeated measurement of HrQoL of oncological in- and outpatients generalized for all cancer entities. Use of the new instrument in clinical practice is expected to improve patient-centered care, as well as data management for continuous health care research.

Methods

Design

In order to develop a validated and reliable instrument, an observational study with a mixed methods design was conducted (Figure 1). The study consists of two phases, making use of qualitative and quantitative data and analyses. Recruitment of study participants took place at the University Medical Center Hamburg-Eppendorf, where the developed instrument will also be implemented. The implementation process is outlined elsewhere [32]. Inclusion criteria for patients are a cancer diagnosis, sufficient language skills in German, and no cognitive or verbal impairments in providing information and giving informed consent.

Figure 1. Study design.



Study Phase I

The aim of study phase I is to develop five to six relevant dimensions of HrQoL for cancer patients. For this purpose, interviews with oncological patients (n=28) were conducted. To facilitate further discussion and exchange, five focus groups with oncologists, oncological nurses, and psychologists on relevant dimensions of HrQoL were undertaken. Patients as well as clinicians were asked to evaluate the HrQoL dimensions in general and in regard to cancer treatment. Since senior clinicians could not be present at the focus groups, interviews (n=4) were conducted instead.

The outcome of attained qualitative data was presented to a group of eight experts for discussion. Psychooncologists, oncologists, patient representatives (leaders of self-help groups), quality of life scientists, staff nurses, a quality management representative, and a health insurance representative were included. On the grounds of these outcomes and of the current state of research, the dimensions for the instrument were identified. Items were phrased and discussed among project group members. Wording, meaning, and overall feasibility of the items were verified by means of a survey of health care researchers (n=5). This phase began in December 2017 and ended in April 2018. For additional feasibility testing, a pilot study was carried out. Three patients were asked to evaluate the newly developed instrument by using the reading-out-loud technique. Since no requests for modification of the instrument were voiced, the instrument was readied for psychometrical testing.

Study Phase II

To psychometrically test the developed questionnaire, oncological in- and outpatients with different cancer diagnoses and stages of disease were asked to participate. The questionnaire was presented to the subjects in paper-pencil format. Furthermore, medical data were retrieved from the Soarian Clinicals patient documentation system of the University Medical Center Hamburg-Eppendorf. A pilot run was conducted in May 2018. Three patients were asked to provide their opinion using the reading-out-loud technique in order to assess the comprehensibility and feasibility of the questionnaire. The statistical survey started in June 2018 and ended in February 2019.

Cooperation Partners

Recruitment of patients in study phases I and II was carried out in cooperation with the Medical Clinic and Polyclinic, the Department of Stem Cell Transplantation, the Department of Gynecology, the Department of Radiotherapy and Radiation Oncology, and the Institute and Polyclinic for Medical Psychology.

Recruitment and Procedures

Study Phase I

Potential patients to be questioned were pointed out by staff. The appointed patients were asked to participate and interviewed by research staff. We planned to conduct 28 interviews with oncological patients; four additional interviews with senior clinicians were conducted. Medical staff and external experts were approached and asked to participate. After written consent, they were invited to either an interview, a focus group, or a summarizing discussion. We planned to conduct five focus groups and one expert discussion.

Study Phase II

Potential inpatients to be questioned were pointed out by staff in the outpatient departments; oncological patients were addressed directly by research staff. Inpatients were questioned twice, once at the beginning of their treatment and then again 3-7 days later. The interval of time for questioning outpatients differed due to practice procedures. They were asked to participate once during their treatment and again 1 week later.

Patient and Clinician Involvement

Patients and clinicians were not involved in the study design. Patients first became involved during study phase I when they were interviewed regarding their HrQoL appraisal. Clinicians were involved in the recruitment process and execution of the study. In study phase I, chief physicians were asked to support recruitment of clinicians by asking their staff to participate. For study phases I and II, clinicians were asked to point out potential patients to be questioned. Patients were selected on the basis of assessments made by the clinicians. For example, severe pain or low responsiveness in some cases prevented patients from participating. In order to assess the comprehensibility and feasibility of the questionnaire, three patients were asked to give their opinion using the reading-out-loud technique (pilot study).

Measurements and Outcomes

Study Phase I

A semistructured interview guide was developed based on Helfferich [33], asking one main question concerning relevant dimensions of HrQoL to be assessed in routine care. An example of such a question is “If you imagine that your current doctor asks you about your quality of life, physical and mental stress, what would be important for you? / What should not be forgotten?”. For focus groups, a focus group guide was developed based on Barbour [34], including the same main question used in the interview guide.

Study Phase II

To test the validity and reliability of the developed questionnaire, a series of established standardized measurements were included in the quantitative survey. In addition to the developed questionnaire, sociodemographic and standardized questionnaires assessing HrQoL (Fact-G [28]), Distress Thermometers [30], Short Form 8 Health Survey (SF-8) [35]), dignity (German version of the Patient Dignity Inventory [PDI-G] [36]), as well as depressive and anxiety symptoms (Patient Health Questionnaire-4 [PHQ-4] [37]), were included for psychometric purposes. These standardized questionnaires were included to validate the newly developed questionnaire. The priority objective of study phase II is a reduction to five to six HrQoL dimensions with one item each. The final result of this study phase is a psychometrically validated short instrument to assess HrQoL in cancer patients for use in routine clinical practice.

Data Analysis

Qualitative Analysis

Interviews, focus groups, and expert discussion were carried out by scientists, recorded, and afterwards transcribed by study staff. The qualitative data was structured via the software program MAXQDA 10 and analyzed using qualitative content analysis based on Mayring [38]. Within the procedure of analyzing the data, deductive-inductive category application was used: deductive main categories (generated through literature research) and inductive subcategories (derived from the qualitative text analysis of the interviews and focus groups). Quality criteria to be examined for the qualitative content analysis are interrater reliability and communicative validation.

Quantitative Analysis

For study phase II data, an exploratory structural equation model (principal component analysis) was planned to be computed via SPSS (IBM). Reliability as well as validity (internal consistency, construct validity, content validity, criterion validity, correlations, and responsiveness) of the instrument were assessed through item and scale analysis. Missing data were compensated for by an expectation–maximization algorithm [28]; in cases of missing data of more than 30% per case, exclusion of data was carried out. Transformations of data were only applied if required by the data structure (ie, nonnormality of residuals). Exclusion of data due to systematic bias or false statement was not necessary. Further exploration of the data to look for unexpected differences or relationships were undertaken using subgroup analysis.

Sample Size and Power

Confirmative models allowed for the determination of an appropriate sample size; based on Monte Carlo study results, for a power of 80%, a sample size of at least 460 patients is needed [39]. Calculating a dropout rate of 40%, a minimum number of 770 addressed patients ensures enough data will be obtained.

Ethics and Dissemination

The intention of this project is to improve psychosocial care for cancer patients in routine clinical practice. Patients and health care professionals were asked to participate by joining focus groups and interviews and by completing questionnaires. The written survey methodology does not involve direct intervention in medical procedures. We expect no risks or disadvantages for patients, although one potential but unlikely stressor may arise as participants confront the shortcomings of their quality of life. This could have a negative influence on adjustment to and handling of the illness. However, the participating clinics of this project already offer psychooncological support, which is

also available for the patients in this study. A written informed consent is mandatory for participation in the study. Patients interested in the study were informed about the voluntary nature of participation and the possibility to refuse or discontinue participation at any time without any negative consequences. Additionally, patients were informed about the study's aims and personal risks. For further questions concerning the study, the contact details of study assistants were provided. The study received approval by the ethics committee of the Medical Association of Hamburg (reference number: PV5636).

The project started in May 2017 and is planned for 36 months. In December 2017, the first interviews were carried out. Qualitative data of the first study phase were evaluated by April 2018. Quantitative data collection was conducted from June 2018 to February 2019 with subsequent analysis of the obtained data.

Regarding the dissemination plan, two further publications regarding the development of the short instrument for cancer patients will be published (eg, one paper on study phase I and one paper on study phase II).

Results

This project is funded by Innovationsfond des Gemeinsamen Bundesausschusses (grant number: 01VSF16024). Recruitment was completed in February 2019.

So far, 32 interviews, 5 focus groups, and 1 expert discussion have been conducted. On the grounds of the qualitative analyses of the obtained material, six dimensions with 10 items were identified. After study phase II (n=630) and psychometrical analyses, the newly developed questionnaire (HELP-5 [Hamburger Inventar zur Erfassung von Lebensqualität bei onkologischen Patienten]; English translation: Hamburg Inventory for Measuring Quality of Life in Oncological Patients), comprising five dimensions with one item each to measure HrQoL in all cancer patients in routine care, was finalized. The first results of both study phases are expected to be submitted for publication by the end of 2020.

Discussion

HrQoL is of vast importance for cancer patients. In the context of improving oncological patient-centered care, continuous PRO monitoring represents an important addition to current routine care to identify and address patients' needs [40,41]. As patients are highly affected by their disease and its treatment, tools for measuring HrQoL need to be a permanent feature of routine care. At present, instruments measuring HrQoL do not match the requirements of routine care (ie, brevity, adaptiveness, simplicity). The questionnaire developed in this study should be able to meet the above-mentioned requirements. With five to six dimensions and one item per dimension, the developed questionnaire is short enough to not disrupt routine procedures during treatment but is profound enough to inform clinicians about the patient's impairments and course concerning HrQoL.

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Authors' Contributions

HS, C Bokemeyer, NK, CP, C Bleich, and VM wrote the grant proposal and obtained funding. All authors were involved in the conception and design of this study. TS and MG developed the study materials and acquired the data. TS and MG analyzed and interpreted the data. TS wrote the draft of this manuscript; HS, MG, and C Bleich provided revisions. All authors gave final approval of the version to be published.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Funding report.
[PDF File (Adobe PDF File), 112 KB - resprot_v9i7e17854_app1.pdf]

References

1. Rowland JH, Bellizzi KM. Cancer Survivorship Issues: Life After Treatment and Implications for an Aging Population. JCO 2014 Aug 20;32(24):2662-2668. [doi: 10.1200/jco.2014.55.8361]
2. Mehnert A, Brähler E, Faller H, Härter M, Keller M, Schulz H, et al. Four-Week Prevalence of Mental Disorders in Patients With Cancer Across Major Tumor Entities. JCO 2014 Nov 01;32(31):3540-3546. [doi: 10.1200/jco.2014.56.0086]
3. Bumeder I. Lebensqualität - Begriff und Operationalisierung. In: Dorfmüller M, Dietzfelbinger H, editors. Psychoonkologie - Diagnostik - Methoden - Therapieverfahren. München: Urban & Fischer Verlag; 2013:455-461.
4. Bergelt C, Schölermann C, Koch U. Psychoonkologische Versorgung im Akutkrankenhaus. In: Weis J, Brähler E, editors. Psychoonkologie in Forschung und Praxis. Stuttgart: Schattauer Verlag; 2013:79-90.

5. Kusch M, Labouvie H, Hein-Nau B. Klinische Psychoonkologie. Berlin Heidelberg: Springer-Verlag; 2013.
6. Singer S, Das-Munshi J, Brähler E. Prevalence of mental health conditions in cancer patients in acute care--a meta-analysis. Ann Oncol 2010 May;21(5):925-930 [FREE Full text] [doi: 10.1093/annonc/mdp515] [Medline: 19887467]
7. Dietzfelbinger H, Heußner P. Kriterien der Lebensqualität. In: Dorfmüller M, Dietzfelbinger H, editors. Psychoonkologie - Diagnostik - Methoden - Therapieverfahren. München: Urban & Fischer Verlag; 2013:E-70.
8. Graefen M. Prostatakarzinom. In: Hautmann R, Gschwend J, editors. Urologie. Berlin Heidelberg: Springer-Verlag; 2014:217-229.
9. Saeger W. Hypophyse. In: Klöppel G, Kreipe HH, Remmele W, editors. Pathologie. Urogenitale und Edokrine Organe, Gelenke und Skelett. Berlin Heidelberg: Springer-Verlag; 2016:587-629.
10. Aigner K, Stephens F, Allen-Mersh T, Hortobagyi G, Khayat D, Picksley S. Krebstherapie. In: Aigner KR, Stephens FO, editors. Onkologie Basiswissen. Berlin Heidelberg: Springer-Verlag; 2016:77-105.
11. Bullinger M, Blome C, Sommer R, Lohrberg D, Augustin M. [Health-related quality of life: a pivotal endpoint in benefit assessment of medical procedures]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2015 Mar 15;58(3):283-290. [doi: 10.1007/s00103-014-2107-0] [Medline: 25589357]
12. Berhnhard J, Ribi K. Lebensqualität in der Onkologie - Klinik und Forschung. In: Weis J, Brähler E, editors. Psychoonkologie in Forschung und Praxis. Stuttgart: Schattauer Verlag; 2013:3-15.
13. Basch E. The Missing Voice of Patients in Drug-Safety Reporting. N Engl J Med 2010 Mar 11;362(10):865-869. [doi: 10.1056/nejmp0911494]
14. Darzi L. High Quality Care For All: NHS Next Stage Review Final Report. London: Department of Health UK; 2008.
15. Devlin N, Appleby J. Getting the most out of PROMs: Putting health outcomes at the heart of NHS decision making. London: The King's Fund; 2010.
16. Fashoyin-Aje LA, Martinez KA, Dy SM. New patient-centered care standards from the commission on cancer: opportunities and challenges. J Support Oncol 2012 May;10(3):107-111. [doi: 10.1016/j.suponc.2011.12.002] [Medline: 22440532]
17. McGrail K, Bryan S, Davis J. Let's all go to the PROM: the case for routine patient-reported outcome measurement in Canadian healthcare. Healthc Pap 2011 Jan 2;11(4):8-18; discussion 55. [doi: 10.12927/hcpap.2012.22697] [Medline: 22543287]
18. Mitchell AJ. Pooled Results From 38 Analyses of the Accuracy of Distress Thermometer and Other Ultra-Short Methods of Detecting Cancer-Related Mood Disorders. JCO 2007 Oct 10;25(29):4670-4681. [doi: 10.1200/jco.2006.10.0438]
19. Health Outcomes of Care: An idea whose time has come. Ottawa: Canadian Instiute for Health Information; 2012.
20. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. The Lancet 2009 Aug;374(9687):369-370. [doi: 10.1016/s0140-6736(09)61400-8]
21. Schlag PM. Anforderungen und Erwartungen an die Psychoonkologie aus Sicht des chirurgischen Onkologen. In: Weis J, Brähler E, editors. Psychoonkologie in Forschung und Praxis. Stuttgart: Schattauer Verlag; 2013:139-144.
22. Nationaler Krebsplan: Handlungsfelder, Ziele und Umsetzungsempfehlungen. Bonn: Bundesministerium für Gesundheits; 2017 Dec. URL: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Praevention/Broschueren/Broschuere_Nationaler_Krebsplan.pdf [accessed 2020-05-16]
23. Schmidt H, Merkel D, Koehler M, Flechtner H, Sigle J, Klinge B, et al. PRO-ONKO-selection of patient-reported outcome assessments for the clinical use in cancer patients-a mixed-method multicenter cross-sectional exploratory study. Support Care Cancer 2016 Jun 16;24(6):2503-2512. [doi: 10.1007/s00520-015-3055-4] [Medline: 26676238]
24. Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993;85(5):365-376. [doi: 10.1037/t01822-000]
25. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer 2002 Mar;38(4):125-133. [doi: 10.1016/s0959-8049(01)00448-8]
26. Bascioni R, Giorgi F, Esperide B, Iacopini D, Brugni M, Giustini L, et al. Quality of life (QOL) assessment with EORTC QLQ-C30 in daily clinical practice. JCO 2005 Jun;23(16):8205-8205. [doi: 10.1200/jco.2005.23.16_suppl.8205]
27. Boyce MB, Browne JP, Greenhalgh J. The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. BMJ Qual Saf 2014 Feb 06;23(6):508-518. [doi: 10.1136/bmjqs-2013-002524]
28. Bonomi AE, Cella DF, Hahn EA, Bjordal K, Sperner-Unterweger B, Gangeri L, et al. Multilingual translation of the Functional Assessment of Cancer Therapy (FACT) quality of life measurement system. Qual Life Res 1996 Jun;5(3):309-320. [doi: 10.1007/bf00433915]
29. Angermeyer M, Kilian R, Matschinger H. WHOQOL-100 und WHOQOL-BREF. Göttingen: Hogrefe; 2000.
30. Mehnert A, Müller D, Lehmann C, Koch U. Die deutsche Version des NCCN Distress-Thermometers. Zeitschrift für Psychiatrie, Psychologie und Psychotherapie 2006 Jan;54(3):213-223. [doi: 10.1024/1661-4747.54.3.213]
31. Robbeson C, Hugenholtz-Wamsteker W, Meeus M, Devoogdt N, Nijs J, De Groef A. Screening of physical distress in breast cancer survivors: Concurrent validity of the Distress Thermometer and Problem List. Eur J Cancer Care 2018 Jul 24;28(1):e12880. [doi: 10.1111/ecc.12880]

32. Görlach MG, Schrage T, Bokemeyer C, Kröger N, Müller V, Petersen C, et al. Implementation analysis of patient reported outcomes (PROs) in oncological routine care: an observational study protocol. Health Qual Life Outcomes 2020 Jan 2;18(1). [doi: 10.1186/s12955-019-1262-2]
33. Helfferich C. Die Qualität qualitativer Daten. Wiesbaden: VS Verlag für Sozialwissenschaften; 2009.
34. Barbour R. Doing Focus Groups. London: Sage Publications Ltd; 2007.
35. Beierlein V, Morfeld M, Bergelt C, Bullinger M, Brähler E. Messung der gesundheitsbezogenen Lebensqualität mit dem SF-8. Diagnostica 2012 Jul;58(3):145-153. [doi: 10.1026/0012-1924/a000068]
36. Sautier LP, Vehling S, Mehnert A. Assessment of patients' dignity in cancer care: preliminary psychometrics of the German version of the Patient Dignity Inventory (PDI-G). J Pain Symptom Manage 2014 Jan;47(1):181-188 [FREE Full text] [doi: 10.1016/j.jpainsymman.2013.02.023] [Medline: 23830532]
37. Löwe B, Wahl I, Rose M, Spitzer C, Glaesmer H, Wingenfeld K, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord 2010 Apr;122(1-2):86-95. [doi: 10.1016/j.jad.2009.06.019] [Medline: 19616305]
38. Mayring P. Qualitative Inhaltsanalyse: Grundlagen und Techniken. Weinheim: Beltz; 2008.
39. Wolf EJ, Harrington KM, Clark SL, Miller MW. Sample Size Requirements for Structural Equation Models: An Evaluation of Power, Bias, and Solution Propriety. Educ Psychol Meas 2013 Dec 09;76(6):913-934 [FREE Full text] [doi: 10.1177/0013164413495237] [Medline: 25705052]
40. Snyder CF, Aaronson NK, Choucair AK, Elliott TE, Greenhalgh J, Halyard MY, et al. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations. Qual Life Res 2012 Oct;21(8):1305-1314. [doi: 10.1007/s11136-011-0054-x]
41. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. JCO 2016 Feb 20;34(6):557-565. [doi: 10.1200/jco.2015.63.0830]

Abbreviations

DT: Distress Thermometer
EORTC QoL-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
Fact-G: Functional Assessment of Cancer Therapy
HELP-5: Hamburger Inventar zur Erfassung von Lebensqualität bei onkologischen Patienten (Hamburg Inventory for Measuring Quality of Life in Oncological Patients)
HrQoL: health-related quality of life
NCCN: National Comprehensive Cancer Network
PDI-G: Patient Dignity Inventory—German version
PHQ-4: Patient Health Questionnaire-4
PRO: patient reported outcome
SF-8: Short Form 8 Health Survey
WHOQOL: World Health Organization Quality of Life

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Protocol

Decentralized, Community-Based Hepatitis C Point-of-Care Testing and Direct-Acting Antiviral Treatment for People Who Inject Drugs and the General Population in Myanmar: Protocol for a Feasibility Study

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Abstract

Background: The advent of direct-acting antivirals (DAAs) and point-of-care (POC) testing platforms for hepatitis C allow for the decentralization of care to primary care settings. In many countries, access to DAAs is generally limited to tertiary hospitals, with limited published research documenting decentralized models of care in low-and middle-income settings.

Objective: This study aims to assess the feasibility, acceptability, effectiveness, and cost-effectiveness of decentralized community-based POC testing and DAA therapy for hepatitis C among people who inject drugs and the general population in Yangon, Myanmar.

Methods: Rapid diagnostic tests for anti-hepatitis C antibodies were carried out on-site and, if reactive, were followed by POC GeneXpert hepatitis C RNA polymerase chain reaction tests. External laboratory blood tests to exclude other major health issues were undertaken. Results were given to participants at their next appointment, with the participants commencing DAA therapy that day if a specialist review was not required. Standard clinical data were collected, and the participants completed behavioral questionnaires. The primary outcome measures are the proportion of participants receiving GeneXpert hepatitis C RNA test, the proportion of participants commencing DAA therapy, the proportion of participants completing DAA therapy, and the proportion of participants achieving sustained virological response 12 weeks after completing DAA therapy.

Results: Recruitment was completed on September 30, 2019. Monitoring visits and treatment outcome visits are scheduled to continue until June 2020.

Conclusions: This feasibility study in Myanmar contributes to the evidence gap for community-based hepatitis C care in low- and middle-income settings. Evidence from this study will inform the scale-up of hepatitis C treatment programs in Myanmar and globally.

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KEYWORDS

hepatitis C; primary health care; community health services; delivery of health care; point-of-care testing; retention in care; Asia, Southeastern

Introduction

Globally, an estimated 71 million people are living with hepatitis C virus infection [1]. Left untreated, hepatitis C can lead to complications, including cirrhosis, liver failure, and hepatocellular carcinoma [2]. The advent of direct-acting antivirals (DAAs) revolutionized hepatitis C treatment [3-6]. DAAs have few side effects, involve an all-oral regimen, and most people require treatment for only 8-12 weeks [7]. Given that hepatitis C treatment is now simple and safe, there is a push to simplify clinical care pathways to enable rapid scale-up and access to treatments. Although the advent of DAAs made decentralized models of care led by general practitioners (GPs) in primary care settings possible [8,9], the dominant model remains as specialist physicians prescribing at tertiary hospitals. Alongside the introduction of these new treatments, there are various World Health Organization (WHO) prequalified point-of-care (POC) testing and diagnostic technologies available for hepatitis C [10,11]. The availability of POC testing technologies means same-day on-site diagnosis is now possible, reducing the number of times a participant needs to attend the clinic to receive a diagnosis and initiate treatment [7].

Decentralized testing and treatment approaches are supported by the WHO Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection (July 2018) [7], specifically at primary health facilities or harm reduction sites, to promote access to care. These models of care can be implemented using a differentiated care approach that allows for specialist referral as required [7]. Implementation of this model requires simplified diagnostic pathways, training of GPs, specified referral pathways for complicated cases, and access to DAAs in community settings. In this paper, we have defined GPs as medical doctors with no further specialized training after completing their university qualifications. They are sometimes referred to as generalist doctors or primary care physicians in other settings, although it should be noted that in many settings, primary care physicians/GPs often have specialized training. Globally, research trials and programs led by non-government organizations have included decentralized community-based, GP-led models of care [12,13] and, more recently, trials of same-day treatment initiation models [12,14]. However, there is little well-documented evidence of these models of care and their feasibility and effectiveness, particularly in resource-limited settings [12].

In the Republic of the Union of Myanmar (hereafter, Myanmar), an estimated 1.4 million people have hepatitis C infection, and the estimated overall population prevalence is 2.7% [15]. Similar to many resource-limited settings, it is likely that most people acquired hepatitis C in official and nonofficial health care settings, including via unsafe surgery, contaminated blood transfusions, repeated use of syringes for vaccinations/injections, or unsafe dental treatment [7]. At the same time, there is a substantial level of infection among people who inject drugs (PWID), with an estimated 56% prevalence across Myanmar, reaching 84% in some regions [16]. The likely mode of acquisition in this population is through shared injecting equipment.

Currently, in Myanmar, DAAs are mostly available through the National Hepatitis Control Program in tertiary hospitals, the private sector, some international and local nongovernmental organizations, and research projects (generally focusing on people with HIV and hepatitis C co-infection). There is currently limited capacity in centralized laboratories in Myanmar to provide hepatitis C RNA polymerase chain reaction (PCR) testing, other than those utilizing the Cepheid GeneXpert platform.

Given the large numbers of people infected, if treatment is to be accessible to everyone with hepatitis C infection, it is important that treatment is available in both community settings and tertiary hospital settings. Few countries allow GPs to prescribe DAA therapy [17], and Myanmar is one of them [18]. The National Guidelines for the Simplified Treatment of Hepatitis C Virus Infection allow GPs to prescribe DAA therapy and for the use of the Cepheid GeneXpert hepatitis C RNA PCR test to assess if someone has current hepatitis C infection [18]. However, to date, there is insufficient data to assess the success of this decentralized approach, including the use of the community-based diagnostic and treatment pathway in Myanmar and other low-and middle-income settings globally [12,14,19].

The Hepatitis C: Community-based Testing and Treatment Study (CT2 study), undertaken by the Burnet Institute, is part of the Foundation for Innovative New Diagnostics (FIND)–led Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) program funded by Unitaid. It was designed to assess the feasibility of a decentralized hepatitis C model of care in a resource-constrained setting, utilizing POC testing technologies with a GP initiating DAA therapy in the majority of participants, with a pathway of care to tertiary hospitals for people with decompensated cirrhosis. This paper describes the protocol of the CT2 study.

Methods

Study Design

The CT2 study is a feasibility trial of decentralized community-based hepatitis C testing utilizing POC testing

technologies and GP-led DAA treatment initiation and measures on the outcomes of completion of the hepatitis C diagnostic pathway, treatment initiation, and treatment outcomes. The study aimed to treat 450 participants for hepatitis C infection with the pangenotypic regimen sofosbuvir 400 mg and daclatasvir 60 mg.

The study protocol (version 7, June 27, 2019) follows the Standard Protocol Items: Recommendations for Interventional Trials statement. The trial was registered at ClinicalTrials.gov NCT03939013 on May 6, 2019.

Trial Status

Recruitment commenced on January 30, 2019 and was completed on September 30, 2019.

Objectives

This study will determine if implementing this model of care is feasible in Myanmar. It assesses the key requirements for implementation in a resource-constrained setting, the acceptability of the model of care to participants and providers, and the cost of implementing the model in this setting.

Primary Outcome Measures

The primary outcome measures include:

1. The proportion of anti-hepatitis C antibody (Ab)-positive participants who receive a GeneXpert hepatitis C RNA PCR test
2. The proportion of hepatitis C RNA PCR-positive participants who are initiated on DAAs
3. The proportion of participants initiated on treatment who complete therapy (defined as picking up the last 28-day bottle of medication and not reporting >7 days missed doses)
4. The proportion of participants who completed treatment who achieve a sustained virologic response (SVR12).

Secondary Outcome Measures

The secondary outcome measures include:

1. The proportion of participants requiring specialist review
2. Feasibility of the testing and treatment pathways from the provider perspective
3. Acceptability of the testing and treatment pathways participant
4. Costing of POC testing and treatment pathways at community sites
5. Time from the collection of hepatitis C RNA test samples to treatment initiation.

Feasibility Assessment

To assess the feasibility of this model of care, we will focus on 3 of the domains identified by the study by Bowen et al [20]—*How We Design Feasibility Studies*: demand, implementation, and practicality. Demand will be assessed using testing and treatment uptake (primary outcome measures number 1 and number 2). Implementation and practicality will be assessed using the Gericke et al [21] *Intervention Complexity* framework: (1) characteristics of basic intervention, (2) characteristics of delivery, (3) requirements on government capacity, and (4) usage characteristics. For these dimensions, we will focus on the requirements for the GeneXpert device and GP-initiated DAAs.

Study Setting and Recruitment

Study Setting

This study is being conducted in Yangon, Myanmar. Yangon is the largest city in Myanmar, with a population of over 7 million people [22]. Yangon has five hospital sites (three for HIV/hepatitis C co-infected patients, two for hepatitis C mono-infected patients) that can provide hepatitis C treatment at no cost as part of the government-led National Hepatitis Control QuickStart program; a subset of hospitals also provide a subsidized treatment program to patients. However, only a small proportion of patients requiring treatment can currently access treatment through the government-led program. As a consequence, there is a high unmet need for no-cost/low-cost hepatitis C testing and treatment programs among the general population in Yangon as well as for PWID, who are often unable to access hospital-based programs.

Study Sites

The study is being conducted at 2 community clinics in Yangon: the Burnet Institute Thingangyun Key Population Service Clinic (hereafter referred to as the Burnet clinic) and the Myanmar Liver Foundation (MLF) Than Sitt Charity Clinic (hereafter referred to as the MLF clinic). Clinics are staffed by a trained GP (study medical officer), a nurse, and a laboratory technician for the duration of the study, plus a peer worker at the Burnet clinic and reception staff at MLF clinic. These study sites are separate from the hospital program sites described earlier.

The Burnet clinic provides health care services primarily to PWID, including needle and syringe distribution. The Burnet clinic is located in the Thingangyun township near the major methadone treatment center in central Yangon.

The MLF clinic serves the general population of patients with liver disease, with a focus on hepatitis B and hepatitis C care. MLF is well known across Myanmar for providing hepatitis B vaccination and treatment and hepatitis C testing and treatment; it runs several clinics across the country. MLF clinics provide outreach hepatitis C screening to various townships on an ad hoc basis, with those who test positive referred to MLF clinics for further testing and, if available, treatment through research studies, philanthropic projects, and other cost-sharing arrangements. The MLF clinic in Yangon also advertises its services via Facebook and accepts referrals from physicians for patients with elevated liver enzymes and other indicators of hepatitis B or hepatitis C.

Recruitment

Recruitment into the study was based on prescreening eligibility assessment (criteria described further in *Study Assessments, Pretreatment Assessments* section). At the Burnet clinic, the study was advertised to potential participants using flyers displayed at the methadone treatment centers in Yangon and through Burnet peer outreach workers distributing flyers and speaking with PWID about the study. Burnet peer outreach workers also assessed potential participants for eligibility for

enrollment in the study and made initial screening appointments with the nurse and medical officer at the clinic.

MLF clinic medical officers registered potential participants (including those previously screened anti-hepatitis C Ab positive) before commencement of the study and then invited them to attend the clinic in order of registration date. Patients attending the clinic on specified recruitment days (3 to 5 days per week) were also offered participation in the study.

At the initial study visit, the study nurse explained the purpose and procedure of the study to interested participants. Pre-enrollment eligibility was then assessed by the study nurse, and the consent procedure was conducted by the study nurse and medical officer.

Study recruitment commenced at the MLF clinic on January 30, 2019, and at the Burnet clinic on February 4, 2019; the last participant was recruited on September 30, 2019. Each clinic aimed to start 225 participants on DAA therapy; a total of 585 3-month treatment courses were available for the study, including some 6-month courses allocated to treat cirrhotic participants.

Eligibility

Before enrollment, participants had to be:

1. Aged 18 years or older
2. Willing and able to provide written informed consent
3. Not previously tested for hepatitis C virus (HCV) RNA
4. Hepatitis C treatment naïve (no prior pegylated interferon-based therapy or DAA therapy)
5. Without HIV or hepatitis B infection and active tuberculosis/being treated for tuberculosis, with known estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 and not pregnant (all self-reported)
6. Taking no medications with serious drug-drug interactions with sofosbuvir/daclatasvir that the participant would be unable/unwilling to cease.

Eligible participants were consented by delegated study staff (nurse and medical officer), provided written informed consent, and then study procedures commenced.

Study Interventions

Point-of-Care Anti-Hepatitis C Antibody Test

Trained laboratory technicians performed phlebotomy and conducted a POC immunochromatographic rapid test for anti-hepatitis C antibodies, using whole blood venous samples. This study used the WHO-prequalified SD BIOLINE hepatitis C test (Standard Diagnostics Inc, South Korea). It has 99.3% (95% CI 97.9%-99.8%) sensitivity and 100% (95% CI 99.7%-100%) specificity [23], with the result read within 5 to 20 min of the test start time.

The results were then communicated to the medical officer using internal laboratory test forms filled out by the laboratory technician; the medical officer returned the test results to the participants and provided relevant posttest counseling. If reactive, the participants were offered a near-POC hepatitis C RNA test using the remaining blood sample to determine if they had active hepatitis C infection.

Point-of-Care Hepatitis C RNA Test

Participants who were anti-hepatitis C Ab positive underwent a near-POC hepatitis C RNA test at the study site (Cepheid GeneXpert Hepatitis C RNA test). The WHO-prequalified GeneXpert hepatitis C RNA test is a reverse transcriptase PCR test performed on blood plasma samples using fluorescence to detect RNA; it is designed to quantify the viral load of hepatitis C RNA [10]. Its sensitivity was 100% (95% CI 94.6%-99.9%) and specificity was 100% (95% CI 75.9%-99.4%); the device error rate was 1.67% [10].

The blood sample was first spun in a centrifuge at 1500 rpm for 10 to 15 min (as per the manufacturer's instructions) to separate plasma from the whole blood sample, within 2 hours of sample collection. The plasma was then pipetted into the GeneXpert cartridge, and the cartridge was placed in an available module in the GeneXpert machine, the module cover was closed, and the assay commenced; the run time was 105 minutes. Tests were not batched, so they can be performed individually without delay.

GeneXpert results can be hepatitis C RNA detected (within the quantitative range, above the quantitative range [>1.00E08 IU/mL] or below the quantitative range [<10 IU/mL]) or hepatitis C RNA not detected. If the result is RNA detected, but below the quantitative range, the participant will be retested in 12 weeks. If the result is RNA detected and within or above the quantitative range, then the participant is considered to currently have hepatitis C infection.

Participants with an RNA-detected result then have an HIV antibody (Ab) rapid test and hepatitis B surface antigen (HBsAg) rapid test; if both these tests are negative, blood samples are sent to an external laboratory for standard pretreatment laboratory investigations (refer to the *Pretreatment Assessments* section). If the HBsAg test is positive, hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) tests were performed at the laboratory. If the HIV Ab rapid test was s positive, the participant was referred for confirmatory testing and withdrawn from the study if HIV positive.

Generally, all blood required for diagnostic testing and pretreatment assessments was collected in one blood draw.

Direct-Acting Antiviral Therapy

Participants who tested RNA detected (or positive) in the study could then receive a combination DAA therapy of sofosbuvir (400 mg) and daclatasvir (60 mg). Those with an aspartate aminotransferase to platelet ratio index (APRI) <2.0 (noncirrhotic) were offered a 12-week course. Those with an APRI ≥ 2.0 (cirrhotic) were offered a 24-week course, consistent with the national Simplified Treatment Guidelines for Hepatitis C Infection. A previous APRI validation study found that an APRI <2.0 reliably excluded cirrhosis in 85% of patients, with a negative predictive value of 91% [24]. (In line with the updated National Guidelines [second edition, July 18, 2019], the APRI cutoff was changed to 1.5 from August 6, 2019.)

All participants were reviewed and initiated on therapy by the study medical officer (a trained GP) at the study site. A specialist review was only required for those with signs of liver

decompensation; the study medical officer referred to a consulting hepatologist as necessary and to other specialists at the local tertiary hospital at his or her discretion for other major comorbidities. A total of 4 weeks of medication is dispensed at the study site by the medical officer or nurse (site dependent) at baseline, week 4, and week 8 of treatment and at weeks 12, 16, and 20 for those on a 24-week course. Participants self-administer the combination therapy daily; adherence is monitored using self-report and pill counting if the participants return medication bottles.

The exclusion criteria for commencing DAA therapy in the study included (1) no active hepatitis C infection, (2) HIV co-infection, (3) hepatitis B virus co-infection, (4) active tuberculosis/on tuberculosis treatment, (5) eGFR <30 mL/min/1.73m^2, (6) pregnancy, and (7) taking medications with serious drug-drug interactions with sofosbuvir/daclatasvir, which that participant is unable/unwilling to cease.

Participants with decompensated cirrhosis are eligible to access therapy through the study under the supervision of a consultant hepatologist if recommended after a consultant review. Consultant hepatologists are available on the weekends at the MLF clinic to see participants from the Burnet and MLF clinics; participants must attend the MLF clinic or Yangon Specialty Hospital to complete a specialist review. Advice from the consultant hepatologist is available via phone call and, if required, at other times.

Study Assessments

Following consent and study enrollment, participants completed assessments, as outlined in the schedule of assessments (Figure 1). The visit schedule is described in Figure 2.

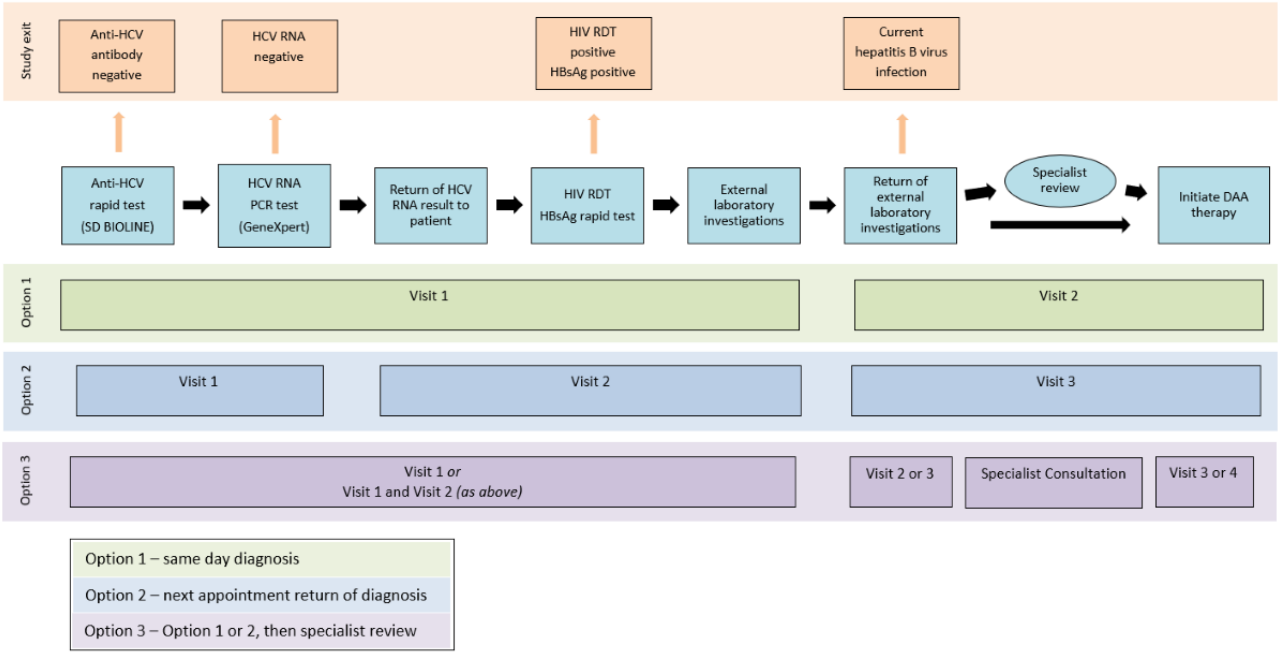
Figure 1. Study assessments overview.

	Visit 1 HCV Screening / Diagnosis	Visit 2 HCV Diagnosis	Specialist Consultation	Visit 3 Baseline	Monitoring	Monitoring	EOT Monitoring	Monitoring	Monitoring	EOT	SVR12
	Week <0	Week <0	Week <0	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 24 or 48
Study procedure											
Eligibility checklist	X										
Informed consent	X										
Baseline behavioral survey	X										
Acceptability survey		X									
Dispense DAAs				X	X	X	X	X	X		
Adherence assessment					X	X	X	X	X	X	
Alcohol and injecting drug use Assessment	X				X	X	X	X	X	X	
SVR12 behavioral and acceptability survey											X
Clinical assessments											
Anti-HCV antibody test	X										
HCV RNA test	X										
Complete blood picture (platelets, hemoglobin)		X	X								
Renal function tests (creatinine, eGFR)		X	X								
Liver function tests (ALT, AST, Albumin, Bilirubin, ALP)		X	X								
Pregnancy test (females only)		X									
HIV RDT (plus confirmatory serology if reactive)		X									
HBV RDT plus serology if applicable		X									
Dry blood spot samples obtained		X									
Physical signs and symptoms of cirrhosis			X	X							
Physical signs and symptoms of decompensation			X	X							

Figure 1 - Study Assessments Overview: DAA (direct-acting antivirals), SVR12 (sustained virological response, 12 weeks post treatment completion), HCV (Hepatitis C virus), eGFR (estimated glomerular filtration rate), ALT (Alanine transaminase), AST (Aspartate transaminase), ALP (Alkaline phosphatase), RDT (rapid diagnostic test), HBV (hepatitis B virus), EOT (end of treatment)

Note: Visit 1 and 2 can be conducted on the same date; Specialist Consultation is only for subset of participants; Week 16, 20, 24 are only for participants on 24 week treatment course; SVR12 is at Week 24 for participants on a 12 week treatment course and Week 48 for those on 24 week treatment course

Figure 2. Study Visit Schedule.



Visit 1: Screening and Diagnosis

This visit included a POC anti-hepatitis C Ab rapid test and POC hepatitis C RNA test, followed by an HIV Ab rapid test and a HBsAg rapid test. Blood samples were sent for pretreatment assessment investigations (further details given in *Pretreatment Assessment*). The hepatitis C RNA test result was returned to the participant during visit 1 or at the next appointment (visit 2).

Visit 2: Diagnosis (Return of Hepatitis C RNA Test Result)

If participants do not wait to receive the POC hepatitis C RNA test result during visit 1, they returned to the clinic to receive it at the next appointment.

Participants who tested hepatitis C RNA not detected were classified as having cleared their virus spontaneously (participants are not eligible if previously treated). They were informed of their results and do not require treatment.

Visit 2/3: Baseline (Pretreatment Assessment and Direct-Acting Antiviral Initiation)

Pretreatment Assessment

Pretreatment assessment included the following laboratory investigations:

- HIV Ab test (Alere Determine HIV-1/2 Ab rapid diagnostic test; performed at the study site)
- Hepatitis B surface antigen test (Alere Determine HBsAg rapid test performed at the study site)
- HBsAb test and HBcAb serology; hepatitis B DNA test performed if required
- Liver function tests: alanine aminotransferase (ALT), aspartate transaminase (AST), bilirubin, albumin, alkaline phosphatase
- Full blood examination: platelets and hemoglobin
- Renal tests: creatinine and eGFR.

These investigations were performed by a laboratory technician and at an external laboratory after RNA test results were available and returned to the participant at the next appointment (visit 2/3).

Cirrhosis/Decompensation Assessment

The APRI score was calculated to assess if liver cirrhosis was present. The medical officer calculated the APRI using the formula APRI=([AST/ULN]/ ([Platelet count × 10^9/L])) × 100 [24], where ULN is the upper limit of normal. The AST ULN was set at 40 U/L for consistency across the study because laboratory reporting can vary.

The medical officer performed physical examinations for clinical signs of cirrhosis, including (1) liver enlargement with a firm liver edge, (2) spider nevi, (3) jaundice, (4) palmar erythema, (5) leukonychia, (6) gynecomastia, and (7) proximal muscle wasting/generalized sarcopenia. The medical officer also performed physical examinations and took a history of the clinical symptoms and signs of decompensation, including ascites, hepatic encephalopathy, and hematemesis and melena.

HIV and Hepatitis B Virus Co-Infection

Participants with HIV infection and chronic or acute hepatitis B infection were not eligible to commence treatment as part of the study. Participants with HIV or hepatitis B co-infection were referred to government-led QuickStart program hospital sites for further assessment of eligibility for this program or to the MLF clinic for other research studies or cost-sharing programs. Participants were referred to a local HIV treatment center if newly diagnosed.

Referral to a Hepatologist

Participants with (1) ALT or AST >200 U/L, (2) bilirubin above ULN (1.14 mg/dL), (3) albumin <35 g/L without other obvious cause, (4) jaundice, (5) ascites, (6) hepatic encephalopathy, or

(7) hematemesis and melena were referred to a hepatologist for review.

Participants with ALT or AST levels between 100 and 200 U/L were advised to reduce alcohol intake, and the medical officer could consider locally available liver-supportive supplements as per the hepatologist's advice. Liver function tests (LFTs) were retested after 2 weeks, with updated LFT results to inform if a referral to a hepatologist was required, and the updated APRI score was used to inform the treatment duration.

If the participants were identified with hepatic decompensation, they were referred to a specialist for care.

Direct-Acting Antiviral Therapy Initiation

DAAs were initiated by the study medical officer during visit 2/3 after reviewing and returning pretreatment assessment results to the participant. If the participant required a specialist review, DAAs were initiated (when appropriate) by the medical officer after the participant returned from the specialist review appointment.

On-Treatment Monitoring Visits

Participants commenced DAA therapy and received short on-treatment monitoring visits every 4 weeks (weeks 4, 8, and 12 for a 12-week course, plus weeks 16, 20, and 24 for a 24-week course). These visits include medication dispensing and questions about alcohol use, injecting drug use, medication adherence, and side effects. On-treatment visits are not required by the National Guidelines; they are included to collect study-related data.

Sustained Virologic Response 12 Assessment

After 12 weeks of treatment completion, the participants return to the clinic for the assessment of SVR12 using the Cepheid GeneXpert hepatitis C RNA test. If hepatitis C RNA is detected but <10 IU/mL, then the participant is retested in 12 weeks. If RNA is detected and within or above the quantitative range, the participant undergoes further testing using dried blood spot samples collected at screening and SVR12 to determine the next potential treatment course.

Data Sources

Clinical Case Report Forms

Clinical data are collected in case report forms (CRFs) using the electronic database Open Medical Records System (OpenMRS); medical officers at the study site complete electronic CRFs (eCRFs) in OpenMRS first, but paper CRFs were used at the beginning of the study before eCRFs were finalized and are available if there are extended power outages or the database does not function properly. OpenMRS is an open-source medical records system; the database and the system are tailored to meet disease- and clinic-specific requirements. The OpenMRS database is run from a secure local server at each study site; backups of participant data are encrypted. Regular de-identified data exports are emailed to the data management team as a CSV (comma-separated values) file.

Visit 1/2 (Screening and Diagnosis): Case Report Forms 1 and 2

At visit 1/2 (Screening and Diagnosis), demographic data, drug use data, medical history, hepatitis C test results, and when participants received their diagnosis results were recorded.

Demographic data include age, sex, education level, employment status, income level, and residence locality. Drug use data include a history of injecting drug use, frequency of injecting, substances injected, receptive sharing of injecting equipment, history of and current methadone maintenance therapy, and alcohol consumption via the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) questionnaire.

Visit 2/3 (Baseline): Case Report Form 3 and Visit 3 /4 (Specialist Review) Case Report Form 7

At visit 2/3 (Baseline), pretreatment assessment laboratory results, clinical review, and treatment plan were recorded in eCRFs. A specialist review is captured in an eCRF by the medical officer when the participant returns to the study site, including laboratory investigation results, examination notes, and the recommended treatment plan.

On-Treatment Monitoring—Case Report Form 4

At monitoring visits (on treatment, end of treatment), the following data are collected: alcohol use in the past month using the adapted AUDIT-C questionnaire, injecting drug use in the past month (including frequency of injecting, substance/s most commonly injected), receptive sharing of injecting drug use equipment, current methadone maintenance therapy, side effects experienced, medication adherence (any missed doses, how many missed doses, and whether the doses were missed on consecutive days), and any new medications.

Sustained Virologic Response 12 Weeks Post-Treatment Completion Assessment: Case Report Form 5

At SVR12 visit (12 weeks after treatment completion), the following data are collected: alcohol use via the AUDIT-C questionnaire, injecting drug use in the past month (including frequency and substance), receptive sharing of injecting drug use equipment, current methadone maintenance therapy, hepatitis C RNA test result (SVR12 assessment), and details on when the participant received the result (on the same day or the next appointment).

Study Discontinuation: Case Report Form 6

When a participant exits the study, the date of exit and the reason for discontinuation (ineligible, loss to follow-up, participant decision, etc) are recorded. Participants are contacted at least three times over 4 weeks by phone and via their secondary contact at least once. A peer worker from the Burnet clinic also tries to contact the participant via outreach work. If there is no response or the participant is incarcerated, they are classified as lost to follow-up; if the participant has withdrawn from the study, this decision and the reason are recorded.

Participant-Completed Questionnaires

Participant-completed questionnaire data are collected in Research Electronic Data Capture (REDCap) [25]. REDCap is a web-based database system that hosts customized

project-specific questionnaires. All participants completed a behavioral questionnaire at the first study visit (Screening visit). It collects data on demographics, lifetime health care utilization (locations and providers), alcohol use, injecting drug use, incarceration history, sexual behaviors, experiences of stigma/discrimination, and reason for seeking a hepatitis C test.

All participants also complete an acceptability survey at the Screening/Diagnosis visit, after receiving the results of anti-hepatitis C Ab and/or hepatitis C RNA tests. It collects information on referral to the clinic, how they found out about the clinic, how they got to the clinic (including transport mode, time spent, and cost), level of comfort in talking with a health provider about risk behaviors, confidence in the knowledge of hepatitis C, hepatitis C knowledge, acceptability of the Ab rapid diagnostic test (including the collection of blood samples, trust in test accuracy, and wait to receive results), and acceptability of POC GeneXpert hepatitis C RNA test (including the collection of blood samples, trust in test accuracy, and wait to receive results) using a 5-point Likert scale for acceptability and confidence, and testing preferences by asking which test option participants would choose.

Participants complete a combined behavioral and acceptability survey at the SVR12 visit. The survey collects data on the past months' health care utilization, alcohol use (modified AUDIT-C questions for the past month), injecting drug use, acceptability of the testing and treatment process, details of how often participants attended the clinic, any costs to the participant, confidence in the knowledge of ongoing liver-related care required, and how to prevent reinfection.

Participant Interviews

Semistructured interviews will be conducted with 10 to 15 participants from each study site. The interview guide includes questions related to the experiences and views participants have toward services at the clinic, POC hepatitis C testing (both Ab and RNA testing), and treatment course. These data complement the acceptability survey data.

Provider Interviews, Surveys, and Clinical Workflow Observations

Semistructured interviews will be conducted with providers from each study site. Provider interviews will ask about the processes involved in conducting the tests, the processes involved in providing treatment, the referral process, and the processes for following up participants. These data will contribute to assessing the feasibility of the model of care from the provider perspective, contributing to domains of practicality and implementation. The provider survey will be completed by providers at each study site and will cover the acceptability and usability of Ab and RNA test devices and procedures. Clinical workflow observations recording workflow and time taken by staff members to complete specific aspects of workflow were completed midway through the study. These workflow observations will contribute to intervention complexity assessments.

Document Review

A document review of the GeneXpert device requirements, DAA requirements, training requirements, project meeting minutes, and monitoring visit reports will be used to inform intervention complexity assessments and practicality and implementation feasibility domains. GeneXpert device error reports and maintenance reports will also be included in the feasibility and intervention complexity assessment.

Data Management

All quantitative CRF and survey data are managed in Stata SE 15 (Stata Statistical Software: Release 15, StataCorp LLC). OpenMRS and REDCap CSV file exports are imported into Stata and labeled and cleaned before conducting data quality checks and analysis. Regular data quality checks (every 2-4 weeks) and subsequent timely query resolution (<14 days) are performed to ensure quality assurance by the Burnet Institute project staff. The list of study IDs from the enrollment log is compared with OpenMRS and REDCap exports to ensure that no records are missing. Key data, including visit dates, test dates, test results, DAA therapy regimen and commencement date, and study discontinuation information, are checked for completion and logical responses.

Interviews will be audio recorded, transcribed, and translated into English. Transcript data will be managed using NVivo (QSR International).

Statistical Analysis

Primary Outcomes

Outcomes 1-4 measuring the proportion of uptake across the cascade of care will be used to assess the feasibility of the model of care in terms of demand and practicality.

Outcome 1: The Proportion of Anti-Hepatitis C Antibody-Positive Participants who Received a GeneXpert Hepatitis C RNA Polymerase Chain Reaction Test

Descriptive statistics of the number and proportion of anti-hepatitis C antibody-positive participants who receive a GeneXpert hepatitis C RNA PCR test are provided. Any difference between sites will be determined using chi-square tests.

Outcome 2: The Proportion of Hepatitis C RNA Polymerase Chain Reaction-Positive Participants who Are Initiated on Direct-Acting Antiviral Therapy

Descriptive statistics of the number and proportion of hepatitis C RNA PCR-positive participants who are initiated on DAAs are provided. Any difference between sites will be determined using chi-square tests.

Outcome 3: The Proportion of Participants Initiated on Treatment who Complete Therapy

Descriptive statistics of the number and proportion of participants initiated on treatment who complete the therapy (defined as picking up the last 28-day bottle of medication and reporting ≤7 days missed doses) are provided. Any difference between sites will be determined using chi-square tests.

Outcome 4: The Proportion of Participants who Completed Treatment who Achieve Sustained Virologic Response 12

SVR12 is defined a priori as an undetectable hepatitis C RNA viral load using hepatitis C RNA PCR testing on the GeneXpert platform at least 12 weeks after therapy completion. Intention-to-treat SVR is defined by undetectable HCV RNA among all participants initiating treatment. Modified intention-to-treat SVR is calculated for participants who initiated treatment and have SVR data available (ie, the SVR test was performed, and the results are available).

Care cascade outcomes (primary outcomes 1-4) describe the proportion who have completed diagnosis, pretreatment assessments, and initiation of DAA therapy; completed DAA therapy; and achieved SVR12. These care cascade outcomes will be descriptively compared with historical outcomes to give context to these results in the study results paper.

Secondary Outcomes

Outcome 5: The Proportion of Participants Requiring Specialist Review

Descriptive statistics of the number and proportion of RNA-positive participants who require specialist review before commencing DAA therapy will be presented in aggregate format and by site. The reasons for specialist review and the outcome of the review will be presented.

Outcome 6: The Feasibility of the Testing and Treatment Pathway From the Provider Perspective

Interview data will be thematically and inductively analyzed using the intervention complexity framework to assess the feasibility and implementation requirements of the model of care from the provider perspective. This will be complemented by a document review of project documentation.

The framework includes (1) the characteristics of the interventions (device: GeneXpert device, cartridges; DAA prescription: DAA import, storage, and prescribing), (2) characteristics of delivery (facility and human resource requirements), (3) government capacity requirements (regulations and registrations), and (4) usage characteristics: ease of use, error rates and causes, and pre-existing demand.

Outcome 7: The Acceptability of the Testing and Treatment Pathways Among Participants

Descriptive statistics will be reported for measures of the acceptability of the testing and treatment pathways among participants and preferences for testing and treatment pathways. Categorical data will be reported using numbers and proportions in aggregate and by site. Questions using 5-point Likert scales will be collapsed into dichotomous variables, where appropriate for ease of reporting. Participant interview data will be analyzed using the theoretical framework for acceptability by Sekhon et al [26] and using inductive thematic analysis to identify any themes not captured by the framework analysis.

Outcome 8: Costing of the Point-of-Care Testing and Treatment Pathways at the Community Site

An ingredients-based costing method will be used to record the cost of consumables, staff time, and fractional costs of infrastructure and overheads for each person treated.

Outcome 9: Time From Hepatitis C RNA Test/Diagnosis to Treatment Initiation

The mean or median number of days and SD or IQR (depending on normality of results) of time from hepatitis C RNA test run date to treatment initiation will be presented in an aggregate format and by site.

Trial Management

Reporting of Adverse Events

Adverse events are recorded in the participant adverse event report form, which collates adverse events per participant across the study. Serious adverse events are recorded in the serious adverse event report form and reported immediately to the study team, the study sponsor (FIND), the ethical review boards, and relevant local authorities/distributor companies if necessary.

Trial Monitoring Procedures

The Burnet Institute project coordinator makes monthly site monitoring visits and uses a site monitoring checklist covering completion of enrollment log, informed consent forms (correct version, signed and dated by participants and study staff), and observation of consent procedure (monthly only). The coordinator verifies that stock is stored correctly and sufficient stock is available to continue the study. Sponsor-led site monitoring visits are performed ad hoc by the FIND hepatitis C projects trial manager to verify informed consent forms and source data. The Myanmar Department of Medical Research Ethics Review Committee performs ad hoc monitoring visits, with two visits completed in the first 6 months. This study is not a safety/efficacy trial—it uses approved interventions, so it does not have a data safety monitoring board.

Results

Research Ethics Approval

Ethics approval was obtained from the Myanmar Department of Medical Research Ethics Review Committee (no. 2019-144) in December 2018 and the Alfred Hospital Human Research Ethics Committee (no. 244/17) in July 2017. All participants sign written informed consent forms.

Project Status

As of September 30, 2019, 634 participants were enrolled in the study. All SVR12 data will be available by September 30, 2020, with results expected to be published by December 2020.

Discussion

Globally, international and national guidelines support the implementation of decentralized community-based, GP-led models of care for hepatitis C [7,17]. However, few publications document such models of care in detail or their outcomes regarding the completion of the diagnostic pathway and

treatment uptake and outcomes [12-14,19]. This study allows us to assess the implementation requirements of this clinical pathway, its feasibility, acceptability to both patients and providers, and its cost, along with the effectiveness of providing decentralized testing and treatment to patients in terms of the uptake of treatment and achievement of cure among those diagnosed. These results will inform the scale-up of services in Myanmar and other resource-constrained settings. In Myanmar, this will be particularly useful in informing the scale-up of services established to reach PWID who are not accessing the hospital-based program.

The study design has several limitations. It includes only two study sites in one large city, where amenities are more available than in more remote locations. Convenience recruitment, including a high proportion of study participants with known anti-hepatitis C Ab-positive test results, indicates that the study sample is not representative of case finding for hepatitis C infection. In addition, we were unable to treat people with HIV/hepatitis C co-infection; we aim to address this in further research studies in this setting.

Previous studies have demonstrated that treating people with hepatitis C infection with DAAs in community settings is feasible and that people achieve similar SVR12 rates to those treated in tertiary settings [12]; however, there is still little evidence for the feasibility and effectiveness of this model of care in low- and middle-income settings [13,14,19]. Decentralizing diagnostic testing and treatment initiation and offering these services at a one-stop shop has the potential to reduce time to DAA initiation, increase retention in care, and provide curative treatment to many people unable to access tertiary hospital services.

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Conflicts of Interest

BD has received the Australian National Health Medical Research Council postgraduate scholarship and investigator-initiated research funding from Abbvie. WY has received a Gilead Sciences Fellowship. JH has received a Gilead Sciences Fellowship. AP has received investigator-initiated research funding from Abbvie, Gilead, and Merck Sharp & Dohme. MH has received investigator-initiated research funding from Abbvie, Gilead, and Bristol-Myers Squibb.

References

1. World Health Organization. 2017. Global Hepatitis Report, 2017 URL: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ [accessed 2019-10-28]
2. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3(2):47-52 [FREE Full text] [doi: 10.7150/ijms.3.47] [Medline: 16614742]
3. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014 Apr 24;370(17):1594-1603. [doi: 10.1056/NEJMoa1315722] [Medline: 24720703]
4. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014 May 15;370(20):1879-1888. [doi: 10.1056/NEJMoa1402355] [Medline: 24720702]
5. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, ALLY-2 Investigators. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015 Aug 20;373(8):714-725. [doi: 10.1056/NEJMoa1503153] [Medline: 26196502]
6. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014 Aug 2;384(9941):403-413. [doi: 10.1016/S0140-6736(14)60494-3] [Medline: 24907225]
7. World Health Organization. 2018. Guidelines for the Care and Treatment of Persons Diagnosed With Chronic Hepatitis C Virus Infection URL: https://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/ [accessed 2019-10-28]
8. Wade AJ, Macdonald DM, Doyle JS, Gordon A, Roberts SK, Thompson AJ, et al. The cascade of care for an Australian community-based hepatitis C treatment service. PLoS One 2015;10(11):e0142770 [FREE Full text] [doi: 10.1371/journal.pone.0142770] [Medline: 26562516]
9. Wade AJ, Doyle JS, Gane E, Stedman C, Draper B, Iser D, et al. Outcomes of treatment for hepatitis C in primary care, compared to hospital-based care: a randomized, controlled trial in people who inject drugs. Clin Infect Dis 2020 Apr 15;70(9):1900-1906. [doi: 10.1093/cid/ciz546] [Medline: 31233117]
10. World Health Organization. 2017. WHO Prequalification of in Vitro Diagnostics: Public Report - Xpert HCV Viral Load with GeneXpert Dx, GeneXpert Infinity-48s, and GeneXpert Infinity-80 WHO Reference Number: PQDx 0260-070-00

URL: https://www.who.int/diagnostics_laboratory/evaluations/pq-list/hcv/170404_final_pq_report_pqdx_0260-070-00.pdf?ua=1 [accessed 2019-04-28]
11. World Health Organization. 2016. WHO Prequalification of in Vitro Diagnostics: Public Report URL: https://www.who.int/diagnostics_laboratory/evaluations/pq-list/hcv/170309_amended_final_pr_0257-012-00_v5.pdf [accessed 2020-05-05]
12. Radley A, Robinson E, Aspinall EJ, Angus K, Tan L, Dillon JF. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments. BMC Health Serv Res 2019 Oct 28;19(1):765. [doi: 10.1186/s12913-019-4635-7] [Medline: 31660966]
13. Khalid GG, Kyaw KW, Bousquet C, Auat R, Donchuk D, Trickey A, et al. From risk to care: the hepatitis C screening and diagnostic cascade in a primary health care clinic in Karachi, Pakistan-a cohort study. Int Health 2020 Jan 1;12(1):19-27 [FREE Full text] [doi: 10.1093/inthealth/ihy096] [Medline: 30597008]
14. Shiha G, Soliman R, Serwah A, Mikhail NN, Asselah T, Easterbrook P. A same day 'test and treat' model for chronic HCV and HBV infection: results from two community-based pilot studies in Egypt. J Viral Hepat 2020 Jan 30:- epub ahead of print. [doi: 10.1111/jvh.13268] [Medline: 31999866]
15. Lwin AA, Aye KS, Htun MM, Kyaw YY, Zaw KK, Aung TT, et al. Myanmar Health Sciences Research Journal. 2017. Sero-Prevalence of Hepatitis B and C Viral Infections in Myanmar: National and Regional Survey in 2015 URL: http://myanmarhsrj.com/index.php?page=sviewabstract&articleid=Reg-000855&articleyear=2017&articlevolume=29&articleissue=3&s= [accessed 2020-05-05]
16. National AIDS Program, Ministry of Health and Sports Myanmar. Myanmar Integrated Biological and Behavioural Survey & Population Size Estimates Among People Who Inject Drugs (PWID) 2017-2018 URL: https://www.aidsdatahub.org/sites/default/files/highlight-reference/document/Myanmar_IBBS_and_Population_size_estimates_among_PWID_2017-2018.pdf [accessed 2019-10-28]
17. Marshall AD, Cunningham EB, Nielsen S, Aghemo A, Alho H, Backmund M, International Network on Hepatitis in Substance Users (INHSU). Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. Lancet Gastroenterol Hepatol 2018 Feb;3(2):125-133. [doi: 10.1016/S2468-1253(17)30284-4] [Medline: 28986139]
18. Ministry of Health and Sports: Myanmar. 2019. Myanmar National Simplified Treatment Guidelines for Hepatitis C Infection, Second Edition URL: http://mohs.gov.mm/Main/content/publication/hepatitis-national-simplified-treatment-guidelines-of-viral-hepatitis-c-infection-second-edition-july-2019 [accessed 2019-10-28]
19. Alavi M, Poustchi H, Merat S, Kaveh-Ei S, Rahimi-Movaghar A, Shadloo B, et al. An intervention to improve HCV testing, linkage to care, and treatment among people who use drugs in Tehran, Iran: the ENHANCE study. Int J Drug Policy 2019 Oct;72:99-105. [doi: 10.1016/j.drugpo.2019.07.002] [Medline: 31303262]
20. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
21. Gericke CA, Kurowski C, Ranson MK, Mills A. Intervention complexity-a conceptual framework to inform priority-setting in health. Bull World Health Organ 2005 Apr;83(4):285-293 [FREE Full text] [Medline: 15868020]
22. UNFPA Myanmar. 2014. Population and Housing Census of Myanmar - Data Sheet URL: https://myanmar.unfpa.org/en/publications/2014-population-and-housing-census-myanmar-data-sheet [accessed 2019-10-28]
23. Alere. SD Bioline: HCV Hepatitis C Virus Test. Product Details URL: https://www.alere.com/en/home/product-details/sd-bioline-hcv.html [accessed 2019-10-28]
24. Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology 2005 Jun;41(6):1376-1382. [doi: 10.1002/hep.20717] [Medline: 15915455]
25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
26. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017 Jan 26;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]

Abbreviations

Ab: antibody
ALT: alanine aminotransferase
APRI: aspartate aminotransferase to platelet ratio index
AST: aspartate aminotransferase
AUDIT-C: Alcohol Use Disorders Identification Test – Consumption
CRF: case report form

CSV: comma separated value
CT2 Study: Hepatitis C: Community-based testing and treatment Study
DAAs: direct-acting antivirals
eCRF: electronic case report form
eGFR: estimated glomerular filtration rate
FIND: Foundation for Innovative New Diagnostics
GP: general practitioner
HBcAb: hepatitis B core antibody
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HEAD-Start: Hepatitis C Elimination through Access to Diagnostics
MLF: Myanmar Liver Foundation
OpenMRS: Open Medical Records System
PCR: polymerase chain reaction
REDCap: Research Electronic Data Capture
SVR12: sustained virologic response 12 weeks after treatment completion
ULN: upper limit of normal

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Protocol

Promoting Employees' Recovery During Shift Work: Protocol for a Workplace Intervention Study

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Abstract

Background: Shift work can be demanding owing to disturbances in the biological and social rhythms. This can cause short-term negative effects in employees, such as increased fatigue and reduced alertness. A potential way to counteract these negative effects is to enhance employees' recovery from work during working hours.

Objective: The aim of this study is to develop and implement an intervention that focuses on promoting "on-job" recovery of shift workers.

Methods: This study is performed in 2 department units with shift workers at a multinational company in the steel industry. For each department, an intervention will be developed and implemented through an iterative process of user-centered design and evaluation. This approach consists of various sessions in which employees and a project group (ie, researchers, line managers, human resource managers, and occupational health experts) provide input on the intervention content and implementation. Intervention effects will be evaluated using pretest and posttest web-based surveys. Digital ecological momentary assessment will be performed to gain insight into the link between the intervention and daily within-person processes. The intervention process and participants' perception of the interventions will be assessed through a process evaluation. Intervention results will be analyzed by performing mixed model repeated measures analyses and multilevel analyses.

Results: This study is supported by the Netherlands Organization for Applied Scientific Research Work and Health Research Program, which is funded by the Ministry of Economic Affairs and supported by the Dutch Ministry of Social Affairs and Employment, program number 19.204.1-3. This study was approved by the institutional review board on February 7, 2019. From June to August 2019, baseline data were collected, and from November to December 2019, the first follow-up data were collected. The second follow-up data collection and data analysis are planned for the first two quarters of 2020. Dissemination of the results is planned for the last two quarters of 2020.

Conclusions: A strength of this study design is the participatory action approach to enhance the stakeholder commitments, intervention adherence, and compliance. Moreover, since the target group will be participating in the development and implementation of the intervention, the proposed impact will be high. In addition, the short-term as well as the long-term effects will be evaluated. Finally, this study uses a unique combination of quantitative and qualitative evaluation methods. A limitation of this study is that it is impossible to randomly assign participants to an intervention or control group. Furthermore, the follow-up period (6 months) might be too short to establish health-related effects. Lastly, the results of this study might be specific to the department, organization, or sector, which limits the generalizability of the findings. However, as workplace intervention research for shift workers is scarce, this study might serve as a starting point for future research on shift work interventions.

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KEYWORDS

shift work; recovery during work; fatigue; intervention study; participatory action research; ecological momentary assessment; mobile phone

Introduction

Background

The expanding 24-hour economy, ongoing globalization, and technological developments have resulted in about 19% of the workforce working during the night and about 21% involved in work schedules with permanent or rotating shifts [1]. In the Netherlands, about 1.2 million employees are involved in shift work, including night shifts, and in sectors such as the heavy industry, the percentage of employees working in shifts is about 25% [2]. Short-term irregular working hours have been reported to lead to fatigue, sleep loss, and an increased accident risk [3,4]. Long-term shift work has been reported to result in severe health issues, including gastrointestinal, reproductive, metabolic, and cardiovascular disorders [5]. Despite these health problems, there are hardly any evidence-based interventions that can mitigate the negative effects of shift work [6]. A potential starting point for interventions to reduce the negative short-term effects of shift work is recovery from work. Recovery from work is defined as the psychophysiological unwinding following effort expenditure at work [7]. When refraining from work demands, activated bodily systems can unwind and return to baseline levels. This process of unwinding has the potential to reduce fatigue, subsequent alertness problems, and accident risks [8]. Research has indeed shown beneficial effects of recovery after work (eg, evenings, weekends), such as decreased burnout, increased performance [9], and lowered levels of blood pressure, heart rates, and epinephrine excretion [10]. However, little research has been performed to investigate the recovery during working hours [11]. Recovery during work may be particularly relevant for shift workers, as it has the potential to directly counteract the increased levels of sleepiness, fatigue, and the associated accident risk. Moreover, it has been shown that good recovery practices can be learned and that differences between individual preferences for recovery practices can be accounted for in recovery interventions [12,13]. In short, recovery during work seems to be a promising direction for tailored interventions that aim to mitigate the negative effects of shift work. In this paper, we will therefore start with a brief discussion of recent literature on recovery research to identify the potentially effective ingredients for recovery interventions. Subsequently, we will describe the development, implementation, and evaluation of a tailored workplace intervention aimed at enhancing recovery during the work of shift work employees.

Effective Ingredients for Recovery Interventions

Psychological Detachment

Studies have shown that a particularly powerful recovery experience is mental disengagement from work [14,15]. This is also referred to as psychological detachment from work or, in everyday terms, it is called as “switching off” [16]. It implies being occupied with things other than work and allows for physiological and psychological restorative processes to occur. In order to achieve this type of recovery, employees should refrain from job-related activities for a certain amount of time. Moreover, they should engage in activities that help them to temporarily take work off their mind. On a more critical note, it remains to be seen to what extent psychological detachment from work is actually possible during the working hours because contact with coworkers and the overall work setting cannot be avoided and therefore, this setting would most likely not result in full detachment [13]. Further, the single time periods for recovery activities are short. Thus, it is important to develop an intervention that allows for recovery activities that encourage psychological detachment during a limited period of time. For instance, some types of recovery activities (eg, mindfulness practices, exposure to a natural environment) may provide some degree of recovery rather quickly [13], while others may require more time and organization (eg, engaging in team sports). Two important types of recovery activities that may foster psychological detachment from work are relaxation and activation [13]. We have discussed both these types in the following section.

Recovery Activities: Relaxation and Activation

Relaxation is a positively toned state of low arousal that can benefit people in recuperating after a busy day at work [13]. In terms of relaxation, studies on interventions for shift workers have mainly focused on the recovery effect of napping. Napping allows employees to both physically and mentally detach from work for a short period of time. Richter et al [16] reported that basic conditions such as a pleasant, clean, and undisturbed surrounding for a healthy meal and a silent dark room for taking a nap are essential for the prolonged well-being of shift workers. In addition, the Health Council of the Netherlands [6] indicated that taking a short nap during the night shift may have a positive effect on alertness and may reduce sleepiness and fatigue. However, the Council also concluded that there is not enough knowledge regarding the optimal timing of such a nap. Ruggiero and Redeker [17] found that many individual characteristics such as age, gender, and years of experience can influence the potential positive effects of napping. Naps of 20-40 minutes have been reported to have the most beneficial effects, while the effects of short naps lasting to a maximum of 10 minutes are largely unknown [18]. Despite these potential positive effects, many workers do not apply napping as a recovery activity since they presume that naps take too much time and they fear feeling worse afterwards. Moreover, they feel they are too busy or do not have a comfortable napping space and they feel that the management would not support them in taking a nap during work [18]. We are not aware of articles that describe intervention studies focusing on other types of relaxations or work stress reduction techniques for shift workers.

Detachment from work may also be accomplished by ways other than a reduction in activity (ie, relaxation). There is ample evidence that an increase in social or physical activities can contribute to unwinding from work as well [13,19,20]. For instance, Sianoja et al [21] found that employees experienced less fatigue and high levels of well-being at the end of a working day on which they engaged in recovery activities such as park walks during lunch breaks. Furthermore, social activities during lunch breaks can be conducive to recovery [20] as long as employees have a high sense of autonomy in selecting their social activities during a work break [11]. In other words, a sense of autonomy or control over the break activities during

work seems to be one of the basic conditions for recovery to occur [12].

Hardly any study has shown the effect of activation as a means for recovery during shift work. Stimuli such as social interactions, job variations, physical activities such as standing or walking, and exposure to sound and light are thought to increase alertness, but more research is needed to establish the usefulness of such interventions as countermeasures to the negative effects of irregular working hours [22]. Instead, shift work interventions have primarily focused on optimizing the physical capacity of the employees and, thereby, the proposed tolerance of shift workers through off-job training programs [23]. A study has shown that appropriately timed physical exercise may be used to adapt to a certain shift schedule or readapt to a daytime schedule [22]. In one experimental study, physical exercise (2-6 training sessions per week) was found to lead to not only increased physical performance but also increased alertness and increased short-term memory during the night shifts of female shift workers [24]. Although these training sessions may be effective, this intervention may be very difficult to implement during the actual working hours of the employees.

Study Objectives

Studies have shown that the experience of psychological detachment from work is an effective ingredient for an intervention aimed at enhancing recovery during work [13-15]. This experience may be evoked through either relaxing or activating recovery activities as long as employees have a sense of control with regard to choosing their recovery activities. Nevertheless, the optimal intervention for enhancing recovery during the work of shift workers has not been elucidated in practical settings. Therefore, the main objective of this study is to develop, implement, and evaluate an intervention aimed at improving recovery during work and thereby reduce the negative short-term effects of shift work. Not only the content but also the intervention development and implementation process can affect the outcomes of the respective intervention [25,26]. The evaluation will therefore focus on the effects of the intervention as well as the process of intervention development and implementation. The corresponding research questions of this study are as follows:

1. What is an optimal intervention to enhance recovery during work for shift workers in practice?
2. To what extent is this intervention effective in enhancing recovery during work and in reducing the negative short-term effects of shift work?
3. What are the hindering and facilitating factors for the development and implementation of the intervention?

Methods

Ethical Approval and Consent to Participate

This study protocol and materials have been approved by the Netherlands Organization for Applied Scientific Research's review board, which is an internal ethics committee that assesses the ethical aspects of working with participants in experiments. In addition, both the higher and lower management of the shift work organization provided their consent for the execution of the research plan. Employees will be extensively informed about the study purpose and the protocols and asked to sign an informed consent form before participation. The confidentiality of the research data will be guaranteed and participation will strictly happen on a voluntary basis; thus, participants can withdraw from the study at any moment.

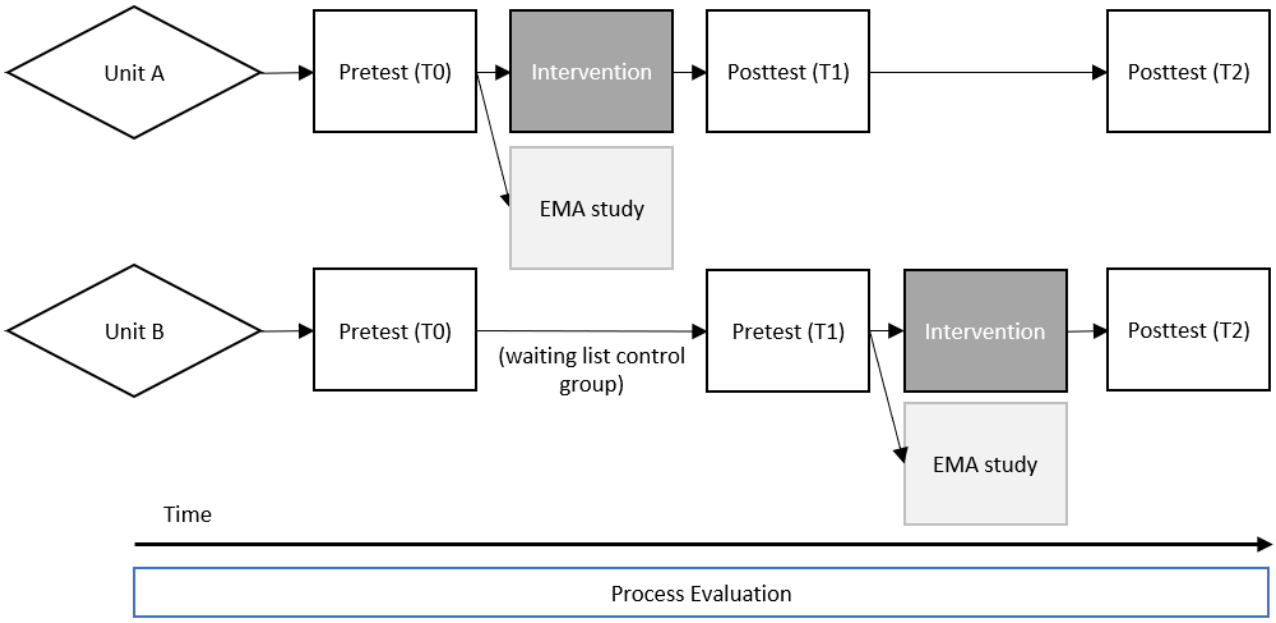
Quasi-Experimental Field Study

A randomized controlled trial is generally considered as the gold standard in evaluative health-related research, as causal inferences about the therapy under study can be drawn [27]. However, in this project, there are several practical and ethical issues that do not allow for such a design. Most importantly, a precondition set by the participating organization was that their management would select 2 preexisting departmental units for the study and that both units would receive the intervention. However, a control group is needed to distinguish between the change in the outcome over time due to the planned intervention or to evaluate the changes over time due to unmeasured or unknown factors [27]. Therefore, this study was designed as a quasi-experimental field study with a waiting list control group and pretest-posttest design. This means that one part of the experimental group (ie, unit A) will receive the intervention first, while another part of the group (ie, unit B) waits for an additional 3 months before they can make use of the intervention. Thus, the second unit acts as a temporary control group.

Three types of research methods can be distinguished in this study: (1) a longitudinal web-based survey study, (2) an ecological momentary assessment (EMA) study, and (3) a process evaluation. After the baseline measures (T0) of the web-based survey study are recorded, the yet-to-be-developed intervention aimed at recovery during work will be implemented within the experimental group.

Figure 1 presents a flowchart of the study design and the measurement moments. To analyze the effectiveness of the intervention, follow-up measurements will be performed at 3 months (T1) and at 6 months (T2) after the implementation of the intervention. This timeline seems adequate as the primary study outcomes (recovery during work and short-term negative effects of shift work) are expected to change over a relatively short period of time. In addition, an EMA study will be carried out shortly after the implementation of the intervention to provide insight into the short-term within-person intervention effects. Finally, a process evaluation will be performed to determine the factors that may have either enhanced or mitigated the effectiveness of the intervention.

Figure 1. Study design. EMA: ecological momentary assessment; T0: baseline measurements; T1: measurements after 3 months; T2: measurements after 6 months.



Setting and Study Population

This study is performed at the logistics department of a multinational steel company. This department consists of 160 employees in rotating shift work who are predominantly men, and they are divided into 2 units. These units do not share physical workspaces and are managed separately, thereby minimizing the chance of potential crossover effects. With respect to the demographics and the workload, the units are highly comparable. The typical job positions in both the units are machine operators and logistics coordinators. Open air working conditions are limited for both the participating units. One of the units will be selected to serve as the waiting list control group. This selection will be made in close consultation with the management, considering factors such as organizational planning, expected availability of time, and resources available for each unit.

Inclusion Criteria

All questionnaires used during the study will be distributed using an app. Therefore, the only inclusion criteria are that employees have to work for one of the 2 participating units and they need to possess their own personal smartphone to be able to participate in the study.

Intervention Development and Implementation

The current protocol for intervention development and implementation is based on close alignment between the researchers and human resource (HR)/occupational health representatives of the respective multinational steel company. Before the start of the participatory process (phase 1: needs assessment), the company already signaled issues with respect to fatigue and recovery on the basis of the internal employee surveys. However, as mentioned before, for recovery interventions to be effective, it is essential that employees have a sense of autonomy and control with regard to choosing their recovery activities [11,12]. To provide this sense of control, it seems vital to actively involve the target group in the intervention design and implementation process. In fact, Nielsen et al [28] argued that the effect of occupational health–promoting interventions heavily depends on the participation of the various organizational stakeholders. Therefore, in this study, a bottom-up participatory action research (PAR) approach will be used for intervention development and implementation [29]. By establishing a participatory group and making use of the management's and workers' knowledge, skills, and perceptions, a feeling of joint ownership of both problems and solutions is created [30]. Further, involving organizational stakeholders in the process of intervention development and implementation may enhance their general capacity to successfully address workplace issues [29]. The participatory group will be led by researchers with expertise in occupational health and PAR approaches. The effectiveness of PAR approaches has been demonstrated in various intervention studies [31,32].

The PAR approach toward intervention development and implementation consists of various sessions for each participating unit, in which employees and a project group (ie, researchers, line managers, HR managers, occupational health experts) provide input on the intervention content and implementation. The development and implementation process can be divided into 3 phases, which are described below.

Phase 1: Needs Assessment

In phase 1, we aim to assess the initial design specifications and the user requirements for the intervention to meet the needs of the target group. The basic needs and requirements of the intervention will be determined in close consultation with the target group. To this end, we will apply a user-centered design approach. First, the researchers will observe the workplace of the participating departmental units and conduct semistructured interviews with the employees and departmental and unit managers to gain insight into the characteristics of the target group, their specific work activities, and their current recovery practices. Second, the employees from the participating units (ie, intervention groups) will be invited to participate in 2

successive so-called user sessions that are led by the researchers. In these sessions, evidence-based and theory-based recovery practices (ie, psychological detachment, relaxation and activating recovery activities) will be presented and discussed. Specifically, employees will be asked for their recovery needs (eg, preferred work break activities) in context to specific work shifts (ie, morning, evening, night). In addition, they will be asked for ideas on how to incorporate new recovery practices into their current work and recovery routines. For reasons of feasibility, the focus will be on their formal work breaks. These ideas will then be rated on desirability by all employees. A voting procedure will be used to reach consensus. Phase 1 will result in an overview of the general intervention requirements.

Phase 2: Intervention Development

The aim of phase 2 is the development of an intervention prototype that can be tested in practice. To ensure that the intervention will meet the individual needs of various employees, the prototype should include the introduction and facilitation of a minimum of three recovery practices. These practices may be directed at both the individual and the work environment, depending on the outcomes of phase 1. The development of the intervention will again take place in consultation with the project group and the target group (ie, employees of the departmental units A and B). An intervention development and implementation team will be set up, consisting of various target group representatives (ie, employees, managers, and possibly HR advisors and works council members). We will use an iterative design to transform a paper prototype into a working prototype, considering the general intervention requirements that are identified in phase 1. Phase 2 will result in an intervention prototype and an accompanying implementation plan.

Phase 3: Intervention Implementation

In phase 3, the implementation plan that was set up in phase 2 will be executed and rolled out over the 2 subunits according to the schedule in Figure 1. A part of this plan will be the organization of informal small-scale meetings at work wherein the use of the intervention will be demonstrated and explained by the members of the implementation team. In addition, flyers with a brief intervention user manual will be distributed throughout the department.

Study Procedure

All employees of the participating units will be asked to participate in the intervention evaluation on a voluntary basis. During small-group information sessions, employees will be informed about the study purposes and procedures.

An information letter will show the participants how to install a smartphone-based questionnaire app, after which they will be asked to activate a user account by filling in a unique login username and password. Information letters will be handed out blindly, ensuring that user accounts are anonymous and only used for linking the participant data of different measurement moments (ie, T0, T1, T2, and EMA data). After logging in, the employees will be directed to the baseline questionnaire. The first question of the baseline questionnaire refers to the informed consent and asks the employees if they agree to participate. If they do not agree, the questionnaire will be ended. If they do agree, the participant acknowledges that the information provided was clear. No further follow-up of the nonparticipants will be performed. In addition, during the information sessions and in the information letter, it is indicated that participants are free to quit the study whenever they wish to do so, without having to provide an explanation.

Intervention Evaluation

Web-Based Survey

Intervention effects will be evaluated using pretest (T0/T1) and posttest (T1/T2) web-based surveys (see Figure 1). Participants will be invited to complete the surveys through the smartphone-based questionnaire app. The primary outcome variables used are as follows.

1. Recovery during work: Recovery during work will be measured using 3 items, which reflect the cognitive, emotional, and physical dimension of detachment from work [31,33]. A sample item is as follows: “During a work break, I think of things other than work.” Items will be scored on a 5-point frequency scale ranging from 1 (never or very rarely) to 5 (very often or always).

2. Need for recovery: The need for recovery will be assessed with the “need for recovery scale” from the Dutch questionnaire on the experience and evaluation of work (Dutch abbreviation, VBBA) [34]. A sample item is “Often, after a day’s work, I feel so tired that I cannot get involved in other activities.” All items have 2 response choices: yes or no.

3. Fatigue: Fatigue levels will be measured using the 4-item shortened version of the Checklist Individual Strength [35]. A sample item is as follows: “I feel physically exhausted.” Items will be scored on a 7-point scale ranging from 1 (completely disagree) to 7 (completely agree).

The secondary outcome variables are as follows.

1. General perceived health: The general perceived health will be measured using 1 item of the Dutch version of the short form 36-item Health Survey [36].

2. Vigor: Vigor will be assessed using 3 items of the vigor scale of the Utrecht Work Engagement Scale [37]. A sample item is as follows: “At my work, I am bursting with energy.” All the items will be scored on a 7-point rating scale, ranging from 0 (never) to 6 (every day).

3. Work ability: Work ability will be measured using 3 items of the Work Ability Index [38]. One item is used for subjective estimation of the current work ability compared with lifetime best work ability (11-point scale, ranging from 0 [not able to work at all] to 10 [best work ability in lifetime]), whereas the other 2 items assess the subjective work ability in relation to the physical and mental demands of the work (5-point scale, ranging from 1 [very poor] to 5 [very good]).

4. Safety and performance: Safety and performance at work will be assessed with a self-constructed item for each type of shift (ie, morning/evening/night). A sample item is as follows: “Given the current working conditions, I manage to work safely and productively every morning shift.” The items will be scored

on a 7-point scale ranging from 1 (completely disagree) to 7 (completely agree).

The other confounding and effect-modifying parameters that will be collected at baseline are as follows.

1. Sociodemographic variables: Information on age, gender, work unit, job title, and household composition will be collected.

2. Morningness-eveningness preferences: Personal morningness-eveningness preferences will be measured using 1 item based on the Morningness-Eveningness questionnaire [39].

3. Lifestyle: Physical activity and smoking behavior will be measured with 1 item each, based on the Study on Transitions in Employment, Ability, and Motivation cohort study [40].

4. Sleep patterns: Sleep disturbances will be measured using the Jenkins Sleep Questionnaire [41]. This questionnaire consists of the following 4 items: frequency in the difficulty of falling asleep in the previous month, difficulty sleeping continuously, waking up several times each night, and waking up feeling tired and worn out after the usual amount of sleep. The response alternatives range from 1 (not at all) to 6 (22-31 days).

EMA

During the intervention period, all employees will also be asked to participate in the EMA. EMA is a method for self-monitoring through the collection of self-reports on indices of behavior, cognition, or emotions in near real time in the daily lives of the participants, often through digital devices [42-44]. The smartphone-based questionnaire app allows us to digitally collect daily life momentary assessments of changes in employees' levels of fatigue and recovery behavior, in relation to momentary context and activity. As such, it provides insight into the short-term, within-person mechanisms linking fatigue and recovery with short-term intervention effects. Event-contingent data collection protocols will be used, indicating that data entry takes place when a predefined event occurs [45,46]. The predefined event in this study is the formal work break. Participants will be asked to fill the data in the EMA app for a period of 14 consecutive days (1) directly before taking a work break, (2) directly after taking a work break, and (3) directly after the end of their shift. Each measurement moment will take about 1-2 minutes. In alignment with organizational management, we chose a period of 14 days to ensure enough day-level data points (despite rotating shift schedules and possible dropouts) without overburdening the participants. The use of the intervention, however, can continue after data has been collected.

Table 1 shows the variables that will be measured. The information provided will give insight into the effectiveness of the different recovery strategies (eg, relaxation and activation) and the influence of work break control, shift types, and personal characteristics (eg, age, chronotype, job position) on recovery outcomes. The start of the 14-day EMA period will be communicated through (1) the app via prompts, (2) the manager of the specific unit, and (3) through communication at the workplace (eg, posters, newsletters).

Table 1. Variables retrieved through EMA.

Variable	Items	Questionnaire	Before break	After break	After shift
Shift type	1	What shift are you working today?	✓		
Sleepiness	1	Karolinska Sleepiness Scale [47]: scored on a scale from 1 (extremely alert) to 10 (very sleepy, difficulty in staying awake)	✓	✓	✓
Stress	1	Self-developed: "How do you currently feel?" scored on a visual analog scale (ranging from "stressed" to "relaxed")	✓	✓	✓
Need for work break	1	Self-developed: "To what extent are you in need of a work break right now?" scored on a scale ranging from 1 (not at all) to 10 (to a great extent)	✓		
Detachment from work	3	Based on de Jonge et al [33]: scored on a scale ranging from 1 (completely disagree) to 10 (completely agree)		✓	
Recovery activities	2	Self-developed: "During this work break, I spent my time mainly…". • 1 item scored with 3 answering categories: 1 (on activation activities such as walking, exercising, playing a game); 2 (on relaxation activities such as sitting, reading, listening to music, and power nap); and 3 ((other activities (please specify)) • 1 item scored with 2 answering categories: 1 (alone) and 2 (with others).		✓	
Control	1	Self-developed: "I was able to decide for myself how to spend my time during this work break" scored on a scale ranging from 1 (completely disagree) to 10 (completely agree)		✓	
Work break satisfaction	1	Self-developed: "I am satisfied with the way I spend my time during this work break" scored on a scale ranging from 1 (completely disagree) to 10 (completely agree)		✓	
Level of recovery	1	Based on Demerouti et al [20]: "At this moment, I feel sufficiently recovered" scored on a scale ranging from 1 (completely disagree) to 10 (completely agree)		✓	
Productivity	1	Self-developed: "To what extent were you able to work productively during this shift?" scored on a scale ranging from 1 (not at all) to 10 (a great extent)			✓
Safety	1	Self-developed: "To what extent were you able to work safely during this shift?" scored on a scale ranging from 1 (not at all) to 10 (a great extent)			✓

Process Evaluation

It is not only important to develop an intervention with the right ingredients but also to design a good implementation process [48]. Studies have shown that the intervention development and implementation process can affect the outcomes of the respective intervention [27,28]. For instance, activities aimed at raising support from the employees and the management for the intervention may enhance the effectiveness of an intervention. However, failing to fully implement a planned intervention after raising support may result in unfulfilled expectations and negative employee attitudes. By evaluating the intervention process, the outcomes of organizational interventions can be better understood [48,49]. These insights can be used to further improve the intervention effectiveness.

In this study, we will use Nielsen and Randall's [50] framework for process evaluations, which is specifically designed for the implementation process of organization-level interventions. It provides a broad perspective on the intervention process by not only including the intervention design and implementation but also the organizational context and the participant's perceptions of the intervention. Evaluation of these factors will enable us to answer the questions of what works for whom under which circumstances [48]. Data on the process factors will be collected during and after the implementation of the intervention. A variety of data sources will be used: (1) data logs of the researchers and the organizational management, (2) interviews with the management and the employees, and (3) the T1/T2 web-based employee survey. Table 2 provides an overview of the process factors, associated questions, and data sources.

Table 2. Overview of the process evaluation factors.

Process factor	Question	Data logs	Interviews	T1/T2[a] survey
Intervention design and implementation				
Initiation	Who initiated the intervention and for what purpose?	✓	✓	
Developing intervention activities	Did the intervention activities target the problems of the workplace?	✓	✓	✓
Implementing intervention activities	Did the intervention reach the target group?	✓	✓	✓
Implementation strategy				
Drivers of change and the roles of key stakeholders	Who were/are the drivers of change?	✓	✓	
Employee involvement	Did employees participate significantly in decision making and how many were involved?	✓	✓	✓
Management support	What was the role of the senior/middle managers?	✓	✓	✓
External consultants	What was the role of the external consultants? *(Not Applicable)*			
Information and communication	What kind of information was provided to the participants during the study?	✓	✓	✓
Context				
Omnibus context	How did the intervention fit in with the culture and the conditions of the intervention group?	✓	✓	✓
Discrete context	Which events took place during the intervention phase?	✓	✓	
Mental models				
Readiness for change	To what extent are/were the participants ready for change?		✓	✓
Shared mental models	To what degree do the participants have shared mental models?		✓	✓
Appraisal of the intervention and its activities	How did the participants perceive the intervention and its activities?		✓	✓
Changes in mental models	Did the intervention bring about a change in the participants' mental models?		✓	✓

[a]T1/T2: Posttest web-based survey.

Statistical Analysis

First, intervention results will be analyzed by performing mixed model repeated measures analyses (multivariate analysis of variance; time*group interaction) on longitudinal survey data with the outcome measures at follow-up (T0-T1, T1-T2, and T0-T2 comparisons) as the dependent variables. Furthermore, the effectiveness of the intervention will be analyzed by applying multilevel analyses on data collected within the EMA study (before break-after break and before break-after shift comparisons). Data will be collected and analyzed at 3 levels: (1) day level, (2) employee level, and (3) work unit level. Dropouts will be documented and included in the data analysis to the point of dropout. Potential confounders or effect modifiers (eg, age, gender, chronotype) will be compared between the intervention and the waiting list control group by *t* tests for independent samples and chi-square tests. For all analyses, a two-tailed significance level of $P<.05$ will be applied. The multilevel analyses will be conducted using R and the mixed model repeated measures analyses will be performed using SPSS software (IBM Corp, Version 25.0). A detailed analysis plan will be developed prior to finalization of the dataset.

Sample Size

The sample size calculation is based on finding an effect on the need for recovery. This variable was chosen because of its test-retest reliability and sensitivity to detect change, indicating that the need for recovery may be a useful tool for evaluating interventions related to occupational health [34]. Based on previous studies [47,51], a small effect size is expected. Power calculations indicate that to detect a small effect in the context of a repeated measurements analysis of variance (Cohen f=0.15), at least 37 subjects are necessary in each study group (power=0.80 and α=.05), and calculations were performed using G*power [52]. The response rates of similar PAR studies have been shown to be around 75% or higher [31,32]. Given the intended sample size of 150 subjects and the expected response rate of 75%, resulting in 56 subjects per group, the study has sufficient power to even detect slightly smaller effects [53].

Results

This study is supported by the Netherlands Organization for Applied Scientific Research Work and Health Research Program, which is funded by the Ministry of Economic Affairs and supported by the Dutch Ministry of Social Affairs and Employment, program number 19.204.1-3. This study was approved by the institutional review board on February 7, 2019. From June to August 2019, baseline data were collected, and from November to December 2019, the first follow-up data were collected. The second follow-up data collection and data analysis are planned for the first two quarters of 2020. Dissemination of the results is planned for the last two quarters of 2020.

Discussion

Principal Aspects of This Study

Shift work (ie, irregular working hours) can cause negative short-term effects for both employees and employers, such as increased fatigue levels, concentration problems, and consequently, an augmented risk of accidents and productivity loss. Unfortunately, evidence-based interventions to mitigate the negative effects of shift work are still lacking. Previous research studies have shown that a possible way to counteract the negative short-term effects of shift work is by enhancing the recovery of the employees during work. Therefore, the aim of this study is to develop, implement, and evaluate an intervention focused on enhancing the recovery of shift workers during working hours.

Study Strengths

The design of this study has several strengths. First, by making use of the PAR approach, stakeholders at all levels of the company are involved. This bottom-up involvement of the stakeholders will contribute to the commitment to the proposed interventions, which will likely translate into better overall intervention adherence and compliance. Moreover, it allows the target group to participate in the development and implementation of the intervention. This approach will stimulate problem ownership and commitment at all levels of the organization and has the potential to contribute to organizational sustainability [29], for which the interventions are more likely to have the proposed impact [28]. Another strength of the study design is that the timeline for the experimental unit allows us to compare the short-term intervention effects (T1) with the long-term effects (T2). In addition, the intervention development is conducted in a similar way in both the departments, but the eventual workplace interventions can differ. As a consequence, we can compare different solutions on similar proposed outcomes, further contributing to both theory and evidence-based practice [54]. In addition, to determine the effects of the workplace intervention, we use a rather unique data triangulation. Next to group-level outcome measurements with a web-based questionnaire, EMA measurements are used to gain insight into the working mechanisms of the intervention and to determine the influence of the type of recovery strategy chosen, the time of day, the type of shift, and intraindividual differences. Moreover, a process evaluation will be performed in order to gain more insight into what aspects of the intervention work for whom and why [48]. The process evaluation outcomes are assessed qualitatively (ie, group interviews, observations, data logs) and quantitatively (ie, self-reported measures in digital surveys) and whenever possible, complemented with objective organizational data (eg, sickness absence registration).

Study Limitations

From an occupational and epidemiological point of view, this study can be classified as a prevention-effectiveness study [27,55,56]. The characteristics of a prevention-effectiveness study design are as follows: small sample size, no randomization or blinding, and quantitative and qualitative measures. These characteristics ensure the internal validity of the study [55]. However, this type of study, as does ours, contains some limitations as well. First, because we do not use randomization, allocation bias could take place. However, in this study, it is impossible to randomly assign participants to an intervention and control group for practical and ethical reasons. Therefore, the waiting list control group principle was introduced. Moreover, one could argue that owing to the preallocation of the departments, the commitment of the management to the study is assured (ie, they know that an actual intervention is taking place and things have to be arranged to get this done), which enhances the feasibility of this study. A second limitation is the timeframe of the study. Behavioral and organizational changes do not occur easily or quickly. Therefore, the follow-up period (6 months) might be too soon to establish health-related effects. It might be, for instance, that changing recovery habits initially requires additional effort before it pays off in long-term reduced levels of fatigue. By combining quantitative data with qualitative data, we aim to gain further insight into this matter. A third limitation is that the evaluation of the effectiveness of the intervention fully relies on self-reported data. It would be interesting, for instance, to also assess fatigue levels through simple cognitive tests. For reasons of feasibility (ie, extensiveness of current research activities and accompanying time investment from the participants), we did not include such tests in the current design, but it might be a useful addition to the EMA method in the future studies. Another study limitation is the lack of generalizability of the findings. These study results may be organization-specific or sector-specific. However, workplace intervention studies for shift workers are still very scarce. The intervention in this study may therefore offer a starting point for future intervention studies in other organizations and sectors with shift work. Thereafter, aspects of the intervention should again be tailored to the workplace-specific context and target group through a participatory development and implementation process, as this has been argued to be a crucial condition for organizational interventions to be effective. An inevitable implication of this approach is that the effects have to be interpreted by considering unique contextual factors. A process evaluation will be performed to identify such contextual factors.

In summary, this study will investigate whether a workplace intervention study can reduce fatigue and improve the recovery of shift workers during work by using a PAR-designed

workplace intervention at a large steel company in the Netherlands.

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Authors' Contributions

All authors were involved in the design of the study. IN and AvD were responsible for drafting the paper, which was commented by all the authors. EdK is the coordinator in the Work and Health Research Program. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Arditon C, d'Errico A, Leombruni R, Pacelli L. Dublin: Eurofound; 2012. Health and well-being at work. A report based on the fifth European Working Conditions Survey URL: http://csdle.lex.unict.it/docs/labourweb/Health-and-well-being-at-work-A-report-based-on-the-fifth-European-Working-Conditions-Survey/4195.aspx [accessed 2020-05-29]
2. Hooftman W, Mars G, Janssen B, de VE, Michiels J, Pleijers A. Nationale Enquête Arbeidsomstandigheden 2016 (Netherlands Working Conditions Survey 2016). Leiden, Heerlen: TNO, CBS; 2016. URL: https://www.monitorarbeid.tno.nl/dynamics/modules/SFIL0100/view.php?fil_Id=188
3. Akerstedt T, Wright KP. Sleep Loss and Fatigue in Shift Work and Shift Work Disorder. Sleep Med Clin 2009 Jun 01;4(2):257-271 [FREE Full text] [doi: 10.1016/j.jsmc.2009.03.001] [Medline: 20640236]
4. Fischer D, Lombardi DA, Folkard S, Willetts J, Christiani DC. Updating the "Risk Index": A systematic review and meta-analysis of occupational injuries and work schedule characteristics. Chronobiol Int 2017;34(10):1423-1438. [doi: 10.1080/07420528.2017.1367305] [Medline: 29064297]
5. Wang X, Armstrong MEG, Cairns BJ, Key TJ, Travis RC. Shift work and chronic disease: the epidemiological evidence. Occup Med (Lond) 2011 Mar;61(2):78-89 [FREE Full text] [doi: 10.1093/occmed/kqr001] [Medline: 21355031]
6. Health Council of the Netherlands. Healthcouncil.nl. The Hague: Health Council of the Netherlands; 2015. Shiftwork and health risks: possibilities for prevention URL: https://www.healthcouncil.nl/documents/advisory-reports/2015/11/10/shiftwork-and-health-risks-possibilities-for-prevention [accessed 2020-05-20]
7. Geurts SAE, Sonnentag S. Recovery as an explanatory mechanism in the relation between acute stress reactions and chronic health impairment. Scand J Work Environ Health 2006 Dec;32(6):482-492 [FREE Full text] [doi: 10.5271/sjweh.1053] [Medline: 17173204]
8. Härmä M. Workhours in relation to work stress, recovery and health. Scand J Work Environ Health 2006 Dec;32(6):502-514 [FREE Full text] [doi: 10.5271/sjweh.1055] [Medline: 17173206]
9. Fritz C, Sonnentag S. Recovery, well-being, and performance-related outcomes: the role of workload and vacation experiences. J Appl Psychol 2006 Jul;91(4):936-945. [doi: 10.1037/0021-9010.91.4.936] [Medline: 16834516]
10. Frankenhaeuser M, Lundberg U, Fredrikson M, Melin B, Tuomisto M, Myrsten A, et al. Stress on and off the job as related to sex and occupational status in white-collar workers. J. Organiz. Behav 1989 Oct;10(4):321-346. [doi: 10.1002/job.4030100404]
11. Trougakos J, Hideg I. Momentary work recovery: The role of within-day work breaks. In: Sonnentag S, Perrewé PL, Ganster DC, editors. Current perspectives on job-stress recovery. Bingley: Emerald Group Publishing Limited; 2009:37-84.
12. Hunter EM, Wu C. Give me a better break: Choosing workday break activities to maximize resource recovery. J Appl Psychol 2016 Feb;101(2):302-311. [doi: 10.1037/apl0000045] [Medline: 26375961]
13. Sonnentag S, Venz L, Casper A. Advances in recovery research: What have we learned? What should be done next? J Occup Health Psychol 2017 Jul;22(3):365-380. [doi: 10.1037/ocp0000079] [Medline: 28358572]
14. Sonnentag S, Fritz C. Recovery from job stress: The stressor-detachment model as an integrative framework. J. Organiz. Behav 2014 Apr 11;36(S1):S72-S103. [doi: 10.1002/job.1924]

15. Sonnentag S, Fritz C. The Recovery Experience Questionnaire: development and validation of a measure for assessing recuperation and unwinding from work. J Occup Health Psychol 2007 Jul;12(3):204-221. [doi: 10.1037/1076-8998.12.3.204] [Medline: 17638488]
16. Richter K, Acker J, Adam S, Niklewski G. Prevention of fatigue and insomnia in shift workers-a review of non-pharmacological measures. EPMA J 2016;7:16 [FREE Full text] [doi: 10.1186/s13167-016-0064-4] [Medline: 27486484]
17. Ruggiero JS, Redeker NS. Effects of napping on sleepiness and sleep-related performance deficits in night-shift workers: a systematic review. Biol Res Nurs 2014 Apr;16(2):134-142 [FREE Full text] [doi: 10.1177/1099800413476571] [Medline: 23411360]
18. Banks S, Hilditch C, Centofanti S, Dorrian J. Napping on night shift: Powerful tool or hazard? ESW 2016 Jun 20;1(1). [doi: 10.21913/jdrssesw.v1i1.1042]
19. Coffeng JK, Hendriksen IJM, Duijts SFA, Twisk JWR, van Mechelen W, Boot CRL. Effectiveness of a combined social and physical environmental intervention on presenteeism, absenteeism, work performance, and work engagement in office employees. J Occup Environ Med 2014 Mar;56(3):258-265. [doi: 10.1097/JOM.0000000000000116] [Medline: 24603201]
20. Demerouti E, Bakker A, Geurts S, Taris T. Daily recovery from work-related effort during non-work time. In: Sonnentag S, Perrewé PL, Ganster DC, editors. Current Perspectives on Job-Stress Recovery (Research in Occupational Stress and Well Being, Vol. 7). Bingley: Emerald Group Publishing Limited; 2009:85-123.
21. Sianoja M, Syrek CJ, de Bloom J, Korpela K, Kinnunen U. Enhancing daily well-being at work through lunchtime park walks and relaxation exercises: Recovery experiences as mediators. J Occup Health Psychol 2018 Jul;23(3):428-442. [doi: 10.1037/ocp0000083] [Medline: 28358570]
22. Pallesen S, Bjorvatn B, Magerøy N, Saksvik IB, Waage S, Moen BE. Measures to counteract the negative effects of night work. Scand J Work Environ Health 2010 Mar;36(2):109-120 [FREE Full text] [doi: 10.5271/sjweh.2886] [Medline: 20011984]
23. Atkinson G, Fullick S, Grindey C, Maclaren D. Exercise, energy balance and the shift worker. Sports Med 2008;38(8):671-685 [FREE Full text] [doi: 10.2165/00007256-200838080-00005] [Medline: 18620467]
24. Härmä MI, Ilmarinen J, Knauth P, Rutenfranz J, Hänninen O. Physical training intervention in female shift workers: I. The effects of intervention on fitness, fatigue, sleep, and psychosomatic symptoms. Ergonomics 1988 Jan;31(1):39-50. [doi: 10.1080/00140138808966647] [Medline: 3359987]
25. Schelvis RMC, Wiezer NM, Blatter BM, van Genabeek JAGM, Oude Hengel KM, Bohlmeijer ET, et al. Evaluating the implementation process of a participatory organizational level occupational health intervention in schools. BMC Public Health 2016 Dec 01;16(1):1212 [FREE Full text] [doi: 10.1186/s12889-016-3869-0] [Medline: 27905904]
26. Nielsen K, Fredslund H, Christensen KB, Albertsen K. Success or failure? Interpreting and understanding the impact of interventions in four similar worksites. Work & Stress 2006 Jul;20(3):272-287. [doi: 10.1080/02678370601022688]
27. Schelvis RMC, Oude Hengel KM, Burdorf A, Blatter BM, Strijk JE, van der Beek AJ. Evaluation of occupational health interventions using a randomized controlled trial: challenges and alternative research designs. Scand J Work Environ Health 2015 Sep 01;41(5):491-503 [FREE Full text] [doi: 10.5271/sjweh.3505] [Medline: 26030719]
28. Nielsen K, Randall R, Holten A, González ER. Conducting organizational-level occupational health interventions: What works? Work & Stress 2010 Jul;24(3):234-259. [doi: 10.1080/02678373.2010.515393]
29. Dollard MF, Le Blanc PM, Cotton SJ. Participatory action research as work stress intervention. In: Näswall K, Hellgren J, Sverke M, editors. The individual in the changing working life. Cambridge: Cambridge University Press; 2008:353-379.
30. Schelvis RMC, Oude Hengel KM, Wiezer NM, Blatter BM, van Genabeek JAGM, Bohlmeijer ET, et al. Design of the Bottom-up Innovation project--a participatory, primary preventive, organizational level intervention on work-related stress and well-being for workers in Dutch vocational education. BMC Public Health 2013 Aug 15;13:760 [FREE Full text] [doi: 10.1186/1471-2458-13-760] [Medline: 23947538]
31. Niks I, de Jonge J, Gevers J, Houtman I. Work Stress Interventions in Hospital Care: Effectiveness of the DISCovery Method. Int J Environ Res Public Health 2018 Feb 13;15(2) [FREE Full text] [doi: 10.3390/ijerph15020332] [Medline: 29438350]
32. Mikkelsen A, Saksvik P, Landsbergis P. The impact of a participatory organizational intervention on job stress in community health care institutions. Work & Stress 2000 Apr;14(2):156-170. [doi: 10.1080/026783700750051667]
33. de Jonge J, Spoor E, Sonnentag S, Dormann C, van den Tooren M. "Take a break?!" Off-job recovery, job demands, and job resources as predictors of health, active learning, and creativity. European Journal of Work and Organizational Psychology 2012 Jun;21(3):321-348. [doi: 10.1080/1359432x.2011.576009]
34. van Veldhoven M, Broersen S. Measurement quality and validity of the "need for recovery scale". Occup Environ Med 2003 Jun;60 Suppl 1:i3-i9 [FREE Full text] [doi: 10.1136/oem.60.suppl_1.i3] [Medline: 12782740]
35. Beurskens AJ, Bültmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occup Environ Med 2000 May;57(5):353-357 [FREE Full text] [doi: 10.1136/oem.57.5.353] [Medline: 10769302]
36. Ware JE, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998 Nov;51(11):903-912. [doi: 10.1016/s0895-4356(98)00081-x] [Medline: 9817107]

37. Schaufeli W, Bakker A. Utrecht Work Engagement Scale: Preliminary Manual. Utrecht: Occupational Health Psychology Unit; Utrecht University; 2004.
38. Tuomi K, Ilmarinen J, Jahkola A, Katajarinne L, Tulkki A. Work Ability Index. Helsinki: Institute of Occupational Health Helsinki; 1998.
39. Loureiro F, Garcia-Marques T. Morning or Evening person? Which type are you? Self-assessment of chronotype. Personality and Individual Differences 2015 Nov;86:168-171. [doi: 10.1016/j.paid.2015.06.022]
40. Van den Heuvel S, Geuskens G, Bouwhuis S, Niks I. Study on transitions in employment, ability and motivation (STREAM): technical report (2010-2017). Leiden: TNO; 2017. URL: http://www.monitorarbeid.tno.nl/dynamics/modules/SFIL0100/view.php?fil_Id=254 [accessed 2020-05-29]
41. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41(4):313-321. [doi: 10.1016/0895-4356(88)90138-2] [Medline: 3351539]
42. Stone A, Shiffman S. Ecological momentary assessment (EMA) in behavorial medicine. Annals of Behavioral Medicine 1994 Apr;16(3):199-202 [FREE Full text] [Medline: 32426007]
43. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4:1-32. [doi: 10.1146/annurev.clinpsy.3.022806.091415] [Medline: 18509902]
44. Trull TJ, Ebner-Priemer UW. Using experience sampling methods/ecological momentary assessment (ESM/EMA) in clinical assessment and clinical research: introduction to the special section. Psychol Assess 2009 Dec;21(4):457-462 [FREE Full text] [doi: 10.1037/a0017653] [Medline: 19947780]
45. Wheeler L, Reis HT. Self-recording of everyday life events: Origins, types, and uses. Journal of Personality 1991;59(3):339-354. [doi: 10.1111/j.1467-6494.1991.tb00252.x]
46. Burke LE, Shiffman S, Music E, Styn MA, Kriska A, Smailagic A, et al. Ecological Momentary Assessment in Behavioral Research: Addressing Technological and Human Participant Challenges. J Med Internet Res 2017 Mar 15;19(3):e77 [FREE Full text] [doi: 10.2196/jmir.7138] [Medline: 28298264]
47. van Drongelen A, Boot CR, Hlobil H, Twisk JW, Smid T, van der Beek AJ. Evaluation of an mHealth intervention aiming to improve health-related behavior and sleep and reduce fatigue among airline pilots. Scand J Work Environ Health 2014 Nov;40(6):557-568 [FREE Full text] [doi: 10.5271/sjweh.3447] [Medline: 25121620]
48. Nielsen K, Miraglia M. What works for whom in which circumstances? On the need to move beyond the 'what works?' question in organizational intervention research. Human Relations 2016 Nov 12;70(1):40-62. [doi: 10.1177/0018726716670226]
49. Biron C, Karanika-Murray M. Process evaluation for organizational stress and well-being interventions: Implications for theory, method, and practice. International Journal of Stress Management 2014;21(1):85-111. [doi: 10.1037/a0033227]
50. Nielsen K, Randall R. Opening the black box: Presenting a model for evaluating organizational-level interventions. European Journal of Work and Organizational Psychology 2013 Oct;22(5):601-617. [doi: 10.1080/1359432x.2012.690556]
51. Gupta N, Wåhlin-Jacobsen CD, Abildgaard JS, Henriksen LN, Nielsen K, Holtermann A. Effectiveness of a participatory physical and psychosocial intervention to balance the demands and resources of industrial workers: A cluster-randomized controlled trial. Scand J Work Environ Health 2018 Jan 01;44(1):58-68 [FREE Full text] [doi: 10.5271/sjweh.3689] [Medline: 29095478]
52. Faul F, Erdfelder E, Buchner A, Lang A. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009 Nov;41(4):1149-1160. [doi: 10.3758/BRM.41.4.1149] [Medline: 19897823]
53. Cohen J. A power primer. Psychological Bulletin 1992;112(1):155-159. [doi: 10.1037/0033-2909.112.1.155]
54. Richardson KM, Rothstein HR. Effects of occupational stress management intervention programs: a meta-analysis. J Occup Health Psychol 2008 Jan;13(1):69-93. [doi: 10.1037/1076-8998.13.1.69] [Medline: 18211170]
55. Skov T, Kristensen TS. Etiologic and prevention effectiveness intervention studies in occupational health. Am J Ind Med 1996 Apr;29(4):378-381. [doi: 10.1002/(SICI)1097-0274(199604)29:4<378::AID-AJIM19>3.0.CO;2-Z] [Medline: 8728143]
56. Kristensen TS. Intervention studies in occupational epidemiology. Occup Environ Med 2005 Mar;62(3):205-210 [FREE Full text] [doi: 10.1136/oem.2004.016097] [Medline: 15723887]

Abbreviations

EMA: ecological momentary assessment
HR: human resource
PAR: participatory action research

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Protocol

Extended Support Within a Person-Centered Practice After Surgery for Patients With Pituitary Tumors: Protocol for a Quasiexperimental Study

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Abstract

Background: Patients with pituitary tumors often live with lifelong consequences of their disease. Treatment options include surgery, radiotherapy, and medical therapy. Symptoms associated with the tumor or its treatment affect several areas of life. Patients need to adhere to long-term contact with both specialist and general health care providers due to the disease, complex treatments, and associated morbidity. The first year after pituitary surgery constitutes an important time period, with medical evaluations after surgery and decisions on hormonal substitution. The development and evaluation of extended patient support during this time are limited.

Objective: The aim of this study is to evaluate whether support within a person-centered care practice increases wellbeing for patients with pituitary tumors. Our main hypothesis is that the extended support will result in increased psychological wellbeing compared with the support given within standard of care. Secondary objectives are to evaluate whether the extended support, compared with standard care, will result in (1) better health status, (2) less fatigue, (3) higher satisfaction with care, (4) higher self-efficacy, (5) increased person-centered content in care documentation, and (6) sustained patient safety.

Methods: Within a quasiexperimental design, patients diagnosed with a pituitary tumor planned for neurosurgery are consecutively included in a pretest-posttest study performed at a specialist endocrine clinic. The control group receives standard of care after surgery, and the interventional group receives structured patient support for 1 year after surgery based on person-centeredness covering self-management support, accessibility, and continuity. A total of 90 patients are targeted for each group.

Results: Recruitment into the control group was performed between Q3 2015 and Q4 2017. Recruitment into the intervention group started in Q4 2017 and is ongoing until Q4 2020. The study is conducted according to the Declaration of Helsinki, and the protocol has received approval from a regional ethical review board.

Conclusions: This study entails an extensive intervention constructed in collaboration between clinicians, patients, and researchers that acknowledges accessibility, continuity, and self-management support within person-centeredness. The study has the potential to compare standard care to person-centered practice adapted specifically for patients with pituitary tumors and evaluated with

a combination of patient-reported outcomes and patient-reported experience measures. Following the results, the person-centered practice may also become a useful model to further develop and explore person-centered care for patients with other rare, lifelong conditions.

Trial Registration: Researchweb.org. https://www.researchweb.org/is/sverige/project/161671

International Registered Report Identifier (IRRID): DERR1-10.2196/17697

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KEYWORDS

pituitary tumor; person-centered care; clinical pathway; intervention; quasiexperimental

Introduction

Background

Pituitary tumors occur at any age, but most often occur in persons at the peak of their professional career [1]. The annual incidence of pituitary tumors is approximately 4.0 per 100,000 inhabitants [1-4]. Pituitary tumors can be divided into nonfunctioning tumors (nonfunctioning pituitary adenoma and craniopharyngioma) and hormone-producing adenomas (prolactinomas, Cushing's disease, and acromegaly). Although they are histologically benign, the tumor itself and its treatment often lead to lifelong hormone deficiencies, obesity, neurocognitive dysfunction, visual field defects, diabetes insipidus, and other adverse effects due to the pituitary gland's vital regulatory function and its proximity to the hypothalamus and optic chiasm [5,6]. Patients with pituitary tumors therefore have excess morbidity and mortality [1,2,4,7-9]. The tumors are treated with surgery and, in some cases, radiotherapy, while endocrine-active tumors can also be managed with medical therapy [6]. A substantial proportion of patients experience tumor recurrence during their follow-up [10]. Recurrence is associated with excess mortality; disease control is therefore of vital importance for patient outcomes [11].

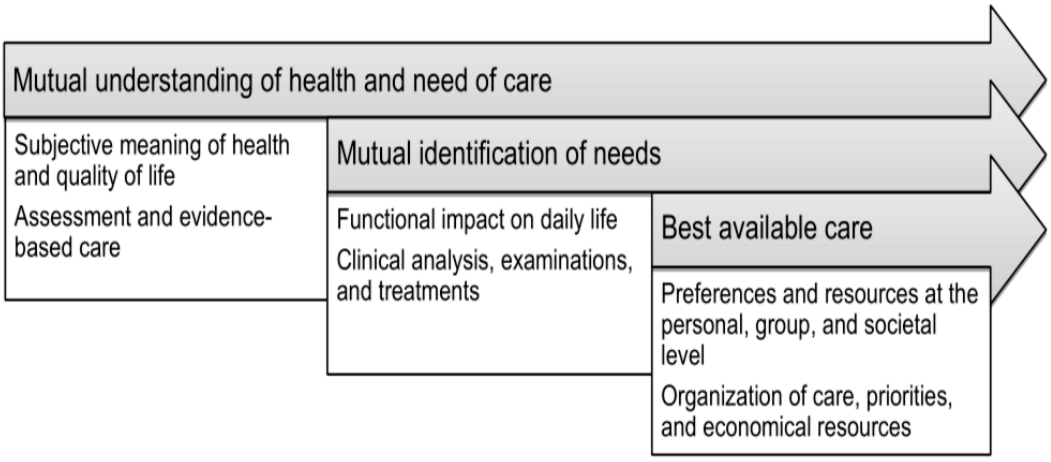
Pituitary tumors constitute a substantial chronic disease burden for patients, affecting several areas of life [12,13]. Low self-reported health is evident with symptoms such as fatigue, memory and concentration difficulties, sleeping problems, and sexual dysfunction [14,15]. Partners of patients have described a lack of information regarding the disease and its treatment as well as concerns related to changes in relational aspects, social life, and family life [16]. Unemployment is also more common among patients with pituitary disease, and a substantial number of patients report having missed work or not performing to their potential at work due to their illness [17].

The disease, its treatment, and related morbidity necessitate that patients adhere to long-term contact with specialist and general health care providers. There is limited knowledge on how to support patients with pituitary tumors to better cope with their lifelong condition. Andela and colleagues [18] evaluated structured patient and partner group education introduced to patients several years after their diagnosis. The 8-week program showed increased and sustained self-efficacy 6 months after the education program and, to some extent, improved patient mood. However, patients did not report any significant differences in perceived quality of life, symptoms, coping style, or illness perception. A nurse-led, 9-month educational program specifically designed for patients with Cushing's syndrome showed improvement in health outcomes such as pain, physical activity, and aspects of quality of life [19].

Recent reforms covering health and medical care have highlighted the importance of designing care in collaboration with each patient through participation in decisions, providing explicit information, and determining patients' preferences and abilities [20,21]. Care based on person-centeredness has been promoted, whereby care providers inquire how patients view their health situation and about their needs, resources, and preferences [22,23]. Person-centeredness focuses on preserving patient autonomy, function, and wellbeing and strives to emphasize patient involvement through equalizing power between health care professionals and patients with the main goal of an enhanced health situation for each patient.

This project focuses on how a nurse-led, person-centered practice with a state-of the-art medical team might be beneficial for patients after surgery for pituitary tumors (Figure 1). To our knowledge, this has not been previously studied. This study is presented according to the SPIRIT statement for reporting study protocols [24].

Figure 1. Person-centered practice: integrating person-centered care and the clinical pathway.



Study Objectives

The aim of the study is to evaluate whether support within a person-centered care practice increases wellbeing for patients with pituitary tumors. Our main hypothesis is that the extended support will result in increased psychological wellbeing compared with the support given within standard of care. Secondary objectives are to evaluate whether the extended support, compared with standard care, will result in (1) better health status, (2) less fatigue, (3) higher satisfaction with care, (4) higher self-efficacy, (5) increased person-centered content in care documentation, and (6) sustained patient safety.

Methods

Study Design

The study utilizes a quasiexperimental design with a nonequivalent control group and a pretest-posttest study design. The study is carried out in two sequential steps: (1) a control group of patients receiving standard care up to 1 year after surgery followed by (2) an interventional group where patients receive extended support within a person-centered practice up to 1 year after surgery.

The study is conducted according to the Declaration of Helsinki. All participants in the study have rights to confidentiality and provide written informed consent [25]. Approval for the protocol has been obtained from the regional ethical review board (approval reference 387-15). Any modifications to study procedures have to be reported as formal amendments to the ethical review board for approval.

Study Setting

A university clinic in western Sweden constitutes the clinical setting for the study. An inpatient neurosurgical unit, an inpatient endocrine unit following surgery, and an outpatient endocrine unit collectively comprise the patients' care pathway before and after surgery.

Study Population

All consecutive patients diagnosed with a pituitary tumor planned for neurosurgery at the study center will be asked to participate in the study. Inclusion criteria are planned neurosurgery and ≥18 years of age. Exclusion criteria comprise health conditions that might restrict understanding of the study or ability to adhere to the protocol (eg, cognitive impairments or drug addiction). The power calculation for estimation of sample size was based on two previous hormonal replacement therapy interventions evaluating improvement in psychological general wellbeing [26,27]. We used a range of d values due to different study designs; based on d=0.3326 (no treatment vs treatment in a crossover design) [27] to d=2.826 (before and after intervention) [26], 64-100 patients are needed in each group to obtain an 80% power with a 95% significance. Considering the different design of the study, 90 patients are targeted in each group, also taking into account a 10% discontinuation rate.

Recruitment

Recruitment is coordinated by a research nurse (ACO) experienced in the care of patients with pituitary tumors and specifically trained in endocrine research studies. Patients who are planned for surgery and are eligible for the study will be contacted by phone about 1 week before surgery to receive information regarding the study. A written description of the study is sent to the patients after this initial contact. The same nurse meets the patient on the day before surgery to inform about the study again. After answering any potential questions regarding the study, patients provide written informed consent. In the case of acute surgery, the neurosurgeon responsible for the patient obtains verbal and written consent before surgery. No study activities are initiated before verbal and written informed consent.

Patient and Public Involvement

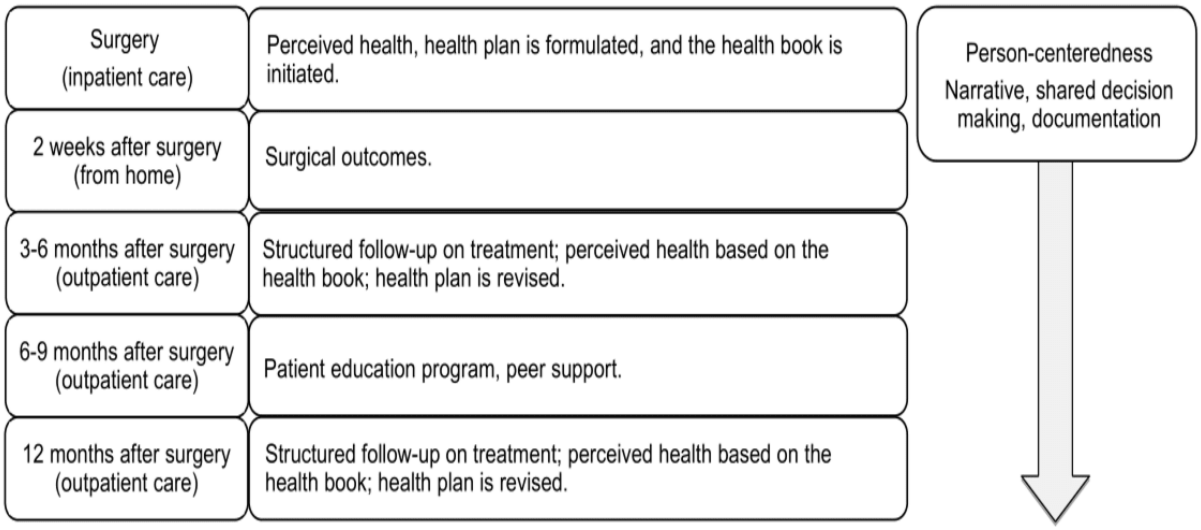
To be able to develop a valid person-centered practice from the patients' point of view, a group of patients with pituitary tumors who have experienced long-term care participated in the development of the intervention. In two workshops, discussions were held between patients, clinicians, and researchers on current care and specific needs stated by the patients. The expressed preferences in care were integrated into the content of the intervention. Specifically, these preferences included increased accessibility, an identified contact person within care, patient education program early after surgery, relatives included in care, and knowledge of medical treatment, surgery, and tumor

recurrence. When results from the study are assessable, efforts will be made to disseminate the results in appropriate forums for patients and their relatives. In addition, the findings of the study will be communicated in peer-reviewed publications in scientific journals, in PhD theses, and at scientific meetings.

Intervention

The structure and content of the intervention are built on principles for person-centeredness. Within the intervention, repeated patient narratives and continuously revised, documented health care planning ensure that the care is systematically practiced according to principles for person-centeredness (Figure 2). Self-management support, being an important component in the intervention, is primarily conducted between the patient and a nurse care manager. Each patient in the intervention is allocated a hospital-initiated nurse care manager, who initiates the first contact with the patient at the inpatient unit before discharge after surgery. The primary goal of the support from the nurse care manager is to facilitate the patient's own resources in managing illness as well as giving specific health education on, for example, physical activity and diet. Patient-held documentation, the health book, frames the content of self-management support. The health book includes detailed information on the structured clinical care pathway, contact information for the nurse care manager, and preparatory questions that could be used before appointments with the health care team. Questions to encourage reflections on good and bad days and what constitutes or hinders good health are also included in the health book. After each contact between the patient and nurse care manager, a health plan, including agreed goals, is revised. Within the health book, it is also possible for the patient to self-assess and monitor symptoms and health in writing or by drawing. They are also able to reflect and self-assess issues related to work, social support, economy, and other health factors such as physical activity, sleep, sex life, and diet.

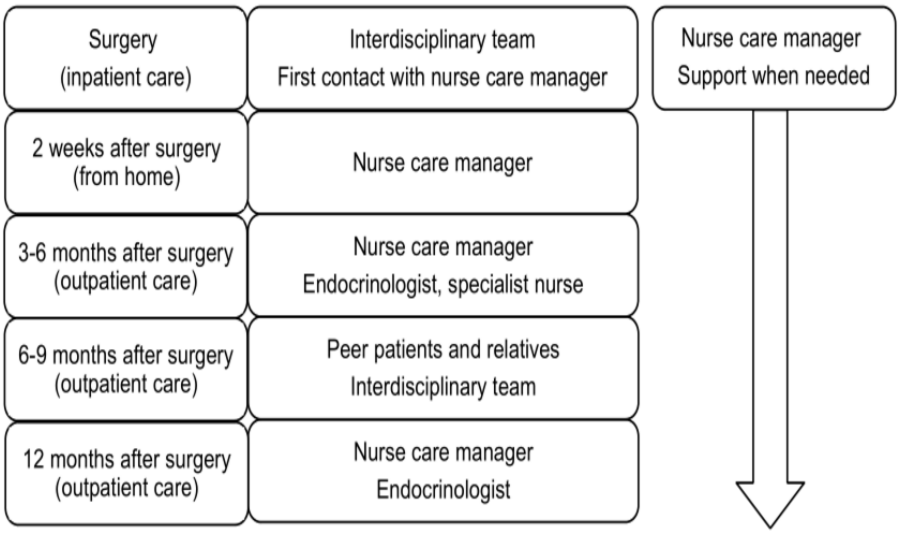
Figure 2. Content of the extended support within a person-centered practice until 1 year after surgery.



Other components of the intervention comprise accessibility and continuity, which are secured by a structured clinical care pathway (Figure 3). The patient has continuous access to the nurse care manager by telephone and face-to-face contact according to a structured follow-up plan for 1 year after surgery. An interdisciplinary team as well as a patient education program constitute distinct parts of support. The structured clinical care pathway visualizes the care that is preplanned and defines the roles of the different heath care providers. The patient education program at 6-9 months after surgery comprises education for both the patient and their relatives. It is aimed at promoting the development of skills and knowledge needed to self-manage health. The content includes information about surgical treatment, symptoms, and signs as well as issues related to health and quality of life. The patients' knowledge of diagnosis and surgery is increased by lectures. Discussions during the program are targeted at including common experiences and skills needed to manage different symptoms in daily life. The patient education program also provides requisites for peer support in nonclinical aspects.

To qualify as an outpatient nurse care manager, the nurse must have experience caring for patients with pituitary tumors. Further, it is mandatory to attend a 1-day education course covering updated information on signs and symptoms, hormonal treatments, neurosurgical aspects, person-centered care, health promotion, and the role of the nurse care manager. Each nurse, depending on their experience and needs, completes observation in different care units such as neurosurgery or inpatient care or with specific team members, such as dietitians and physical therapists, included in the patient care pathway. Literature and other materials are made available to the nurse care managers.

Figure 3. Care contacts in the structured clinical care pathway from surgery until 1 year after surgery. The interdisciplinary team includes endocrinologists, neurosurgeons, nurses, dietitians, and physical therapists.



Standard Care

All patients in the control group will receive standard care. Standard care is primarily hospital-based. In short, during the first 24 postoperative hours, the patients are monitored at a medium care unit for neurological status as well as fluid and electrolyte balance. Thereafter, monitoring for a further 5 days is conducted at the inpatient department of endocrinology. Before discharge, on postoperative day 6, evaluation of endocrine deficiencies is performed. At an outpatient visit at the department of endocrinology, 4-5 weeks postoperatively, hormonal status is rechecked, and information on any complications is collected. Thereafter, the frequency of visits to the outpatient clinic depends on tumor types, surgical outcome, hypopituitarism, and perceived symptoms.

Strategies to Secure the Intervention Over Time

To facilitate and secure the implementation of the intervention over time, and specifically the nurse care manager's role, the nurse assigned for quality and safety improvement at the clinic (EA) and a researcher from the research group (EJU) meet the nurse care managers regularly to support and discuss the different components of the intervention and its implementation in patient care. In addition, all staff members at the inpatient and outpatient units are informed about the study prior to starting. Specific nurses at the postsurgical endocrinology unit were identified and are involved in the performance of the study; these nurses also attend the 1-day education course. Every 3 months, the nurse assigned for quality and safety improvement at the clinic and the researcher from the research group meet with inpatient and outpatient team members including nurses, endocrinologists, neurosurgeons, research nurses, the head of nurses, and the head of physicians to provide an update on the intervention and discuss issues related to the structured clinical care pathway and other issues of relevance.

Outcome Measures

The primary outcome measure is self-reported psychological wellbeing. Secondary outcome measures will be self-reported satisfaction of care, health status, fatigue, and self-efficacy. Additional secondary outcomes include person-centered content in documentation and patient safety.

Participant Timeline

The patient-reported outcome measures are reported by the patients on the day before surgery and repeated at discharge from inpatient care, approximately 1 week after surgery. Two follow-ups are performed at 4-6 months and 11-13 months after surgery (Figure 4). All questionnaires for self-assessment were chosen due to their widespread use in research and good psychometric validity in both patients and healthy populations. Medical records are also reviewed.

Figure 4. Schedule of enrollment, intervention and assessments for each included patient. EQ-5D-5L: Euro- Qual Five Dimensions; GSE: Generalized Self-Efficacy Scale; MFI-20: The Multidimensional Fatigue Inventory; MIDAS: The Migraine Disability Assessments; PGWB: The Psychological General Well-being instrument; QPP: Quality from the Patient Perspective Questionnaire; SNOT-22: Sino-nasal Outcome Test.

	Study period				
	Enrollment	Longitudinal assessments			
TIMEPOINT	Before surgery	Surgery	At discharge after surgery	6 months after surgery	12 months after surgery
Enrollment					
Eligibility screening	x				
Informed consent	x				
Control or intervention group	**Enrollment period**				
Standard care	Q3, 2015- Q4, 2017	←	—	—	→
Person-centred practice	Q4, 2017-Q4, 2020	←	—	—	→
Primary and secondary assessments					
Patient characteristics	x				
Psychological wellbeing (PGWB)	x		x	x	x
Health status (EQ-5D-5L)	x		x	x	x
Self-efficacy (GSE)	x		x	x	x
Fatigue (MFI-20)	x		x	x	x
Satisfaction of care (QPP)			x	x	x
Other assessments					
Sino-nasal symptoms (SNOT-22)	x			x	x
Headache (MIDAS)	x			x	x
Neuropsychological testing	x				x

Data Collection

Primary Outcome

Self-perceived psychological wellbeing is assessed with the Psychological General Well-Being scale, a 22-item questionnaire comprising 6 dimensions: anxiety, depression, positive wellbeing, self-control, general health, and vitality [28]. The Swedish version of the questionnaire has been externally validated [29]. A total score of 132 is calculated from 6-point Likert scales for each item and represents excellent psychological wellbeing.

Secondary Outcomes

The Euro-Qual Five Dimensions questionnaire is used to assess self-reported health status. It includes 5 specific dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [30-32]. The questionnaire also comprises a visual analogue scale from 0 to 100 in which the patient rates health from the worst to the best health imagined. To further explore effects on the patients' perceived perception and intensity of fatigue, the Multidimensional Fatigue Inventory-20 is used [33,34]. Within the Multidimensional Fatigue Inventory-20, general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue represent the 5 dimensions of fatigue. The Generalized Self-Efficacy scale is used to measure how the patient perceives their possibility of adhering to the goals being set and find solutions to unforeseen or surprising situations and challenges [35]. As a patient-experience measure, the Quality from the Patient's Perspective questionnaire is used [36,37]. Patients rate their

experience and subjective importance in aspects of care: medical-technical competence, identity-oriented approach, sociocultural atmosphere, and physical-technical conditions. Documentation held by both health care professionals (eg, medical records) and patients (eg, the health book) are reviewed with respect to person-centered content [38]. Aspects of patient safety are reviewed from medical records (eg, the assessment of symptoms and vital signs) and care planning as well as specific aspects of care following surgery and introduction of hormonal replacement therapy.

Retention and Data Management

The research nurse is responsible to schedule follow-up visits in the longitudinal assessment. The research nurse ensures that the scheduled appointments are kept and that data are collected. Reasons for missing data or discontinuation from the study are documented. Updated information on recruitment and follow-up are continuously discussed within the research group to identify structural barriers for inclusion or data collection. A file for data collection on the patients including their social security number and assigned code number is kept in a locked safe at the clinic. Self-reported measures are primarily collected through electronic devices. Data are entered with the code number assigned to each patient. Clinical data such as diagnosis, surgery, medical treatment, radiotherapy, mortality, morbidity, care contacts, and hospitalization are collected from the patients' medical records and entered into data files. Researchers within the research group are responsible for monitoring data collection.

Plan for Statistical Analysis

Statistical analysis will include descriptive analysis and comparisons between the control and intervention groups. For numerical data, mean, SD, median, and interquartile range will be calculated. Categorical data will be expressed as proportions (%). Background and clinical characteristics for the two groups will be expressed with descriptive data, and differences will be analyzed with the chi - squared test, independent samples *t* test, or Mann-Whitney U test. The primary outcome will primarily be evaluated by comparing changes in psychological wellbeing between baseline and 1 year after surgery in the two groups. Parametric or nonparametric tests will be used depending on whether data are normally distributed for the purpose of comparing data between the intervention group and control group. Effects will be described as mean differences with 95% CIs. Data will be analyzed using SPSS software package (IBM Inc, Armonk, NY). The significance level will be set at $P<.05$, and all tests will be two-tailed. Subgroup analyses will be performed based on demographic characteristics and disease and treatment characteristics.

Ancillary Studies

Identification of Factors Predicting a Poor Outcome

Tumor remission is highly dependent on the type and growth pattern of the tumor. Excess mortality is highest in patients with craniopharyngioma and lowest in patients with nonfunctioning pituitary adenoma [1,2]. Further, factors often associated with excess mortality and morbidity in these patients are hypopituitarism, female gender, young age at diagnosis, and tumor characteristics needing additional treatment [1,2,4,7,9]. Patient characteristics, magnetic resonance imaging evaluations of the tumor, laboratory results, and tumor tissues are studied to explore factors that may predict long-term outcomes. The anatomical structures surrounding the tumor (hypothalamus and basal forebrain) are visualized on magnetic resonance imaging using sequences for anatomical imaging (T1) as well as sequences for detecting damage (3D T2/FLAIR). Tumor tissue is analyzed to investigate DNA, RNA, expressed proteins, and DNA methylation pattern. This integrated part of the project enhances knowledge with respect to identification of persons at risk for tumor progression.

Brain Injury Biomarkers

Resection of large pituitary tumors may lead to manipulation of adjacent structures such as the hypothalamus and the basal forebrain. In an effort to study possible brain damage caused by surgery, we examine peripheral blood biomarkers of brain injury before surgery, immediately after surgery, and during follow-up. This allows us to study the potential relationship between brain injury markers during surgery and long-term outcomes.

Consequences and Complications of Surgical Treatment

Surgery for pituitary tumors is usually performed using a transsphenoidal route, which affects sino-nasal structures and may lead to nasal symptoms postoperatively and impaired quality of life [39]. The aim of this part of the study is to examine postoperative effects focusing on sino-nasal symptoms [40]. As headache can occur both as a consequence of the tumor itself and as a complication after surgery, a further aim is to study the occurrence and type of headache before surgery and during follow-up [41].

Cognitive Functioning

For an evaluation of cognitive functioning in conjunction with surgery, cognitive functioning is assessed using the Repeatable Battery for the Assessment of Neuropsychological Status, which measures immediate memory, visuospatial functions, language, attention, and delayed memory [42]. The cognitive testing is performed by a neurorehabilitation psychologist before surgery and 1 year after surgery. Together with self-reported quality of life, cognitive function is an important outcome against which intervention, tumor size, surgery, and brain injury markers can be evaluated.

Methodological Development

An additional measure of self-efficacy, the Self-Efficacy Scale for chronic disease [43], is used for psychometric evaluation and compared directly with the Generalized Self-Efficacy scale regarding responsiveness and sensitivity.

Results

Inclusion in the control group receiving standard care was completed from Q3 2015 to Q4 2017 with the number of patients needed to evaluate the primary outcome. Recruitment to the group exposed to the intervention has been ongoing since Q4 2017, and the estimated timepoint for completed recruitment is Q4 2020. Final data collection is expected in Q4 2021.

Discussion

The primary aim of this study is to evaluate whether support within a person-centered care practice increases psychological wellbeing for patients with pituitary tumors. The project addresses the effects of extended support from surgery to the start of lifelong endocrine treatment and tumor surveillance for patients with pituitary tumors. The year after pituitary surgery constitutes an important time period, with medical evaluations of surgery and decisions on hormonal substitution, all resulting in a critical time for the patients [44].

Clinical care is currently standardized and evidence-based within the framework of a clinical pathway and is based on the medical needs patients have as a group. While it is important to ensure that patients receive safe, high-quality medical care, the patients' experiences, will, resources, and motivation often have a smaller role in a standardized care model. In this intervention, the clinical pathway and care based on person-centeredness will be integrated (Figure 1). Person-centered practice may create a better foundation for offering care at the right time with the right effort and at the right level, since the patients' experiences with their own health situation and confidence in their own ability to cope with the situation are the focus.

Recent research has shown that shared decision making can increase physical and mental wellbeing, self-care, and confidence in one's own abilities [45]. Ekman and colleagues [46] described three integrated procedures when initiating, integrating, and securing the practice of person-centered care: (1) the narrative that puts the person and his or her health and life situation at the center of care, (2) shared information and shared decision making, and (3) documentation that gives legitimacy to the patient's experiences, preferences, beliefs, and values [46]. After receiving care based on these procedures, patients have reported increased satisfaction with care, increased participation in decisions, and care in accordance with needs [38,47]. Furthermore, there was increased confidence in one's own abilities and reduced uncertainty [48-50]. Person-centered care has also resulted in reduced durations of inpatient care [51].

The core element of the intervention, a nurse care manager, has the potential to give extended support to the patients. The role of a nurse care manager has mainly evolved within cancer care [52]. The role has changed over recent years from facilitating cancer screening to including provision for education to support informed decision making, assessing and addressing psychosocial needs, and facilitating transitions between care providers [52]. The role of the nurse care manager described within our intervention is to provide self-management support based on patient education, the patients' own resources, access to the interdisciplinary team, and through peer support. In reviewing 35 studies on nurse-led self-management programs in different long-term conditions, interventions aimed at combining both education and skill advancement in relation to individual needs were the most effective in increasing self-efficacy, coping, and behavioral changes, especially when also involving partners [53]. Educating patients about their disease should be individualized and extended to different ways of teaching [54]. The most effective support to increase patients' health and quality of life by a nurse care manager is to include education and support for self-care specifically adapted to the patient population and provided within an interdisciplinary team [55].

The quasiexperimental design has the potential to compare person-centered practice to standard care. A design based on randomization of parallel groups was considered impossible as the intervention consists of reorganizational as well as relational components and would thereby create potential bias in the standard care group. Developing, implementing, and evaluating a person-centered care practice contains several interacting components that make it a complex intervention [56]. Evaluations of conducting person-centered care have shown that interventional studies demanded specific adaptation to the different clinical settings including time, workload, care culture, and documentation systems that would otherwise constrain the intervention unless continued education and follow-up were performed during the intervention [57,58]. The person-centered practice within our study demands a transformation from disease-oriented care to care based on person-centeredness; therefore, extensive implementation of both structural and relational components is addressed. The study protocol has a design in which the evaluation of the intervention is being made within the setting where it is later supposed to work in clinical practice adapted specifically for patients with pituitary tumors. Following our study's results, the person-centered practice may also become a useful model to further develop and explore person-centered care for patients with other rare, lifelong conditions.

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Authors' Contributions

All authors contributed to the design of the study. SJ, DO, GJ, and EJU wrote the protocol, and all other authors contributed with critical review and editing. All authors read and approved the final version of the protocol.

Conflicts of Interest

SJ, EA, TH, DK, ACO, and EJU declare that they have no conflicts of interest. DSO has served as a consultant for Pfizer, Sandoz, and Ipsen. TS has received lecture fees from Abbott. OR has received lecture fees from Novo Nordisk, Ipsen, Sandoz, and Pfizer; an unrestricted research grant from HRA-pharma; and consultancy fees from Novartis and HRA-pharma. GJ has served as a consultant to Shire and AstraZeneca and has received lecture fees from Ipsen, Novartis, Novo Nordisk, Pfizer, Sandoz, Merck Serono, and Otsuka.

References

1. Olsson DS, Nilsson AG, Bryngelsson I, Trimpou P, Johannsson G, Andersson E. Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study. J Clin Endocrinol Metab 2015 Jul;100(7):2651-2658. [doi: 10.1210/jc.2015-1475] [Medline: 25946030]
2. Olsson DS, Andersson E, Bryngelsson I, Nilsson AG, Johannsson G. Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab 2015 Feb;100(2):467-474. [doi: 10.1210/jc.2014-3525] [Medline: 25375987]
3. Tjörnstrand A, Gunnarsson K, Evert M, Holmberg E, Ragnarsson O, Rosén T, et al. The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. Eur J Endocrinol 2014 Oct;171(4):519-526. [doi: 10.1530/EJE-14-0144] [Medline: 25084775]
4. Ragnarsson O, Olsson DS, Chantzichristos D, Papakokkinou E, Dahlqvist P, Segerstedt E, et al. The incidence of Cushing's disease: a nationwide Swedish study. Pituitary 2019 Apr;22(2):179-186 [FREE Full text] [doi: 10.1007/s11102-019-00951-1] [Medline: 30799512]
5. Karavitaki N, Cudlip S, Adams CBT, Wass JAH. Craniopharyngiomas. Endocr Rev 2006 Jun;27(4):371-397. [doi: 10.1210/er.2006-0002] [Medline: 16543382]
6. Esposito D, Olsson DS, Ragnarsson O, Buchfelder M, Skoglund T, Johannsson G. Non-functioning pituitary adenomas: indications for pituitary surgery and post-surgical management. Pituitary 2019 Aug;22(4):422-434 [FREE Full text] [doi: 10.1007/s11102-019-00960-0] [Medline: 31011999]
7. Olsson DS, Bryngelsson I, Ragnarsson O. Higher incidence of morbidity in women than men with non-functioning pituitary adenoma: a Swedish nationwide study. Eur J Endocrinol 2016 Jul;175(1):55-61. [doi: 10.1530/EJE-16-0173] [Medline: 27147638]
8. Olsson DS, Hammarstrand C, Bryngelsson I, Nilsson AG, Andersson E, Johannsson G, et al. Incidence of malignant tumours in patients with a non-functioning pituitary adenoma. Endocr Relat Cancer 2017 May;24(5):227-235. [doi: 10.1530/ERC-16-0518] [Medline: 28274953]
9. Esposito D, Ragnarsson O, Granfeldt D, Marlow T, Johannsson G, Olsson DS. Decreasing mortality and changes in treatment patterns in patients with acromegaly from a nationwide study. Eur J Endocrinol 2018 May;178(5):459-469. [doi: 10.1530/EJE-18-0015] [Medline: 29483205]
10. Ferrante E, Ferraroni M, Castrignanò T, Menicatti L, Anagni M, Reimondo G, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol 2006 Dec;155(6):823-829. [doi: 10.1530/eje.1.02298] [Medline: 17132751]
11. Erfurth EM, Bulow B, Nordström CH, Mikoczy Z, Hagmar L, Strömberg U. Doubled mortality rate in irradiated patients reoperated for regrowth of a macroadenoma of the pituitary gland. Eur J Endocrinol 2004 Apr;150(4):497-502. [doi: 10.1530/eje.0.1500497] [Medline: 15080779]
12. Andela CD, Lobatto DJ, Pereira AM, van Furth WR, Biermasz NR. How non-functioning pituitary adenomas can affect health-related quality of life: a conceptual model and literature review. Pituitary 2018 Apr;21(2):208-216 [FREE Full text] [doi: 10.1007/s11102-017-0860-4] [Medline: 29302835]
13. Romijn JA. The chronic syndromes after previous treatment of pituitary tumours. Nat Rev Endocrinol 2016 Sep;12(9):547-556. [doi: 10.1038/nrendo.2016.84] [Medline: 27259177]
14. Andela CD, Scharloo M, Pereira AM, Kaptein AA, Biermasz NR. Quality of life (QoL) impairments in patients with a pituitary adenoma: a systematic review of QoL studies. Pituitary 2015 Oct;18(5):752-776. [doi: 10.1007/s11102-015-0636-7] [Medline: 25605584]
15. Andela CD, Niemeijer ND, Scharloo M, Tiemensma J, Kanagasabapathy S, Pereira AM, et al. Towards a better quality of life (QoL) for patients with pituitary diseases: results from a focus group study exploring QoL. Pituitary 2015 Feb;18(1):86-100. [doi: 10.1007/s11102-014-0561-1] [Medline: 24682940]
16. Andela CD, Tiemensma J, Kaptein AA, Scharloo M, Pereira AM, Kamminga NG, et al. The partner's perspective of the impact of pituitary disease: Looking beyond the patient. J Health Psychol 2017 Mar 01;24(12):1687-1697 [FREE Full text] [doi: 10.1177/1359105317695427] [Medline: 28810427]
17. Lobatto DJ, Steffens ANV, Zamanipoor Najafabadi AH, Andela CD, Pereira AM, van den Hout WB, et al. Work disability and its determinants in patients with pituitary tumor-related disease. Pituitary 2018 Dec;21(6):593-604 [FREE Full text] [doi: 10.1007/s11102-018-0913-3] [Medline: 30288666]

18. Andela CD, Repping-Wuts H, Stikkelbroeck NMML, Pronk MC, Tiemensma J, Hermus AR, et al. Enhanced self-efficacy after a self-management programme in pituitary disease: a randomized controlled trial. Eur J Endocrinol 2017 Jul;177(1):59-72. [doi: 10.1530/EJE-16-1015] [Medline: 28566534]
19. Martínez-Momblán MA, Gómez C, Santos A, Porta N, Esteve J, Úbeda I, et al. A specific nursing educational program in patients with Cushing's syndrome. Endocrine 2016 Jul;53(1):199-209. [doi: 10.1007/s12020-015-0737-0] [Medline: 26400845]
20. Institute OM(COQOCIA. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: The National Academies Press; 2001:a.
21. World Health Organization. Framework on integrated, people-centered health services. 2016. URL: https://www.who.int/servicedeliverysafety/areas/people-centred-care/en/ [accessed 2020-02-28]
22. Harding E, Wait S, Scrutton J. The Health Policy Partnership Ltd. 2015 Dec 11. The state of play in person-centered care: a pragmatic review of how person-centered care is defined, applied and measured URL: http://www.healthpolicypartnership.com/wp-content/uploads/State-of-play-in-person-centred-care-full-report-Dec-11-2015.pdf [accessed 2017-12-01]
23. McCormack B, McCance T. Person-Centred Nursing: Theory and practice. Oxford: Wiley-Blackwell; Jul 12, 2010.
24. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
25. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-2194. [doi: 10.1001/jama.2013.281053] [Medline: 24141714]
26. Wirén L, Bengtsson BA, Johannsson G. Beneficial effects of long-term GH replacement therapy on quality of life in adults with GH deficiency. Clin Endocrinol (Oxf) 1998 May;48(5):613-620. [doi: 10.1046/j.1365-2265.1998.00462.x] [Medline: 9666873]
27. Filipsson Nyström H, Barbosa EJL, Nilsson AG, Norrman L, Ragnarsson O, Johannsson G. Discontinuing long-term GH replacement therapy--a randomized, placebo-controlled crossover trial in adult GH deficiency. J Clin Endocrinol Metab 2012 Sep;97(9):3185-3195. [doi: 10.1210/jc.2012-2006] [Medline: 22791760]
28. Wiklund I, Karlberg J. Evaluation of quality of life in clinical trials. Controlled Clinical Trials 1991 Aug;12(4):S204-S216. [doi: 10.1016/s0197-2456(05)80024-8] [Medline: 1663856]
29. Lundgren-Nilsson A, Jonsdottir IH, Ahlborg G, Tennant A. Construct validity of the Psychological General Well Being Index (PGWBI) in a sample of patients undergoing treatment for stress-related exhaustion: a Rasch analysis. Health Qual Life Outcomes 2013 Jan 07;11:2 [FREE Full text] [doi: 10.1186/1477-7525-11-2] [Medline: 23295151]
30. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [doi: 10.1016/0168-8510(90)90421-9] [Medline: 10109801]
31. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
32. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013 Sep;22(7):1717-1727 [FREE Full text] [doi: 10.1007/s11136-012-0322-4] [Medline: 23184421]
33. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995 Apr;39(3):315-325. [doi: 10.1016/0022-3999(94)00125-o] [Medline: 7636775]
34. Hagelin CL, Wengström Y, Runesdotter S, Fürst CJ. The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations. Acta Oncol 2007;46(1):97-104. [doi: 10.1080/02841860601009430] [Medline: 17438711]
35. Schwarzer R, Jerusalem M. Generalized self-efficacy scale. In: Measures in health psychology: A users portfolio. Causal and control beliefs. Vol. England: NFER-NELSON: Windsor; 1995:35-37.
36. Wilde B, Larsson G, Larsson M, Starrin B. Quality of care. Development of a patient-centred questionnaire based on a grounded theory model. Scand J Caring Sci 1994;8(1):39-48. [doi: 10.1111/j.1471-6712.1994.tb00223.x] [Medline: 8159889]
37. Wilde Larsson B, Larsson G. Development of a short form of the Quality from the Patient's Perspective (QPP) questionnaire. J Clin Nurs 2002 Sep;11(5):681-687. [doi: 10.1046/j.1365-2702.2002.00640.x] [Medline: 12201896]
38. Jakobsson S, Eliasson B, Andersson E, Johannsson G, Ringström G, Simrén M, et al. Person-centred inpatient care - A quasi-experimental study in an internal medicine context. J Adv Nurs 2019 Aug;75(8):1678-1689. [doi: 10.1111/jan.13953] [Medline: 30793351]
39. Little AS, Kelly D, Milligan J, Griffiths C, Prevedello DM, Carrau RL, et al. Predictors of sinonasal quality of life and nasal morbidity after fully endoscopic transsphenoidal surgery. J Neurosurg 2015 Jun;122(6):1458-1465. [doi: 10.3171/2014.10.JNS141624] [Medline: 25839931]
40. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol 2009 Oct;34(5):447-454. [doi: 10.1111/j.1749-4486.2009.01995.x] [Medline: 19793277]

41. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology 2001;56(6 Suppl 1):S20-S28. [doi: 10.1212/wnl.56.suppl_1.s20] [Medline: 11294956]
42. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998 Jun;20(3):310-319. [doi: 10.1076/jcen.20.3.310.823] [Medline: 9845158]
43. Freund T, Gensichen J, Goetz K, Szecsenyi J, Mahler C. Evaluating self-efficacy for managing chronic disease: psychometric properties of the six-item Self-Efficacy Scale in Germany. J Eval Clin Pract 2013 Feb;19(1):39-43. [doi: 10.1111/j.1365-2753.2011.01764.x] [Medline: 21883720]
44. Jakobsson Ung E, Olofsson A, Björkman I, Hallén T, Olsson DS, Ragnarsson O, et al. The pre- and postoperative illness trajectory in patients with pituitary tumours. Endocr Connect 2019 Jul;8(7):878-886 [FREE Full text] [doi: 10.1530/EC-19-0202] [Medline: 31176303]
45. Coulter A, Entwistle VA, Eccles A, Ryan S, Shepperd S, Perera R. Personalised care planning for adults with chronic or long-term health conditions. Cochrane Database Syst Rev 2015 Mar 03(3):CD010523 [FREE Full text] [doi: 10.1002/14651858.CD010523.pub2] [Medline: 25733495]
46. Ekman I, Swedberg K, Taft C, Lindseth A, Norberg A, Brink E, et al. Person-centered care--ready for prime time. Eur J Cardiovasc Nurs 2011 Dec;10(4):248-251. [doi: 10.1016/j.ejcnurse.2011.06.008] [Medline: 21764386]
47. Ulin K, Olsson L, Wolf A, Ekman I. Person-centred care - An approach that improves the discharge process. Eur J Cardiovasc Nurs 2016 Apr;15(3):e19-e26. [doi: 10.1177/1474515115569945] [Medline: 25648848]
48. Dudas K, Olsson L, Wolf A, Swedberg K, Taft C, Schaufelberger M, et al. Uncertainty in illness among patients with chronic heart failure is less in person-centred care than in usual care. Eur J Cardiovasc Nurs 2013 Dec;12(6):521-528. [doi: 10.1177/1474515112472270] [Medline: 23303766]
49. Fors A, Taft C, Ulin K, Ekman I. Person-centred care improves self-efficacy to control symptoms after acute coronary syndrome: a randomized controlled trial. Eur J Cardiovasc Nurs 2016 Apr;15(2):186-194. [doi: 10.1177/1474515115623437] [Medline: 26701344]
50. Fors A, Swedberg K, Ulin K, Wolf A, Ekman I. Effects of person-centred care after an event of acute coronary syndrome: Two-year follow-up of a randomised controlled trial. Int J Cardiol 2017 Dec 15;249:42-47 [FREE Full text] [doi: 10.1016/j.ijcard.2017.08.069] [Medline: 28893432]
51. Ekman I, Wolf A, Olsson L, Taft C, Dudas K, Schaufelberger M, et al. Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. Eur Heart J 2012 May;33(9):1112-1119 [FREE Full text] [doi: 10.1093/eurheartj/ehr306] [Medline: 21926072]
52. Lubejko BG, Bellfield S, Kahn E, Lee C, Peterson N, Rose T, et al. Oncology Nurse Navigation: Results of the 2016 Role Delineation Study. Clin J Oncol Nurs 2017 Feb 01;21(1):43-50. [doi: 10.1188/17.CJON.43-50] [Medline: 28107327]
53. van Hooft SM, Been-Dahmen JMJ, Ista E, van Staa AL, Boeije HR. A realist review: what do nurse-led self-management interventions achieve for outpatients with a chronic condition? J Adv Nurs 2017 Jun;73(6):1255-1271. [doi: 10.1111/jan.13189] [Medline: 27754557]
54. Friedman AJ, Cosby R, Boyko S, Hatton-Bauer J, Turnbull G. Effective teaching strategies and methods of delivery for patient education: a systematic review and practice guideline recommendations. J Cancer Educ 2011 Mar;26(1):12-21. [doi: 10.1007/s13187-010-0183-x] [Medline: 21161465]
55. Hickam D, Weiss J, Guise JM, Buckley D, Motuápuaka M, Graham E, et al. Outpatient case management for adults with medical illness and complex care needs. Rockville (MD): Agency for Healthcare Research and Quality; Jan 2013.
56. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008 Sep 29;337:a1655 [FREE Full text] [doi: 10.1136/bmj.a1655] [Medline: 18824488]
57. Moore L, Britten N, Lydahl D, Naldemirci O, Elam M, Wolf A. Barriers and facilitators to the implementation of person-centred care in different healthcare contexts. Scand J Caring Sci 2017 Dec 08;31(4):662-673. [doi: 10.1111/scs.12376] [Medline: 27859459]
58. Britten N, Moore L, Lydahl D, Naldemirci O, Elam M, Wolf A. Elaboration of the Gothenburg model of person-centred care. Health Expect 2017 Jun;20(3):407-418 [FREE Full text] [doi: 10.1111/hex.12468] [Medline: 27193725]

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Protocol

Exploring the Paradoxical Relationship of a Creb 3 Regulatory Factor Missense Variant With Body Mass Index and Diabetes Among Samoans: Protocol for the Soifua Manuia (Good Health) Observational Cohort Study

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Abstract

Background: The prevalence of obesity and diabetes in Samoa, like many other Pacific Island nations, has reached epidemic proportions. Although the etiology of these conditions can be largely attributed to the rapidly changing economic and nutritional environment, a recently identified genetic variant, rs373863828 (CREB 3 regulatory factor, CREBRF: c.1370G>A p.[R457Q]) is associated with increased odds of obesity, but paradoxically, decreased odds of diabetes.

Objective: The overarching goal of the Soifua Manuia (Good Health) study was to precisely characterize the association of the *CREBRF* variant with metabolic (body composition and glucose homeostasis) and behavioral traits (dietary intake, physical activity, sleep, and weight control behaviors) that influence energy homeostasis in 500 adults.

Methods: A cohort of adult Samoans who participated in a genome-wide association study of adiposity in Samoa in 2010 was followed up, based on the presence or absence of the *CREBRF* variant, between August 2017 and March 2019. Over a period of 7-10 days, each participant completed the main study protocol, which consisted of anthropometric measurements (weight, height, circumferences, and skinfolds), body composition assessment (bioelectrical impedance and dual-energy x-ray absorptiometry), point-of-care glycated hemoglobin measurement, a fasting blood draw and oral glucose tolerance test, urine collection, blood pressure measurement, hand grip strength measurement, objective physical activity and sleep apnea monitoring, and questionnaire measures (eg, health interview, cigarette and alcohol use, food frequency questionnaire, socioeconomic position, stress, social support, food and water insecurity, sleep, body image, and dietary preferences). In January 2019, a subsample of the study participants (n=118) completed a buttock fat biopsy procedure to collect subcutaneous adipose tissue samples.

Results: Enrollment of 519 participants was completed in March 2019. Data analyses are ongoing, with results expected in 2020 and 2021.

Conclusions: While the genetic variant rs373863828, in CREBRF, has the largest known effect size of any identified common obesity gene, very little is currently understood about the mechanisms by which it confers increased odds of obesity but paradoxically lowered odds of type 2 diabetes. The results of this study will provide insights into how the gene functions on a whole-body level, which could provide novel targets to prevent or treat obesity, diabetes, and associated metabolic disorders. This study represents the human arm of a comprehensive and integrated approach involving humans as well as preclinical models that will provide novel insights into metabolic disease.

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KEYWORDS

cohort studies; CREBRF; type 2 diabetes; obesity; Samoa

Introduction

Background

As is now the case in many Pacific Island nations, the prevalence of obesity and diabetes in Samoa have reached epidemic proportions. In 2013 (the most recent estimates), 41.2% of men and 65.1% of women could be classified as having obesity based on Polynesian-specific body mass index (BMI) cutoff points (>32 kg/m^2) [1]. Data from the same survey indicated that type 2 diabetes mellitus was present in 19.6% of men and 19.5% of women and projections suggest that the proportion of the population with diabetes may exceed 26% by 2020 [1].

The underlying etiology of the rapidly increasing prevalence of obesity and related cardiometabolic disorders in the Pacific generally [2,3], and Samoa specifically [1], can be attributed in large part to the rapidly changing economic and nutritional environment. While energy availability, often in the form of calorie-dense, nutrient-poor, imported foods has increased rapidly in recent decades [4], opportunities for subsistence agriculture-related physical activity have simultaneously declined, resulting in chronic positive energy balance and associated metabolic disease. Perhaps compounding the effect of the changing nutritional and physical activity environment, however, is a recently identified genetic variant, rs373863828 (CREB 3 regulatory factor, *CREBRF*: c.1370G>A p.[R457Q]), which is associated with increased odds of obesity, but paradoxically, decreased odds of diabetes [5].

The *CREBRF* missense variant (*CREBRF*), first identified in a genome-wide association study (GWAS) we conducted in 2010 [5], is common among Samoans (minor allele frequency=0.259) and has a larger effect on BMI than any previously identified common genetic variant. The minor allele (A) is associated with greater average adult BMI of 1.36 kg/m^2 per copy, an effect size approximately 3-fold greater than variation near *FTO* (0.39 kg/m^2 per copy) [6]. Interestingly, however, the higher-BMI allele is associated with *decreased* odds of type 2 diabetes and *lower* fasting serum glucose levels. Several studies in New Zealand Māori and Pacific Islanders (Tongans, Cook Islanders, and Niueans) have recently replicated these findings [7-11], demonstrating comparable minor allele frequencies and reproducing the incongruent effects on BMI and type 2 diabetes. The variant is nearly absent in non-Pacific Islanders (14 alleles in 198,121 individuals, allele frequency=0.00004 in BRAVO and the Genome Aggregation Database (gnomAD) combined) [12,13].

Findings from mouse cell models indicate that the *CREBRF* genetic variant plays a role in both adipogenesis and improving cell survival under starvation conditions [5]. It appears to function by reducing energy substrate utilization for basic cellular processes and reallocating energy to lipid storage, perhaps functioning as a “thrifty gene” [5]. How the gene

functions on a whole-body level and the underlying explanation for its paradoxical association with obesity and diabetes, however, remains unknown.

Objectives

The overarching goal of this study was to precisely characterize the impact of the *CREBRF* variant on metabolic (body composition and glucose homeostasis) and behavioral traits (dietary intake, physical activity, sleep, and weight control behaviors) that influence energy homeostasis in 500 adults. Specifically, we aimed to (1) determine if the *CREBRF* variant's paradoxical association with BMI and diabetes could be explained by the amount (total fat mass) and distribution of adiposity (subcutaneous relative to visceral or central versus peripheral); (2) determine the association of the *CREBRF* variant with measures of glucose homeostasis and insulin action; (3) explore gene-environment interactions among the *CREBRF* variant and dietary intake, physical activity, and other behavioral traits; and (4) understand how the *CREBRF* variant influences metabolic homeostasis and gene expression in human adipose tissue.

Methods

Study Design

The Soifua Manuia (*Good Health* in Samoan) study described here follows a cohort of adult Samoans who participated in a GWAS of adiposity in Samoa in 2010 and who were followed up, based on the presence or absence of the *CREBRF* genetic variant, between August 2017 and March 2019. The recruitment procedures and protocols associated with the 2010 GWAS study have been described in detail previously [14]. *This study protocol describes the procedures used during the 2017-2019 interaction with study participants*.

The study underwent initial and annual continuing ethical review by institutional review boards (IRBs) at Yale and Brown Universities (there was a reliance agreement between Brown and Yale, with Yale serving as the IRB of record, IRB #1604017547). Data analysis activities at the University of Pittsburgh were reviewed by their IRB and were determined to be exempt (IRB #PRO16040077) based on their receipt of only deidentified data. The PartnersHealth Office of Research approved protocols for sleep apnea studies, and all aspects of the protocol were reviewed and approved by the Health Research Committee of the Samoan Ministry of Health. All participants provided written informed consent for their participation.

Setting

Samoa is an independent Pacific Island nation consisting of 2 large (*Upolu and Savai'i*) and several smaller islands. The majority of the Samoan population is rural (81%), and 78% are residents on the island of *Upolu* [15], which is divided into 3 census regions: the Apia urban area (AUA), Northwest Upolu (NWU), and the rest of Upolu (ROU).

Classified as an upper middle-income economy by the World Bank, Samoa's gross national income was US $4120 per capita in 2017 [16], and the country ranked 104 out of 188 globally based on the Human Development Index (HDI value=0.704) [17]. In 2017, the population of Samoa was 195,352, with an anticipated annual growth rate of 0.9%. Life expectancy at birth in 2016 was 78 for women and 72 for men [18].

Participants

Participants included in the 2017-2019 Soifua Manuia study were purposively recruited to study genetic and environmental influences on adiposity and cardiometabolic health. Specifically, we aimed to recruit a sample of 500 participants, with equal numbers of men and women, 100 of whom had 2 copies of the *CREBRF* minor/risk allele (AA), 200 of whom had one copy (AG), and 200 of whom had zero copies (GG). We carried out this nonrepresentative sampling by genotype to have higher power to detect contrasts between the genotype groups, while recognizing what was feasible in terms of recruitment given the overall rarity of the AA genotype in the population.

CREBRF genotypes were determined based on participants' data from the 2010 GWAS study [5,14]. The original eligibility criteria for the GWAS study included Samoan ethnicity (which was determined based on participant report that they had 4 Samoan grandparents), were aged 24.5 years to less than 65 years, nonpregnant, and had no physical or cognitive impairment that would prohibit completion of study procedures. To create a list of potential participants to be recruited for the 2017-2019 follow-up a number of selection criteria were applied to the 2010 data (Figure 1): only participants who consented in 2010 to being recontacted for additional research studies were included; participants must have had genotype data from the 2010 study and complete data on key outcomes of interest (BMI and serum glucose levels) and must have been resident on the island of Upolu (because study equipment could not be transported to the less developed and less densely populated island of Savai'i, where 9 of 33 of the 2010 GWAS villages were located). Then, kinship estimates were used (GenABEL [19]) to restrict the sample to those who were only minimally related to one another (less than first cousins, maximum kinship estimate 6.01%) because reducing the genetic correlation among the sampled individuals increases the effective population size. From this sample, individuals with the AA genotype were prioritized for recruitment. Early on in recruitment, we attempted to recruit 2 AG genotype and 2 GG genotype individuals for each recruited AA genotype individual, matching on sex, age within 5 years, and census region. Halfway through the recruitment, this protocol was adjusted to allow for faster recruitment, prioritizing AA and AG genotype individuals without explicitly matching. In this system, target recruitment lists were generated from the list of unrelated individuals and participants were recruited until the desired sample size for each genotype group within sex was achieved.

Recruitment occurred between August 2017 and March 2019 from 23 villages on the island of Upolu (8 urban [AUA], 7 periurban [NWU], and 8 rural [ROU]). After government and village-level permissions were granted, Samoan research assistants (2 out of 4 of whom had assisted with the 2010 GWAS study) used phone calls and visits to the participants' 2010 villages of residence to relocate participants. Village leadership (village mayors and women's committee members) assisted research staff in locating participants' homes. If a participant

could not be located, the reason was noted (Figure 1). In the case of participant death, a death certificate was requested from the Samoa Bureau of Statistics to document the cause.

During visits to participants' homes, research staff provided detailed information about the purpose of the 2017-2019 follow-up study and its protocols, gained written informed consent from all participants (including permission to link their 2017-2019 phenotype data with their 2010 data, which had been shared with the database of Genotypes and Phenotypes (dbGap) [20]), and screened the participants for eligibility. The same eligibility criteria were applied in 2017-2019 as in 2010 [14]; pregnant women were excluded, as were those who had developed physical or cognitive impairments preventing full participation in study procedures. Additional exclusion criteria included having given birth in the past 6 months or current lactation, ongoing use of weight loss medications, weight loss surgery, or significant recent weight loss (>5% of body weight in the past year). Seven to nine years after their original participation in the 2010 GWAS study, participants' age ranged from 30.7 years to 72.7 years. A total of 519 participants agreed to participate in the study (Figure 1): 94 participants with the AA *CREBRF* genotype, 201 with the AG genotype, and 224 with the GG genotype.

Study Procedures

Willing and eligible participants completed study activities over the course of 7-10 days. Two in-person visits took place, one in the participant's home and the other 7-10 days later in the Obesity, Lifestyle, and Genetic Adaptations (OLaGA; *n. life* in Samoan) research laboratory, located in the capital city of Apia, and research assistants contacted participants once by phone between the in-person visits. During the home visit, research assistants collected height, weight, hemoglobin (for assessment of anemia), administered a number of questionnaires, and initiated an accelerometer-based device, which participants wore to objectively measure physical activity for at least seven days before their visit to the OLaGA laboratory. Remaining study procedures were completed during the laboratory visit. A subsample of participants provided a subcutaneous buttock fat biopsy, which was collected at a separate research visit in January 2019. Participants were compensated for time spent completing the protocol, receiving 75 Western Samoan Tala (WST; approximately US $28) for their participation as well as a 10 WST phone card to allow them to complete dietary recalls by telephone. Table 1 provides an overview of the study activities and their timing, and each of the procedures are described in detail below.

Figure 1. Consolidated Standards of Reporting Trials diagram describing recruitment into the Soifua Manuia study and completion of study procedures. GWAS: genome-wide association study; HbA^{1c}: glycated hemoglobin.

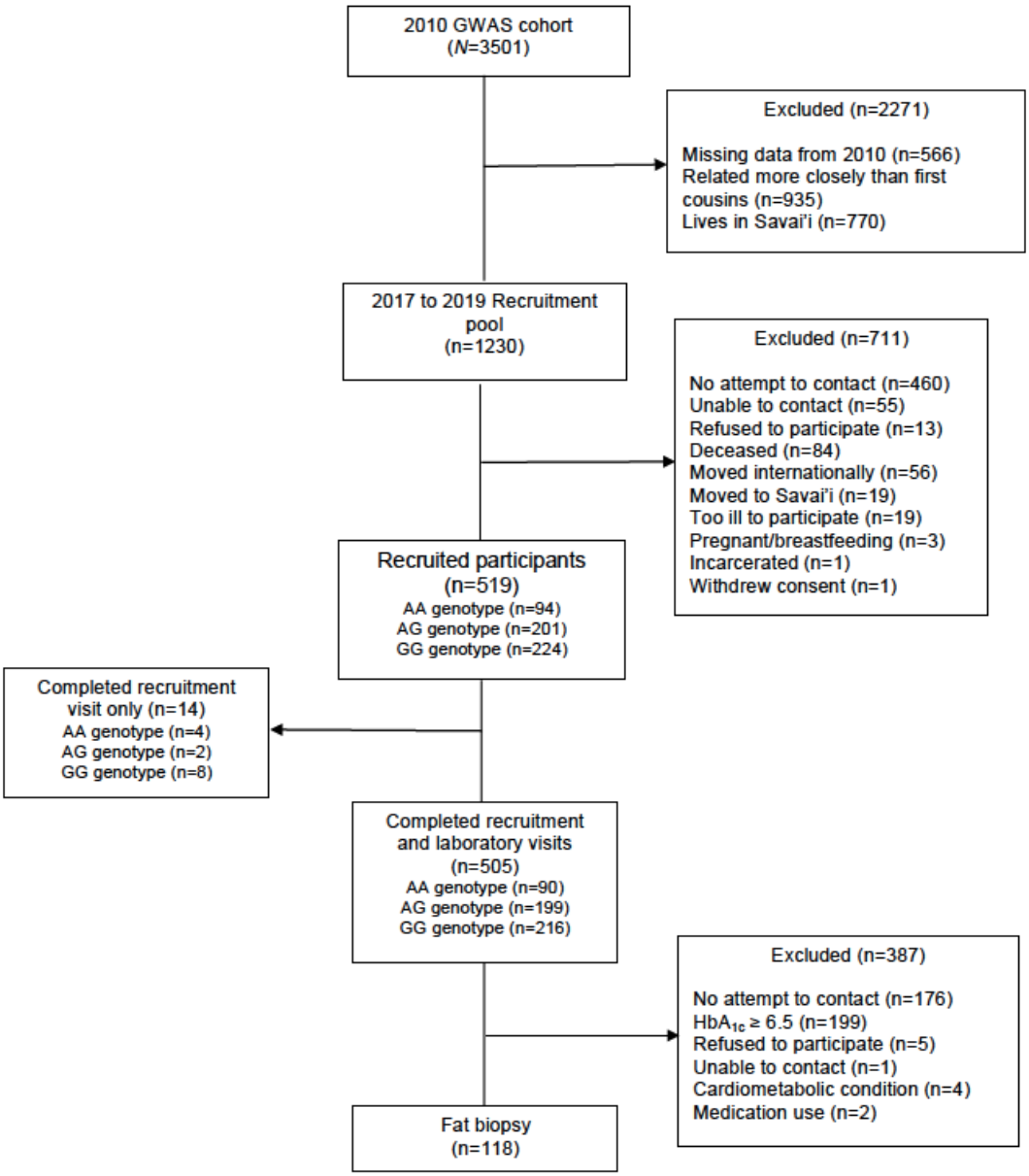

Table 1. Summary of the Soifua Manuia study procedures.

Measures	2010	Home visit, 2017-2019	Laboratory visit, 2017-2019	Fat biopsy visit, 2019
Anthropometric measures				
Weight	X[a]	X	X	X
Height	X	X	X	X
Circumferences (midupper arm, abdominal, hip, and midcalf)	X	—[b]	X	—
Skinfold thicknesses (forearm, tricep, subscapular, abdominal, and suprailiac)	X	—	X	—
Body composition				
BIA[c]	X	—	X	—
DXA[d] (total body, lumbar spine, hip, and forearm)	—	—	X	—
Blood pressure and hand grip strength				
Blood pressure and heart rate	X	—	X	—
Hand grip strength	—	—	X	—
Biospecimen collection				
Hemoglobin	—	X	—	—
Point-of-care HbA_{1c}[e]	—	—	X	X
Point-of-care fasting blood glucose	X	—	X	—
Serum	X	—	X	—
OGTT[f]	—	—	X	—
DNA	X	—	X	—
RNA	—	—	X	—
Urine	—	—	X	—
Objective physical activity monitoring (ActiGraph GT3X+)	—	X	X	—
Sleep monitoring (WatchPAT)	—	—	X	—
24-Hour dietary recalls	—	X	X	—
Questionnaire measures[g]				
Demographic information	X	X	—	—
Health Interview[h]	X	X	—	X
Women's health	X	X	—	—
Cigarette and alcohol use	X	X	—	—
Physical activity	X	X	—	—
Food frequency questionnaire	X	X	—	—
Material lifestyle	X	X	—	—
Health care choices	—	—	X	—
Stress	—	—	X	—
Social support and conflict	—	—	X	—
Health locus of control	—	—	X	—
Self-efficacy	—	—	X	—
Food and water insecurity	—	—	X	—
Sleep	—	—	X	—
Body image	—	—	X	—

Measures	2010	Home visit, 2017-2019	Laboratory visit, 2017-2019	Fat biopsy visit, 2019
Weight stigma and attitudes	—	—	X	—
Weight control behaviors	—	—	X	—
Dietary preferences	—	—	X	—
Living with diabetes	—	—	X	—
Bone and muscle function	—	—	X	—
Buttock fat biopsy	—	—	—	X

[a]Indicates that the measure was completed.

[b]Indicates that the measure was not collected at the specific visit.

[c]BIA: bioelectrical impedance analysis.

[d]DXA: dual-energy x-ray absorptiometry.

[e]HbA_{1c}: glycated hemoglobin.

[f]OGTT: oral glucose tolerance test.

[g]Questionnaire measures are described in detail in Table 2.

[h]An abbreviated health history was collected for the purposes of additional eligibility screening before the buttock fat biopsy.

Body Size and Body Composition

Protocols used in 2010 for the collection of anthropometric data were replicated during the 2017-2019 follow-up study [14]. Weight and height were measured in duplicate to the nearest 0.1 kg and 0.1 cm, respectively, using a digital weighing scale (Tanita HD 351; Tanita Corporation of America) and a portable stadiometer (SECA 213, Seca GmbH & Co). Circumferences (midupper arm, abdomen [at the level of the umbilicus], hip, and midcalf) and skinfold thicknesses (forearm, tricep, subscapular, abdominal, and suprailiac; Lange calipers, Beta Technology Inc) were also measured in duplicate to the nearest 0.1 mm. Measurements exceeding the maximum capacity of the skinfold calipers (>65 mm) were recorded as doing so in participant records. Bioelectrical impedance analysis (BIA) measures of resistance and reactance were obtained with an RJL BIA-101Q device (RJL Systems) in all participants without metal implants or pacemakers, using standard procedures. These data will be used to estimate fat mass and body fat percentage.

Whole body and regional body composition were also assessed using dual-energy x-ray absorptiometry (DXA; Lunar iDXA, Encore version 17, General Electric (GE) Healthcare Medicine). Additional eligibility criteria were applied to this assessment; participants did not undergo a DXA scan if they had been exposed to additional x-ray or computed tomography scans in the past 12 months (with the exception of dental x-rays). All women of childbearing age (<55 years) were tested for pregnancy before completing the DXA scan. Participants wore standardized clothing, without metal inserts or buttons, for a total body scan administered by 1 of 4 trained DXA operators in *standard* or *thick* mode. Body composition outcomes of interest were fat mass, lean mass, and visceral fat mass and volume (estimated using the CoreScan application, GE Healthcare Medicine). In cases where the participant's body size exceeded the limits of the scan area, participants were placed on the scanning bed such that the first scan captured the limbs on one side of the body and as much of the trunk region as possible. Participants were then repositioned to scan the remaining half of the body. Analyses in these cases will proceed using a mirror mode, where total body composition will be estimated from one half of the body. Among obese adults in other settings, this technique results in nonsignificant differences between mirrored and standard scan data [21].

DXA was also used to assess the bone mineral density and bone mineral content of the whole body, lumbar spine, nondominant hip, and forearm. Bone geometry at the femoral neck was estimated using Hip Structural Software (GE Healthcare Medicine) to calculate section modulus (bone resistance to bending), cross-sectional area, cross-sectional moment of inertia, and minimal neck width.

Blood Pressure and Hand Grip Strength

After a 10-min seated rest period, blood pressure and heart rate were measured 3 times, with a 3-min rest period between measurements, using an Omron HEM-907XL automated blood pressure monitor (Omron Healthcare). Hand grip strength was assessed as a functional measure of overall strength. After adjusting the handle position of a Jamar Plus+ digital hand dynamometer (Patterson Medical) according to participants' optimal comfort, maximal grip strength was measured in triplicate for both hands with 30-second rest periods between measurements. Procedures recommended by the American Society of Hand Therapists were followed for standardization [22].

Biospecimen Collection

Point-of-care testing devices requiring fingerstick blood samples were used to measure hemoglobin (for assessment of anemia; AimStrip Hb test system, Germaine Laboratories Inc) and glycated hemoglobin (HbA_{1c}; DCA vantage analyzer, Siemens Healthcare GmbH). HbA_{1c} values were used to determine if an oral glucose tolerance test (OGTT) could be administered safely: if HbA_{1c} was ≥9.0%, participants did not complete the OGTT, and if HbA_{1c} was ≥6.5% (indicating diabetes) but <9.0%, fasting blood glucose (FBG) was also measured (Bayer Contour Next,

Bayer HealthCare LLC) and only participants with FBG <200 mg/dL were allowed to complete the OGTT.

All participants completed a fasting blood draw, where Samoan phlebotomists collected whole blood for serum separation, DNA extraction, and RNA expression (using PaxGene (R) Blood RNA vacutainers, PreAnalytiX GmbH). Participants who could safely complete the 2-hour 75 g OGTT followed protocols recommended for diabetes diagnosis by the American Diabetes Association [23]. Additional whole blood was collected at 30-min intervals throughout the 2-hour protocol (30-, 60-, 90-, and 120-min postglucose load). Serum from the fasting samples and OGTT draws was separated by centrifugation and stored at −80°C before transport on dry ice to the University of Pittsburgh for analysis. Fasting samples are currently being analyzed for glucose, insulin, free fatty acids, lipid levels (total-, high density lipoprotein, low density lipoprotein, and very low density lipoprotein cholesterol, triglycerides), adiponectin, leptin, and markers of liver function (alanine amino transferase and aspartate aminotransferase). Glucose, insulin, and free fatty acids are being measured in all postglucose load samples.

Whole blood samples for DNA extraction were processed to the cell lysate stage using red blood cell lysis, protein precipitation, and cell lysis solutions following manufacturers protocols (5Prime T-MArchivePure TM, Thermo Fisher Scientific) and shipped at room temperature to the University of Cincinnati where further extraction steps were completed. PAXgene (R) vacutainers were chosen to collect whole blood samples for RNA expression because of their stability during transportation and storage. However, after the initiation of this protocol we learned of United States' import restrictions on the vacutainer reagents, meaning that processing had to be completed at the Samoan site. After storage at −80°C, samples were thawed and incubated at room temperature for up to 24 hours. RNA was isolated using the PAXgene (R) blood miRNA kit (PreAnalytix) according to the manufacturer's protocol with the following modification: step 5 of the Qiagen protocol stipulates, "Pipet the sample into a 1.5 ml microcentrifuge tube. Add 300 µl Buffer BM2 and 40 µl proteinase K. Mix by vortexing for 5 s, and incubate for 10 min at 55°C in a shaker incubator at 400-1400 rpm." A shaker incubator was unavailable for this step; so, after the addition of proteinase K, samples were incubated for 5 min at 55°C, uncapped, recapped, vortexed, and incubated for another 5 min at 55°C. Two elutions of 40 µl of buffer BR5 produced a final volume of 80 µL RNA. Following isolation, RNA was stored at −80°C before transfer to a GenTegra RNA matrix. RNA was applied to the GenTegra matrices per the manufacturer's protocol, distributing each sample among 2 GenTegra tubes (approximately 40 µl each), and dried overnight in a biosafety cabinet by evaporation. Tubes were then capped, stored, and inventoried before transport to the University of Pittsburgh. Recovery of RNA was performed according to the manufacturer's instructions, using the same volume buffer BR5 as was originally added to the matrix.

Random urine specimens were collected and stored for the study biobank. To allow for the later examination of exposure to environmental chemicals, samples were collected in polypropylene containers, and participants were asked not to touch the inside of the specimen cups or cup lids. Urine specific gravity was measured using a handheld digital refractometer (ATAGO, PAS-10S, ATAGO Co. Ltd) to quantify urine dilution. Samples were aliquoted into polypropylene cryovials and stored at −80°C before shipping on dry ice to Brown University.

Questionnaires

Over the course of the 2 study visits and in the midparticipation phone call, participants responded to questionnaires that documented their individual and household demographic and socioeconomic characteristics, current health status and health history, physical activity, dietary intake, and sleep patterns and symptoms. Participants also completed multiple psychosocial measures, including body image, stress, self-efficacy, and weight control behaviors. All questionnaire measures were chosen based on existing literature linking the concepts measured with obesity, diabetes, or other aspects of cardiometabolic health and well-being. All the questionnaire measures employed are listed in Table 2, with a brief summary of their content and references for the original survey instruments.

All questionnaires were translated into the Samoan language and administered in Samoan by bilingual local research assistants. Data were collected on iPads using Research Electronic Data Capture (REDCap) tools hosted by Yale University [24,25]. Each questionnaire was completed once, either at the home visit or laboratory assessment, with the exception of the 24-hour dietary recalls, which were completed on three occasions—twice in person (at the home and laboratory visits) and once by phone on a randomly selected day between the 2 in-person visits. Recall days were selected to include 2 weekdays and one weekend day, and protocols followed the multiple-pass method recommended by the US Department of Agriculture [26]. The timing of administration of each questionnaire was carefully considered. First, questionnaires that were asked in 2010 were repeated at the first contact with participants to protect against any loss to follow-up that may have occurred between the home and laboratory visits and maximize the longitudinal data available for assessment (weight and height were collected at the first contact for a similar reason). Second, questionnaires that may have triggered alterations in behavior during the period of measurement between visits (such as some of the weight control behavior or body image measures) were only asked at the laboratory visit once monitoring of dietary intake and physical activity were complete.

Table 2. Soifua Manuia study questionnaire measures completed in 2017-2019.

Questionnaire	Number of items	Asked in 2010	Description	References[a]
Demographic information	6	X[b]	Basic demographic information including age, sex, marital status, and education	—[c]
Health interview[d]	36	X	Diagnosis with medical conditions (diabetes, hypertension, heart disease, and high cholesterol), medication use, use of traditional healers, and self-reported health and weight	—
Women's health[d]	26	X	Parity, gravidity, age at menarche, menstrual regularity, contraceptive use, infertility, pregnancy history, and menopause (age and symptoms)	Barkan et al [27]
Cigarette and alcohol use	15	X	Use of tobacco products, alcohol consumption, and problems with drunkenness	—
Physical activity	11	X	Global Physical Activity Questionnaire (GPAQ), which estimates time spent in moderate-vigorous work, transport, and leisure-related activities	World Health Orgnaization [28]
Food frequency questionnaire	111	X	Locally validated food frequency questionnaire measuring consumption (never or less than once a month to more than 6 times per day) and usual portion size	—
Material lifestyle[d]	46	X	Household assets inventory, amenities (plumbing, cooking, and toilet facilities), number of household residents, occupation of heads of household, income, village wealth, disparities, and community spirit	—
Health care choices	17	—	Use of and preferences for traditional versus western biomedical health care practitioners	—
Stress	18	—	Cohen Perceived Stress Scale (PSS) and Short Form-8 quality of life measures	Cohen et al [29]; Ware et al [30]
Social support and conflict	19	—	Multidimensional Scale of Perceived Social Support (MSPSS) and perceived social conflict	Zimet et al [31]; O'Brien et al [32]
Health locus of control	18	—	Beliefs about internal versus external control over health and well-being	Wallston et al [33]
Self-efficacy	35	—	General and social self-efficacy and exercise confidence survey	Sherer et al [34] Clark et al [35]; Sallis et al [36]
Food and water insecurity	52	—	Household Food Insecurity Access Scale (HFIAS) and Household Water Insecurity Experiences scale (HWISE)	Coates et al [37]; Young et al [38]
Sleep	23	—	Sleep duration, sleep quality, chronotype, shift work, and Epworth Daytime Sleepiness Scale (EDSS)	Bild et al [39]; Johns [40]
Body image	20	—	Satisfaction with body shape and size and body size preferences	Brewis et al[41]
Weight stigma and attitudes[e]	66	—	Attitudes toward obese persons scale, beliefs about obese people, weight stigma, and discrimination	Allison et al [42]; Myers and Rosen [43]
Self-esteem	19	—	Rosenberg self-esteem scale	Rosenberg [44]
Weight control behaviors	53	—	Eating habits, dietary preferences, and weight control efforts	Neumark-Sztainer et al [45]
Dietary preferences	50	—	Three-factor eating questionnaire (cognitive restraint of eating, disinhibition, and hunger)	Stunkard and Messick [46]
Living with diabetes[f]	86	—	Diabetes symptoms and self-care behaviors, perceived diabetes control, medication adherence, and beliefs about diabetes	Carey et al [47]; DePue et al [48]
Bone and muscle function	9	—	Broken bones, bone-specific supplement use, and SARC-F screen for sarcopenia	Malmstrom et al [49]

[a]References indicate the sources of questionnaire items; questionnaires may not have been used in their entirety and may have been adapted to the Samoan context.

[b]Indicates that the questionnaire was also completed in 2010.

[c]Indicates that the measure was not collected in 2010. In the references column, it indicates that questions cannot be attributed to a single source or were of the authors design.

[d]Some questionnaire items were updated between 2010 and 2017, so not all questions were consistent across time points; health interviews were updated with additional questions about medication adherence and locally available generic medication brands, women's health included more detailed menstrual regularity questions in 2010, and the material lifestyle household assets inventory was updated with newly available household commodities monitored in the Samoa Demographic and Health Survey.

[e]One section of this questionnaire (n=19 questions), concerned with experiences of overweight or obesity, was only asked of participants who self-reported being moderately or much too heavy.

[f]Asked only of those participants who self-reported a diagnosis of type 2 diabetes.

Objective Physical Activity Monitoring

Actigraph GT3X+ accelerometer-based devices (ActiGraph Corporation) were used to objectively measure physical activity during the 7-10 day period between the home and laboratory visits. The GT3X+ was secured to the nondominant wrist using a disposable hospital band. The wrist placement was chosen for several reasons: (1) for continuous monitoring that would allow assessment of sleep patterns, (2) to better accommodate Samoan clothing styles (as compared with waist-worn), and (3) to prevent loss of the devices and minimize missing data associated with participants forgetting to replace their device after removing with clothing or bathing. The GT3X+ devices were initialized to collect raw acceleration at 30 Hz, and participants were asked to wear the devices continuously until the laboratory visit. Devices were removed at the laboratory visit, where data were downloaded and briefly reviewed for completeness. In the event that less than 5 days of data were recorded, participants were asked to repeat the assessment. Expected output from the objective physical activity monitoring includes estimates of daily energy expenditure (metabolic equivalents); daily steps; sedentary time; and time spent in light, moderate, and vigorous physical activity.

Sleep Apnea Detection

We provided 391 participants with a WatchPAT TM 200 Unified (Itamar Medical Ltd.) device, consisting of a finger probe and chest sensor to evaluate sleep apnea and sleep patterns (devices became available several months into the recruitment period, after which all participants completed this assessment). The WatchPAT TM was worn on the nondominant wrist (proximal to the GT3X+, so results could be compared) the night before the laboratory visit. The device measured peripheral arterial tone (PAT TM) signal, oxygen saturation, actigraphy, acoustic decibels (snoring evaluation), and body position. The output was downloaded to a computer, encrypted, and sent to collaborators at Brigham and Women's/Harvard Medical School for interpretation. Sleep studies were reviewed within 48 hours of receipt by expert analysts, and all participants with readings indicative of severe sleep apnea (n=15) were referred to a local sleep clinic in Apia.

Buttock Fat Biopsies

At the time of consent for the overall study, participants were asked to consent separately to completing a subcutaneous buttock fat biopsy so that the effect of the *CREBRF* variant on gene expression in adipose tissue could be determined. To limit variation by disease status, we selected a subsample of participants to recontact and ask to participate in this additional procedure. The participants in this subset were those without diabetes (those without a self-reported diabetes diagnosis at the time of participation in the main protocol and those with HbA_{1c} <6.5%), cancer, or cardiovascular disease. For convenience and efficiency, we sampled participants within a 45-min drive of the AUA. Participants were recontacted either by phone or at their homes during a 2-week period in January 2019. Given the genotype frequencies and diabetes prevalence in the population, we aimed to recruit 26 nondiabetic women and 15 nondiabetic men for each of the 3 genotypes (AA, AG, and GG). Participants were rescreened for the overall study eligibility criteria (pregnancy, lactation, birth within 6 months, and major weight loss) as well as the specific biopsy criteria, including additional point-of-care HbA_{1c} measurement, in their homes. Willing and eligible participants were then scheduled for the biopsy procedure.

Biopsies were completed in a sterile environment at a local medical facility. After the procedure, an adapted version of that described by Beynen and Katan [50] was explained in detail by the study clinician (A Prescott, plastic surgery resident), and additional verbal consent to the procedure was obtained in the Samoan language by study staff. Participants lay in a prone position with the left gluteal soft tissue exposed. Using red light technology, a commercial vein identification device (Illumivein, Easy-RN LLC) was used to identify any venous plexuses in the subcutaneous tissues. The anticipated biopsy site (with the least amount of subcutaneous vessels) was marked with a surgical skin marker, and an ice pack was applied for 1 min to numb the area. The skin was prepped with single-use sterile ChloraPrep (TM; Becton, Dickinson and Company), allowed to dry, and topical Gebauer's ethyl chloride spray was used to anesthetize the anticipated biopsy site. Participants were asked to contract their gluteal muscles, while the clinician performed a pinch test (using single-use, latex-free, sterile gloves) on the anticipated biopsy site. A single-use, sterile 16-gauge needle attached to a single-use, sterile 1 cc syringe was inserted into the biopsy site percutaneously to harvest the adipose tissue samples. Using a handheld aspiration technique (applying gentle negative manual pressure to the syringe or needle apparatus), 10-30 passes were performed at a 45-degree angle, until adipose tissue was visibly seen in the syringe. In cases where the study participant demonstrated more than minimal discomfort (or if samples were too sanguineous), the biopsy was terminated immediately. Once the lipoaspirate was visible in the syringe, the needle or syringe

was completely removed from the biopsy site and handed off to a technician for downstream processing. When the biopsy site was deemed adequately hemostatic, a small gauze was applied and secured gently with adhesive tape. Study participants were observed for up to 60 min before departing the study site. Study participants were provided with postbiopsy care instructions and a contact number to call if any unusual or severe adverse effects were encountered.

Following sample collection, the syringe containing the adipose sample was washed with 0.5-1 ml RNALater (R; Ambion Inc). The mixture of RNALater (R) and lipoaspirate was then expelled into a 1.5 5-ml microcentrifuge tube and incubated at 5°C overnight before transfer to −80°C the next day per the manufacturer's protocol. Samples in RNALater (R) were transported from Apia, Samoa, to the University of Pittsburgh. Although samples in RNALater (R) are stable for up to a week at room temperature, we shipped the samples on ice, with refrigeration and/or refreshed ice between destinations, to maintain a more consistent temperature as temperatures can fluctuate dramatically across climates and altitudes. Upon arrival in Pittsburgh, samples were stored at −80°^{o}C until processing. To process, frozen samples were thawed at room temperature, and RNALater (R) was removed from the sample by straining the RNALater (R) + lipoaspirate through a 0.22- µm nylon cell strainer placed atop a 50- ml conical tube (such that the sample was collected in the strainer and the RNALater was collected in the conical tube). The strainer was weighed before and after the sample was strained to acquire the mass of the lipoaspirate. The tissue was then collected from the strainer into a 14-ml round bottom tube containing 1 ml of QIAzol Lysis Reagent (Qiagen Sciences Inc) and homogenized for 30 seconds with a TissueRuptor (R; Qiagen Sciences Inc). Following homogenization, total RNA was isolated from the homogenate using RNeasy Lipid Tissue Mini Kit (R; also Qiagen) according to the manufacturer's protocol, including optional DNase treatment to remove contaminating genomic DNA and optional full speed spin to remove residual buffer RPE or flow-through. Two elutions of 30-µl nuclease-free water were used in the final step for a final volume of 60 µl RNA.

Participant Feedback and Referrals to Clinical Services

Participant feedback occurred in several stages. First, at the completion of the laboratory visit, all participants received a feedback sheet that used a *traffic light* (green, orange, and red) approach to describe their risk of overweight or obesity, anemia, hypertension, and diabetes (based on HbA_{1c}) as well as recommendations for further follow-up screening and behavioral modifications based on those risks. After serum analyses were completed, participants received individual letters with their cholesterol, triglycerides, fasting glucose, and insulin, and OGTT results as well as a study summary, which described key findings from the overall study and provided village and like-for-like comparisons to allow participants to put their individual results in context (eg, men <40 years of age were provided with summary data for all men in their comparable age range). At both stages, study staff provided referrals to local clinical services where participants met local risk criteria for diabetes, hypertension, or anemia. Participants are able to engage with study progress via the study's Facebook page (@YaleOlaga), and the private message function on the page offered an additional way for participants to contact study staff with questions about their participation (study staff could also be contacted by phone or text message).

Data Management and Statistical Analysis

Descriptive analyses will first be used to characterize the metabolic and behavioral traits of participants. Questionnaire measures that have not previously been validated in the Samoan setting will be examined for validity and internal consistency before analyses proceed. Then, we will test for cross-sectional associations of measured traits with the *CREBRF* variant using methods appropriate for the categorical or continuous nature of the outcomes, while adjusting for relevant covariates including age, sex, and relatedness. While many of our analyses using the newly collected data will initially be hypothesis-free, we will continue to be informed by our parallel mouse and cell models and test the resulting hypotheses using methods appropriate to the questions being addressed. Longitudinal analyses, where there are comparable measures available from the 2010 data collection (eg, weight or BMI) will use appropriate linear-mixed models that explicitly model the dependence between the different time points. After quality control and data cleaning are completed, the cleaned datasets generated during this study will be available in the dbGaP repository under the accession number phs000914 [20].

Results

The study was funded by the US National Institutes of Health (R01HL093093) in March 2016. Data collection was completed among 519 participants between July 2017 and March 2019, and results addressing the main study hypotheses are expected to be published in 2020 and 2021.

Discussion

Significance

Although the genetic variant rs373863828, in *CREBRF*, has the largest known effect size of any identified *obesity gene*, very little is currently understood about the mechanisms by which it confers increased odds of obesity but paradoxically lowered odds of type 2 diabetes. A small number of studies have evaluated the *CREBRF* gene (not this variant specifically) in nonhuman preclinical models. These studies have implicated *CREBRF* in a variety of disparate cellular and physiological processes, including the unfolded protein response [51], glucocorticoid signaling and maternal behaviors [52], reproduction [53,54], viral pathogenesis [55], angiogenesis [56], carcinogenesis [57,58], and starvation resistance [59]. However, this protocol is the first attempt to broadly characterize the association of the variant with a wide variety of metabolic and behavioral traits in humans.

Overweight, obesity, and type 2 diabetes—the complex and chronic conditions that are the focus of this protocol—are major health concerns that are estimated to cause 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life years in high-, low-, and middle-income countries [60]. Every effort

must be made to understand the basic biological underpinnings of these complex, chronic conditions, so that appropriate pathways may be targeted by behavioral and pharmacologic intervention. Although we do not describe our additional ongoing studies here, the activities described in this protocol occurred alongside additional cell and mouse studies, including characterization of the gene networks mediating the effects of the variant on energy and metabolic homeostasis. We will also seek to identify the role of natural selection in the emergence of the *CREBRF* variant and other variants coselected with it that may contribute to its risk.

Strengths and Limitations

Although we believe the approach we have described has the potential to generate new understanding of the genetic basis of obesity and diabetes risk in this population, it is not without limitations. Although several key analyses will be able to take advantage of longitudinal data, many of the phenotypes collected here were measured for the first time in the cohort in 2017-2019, meaning analyses will be cross-sectional and we will have limited ability to infer causality. Several of our measurement tools, particularly those used to measure behavioral traits, were new to the Samoan setting, and despite rigorous protocols for translation and staff training, will require testing for validity and reliability in this population. Most significant though are potential biases in our sampling, stemming from both our initial sampling strategy in the 2010 GWAS study, where a nonrepresentative convenience sampling approach was used, and our selective follow-up of only Upolu residents (necessitated by the near-impossibility of transporting the DXA scanner to the most rural residents of Savai'i). Our nonrepresentational sampling, with strong oversampling of AAs and moderate oversampling of AGs, ensures that we have enough individuals with the rarer genotypes to be able to contrast them against the common GGs. However, it is important to consider the possible effects of the initial matching on sex, age within 5 years, and census region, followed by looser matching; this sampling strategy, which may induce bias, reflects the realities and complexities of fieldwork. Kuo et al [61] found that *matching in loose-matching data can be ignored for negligible loss in testing and estimation if the distributions of matching variables are not extremely different between cases and controls*. To examine this in our own data, we simulated 20,000 replicates of a quantitative trait in the whole sample gathered in 2010 as a function of each individual's observed values for age, sex, rs373863828 genotype (coded 0,1,2), census region, and random normal N(0,1) noise and assumed *true* effect sizes; the effect size of the genotype was set such that its mean *P* value was 2.7×10^{-6} in the larger 2010 sample. Then, we subset the data to the 519 individuals who are in our current sample and examined the percent bias in the estimates of the regression parameters derived ignoring matching. Similar to Kuo et al's results [61], we find that the bias in the estimates is very small, for example, for the genotype effect size estimate, which is of primary interest, the bias is only −0.43%. Although more extensive simulations are merited, it appears that our sampling strategy does not induce strong bias in the estimates relative to their true population-level values. The estimated power in the 519 selected individuals to detect association of the simulated trait with genotype, while adjusting for the other predictors, at the .01 level was 82.8%. This is in line with earlier simulations done when we initially sought funding for this work where we found that, based on simulated sampling from the total set of the 2010 participants, we should have 87.1% power at the 0.01 level to detect our BMI signal and 78.4% power for hip circumference.

This study lays the groundwork for subsequent analysis to understand how the *CREBRF* risk variant influences adiposity and cardiometabolic traits. These studies, in combination with studies to understand the *CREBRF* gene more generally, are expected to be significant because they are likely to reveal entirely new pathways upstream and downstream of *CREBRF* that more broadly influence energy and metabolic traits across multiple populations and ethnic groups and individuals. Such knowledge could provide novel targets to prevent or treat obesity, diabetes, and associated metabolic disorders. This study represents the human arm of a comprehensive and integrated approach involving humans as well as preclinical models that will provide novel insights into metabolic disease.

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Conflicts of Interest

None declared.

References

1. Lin S, Naseri T, Linhart C, Morrell S, Taylor R, McGarvey ST, et al. Trends in diabetes and obesity in Samoa over 35 years, 1978-2013. Diabet Med 2017 May;34(5):654-661 [FREE Full text] [doi: 10.1111/dme.13197] [Medline: 27505623]
2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the global burden of disease study 2013. Lancet 2014 Aug 30;384(9945):766-781 [FREE Full text] [doi: 10.1016/S0140-6736(14)60460-8] [Medline: 24880830]
3. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016 Apr 2;387(10026):1377-1396 [FREE Full text] [doi: 10.1016/S0140-6736(16)30054-X] [Medline: 27115820]
4. Seiden A, Hawley NL, Schulz D, Raifman S, McGarvey ST. Long-term trends in food availability, food prices, and obesity in Samoa. Am J Hum Biol 2012;24(3):286-295 [FREE Full text] [doi: 10.1002/ajhb.22237] [Medline: 22371334]
5. Minster RL, Hawley NL, Su C, Sun G, Kershaw EE, Cheng H, et al. A thrifty variant in CREBRF strongly influences body mass index in Samoans. Nat Genet 2016 Sep;48(9):1049-1054 [FREE Full text] [doi: 10.1038/ng.3620] [Medline: 27455349]
6. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol 2014 Jan;10(1):51-61 [FREE Full text] [doi: 10.1038/nrendo.2013.227] [Medline: 24247219]
7. Naka I, Furusawa T, Kimura R, Natsuhara K, Yamauchi T, Nakazawa M, et al. A missense variant, rs373863828-A (p.Arg457Gln), of CREBRF and body mass index in Oceanic populations. J Hum Genet 2017 Sep;62(9):847-849. [doi: 10.1038/jhg.2017.44] [Medline: 28405013]
8. Berry SD, Walker CG, Ly K, Snell RG, Carr PE, Bandara D, et al. Widespread prevalence of a CREBRF variant amongst Māori and Pacific children is associated with weight and height in early childhood. Int J Obes (Lond) 2018 Apr;42(4):603-607. [doi: 10.1038/ijo.2017.230] [Medline: 28928463]
9. Krishnan M, Major TJ, Topless RK, Dewes O, Yu L, Thompson JM, et al. Discordant association of the CREBRF rs373863828 A allele with increased BMI and protection from type 2 diabetes in Māori and Pacific (Polynesian) people living in Aotearoa/New Zealand. Diabetologia 2018 Jul;61(7):1603-1613 [FREE Full text] [doi: 10.1007/s00125-018-4623-1] [Medline: 29721634]
10. Ohashi J, Naka I, Furusawa T, Kimura R, Natsuhara K, Yamauchi T, et al. Association study of CREBRF missense variant (rs373863828:G > A; p.Arg457Gln) with levels of serum lipid profile in the Pacific populations. Ann Hum Biol 2018 May;45(3):215-219. [doi: 10.1080/03014460.2018.1461928] [Medline: 29877158]
11. Hanson RL, Safabakhsh S, Curtis JM, Hsueh W, Jones LI, Aflague TF, et al. Association of CREBRF variants with obesity and diabetes in Pacific islanders from Guam and Saipan. Diabetologia 2019 Sep;62(9):1647-1652. [doi: 10.1007/s00125-019-4932-z] [Medline: 31280340]
12. Karczewski K, Francioli L, Tiao G, Cummings B, Alföldi J, Wang Q, The Genome Aggregation Database Consortium, et al. Variation across 141,456 human exomes and genomes reveals the spectrum of loss-of-function intolerance across human protein-coding genes. bioRxiv 2019 preprint [FREE Full text] [doi: 10.1101/531210]
13. BRAVO variant browser: University of Michigan and NHLBI. 2018. The NHLBI Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequencing Program URL: https://bravo.sph.umich.edu/freeze5/hg38 [accessed 2020-04-22]
14. Hawley NL, Minster RL, Weeks DE, Viali S, Reupena MS, Sun G, et al. Prevalence of adiposity and associated cardiometabolic risk factors in the Samoan genome-wide association study. Am J Hum Biol 2014;26(4):491-501 [FREE Full text] [doi: 10.1002/ajhb.22553] [Medline: 24799123]
15. Samoa Bureau of Statistics. 2017. 2016 Census Brief No 1: Revised version. Population Snapshot and Household Highlights URL: https://www.sbs.gov.ws/digi/2016_Census_Brief_No.1.pdf [accessed 2020-04-22]
16. World Bank Open Data. 2019. Country Information: Samoa URL: https://data.worldbank.org/country/samoa [accessed 2019-08-22]
17. United Nations Development Programme. Human Development Report 2016: Human Development for Everyone. New York, NY: UNDP; 2016.
18. World Health Organization. 2019. Country Information: Samoa URL: https://www.who.int/countries/wsm/en/ [accessed 2019-08-29]
19. Aulchenko YS, Ripke S, Isaacs A, van Duijn CM. GenABEL: an R library for genome-wide association analysis. Bioinformatics 2007 May 15;23(10):1294-1296. [doi: 10.1093/bioinformatics/btm108] [Medline: 17384015]
20. NCBI - NIH. The Database of Genotypes and Phenotypes (dbGaP). Genome-wide Association Study of Adiposity in Samoans URL: https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000914.v1.p1 [accessed 2020-04-20]

21. Rothney MP, Brychta RJ, Schaefer EV, Chen KY, Skarulis MC. Body composition measured by dual-energy X-ray absorptiometry half-body scans in obese adults. Obesity (Silver Spring) 2009 Jun;17(6):1281-1286 [FREE Full text] [doi: 10.1038/oby.2009.14] [Medline: 19584885]
22. MacDermid J, Solomon G, Fedorczyk J, Valdes K. Impairment based conditions. In: Clinical Assessment Recommendations. Third Edition. Mount Laurel, NJ: American Society of Hand Therapists; 2015.
23. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care 2017 Dec 8;41(Supplement 1):S13-S27. [doi: 10.2337/dc18-s002] [Medline: 29222373]
24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
25. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019 Jul;95:103208. [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
26. Moshfegh A, Rhodes D, Baer DJ, Murayi T, Clemens J, Rumpler W, et al. The US department of agriculture automated multiple-pass method reduces bias in the collection of energy intakes. Am J Clin Nutr 2008 Aug;88(2):324-332. [doi: 10.1093/ajcn/88.2.324] [Medline: 18689367]
27. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, et al. The women's interagency HIV study. WIHS collaborative study group. Epidemiology 1998 Mar;9(2):117-125. [doi: 10.1097/00001648-199803000-00004] [Medline: 9504278]
28. World Health Organization. Global Physical Activity Questionnaire (GPAQ). WHO STEPwise Approach to NCD Risk Factor Surveillance URL: https://www.who.int/ncds/surveillance/steps/GPAQ_EN.pdf [accessed 2019-11-25]
29. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [doi: 10.2307/2136404] [Medline: 6668417]
30. Ware J, Kosinski M, Dewey J, Gandek B. How to Score and Interpret Single-item Health Status Measures: A Manual for Users of the of the SF-8 Health Survey : (with a Supplement on the SF-6 Health Survey). Boston, MA: QualityMetric; 2001.
31. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 1988 Mar;52(1):30-41. [doi: 10.1207/s15327752jpa5201_2]
32. O'Brien K, Wortman CB, Kessler RC, Joseph JG. Social relationships of men at risk for AIDS. Soc Sci Med 1993 May;36(9):1161-1167. [doi: 10.1016/0277-9536(93)90236-w] [Medline: 8511645]
33. Wallston KA, Wallston BS, DeVellis R. Development of the multidimensional health locus of control (MHLC) scales. Health Educ Monogr 1978;6(2):160-170. [doi: 10.1177/109019817800600107] [Medline: 689890]
34. Sherer M, Maddux JE, Mercandante B, Prentice-Dunn S, Jacobs B, Rogers RW. The self-efficacy scale: construction and validation. Psych Rep 1982;51(2):663-671. [doi: 10.2466/pr0.1982.51.2.663]
35. Clark MM, Abrams DB, Niaura RS, Eaton CA, Rossi JS. Self-efficacy in weight management. J Consult Clin Psych 1991;59(5):739-744. [doi: 10.1037/0022-006x.59.5.739] [Medline: 1955608]
36. Sallis JF, Pinski RB, Grossman RM, Patterson TL, Nader PR. The development of self-efficacy scales for health-related diet and exercise behaviors. Health Educ Res 1988 Nov;3(3):283-292. [doi: 10.1093/her/3.3.283]
37. Coates J, Swindale A, Bilinsky P. Food and Nutrition Technical Assistance III Project (FANTA). 2007. Household Food Insecurity Access Scale (HFIAS) for Measurement of Food Access: Indicator Guide URL: https://www.fantaproject.org/monitoring-and-evaluation/household-food-insecurity-access-scale-hfias [accessed 2020-04-24]
38. Young SL, Boateng GO, Jamaluddine Z, Miller JD, Frongillo EA, Neilands TB, HWISE Research Coordination Network. The Household Water Insecurity Experiences (HWISE) Scale: development and validation of a household water insecurity measure for low-income and middle-income countries. BMJ Glob Health 2019;4(5):e001750 [FREE Full text] [doi: 10.1136/bmjgh-2019-001750] [Medline: 31637027]
39. Bild D, Bluemke D, Burke G, Detrano R, Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002 Nov 1;156(9):871-881. [doi: 10.1093/aje/kwf113] [Medline: 12397006]
40. Johns M. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991 Dec;14(6):540-545. [doi: 10.1093/sleep/14.6.540] [Medline: 1798888]
41. Brewis A, McGarvey S, Jones J, Swinburn B. Perceptions of body size in Pacific islanders. Int J Obes Relat Metab Disord 1998 Feb;22(2):185-189. [doi: 10.1038/sj.ijo.0800562] [Medline: 9504327]
42. Allison D, Basile V, Yuker H. The measurement of attitudes toward and beliefs about obese persons. Int J Eat Disord 1991;10:599-607. [doi: 10.1002/1098-108X(199109)10:5<599::AID-EAT2260100512>3.0.CO;2-%23]
43. Myers A, Rosen J. Obesity stigmatization and coping: relation to mental health symptoms, body image, and self-esteem. Int J Obes Relat Metab Disord 1999 Mar;23(3):221-230. [doi: 10.1038/sj.ijo.0800765] [Medline: 10193866]
44. Rosenberg M. Society and the Adolescent Self-Image. Princeton, NJ: Princeton University Press; 1965.
45. Neumark-Sztainer D, Hannan PJ, Story M, Perry CL. Weight-control behaviors among adolescent girls and boys: implications for dietary intake. J Am Diet Assoc 2004 Jun;104(6):913-920. [doi: 10.1016/j.jada.2004.03.021] [Medline: 15175589]

46. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 1985;29(1):71-83. [doi: 10.1016/0022-3999(85)90010-8] [Medline: 3981480]
47. Carey MP, Jorgensen RS, Weinstock RS, Sprafkin RP, Lantinga LJ, Carnrike CL, et al. Reliability and validity of the appraisal of diabetes scale. J Behav Med 1991 Feb;14(1):43-51. [doi: 10.1007/bf00844767] [Medline: 2038044]
48. de Pue JD, Dunsiger S, Seiden AD, Blume J, Rosen RK, Goldstein MG, et al. Nurse-community health worker team improves diabetes care in American Samoa: results of a randomized controlled trial. Diabetes Care 2013 Jul;36(7):1947-1953 [FREE Full text] [doi: 10.2337/dc12-1969] [Medline: 23393217]
49. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle 2016 Mar;7(1):28-36 [FREE Full text] [doi: 10.1002/jcsm.12048] [Medline: 27066316]
50. Beynen A, Katan M. Rapid sampling and long-term storage of subcutaneous adipose-tissue biopsies for determination of fatty acid composition. Am J Clin Nutr 1985 Aug;42(2):317-322. [doi: 10.1093/ajcn/42.2.317] [Medline: 4025201]
51. Audas TE, Li Y, Liang G, Lu R. A novel protein, Luman/CREB3 recruitment factor, inhibits Luman activation of the unfolded protein response. Mol Cell Biol 2008 Jun;28(12):3952-3966 [FREE Full text] [doi: 10.1128/MCB.01439-07] [Medline: 18391022]
52. Martyn AC, Choleris E, Gillis DJ, Armstrong JN, Amor TR, McCluggage AR, et al. Luman/CREB3 recruitment factor regulates glucocorticoid receptor activity and is essential for prolactin-mediated maternal instinct. Mol Cell Biol 2012 Dec;32(24):5140-5150 [FREE Full text] [doi: 10.1128/MCB.01142-12] [Medline: 23071095]
53. Yang Y, Jin Y, Martyn AC, Lin P, Song Y, Chen F, et al. Expression pattern implicates a potential role for Luman recruitment factor in the process of implantation in uteri and development of preimplantation embryos in mice. J Reprod Dev 2013;59(3):245-251 [FREE Full text] [doi: 10.1262/jrd.2012-137] [Medline: 23400243]
54. Yang D, Jiang T, Liu J, Zhang B, Lin P, Chen H, et al. CREB3 regulatory factor-mTOR-autophagy regulates goat endometrial function during early pregnancy. Biol Reprod 2018 May 1;98(5):713-721. [doi: 10.1093/biolre/ioy044] [Medline: 29447354]
55. Audas TE, Hardy-Smith PW, Penney J, Taylor T, Lu R. Characterization of nuclear foci-targeting of Luman/CREB3 recruitment factor (LRF/CREBRF) and its potential role in inhibition of herpes simplex virus-1 replication. Eur J Cell Biol 2016 Dec;95(12):611-622. [doi: 10.1016/j.ejcb.2016.10.006] [Medline: 28029379]
56. Wong N, Cheung H, Solly E, Vanags L, Ritchie W, Nicholls S, et al. Exploring the roles of and in the regulation of angiogenesis by high-density lipoproteins. Int J Mol Sci 2018 Jun 28;19(7):1930 [FREE Full text] [doi: 10.3390/ijms19071903] [Medline: 29958463]
57. Han J, Zhang L, Zhang J, Jiang Q, Tong D, Wang X, et al. CREBRF promotes the proliferation of human gastric cancer cells via the AKT signaling pathway. Cell Mol Biol (Noisy-le-grand) 2018 Apr 30;64(5):40-45. [doi: 10.14715/cmb/2018.64.5.6] [Medline: 29729692]
58. Xue H, Zhang J, Guo X, Wang J, Li J, Gao X, et al. CREBRF is a potent tumor suppressor of glioblastoma by blocking hypoxia-induced autophagy via the CREB3/ATG5 pathway. Int J Oncol 2016 Aug;49(2):519-528. [doi: 10.3892/ijo.2016.3576] [Medline: 27278737]
59. Tiebe M, Lutz M, de la Garza A, Buechling T, Boutros M, Teleman A. REPTOR and REPTOR-BP regulate organismal metabolism and transcription downstream of TORC1. Dev Cell 2015 May 4;33(3):272-284 [FREE Full text] [doi: 10.1016/j.devcel.2015.03.013] [Medline: 25920570]
60. Lim S, Vos T, Flaxman A, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012 Dec 15;380(9859):2224-2260 [FREE Full text] [doi: 10.1016/S0140-6736(12)61766-8] [Medline: 23245609]
61. Kuo C, Duan Y, Grady J. Unconditional or conditional logistic regression model for age-matched case-control data? Front Public Health 2018;6:57 [FREE Full text] [doi: 10.3389/fpubh.2018.00057] [Medline: 29552553]

Abbreviations

AUA: Apia urban area
BIA: bioelectrical impedance analysis
BMI: body mass index
CREBRF: Creb 3 Regulatory Factor
DXA: dual-energy x-ray absorptiometry
FBG: fasting blood glucose
GWAS: genome-wide association study
HbA1c: glycated hemoglobin
IRB: institutional review board
NWU: Northwest Upolu
OGTT: oral glucose tolerance test
OLaGA: obesity, lifestyle, and genetic adaptations

ROU: rest of Upolu
WST: Western Samoan tala

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Protocol

Gaining First Insights on Secondary Progressive Multiple Sclerosis Patients Treated With Siponimod in Clinical Routine: Protocol of the Noninterventional Study AMASIA

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Abstract

Background: A high proportion of patients with relapsing remitting multiple sclerosis convert to secondary progressive multiple sclerosis (SPMS) characterized by irreversibly progressing disability and cognitive decline. Siponimod (Mayzent), a selective sphingosine-1-phosphate receptor modulator, was recently approved by the European Medicines Agency for the treatment of adult SPMS patients with active disease, as evidenced by relapses or magnetic resonance imaging features of ongoing inflammatory activity. Approval by the Food and Drug Administration covers a broader range of indications, comprising clinically isolated syndrome, relapsing remitting multiple sclerosis, and active SPMS. However, treatment effects of siponimod have not been assessed in a structured setting in clinical routine so far.

Objective: The objectives of AMASIA (imp**A**ct of **M**ayzent [siponimod] on second**A**ry progressive multiple **S**clerosis patients in a long-term non-**I**nterventional study in Germ**A**ny), a prospective noninterventional study, are to assess the long-term effectiveness and safety of siponimod in clinical routine and to evaluate the impact of disease burden on quality of life and socioeconomic conditions. Here, we report the study design of AMASIA.

Methods: Treatment effects of siponimod will be evaluated in 1500 SPMS patients during a 3-year observational phase. According to the genetic polymorphism of CYP2C9, the initial dose will be titrated to the maintenance dose of 1 mg (CYP2C9*1*3 and *2*3) or 2 mg (all other polymorphisms of CYP2C9 except *3*3, which is contraindicated) taken orally once daily. Primary endpoint is the 6-month confirmed disability progression, as assessed by a functional composite endpoint comprising the Expanded Disability Status Scale and symbol digit modalities test to take appropriate account of cognitive changes and increase sensitivity. Further measures including multiple sclerosis activity data; assessments of functional domains; questionnaires addressing the patients', physicians', and relatives' perspectives of disability progression; cognitive worsening; quality of life; and socioeconomic aspects will be documented using the multiple sclerosis documentation system MSDS3D.

Results: AMASIA is being conducted between February 2020 and February 2025 in up to 250 neurological centers in Germany.

Conclusions: AMASIA will complement the pivotal phase III–derived efficacy and safety profile of siponimod with real-world data and will further evaluate several individual treatment aspects such as quality of life and socioeconomic conditions of patients and caregivers. It might help to establish siponimod as a promising option for the treatment of SPMS patients in clinical routine.

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KEYWORDS

secondary progressive multiple sclerosis; siponimod (Mayzent); S1P modulator; oral therapy; noninterventional study; clinical routine; real-world evidence; disability; cognition; multiple sclerosis; drug therapy; chronic disease

Introduction

Most patients with multiple sclerosis (MS), a disabling chronic inflammatory disease of the central nervous system (CNS), initially experience episodes of focal neurological symptoms interspersed by periods of remission (relapsing remitting multiple sclerosis [RRMS]) [1]. Over time, 60% to 90% of RRMS patients convert to secondary progressive multiple sclerosis (SPMS) that is characterized both by an irreversibly increasing disability, with or without new magnetic resonance imaging (MRI) lesions or relapses [1-3], and by the worsening of cognitive function [4]. Cognitive deficits occur more frequently and with higher severity in SPMS patients than in RRMS patients [4].

In individual patients, the risk and timing of the transition from RRMS to SPMS remain largely unpredictable as there are currently no suitable immunologic, clinical, and imaging predictive markers [1,5]. Due to a lack of distinct diagnostic criteria, SPMS is usually diagnosed in retrospect, particularly because pathological parenchymal processes precede clinical symptoms [6,7]. Delineating the clinical profile of RRMS patients at risk of developing SPMS and identifying MRI parameters indicative of SPMS conversion are therefore of primary interest. For this purpose, the real-world evidence study PANGAEA 2.0 [8] has recently been expanded by the additional EVOLUTION study arms [9]. The long-term objective of PANGAEA2.0 EVOLUTION is to establish more accurate and unified diagnostic criteria for the detection of SPMS [10].

As with diagnosis, treatment options for SPMS are limited. Disease-modifying therapies indicated for RRMS as well as investigational RRMS treatments have failed to prevent or slow down disability progression in progressive MS in general [11] and, in particular, in SPMS [5,12-15]. The European Medicines Agency (EMA) has approved only interferon β-1b specifically for SPMS with superimposed relapses [13]. Until now, no immunomodulatory and immunosuppressive drugs have been available for the treatment of SPMS patients without superimposed relapses [16,17]. Siponimod (Mayzent) was approved by the EMA in 2020 for the treatment of adult SPMS patients with active disease, as evidenced by relapses or MRI features of inflammatory activity, commonly interpreted as gadolinium (Gd)-enhancing T1 lesions or active, new, or enlarging T2 lesions [18]. In 2019, the Food and Drug Administration had already approved siponimod with a broader label for the treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults [19].

Siponimod has been developed to selectively modulate the two sphingosine-1-phosphate (S1P) receptor (S1PR) subtypes S1PR1 and S1PR5, which are expressed on lymphocytes (S1PR1), astrocytes, oligodendrocytes, and neurons (S1PR1 and S1PR5) [20]. S1P interaction with S1PR1 expressed on autoreactive lymphocytes appears to be a major driver in early MS pathogenesis, because this interaction is essential for the egression of these cells from secondary lymphoid organs and their infiltration into the CNS [21]. Compared to RRMS, peripheral inflammatory infiltration plays a smaller role in SPMS, as reflected by a low frequency of new Gd-enhancing lesions. Instead, neurodegeneration driven by CNS-intrinsic inflammation is regarded as the predominant feature leading to progressive brain volume loss. Preclinical studies have identified direct neuroprotective properties of siponimod mediated through S1PR1 and S1PR5 receptors (ie, the prevention of synaptic degeneration and promotion of CNS remyelination) [22-24]. In this respect, siponimod represents an improvement over fingolimod (Gilenya), an oral S1P analogue targeting all 5 S1P receptors except S1PR2, for use in patients with highly active or rapidly evolving, severe RRMS [25,26]. The higher S1PR-selectivity of siponimod lowers the risk of adverse events (AEs) [27,28], and the shorter elimination half-life [27] allows patients more flexibility (eg, in case of planned pregnancy).

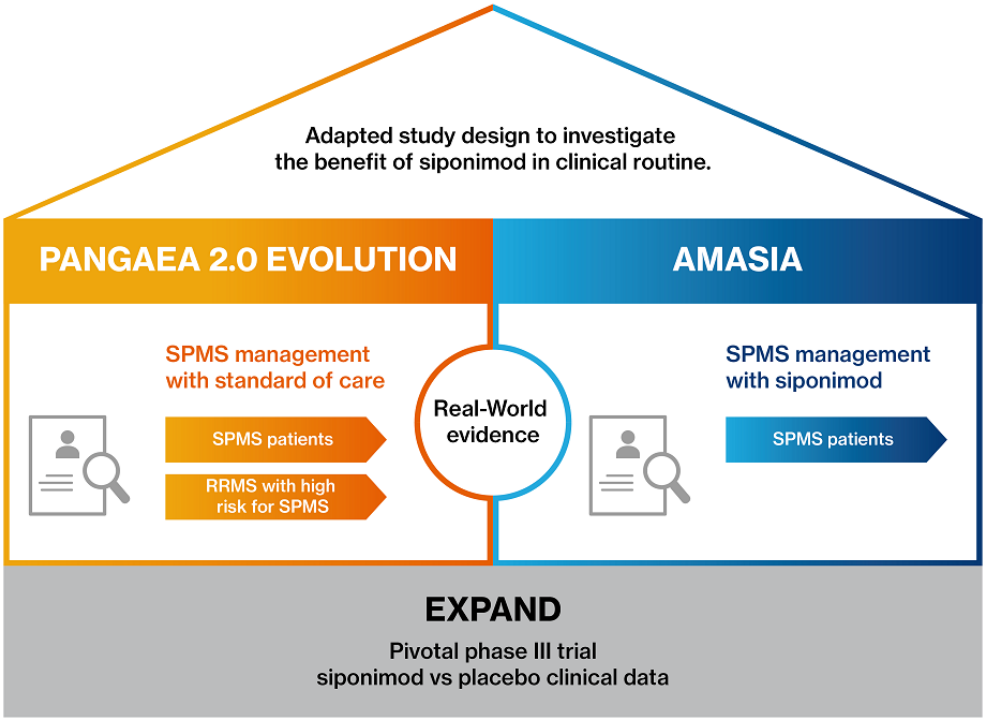
The phase III study EXPAND (EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis; CBAF312A2304) on the efficacy and safety of siponimod in SPMS patients [29] showed three favorable effects of particular importance for SPMS. First, siponimod attenuated inflammatory activity in SPMS patients. When compared to placebo-treated patients, more siponimod patients were found free from both Gd-enhancing lesions and new or enlarging T2 lesions. Second, siponimod reduced the risk of disability progression and lowered rates of brain volume decrease indicating that siponimod slows down neurodegeneration. Third, analyses of participants of the EXPAND study revealed significant and clinically meaningful effects of siponimod on cognitive processing speed, as demonstrated by increased scores in the symbol digit modalities test (SDMT) [30]. Compared to placebo, siponimod increased the proportion of patients with sustained SDMT improvement, while the proportion with sustained SDMT deterioration was reduced [31].

By nature, a pivotal study such as EXPAND with limited follow-up and a narrowly defined patient population cannot address the real-world situation of SPMS patients treated by siponimod in clinical routine [32]. We therefore planned

AMASIA (imp**A**ct of **M**ayzent [siponimod] on second**A**ry progressive multiple **S**clerosis patients in a long-term non-**I**nterventional study in Germ**A**ny), a noninterventional study (NIS) to assess the treatment effects of siponimod on SPMS patients in clinical routine. While EXPAND included a representative SPMS population with advanced progression, AMASIA focuses on the much narrower EMA label of SPMS with active disease. In addition to long-term clinical effectiveness and safety of siponimod in real-world situations, AMASIA will assess the effects of siponimod on disease progression of SPMS patients by a wide range of clinical and functional tests and questionnaires concerning the patients', physicians', and relatives' perspectives on disability progression and its consequences, including quality of life and socioeconomic aspects [33]. Furthermore, the study design of AMASIA has been developed following the methodology of PANGAEA 2.0 EVOLUTION [9] to enable a propensity score–matched comparison of SPMS patients receiving either siponimod or standard of care. Therefore, on the one hand, AMASIA will assess real-world treatment effects beyond the clinical data obtained by the phase III study EXPAND. On the other hand, it will allow a comparison of real-world treatment effects of siponimod and current standard of care in SPMS patients (Figure 1). With clinical data of the pivotal trial EXPAND as the base, AMASIA aims to analyze the benefit of siponimod treatment for SPMS patients in clinical routine. Results will be set in relation to the matched study PANGAEA 2.0 EVOLUTION, which analyzes patients with SPMS and high risk for SPMS treated by standard of care [8].

In this paper, we report the study protocol of AMASIA, a multicentric, open-label, prospective NIS. The study started in February 2020 and is planned to continue until February 2025. During the 3-year observational phase, data on 1500 SPMS patients treated by siponimod in up to 250 neurological centers in Germany will be documented.

Figure 1. AMASIA within the study framework of siponimod studies. AMASIA: imp**A**ct of **M**ayzent [siponimod] on second**A**ry progressive multiple **S**clerosis patients in a long-term non-**I**nterventional study in Germ**A**ny; EXPAND: EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis [29]; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.



Methods

Study Design

AMASIA is a multicentric, open-label, prospective NIS on adult SPMS patients with active disease as evidenced by relapses or MRI features of inflammatory activity. Clinical diagnosis and decision for siponimod therapy will exclusively be made by the treating physician prior to enrollment and according to clinical routine practice and drug label information [34] to ensure real-world conditions.

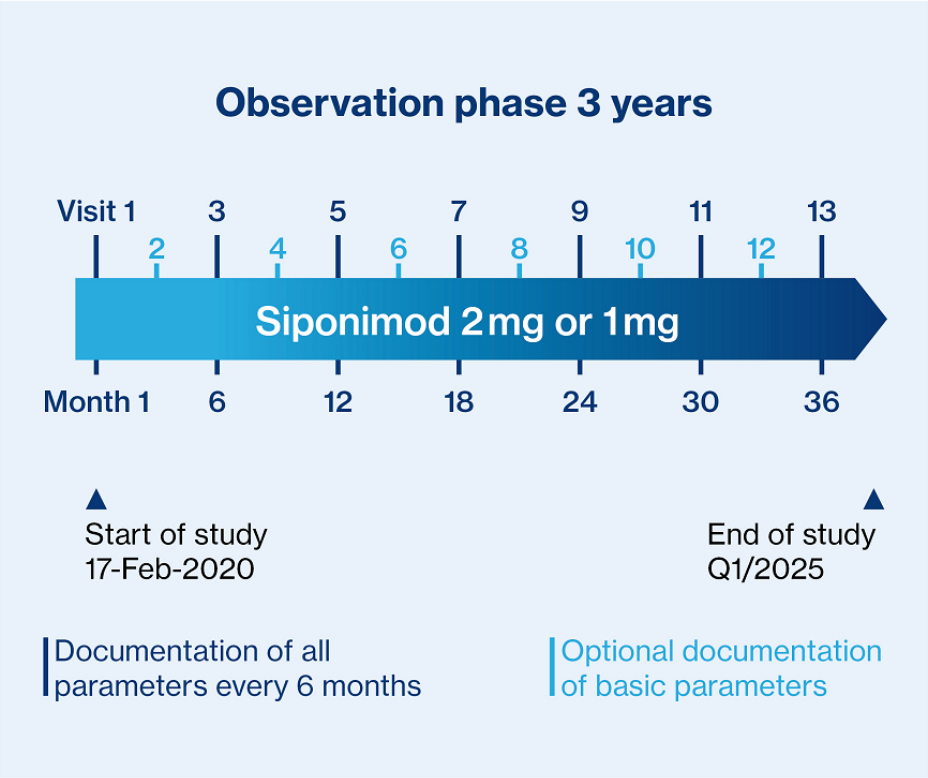
Both disability progression, as assessed by an increase in Expanded Disability Status Scale (EDSS) scores, and decline of cognitive processing speed are important indicators of disease burden in MS [35-37]. Therefore, in AMASIA, a novel functional composite primary endpoint combining the 6-month confirmed disease progression (6M-CDP) of the EDSS score and SDMT score is utilized. This composite endpoint has been validated in Germany [38] and will be analyzed after 36 months of siponimod therapy to assess long-term effects of siponimod under real-world conditions. This combined 6M-CDP has been successfully applied for the evaluation of EXPAND patients to increase the sensitivity for SPMS progression of both single measures [38,39]. Confirmed disability progression on EDSS is defined as ≥1.0-point worsening in patients with baseline scores ≤5.0 or 0.5-point worsening in patients with baseline scores >5.0. Concomitantly, a ≥4.0-point SDMT worsening from baseline is considered as clinically relevant [40].

To further evaluate the long-term benefits from siponimod treatment in clinical routine, changes in EDSS (after 36 months) and quality of life scores as well as data on safety and long-term adherence (treatment discontinuation and interruption) will be assessed as secondary endpoints. Adherence will be evaluated on the basis of duration of siponimod intake as well as frequency of discontinuation and dose retitration per patient-year. Additional secondary endpoints are exploratory in nature and concern socioeconomic aspects [41], the characteristics of patients receiving their first dose of siponimod, the timing of therapy initiation, and its impact on disease progression. Furthermore, the utility of progression questionnaires (aligned with the online tool MSProDiscuss) and mobile/digital apps for MS monitoring will be documented [42].

Because data are obtained in clinical routine, there is no protocol-defined visit schedule during the 3-year observational phase. However, the most probable frequency of visits in clinical routine is every 6 months after the first visit for dose titration. Basically, functional tests will be performed, and questionnaires will be collected in this interval. These regular visits will be complemented by additional visits to obtain basic parameters on clinical characteristics and MS disease activity every 3 months (Figure 2).

AMASIA will be conducted in accordance with the FSA code (voluntary self-regulation for the pharmaceutical industry [43]); joint recommendations of the German Federal Institute for Drugs and Medical Devices and Paul-Ehrlich-Institute on planning, conducting, and evaluating observational studies [44]; and German Association of Research-Based Pharmaceutical Companies recommendations on improving the quality and transparency of NIS [45]. The guidelines for good pharmacoepidemiology practices [46] as well as the STROBE guidelines for the reporting of observational studies will be applied [47]. Study procedures will be carried out in accordance with the Declaration of Helsinki. The Ethics Committee of TU Dresden (Technische Universität Dresden) approved AMASIA.

Figure 2. Study design of AMASIA (imp**A**ct of **M**ayzent [siponimod] on second**A**ry progressive multiple **S**clerosis patients in a long-term non-**I**nterventional study in Germ**A**ny), a non-interventional study involving an initial dose titration (visit 1), followed by a 3-year observational phase (visits 2-13).



Study Population

Sample Size

We intend to include 1500 SPMS patients in our study. In the EXPAND study [29], 62.2% of siponimod-treated patients had no disease progression, as determined by the combined 6M-CDP assessed using EDSS and SDMT scores (placebo: 52.3%). Since we expect comparable percentages for AMASIA, a total of 1000 patients completing the 36-month observational phase of AMASIA will be sufficient to estimate the combined 6M-CDP with a precision of 3.0%. With an assumed annual dropout rate of 13%, recruitment of 1500 patients will be required to achieve the intended sample size. Likewise, the same sample size is sufficient to assess EDSS changes over 36 months (secondary endpoint). The calculation is based on the assumed annual dropout rate of 13% and assumed standard deviation of 0.6 for EDSS changes from baseline to month 12 and month 24, as observed in EXPAND [29].

Eligibility of Patients

Treatment initiation with siponimod as routine therapy is at the discretion of the treating physician. The decision for siponimod treatment according to drug label information needs to be made

before enrollment and independently of study participation. Participants of all genders are eligible if they are 18 years or older, are diagnosed with SPMS, and provide written informed consent. Patients will be excluded due to off-label therapy, pregnancy and breastfeeding, treatment with siponimod before enrollment, and participation in interventional trials or PANGAEA 2.0 EVOLUTION. Patients who do not attend study visits for more than 12 months will exit the study.

Procedures

Dose Titration

After treatment decision and for dose selection, genetic variants of CYP2C9, a cytochrome P450 isoform involved in the metabolism of exogenous compounds by the liver [48], need to be determined in SPMS patients before the first dose of siponimod [34]. These CYP2C9 variants exhibit reduced enzymatic activity, leading to substantially elevated siponimod plasma levels [49,50]. Patients with CYP2C9 genotypes *1*1, *1*2, and *2*2 as well as patients with CYP2C9 genotypes *1*3 or *2*3 undergo a 5-day titration phase. In this titration phase, dosage is gradually increased from days 1 and 2 (0.25 mg) to day 3 (0.5 mg), day 4 (0.75 mg), and day 5 (1.25 mg). The maintenance dose is then 2 mg (CYP2C9*1*1, *1*2, *2*2) or 1 mg (CYP2C9*1*3, *2*3) taken orally once daily. If one dose is missed during the first 6 days of treatment or treatment at maintenance dose is interrupted for 4 or more consecutive days, titration needs to be reinitiated. Siponimod is contraindicated in patients with CYP2C9*3*3 genotype.

In patients with pre-existing cardiac conditions (ie, sinus bradycardia, first-degree or second-degree AV block, or a history of myocardial infarction or heart failure), a first-dose 6-hour monitoring of pulse and blood pressure is recommended, with an electrocardiogram at the beginning and end. Additional monitoring in case of clinically relevant cardiac symptoms as well as appropriate clinical management will be initiated according to the product information [34]. In AMASIA, SPMS diagnosis according to ICD-10, demographic and clinical data including MS-disease and non-MS-disease history, and varicella zoster virus immune status will be obtained during the initial dose titration phase. Varicella zoster virus vaccination of antibody-negative patients is recommended prior to siponimod treatment.

Observational Phase

Assessments during the 3-year observational period are depicted in Figure 3. Data on clinical examinations and MS disease status are obtained quarterly, if available. Data on MS disease status include MRI findings concerning number and volume of T2 hyperintense lesions, Gd-enhancing lesions, T1 hypointense lesions, and brain volume changes as well as EDSS and MS activity scale scores. The latter documents time, duration, intensity, treatment, and recovery of relapses.

Results of functional tests and questionnaires are obtained every 6 months (except for the questionnaire on the quality of life of caregivers [51]). Functional tests comprise the SDMT [36], timed 25-foot walk [52,53], and the nine-hole peg test [54] to assess neurological dysfunction and disability of lower and upper extremities. Furthermore, different questionnaires address the patients' [55-58], physicians' [59,60], and relatives' perspectives as well as socioeconomic aspects [61]. Disease progression will be additionally judged by means of a progression questionnaire aligned with the online tool MSProDiscuss, which is intended to facilitate the discussion between physicians and patients about SPMS [42,60].

Occurrence, duration, causal relationship to therapy, counteractive measures to and outcomes of AEs, and treatment discontinuation and interruption will be documented throughout the study. AEs are defined as any unfavorable change in the patients' pretreatment condition, regardless of their potential relation to treatment and irrespective of whether medication was taken as intended. Serious AEs comprise lethal or life-threatening events leading to persistent or significant disability, congenital anomaly or birth, hospitalizations, and other medically significant events that compromise the safety of patients.

Figure 3. Study visits during AMASIA (imp**A**ct of **M**ayzent [siponimod] on second**A**ry progressive multiple **S**clerosis patients in a long-term non-**I**nterventional study in Germ**A**ny). 9Hole Peg test: nine-hole peg test; AE: adverse event; CBC: complete blood count; CGI: clinical global impression; EDSS: Expanded Disability Status Scale; FSMC: Fatigue Scale For Motor And Cognitive Functions; MRI: magnetic resonance imaging; MS: multiple sclerosis; MS-AS: MS activity scale; MS-HRS: Multiple Sclerosis Health Resource Utilization Survey; SAE: serious adverse event; SDMT: symbol digit modalities test; T25-FW: timed 25-foot walk; TSQM-9: Treatment Satisfaction Questionnaire for Medication; UKNDS: United Kingdom Neurological Disability Scale.

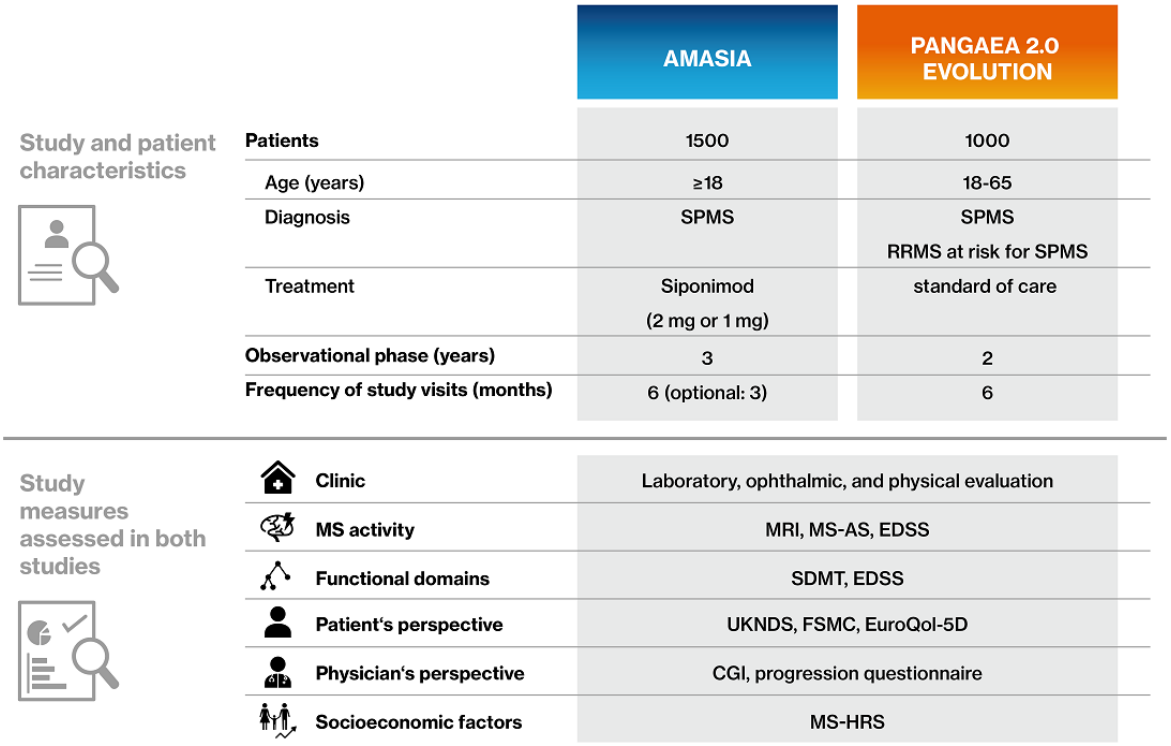
	Initial dose titration	Observational phase		
Visit	**1**	**2-12**		**13**
		optional every 3 months	app. every 6 months	
Informed consent	x			
Demography/diagnosis/anamnesis	x			
MS medical history	x			
Clinical characteristics				
CYP2C9 genotyping	x			
First dose monitoring	*if required*			
Varicella zoster virus immune status	x			
Laboratory (CBC, liver)	x	*if available*		x
Vital signs and physical examination	x	*if available*		
Ophthalmic evaluation	x	*as required*		x
Pregnancy status	x	*as required*		x
Co-medications (incl. prior medications)	x	*if available*		x
Use of an app for MS monitoring	x	*if available*		
MS disease status				
MRI parameters	x	*if available*		x
MS-AS	x	*if available*		x
EDSS	x	*if available*		x
Functional Domains				
SDMT, T25-FW, 9Hole Peg test	x		x	x
Questionnaires, patient's perspective				
UKNDS, FSMC, EuroQol-5D, TSQM-9	x		x	x
Physician's perspective				
CGI, progression questionnaire	x		x	x
Questionnaires care giver's perspective				
Scale of quality of life of care-givers	x			x
Questionnaires on socioeconomic factors				
MS-HRS	x		x	x
Adverse events				
AE	*continously*			
SAE	*continously*			
Treatment interruption/discontinuation	*as required*			

Propensity Score–Matched Comparison With PANGAEA 2.0 EVOLUTION

The real-world evidence study PANGAEA 2.0 [8] has been expanded by the EVOLUTION study arms [9] to clinically characterize SPMS patients and RRMS patients at risk for SPMS. In EVOLUTION, patients aged 18 to 65 years and with moderate to severe disability (EDSS 3.0-6.5) are included if they were previously diagnosed with RRMS and have a current diagnosis of SPMS or RRMS at risk for SPMS. Treatment options at inclusion are current disease-modifying therapies or no treatment during the last 12 months. Any treatment option as well as change of treatment are permitted, thereby representing the standard of care for SPMS prior to availability of siponimod. By having aligned the objectives and measures of EVOLUTION and AMASIA, it will be feasible to compare

the demographic and clinical parameters as well as the disease impact on functional domains, cognition, quality of life, and socioeconomic parameters. Since patients in EVOLUTION receive standard of care currently available to these patients, the propensity score–matched comparison with data obtained by AMASIA will provide further insights into the long-term effectiveness and safety of siponimod in clinical practice (Figure 4).

Figure 4. Pairwise comparison of data obtained during AMASIA (imp**A**ct of **M**ayzent [siponimod] on second**A**ry progressive multiple **S**clerosis patients in a long-term non-**I**nterventional study in Germ**A**ny) and PANGAEA 2.0 EVOLUTION, including study design, patient characteristics, and concordant and additional measures of multiple sclerosis (MS) activity, disability progression, functional domains, quality of life, and socioeconomic factors. Standard of care includes current disease-modifying therapy or no treatment at inclusion. CGI: clinical global impression; EDSS: Expanded Disability Status Scale; FSMC: Fatigue Scale For Motor And Cognitive Functions; MRI: magnetic resonance imaging; MS-AS: MS activity scale score; MS-HRS: Multiple Sclerosis Health Resource Utilization Survey; RRMS: relapsing remitting multiple sclerosis; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis; UKNDS: United Kingdom Neurological Disability Scale.



Data Collection and Management Using the Multiple Sclerosis Documentation System MSDS3D

Data will be recorded exclusively online by the physician responsible, using the electronic case report form in the MS documentation system MSDS3D [62,63]. The MSDS3D software combines data documentation with patient management. It now has expanded safety management with regard to the characteristics of different treatments and populations [64,65]. Data will be computerized in a pseudonymous form, and all entries will be automatically controlled for plausibility at the time of data entry and reviewed daily by the database coordinator. Data management processes including data analyses will be conducted by the data management team of the responsible clinical research organization (Winicker Norimed GmbH Medical Research).

Statistical Analysis

For analysis, descriptive statistics will be primarily used. The full analysis set includes all patients receiving at least one dose of siponimod with at least one available post-dose data recording. Sample statistics such as median, mean (SD), minimum, maximum, 5% percentile, 1st quartile, 3rd quartile, 95% percentile, and number of valid and missing values will be presented in tabular form. Distributions of absolute and relative frequencies will be reported for nominal and ordinal-level data. Incidence rates of all safety outcomes (events per patient-year) will be evaluated for the patient population included. A propensity score matching adjustment, possibly using a caliper-based nearest-neighbor approach as seen in Alsop et al [66], will be used to compare data from AMASIA with data from the PANGAE 2.0 EVOLUTION arm. Possible predictive baseline and prestudy variables to be included in the model are as follows: age at baseline (years), sex, time since diagnosis at baseline (years), treatment at baseline, number of relapses in the past 12 months before baseline, and EDSS score at baseline. A multivariable logistic regression model will be fitted with the treatment arm as the dependent variable. The distribution of propensity scores before and after matching will be analyzed. Using the Medical Dictionary for Regulatory Activities, AEs are categorized according to system organ class and preferred term for individual adverse events (for AEs, serious AEs, adverse drug reactions, serious adverse drug reactions). For all analyses, SAS version 9.2 will be used.

Results

The study will last from February 2020 through February 2025, with an observational phase of 3 years. Recruitment will end after 2 years or after enrollment of 1500 patients, whichever occurs first (Figure 2).

Discussion

Here, we report the study design of AMASIA, a NIS prospectively including 1500 SPMS patients to be treated with siponimod in the clinical routine of up to 250 German neurological centers. This study will provide first insights on the benefit of siponimod treatment in clinical routine. During the 3-year observational phase, the long-term effectiveness and safety of siponimod will be assessed under real-world conditions, along with data on the quality of life of both patients and caregivers as well as socioeconomic aspects. Overall, the study aims at obtaining a detailed real-world safety and benefit profile of siponimod, complementing both the phase-III study data of EXPAND [29] and the NIS data of PANGAEA 2.0 EVOLUTION [9] (Figure 1).

The primary endpoint of the study is the 6-month confirmed progression of both disability worsening and cognitive decline, as assessed by a novel composite endpoint comprising 6M-CDP in EDSS and SDMT [38]. In clinical trials, EDSS is the most common outcome measure to determine disability progression in MS and a widely used inclusion criterion to define study populations [67]. However, EDSS alone suffers from limited sensitivity, as it is restricted in assessing impairments of upper extremities and cognition, especially at higher scores [68,69]. Since cognition is more severely and more frequently affected in SPMS patients than in RRMS and even primary progressive MS patients [70-72], the SDMT, indexing the most frequently affected information processing speed domain, was chosen as an additional primary outcome measure. In the assessment of information processing speed, SDMT has been proven to be superior to other tests such as the Paced Auditory Serial Addition Test. Moreover, it is simple and requires less time and assessor expertise to complete [73], and several trials have demonstrated its sensitivity in the evaluation of treatment effects [30,74]. Since Kappos et al [38] showed that 6M-CDP, as assessed by either EDSS or SDMT, is of limited sensitivity when compared to the combined 6M-CDP considering both, we decided to employ this novel composite endpoint to increase sensitivity for changes and therapeutic effects of siponimod.

Additional measures aim at completing the picture of siponimod-treated SPMS patients in clinical routine (Figure 3). The clinical disease course will be characterized by MRI, EDSS, and MS activity scale scores. Since EDSS alone does not comprehensively reflect the disability status of patients, long-term effects on disability of lower and upper extremities are determined by the timed 25-foot walk and nine-hole-peg test, respectively. Questionnaires will capture data on symptoms and disease progression, perceived from the perspective of patients, physicians, and relatives. Importantly, the pairwise comparison with data obtained by PANGAEA 2.0 EVOLUTION [8,9] will extend the safety and efficacy profile of siponimod in clinical routine. Comparability is ensured by sample size, population characteristics, length of observational period, visit interval, and test selection (Figure 4). The combination of data obtained by both NIS will extend the efficacy and safety profile of siponimod obtained by the pivotal phase III study EXPAND [29]. In AMASIA, patient selection is less restricted in terms of age and not restricted in terms of comorbidities, EDSS status at baseline, and history of relapses before enrollment. Furthermore, while EXPAND included a much broader SPMS population, AMASIA concentrates completely on the siponimod EMA-label population with active disease. Therefore, AMASIA will better represent the real-world population of siponimod patients with supposedly earlier stages of SPMS.

AMASIA might provide additional mechanistic information on both the anti-inflammatory effects of siponimod (ie, fewer Gd-enhancing lesions and new or enlarging T2 lesions) and the prevention of neurodegeneration. Traditionally, neurodegeneration during MS pathogenesis is considered to be the consequence of inflammatory attacks mediated by the infiltration of leukocytes in the CNS and the release of inflammatory mediators. However, recent publications suggest that inflammation and neurodegeneration might be two separate aspects in progressive MS, with diffuse white matter injury and cortical demyelination on a background of meningeal, perivascular, and parenchymal inflammation [75]. Indeed, preclinical studies indicated that siponimod prevents and attenuates neurodegeneration [22,76] and promotes remyelination of the CNS [23]. While the EXPAND study indicated that patients with ongoing inflammatory activity (ie, superimposed relapses in the 2 years before enrollment) benefited most from siponimod treatment [29], a recent subgroup analysis suggested that treatment effects on disability are largely independent from that on relapses because siponimod reduced the risk for confirmed disability progression in both relapsing and nonrelapsing SPMS patients [77]. AMASIA might confirm these findings with long-term data from clinical routine.

As AMASIA is an observational NIS, it might be associated with some limitations. The lack of randomization to siponimod treatment and the heterogeneity of patients in real-life settings might limit robust conclusions regarding efficacy. However, propensity score–matched comparisons of SPMS patients receiving either siponimod (AMASIA) or standard care (PANGAEA 2.0 EVOLUTION) are thought to assess real-world treatment effects and, therefore, complement phase III data on efficacy. Another limitation to be considered is the potential incompleteness of data obtained during visits not following a predefined visit schedule. Obviously, this risk must be assumed to exist, but the intended systematic, standardized data collection, along with regular monitor visits to ensure data integrity, might be sufficient to minimize bias resulting from incomplete data.

In summary, AMASIA will be the first longitudinal study expanding the approval efficacy and safety profile of siponimod with real-world data. Data collected from this study are differentiated from the phase-III study on one hand and from pure registry studies on the other, through the use of the specialized MS management software tool MSDS3D. In particular, the comparison with data obtained from patients of

the PANGAEA 2.0 comparator arm EVOLUTION, who are treated according to the current standard of care, will provide even deeper insights into the long-term effectiveness and safety of siponimod as well as its effects on the quality of life and socioeconomic conditions of SPMS patients. After the United States [19], Germany is the second country in which patients have access to commercially available siponimod. Therefore, the results of AMASIA will be particularly helpful for physicians in other countries to expand the long-term efficiency and safety profile of siponimod and to establish a promising treatment option for SPMS patients.

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Authors' Contributions

TZ developed the study design, which is part of this manuscript, and contributed to this manuscript. OH, LK, HS, and MSW participated in the design of the study and contributed to the manuscript. BR wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

TZ received speaking honoraria and financial support for research activities from Almirall, Biogen, Celgene, Novartis, Roche, Teva, and Sanofi. OH served on scientific advisory boards and received speaker honoraria from Bayer Healthcare, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, and Teva and received financial support for research activities from Biogen, Novartis, and Sanofi. LK received compensation for serving on scientific advisory boards (Alexion, Janssen, Novartis, Merck Serono, Sanofi Genzyme, Roche), speaker honoraria and travel support (Biogen, Novartis, Merck Serono, Sanofi Genzyme, Roche, TEVA), and research support (Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme). She receives research funding from the Deutsche Forschungsgemeinschaft (DFG), German Ministry for Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, and Innovative Medical research Muenster. HS has received research grants and honoraria for serving as a speaker and member of scientific advisory boards from Almirall, Bayer Healthcare, Biogen, Merck, Novartis, Roche, and Teva. MSW receives research support from the Deutsche Forschungsgemeinschaft (DFG; WE 3547/5-1), Novartis, TEVA, Biogen-Idec, Roche, Merck, and the ProFutura Programm of the Universitätsmedizin Göttingen. MSW is serving as an editor for PLoS One. He received travel funding and/or speaker honoraria from Biogen-Idec, Merck Serono, Novartis, Roche, TEVA, Bayer, and Genzyme. BR is an employee of Novartis Pharma GmbH, Nuremberg, Germany.

References

1. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014 Jul 15;83(3):278-286 [FREE Full text] [doi: 10.1212/WNL.0000000000000560] [Medline: 24871874]
2. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996 Apr 01;46(4):907-911. [doi: 10.1212/wnl.46.4.907] [Medline: 8780061]
3. Lorscheider J, Buzzard K, Jokubaitis V, Spelman T, Havrdova E, Horakova D, MSBase Study Group. Defining secondary progressive multiple sclerosis. Brain 2016 Sep;139(Pt 9):2395-2405. [doi: 10.1093/brain/aww173] [Medline: 27401521]
4. Brochet B, Ruet A. Cognitive Impairment in Multiple Sclerosis With Regards to Disease Duration and Clinical Phenotypes. Front Neurol 2019 Mar 20;10:261 [FREE Full text] [doi: 10.3389/fneur.2019.00261] [Medline: 30949122]
5. Shirani A, Okuda DT, Stüve O. Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis. Neurotherapeutics 2016 Jan 4;13(1):58-69 [FREE Full text] [doi: 10.1007/s13311-015-0409-z] [Medline: 26729332]
6. Scalfari A, Neuhaus A, Daumer M, Muraro PA, Ebers GC. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. J Neurol Neurosurg Psychiatry 2014 Jan;85(1):67-75. [doi: 10.1136/jnnp-2012-304333] [Medline: 23486991]
7. Inojosa H, Proschmann U, Akgün K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. J Neurol 2019 Jul 30. [doi: 10.1007/s00415-019-09489-5] [Medline: 31363847]
8. Ziemssen T, Kern R, Cornelissen C. Study design of PANGAEA 2.0, a non-interventional study on RRMS patients to be switched to fingolimod. BMC Neurol 2016 Aug 08;16(1):129 [FREE Full text] [doi: 10.1186/s12883-016-0648-6] [Medline: 27502119]
9. Ziemssen T, Schulze-Topphoff U. PANGAEA 2.0 EVOLUTION: state of the art multiple sclerosis patient management in daily clinical practice to identify key parameters for a more unified and early diagnosis of SPMS. 2019 Sep 11 Presented at: ECTRIMS; 2019-09-11; Stockholm.

10. Ziemssen T, Kern R, Thomas K. Multiple sclerosis: clinical profiling and data collection as prerequisite for personalized medicine approach. BMC Neurol 2016 Aug 02;16(1):124 [FREE Full text] [doi: 10.1186/s12883-016-0639-7] [Medline: 27484848]
11. Correale J, Gaitán MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain 2017 Mar 01;140(3):527-546. [doi: 10.1093/brain/aww258] [Medline: 27794524]
12. Panitch H, Miller A, Paty D, Weinshenker B, North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004 Nov 23;63(10):1788-1795. [doi: 10.1212/01.wnl.0000146958.77317.3e] [Medline: 15557491]
13. Kappos L. Placebo-controlled multicentre randomised trial of interferon β-1b in treatment of secondary progressive multiple sclerosis. The Lancet 1998 Nov;352(9139):1491-1497. [doi: 10.1016/s0140-6736(98)10039-9]
14. Kappos L, Weinshenker B, Pozzilli C, Thompson AJ, Dahlke F, Beckmann K, European (EU-SPMS) Interferon beta-1b in Secondary Progressive Multiple Sclerosis Trial Steering CommitteeIndependent Advisory Board, North American (NA-SPMS) Interferon beta-1b in Secondary Progressive Multiple Sclerosis Trial Steering CommitteeIndependent Advisory Board. Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. Neurology 2004 Nov 23;63(10):1779-1787. [doi: 10.1212/01.wnl.0000145561.08973.4f] [Medline: 15557490]
15. Kapoor R, Ho P, Campbell N, Chang I, Deykin A, Forrestal F, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. The Lancet Neurology 2018 May;17(5):405-415. [doi: 10.1016/s1474-4422(18)30069-3]
16. Ontaneda D, Fox RJ, Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. The Lancet Neurology 2015 Feb;14(2):208-223. [doi: 10.1016/s1474-4422(14)70264-9]
17. Baldassari LE, Fox RJ. Therapeutic Advances and Challenges in the Treatment of Progressive Multiple Sclerosis. Drugs 2018 Oct 25;78(15):1549-1566. [doi: 10.1007/s40265-018-0984-5] [Medline: 30255442]
18. EPAR - An overview of Mayzent and why it is authorised in the EU. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/mayzent [accessed 2020-02-05]
19. Crump LH, Benfield M, Ramey C, Arcara A, Yang S, Brown J, et al. Drug updates and approvals. The Nurse Practitioner 2019;44(12):21-32. [doi: 10.1097/01.npr.0000605508.04187.b2]
20. Pan S, Gray NS, Gao W, Mi Y, Fan Y, Wang X, et al. Discovery of BAF312 (Siponimod), a Potent and Selective S1P Receptor Modulator. ACS Med Chem Lett 2013 Mar 14;4(3):333-337 [FREE Full text] [doi: 10.1021/ml300396r] [Medline: 24900670]
21. Oo ML, Thangada S, Wu M, Liu CH, Macdonald TL, Lynch KR, et al. Immunosuppressive and Anti-angiogenic Sphingosine 1-Phosphate Receptor-1 Agonists Induce Ubiquitinylation and Proteasomal Degradation of the Receptor. J. Biol. Chem 2007 Jan 21;282(12):9082-9089. [doi: 10.1074/jbc.m610318200]
22. Gentile A, Musella A, Bullitta S, Fresegna D, De Vito F, Fantozzi R, et al. Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis. J Neuroinflammation 2016 Aug 26;13(1):207 [FREE Full text] [doi: 10.1186/s12974-016-0686-4] [Medline: 27566665]
23. Jackson SJ, Giovannoni G, Baker D. Fingolimod modulates microglial activation to augment markers of remyelination. J Neuroinflammation 2011 Jul 05;8(1):76 [FREE Full text] [doi: 10.1186/1742-2094-8-76] [Medline: 21729281]
24. Behrangi N, Fischbach F, Kipp M. Mechanism of Siponimod: Anti-Inflammatory and Neuroprotective Mode of Action. Cells 2019 Jan 07;8(1):24 [FREE Full text] [doi: 10.3390/cells8010024] [Medline: 30621015]
25. Gilenya (fingolimod) Product information EMEA/H/C/002202 -II-26-G. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/gilenya [accessed 2020-01-07]
26. Brinkmann V. FTY720 (fingolimod) in Multiple Sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol 2009 Nov;158(5):1173-1182 [FREE Full text] [doi: 10.1111/j.1476-5381.2009.00451.x] [Medline: 19814729]
27. Gergely P, Nuesslein-Hildesheim B, Guerini D, Brinkmann V, Traebert M, Bruns C, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. Br J Pharmacol 2012 Nov;167(5):1035-1047 [FREE Full text] [doi: 10.1111/j.1476-5381.2012.02061.x] [Medline: 22646698]
28. Gajofatto A. Spotlight on siponimod and its potential in the treatment of secondary progressive multiple sclerosis: the evidence to date. DDDT 2017 Nov;Volume 11:3153-3157. [doi: 10.2147/dddt.s122249]
29. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. The Lancet 2018 Mar;391(10127):1263-1273. [doi: 10.1016/s0140-6736(18)30475-6]
30. Benedict R, Cree B, Tomic D, Fox R, Giovannoni G, Bar-Or A. Impact of Siponimod on Cognition in Patients With Secondary Progressive Multiple Sclerosis: Results From Phase 3 EXPAND Study (S44.004). In: Neurology. 2018 Presented at: AAN; 2018-04-21; Los Angeles.
31. Benedict R, Fox R, Tomic D, Cree B, Vermersch P, Giovannoni G. Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis (P3.2-051). 2019 Presented at: AAN 2019; 2019-05-21; Philadelphia p. 2-051.
32. Ziemssen T, Hillert J, Butzkueven H. The importance of collecting structured clinical information on multiple sclerosis. BMC Med 2016 May 31;14(1):81 [FREE Full text] [doi: 10.1186/s12916-016-0627-1] [Medline: 27246898]

33. D'Amico E, Haase R, Ziemssen T. Review: Patient-reported outcomes in multiple sclerosis care. Mult Scler Relat Disord 2019 Aug;33:61-66. [doi: 10.1016/j.msard.2019.05.019] [Medline: 31154262]
34. Novartis. 2019. MAYZENT® (siponimod) prescribing information. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209884s000lbl.pdf [accessed 2020-01-21]
35. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983 Nov 01;33(11):1444. [doi: 10.1212/WNL.33.11.1444]
36. Smith A. Symbol Digit Modalities Test (SDMT). Manual (revised). Los Angeles, CA: Western Psychological Services; 1982.
37. Papadopoulou A, Müller-Lenke N, Naegelin Y, Kalt G, Bendfeldt K, Kuster P, et al. Contribution of cortical and white matter lesions to cognitive impairment in multiple sclerosis. Mult Scler 2013 Sep 04;19(10):1290-1296. [doi: 10.1177/1352458513475490] [Medline: 23459568]
38. Kappos L, Vermersch P, Cree B, Benedict R, Giovannoni G, Bar-Or A. A Novel Functional Composite Endpoint to Characterize Disease Progression in Patients with Secondary Progressive Multiple Sclerosis (S12.006). 2019 Presented at: AAN 2019; 2019-05-21; Philadelphia.
39. Inojosa H, Schriefer D, Ziemssen T. Clinical outcome measures in multiple sclerosis: A review. Autoimmun Rev 2020 May;19(5):102512. [doi: 10.1016/j.autrev.2020.102512] [Medline: 32173519]
40. Benedict RH, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R, Multiple Sclerosis Outcome Assessments Consortium. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 2017 Apr 16;23(5):721-733 [FREE Full text] [doi: 10.1177/1352458517690821] [Medline: 28206827]
41. Ness N, Schriefer D, Haase R, Ettle B, Cornelissen C, Ziemssen T. Differentiating societal costs of disability worsening in multiple sclerosis. J Neurol 2020 Apr 17;267(4):1035-1042. [doi: 10.1007/s00415-019-09676-4] [Medline: 31848738]
42. Ziemssen T, Piani-Meier D, Bennett B, Johnson C, Tinsley K, Trigg A, et al. A Physician-Completed Digital Tool for Evaluating Disease Progression (Multiple Sclerosis Progression Discussion Tool): Validation Study. J Med Internet Res 2020 Feb 12;22(2):e16932 [FREE Full text] [doi: 10.2196/16932] [Medline: 32049062]
43. V. Freiwillige Selbstkontrolle für die Arzneimittelindustrie e. 2018. URL: https://www.fsa-pharma.de/de/kodizes/zusammenarbeit/fachkreise [accessed 2020-01-21]
44. Bundesinstitut F, Paul-Ehrlich-Institut (. 2010. Empfehlungen des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen (AWB) vom 7. URL: https://www.pei.de/SharedDocs/Downloads/DE/regulation/klinische-pruefung/awb-empfehlung-bfarm-pei-7-7-2010.pdf?__blob=publicationFile&v=2 [accessed 2020-01-21]
45. V. Verband Forschender Arzneimittelhersteller e. 2014. URL: https://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/nisdb/nis-empfehlungen [accessed 2020-01-21]
46. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf 2008 Feb 17;17(2):200-208. [doi: 10.1002/pds.1471] [Medline: 17868186]
47. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008 Apr;61(4):344-349. [doi: 10.1016/j.jclinepi.2007.11.008] [Medline: 18313558]
48. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 2013 Apr;138(1):103-141 [FREE Full text] [doi: 10.1016/j.pharmthera.2012.12.007] [Medline: 23333322]
49. Gardin A, Ufer M, Legangneux E, Rossato G, Jin Y, Su Z, et al. Effect of Fluconazole Coadministration and CYP2C9 Genetic Polymorphism on Siponimod Pharmacokinetics in Healthy Subjects. Clin Pharmacokinet 2019 Mar 7;58(3):349-361 [FREE Full text] [doi: 10.1007/s40262-018-0700-3] [Medline: 30088221]
50. Huth F, Gardin A, Umehara K, He H. Prediction of the Impact of Cytochrome P450 2C9 Genotypes on the Drug-Drug Interaction Potential of Siponimod With Physiologically-Based Pharmacokinetic Modeling: A Comprehensive Approach for Drug Label Recommendations. Clin Pharmacol Ther 2019 Nov 11;106(5):1113-1124 [FREE Full text] [doi: 10.1002/cpt.1547] [Medline: 31199498]
51. Glozman JM, Bicheva KG, Fedorova NV. Scale of Quality of Life of Care-Givers (SQLC). J Neurol 1998 May 24;245 Suppl 1(S1):S39-S41. [doi: 10.1007/pl00007738] [Medline: 9617723]
52. Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. Mult Scler 2012 Jul 24;18(7):914-924. [doi: 10.1177/1352458512444498] [Medline: 22740603]
53. Motl RW, Cohen JA, Benedict R, Phillips G, LaRocca N, Hudson LD, Multiple Sclerosis Outcome Assessments Consortium. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 2017 Apr 16;23(5):704-710 [FREE Full text] [doi: 10.1177/1352458517690823] [Medline: 28206828]
54. Feys P, Lamers I, Francis G, Benedict R, Phillips G, LaRocca N, Multiple Sclerosis Outcome Assessments Consortium. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler 2017 Apr 16;23(5):711-720 [FREE Full text] [doi: 10.1177/1352458517690824] [Medline: 28206826]
55. Sharrack B, Hughes RA. The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. Mult Scler 1999 Aug 02;5(4):223-233. [doi: 10.1177/135245859900500406] [Medline: 10467380]

56. Penner I, Raselli C, Stöcklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler 2009 Dec 07;15(12):1509-1517. [doi: 10.1177/1352458509348519] [Medline: 19995840]
57. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [doi: 10.1016/0168-8510(90)90421-9]
58. Bharmal M, Payne K, Atkinson MJ, Desrosiers M, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009 Apr 27;7(1):36 [FREE Full text] [doi: 10.1186/1477-7525-7-36] [Medline: 19397800]
59. Busner J, Targum S. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007 Jul;4(7):28-37 [FREE Full text] [Medline: 20526405]
60. Ziemssen T, Tolley C, Bennett B, Kilgariff S, Jones E, Pike J, et al. A mixed methods approach towards understanding key disease characteristics associated with the progression from RRMS to SPMS: Physicians' and patients' views. Mult Scler Relat Disord 2020 Feb;38:101861 [FREE Full text] [doi: 10.1016/j.msard.2019.101861] [Medline: 31865132]
61. Ness N, Haase R, Kern R, Schriefer D, Ettle B, Cornelissen C, et al. The Multiple Sclerosis Health Resource Utilization Survey (MS-HRS): Development and Validation Study. J Med Internet Res 2020 Mar 17;22(3):e17921 [FREE Full text] [doi: 10.2196/17921] [Medline: 32181745]
62. Schultheiss T, Kempcke R, Kratzsch F, Eulitz M, Pette M, Reichmann H, et al. [Multiple sclerosis management system 3D. Moving from documentation towards management of patients]. Nervenarzt 2012 Apr 20;83(4):450-457. [doi: 10.1007/s00115-011-3376-6] [Medline: 22038386]
63. Ziemssen T, Kempcke R, Eulitz M, Großmann L, Suhrbier A, Thomas K, et al. Multiple sclerosis documentation system (MSDS): moving from documentation to management of MS patients. J Neural Transm (Vienna) 2013 Sep 1;120 Suppl 1(S1):S61-S66. [doi: 10.1007/s00702-013-1041-x] [Medline: 23728704]
64. Haase R, Wunderlich M, Dillenseger A, Kern R, Akgün K, Ziemssen T. Improving multiple sclerosis management and collecting safety information in the real world: the MSDS3D software approach. Expert Opin Drug Saf 2018 Apr 13;17(4):369-378. [doi: 10.1080/14740338.2018.1437144] [Medline: 29436244]
65. Kern R, Haase R, Eisele JC, Thomas K, Ziemssen T. Designing an Electronic Patient Management System for Multiple Sclerosis: Building a Next Generation Multiple Sclerosis Documentation System. Interact J Med Res 2016 Jan 08;5(1):e2 [FREE Full text] [doi: 10.2196/ijmr.4549] [Medline: 26746977]
66. Alsop J, Medin J, Cornelissen C, Vormfelde SV, Ziemssen T. Two studies in one: A propensity-score-matched comparison of fingolimod versus interferons and glatiramer acetate using real-world data from the independent German studies, PANGAEA and PEARL. PLoS One 2017;12(5):e0173353 [FREE Full text] [doi: 10.1371/journal.pone.0173353] [Medline: 28475587]
67. van Munster CEP, Uitdehaag BMJ. Outcome Measures in Clinical Trials for Multiple Sclerosis. CNS Drugs 2017 Mar 9;31(3):217-236 [FREE Full text] [doi: 10.1007/s40263-017-0412-5] [Medline: 28185158]
68. Tur C, Moccia M, Barkhof F, Chataway J, Sastre-Garriga J, Thompson AJ, et al. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. Nat Rev Neurol 2018 Feb 12;14(2):75-93. [doi: 10.1038/nrneurol.2017.171] [Medline: 29326424]
69. Whitaker J, McFarland H, Rudge P, Reingold S. Outcomes assessment in multiple sclerosis clinical trials: a critical analysis. Mult Scler 1995 Apr 02;1(1):37-47. [doi: 10.1177/135245859500100107] [Medline: 9345468]
70. Planche V, Gibelin M, Cregut D, Pereira B, Clavelou P. Cognitive impairment in a population-based study of patients with multiple sclerosis: differences between late relapsing-remitting, secondary progressive and primary progressive multiple sclerosis. Eur J Neurol 2016 Feb 22;23(2):282-289. [doi: 10.1111/ene.12715] [Medline: 25903918]
71. Dackovic J, Pekmezovic T, Mesaros S, Dujmovic I, Stojsavljevic N, Martinovic V, et al. The Rao's Brief Repeatable Battery in the study of cognition in different multiple sclerosis phenotypes: application of normative data in a Serbian population. Neurol Sci 2016 Sep 20;37(9):1475-1481. [doi: 10.1007/s10072-016-2610-1] [Medline: 27207679]
72. Huijbregts SC, Kalkers NF, de Sonneville LM, de Groot V, Reuling IE, Polman CH. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. Neurology 2004 Jul 27;63(2):335-339. [doi: 10.1212/01.wnl.0000129828.03714.90] [Medline: 15277630]
73. Benedict RH, Smerbeck A, Parikh R, Rodgers J, Cadavid D, Erlanger D. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: implications for multiple sclerosis clinical trials. Mult Scler 2012 Sep 25;18(9):1320-1325. [doi: 10.1177/1352458511435717] [Medline: 22277740]
74. Benedict RH, Cohan S, Lynch SG, Riester K, Wang P, Castro-Borrero W, et al. Improved cognitive outcomes in patients with relapsing-remitting multiple sclerosis treated with daclizumab beta: Results from the DECIDE study. Mult Scler 2018 May 09;24(6):795-804. [doi: 10.1177/1352458517707345] [Medline: 28485186]
75. Kutzelnigg A, Lucchinetti C, Stadelmann C, Brück W, Rauschka H, Bergmann M, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005 Nov;128(Pt 11):2705-2712. [doi: 10.1093/brain/awh641] [Medline: 16230320]

76. O'Sullivan C, Schubart A, Mir AK, Dev KK. The dual S1PR1/S1PR5 drug BAF312 (Siponimod) attenuates demyelination in organotypic slice cultures. J Neuroinflammation 2016 Feb 08;13(1):31 [FREE Full text] [doi: 10.1186/s12974-016-0494-x] [Medline: 26856814]
77. Cree B, Fox R, Giovannoni G, Vermersch P, Bar-Or A, Gold R. Uncoupling the Impact on Relapses and Disability Progression: Siponimod in Relapsing and Non-relapsing Patients With Secondary Progressive Multiple Sclerosis in the Phase III EXPAND Study (S8.005). 2018 Presented at: AAN 2018; 2018-04-21; Los Angeles.

Abbreviations

6M-CDP: 6-month confirmed disease progression
9Hole Peg test: nine-hole peg test
AE: adverse events
AMASIA: impAct of Mayzent [siponimod] on secondAry progressive multiple Sclerosis patients in a long-term non-Interventional study in GermAny
CBC: complete blood count
CGI: clinical global impression
CNS: central nervous system
EDSS: Expanded Disability Status Scale
EMA: European Medicines Agency
EXPAND: EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis
FSMC: Fatigue Scale for Motor and Cognitive Functions
Gd: gadolinium
MRI: magnetic resonance imaging
MS: multiple sclerosis
MS-AS: MS activity scale score
MS-HRS: Multiple Sclerosis Health Resource Utilization Survey
NIS: noninterventional study
RRMS: relapsing remitting multiple sclerosis
S1P: sphingosine-1-phosphate
S1PR: S1P receptor
SAE: serious adverse event
SDMT: symbol digit modalities test
SPMS: secondary progressive multiple sclerosis
T25-FW: timed 25-foot walk
TSQM-9: Treatment Satisfaction Questionnaire for Medication
UKNDS: United Kingdom Neurological Disability Scale

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Protocol

Visual Fixations and Motion Sensitivity: Protocol for an Exploratory Study

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Abstract

Background: Motion sensitivity after vestibular disorders is associated with symptoms of nausea, dizziness, and imbalance in busy environments. Dizziness and imbalance are reported in places such as supermarkets and shopping malls which have unstable visual backgrounds; however, the mechanism of motion sensitivity is poorly understood.

Objective: The main aim of this exploratory observational study is to investigate visual fixations and postural sway in response to increasingly complex visual environments in healthy adults and adults with motion sensitivity.

Methods: A total of 20 healthy adults and 20 adults with motion sensitivity will be recruited for this study. Visual fixations, postural sway, and body kinematics will be measured with a mobile eye tracker device, force plate, and 3D motion capture system, respectively. Participants will be exposed to experimental tasks requiring visual fixation on letters, projected on a range of backgrounds on a large screen during quiet stance. Descriptive statistics (mean and standard deviation) will be calculated for each of the variables. One-way independent-measures analyses of variance will be performed to investigate the differences between groups for all variables.

Results: Data collection was started in May 2019 and was completed by February 2020. It was approved by Health and Disability Ethics Committees, Ministry of Health, New Zealand on November 2, 2018 (Ethics ref: 18/CEN/193). We are currently processing the data and will begin data analysis in July 2020. We expect the results to be available for publication by the end of 2020. The trial was funded by the Neurology Special Interest Group, Physiotherapy New Zealand, and the Eisdell Moore Centre in November 2018.

Conclusions: This study will provide a detailed investigation of visual fixations in response to increasingly complex visual environments. Investigating characteristics of visual fixations in healthy adults and those with motion sensitivity will provide insight into this disabling condition and may inform the development of new intervention strategies which explicitly cater to the needs of this population.

Trial Registration: Australian New Zealand Clinical Trials Registry, ACTRN12619000254190; https://tinyurl.com/yxbn7nks

International Registered Report Identifier (IRRID): PRR1-10.2196/16805

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KEYWORDS

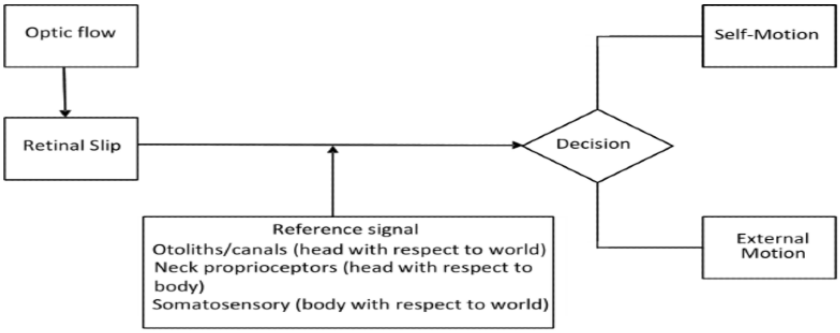
motion sensitivity; vestibular disorder; complex environments; visual fixations; postural control; posture; kinematics; inner ear; visual

Introduction

Motion sensitivity is characterized by nausea, dizziness, and imbalance in response to motion of the visual environment [1]. It can develop as a sequela of a vestibular disorder and is one of the diagnostic criteria for persistent postural perceptual dizziness [1-3]. The symptoms are due to a misinterpretation of, or overreliance on, visual cues for orientation in space [1,3-6]. Dizziness and imbalance are triggered in busy surroundings with visual motion or complex repetitive patterns. Consequently, people with motion sensitivity tend to avoid crowded or busy environments such as supermarkets or driving on motorways [7]. This frequently leads to an interruption of daily activities, sick leave from work, and in extreme cases a reluctance to leaving the house [8,9]. Motion sensitivity may affect people following an acute vestibular insult or people with chronic recurrent dizziness [10].

Information from the visual system has a role in differentiating self-motion from external motion [11]. This differentiation is dependent on perceiving whether motion on the retina is due to an object moving relative to the person or the person moving relative to the object [12,13]. This distinction between self-motion and external motion is achieved by a mechanism that compares the retinal signal and the reference signal. The reference signal comprises information from vision, vestibular afferents, proprioceptive feedback from the extraocular muscles, somatosensory kinaesthetic proprioception, and cognition [14] (Figure 1).

Figure 1. The sources of information to allow differentiation of self-motion and object motion components. The various sources are shown as giving information with respect to different reference frames.



A crucial aspect of the stabilization of posture is dependent on the visual input received from the environment. An essential component of visual input is optic flow [15,16]. Optic flow helps perception of spatiotemporal information from the environment which is then used to move around and maintain orientation in space [12,17]. Optic flow generates retinal slip, defined as motion of the visual image of the environment on the surface of the retina [18]. This information is used to adjust the amount of postural sway. The main aim of visually induced postural movements is to reduce the overall amplitude of the optic flow field by minimizing retinal slip [19-21].

Because optic flow plays a vital role in postural correction, perceiving inaccurate information can be destabilizing. Optic flow that is a part of the background motion behind a target is not normally used as a visual input for postural control as it can stimulate an optokinetic response (which evokes a combination of a slow-phase and fast-phase eye movements where the eyes momentarily follow the moving object and then rapidly reset back to the initial position) [22]. This response can induce a standing subject to move in response to the direction of the motion and can be destabilizing [22]. In normal circumstances, this optokinetic response to background motion is suppressed by visually fixating on a target [23].

Visual fixations contribute to 80% of the total visual experience [24], and help to reduce optic flow, minimize retinal slip, and suppress the optokinetic response [23]. When fixating on a stationary target, there is almost no retinal slip, and the vestibulo-ocular reflex keeps the gaze on target during head movements [21]. By contrast, maintaining fixation on a moving object requires suppression of the vestibulo-ocular reflex for the eyes and the head to move in the same direction [21,25,26].

Fixations contribute to a person's sense of spatial orientation. Fixations suppress visual field motion perception by maximizing the peripheral vision and rendering a stable image to enhance the visual signals of self-motion [27]. Sensations of small body movements then facilitate the execution of compensatory postural reactions [28].

Fixational instability may predispose a person to develop motion sensitivity [29-31]. Studies have shown that people with motion sensitivity after vestibular disorders exhibit fixational instability and have increased perceptual and postural responses to complex visual surroundings [31-34]. Several studies have investigated the relationship between fixational instability and the strength of illusionary motion [29-31]. Fixational instability can be detected by frequency of refixations and saccades [32,34]. Studies have reported that a person with fixational instability would have a high frequency of saccades and refixations while attempting fixation [32,34].

Any difficulty in differentiating self-motion from external motion will require adjustments to determine the correct orientation in space. A peripheral or central vestibular disorder disrupts the normal visual–vestibular interaction [35], which can alter the perception of motion. It can lead to illusionary motion perception, thereby degrading postural stability. Adults with motion sensitivity report worsening of symptoms and reduced postural control in visually stimulating environments which may be explained by fixation instability. However, to date, visual fixations have not been well investigated in people

with motion sensitivity. Previous studies have used video oculography or electrooculogram and optokinetic stimulation rotating around the naso-occipital center to study eye movements in adults with motion sensitivity [32-34]. This study aims to investigate the characteristics of fixations in people with motion sensitivity and how they differ from those of healthy adults by using a mobile eye tracker device in a more naturalistic yet controlled laboratory setting.

This research will investigate visual fixations, postural sway, and kinematics of adults with motion sensitivity, compared with healthy adults, in complex visual environments. Center of pressure (COP) measurement will be used to evaluate postural sway. COP parameters have been used widely to describe stability and quantify alterations in postural control [36,37]. The exploratory nature of this study will also allow the investigation of mean saccadic velocity and saccadic peak amplitude between groups. Several studies have identified anomalies in mean saccadic velocities in a range of health conditions [38,39].

This study is the first step toward recognizing the components that may be essential in a rehabilitation programme addressing the challenging clinical issue of motion sensitivity and may guide the development of rehabilitation programs for adults with motion sensitivity.

Methods

Aim

To conduct an observational study with 40 adults (20 in each group; healthy adults and adults with motion sensitivity). The study will determine whether complex visual environments are associated with fixational instability, altered COP displacement, and altered center of mass (COM) displacements of the head and body in adults with motion sensitivity compared with healthy adults.

Hypothesis

Complex visual environments in people with motion sensitivity compared with healthy adults will be associated with (1) increased number of visual refixations, (2) increased displacement of COP, and (3) differences in the body COM displacement and differences in the head COM displacement.

Trial Design, Setting, and Participants

This is a cross-sectional exploratory single-session experimental study that will be laboratory based in Auckland University of Technology. A total of 40 adults will participate in the study (20 healthy adults and 20 adults with motion sensitivity after vestibular disorder). Healthy adults aged between 18 and 60 who are independently mobile and have no history of neurological conditions will be recruited through neurorehabilitation research team networks and community advertisements. Adults with motion sensitivity will be recruited through a specialized vestibular disorders clinic. They will be included if they have had a history of vestibular disorder (confirmed by a clinician in the vestibular disorder clinic) but have no current signs of acute vestibular deficits, are aged between 18 and 60 [40,41], have a history of motion sensitivity symptoms as reported by the Visual Vertigo Analogue Scale (score >5) [42-44], and score >40 on the Dizziness Handicap Inventory [44]. People with a history of previous eye surgery, or a medical condition that may influence eye movements such as sarcoidosis, Lyme disease, diabetes mellitus, traumatic brain injury, and migraine will be excluded from the study.

Recruitment

Potential participants will be provided with a Participant Information Sheet and be requested to contact the corresponding author by email or telephone. All potential participants will be made aware that participating in this study will not influence their current health care.

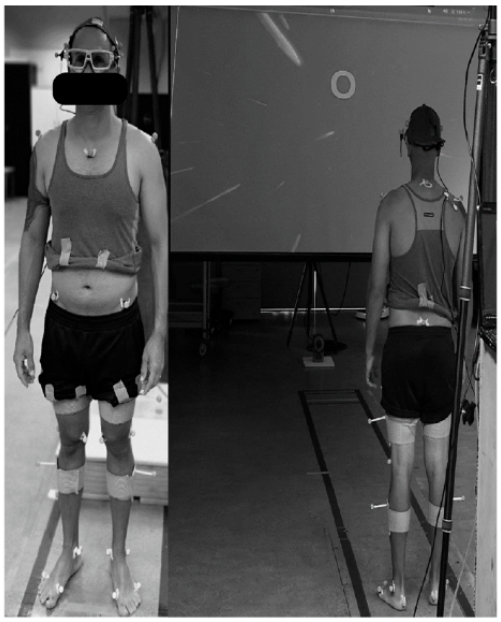
Screening

Potential participants will be screened against the study's inclusion and exclusion criteria via telephone or through a face-to-face meeting with the researcher (SC). Eligible potential participants will be asked to provide written informed consent.

Experimental Setup

The experimental setup consists of a projector screen (Brateck Lumi), a mobile eye tracker device (SensoMotoric Instruments), a force plate (Advanced Mechanical Technology Inc.), and a 3D motion capture system (Qualisys Motion Analysis Capture System; Qualisys Medical AB). Visual fixations will be recorded using a mobile eye tracker (SMI BeGaze; SensoMotoric Instruments). A 3D motion capture system and a force plate will be used to record kinematics and postural sway, respectively. The projector screen (135 in., 16:9 aspect ratio) will be mounted at 3.5-m distance from the force plate for projecting the visual environments (Figure 2).

Figure 2. The experimental setup.



Sensor Motoric Instruments Eye Tracking Glasses (SMI ETG)

The SMI Eye Tracking Glasses (SMI ETG) are a mobile eye-tracking device with a binocular sampling rate of 120 Hz (Figure 3). SMI uses infrared light of wavelength around 789-880 nm to increase the contrast between the pupil and iris which is easily detected by the camera. SMI is a video-based eye tracker based on the concept of pupil center corneal reflection. The scene camera has a resolution of 1280 × 960 pixels @ 24FPS, 960 × 720 pixels @ 30 FPS with a 60° horizontal and 46° vertical field of view. The gaze position accuracy is 0.5° for all distances and the gaze tracking range is 80° horizontal and 60° vertical.

The SMI software uses a frame-by-frame analysis of the gaze data. These data involve defining the location and type of gaze behavior for each frame of data collected. Frame numbers are used to determine the duration of the eye movement. SMI uses an in-built detector for identifying saccades, fixations, and blinks. According to the detector, a blink is identified by points where eye data are not present, a saccade represents a quick change in gaze location, and a fixation is bordered by 2 saccades.

Data collected by the eye-tracking glasses identify the primary event as fixation and therefore a dispersion-based algorithm is used. The algorithm identifies fixations as groups of successive points within a dispersion, or maximum separation. A blink is determined based on the whole trial data where the pupil diameter is either zero, or the horizontal and vertical gaze positions are zero, or they lie outside a calculated valid pupil range. Once fixations and blinks are identified, a saccadic event is created between the detected blinks and fixations.

Figure 3. SMI Eye Tracking Glasses with 3D reflective markers.

Qualisys System

Qualisys is a motion capture system used to track movement. Small retro-reflective markers reflecting infrared light are attached to the participant's skin. Frame-by-frame analysis is used to track each marker from one frame to the next. Each marker data and their 3D position trajectory can be used to calculate joint and movement trajectories. The force plates and SMI eye tracker are integrated and time synced in the Qualisys system. The SMI program is installed on the Qualisys system. The data from the SMI system are synchronized to Qualisys via a start command, so as to capture its data together with all the other data in the Qualisys system. The force plates are connected to the Qualisys computer via an analog board to capture analog signals from the force plate with the motion capture data. The data from the force plates are synchronized with the motion capture data via a synchronization signal between the Qualisys camera system and the analog board. The sync signal from the camera system is connected to an external trigger input on the analog board to start the capture of analog data using hardware synchronization.

Kinematics will be measured using an infrared motion analysis capture system, consisting of 9 Oqus 3D Motion analysis capture units. A set of 27 reflective markers will be placed on the participant. Markers will be attached using a double-sided tape

directly onto the skin. Pelvis markers will be placed in accordance with the modified Helen Hayes model as a set of 3: 1 marker on each anterior superior iliac spine and 1 on sacrum (midpoint). For the thigh segment, markers will be placed on midthigh, medial femur epicondyle, and femur lateral epicondyle for each extremity. The shank segment includes markers on midshank, medial malleolus, and lateral malleolus. The foot segment will be created using a set of markers on the head of the fifth metatarsus, head of the first metatarsus, and posterior surface of the calcaneus. Further, markers will be placed on the right and left acromion process, sternoclavicular notch, and C7 vertebra to create the thorax segment. To create the head segment, 1 marker will be placed on each side of the head.

3D co-ordinates of each reflective marker will be tracked using Qualisys Track Manager. Visual 3D software will be used to process the data files. After placement of markers, a static image of the participant standing in an anatomical position will be taken.

AMTI Force Plates

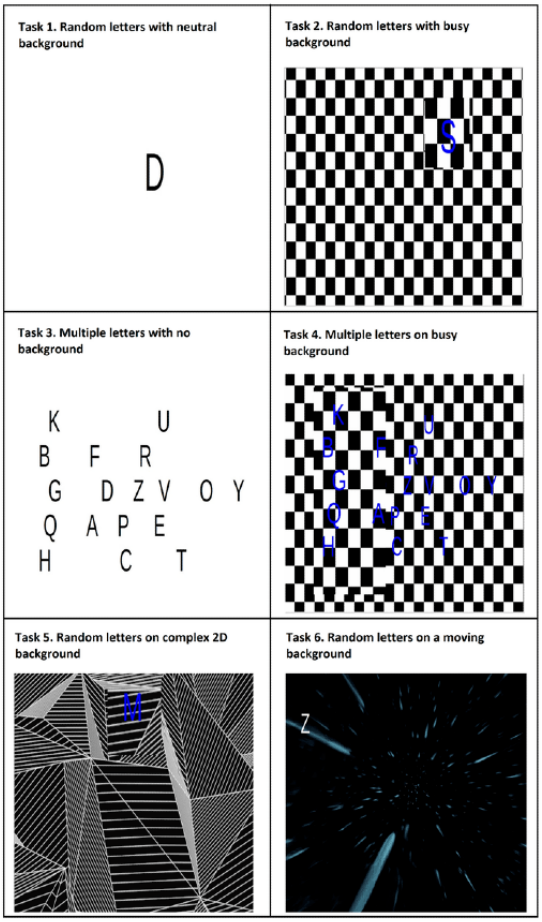
Postural control as the COP movement will be measured with an AMTI force platform (Advanced Mechanical Technology Inc.). The force platform measures the 3 force components, F_x, F_y, and F_z (where x, y, and z are the medial–lateral, anterior–posterior, and vertical directions, respectively), at the sampling frequency of 1200 Hz. The AMTI force plate is a static-force measurement system and is a computer-based system which synchronizes with a computer using a serial link. The COP movement track data (in millimeter) will be collected for each participant and will be converted into mediolateral and anterior–posterior components for analysis.

Participants will stand on the force plate with arms relaxed at their sides. Participants will be asked to stand with their feet shoulder width apart. They will be instructed to maintain their gaze on the letter while maintaining a quiet stance for the duration of a task.

Experimental Tasks

The experimental tasks have been designed to simulate eye movements in visually complex environments. Tasks will increase in the level of complexity, starting from easy visual tasks progressing to more visually complex tasks. Letters will be projected in a random sequence on to a range of visually complex background images (Figure 4). The font of the letters, backgrounds, and duration of each task were finalized after piloting. There are 6 tasks, each lasting 70 seconds. The letters appear on the screen for 7 seconds each, at different positions on the screen. Python programming language has been used to select letters and their positions on screen. Participants will be instructed to focus on a letter as they appear on the screen. The tasks increase in difficulty in two ways: (1) the background behind the letter progresses from neutral to busy (ie, to a complex moving background), and (2) by the appearance of either a single letter or multiple letters on screen. In the single-letter tasks (tasks 1, 2, 5, and 6), the participants will be instructed to focus their gaze on each projected letter for the duration of the task. In the multiple letters' tasks (tasks 3 and 4), the participant will be instructed to find letter *E* and maintain visual fixation on it for the duration of the task. The tasks will be presented from the lowest to highest difficulty of background and number of letters (as described in Figure 4). The tasks will not be randomized as the more difficult tasks might provoke symptoms of dizziness which would hinder the performance of participants in the subsequent tasks.

Figure 4. The experimental tasks. *Letters have been magnified for clear visibility.



Data Collection

Data will be collected for all tasks in 1 session. The motion analysis system and force plate will be calibrated before the participant arrives in the laboratory. Upon arrival, the participant will be orientated to the laboratory setup. The Dizziness Handicap Inventory and Visual Vertigo Analogue Scale screening will be completed. After setting up the markers, experimental tasks will be explained, and the eye tracker glasses will be fitted for comfort and calibrated. The participant will then stand on the force plate wearing the calibrated eye tracker with reflective markers (Figure 5). During the experimental tasks, appropriate rest intervals will be provided after each task to minimize provocation of symptoms such as dizziness and nausea.

Figure 5. Data collection procedure.

Outcome Measures

The following outcome measures will be explored and analyzed for this study.

Visual Fixations

Fixation characteristics for each group will be computed using the SMI ETG software and will measure the total number of refixations, the maximum fixation duration, and the number of saccades. The software determines a fixation as a window with a minimum duration of 80 ms and a maximum dispersion of 100 pixels. Refixations are calculated if the eye crosses the maximum dispersion threshold of 100 pixels. The fixation duration will be calculated as the total time spent in fixating during a trial. The maximum fixation duration will be calculated

as the longest fixation within each trial. A saccade event is computed as any event that does not meet the fixation criteria between the new and the previous fixation.

Postural Sway: Center of Pressure

COP displacement times series obtained from the force platform will be down sampled to 100 Hz and subsequently will be processed using a low-pass filter at 5 Hz (fourth-order, zero-phase-lag, Butterworth) [45]. The mean velocity, root mean square, and maximum range of the COP displacement will be computed to evaluate postural sway [46].

Kinematics

Raw data from the Qualisys motion analysis will be imported into Visual 3D, where a 6 degree-of-freedom model will be constructed. Data will be interpolated and processed using a fourth-order Butterworth low-pass filter with cutoff frequency of 12 Hz. The body COM and the COM of the head segment will be calculated using a pipeline in Visual 3D. The mean velocity, root mean square, and maximum range of the COM of the head and whole-body displacement will be calculated [47].

Safety Measures

The study will be using moving background/moving images, which may induce dizziness, imbalance, or nausea in some participants. An assistant will stand close to the participant to provide assistance and prevent a fall in case of imbalance. We will monitor how a participant is feeling throughout each task, and appropriate rest intervals will be provided. The session would be stopped at any stage if required.

In the unlikely event of a physical injury, rehabilitation and compensation for injury by accident may be available from the Accident Compensation Corporation, provided the incident details satisfy the requirements of the law and the Corporation's regulations.

Statistical Analysis

Sample Size Calculation

There is a lack of experimental evidence in the population of interest to conduct a power calculation for the required sample size. It is unclear if factors such as age or gender affect visual fixations and there is minimal information on population variation. Therefore, an arbitrary sample size of 20 in each group has been selected. This has been selected in accordance with studies performed in adults with motion sensitivity [33,34]. The data from this study may help inform future studies for the required sample size.

Analysis

Descriptive statistics (mean and standard deviation) will be calculated for each of the variables. Data normality will be examined using the Kolmogorov–Smirnov statistic. One-way independent-measures analyses of variance will be performed to investigate the differences between groups for all variables. Post-hoc analysis with Šidák adjustment will be used for multiple comparisons [48]. Finally, a receiver operating characteristic curve analysis will be applied to determine threshold values in gaze, COP, and COM parameters, allowing identification of the impairment induced by motion sensitivity. The optimal cutoff point will be determined using the Youden Index. Areas under the curve, specificity, and sensitivity will also be calculated. Values of areas under the curve will be categorized as follows: excellent (≥0.90), good (0.80-0.90), fair (0.70-0.79), and poor (<0.70).

Confidentiality

During the screening, the researcher will make note of whether the potential participant meets the study criteria. For those who do not meet the criteria, only the reason for exclusion from the project will be recorded in a database and will not be identifiable.

Ethics Approval and Consent to Participate

Ethical approval for this study has been obtained from the New Zealand Health and Disability Ethics Committee (HDEC) and Auckland University of Technology Ethics Committee (AUTEC). Eligible potential participants will be asked to provide written informed consent. Ethics committee approval for any protocol modifications will be sought from HDEC and AUTEC. Any changes will lead to an amendment in the Australian New Zealand Clinical Trials Registry (HDEC reference number: 18/CEN/193; AUTEC reference number: 19/38).

Dissemination of Study Data

A summary of the results from the study will be offered to all participants as per the consent form. Results from the study will be published in a peer-reviewed journal and presented at national and international conferences.

Availability of Data and Materials

All participants will be given a numerical code upon acceptance into the project. All health information will be stored in physical and electronic records that are identified by the participant code only. Only the named investigators will have access to the forms that contain information about the participant's name and their code. These forms will be stored in a secured cabinet in co-ordinating investigator's office, separate from any records containing health information.

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

Results

Data collection was started in May 2019 and was completed by February 2020. It was approved by the Institutional Review Board on November 2, 2018 (Ethics ref: 18/CEN/193). We are currently processing the data and will begin data analysis in July 2020. We expect the results to be available for publication by the end of 2020. The trial was funded by the Neurology Special Interest Group, Physiotherapy New Zealand, and the Eisdell Moore Centre in November 2018.

Discussion

This is an exploratory study with the primary aim to identify whether fixational instability is associated with motion

sensitivity and whether it leads to increased postural sway and altered kinematics in adults with motion sensitivity.

This study will provide a detailed investigation of visual fixations, postural sway, and kinematics in complex visual environments. The use of a mobile eye tracker device will investigate naturalistic eye behavior when exposed to experimental stimuli. The task hierarchy will help in understanding how characteristics of visual fixations change when a person views a complex visual environment as opposed to neutral environments. The experimental tasks might provoke symptoms in some participants; however, we expect that all participants will be able to complete the protocol with appropriate rest intervals between tasks. Our sample size of 20 participants in each group is a foundational step in exploring whether visual fixations contribute to motion sensitivity after vestibular disorder. We anticipate the outcomes will be able to detect a difference between healthy adults and those with motion sensitivity. Results from this study will inform future trials and will be used to inform development of diagnostic and rehabilitation programs.

We hope that this study will increase our understanding of the complex interactions of vision and balance in people with motion sensitivity. If we determine that gaze and postural control characteristics are altered, we will develop an intervention that is designed to re-align the gaze and postural control characteristics closer to those of the control population. This intervention would then be tested in a series of clinical trials to determine effectiveness.

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Authors' Contributions

SC, DT, and NS conceptualized and designed the project and obtained the funding. AK developed the experimental tasks and contributed to protocol. SC drafted the manuscript. DT and NS are providing PhD supervision for SC. All authors critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Bronstein A, Golding J, Gresty M. ‘Visual vertigo’ and motion sickness. In: Vestibular Migraine and Related Syndromes. Berlin: Springer; 2014:91-104.
2. Popkirov S, Staab JP, Stone J. Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. Pract Neurol 2018 Feb;18(1):5-13. [doi: 10.1136/practneurol-2017-001809] [Medline: 29208729]
3. Chin S. Visual vertigo: Vertigo of oculomotor origin. Med Hypotheses 2018 Jul;116:84-95 [FREE Full text] [doi: 10.1016/j.mehy.2018.04.025] [Medline: 29857916]
4. Zur O, Schoen G, Dickstein R, Feldman J, Berner Y, Dannenbaum E, et al. Anxiety among individuals with visual vertigo and vestibulopathy. Disabil Rehabil 2015;37(23):2197-2202. [doi: 10.3109/09638288.2014.1002577] [Medline: 25597835]
5. Bronstein AM. Vision and vertigo: some visual aspects of vestibular disorders. J Neurol 2004 Apr;251(4):381-387. [doi: 10.1007/s00415-004-0410-7] [Medline: 15083281]
6. Guerraz M, Yardley L, Bertholon P, Pollak L, Rudge P, Gresty MA, et al. Visual vertigo: symptom assessment, spatial orientation and postural control. Brain 2001 Aug;124(Pt 8):1646-1656. [doi: 10.1093/brain/124.8.1646] [Medline: 11459755]
7. Bronstein AM. Visual vertigo syndrome: clinical and posturography findings. J Neurol Neurosurg Psychiatry 1995 Nov;59(5):472-476 [FREE Full text] [doi: 10.1136/jnnp.59.5.472] [Medline: 8530928]
8. Neuhauser HK, Radtke A, von Brevern M, Lezius F, Feldmann M, Lempert T. Burden of dizziness and vertigo in the community. Arch Intern Med 2008 Oct 27;168(19):2118-2124. [doi: 10.1001/archinte.168.19.2118] [Medline: 18955641]
9. Benecke H, Agus S, Kuessner D, Goodall G, Strupp M. The Burden and Impact of Vertigo: Findings from the REVERT Patient Registry. Front Neurol 2013;4:136 [FREE Full text] [doi: 10.3389/fneur.2013.00136] [Medline: 24106487]
10. Roberts E, Bronstein A, Seemungal B. Visualvestibular interaction: basic science to clinical relevance. Adv Clin Neurosci Rehab 2013;13(5):8-12. [doi: 10.1007/978-3-642-69950-4_6]
11. Redfern MS, Yardley L, Bronstein AM. Visual influences on balance. J Anxiety Disord 2001;15(1-2):81-94. [doi: 10.1016/s0887-6185(00)00043-8] [Medline: 11388359]
12. Angelaki DE, Hess BJM. Self-motion-induced eye movements: effects on visual acuity and navigation. Nat Rev Neurosci 2005 Dec;6(12):966-976. [doi: 10.1038/nrn1804] [Medline: 16340956]

13. Fajen BR, Matthis JS. Visual and non-visual contributions to the perception of object motion during self-motion. PLoS One 2013;8(2):e55446 [FREE Full text] [doi: 10.1371/journal.pone.0055446] [Medline: 23408983]
14. Wertheim AH. Motion perception during selfmotion: The direct versus inferential controversy revisited. Behav Brain Sci 2010 Feb 04;17(2):293-311. [doi: 10.1017/S0140525X00034646]
15. Lee DN. The optic flow field: the foundation of vision. Philos Trans R Soc Lond B Biol Sci 1980 Jul 08;290(1038):169-179. [doi: 10.1098/rstb.1980.0089] [Medline: 6106236]
16. Koenderink JJ. Optic flow. Vision Res 1986;26(1):161-179. [doi: 10.1016/0042-6989(86)90078-7] [Medline: 3716209]
17. Warren WH, Kay BA, Zosh WD, Duchon AP, Sahuc S. Optic flow is used to control human walking. Nat Neurosci 2001 Feb;4(2):213-216. [doi: 10.1038/84054] [Medline: 11175884]
18. Guerraz M, Bronstein AM. Ocular versus extraocular control of posture and equilibrium. Neurophysiol Clin 2008 Dec;38(6):391-398. [doi: 10.1016/j.neucli.2008.09.007] [Medline: 19026959]
19. Masson G, Mestre DR, Pailhous J. Effects of the spatio-temporal structure of optical flow on postural readjustments in man. Exp Brain Res 1995;103(1):137-150. [doi: 10.1007/BF00241971] [Medline: 7615029]
20. Barela AMF, Barela JA, Rinaldi NM, de Toledo DR. Influence of imposed optic flow characteristics and intention on postural responses. Motor Control 2009 Apr;13(2):119-129. [doi: 10.1123/mcj.13.2.119] [Medline: 19454775]
21. Strupp M, Glasauer S, Jahn K, Schneider E, Krafczyk S, Brandt T. Eye movements and balance. Ann N Y Acad Sci 2003 Oct;1004:352-358. [doi: 10.1196/annals.1303.033] [Medline: 14662475]
22. Wallman J. Subcortical optokinetic mechanisms. Rev Oculomot Res 1993;5:321-342. [Medline: 8420557]
23. Pola J, Wyatt HJ, Lustgarten M. Visual fixation of a target and suppression of optokinetic nystagmus: effects of varying target feedback. Vision Res 1995 Apr;35(8):1079-1087 [FREE Full text] [doi: 10.1016/0042-6989(94)00215-8] [Medline: 7762164]
24. Martinez-Conde S. Fixational eye movements in normal and pathological vision. Prog Brain Res 2006;154:151-176. [doi: 10.1016/s0079-6123(06)54008-7] [Medline: 17010709]
25. Glasauer S, Schneider E, Jahn K, Strupp M, Brandt T. How the eyes move the body. Neurology 2005 Oct 25;65(8):1291-1293. [doi: 10.1212/01.wnl.0000175132.01370.fc] [Medline: 16051645]
26. Laurens J, Awai L, Bockisch CJ, Hegemann S, van Hedel HJA, Dietz V, et al. Visual contribution to postural stability: Interaction between target fixation or tracking and static or dynamic large-field stimulus. Gait Posture 2010 Jan;31(1):37-41. [doi: 10.1016/j.gaitpost.2009.08.241] [Medline: 19775892]
27. Martinez-Conde S, Macknik SL, Hubel DH. The role of fixational eye movements in visual perception. Nat Rev Neurosci 2004 Mar;5(3):229-240. [doi: 10.1038/nrn1348] [Medline: 14976522]
28. Thomas NM, Bampouras TM, Donovan T, Dewhurst S. Eye Movements Affect Postural Control in Young and Older Females. Front Aging Neurosci 2016;8:216 [FREE Full text] [doi: 10.3389/fnagi.2016.00216] [Medline: 27695412]
29. Beer AL, Heckel AH, Greenlee MW. A motion illusion reveals mechanisms of perceptual stabilization. PLoS One 2008 Jul 23;3(7):e2741 [FREE Full text] [doi: 10.1371/journal.pone.0002741] [Medline: 18648651]
30. Poletti M, Listorti C, Rucci M. Stability of the visual world during eye drift. J Neurosci 2010 Aug 18;30(33):11143-11150 [FREE Full text] [doi: 10.1523/JNEUROSCI.1925-10.2010] [Medline: 20720121]
31. Otero-Millan J, Macknik SL, Martinez-Conde S. Microsaccades and blinks trigger illusory rotation in the "Rotating Snakes" illusion. J Neurosci 2012 Apr 25;32(17):6043-6051 [FREE Full text] [doi: 10.1523/JNEUROSCI.5823-11.2012] [Medline: 22539864]
32. Lencer RM, Clarke AH. Influence of optokinetic and vestibular stimuli on the performance of smooth pursuit eye movements: implications for a clinical test. Acta Otolaryngol 1998 Mar;118(2):161-169. [doi: 10.1080/00016489850154856] [Medline: 9583782]
33. Van Ombergen A, Lubeck AJ, Van Rompaey V, Maes LK, Stins JF, Van de Heyning PH, et al. The Effect of Optokinetic Stimulation on Perceptual and Postural Symptoms in Visual Vestibular Mismatch Patients. PLoS One 2016;11(4):e0154528 [FREE Full text] [doi: 10.1371/journal.pone.0154528] [Medline: 27128970]
34. Winkler PA, Ciuffreda KJ. Ocular fixation, vestibular dysfunction, and visual motion hypersensitivity. Optometry 2009 Sep;80(9):502-512. [doi: 10.1016/j.optm.2009.01.014] [Medline: 19716078]
35. Redfern MS, Furman JM. Postural sway of patients with vestibular disorders during optic flow. J Vestib Res 1994;4(3):221-230. [Medline: 7921340]
36. Cotton S, Murray A, Fraisse P. Estimation of the Center of Mass: From Humanoid Robots to Human Beings. IEEE/ASME Trans. Mechatron 2009 Dec;14(6):707-712. [doi: 10.1109/tmech.2009.2032687]
37. Palmieri R, Ingersoll C, Stone M, Krause B. Center-of-pressure parameters used in the assessment of postural control. Journal of Sport Rehabilitation 2002;11(1):51-66. [doi: 10.1123/jsr.11.1.51]
38. Di Stasi LL, Renner R, Catena A, Cañas JJ, Velichkovsky BM, Pannasch S. Towards a driver fatigue test based on the saccadic main sequence: A partial validation by subjective report data. Transportation Research Part C: Emerging Technologies 2012 Apr;21(1):122-133. [doi: 10.1016/j.trc.2011.07.002]
39. Di Stasi LL, Catena A, Cañas JJ, Macknik SL, Martinez-Conde S. Saccadic velocity as an arousal index in naturalistic tasks. Neurosci Biobehav Rev 2013 Jun;37(5):968-975. [doi: 10.1016/j.neubiorev.2013.03.011] [Medline: 23541685]

40. Agarwal K, Bronstein AM, Faldon ME, Mandalà M, Murray K, Silove Y. Visual dependence and BPPV. J Neurol 2012 Jun;259(6):1117-1124. [doi: 10.1007/s00415-011-6311-7] [Medline: 22113702]
41. Bisdorff A, Bosser G, Gueguen R, Perrin P. The epidemiology of vertigo, dizziness, and unsteadiness and its links to co-morbidities. Front Neurol 2013;4:29 [FREE Full text] [doi: 10.3389/fneur.2013.00029] [Medline: 23526567]
42. Dannenbaum E, Chilingaryan G, Fung J. Visual vertigo analogue scale: an assessment questionnaire for visual vertigo. J Vestib Res 2011;21(3):153-159. [doi: 10.3233/VES-2011-0412] [Medline: 21558640]
43. Sharon JD, Hullar TE. Motion sensitivity and caloric responsiveness in vestibular migraine and Meniere's disease. Laryngoscope 2014 Apr;124(4):969-973 [FREE Full text] [doi: 10.1002/lary.24285] [Medline: 23818082]
44. Grigol TADAES, Silva AM, Ferreira MM, Manso A, Ganança MM, Caovilla HH. Dizziness Handicap Inventory and Visual Vertigo Analog Scale in Vestibular Dysfunction. Int Arch Otorhinolaryngol 2016 Jul;20(3):241-243 [FREE Full text] [doi: 10.1055/s-0035-1567808] [Medline: 27413406]
45. Lin D, Seol H, Nussbaum MA, Madigan ML. Reliability of COP-based postural sway measures and age-related differences. Gait Posture 2008 Aug;28(2):337-342. [doi: 10.1016/j.gaitpost.2008.01.005] [Medline: 18316191]
46. Prieto TE, Myklebust JB, Hoffmann RG, Lovett EG, Myklebust BM. Measures of postural steadiness: differences between healthy young and elderly adults. IEEE Trans Biomed Eng 1996 Sep;43(9):956-966. [doi: 10.1109/10.532130] [Medline: 9214811]
47. Lee S, Powers CM. Individuals with diminished hip abductor muscle strength exhibit altered ankle biomechanics and neuromuscular activation during unipedal balance tasks. Gait Posture 2014 Mar;39(3):933-938. [doi: 10.1016/j.gaitpost.2013.12.004] [Medline: 24373699]
48. Kahya M, Wood TA, Sosnoff JJ, Devos H. Increased Postural Demand Is Associated With Greater Cognitive Workload in Healthy Young Adults: A Pupillometry Study. Front Hum Neurosci 2018;12:288 [FREE Full text] [doi: 10.3389/fnhum.2018.00288] [Medline: 30072883]

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Protocol

Alterations of Gut Microbiota and the Brain-Immune-Intestine Axis in Patients With Relapsing-Remitting Multiple Sclerosis After Treatment With Oral Cladribine: Protocol for a Prospective Observational Study

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Abstract

Background: Immunological factors are the key to the pathogenesis of multiple sclerosis (MS). Conjointly, environmental factors are known to affect MS disease onset and progression. Several studies have found that the intestinal microbiota in MS patients differs from that of control subjects. One study found a trend toward lower species richness in patients with active disease versus in patients in remission. The microbiota plays an important role in shaping the immune system. Recent studies suggest the presence of an association between the gut microbiota and inflammatory pathways in the central nervous system. However, the function of this brain-immune-intestine axis and its possible value for predicting treatment effect in MS patients is currently unknown.

Objective: Our goal is to examine if the changes in gut and oral microbiota and simultaneous changes in the immune response are a predictor for the treatment response in subjects with active relapsing-remitting MS (RRMS) who are being treated with oral cladribine.

Methods: This is a prospective, observational, multicenter study. Eligible subjects are patients with RRMS, between the ages of 18 and 55 years, who will start treatment with oral cladribine. Patients who used probiotics 1 month prior to the start of oral cladribine will be excluded. At baseline (ie, before start) and after 3, 12, and 24 months, the Expanded Disability Status Scale (EDSS) score will be assessed and fecal, oral, and blood samples will be collected. Also, subjects will be asked to register their food intake for 7 consecutive days following the visits. After 24 months, a magnetic resonance imaging (MRI) assessment of the brain will be performed. Responders are defined as subjects without relapses, without progression on the EDSS, and without radiological progression on MRI.

Results: Inclusion started in January 2019. A total of 30 patients are included at the moment. The aim is to include 80 patients from 10 participating centers during a period of approximately 24 months. Final results are expected in 2024.

Conclusions: The results of the BIA Study will contribute to precision medicine in patients with RRMS and will contribute to a better understanding of the brain-immune-intestine axis.

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KEYWORDS

multiple sclerosis; cladribine; brain-immune-intestine axis; brain-gut axis; gut-brain axis; microbiota

Introduction

Immunological and environmental factors are known to be important in the pathogenesis of multiple sclerosis (MS) [1-3]. Recent studies have found that the gut microbiota in MS patients is different from healthy controls [4-7]. One study found a trend toward a decreased species richness in patients with active disease compared to healthy controls and patients who are in remission [6]. The microbiota plays an important role in shaping the immune system, and recent studies suggest an association between the gut and the central nervous system inflammatory demyelination [2-4,7-11].

The connection between microbiota, treatment, and changes in immunity in MS has not yet been examined well. Several recent studies showed that MS patients treated with interferon, glatiramer acetate, or dimethyl fumarate had an altered microbiota in comparison to the patients who did not use immunomodulatory treatment (IMT) [4,8,12].

For cladribine, it is known that after 2 years approximately 50% of the patients have reached the goal of no evidence of disease activity-3 (NEDA-3); that is, patients do not have relapses, show no disability progression, and do not have active disease as seen by magnetic resonance imaging (MRI), as measured by the number and volume of the T2 lesions and the presence of gadolinium-enhancing lesions on T1 images [13]. Cladribine is also used for the treatment of celiac disease, a condition in which there is inflammation of the small intestine due to exposure to gluten. It has been shown that cladribine has a positive effect on the gut immunological system [14].

This study aims to investigate whether the gut and oral microbiota, or changes in gut and oral microbiota after therapy, are a predictor for treatment response in subjects with active relapsing-remitting MS (RRMS) and whether these changes result in downgrading the immune response. To our knowledge, this is the first study to investigate changes in microbiota and immune response in patients with RRMS in a longitudinal follow-up setting.

Methods

Study Objectives and Hypotheses

The main aim of this study is to determine if the gut and oral microbiota at baseline, or the change in gut and oral microbiota in the first 3 months after start of cladribine, is a predictor for treatment response in subjects with active RRMS. The time point of 3 months after the start of treatment was chosen in order to be able to predict early in the treatment regimen whether a treatment response can be expected. Only one previous study investigated changes in microbiota after IMT and found a trend toward changes in microbiota after 2 and 12 weeks [15]. However, possibly due to a small sample size, after correction for multiple comparisons, none of their results seem to be significant. Nevertheless, we expect that 12 weeks (ie, 3 months) is a good moment to measure changes, because changes in different immune cell subsets after administration of oral cladribine have been shown to already appear after 5 weeks and stabilize after 13 weeks [16]. The hypothesis that there is an interaction between the immune system and gut microbiota suggests that we can also expect changes in microbiota at that moment.

The secondary objectives are to answer the following questions:

1. What is the difference between the gut and oral microbiota in patients who experience disease activity (ie, relapse, radiological activity, or disability progression) in comparison to patients without disease activity at baseline and at 3, 12, or 24 months?
2. What is the difference between the immune profile in patients who experience disease activity in comparison to patients without disease activity at baseline and at 3, 12, or 24 months?
3. Will cladribine treatment result in a more balanced microbial profile and a less inflammatory immune profile at 3, 12, or 24 months?

Our hypothesis is that RRMS patients treated with oral cladribine who have NEDA-3 after a follow-up period of 2 years will have a more balanced microbial profile together with a reduced proinflammatory profile of circulating immune cells when compared to the patients who do not have NEDA-3 after 2 years of follow-up. We expect that this study may contribute to a better understanding of the association between the gut, the immune system, and the central nervous system in patients with RRMS.

Design

The BIA (brain-immune-intestine axis) Study is a prospective, observational, multicenter study. Subjects with active RRMS who start with oral cladribine treatment, as per standard of care, will be asked to participate in this study. Participation includes four to five visits over 24 months.

Population

Patients will be recruited from the outpatient clinics of the participating neurological departments. Enrollment will take place at 10 participating centers in the Netherlands during a period of approximately 24 months. Eligible subjects are patients with clinically definite RRMS, between the ages of 18 and 55 years, with a planned start of cladribine treatment. We excluded patients who used probiotics within 1 month prior to the planned start of cladribine. We have chosen not to exclude patients with other potentially confounding factors, such as recent treatment with antibiotics or corticosteroids and a medical history of bowel disease, to make sure our population reflects daily practice. However, these factors will be collected throughout the study to be able to take them into account during analysis.

Sample Size Calculation

This is an exploratory study. No previous studies assessing the primary outcome have been performed. Other studies examining the gut microbiota in MS patients usually included 30-60 patients [4,6-8,11]. With 30-60 patients, these studies were able to clearly show differences in the gut microbiota between MS patients and healthy controls. We want to assess whether there is a difference in the gut microbiota in responders versus nonresponders in patients treated with oral cladribine. Previous studies with oral cladribine in MS patients have shown that approximately half of the patients will reach NEDA-3.

In order to obtain sufficient statistical power for a reliable prediction, we follow the rule of thumb of having at least 10 patients per event [17].

Taking into account that about 50% of the participants will have the event (ie, disease activity, which can include relapses, disability progression, or radiological progression) and that four facets of the gut microbiota profile will be used to predict the event, we need 80 patients (ie, $4 \times 10 \times 2 = 80$). These four facets will be derived from the different approaches described in the Statistical Analysis section of this protocol.

Ethics Committee Approval

This study was approved by the medical ethics committee of Brabant, based in Tilburg, the Netherlands. Written informed consent will be obtained from all participants.

Procedures

This study will include four to five visits—a screening and baseline visit and visits after 3, 12, and 24 months—of which only the baseline visit is an additional visit. Procedures in the screening visit can be partly performed during the baseline visit or by telephone contact. All other visits will be combined with routine hospital visits. During these visits, patients will undergo neurological examination and several study-specific invasive and noninvasive measurements. Blood samples and an oral swab will be taken at baseline and after 3, 12, and 24 months, and one additional MRI (ie, T1-weighted, T2-weighted, fluid-attenuated inversion recovery [FLAIR], and T1-weighted imaging with gadolinium) will be performed after 2 years. A stool sample will be collected at baseline and at months 3, 12, and 24, and subjects will be asked to rate their feces on the Bristol Stool Scale. Subjects will also be asked to register their food and drink intake for 7 consecutive days following the baseline visit and the visits at months 3, 12, and 24.

Table 1 provides an overview of all procedures per visit. A distinction is made between routine assessments and study-specific assessments.

The treating physician will be responsible for all procedures, which can be partially delegated to a research nurse. MRIs will be assessed by a central reader. A central laboratory will analyze gut and oral microbiota from stool samples and oral swabs and an immunological profile from blood samples.

Table 1. Schedule of visits and assessments.

Assessment	Screening visit: Day –28 to 0[a]	Baseline visit: Day –7 to 0[a]	Visit at 3 months	Visit at 12 months	Visit at 24 months	Unscheduled visit (<10 days of relapse)
Informed consent	X[b]					
Inclusion and exclusion criteria check	X	X				
Demography	Y[c]					
Medical history	Y					
Height	Y					
Weight	Y			Y		
Vital signs	Y	X	Y	Y	Y	
Bristol Stool Scale		X	X	X	X	
Disease assessment: Expanded Disability Status Scale (EDSS)	X		X	X	X	X
Magnetic resonance imaging (MRI): brain	Y			Y	X	
Oral swab		X	X	X	X	
Stool sample collection for microbiota assessment		X	X	X	X	
Blood sampling for immunological assessment		X	X	X	X	
Concomitant medication	Y		Y	Y	Y	Y
Adverse events		Y	Y	Y	Y	Y
Food registration by patient		X	X	X	X	

[a]Screening and baseline visit activities can be performed on the same day.

[b]X: study-specific assessment.

[c]Y: routine assessment.

Withdrawal of Subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Subjects who discontinue cladribine, prior to completing the week 2 intake in the second year, and switch to another MS medication will be asked to continue participation in the BIA Study. The new MS medication will be documented as concomitant medication.

Materials and Measures

Expanded Disability Status Score

During the screening visit and the visits at months 3, 12, and 24, the Expanded Disability Status Scale (EDSS) score will be recorded by performing a neurological examination. In case the subject experiences a relapse between screening and baseline, the EDSS will have to be repeated at the Day 0 visit to assess a new baseline value.

Microbiota Assessment

Oral swabs and stool samples will be collected using eNAT tubes (Copan Diagnostics, Inc) at baseline and at months 3, 12, and 24 for microbiota assessment. These tubes contain a guanidine-thiocyanate-based medium that stabilizes RNA and DNA and can be stored at room temperature for 4 weeks and at –20°C after that [18]. This allows patients to collect their stool samples at home and bring them to their hospital visits. Oral swabs will be collected during their hospital visits. After the visits, both tubes will be stored at –20°C until analysis. Composition of the gut microbiota will be determined using the IS-pro (interspace profiling) technique, a clinically validated molecular assay for analysis of complex microbiota [19]. The IS-pro technique (inBiome) identifies bacteria based on specific-length polymorphisms in the 16S-23S rDNA interspace (IS) region, combined with phylum-specific sequence polymorphisms in the 16S rDNA. Resulting data consist of peak profiles, with different colors relating to the different phylum groups (ie, Bacteroidetes; Proteobacteria; and Firmicutes, Actinobacteria, Fusobacteria, and Verrucomicrobia) and length signatures corresponding to the specific species.

Blood Samples

Blood samples will be drawn at baseline and at months 3, 12, and 24 for immunological assessment. Blood will be collected in cell preparation tubes, which allow for direct isolation of the peripheral blood mononuclear cells (PBMCs). Cells will be stored at –80°C for a maximum of 3 months and then in liquid nitrogen. Subsequently, the cells will be used for single-cell mass cytometry analysis using cytometry by time-of-flight (CyTOF).

Bristol Stool Scale

Subjects will be asked to rate their feces on the Bristol Stool Scale at baseline and at months 3, 12, and 24. This information will be used to correct for stool consistency. Previous research investigating features that accounted for gut microbiome variation showed that the Bristol Stool Scale score is the most important feature covarying with fecal microbiome composition [20].

Food Intake Registration

Subjects will be requested to record their food intake for 7 consecutive days following the baseline visit and visits at 3, 12, and 24 months. This information will be used to correct for diet as a potential confounder (eg, vegetarian diet). Also, we will use this information to check for changes in diet throughout the study period, which could possibly explain some changes in the microbiota.

MRI

Gadolinium-enhanced MRI of the brain will be performed at the screening visit, after 12 months (ie, standard care) and after 24 months (ie, study-specific assessment). This MRI will include FLAIR, T2-weighted, and T1-weighted scanning before and after intravenous gadolinium has been given. The MRI parameters will be as follows: T1-lesion load, T2-lesion load, number of enhancing lesions, and number of new and enlarging lesions. If a routine (ie, standard care) MRI has been made within 3 months prior to the start of cladribine, this MRI will not have to be repeated.

Other Measures

At the screening visit, demographic data; medical history, including MS disease activity and gastrointestinal diseases; prior use of IMTs, antibiotics, and glucocorticoids; height and weight; and smoking status will be recorded. At month 12, weight will again be recorded. Vital signs, including blood pressure and pulse, will be measured at screening and baseline visits and at months 3, 12, and 24 visits. Concomitant medication and adverse events, both serious and nonserious, will be registered throughout the study. All these measures can be used to find out whether they are important confounders for microbiota composition.

Statistical Analysis

Primary Study Parameters

The primary study parameter is difference in gut and oral microbiota at baseline or during the first 3 months after the start of oral cladribine between responders and nonresponders. Response to cladribine treatment will be determined using various data:

1. EDSS: score ranging from 0.0 (normal neurological examination) to 10.0 (death due to MS).
2. MRI (brain): radiological changes, including T1-lesion load, T2-lesion load, number of enhancing lesions, and number of new and enlarging lesions, as assessed by a central reader.
3. Documented relapses.

We will evaluate whether responders and nonresponders have a distinct gut and oral microbiota and whether they can be classified based on intestinal or oral microbiota composition prior to therapy and after an initial period of 3 months after the first treatment.

Microbiota composition will be evaluated in different ways. As microbiota data contain many variables, a first approach is to reduce the number of variables. The most commonly used approaches, that we will also use here, are to calculate the

diversity of the microbiota with the Shannon diversity index and to analyze the microbiota on the phylum level, a high-level taxonomic classification. Differences between responders and nonresponders in Shannon diversity indices and phylum abundance will be calculated by classical statistical approaches, the Mann-Whitney U test, or the Student *t* test where appropriate. Bonferroni corrections will be applied where appropriate.

A second approach will be evaluation by time series analysis. Using these longitudinal analyses, subjects will act as their own control. An important advantage of this type of analysis is that the impact of confounding factors is small, because samples are derived from one subject. Changes in potentially confounding factors, such as diet or recent use of antibiotics, can be accounted for based on knowledge from previous studies [21-23]. Changes found using this analysis can be used to create insight into potentially useful parameters to predict response to treatment and can be used in the following approaches.

A third approach for evaluation will be by unsupervised clustering of microbiota profiles. This will be done by generating a correlation matrix based on cosine-correlations of paired microbiota profiles. The matrix will be further clustered with the unweighted-pair group method with arithmetic mean. Resulting clusters will be analyzed for over- or underrepresentation of responders or nonresponders, again using the Mann-Whitney U test or the Student *t* test where appropriate.

The fourth approach for evaluation that we will use is a supervised classification approach. The classifier of choice is adaptive group-regularized logistic ridge regression (AGRR). This classifier has several advantages. First, it enables estimation and predictor selection when the number of features (ie, bacterial features) exceeds the number of observations. Hence, in contrast to standard classifiers, it can deal with high-dimensional data. Second, it allows for the structural use of codata in order to improve predictive performance. Codata refers to additional information on the measured variables. In this case, we will have information on the phylum that each bacterial feature belongs to. Considering this information implies that we will take into account that phylum composition may have additional predictive value. Moreover, information on predictive power at the phylum level will also facilitate feature selection (eg, if Bacteroidetes are most predictive, then the model will give more weight to the selection of bacteria belonging to this phylum). The prediction model will include corrections for clinical variables, such as gender and age, and will take into account potential confounders. Because of a relatively small sample size, we will consider which are the most important confounders based on previous findings and use stratification of these confounders into only a small number of categories, to make sure there are enough subjects in each category. The AGRR depends, as do all regularized classifiers, on penalty parameters. Tuning of these penalties will rest on efficient cross-validation and empirical Bayes estimation. Predictive performance of the model will be assessed by receiver operating characteristic (ROC) curves and area under the ROC curves based on cross-validated predictions obtained from 10-fold cross-validation. The AGRR was developed and implemented by the Statistics for Omics group of the Department of Epidemiology and Biostatistics of the Vrije Universiteit Medical Center [24].

Using these four approaches, we can evaluate our data and decide which parameters can be used to create a model that can predict whether a patient will or will not respond to therapy.

Secondary Study Parameters

Differences between responders and nonresponders in the composition of the gut and oral microbiota after 12 and 24 months will be determined using the same test as used for baseline samples and samples after 3 months.

High-dimensional immune profiling of the RRMS patients on cladribine will be performed using the Maxpar Direct Immune Profiling System (Fluidigm) with CyTOF. This assay uses a 30-marker antibody panel and automated Maxpar Pathsetter software (Fluidigm) that can identify 37 immune cell populations based on the single-cell expression of 30 protein markers. The software is developed using probability state modelling, eliminates the variability of manual gating, and provides an efficient and reliable solution for data analysis in longitudinal and multisite studies.

For each sample, 500,000 PBMCs will be measured on a single-cell level using a Helios mass cytometer (Fluidigm). Subsequently, CyTOF Software v6.7 for Maxpar Direct Immune Profiling Assay (v6.7.1016 or higher) with default flow cytometry software (FCS) processing settings will be used to normalize the final FCS files. After sample acquisition and data normalization, normalized FCS files will be analyzed using the above-mentioned Maxpar Pathsetter software.

Results

Participant inclusion started in January 2019. A total of 30 patients are included at the moment. The aim is to include 80 patients from 10 participating centers during a period of approximately 24 months. Final results are expected in 2024.

Discussion

The BIA Study investigates whether patients with active RRMS on oral cladribine, with or without disease activity after 2 years, have a distinct gut and oral microbiota and an altered immune profile. The results may be applicable in daily practice when deciding which patient is likely to have a response to oral cladribine or, after 3 months, which patient should switch to another immunomodulatory drug. Unnecessary side effects, potential risks, and useless treatment can be avoided this way. Also, this study may contribute to a better understanding of the association between the gut and central nervous system inflammation.

This study has several strengths. First, to our knowledge, this is the first study to investigate changes in gut microbiota and immune response in a longitudinal follow-up setting in patients with RRMS on oral cladribine treatment. Prior studies have only investigated gut microbiota profiles and immune responses in a cross-sectional design, which means they compared samples of different subgroups with each other or compared samples of patients with samples of healthy controls [4-8,11,12]. Changes

due to IMT can be measured only on a group level this way. Interindividual variability in microbiota profiles is high, so it is better to let each subject act as his or her own control. In this study, due to its longitudinal design, we will be able to describe the changes in microbiota and the immune response due to cladribine on an individual level. Also, we will be able to determine the predictive value of the changes in the microbiota and/or immune system on the treatment effect.

Second, this is the first clinical study to combine investigation of changes in the gut microbiota with the oral microbiota. If changes in oral microbiota can be found that are equally predictive as those found in the gut microbiota, this would be highly beneficial for clinical implementation, as oral samples are much easier to obtain than fecal samples.

Third, this is the first study to investigate the effect of cladribine on the immune system on a high-dimensional and single-cell level using CyTOF. These data will not only give extensive insight into the effect of cladribine on the immune system, but also on the role the immune system plays in responders versus nonresponders.

This study also has several limitations. First, subjects were allowed to use IMT prior to the start of oral cladribine. The baseline samples can, therefore, be influenced by this therapy. Also, we did not exclude other confounding factors, such as recently used antibiotics or corticosteroids and bowel disease. However, we will collect data on all these potential confounders in order to take them into account. Also, we will collect data on the consistency of the feces and on dietary habits, which are known confounders [1,20].

Second, generalizability of results may be limited because subjects only used oral cladribine and no other IMT. However, previous research has shown that different IMTs influence the same inflammatory pathways, so it may provide an excellent basis for further research on the brain-immune-intestine axis [12]. Cladribine was chosen for several reasons: its approximately 50% response rate, to create even groups; its known positive effect on the gut immunological system from previous research in celiac disease; and to include a more homogeneous group of patients, based on type of MS, disease severity, and type of IMT [13,25].

In summary, the results of the BIA Study are likely to contribute to more individualized medicine in patients with RRMS and to contribute to a better understanding of the brain-immune-intestine axis.

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Authors' Contributions

JvP, LvO, AEB, HEdV, and LHV contributed to the study conception and design. LHV obtained funding for the study. JvP is coordinating the study, is managing the study and data collection, and wrote the first drafts of the manuscript. All authors have read, commented on, and approved the final draft of this manuscript.

Conflicts of Interest

The BIA Study is funded by Merck. JvP received a travel grant for a scientific meeting by Merck, outside the submitted work. AEB is Chief Executive Officer of inBiome, the company that developed the IS-pro technique used in this study. LHV received honoraria for lectures, grants for research, and honoraria for advisory boards from Sanofi Genzyme, Merck, and Novartis.
Dr WIM Verhagen, a member of the group author, received honoraria for lectures from Biogen Idec and Merck; reimbursement for hospitality from Biogen Idec, Teva, Genzyme, and Merck; and honoraria for advisory boards from Merck, outside the submitted work. Prof Dr RMM Hupperts, a member of the group author, received honoraria for lectures, research, and patient care from Merck and Sanofi Genzyme, outside the submitted work; he is involved in trials from Novartis, Merck, Sanofi Genzyme, Biogen, and Roche. The other authors have nothing to declare.

References

1. Riccio P, Rossano R. Nutrition facts in multiple sclerosis. ASN Neuro 2015 Feb 18;7(1):1-20 [FREE Full text] [doi: 10.1177/1759091414568185] [Medline: 25694551]
2. Glenn JD, Mowry EM. Emerging concepts on the gut microbiome and multiple sclerosis. J Interferon Cytokine Res 2016 Jun;36(6):347-357 [FREE Full text] [doi: 10.1089/jir.2015.0177] [Medline: 27145057]

3. Wekerle H. The gut-brain connection: Triggering of brain autoimmune disease by commensal gut bacteria. Rheumatology (Oxford) 2016 Dec;55(suppl 2):ii68-ii75. [doi: 10.1093/rheumatology/kew353] [Medline: 27856664]
4. Jangi S, Gandhi R, Cox LM, Li N, von Glehn F, Yan R, et al. Alterations of the human gut microbiome in multiple sclerosis. Nat Commun 2016 Jun 28;7:12015 [FREE Full text] [doi: 10.1038/ncomms12015] [Medline: 27352007]
5. Miyake S, Kim S, Suda W, Oshima K, Nakamura M, Matsuoka T, et al. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to Clostridia XIVa and IV clusters. PLoS One 2015 Sep 14;10(9):e0137429 [FREE Full text] [doi: 10.1371/journal.pone.0137429] [Medline: 26367776]
6. Chen J, Chia N, Kalari KR, Yao JZ, Novotna M, Paz Soldan MM, et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci Rep 2016 Jun 27;6:28484 [FREE Full text] [doi: 10.1038/srep28484] [Medline: 27346372]
7. Tremlett H, Fadrosh DW, Faruqi AA, Zhu F, Hart J, Roalstad S, US Network of Pediatric MS Centers. Gut microbiota in early pediatric multiple sclerosis: A case-control study. Eur J Neurol 2016 Aug;23(8):1308-1321 [FREE Full text] [doi: 10.1111/ene.13026] [Medline: 27176462]
8. Tremlett H, Fadrosh DW, Faruqi AA, Hart J, Roalstad S, Graves J, US Network of Pediatric MS Centers. Associations between the gut microbiota and host immune markers in pediatric multiple sclerosis and controls. BMC Neurol 2016 Sep 21;16(1):182 [FREE Full text] [doi: 10.1186/s12883-016-0703-3] [Medline: 27652609]
9. Budhram A, Parvathy S, Kremenchutzky M, Silverman M. Breaking down the gut microbiome composition in multiple sclerosis. Mult Scler 2017 Apr;23(5):628-636. [doi: 10.1177/1352458516682105] [Medline: 27956557]
10. Adamczyk-Sowa M, Medrek A, Madej P, Michlicka W, Dobrakowski P. Does the gut microbiota influence immunity and inflammation in multiple sclerosis pathophysiology? J Immunol Res 2017;2017:7904821 [FREE Full text] [doi: 10.1155/2017/7904821] [Medline: 28316999]
11. Tremlett H, Fadrosh DW, Faruqi AA, Hart J, Roalstad S, Graves J, US Network of Pediatric MS Centers. Gut microbiota composition and relapse risk in pediatric MS: A pilot study. J Neurol Sci 2016 Apr 15;363:153-157 [FREE Full text] [doi: 10.1016/j.jns.2016.02.042] [Medline: 27000242]
12. Katz Sand I, Zhu Y, Ntranos A, Clemente JC, Cekanaviciute E, Brandstadter R, et al. Disease-modifying therapies alter gut microbial composition in MS. Neurol Neuroimmunol Neuroinflamm 2019 Jan;6(1):e517 [FREE Full text] [doi: 10.1212/NXI.0000000000000517] [Medline: 30568995]
13. Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, Vermersch P, CLARITY study group. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: A post-hoc and subgroup analysis. Lancet Neurol 2011 Apr;10(4):329-337. [doi: 10.1016/S1474-4422(11)70023-0] [Medline: 21397565]
14. van Gils T, Nijeboer P, van Wanrooij RL, Bouma G, Mulder CJJ. Mechanisms and management of refractory coeliac disease. Nat Rev Gastroenterol Hepatol 2015 Oct;12(10):572-579. [doi: 10.1038/nrgastro.2015.155] [Medline: 26347156]
15. Storm-Larsen C, Myhr KM, Farbu E, Midgard R, Nyquist K, Broch L, et al. Gut microbiota composition during a 12-week intervention with delayed-release dimethyl fumarate in multiple sclerosis: A pilot trial. Mult Scler J Exp Transl Clin 2019 Nov 15;5(4):1-13 [FREE Full text] [doi: 10.1177/2055217319888767] [Medline: 31798939]
16. Stuve O, Soelberg Soerensen P, Leist T, Giovannoni G, Hyvert Y, Damian D, et al. Effects of cladribine tablets on lymphocyte subsets in patients with multiple sclerosis: An extended analysis of surface markers. Ther Adv Neurol Disord 2019 Jun 18;12:1-16 [FREE Full text] [doi: 10.1177/1756286419854986] [Medline: 31244898]
17. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York, NY: Springer Science+Business Media; 2009.
18. eNAT brochure. COPAN Diagnostics. URL: https://www.copanusa.com/wp-content/uploads/2019/08/eNat_Brochure_COPAN_0814191.pdf [accessed 2020-07-02]
19. Budding AE, Grasman ME, Lin F, Bogaards JA, Soeltan-Kaersenhout DJ, Vandenbroucke-Grauls CMJE, et al. IS-pro: High-throughput molecular fingerprinting of the intestinal microbiota. FASEB J 2010 Nov;24(11):4556-4564. [doi: 10.1096/fj.10-156190] [Medline: 20643909]
20. Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, et al. Population-level analysis of gut microbiome variation. Science 2016 Apr 29;352(6285):560-564 [FREE Full text] [doi: 10.1126/science.aad3503] [Medline: 27126039]
21. Aguirre M, Eck A, Koenen ME, Savelkoul PHM, Budding AE, Venema K. Diet drives quick changes in the metabolic activity and composition of human gut microbiota in a validated in vitro gut model. Res Microbiol Feb–Mar 2016;167(2):114-125. [doi: 10.1016/j.resmic.2015.09.006] [Medline: 26499094]
22. de Meij TGJ, Budding AE, de Groot EFJ, Jansen FM, Frank Kneepkens CM, Benninga MA, et al. Composition and stability of intestinal microbiota of healthy children within a Dutch population. FASEB J 2016 Apr;30(4):1512-1522. [doi: 10.1096/fj.15-278622] [Medline: 26655704]
23. Hertz FB, Budding AE, van der Lugt-Degen M, Savelkoul PH, Løbner-Olesen A, Frimodt-Møller N. Effects of antibiotics on the intestinal microbiota of mice. Antibiotics (Basel) 2020 Apr 17;9(4):191 [FREE Full text] [doi: 10.3390/antibiotics9040191] [Medline: 32316518]
24. van de Wiel MA, Lien TG, Verlaat W, van Wieringen WN, Wilting SM. Better prediction by use of co-data: Adaptive group-regularized ridge regression. Stat Med 2016 Feb 10;35(3):368-381. [doi: 10.1002/sim.6732] [Medline: 26365903]

25. Tack GJ, Verbeek WHM, Al-Toma A, Kuik DJ, Schreurs MWJ, Visser O, et al. Evaluation of cladribine treatment in refractory celiac disease type II. World J Gastroenterol 2011 Jan 28;17(4):506-513 [FREE Full text] [doi: 10.3748/wjg.v17.i4.506] [Medline: 21274381]

Abbreviations

AGRR: adaptive group-regularized logistic ridge regression
BIA: brain-immune-intestine axis
CyTOF: cytometry by time-of-flight
EDSS: Expanded Disability Status Scale
FCS: flow cytometry software
FLAIR: fluid-attenuated inversion recovery
IMT: immunomodulatory treatment
IS: interspace
IS-pro: interspace profiling
MRI: magnetic resonance imaging
MS: multiple sclerosis
NEDA: no evidence of disease activity
PBMC: peripheral blood mononuclear cell
ROC: receiver operating characteristic
RRMS: relapsing-remitting multiple sclerosis

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Protocol

Identification of Potential Biomarkers of Chronic Kidney Disease in Individuals with Diabetes: Protocol for a Cross-sectional Observational Study

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Abstract

Background: The importance of identifying people with diabetes and progressive kidney dysfunction relates to the excess morbidity and mortality of this group. Rates of cardiovascular disease are much higher in people with both diabetes and kidney dysfunction than in those with only one of these conditions. By the time these people are identified in current clinical practice, proteinuria and renal dysfunction are already established, limiting the effectiveness of therapeutic interventions. The identification of an epigenetic or blood metabolite signature or gut microbiome profile may identify those with diabetes at risk of progressive chronic kidney disease, in turn providing targeted intervention to improve patient outcomes.

Objective: This study aims to identify potential biomarkers in people with diabetes and chronic kidney disease (CKD) associated with progressive renal injury and to distinguish between stages of chronic kidney disease. Three sources of biomarkers will be explored, including DNA methylation profiles in blood lymphocytes, the metabolomic profile of blood-derived plasma and urine, and the gut microbiome.

Methods: The cross-sectional study recruited 121 people with diabetes and varying stages (stages 1-5) of chronic kidney disease. Single-point data collection included blood, urine, and fecal samples in addition to clinical data such as anthropometric measurements and biochemical parameters. Additional information obtained from medical records included patient demographics, medical comorbidities, and medications.

Results: Data collection commenced in January 2018 and was completed in June 2018. At the time of submission, 121 patients had been recruited, and 119 samples remained after quality control. There were 83 participants in the early diabetes-associated CKD group with a mean estimated glomerular filtration rate (eGFR) of 61.2 mL/min/1.73 m2 (early CKD group consisting of stage 1, 2, and 3a CKD), and 36 participants in the late diabetic CKD group with a mean eGFR of 23.9 mL/min/1.73 m2 (late CKD group, consisting of stage 3b, 4, and 5), $P<.001$. We have successfully obtained DNA for methylation and microbiome analyses using the biospecimens collected via this protocol and are currently analyzing these results together with the metabolome of this cohort of individuals with diabetic CKD.

Conclusions: Recent advances have improved our understanding of the epigenome, metabolomics, and the influence of the gut microbiome on the incidence of diseases such as cancers, particularly those related to environmental exposures. However, there

is a paucity of literature surrounding these influencers in renal disease. This study will provide insight into the fundamental understanding of the pathophysiology of CKD in individuals with diabetes, especially in novel areas such as epigenetics, metabolomics, and the kidney-gut axis.

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KEYWORDS

epigenetics; metabolomics; gut microbiome; diabetes; chronic kidney disease

Introduction

In 2011-2012, an estimated 1.7 million Australian adults had clinical and biochemical features of Chronic Kidney Disease (CKD), with similar numbers of males and females affected [1]. As kidney disease is mostly asymptomatic, the majority of people are unaware they have this chronic condition. Therefore, opportunistic testing in people with identifiable risk factors is of paramount significance to the individual's health and Australia's health economy. One of the leading risk factors for CKD is diabetes mellitus (DM), both type I and type II, which, together with associated micro and macrovascular complications, have reached epidemic proportions in Australia [2]. The prevalence of CKD is about three times higher in those with diabetes compared to those without [3]. One of the major microvascular complications of diabetes is kidney injury, termed diabetic chronic kidney disease. It is characterized by persistent albuminuria, proteinuria, and eventual decline in kidney function (estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2).

Among people with diabetes and CKD, the rate of cardiovascular events is more than twice the rate of those with diabetes alone [4]**.** Cardiovascular causes are the leading cause of mortality in people with diabetes and kidney disease, and this is more likely than the progression to end-stage renal disease (ESRD) [5]. These problems are only projected to escalate, given the growing epidemic of diabetes and obesity in Australia and worldwide.

Epigenetics is the study of a range of biochemical processes that regulate gene expression and phenotype in the absence of underlying alterations to the DNA sequence [6]**.** Epigenetic mechanisms play a crucial role in differentiation, cell specification, and function and may be regulated by external cues such as exposure to environmental pollutants and poor dietary choices. Consequently, this can induce abnormal metabolic phenotypes that can be further compounded by genetic susceptibility [7]**.** DNA methylation (DNAm) is the most studied epigenetic marker and is highly stable due to the covalent link to the underlying DNA. DNA methylation usually occurs at 5′-cytosines (5mC) of CpG dinucleotides. The regions of DNA with a higher number of CpG clusters are designated "CpG islands" and are generally methylated in a tissue-specific manner. Low methylation status of promoter CpG islands is associated with gene expression, while a high methylation status causes repression of transcription [8]**.**

Multiple factors such as inflammation, accelerated oxidative stress, accumulation of toxins, and aberrant metabolism are involved in the progressive deterioration of kidney function. Abnormal epigenetic mechanisms may be involved in mediating the likely gene-environment interactions underlying diabetes and chronic kidney disease [9]. This area of research is novel as we now know that pro-inflammatory and pro-fibrotic genes can be regulated by hyperglycemia via epigenetic mechanisms in vascular cells, monocytes, and mesangial cells [10]. The epigenetic mechanisms involved in the regulation of gene expression, including DNA methylation, appear to play a pivotal role in the development of diabetes-associated complications [11].

Metabolomics is the large-scale study of small molecules referred to as metabolites (such as sugars, amino acids, and lipids) in a given organism. Just as each individual will have a unique epigenetic profile, each will also have a characteristic metabolomic profile, leading to the concept of personalized metabolomics. In the future, this may provide the ability to track the trends of individual metabolomes over time, thus enabling personalized drugs and improved treatment strategies. Such personalized treatment is likely to be more effective than current medical population-based approaches. Metabolomic approaches are particularly promising in nephrology research as a consequence of the significant and varied impact kidney function has on circulating metabolite levels and because the metabolites may themselves play functional roles in CKD pathogenesis and its complications [12]. In experimental studies, metabolomics has been used to identify a signature of decreased mitochondrial function in diabetic chronic kidney disease, and these studies have outlined new therapeutic options [12].

Each individual's microbiome composition is thought to be unique and influenced by genetics, geographical location, diet, age, and exposure to antibiotics, in addition to factors operational in early life such as mode of delivery and nature of early feeding. Gut bacteria play a crucial role in food digestion and nutrient absorption. More recently, the role of the gut in modulating the immune system has been recognized, and dysbiosis has subsequently been linked to an increasing number of non-communicable diseases such as diabetes, obesity, and heart disease.

Kidney disease is associated with inadequate nutrition, frequent use of antibiotics, metabolic acidosis, and volume overload. These factors are associated with microbial dysbiosis and may also affect gastrointestinal permeability, which together may account for the systemic inflammation that is associated with and contributes to worsening CKD and cardiovascular disease. CKD alters gut microbiota and contributes to dysbiosis. Vaziri et al reported altered gut microbiota composition in people with

CKD: specifically, they noted lower numbers of *Lactobacillaceae* and *Prevotellaceae* families and 100 times higher *Enterobacteria* and *Enterococci* species [13].

The primary aim of this study is to compare DNA methylation, blood and urinary metabolomic, and gut microbiome profiles between people with diabetes and various stages of CKD. A component of this aim is to determine whether there are distinct profiles at each stage of diabetic CKD.

Methods

A sample size of 120 provides 80% power to detect a minimum correlation of 0.25 between epigenetic/metabolomics and gut microbiome factors and the stage of diabetic kidney disease using a two-sided hypothesis test with a significance level of .05. A correlation of 0.25 is considered a moderately small effect size, and as such, the target sample size has enough power to investigate the primary research question.

The sample size of 120 will also provide more than 90% power to detect an R^2 effect size of 0.20 (moderately small effect size) in a multivariate linear regression setting using an F test with a significance level (alpha) of 0.05.

This cross-sectional study design included a study population of 121 adults with diabetes and CKD stages 1, 2, 3a, 3b, 4, and 5. Participants were recruited from a single site, the Austin Health outpatient diabetes clinic, Victoria, Australia. Approximately 40 patients attend this clinic per week, and it took 6 months to recruit 121 participants. Patient recruitment commenced in January 2018 and was completed by the end of June 2018. Patients who presented to this clinic were offered the option to participate in the study and provided consent to the collection of clinical information, archiving and use of blood, urine, and stool samples, for research into the complications of diabetes.

All biological samples and data were de-identified and assigned a study number at Austin Health. Samples (other than stool samples) were transported from Austin Health to the Murdoch Children's Research Institute (MCRI), Melbourne, for processing, analysis, and storage. Stool samples were transported on dry ice to the Metabolic Research Unit, Deakin University, Geelong for processing, analysis, and storage. Electronic data will be kept indefinitely to allow for continued analyses.

Study Population and Recruitment

Participants (N=121) were recruited from the Austin Health outpatient diabetes clinic. The principal investigator approached patients while they waited for their appointment. The aims of the study were explained, and they were asked if they had an interest in knowing more information about the study. Those interested were provided with a participant information statement and consent form as well as a stool collection kit to be brought to their next diabetes clinic appointment.

Inclusion and Exclusion Criteria

Participants qualified for inclusion if they were aged ≥18 years and diagnosed with diabetes and CKD stages 1, 2, 3a, 3b, 4, or 5.

Participants were excluded if they were aged <18 years, had a history of renal transplant, a single kidney, diabetes secondary to pancreatic pathology, steroid medication-induced diabetes, presence of non-diabetic kidney disease, active drug or heavy alcohol use, an active malignancy within the past five years, inflammatory bowel disease, were pregnant or breastfeeding, or who had a BMI <20 or >40.

Data Collection

Patient Information

Participant data inclusive of age, gender, height weight, blood pressure, medical comorbidities, duration of diabetes, stage of CKD and its associated complications, medications, and pathology results were collected. The anthropometric data were obtained on the day of the clinic visit while the remainder of the patient's information was gathered via access to Austin Health's electronic medical records. All of this selected information was then entered into the study database.

Sample Storage

Serum/Plasma samples

Peripheral blood was collected at each outpatient clinic visit by venepuncture for assessment of epigenetics and metabolomics profiles. A total of 15mL of blood was collected at each visit: 10 mL in a 10-mL coagulant tube (for serum) and 5 mL in a 5-mL ethylene diamine tetraacetic acid (EDTA) anticoagulant tube (plasma, white blood cells). Samples were transported to the Austin Health laboratory within two hours of collection for processing by the principal investigator. The clot was initially separated from the 10ml coagulant tube. Subsequently, the 10-mL coagulant tube (for serum) was centrifuged at 3500 rcf at 4°C. The serum was separated into 0.5-mL aliquots. The clot and serum aliquots were then stored at –80°C. The 5-mL EDTA anticoagulant tube was also centrifuged at 3500 rcf at 4°C. The resultant plasma was separated into 0.5-mL aliquots, and the buffy coat separated into 0.2-mL aliquots. All samples were stored at –80°C.

Urine Samples

A spot urine sample was collected at each outpatient diabetic clinic visit and transported to the laboratory within 24-48 hours of collection. The samples were centrifuged at 3500 rcf at 4°C and then aliquoted into 5-mL tubes and stored at –80°C within 30 mins of processing. Subsequently, the urine and plasma samples were sent to Nightingale (Finland) for metabolomic biomarker analysis.

Stool Samples

Following collection in a specimen container, the samples were aliquoted into smaller 1.5-mL Eppendorf tubes before freezing at –80°C, then stored for DNA extraction to avoid multiple freeze/thaw cycles. The stool sample volume required for microbiome analysis was about 0.5-1.0 g.

Data Generation

DNA methylation profile: Genomic DNA was extracted from blood lymphocytes (buffy coat) for methylation analysis. Peripheral blood was collected from Austin Health and transported to MCRI. Buffy coats were lysed with proteinase

K for 2 hours, and the DNA was extracted using the Qiagen QIAamp DNA Mini spin kit (Ref 51306) according to the manufacturer's protocol. DNA was quantified, and purification assessed by Qubit fluorometric quantitation (Thermo Fisher).

Genomic DNA (1000 ng) from adult buffy coat samples were randomized into 96-well plates and sent to the Australian Genome Research Facility (AGRF, Victoria) for sodium bisulfite treatment and genome-wide methylation analysis using Illumina InfiniumMethylationEPIC BeadChips (HM850K) [14]. The EPIC array measures DNA methylation at more than 850,000 CpG sites and covers all gene promoters, gene bodies, and ENCODE-assigned distal regulatory elements (Encyclopedia of DNA elements) [15]. Quality assessment was performed by QuantiFluor, and a subset of samples was resolved on a 0.8% agarose gel at 130 V for 60 minutes. Samples were then normalized to approximately 500 ng of DNA in 45 µL and bisulfite converted with the Zymo EZ DNA Methylation kit. All samples were above 860,000 detected CpG sites (P<.01). Raw IDAT files were received on a hard disk from AGRF and used for data analysis.

In order to assess blood and urine metabolites, plasma was isolated from peripheral blood and corresponding urine samples sent to Nightingale (Finland) for metabolomic biomarker analysis. This platform analyzes metabolites using nuclear magnetic resonance (NMR) spectroscopy, which is an NMR-based metabolomics platform [16]. Robotic sample preparation is followed by spectral acquisition in a fully automated manner. The NMR platform has been used to profile approximately 350,000 blood samples in over 1000 epidemiological and clinical studies. The biomarker measurements are acquired from native serum or EDTA plasma and are possible with 100 µL to 350 µL sample volume. The platform provides quantification of 228 metabolic measures, which are quantified in absolute concentrations (ie, mmol/L) [16].

In order to assess the gut microbiome, stool samples were sent on dry ice to the Metabolic Research Unit, Deakin University, Geelong, where they were stored in a –80°C freezer. DNA was extracted using the commercial Qiagen QIAamp DNA Stool Mini Kit (Ref 51504) according to the manufacturer's protocol. DNA quantity and purity were assessed using Qubit (Thermo Fisher).

The Australian Genome Research Facility performed PCR amplification and sequencing. PCR amplicons were generated using the primers and conditions outlined in Table 1.

Thermocycling was performed on an Applied Biosystem 384 Veriti using AmpliTaq Gold 360 Mastermix (Life Technologies, Australia) for the primary PCR. The first stage PCR product was purified using magnetic beads, and samples were visualized by electrophoretic separation in a 2% Sybr Egel (Thermo Fisher). A secondary PCR to index the amplicons was performed with TaKaRa Taq DNA Polymerase (Clontech). The resulting amplicons were purified using magnetic beads, quantified by fluorometry (Promega Quantifluor), and normalized. The equimolar pool was purified a final time using magnetic beads to concentrate the pool and then measured using a High-Sensitivity D1000 Tape on an Agilent 2200 TapeStation. The pool was diluted to 5 nM, and molarity was confirmed using a High-Sensitivity D1000 Tape, then sequenced on an Illumina MiSeq with a V3, 600 cycle kit (2 × 300 base pairs paired-end).

Paired-end reads were assembled by aligning the forward and reverse reads using PEAR (version 0.9.5) [17]. Primers were identified & trimmed. Trimmed sequences were processed using Quantitative Insights into Microbial Ecology (QIIME 1.8) [18], USEARCH (version 7.1.1090) [19,20], and UPARSE [21] software. USEARCH sequences were quality filtered, and full-length duplicate sequences were removed and sorted by abundance. Singletons or unique reads in the data set were discarded. Sequences were clustered and chimera filtered using the "rdp_gold" database as the reference. Reads were mapped back to OTUs with a minimum identity of 97% to obtain the number of reads in each OTU. QIIME taxonomy was assigned using the Greengenes database (version 13_8) [22].

Demographic and clinical information stored on the Austin Health patient database was accessed and recorded in the study database. The information included but was not limited to blood pressure, weight and BMI, eGFR, albumin to creatinine ratio, medical comorbidities, and medication history. This information was de-identified and given a study ID number corresponding to their matched biological samples.

Table 1. Primers and conditions used to amplify the 16S: V3-V4 target sequence.

Primers and conditions	Description
Primer	
Target	341F-806R
Forward (341F)	CCTAYGGGRBGCASCAG
Reverse (806R)	GGACTACNNGGGTATCTAAT
Condition	
Target	16S: V3 - V4
Cycle	29
Initial	95°C for 7 min
Disassociate	94°C for 60 sec
Anneal	50°C for 60 sec
Extension	72°C for 60 sec
Finish	72°C for 7 min

Results

This study was approved in July 2017 by the Human Research Ethics Committee of Austin Health, Victoria, Australia (HREC/17/Austin/166) and Deakin University, Geelong, Australia. The study was funded in July 2017. Data will be published in peer-reviewed medical and scientific research journals and any molecular data published in the appropriate public repositories. Data collection commenced in January 2018 and was completed in June 2018. At the time of this submission, 121 patients had been recruited. After sample quality control, data were available for 119 patient samples. The proportion of the 119 recruited patients in each stage of CKD is illustrated in Table 2. The clinical and biochemical characteristics of our patient cohort are shown in Table 3.

The majority of participants had type 2 diabetes (n= 99), while 20 had type 1 diabetes. Only 2 of the 20 patients with type 1 diabetes were characterized as having latent autoimmune diabetes of adulthood (LADA). There were 83 participants in the early diabetes-associated CKD group with a mean eGFR of 61.2 mL/min/1.73 m^2 (early CKD group consisting of stages 1, 2, and 3a), and 36 participants in the late diabetic CKD group with a mean eGFR of 23.9 mL/min/1.73 m^2 (late CKD group, consisting of stages 3b, 4, and 5) (P<.001). We chose to define late diabetes-associated CKD as Stages 3b, 4, and 5 in recognition of the marked increase in death, cardiovascular events, and hospitalizations observed as eGFR decreased below 45 mL/min/1.73 m^2 [23]. The mean age in the early CKD group was significantly younger at 66.1 years versus 72 years in the late CKD group (P=.01). There was a higher proportion of males, with 50 out of 83 participants (60.2%) in the early CKD group versus only 16 males out of 36 participants (44.4%) in the late CKD group.

Biospecimens are currently being used for epigenetic, metabolomic, and gut microbiome analyses. The results from these respective analyses will be completed in June 2020 with the publication of this work expected later this year.

Table 2. The proportion of patients in each stage of chronic kidney disease (N=119).

Disease stage	Patients, n (%)
Stage 1	8 (7)
Stage 2	49 (41)
Stage 3a	26 (22)
Stage 3b	13 (11)
Stage 4	13 (11)
Stage 5	10 (8)

Table 3. Clinical and biochemical characteristics of the patient cohort.

Patient characteristics	Early chronic kidney disease (group 1)	Late chronic kidney disease (group 2)	*P* value
Age (years), mean (SD)	66.14 (11.5)	72.00 (11.5)	.01
Male, n (%)	50 (60.2)	16.00 (44.4)	.16
Type of diabetes, n (%)			.24
Type 1	15 (18.1)	3 (8.3)	
Type 2	66 (79.5)	33 (91.7)	
LADA[a]	2 (2.4)	0 (0.0)	
Duration of DBM[b] (years), mean (SD)	18.71 (11.0)	33.00 (11.2)	.12
Hypertension, n (%)	65 (78.3)	34 (94.4)	.06
Diabetic retinopathy, n (%)	32 (38.6)	15 (41.7)	.91
Cardiovascular disease, n (%)	30 (36.1)	15 (41.7)	.72
Peripheral vascular disease, n (%)	12 (14.5)	10 (27.8)	.14
Dyslipidemia, n (%)	66 (79.5)	31 (86.1)	.55
Depression, n (%)	16 (19.3)	4 (11.1)	.41
Smoking status, n (%)			.51
Nonsmoker	46 (55.0)	24 (66.7)	
Ex-smoker	30 (36.0)	10 (27.8)	
Current smoker	7 (8.4)	2 (5.6)	
BMI (kg/m^2), mean (SD)	29.44 (7.9)	28.53 (7.9)	.58
SBP[c] (mmHg), mean (SD)	109.58 (49.7)	121.09 (50.0)	.26
DBP[d] (mmHg), mean (SD)	63.38 (27.2)	66.20 (20.1)	.59
Hb[e] (g/L), mean (SD)	108.60 (52.3)	88.75 (53.7)	.06
eGFR[f] (mL/min/1.73 m^2), mean (SD)	61.17 (22.8)	23.89 (12.0)	<.001
HbA_{1c}[g] (%), mean (SD)	7.51 (1.8)	7.66 (1.7)	.69
TC[h] (mmol/L), mean (SD)	4.00 (1.1)	3.74 (1.0)	.25
LDL[i] (mmol/L), mean (SD)	1.89 (0.9)	1.78 (0.9)	.54
Urine albumin/creatinine ratio, mean (SD)	20.57 (73.27)	83.71 (178.06)	.28
Urine protein/creatinine ratio, mean (SD)	0.28 (1.57)	4.15 (13.85)	.35

[a]LADA: latent autoimmune diabetes of adulthood.

[b]DBM: diabetes mellitus.

[c]SBP: systolic blood pressure.

[d]DBP: diastolic blood pressure.

[e]Hb: hemoglobin.

[f]eGFR: estimated glomerular filtration rate.

[g]HbA_{1c}: glycated hemoglobin.

[h]TC: total cholesterol.

[i]LDL: low-density lipoprotein.

Discussion

In our preliminary data, we have shown the proportion of individuals with diabetes and various stages of CKD. We have illustrated the clinical and biochemical characteristics of our patient cohort. With this protocol, we have obtained DNA for methylation and microbiome analyses and are currently analyzing these results together with the metabolome of our patient group. There have been separate studies in the areas of epigenetics [24], metabolomics [25], and the gut microbiome [13] that have shown these biomarkers to be potential indicators of renal dysfunction and markers of renal prognosis. However, no studies have simultaneously investigated the possible

combined roles of epigenetics, metabolomics, and gut microbiome, especially across all stages of chronic kidney disease in individuals with diabetes.

One of the strengths of this study protocol is the depth of cross-sectional data across epigenetics, metabolomics, and the gut microbiome as well as varying biospecimens inclusive of serum, plasma, buffy coats, urine, and fecal samples, involving the different stages of kidney disease. This broad scope will enable a comprehensive investigation of the factors contributing to and potential for biomarker identification in people with diabetes-associated CKD. One of the limitations, however, of this study design is its cross-sectional nature and small sample size, especially in the late CKD group. Future prospective cohort designs would necessitate larger sample sizes in each CKD stage as well as longitudinal data collection.

The significance and clinical value of these potential biomarkers are in determining whether the specific profiles across the three domains could help to predict the stages of renal dysfunction, especially if these are demonstrated to precede the change in cellular or clinical phenotype. This protocol provides the first step towards biomarker discovery for future longitudinal studies that would enable longer-term patient follow-up. Demonstrating such a change may lead to targeted, individualized patient treatment and better patient outcomes. There is a paucity of research exploring the clinical impact of epigenetics, metabolomics, and the gut microbiome in renal disease. Our research will generate data relating to epigenomic and metabolomic analyses, which, together with an understanding of the kidney-gut microbiome axis, will be a means of identifying potential novel biomarkers for people with progressive diabetic CKD.

Authors' Contributions

Conceptualization: KMD, EIE, RS. Funding acquisition: KMD. Project administration: AL. Investigation: AL. Methodology: AL, KMD, MM, and RS. KMD, EIE, and RS. Original draft: AL. Review and editing: AL, KMD, EIE, and RS.

Conflicts of Interest

This research received no specific grant from any funding agency in public, commercial, or not-for-profit sectors. EIE was supported by a Viertel Clinical Investigatorship, Royal Australasian College of Physicians (RACP) Fellowship, Sir Edward Weary Dunlop Medical Research Foundation, Stroke Foundation, and NHMRC research grants. EIE's institution has received research funding from Novo Nordisk, Bayer, Sanofi, and Dimerix. The funders had no role in study design, data collection and analysis, the decision to publish, or preparation of the manuscript. The remaining authors have no competing interests to disclose.

References

1. Australian BOS. Kidney Disease Biomarkers. Australian Health Survey: Biomedical Results for Chronic Diseases 2011-12 2013.
2. Baker IDI. Diabetes Australia. Diabetes: The silent pandemic and its impact on Australia 2012.
3. Chadban S, Craig J. National Evidence Based Guideline for Diagnosis, Prevention and Management of Chronic Kidney Disease in Type 2 Diabetes. Diabetes Australia Guideline Development Consortium 2009.
4. Deloitte AE, Kidney HA. The burden of diabetic kidney disease and the cost effectiveness of screening people with type 2 diabetes for chronic kidney disease. Two of a KinD (Kidneys in Diabetes) 2011.
5. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004 Mar 22;164(6):659-663. [doi: 10.1001/archinte.164.6.659] [Medline: 15037495]
6. Kato M, Natarajan R. Diabetic nephropathy--emerging epigenetic mechanisms. Nat Rev Nephrol 2014 Sep;10(9):517-530 [FREE Full text] [doi: 10.1038/nrneph.2014.116] [Medline: 25003613]
7. Ling C, Groop L. Epigenetics: a molecular link between environmental factors and type 2 diabetes. Diabetes 2009 Dec;58(12):2718-2725 [FREE Full text] [doi: 10.2337/db09-1003] [Medline: 19940235]
8. Fan S, Zhang X. CpG island methylation pattern in different human tissues and its correlation with gene expression. Biochemical and Biophysical Research Communications 2009 Jun;383(4):421-425. [doi: 10.1016/j.bbrc.2009.04.023]
9. MacFarlane AJ, Strom A, Scott FW. Epigenetics: deciphering how environmental factors may modify autoimmune type 1 diabetes. Mamm Genome 2009;20(9-10):624-632. [doi: 10.1007/s00335-009-9213-6] [Medline: 19697079]
10. Reddy MA, Natarajan R. Epigenetic mechanisms in diabetic vascular complications. Cardiovasc Res 2011 Jun 01;90(3):421-429 [FREE Full text] [doi: 10.1093/cvr/cvr024] [Medline: 21266525]
11. Villeneuve LM, Reddy MA, Natarajan R. Epigenetics: deciphering its role in diabetes and its chronic complications. Clin Exp Pharmacol Physiol 2011 Jul;38(7):451-459 [FREE Full text] [doi: 10.1111/j.1440-1681.2011.05497.x] [Medline: 21309809]
12. Rhee EP. Metabolomics and renal disease. Current Opinion in Nephrology and Hypertension 2017:1. [doi: 10.1097/mnh.0000000000000136]
13. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. Kidney International 2013 Feb;83(2):308-315. [doi: 10.1038/ki.2012.345]

14. Martino D, Neeland M, Dang T, Cobb J, Ellis J, Barnett A, et al. Epigenetic dysregulation of naive CD4+ T-cell activation genes in childhood food allergy. Nat Commun 2018 Aug 17;9(1):3308 [FREE Full text] [doi: 10.1038/s41467-018-05608-4] [Medline: 30120223]
15. Pidsley R, Zotenko E, Peters TJ, Lawrence MG, Risbridger GP, Molloy P, et al. Critical evaluation of the Illumina MethylationEPIC BeadChip microarray for whole-genome DNA methylation profiling. Genome Biol 2016 Oct 7;17(1). [doi: 10.1186/s13059-016-1066-1]
16. Wüthrich K. NMR Studies of Structure and Function of Biological Macromolecules (Nobel Lecture). Angew. Chem. Int. Ed 2003;42(29):3340-3363. [doi: 10.1002/anie.200300595]
17. Zhang J, Kobert K, Flouri T, Stamatakis A. PEAR: a fast and accurate Illumina Paired-End reAd mergeR. Bioinformatics 2014 Mar 01;30(5):614-620 [FREE Full text] [doi: 10.1093/bioinformatics/btt593] [Medline: 24142950]
18. Caporaso JG, Kuczynski J, Stombaugh J, Bittinger K, Bushman FD, Costello EK, et al. QIIME allows analysis of high-throughput community sequencing data. Nat Methods 2010 May;7(5):335-336 [FREE Full text] [doi: 10.1038/nmeth.f.303] [Medline: 20383131]
19. Edgar RC. Search and clustering orders of magnitude faster than BLAST. Bioinformatics 2010 Oct 01;26(19):2460-2461. [doi: 10.1093/bioinformatics/btq461] [Medline: 20709691]
20. Edgar RC, Haas BJ, Clemente JC, Quince C, Knight R. UCHIME improves sensitivity and speed of chimera detection. Bioinformatics 2011 Aug 15;27(16):2194-2200 [FREE Full text] [doi: 10.1093/bioinformatics/btr381] [Medline: 21700674]
21. Edgar RC. UPARSE: highly accurate OTU sequences from microbial amplicon reads. Nat Methods 2013 Oct;10(10):996-998. [doi: 10.1038/nmeth.2604] [Medline: 23955772]
22. DeSantis TZ, Hugenholtz P, Larsen N, Rojas M, Brodie EL, Keller K, et al. Greengenes, a chimera-checked 16S rRNA gene database and workbench compatible with ARB. Appl Environ Microbiol 2006 Jul;72(7):5069-5072 [FREE Full text] [doi: 10.1128/AEM.03006-05] [Medline: 16820507]
23. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004 Dec 23;351(13):1296-1305. [doi: 10.1056/NEJMoa041031] [Medline: 15385656]
24. Villeneuve LM, Natarajan R. The role of epigenetics in the pathology of diabetic complications. Am J Physiol Renal Physiol 2010 Jul;299(1):F14-F25 [FREE Full text] [doi: 10.1152/ajprenal.00200.2010] [Medline: 20462972]
25. Rhee EP, Clish CB, Wenger J, Roy J, Elmariah S, Pierce KA, et al. Metabolomics of Chronic Kidney Disease Progression: A Case-Control Analysis in the Chronic Renal Insufficiency Cohort Study. Am J Nephrol 2016 May 13;43(5):366-374. [doi: 10.1159/000446484]

Abbreviations

AGRF: Australian Genome Research Facility
CKD: chronic kidney disease
DM: diabetes mellitus
DN: diabetic nephropathy
EDTA: ethylenediaminetetraacetic acid
eGFR: estimated glomerular filtration rate
ENCODE: Encyclopedia of DNA Elements
ESRD: end-stage renal disease
HREC: Human Research Ethics Committee
LDL: low-density lipoprotein
MCRI: Murdoch Children's Research Institute
NMR: nuclear magnetic resonance
RRT: renal replacement therapy

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Protocol

Measurement of Physical Activity and Sedentary Behavior by Accelerometry Among a Nationwide Sample from the KiGGS and MoMo Study: Study Protocol

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Abstract

Background: Currently, no nationwide objective physical activity data exists for children and adolescents living in Germany. The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) and the Motorik-Modul study (MoMo) is a national cohort study that has incorporated accelerometers in its most recent data collection wave (wave 2, since 2014). This wave 2 marks the first nationwide collection of objective data on the physical activity of children and adolescents living in Germany.

Objective: The purpose of this protocol is to describe the methods used in the KiGGS and MoMo study to capture the intensity, frequency, and duration of physical activity with accelerometers.

Methods: Participants (N=11,003, aged 6 to 31 years) were instructed to wear an ActiGraph GT3X+ or wGT3X-BT accelerometer laterally on the right hip. Accelerometers were worn on consecutive days during waking hours, including at least 4 valid weekdays and 1 weekend day (wear time >8 hours) in the evaluation. A nonwear time protocol was also implemented.

Results: Data collection was completed by October 2017. Data harmonization took place in 2018. The first accelerometer results from this wave were published in 2019, and detailed analyses are ready to be submitted in 2020.

Conclusions: This study protocol provides an overview of technical details and basic choices when using accelerometers in large-scale epidemiological studies. At the same time, the restrictions imposed by the specified filters and the evaluation routines must be taken into account.

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KEYWORDS

processing criteria; wear time protocol; epoch length; sampling frequency; intensity classification; Motorik-Modul study

Introduction

The health benefits of regularly performed physical activity are well documented in the public health literature. However, assessment of the physical activity of children remains difficult because the energy expenditure of a small active person can be as high as that of a large inactive person [1-4]. Because children show more complex but less structured movement behaviors than adults [3,5], capturing their many spontaneous and impulsive movements is a great challenge for physical activity

assessment [6]. Currently, questionnaires are still the most commonly used subjective method to assess physical activity. One of the greatest advantages of questionnaires is their versatility. In addition to recording the duration, frequency, and intensity of physical activity, questionnaire methods can also be used to collect information about the type of physical activity, which has only recently become possible with accelerometers. Furthermore, in the context of large-scale epidemiological or health science studies, questionnaires are the only feasible alternative for practical and financial reasons [7]. In contrast, many empirical studies have already shown that the level of physical activity subjectively assessed by questionnaires is often overestimated [7-9]. Especially, the unstructured and irregular activities in everyday life are difficult to retrieve from memory correctly. In recent years, accelerometers have been used more frequently in large-scale studies [10-13] because they have become more feasible, more accurate, and much more affordable.

Although accelerometers are being used more frequently, there is no consensus on the usage of accelerometers for the assessment of physical activity in nationwide studies in adolescents or in children [14-16]. Due to the rapid development in this field and the extremely large amounts of gathered data, many current studies do not accurately document accelerometer use in detail (eg, technical details of settings and evaluation) [16]. This complicates replication and comparison of these studies because there are only a few representative studies worldwide [10,17]. Until 2014, no nationwide study had been performed in Germany in which physical activity was measured with accelerometers.

The aim of the Motorik-Modul study (MoMo), as part of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), was to establish regular monitoring of physical fitness and physical activity of children and adolescents living in Germany and to gain insight into their determinants and consequences for health outcomes. The MoMo study was established in 2003 and is based on a cohort-sequence design; four measurement waves (baseline and waves 1, 2, and 3) were planned from 2003 to 2021. Up to 2014 (baseline and wave 1), physical activity was assessed solely using a validated physical activity questionnaire (PAQ) [7]. In KiGGS and MoMo wave 2, physical activity was additionally assessed by accelerometers.

The purposes of this study protocol are to explain the challenges faced when using accelerometers in the MoMo and KiGGS studies as an example of a large-scale epidemiological study and to detail the methods and protocols used to capture physical activity in children and adolescents with accelerometers in Germany.

Methods

Study Design

KiGGS is part of the German health monitoring system established by the Robert Koch Institute. The KiGGS research topics are physical health, mental health, health-related behavior, health care, prevention, and social and environmental determinants. The study design and sampling procedure are described in detail elsewhere [18]. The core KiGGS survey is supplemented by the MoMo study, an in-depth study to assess the physical activity and motor performance of children and adolescents living in Germany that is being conducted by the Karlsruhe Institute of Technology. MoMo is being carried out with a subsample of KiGGS participants, as described in [19,20]. The KiGGS team established temporary study centers in 167 sample points all over Germany. Participants aged 0 to 17 years were randomly chosen from 167 registration offices and invited for interviews, physical examinations, and laboratory tests. At the study centers, KiGGS participants were asked if they were willing to participate in the MoMo study. If they consented, the interviews and physical examinations for the MoMo study took place approximately six to eight weeks later.

To date, three assessments have been conducted in KiGGS and MoMo: baseline (2003-2006; sample sizes: KiGGS n=17,641; ages: 0 to 17 years; MoMo, n=4528; ages: 4 to 17 years), the first follow-up (wave 1) between 2009 and 2012 (sample sizes: KiGGS, n=12,368; ages: 0 to 17 years; MoMo, n=5106; ages: 4 to 23 years), and the second follow-up (wave 2) between 2014 and 2017 (sample sizes: KiGGS, n=15,023; ages: 0 to 17 years; MoMo, n=5689; ages: 4 to 30 years). Wave 3 of the MoMo Study is currently underway (2018-2020; compare [19-22]). For the follow-up surveys (waves 1, 2, and 3), participants in the baseline survey were reinvited (longitudinal subjects). In addition, for cross-sectional analysis, a new sample of children aged 0 to 6 years was drawn in KiGGS wave 1, and in wave 2, a new sample of participants aged 0 to 17 years was drawn. For detailed sample sizes, see [19,20]. In KiGGS and MoMo wave 2 (2014-2017), accelerometry was used for the first time in this study to measure physical activity.

Accelerometer Sample

In KiGGS wave 2, all longitudinal participants aged ≥10 years (n=6465) were included in the accelerometer sample. In MoMo wave 2, all cross-sectional participants (n=4538) in the MoMo wave 2 sample who did not receive an accelerometer in KiGGS wave 2 were asked to wear one (Figure 1). Thus, a total of 11,003 participants were asked to wear an accelerometer. Participants who had impairments that prevented them from wearing an accelerometer were excluded. Participants who dropped out (did not agree to wear an accelerometer or experienced technical problems) in the MoMo and KiGGS studies are listed in Table 1 and Table 2, respectively.

Figure 1. MoMo study design with the accelerometer sample in wave 2. MoMo: Motorik-Modul.

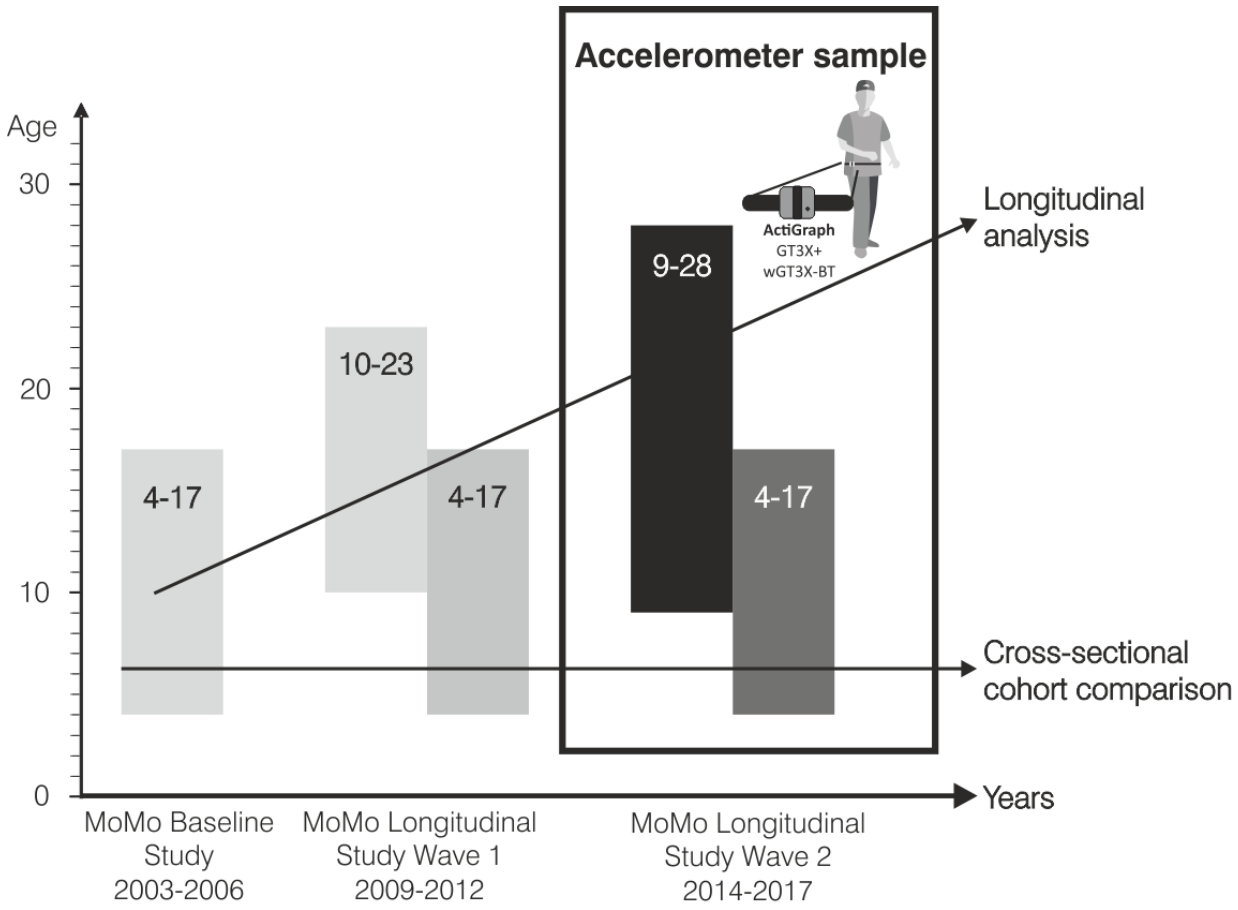

Table 1. Details of the MoMo study participants asked to wear an accelerometer (N=4538), n (%).

Participation	Participants
Agreed to wear an accelerometer	2105 (46.4)
Dropped out because they did not agree to wear an accelerometer	2433 (53.6)
Downloaded accelerometer records	1974 (43.5)
Dropped out due to technical problems or did not wear the accelerometer	131 (2.9)

Table 2. Details of the KiGGS study participants asked to wear an accelerometer (N=6465), n (%).

Participation	Participants
Agreed to wear an accelerometer	5040 (78.0)
Dropped out because they did not agree to wear an accelerometer	1425 (22.0)
Downloaded accelerometer records	4750 (73.5)
Dropped out due to technical problems or did not wear the accelerometer	426 (6.6)

Types of Accelerometers

In KiGGS and MoMo wave 2, ActiGraph accelerometers (models: GT3X+ and wGT3X-BT) were used to enable comparison with other large-scale European studies [10,13]. The heart rate monitor and Bluetooth wireless interface of each accelerometer were both deactivated during testing. The accelerometers were equipped with a tri-axial acceleration sensor (range: ±6g, sensitivity: 3mg, axes: horizontal right-left (x), vertical (y), and horizontal front-back (z)); they could record acceleration data at rates ranging from 30-100 Hertz and store it in epoch lengths from 1-240 seconds (compare with [23]). The settings are described in the "Initializing the Devices" section. The physical dimensions of the devices were 4.6×3.3×1×5 centimeters, their weight was 19 grams, and they used a rechargeable lithium polymer battery.

Assessment Period and Registration Protocol

MoMo and KiGGS accelerometer data sets were considered valid with a minimum wear time of 8 hours of recordings on 4

weekdays and 1 weekend day. These scoring policies are also consistent with the requirements for inclusion in the International Children's Accelerometry Database (ICAD) [24]. Additionally, literature suggests that 4 days is a reasonable measurement time, thereby reducing the burden on participants and making it easier for researchers to collect sufficient data for the formation of recommendations related to general health guidelines [25-28]. To archive the highest possible number of valid data sets, the accelerometer should be worn for 7 days (8 days in the MoMo study) following the day of the examination in the study center. The assessment period of at least seven days ensured the inclusion of weekdays and weekend days. This inclusion is recommended due to differences in physical activity during the week and on weekends [25,29,30].

An additional analysis was planned of data sets with 10 or more hours of recording on each of the 5-7 days. This analysis was included because recent studies [30-33] propose the use of longer accelerometer wear times in hours and days to provide better estimates of daily activity.

The accelerometer should only be removed at bedtime, during activities that risk damaging the device (eg, martial arts), or when the participant is exposed to water (eg, swimming and showering).

Initializing the Devices: Epoch Length, Sampling Frequency, and Filter

Each ActiGraph activity monitor was initialized using a standardized procedure prior to being given to the participant. The monitors used the latest firmware (v1.9.2. for wGT3X-BT and v3.2.1 for GT3X+), a unique output filename, and a sampling frequency of 30 Hz. In research with adults, the accelerometer signal was processed in epoch lengths of 10-60 seconds. Due to the sporadic activity of children, an epoch length between 1 and 5 seconds or the shortest possible epoch length is recommended [16,34-36]. The ActiGraph models used in the KiGGS and MoMo study store the collected raw data. Furthermore, the data are downloaded in epoch lengths of 1 second, reducing memory space and enabling faster data processing afterward. The devices can be used with two different filters when processing the data: a normal filter and a low-frequency extension filter (the implementation and algorithms of the filters are not open to the public). It is known that the normal filter detects accelerations in a range of 0.25-2.5 Hz [37]. To capture slower movements, the low-frequency extension filter establishes an unknown lower threshold [23]. While performing physical activity in a vigorous state, the human body produces accelerations at the hip up to 3.4 Hz [38,39]. Even higher frequencies were documented in the wrist when performing physical activity [40,41]. Considering these limitations, the normal filter was configured to recognize as many accelerations as possible.

In KiGGS, the device was set up to start measurement at 12:00 AM the day after the examination and to stop the measurement at midnight after 7 days of recording. A pilot study prior to data collection in MoMo revealed that many participants were confused by the standard "no flashing" mode of the ActiGraph device while recording. Therefore, "flash mode," in which the device showed a green flashing light-emitting diode (LED), was activated during recording. In MoMo, the device was programmed to start at 12:00 AM on the day the participants underwent their motor performance tests to avoid the "no flashing" confusion noted above. The measurement stopped at midnight after 8 days of recording. In the MoMo study, the recordings of the first day were not considered for data analysis because the participants received the devices at different times throughout the day depending on the initial timing of their examination. Additionally, the first day served as an adaptation period for the participants.

Placement of the Device

In KiGGS and MoMo, the device was placed laterally on top of the right anterior superior iliac spine with the closure on top, then secured with an elastic belt (see Figure 2). Compared to wrist attachment of the device, the hip monitor placement provides better acceleration detection due to the limited frequency range of the normal ActiGraph filter. The higher movement frequencies at the wrist would be out of the range of that filter. Moreover, most cut points for intensity estimation are validated with the device placed on the hip [16,41-43], and it is the most common carrying position for accelerometers [44]. More importantly, studies show more accurate classification of intensities when the device is placed on the hip than on the wrist [16,41,42,45,46].

Figure 2. Participant wearing an accelerometer device on top of the right anterior superior iliac spine.

Nonwear Time Protocol (Logbook)

The accelerometer can only capture accelerations when it is worn; therefore, detailed information about the type of activity and the reasons for not wearing the devices is needed for complete understanding of the assessed physical activity. Therefore, participants were asked to complete a nonwear time protocol (see Figure 3). The combination of self-reports and device-based measures enables better understanding of physical activity behavior [47]. When both self-reported and device-based measured physical activity assessments are available, it is also possible to cross-validate the nonwear time calculated by the algorithms and the self-reported nonwear time. With information about the reasons for not wearing the device, statistics can be created for activities that were not captured and adjustment factors can be calculated.

Figure 3. Sample MoMo wear-time-protocol (translated).

Subject-ID: __ __ __ __ __ __ **Activity wear time protocol**

	Got up in the morning	Accelerometer applied (in the morning)	Gone to bed	Accelerometer put down (in the evening)	Not worn		Activity during unsupported time	Special Events
		(e.g. 8.30 am)	(e.g. 21.30 pm)	(e.g. 22.00 pm)	from	to		
Example Day 1 Date: 20.01.2014	7:00 AM	7:15 AM	10:00 PM	10:15 PM	6:00 PM	7:00 PM	Injury risk at judo	
					7:20 PM	7:45 PM	Showering	

Transfer and Return of the Devices

Trained study assistants at the study centers distributed the devices. The participants chose the appropriate belt size and were shown how to wear the device correctly. Important aspects of wearing the accelerometer (placement, wear times, and return of the device) were summarized in an information sheet that was provided to the participants. At the end of the measurement period, the device, belt, and protocol were returned by mail. Therefore, an addressed and stamped envelope was provided to the participants. A follow-up protocol was implemented by telephone if the devices were not returned after 2 weeks.

Data Download and Preparation

After receiving the devices, the data were downloaded as gt3x files using ActiLife Version 6.13.3 software (ActiGraph). The MoMo team marked all data sets with less than 4+1 days of wear time as invalid. In addition, ActiGraphData (AGD) files with data for all 3 axes and an epoch length of 1 second were created for data analysis. These data sets (1 second epoch length) can be converted into data sets with other epoch lengths, which enables comparison with studies using different data analysis protocols [42,43,48-52]. This is a faster way of processing the data than converting the raw data files (*.gt3x) to data files (*.agd) with different epoch lengths. Additionally, the time saved during the calculation is enormous when analyzing large data sets of several thousand participants. The resulting data sets would be the same. The gt3x files were stored separately to allow more in-depth analysis of the raw data after the planned evaluations (eg, with the GGIR software package [53]).

Planned Data Processing

To ensure comparability with studies already included in the ICAD [24], we decided to conduct the analysis using the ActiGraph "count" system first. Before data analysis, data regarding nonwear time must be preprocessed. Therefore, the wear time values from the nonwear time protocols were compared with the calculated values of different nonwear time algorithms. The algorithms invented by Choi [51] and Troiano [52] were considered for the determination of wear time in this study. The Choi algorithm using a 90-minute window (±30 minutes) for capturing nonwear time was found to be the most practical because there is no need for 24-hour recording and the other nonwear time algorithms with a 60-minute window found too many incorrectly classified nonwear times [54]. Additionally, the nonwear time as identified by Choi is independent of the used epoch length [55].

Different cut points for physical activity intensity classification were calibrated for different epoch lengths. The most frequently used cut points were based on 1-second [42,48], on 15-second [43,49], or on 60-second [50,56] epochs. In our analysis, different cut points for intensity classification will be used for different age groups because the age range of the study sample includes children, adolescents, and adults (6-27 years). The cut points from Evenson [49] for participants aged 6 to 8 years, Hänggi [42] for participants aged 9 to 11 years, Romanzini [43] for participants aged 12 to 19 years, and Sasaki [48] for adult participants are currently under consideration. A summary of the accelerometer data processing criteria (suggested by Migueles et al [16], 2017) can be found in Table 3.

Table 3. List of accelerometer data processing criteria in KiGGS and MoMo (suggested by Migueles et al [16]).

Accelerometer data processing criterion	Definition in this study
Placement of the device	Laterally on top of the right anterior superior iliac spine
Sampling frequency	30 hertz
Filter	Normal ActiGraph GT3X filter
Epoch lengths	1 second with possibility to convert to 5, 10, 15, 30, and 60 seconds
Nonwear time definition	Choi et al 2011 [51]: 90-minute time window for consecutive zero/nonzero counts; allowance of 2-minute intervals of nonzero counts with an up/downstream 30-minute consecutive zero counts window
Valid days/valid weeks	8 hours of recording on at least four weekdays and one additional weekend day
Population age range	6-27 years (children, adolescents, and young adults)
Sedentary and physical activity intensity classification and cut point algorithms[a]	6-8 years: Evenson et al 2008 [49] 9-11 years: Hängii et al 2013 [42] 12-18 years: Romanzini et al 2014 [43] Young adults: Sasaki et al 2011 [48]

[a]To be determined; definitions listed are under consideration.

Results

Data collection was completed in October 2017, and data harmonization was performed in 2018. The first accelerometer results from this wave were published in 2019 [57-59]. Detailed analyses are ready to be submitted in 2020.

First, data analysis should focus on gender and age differences of daily physical activity levels as well as compliance with the physical activity recommendations by the World Health Organization (WHO). Furthermore, we plan to perform in-depth analysis of the associations between physical activity and different health-related parameters (eg, obesity) and socioeconomic parameters (eg, education) by considering various data mining methods. This includes investigation of crosslinks and trends between questionnaires and device-based collected activity data (eg, physical activity differences between groups in both data sets).

Discussion

Summary

Currently, there are different concepts of collecting and processing accelerometer data for the assessment of physical activity among children and adolescents [16]. Many studies do not provide detailed descriptions of their data collection and data handling processes. This complicates replication of and comparability between studies. Therefore, the purposes of this study protocol were to explain the challenges faced when using accelerometers in the MoMo and KiGGS studies as an example of a large-scale epidemiological study and to detail the methods and protocols used to capture physical activity in children and adolescents with accelerometers in Germany.

Strengths

This study protocol provides an extensive list of considerations for measuring physical activity and sedentary behavior by accelerometry in a large sample. These include technical details of the device used and the reasoning behind the device choice, the reasoning behind the a priori data collection proceedings (assessment period and registration protocol, device

initialization, device placement, nonwear time protocol), and the data processing methods. Furthermore, thoughts on feasibility issues (transfer and return of the devices, data download and preparation) are provided. Researchers planning similar studies are given all the information needed for replication. This enables comparability to other large European studies such as the European Youth Heart Study [10] and the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) Study [13,36,60] due to similarities in methodology.

A multimodal approach of using self-reports and accelerometers is recommended [61] and can combine the advantages of the different methods (eg, precision and breadth of detection) because no single procedure provides optimal detection in all situations. The MoMo-PAQ was developed to measure habitual physical activity in general, while the current physical activity was measured by accelerometers over 1 week. Combining these two methods of assessing physical activity provides the opportunity to present a more comprehensive picture of the actual participant's physical activity and can provide a basis for planning health-enhancing physical activity programs for specific target groups.

Challenges

Although ActiGraph accelerometers are being used in many studies to record physical activity, there are technical issues associated with these devices; therefore, their limitations must be considered. The usage of the normal ActiGraph filter removes signals with a frequency greater than 2.5 Hz. However, while performing vigorous physical activity, the human body produces accelerations at the hip up to a frequency of 3.4 Hz [38,39]. Due to this limitation, activities with higher movement frequencies (ie, in the vigorous activity spectrum) may not be assessed correctly. In the context of MoMo and KiGGS, this will not be an issue because all activities in this frequency range will be classified as vigorous, and more detailed investigations are currently not planned. However, evaluating physical activity based on raw data is recommended for unbiased data processing that conforms to the open science approach. This requires more complex and advanced algorithms and evaluation methods. The first applied analysis will resort to a comparable evaluation with counts; however, future discussions on this topic are needed [62,63], and complex data analysis methods must be adapted.

Although unstructured and irregular everyday activities are recorded more accurately by accelerometers than by questionnaires, there are still improvements to be made. Devices can only measure physical activity when they are worn. Therefore, physical activity that occurs during nonwear time is not included in the data sets. This creates a need for methods that include additional information from these nonwear times, such as a nonwear time protocol that adjusts for the missing physical activity.

Taking into account the wide range of ages in the sample, different cut points and epoch lengths are suitable for the data in this study; however, calibration studies for such a broad sample do not exist. This leads to issues with accuracy of the data when only using one calibration study or to comparability issues within the sample when using multiple calibration studies for different subsets of the sample.

Implications and Perspectives

For future waves of data collection, the nonwear time protocol should be improved. The frequency of reasons for nonwear must be analyzed so that the wearing instructions can be refined. This could potentially increase the wear time of the devices. Furthermore, the nonwear time protocol should assess the intensities of physical activity more precisely during nonwear times. This would lead to a more complete assessment of all occurring physical activity, and more detailed feedback could be given to the participants. Future studies should examine the accuracy of different algorithms for detecting nonwear times for different age groups [16]. The impact of different thresholds for physical activity intensity classification and of choosing the right epoch length for the target population based on age will be of interest as long as proprietary counts are used. Therefore, it is recommended to analyze multiple implemented cut point algorithms and identify the one that best fits the sample at hand.

Both methods of assessing physical activity should be compared between different target groups. Moreover, the adherence to physical activity recommendations by the WHO should be examined.

Conclusion

This study protocol will help researchers obtain an overview of the decisions for the methods and protocols used to assess device-based physical activity in children and adolescents with accelerometers in Germany.

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Conflicts of Interest

None declared.

References

1. Cain KL, Sallis JF, Conway TL, Van Dyck D, Calhoon L. Using accelerometers in youth physical activity studies: a review of methods. J Phys Act Health 2013 Mar;10(3):437-450 [FREE Full text] [doi: 10.1123/jpah.10.3.437] [Medline: 23620392]
2. Ekelund U, Yngve A, Brage S, Westerterp K, Sjöström M. Body movement and physical activity energy expenditure in children and adolescents: how to adjust for differences in body size and age. Am J Clin Nutr 2004 May;79(5):851-856. [doi: 10.1093/ajcn/79.5.851] [Medline: 15113725]
3. Gabrys L, Thiel C, Tallner A, Wilms B, Müller C, Kahlert D, et al. Akzelerometrie zur Erfassung körperlicher Aktivität. Sportwiss 2014 Oct 28;45(1):1-9. [doi: 10.1007/s12662-014-0349-5]
4. Rowlands AV, Eston RG. The Measurement and Interpretation of Children's Physical Activity. J Sports Sci Med 2007 Sep 01;6(3):270-276 [FREE Full text] [Medline: 24149412]
5. Graf C, Beneke R, Bloch W, Bucksch J, Dordel S, Eiser S, et al. Vorschläge zur Förderung der körperlichen Aktivität von Kindern und Jugendlichen in Deutschland. Monatsschr Kinderheilkd 2013 Apr 13;161(5):439-446. [doi: 10.1007/s00112-012-2863-6]
6. Müller C, Winter C, Mogwitz M, Rosenbaum D. Validierung von neun Bewegungssensoren bei Kindern und jungen Erwachsenen. Sportwiss 2011 Feb 10;41(1):8-15. [doi: 10.1007/s12662-011-0167-y]
7. Jekauc D, Wagner MO, Kahlert D, Woll A. Reliabilität und Validität des MoMo-Aktivitätsfragebogens für Jugendliche (MoMo-AFB). Diagnostica 2013 Apr;59(2):100-111. [doi: 10.1026/0012-1924/a000083]
8. Wijndaele K, Westgate K, Stephens SK, Blair AN, Bull FC, Chastin SFM, et al. Utilization and Harmonization of Adult Accelerometry Data: Review and Expert Consensus. Med Sci Sports Exerc 2015 Oct;47(10):2129-2139 [FREE Full text] [doi: 10.1249/MSS.0000000000000661] [Medline: 25785929]
9. Slootmaker SM, Schuit AJ, Chinapaw MJ, Seidell JC, van Mechelen W. Disagreement in physical activity assessed by accelerometer and self-report in subgroups of age, gender, education and weight status. Int J Behav Nutr Phys Act 2009 Mar 25;6:17 [FREE Full text] [doi: 10.1186/1479-5868-6-17] [Medline: 19320985]
10. Riddoch CJ, Bo Andersen L, Wedderkopp N, Harro M, Klasson-Heggebø L, Sardinha LB, et al. Physical activity levels and patterns of 9- and 15-yr-old European children. Med Sci Sports Exerc 2004 Jan;36(1):86-92. [doi: 10.1249/01.MSS.0000106174.43932.92] [Medline: 14707773]
11. Wanner M, Richard A, Martin B, Faeh D, Rohrmann S. Associations between self-reported and objectively measured physical activity, sedentary behavior and overweight/obesity in NHANES 2003-2006. Int J Obes (Lond) 2017 Jan;41(1):186-193. [doi: 10.1038/ijo.2016.168] [Medline: 27677618]
12. Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for physical activity research. Br J Sports Med 2014 Jul;48(13):1019-1023 [FREE Full text] [doi: 10.1136/bjsports-2014-093546] [Medline: 24782483]
13. Ruiz JR, Ortega FB, Martínez-Gómez D, Labayen I, Moreno LA, De Bourdeaudhuij I, HELENA Study Group. Objectively measured physical activity and sedentary time in European adolescents: the HELENA study. Am J Epidemiol 2011 Jul 15;174(2):173-184. [doi: 10.1093/aje/kwr068] [Medline: 21467152]
14. Schaefer CA, Nigg CR, Hill JO, Brink LA, Browning RC. Establishing and evaluating wrist cutpoints for the GENEActiv accelerometer in youth. Med Sci Sports Exerc 2014 Apr;46(4):826-833 [FREE Full text] [doi: 10.1249/MSS.0000000000000150] [Medline: 24121241]
15. Ettienne R, Nigg CR, Li F, Su Y, McGlone K, Luick B, et al. Validation of the Actical Accelerometer in Multiethnic Preschoolers: The Children's Healthy Living (CHL) Program. Hawaii J Med Public Health 2016 Apr;75(4):95-100 [FREE Full text] [Medline: 27099804]
16. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sports Med 2017 Sep;47(9):1821-1845 [FREE Full text] [doi: 10.1007/s40279-017-0716-0] [Medline: 28303543]
17. Tudor-Locke C, Ainsworth BE, Adair LS, Popkin BM. Physical activity in Filipino youth: the Cebu Longitudinal Health and Nutrition Survey. Int J Obes Relat Metab Disord 2003 Feb;27(2):181-190. [doi: 10.1038/sj.ijo.802207] [Medline: 12586997]
18. Kurth B, Kamtsiuris P, Hölling H, Schlaud M, Dölle R, Ellert U, et al. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. BMC Public Health 2008 Jun 04;8:196 [FREE Full text] [doi: 10.1186/1471-2458-8-196] [Medline: 18533019]
19. Wagner MO, Bös K, Jekauc D, Karger C, Mewes N, Oberger J, et al. Cohort profile: the Motorik-Modul Longitudinal Study: physical fitness and physical activity as determinants of health development in German children and adolescents. Int J Epidemiol 2014 Oct;43(5):1410-1416. [doi: 10.1093/ije/dyt098] [Medline: 23847291]
20. Woll A, Albrecht C, Worth A. Motorik-Module (MoMo) – the KiGGS Wave 2 module to survey motor performance and physical activity. Journal of Health Monitoring 2017;2(53) [FREE Full text] [doi: 10.17886/rki-gbe-2017-110]
21. Mauz E, Gößwald A, Kamtsiuris P, Hoffmann R, Lange M, Schenck U, et al. Neue Daten für Taten. Die Datenerhebung zur KiGGS Welle 2 ist beendet. Journal of Health Monitoring 2017;02(53). [doi: 10.17886/RKI-GBE-2017-099]
22. Worth A, Woll A, Albrecht C, Karger C, Mewes N, Oberger J, et al. MoMo-Längsschnittstudie "Physical Fitness and Physical Activity as Determinants of Health Development in Children and Adolescents" : Testmanual zu den motorischen Tests und den anthropometrischen Messungen. In: KIT Scientific Reports. Karlsruhe: KIT Scientific Publishing; 2015.

23. ActiGraph. 2013. GT3X+ and wGT3X+ Device Manual URL: http://s3.amazonaws.com/actigraphcorp.com/wp-content/uploads/2018/02/22094126/GT3X-wGT3X-Device-Manual-110315.pdf [accessed 2020-05-27]
24. Sherar LB, Griew P, Esliger DW, Cooper AR, Ekelund U, Judge K, et al. International children's accelerometry database (ICAD): design and methods. BMC Public Health 2011 Jun 21;11:485 [FREE Full text] [doi: 10.1186/1471-2458-11-485] [Medline: 21693008]
25. Matthews CE, Ainsworth BE, Thompson RW, Bassett DR. Sources of variance in daily physical activity levels as measured by an accelerometer. Med Sci Sports Exerc 2002 Aug;34(8):1376-1381. [doi: 10.1097/00005768-200208000-00021] [Medline: 12165695]
26. Toftager M, Kristensen P, Oliver M, Duncan S, Christiansen L, Boyle E, et al. Accelerometer data reduction in adolescents: effects on sample retention and bias. Int J Behav Nutr Phys Act 2013 Dec 23;10:140 [FREE Full text] [doi: 10.1186/1479-5868-10-140] [Medline: 24359480]
27. Mâsse LC, Fuemmeler BF, Anderson CB, Matthews CE, Trost SG, Catellier DJ, et al. Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables. Med Sci Sports Exerc 2005 Nov;37(11 Suppl):S544-S554. [doi: 10.1249/01.mss.0000185674.09066.8a] [Medline: 16294117]
28. Colley R, Connor Gorber S, Tremblay MS. Quality control and data reduction procedures for accelerometry-derived measures of physical activity. Health Rep 2010 Mar;21(1):63-69 [FREE Full text] [Medline: 20426228]
29. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Med Sci Sports Exerc 2005 Nov;37(11 Suppl):S531-S543. [doi: 10.1249/01.mss.0000185657.86065.98] [Medline: 16294116]
30. Donaldson SC, Montoye AHK, Tuttle MS, Kaminsky LA. Variability of Objectively Measured Sedentary Behavior. Med Sci Sports Exerc 2016 Apr;48(4):755-761. [doi: 10.1249/MSS.0000000000000828] [Medline: 26606270]
31. Herrmann SD, Barreira TV, Kang M, Ainsworth BE. How many hours are enough? Accelerometer wear time may provide bias in daily activity estimates. J Phys Act Health 2013 Jul;10(5):742-749. [doi: 10.1123/jpah.10.5.742] [Medline: 23036822]
32. Aadland E, Ylvisåker E. Reliability of Objectively Measured Sedentary Time and Physical Activity in Adults. PLoS One 2015;10(7):e0133296 [FREE Full text] [doi: 10.1371/journal.pone.0133296] [Medline: 26192184]
33. Warren JM, Ekelund U, Besson H, Mezzani A, Geladas N, Vanhees L, Experts Panel. Assessment of physical activity - a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 2010 Apr;17(2):127-139. [doi: 10.1097/HJR.0b013e32832ed875] [Medline: 20215971]
34. Bornstein DB, Beets MW, Byun W, McIver K. Accelerometer-derived physical activity levels of preschoolers: a meta-analysis. J Sci Med Sport 2011 Nov;14(6):504-511. [doi: 10.1016/j.jsams.2011.05.007] [Medline: 21684809]
35. Edwardson CL, Gorely T. Epoch length and its effect on physical activity intensity. Med Sci Sports Exerc 2010 May;42(5):928-934. [doi: 10.1249/MSS.0b013e3181c301f5] [Medline: 19996997]
36. Vanhelst J, Béghin L, Duhamel A, Bergman P, Sjöström M, Gottrand F. Comparison of uniaxial and triaxial accelerometry in the assessment of physical activity among adolescents under free-living conditions: the HELENA study. BMC Med Res Methodol 2012 Mar 12;12:26 [FREE Full text] [doi: 10.1186/1471-2288-12-26] [Medline: 22409718]
37. Tryon WW, Williams R. Fully proportional actigraphy: A new instrument. Behav Res Methods Instrum Comput 1996 Sep;28(3):392-403. [doi: 10.3758/BF03200519]
38. Cavagna GA, Franzetti P. The determinants of the step frequency in walking in humans. J Physiol 1986 Apr;373:235-242 [FREE Full text] [doi: 10.1113/jphysiol.1986.sp016044] [Medline: 3746673]
39. Cavagna GA, Willems PA, Franzetti P, Detrembleur C. The two power limits conditioning step frequency in human running. J Physiol 1991 Jun;437:95-108 [FREE Full text] [doi: 10.1113/jphysiol.1991.sp018586] [Medline: 1890660]
40. Fairclough SJ, Noonan R, Rowlands AV, Van Hees V, Knowles Z, Boddy LM. Wear Compliance and Activity in Children Wearing Wrist- and Hip-Mounted Accelerometers. Med Sci Sports Exerc 2016 Feb;48(2):245-253. [doi: 10.1249/MSS.0000000000000771] [Medline: 26375253]
41. Hildebrand M, VAN Hees VT, Hansen BJ, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. Med Sci Sports Exerc 2014 Sep;46(9):1816-1824. [doi: 10.1249/MSS.0000000000000289] [Medline: 24887173]
42. Hänggi JM, Phillips LR, Rowlands AV. Validation of the GT3X ActiGraph in children and comparison with the GT1M ActiGraph. J Sci Med Sport 2013 Jan;16(1):40-44. [doi: 10.1016/j.jsams.2012.05.012] [Medline: 22749938]
43. Romanzini M, Petroski EL, Ohara D, Dourado AC, Reichert FF. Calibration of ActiGraph GT3X, Actical and RT3 accelerometers in adolescents. Eur J Sport Sci 2014;14(1):91-99. [doi: 10.1080/17461391.2012.732614] [Medline: 24533499]
44. Panagiota A, Shammas L, Hey S. Assessment of human gait speed and energy expenditure using a single triaxial accelerometer. 2020 May 17 Presented at: Ninth International Conference on Wearable and Implantable Body Sensor Networks; 9-12 May 2012; London, UK. [doi: 10.1109/BSN.2012.7]
45. Crouter SE, Flynn JI, Bassett DR. Estimating physical activity in youth using a wrist accelerometer. Med Sci Sports Exerc 2015 May;47(5):944-951 [FREE Full text] [doi: 10.1249/MSS.0000000000000502] [Medline: 25207928]
46. Stec MJ, Rawson ES. Estimation of resistance exercise energy expenditure using triaxial accelerometry. J Strength Cond Res 2012 May;26(5):1413-1422. [doi: 10.1519/JSC.0b013e318248d7b4] [Medline: 22222328]

47. Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. Res Q Exerc Sport 2000 Jun;71 Suppl 2:1-14. [doi: 10.1080/02701367.2000.11082780] [Medline: 25680007]
48. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport 2011 Sep;14(5):411-416. [doi: 10.1016/j.jsams.2011.04.003] [Medline: 21616714]
49. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci 2008 Dec 15;26(14):1557-1565. [doi: 10.1080/02640410802334196]
50. Freedson PS, Lyden K, Kozey-Keadle S, Staudenmayer J. Evaluation of artificial neural network algorithms for predicting METs and activity type from accelerometer data: validation on an independent sample. J Appl Physiol (1985) 2011 Dec;111(6):1804-1812 [FREE Full text] [doi: 10.1152/japplphysiol.00309.2011] [Medline: 21885802]
51. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc 2011 Feb;43(2):357-364 [FREE Full text] [doi: 10.1249/MSS.0b013e3181ed61a3] [Medline: 20581716]
52. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008 Jan;40(1):181-188. [doi: 10.1249/mss.0b013e31815a51b3] [Medline: 18091006]
53. van Hees V, Fang Z, Mirkes E, Heywood J, Zhao JH, Joan CP, et al. Zenodo. 2019. GGIR URL: https://zenodo.org/record/3779893#.Xs66ahNKjfu [accessed 2020-05-27]
54. Jaeschke L, Luzak A, Steinbrecher A, Jeran S, Ferland M, Linkohr B, et al. 24 h-accelerometry in epidemiological studies: automated detection of non-wear time in comparison to diary information. Sci Rep 2017 May 22;7(1):2227 [FREE Full text] [doi: 10.1038/s41598-017-01092-w] [Medline: 28533553]
55. Anedda B, Niessner C, Burchartz A, Oriwol D, Schmidt S, Woll A. Processing accelerometer data of children and adolescents - influence of wear time algorithm, epoch length and cut-off points on age specific subgroups. In: Book of Abstracts of the 23rd Annual Congress of the European College of Sport Science. European College of Sport Science: Book of Abstracts of the 23rd Annual Congress of the European College of Sport Science, 129; 2018 Presented at: 23rd Annual Congress of the European College of Sport Science; July 4-7, 2018; Dublin, Ireland.
56. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998 May;30(5):777-781. [doi: 10.1097/00005768-199805000-00021] [Medline: 9588623]
57. Woll A, Oriwol D, Anedda B, Burchartz A, Hanssen-Doose A, Kopp M, et al. Körperliche Aktivität, motorische Leistungsfähigkeit und Gesundheit in Deutschland: Ergebnisse aus der Motorik-Modul-Längsschnittstudie (MoMo). KIT Scientific Working Papers 2019 Mar 06. [doi: 10.5445/IR/1000095369]
58. Burchartz A, Anedda B, Oriwol D, Kolb S, Schmidt SC, Woll A. Erreichen Kinder und Jugendliche in Deutschland die WHO-Richtlinien für körperliche Aktivität: - erhoben durch Akzelerometer und Fragebogen. In: Schriften der Deutschen Vereinigung für Sportwissenschaft: Vol. 282. Hamburg: Feldhaus; 2019 Presented at: Sport im öffentlichen Raum: 24 dvs-Hochschultag; September 18-20, 2019; Berlin p. 324. [doi: 10.13140/RG.2.2.33511.60322]
59. Anedda B, Burchartz A, Kolb S, Oriwol D, Schmidt SC, Woll A. Untersuchung von Korrelaten der körperlich-sportlichen Aktivität von Kindern und Jugendlichen in Deutschland - Ergebnisse aus Welle 2 der Motorik-Modul-Studie (MoMo). In: Schriften der Deutschen Vereinigung für Sportwissenschaft: Vol. 282. Hamburg: Feldhaus; 2019 Presented at: Sport im öffentlichen Raum: 24 dvs-Hochschultag; September 18-20, 2019; Berlin p. 151.
60. Vicente-Rodriguez G, Libersa C, Mesana MI, Béghin L, Iliescu C, Aznar LAM, et al. Healthy Lifestyle by Nutrition in Adolescence (HELENA). A New EU Funded Project. Therapies 2007 May;62(3):259-270. [doi: 10.2515/therapie:2007050]
61. Jekauc D, Reimers A, Woll A. Methoden der Aktivitätsmessung bei Kindern und Jugendlichen. B & G 2014 Apr 17;30(02):79-82. [doi: 10.1055/s-0033-1361578]
62. Hill H, Ottenbacher J, Ebner-Priemer U. What counts count… A comparison of count and movement acceleration intensity data in the assessment of physical activity. 2015 Jun 25 Presented at: Fourth biennial conference of the Society for Ambulatory Assessment; June 24-27, 2015; State College, PA, USA.
63. Brønd JC, Arvidsson D. Sampling frequency affects the processing of Actigraph raw acceleration data to activity counts. J Appl Physiol (1985) 2016 Feb 01;120(3):362-369 [FREE Full text] [doi: 10.1152/japplphysiol.00628.2015] [Medline: 26635347]

Abbreviations

AGD: ActiGraphData
HELENA: Healthy Lifestyle in Europe by Nutrition in Adolescence
ICAD: International Children's Accelerometry Database
KiGGS: German Health Interview and Examination Survey for Children and Adolescents
LED: light-emitting diode
MoMo: Motorik-Modul
PAQ: physical activity questionnaire
WHO: World Health Organization

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Protocol

The Identification of Native Epitopes Eliciting a Protective High-Affinity Immunoglobulin Subclass Response to Blood Stages of Plasmodium falciparum: Protocol for Observational Studies

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Abstract

Background: Antibodies to blood stages protective against complications of *Plasmodium falciparum* infection were found to be of immunoglobulin G 1 (IgG1) and IgG3 subclasses and of high affinity to the target epitopes. These target epitopes cannot be characterized using recombinant antigens because of a lack of appropriate glycosylation, phosphorylation, methylation, and bisulfide bond formation, which determine the structure of conformational and nonlinear epitopes within the tertiary and quaternary structures of native *P. falciparum* antigens.

Objective: This study aims to develop a method for the comprehensive detection of all *P. falciparum* schizont antigens, eliciting a protective immune response.

Methods: Purified parasitophorous vacuole membrane–enclosed merozoite structures (PEMSs) containing native schizont antigens are initially generated, separated by two-dimensional (2D) gel electrophoresis and blotted onto nitrocellulose. Antigens eliciting a protective antibody response are visualized by incubation with sera from patients with clinical immunity. This is followed by the elution of low-affinity antibodies with urea and detection of protective antibody responses by incubation with anti-IgG1 and anti-IgG3 antibodies, which were conjugated to horseradish peroxidase. This is followed by visualization with a color reaction. Blot signals are normalized by relating to the intensity of blot staining with a reference antibody and housekeeping antigens. Results are corrected for intensity of exposure by the relation of antibody responses to global *P. falciparum* antibody titers. Antigens eliciting the protective responses are identified as immunorelevant from the comparison of spot positions, indicating high-affinity IgG1 or IgG3 responses on the western blot, which is unique to or consistently more intensive in clinically immune individuals compared with nonimmune individuals. The results obtained are validated by using affinity chromatography.

Results: Another group previously applied 2D western blotting to analyze antibody responses to *P. falciparum*. The sera of patients allowed the detection of 42 antigenic spots on the 2D immunoblot. The spots detected were excised and subjected to mass spectrometry for identification. A total of 19 protein spots were successfully identified and corresponded to 13 distinct proteins. Another group used immunoaffinity chromatography to identify antigens bound by IgGs produced by mice with enhanced immunity to *Plasmodium yoelii*. Immunorelevant antigens were isolated and identified by immobilizing immunoglobulin from immune mice to a Sephadex column and then passing a blood-stage antigen mixture through the column followed by the elution of specific bound antigens with sodium deoxycholate and the identification of those antigens by western blotting with specific antibodies.

Conclusions: 2D western blotting using native antigens has the potential to identify antibody responses selective for specific defined isomeric forms of the same protein, including isoforms (*protein species*) generated by posttranscriptional modifications such as phosphorylation, glycosylation, and methylation. The process involved in 2D western blotting enables highly sensitive detection, high resolution, and preservation of antibody responses during blotting. Validation by immunoaffinity chromatography can compensate for the antigen loss associated with the blotting process. It has the potential for indirect quantification of protective antibody responses by enabling quantification of the amount of eluted antibody bound antigens through mass spectrometry.

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KEYWORDS

proteome; immunome; 2D electrophoresis; Plasmodium falciparum; immunoglobulin; affinity; avidity; western blot; conformational epitope; nonlinear epitope

Introduction

Analysis of Immune Responses to Native *Plasmodium falciparum* Antigens

Previously, the transfer of gamma globulins from immune Gambian adults to children with *Plasmodium falciparum* malaria resulted in a reduction of the parasite count to <1% of the initial value and a progressive reduction of clinical symptoms [1]. Antigens from a schizont preparation were selectively precipitated by using an African immune serum [2,3]. This method did not allow the identification of the antigens, the immunoglobulin subclasses, or their avidity. This method allowed visualization of a very limited number of antigen groups [4]**.** Immunoglobulin G 3 (IgG3) is the most effective subclass for activating the complement pathway. It is known to mediate cell lysis by Fc receptor–bearing monocytes or lymphocytes. This is particularly important in the context of immunity to *P. falciparum*. By their ability to link antigens to monocytes, these subclasses can stimulate them to produce tumor necrosis factor. This cytokine induces the production of nitric oxide, which kills intracellular parasites as part of antibody-dependent cellular inhibition. The generated nitric oxide is a vasodilator that prevents cerebral vasospasm, which is significantly involved in the pathogenesis of cerebral malaria [5]. A shift toward the production of IgG1 and IgG3 immunoglobulin subclasses is induced by a T-helper cell 2–mediated immune response involving increased interleukin-10 production by regulatory T-cells [6]. IgG1 antibodies have a half-life of 11 to 23 days versus 7 to 8 days for IgG3 [7]. Antibodies of adults clinically immune to malaria, which reduced the symptoms of malaria in children with symptomatic malaria after infusion, were found to enable antibody-dependent cellular inhibition of *P. falciparum* by monocytes, thereby indicating that its activity may be related to the ability to collaborate with monocytes [8-10]. This antibody response was directed against trophozoites and schizonts but not against ring forms. Field studies in French Guinea, Burkina Faso, Senegal, Ivory Coast, and Thailand found that IgG3 and IgG1 antibodies were significantly higher in patients without parasitemia and clinically immune patients [8,11-15] and were significantly lower in patients with complicated malaria [16,17]. Focusing on specific antigens, studies found that in children, the presence of IgG3 against the C-terminal region of merozoite surface protein (MSP-2) and glutamate-rich protein (GLURP) was associated with a reduced incidence of malaria during a 5-month period [18,19]. A recent systematic review of population-based prospective studies and population-based treatment to reinfection studies found a limited number of studies which were restricted to antigens or components of antigens comprising MSP-119, MSP-1-epidermal growth factor like domain, MSP-1 Wellcome isolate block-1 protein, MSP-1-BL2, MSP-2, MSP-2 from active case detection, MSP-3, GLURP, Apical Membrane Antigen-1, and erythrocyte-binding antigen 175 (EBA-175). The authors concluded that IgG responses to some, but not all, merozoite surface antigens were associated with protection against symptomatic *P. falciparum* infection in malaria endemic areas [20]. Progress in the identification of multiple immunoglobulin subclass responses to native *P.falciparum* blood-stage antigens was made by using one-dimensional (1D) sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis (PAGE) and immunoblotting [21]. The first group which investigated the avidity of antiplasmodial antibodies compared the avidity of immunoglobulin subclass antibodies-as measured by an enzyme immunoassay-against a detergent-soluble extract of *P. falciparum* schizonts in clinically immune Senegalese adults and semi-immune Amazonian adult patients [22]. Avidity was determined by using a thiocyanate elution–based enzyme immunoassay [23-26]. Patients with complicated malaria did not have lower total IgG, M, A, or E level but lower IgG1, 2, and 3 subclasses, and the mean avidity index was significantly lower for IgG1 and 2 subclasses. Most recently, estimations of the affinity of antibodies in serum have been performed using new methods based on surface plasmon resonance association, where dissociation between antigens and antibodies in a continuous flow can be studied in real time. When the time to the next clinical episode of malaria from baseline was assessed, it was found that the 17 individuals with the highest affinity antibodies (higher than 90% of the other 171 samples) against MSP2-3D7 had a longer duration to clinical malaria when compared with individuals with the 10% lowest affinity antibodies. Immunity appeared to be dependent on antibodies to conformational, nonlinear epitopes [27,28].

Analysis of Immune Responses to Recombinant Antigens

P. falciparum has a 23-megabase genome that encodes an estimated 5268 putative proteins [29]. To enlarge the number of antigens identifiable and to analyze antibody responses against all immunologically recognized antigens, the microarray methodology was used. A microarray immunoassay of 18 recombinant antigens derived from MSP1, 2, and 3 and AMA-1 produced in *Escherichia coli*–visualized IgG responses in 53 Gambian asymptomatic parasitemic children, 81 children with clinical malaria, and 55 children without malaria. The analysis took into account only the presence or absence of specific antibodies to individual antigens as markers for immune priming. Antibody titers were not included. No association between clinical outcome and recognition of an individual antigen was observed [30]. This limited number of antigens was soon exceeded by a study using expression vectors encoding 250 *P. falciparum* proteins. Generated by polymerase chain reaction (PCR)/recombination cloning, the proteins were individually expressed with >90% efficiency in *E. coli* cell-free in vitro transcription and translation reactions and printed directly without purification onto microarray slides. The protein

microarrays were probed with human sera from 1 of 4 groups that differed in immune status: sterile immunity or no immunity against an experimental challenge following vaccination with radiation-attenuated *P. falciparum* sporozoites, partial immunity acquired by natural exposure, and no previous exposure to *P. falciparum*. A total of 72 immunoreactive proteins were identified, and 48 were particularly reactive. The average molecular weight of all *P. falciparum* proteins in the proteome is 87 kDa, but the 48 immunodominant antigens averaged nearly two times larger, presumably reflecting the presence of additional B-cell epitopes in the larger sequences [31]. Following this study, screening was extended to 23% of the *P. falciparum* proteome, including 1204 known and hypothetical proteins, using sera from people in Mali exposed to seasonal malaria and monitoring IgG responses to these antigens before and after the malaria season. Of these, 491 antigens were found to be reactive with IgG. Of these, 25.2% (124/491) were derived from sporozoites, 5.5% (27/491) from merozoites, 16.8% (82/491) from trophozoites, 20.6% (101/491) from gametocytes, and 31.9% (157/491) from unknown origin. A total of 40% (196/491) of the immunogenic proteins were expressed in the membrane of the parasite or host erythrocytes. A comparison of antibody profiles of children who did not experience malaria (despite at least one positive blood smear) with those who experienced ≥1 malaria episode during the 8-month study period showed that in the 12 protected children, antibody levels were significantly higher than in the 29 unprotected children for 49 proteins, and in a subsequent study, 107 proteins were associated with a protective antibody response [32-36].

Vaccine Trials in Animals Comparing the Response to Native by Recombinant Parasite Antigens

To generate vaccine antigens for anthelmintic vaccines, 3 different expression systems have been used, that is, bacterial (mainly *E. coli*), yeast, and baculovirus. The bacterial expression system has been by far the most popular choice to express helminth antigens. However, except for the results with cestodes, the levels of protection induced by *E coli* recombinants have been rather disappointing. *E coli* expressing antigens of trematodes and nematodes have had more variable successes, ranging from a 100% reduction in egg counts in mice and sheep for a *Schistosoma mansoni* antigen tested against *Fasciola hepatica* to a 0% reduction for nematode antigens of *Haemonchus contortus* and *Ostertagia ostertagi*. Yeast has been used to express 12 different antigens from 6 helminth species. The levels of protection obtained with these recombinants vary considerably, although all of them appear to induce some level of protection. The best results were obtained with the recombinant Sh28GST antigen from *Schistosoma haematobium* and the Ac-APR-1 antigen from the hookworm *Ancylostoma caninum*: vaccination with these antigens reduced the egg output by 77% and 85%, respectively. Although the yeast and baculovirus expression systems clearly have the capability to glycosylate the recombinant antigens, this glycosylation can differ drastically from the helminth glycans. The yeast *Saccharomyces cerevisiae*, for example, can cover the peptide core with very large glycan trees, which potentially mask important peptide epitopes or which can make the protein hyperantigenic [37-41].

One randomized controlled trial in calves and 3 prospective cohort studies in monkeys, mice, and cattle comparing recombinant and native antigens containing antiparasitic vaccines revealed that native antigens yielded a more effective clinical and immunological response compared with recombinant antigens (Multimedia Appendix 1).

The advantage of using recombinant antigens as vaccines is the relative ease of a large-scale production of these antigens in cell-free expression systems. The advantage of analyzing immunorelevant antigens using protein microarrays is the potential to analyze more protein entities because it allows the analysis of proteins, which may only be expressed under certain conditions in vivo and at certain developmental stages of parasite development simultaneously. There is also less potential for protein loss during the procedure compared with two-dimensional (2D) gel electrophoretic methods. This was illustrated by the example of *Mycobacteriumtuberculosis* by the fact that even with high-resolution 2D electrophoresis, out of 4000 predicted open reading frames, the separation of proteins from whole mycobacterial cells by 2D E resulted in silver-stained patterns comprising only about 1800 distinct protein spots [42].

The limitations associated with a bacterial cell-free expression system used to generate protein microarrays are the lack of posttranslational modifications, such as phosphorylation, methylation, and glycosylation, and the absence of the complexity of protein folding and multimerization forming tertiary and quaternary structures, for example, those formed by disulfide bonds. The potential importance of posttranslational modification in *P. falciparum* is illustrated by the fact that striking visual evidence of widespread posttranslational modifications in the parasite was observed when a study used 2D electrophoresis followed by the mass spectrometric identification of proteins of *P. falciparum* ring stages, with 10 out of the 28 gene products identified in two or more variants of the same protein identified on the 2D gel as placed in different positions due to a different electrophoretic migration [43]. Recombinant proteins expressed in *E coli* lack glycosylation The role of glycosylation was investigated by examining the specific binding of each antibody subclass to *P. falciparum* periodate-sensitive epitopes following treatment of antigen-coated microplate wells with sodium periodate at acidic pH. Such treatment has been shown to cleave carbohydrate vicinal hydroxyl groups without affecting polypeptide chains. The investigators found that 35% to 46% of all anti–*P. falciparum* IgG1 antibodies and 12% to 28% of anti–*P. falciparum* IgG3 naturally acquired by African subjects and Amazonian patients were shown to recognize periodate-sensitive epitopes [22] and would not be detectable in an approach using recombinant antigens.

Rationale for the Project

Vaccines developed against *P. falciparum*, thus far, have only resulted in partial and temporary protection against malaria. Results of previous studies (sections *Analysisof Immune Responses to Native Plasmodium falciparum Antigens* and *Analysis of Immune Responses to Recombinant Antigens)* have not revealed a protective antibody response against a single

antigen of *P. falciparum* blood stages associated with clinical immunity in infected people but are compatible with responses to multiple blood-stage antigens by cytophilic antibodies (IgG1 and IgG3), with high affinity being more protective. Methods to assess antibody responses to multiple blood-stage antigens in previous studies included an analysis of responses to antigens generated by a microarray of recombinant antigens and a very limited analysis of responses to antigens separated by 1D or 2D electrophoresis by western blotting. Recombinant antigens lack posttranscriptional modification, which is found in more than 30% of immunorelevant antigens and do not contain isoforms of the same protein. It is therefore essential to develop an unbiased platform of 2D western blotting combined with the detection of antigens eliciting antibody responses with protective qualities (IgG1 and 3 subclasses and high affinity).

Hypotheses

IgG1 and IgG3 antibodies with high affinity to multiple schizont antigens of *P. falciparum* are associated with clinical immunity to *P. falciparum* malaria. IgG2 or IgG4 responses are not associated with clinical immunity to *P. falciparum* malaria.

Objectives

Objectives of this investigation were:

- To develop a method for comprehensive detection of all *P. falciparum* schizont antigens, eliciting a protective immune response.
- To develop a method for the comprehensive detection of immunoglobulin subclass responses to *P. falciparum* schizont antigens.
- To develop a method for the simultaneous quantification of the affinity of multiple antibodies to multiple antigens.
- To answer the question, whether high-affinity IgG1 and IgG3 antibodies to schizont antigens are associated with clinical immunity to *P. falciparum* malaria.

Methods

Population Studied

Sample Size Calculation

Owing to the lack of previous studies employing the methodology used in this investigation, there was no basis for a sample size calculation. The proposed project includes a pilot study that will inform future sample size calculations. To establish the methodology as a first step, the serum of a patient with afebrile *P. falciparum* parasitemia will be assessed for antiplasmodial immunoglobulin subclass responses with high affinity a total of 10 times during the establishment of the 2D western blot process. This requires taking 35 mL of blood from this patient. Alternatively, lyophilized pooled antiplasmodial hyperimmunoglobulin is reconstituted to give this amount with a dilution titrated to a physiological immunoglobulin concentration. By repeating the blotting process 10 times using the same antigen preparation and immunoglobulin donor (-pool) and comparing the results, an estimate of the intraindividual variability of western blot results will be enabled. Subsequently, a case-control study comparing antibody responses between clinically immune people and people suffering from severe *P. falciparum* malaria will be conducted. This study will provide a preliminary sample size calculation for larger seroepidemiological studies using immunorelevant parts of the immunome. The standard deviation of spot intensity on the image of the immunoblot and the corresponding quantity of antibody measured by immunochromatography for a protein with a known relationship to clinical immunity: IgG3 response and its affinity to merozoite surface protein-2 C-terminal antigen (MSP2-3D7) will be used for the ultimate sample size calculation, and the standard deviation for intraindividual intensity will have to be below the standard deviation used for sample size calculation for the assessment of interindividual differences between cases and controls.

Inclusion Criteria

During the development of the methodology, the serum of a patient known to be clinically immune to malaria from a holoendemic area, that is, asymptomatic malaria using the most common definition—presence of parasites in peripheral thick blood smears, an axillary temperature <37.5°C, and an absence of malaria-related symptoms [44] or *P. falciparum* hyperimmunoglobulin—is analyzed 10 times to be able to assess and achieve reproducibility, as mentioned earlier. After the successful establishment of the methodology, a group of 15 individuals with clinical immunity, defined as at least 10 years old, living in a holoendemic area for *P. falciparum* malaria from birth with at least four to five infections per year with asymptomatic *P. falciparum* malaria (parasitemia on antigen detection of histidine-rich protein or on microscopy) at the time of blood sampling is compared with 15 age-matched individuals from the same ethnic group and holoendemic area hospitalized with acute severe, complicated *P. falciparum* malaria (World Health Organization criteria).

Exclusion Criteria

Patients in whom *P. falciparum* parasitemia by microscopy or antigen detection is not documented, patients whose body temperature is not documented, patients with a known HIV infection, and patients with known acquired or congenital immunodeficiency are excluded.

Ethical Approval and Consent

Ethical approval for the study will be sought from the National Research Ethics Service of the United Kingdom, and the study will be subject to institutional approval by the host institution. Informed written consent for the study will be sought from the participants of this study before its commencement.

Laboratory Methods

2D Western Blot

Immunorelevant antigens are identified by western blotting using participants' serum after 2D electrophoresis of native schizont antigens with discrimination of protective antibody responses by the detection of antibody subclasses and added analysis of affinity. This is followed by the comparison of antibody responses of patients with severe malaria and clinically immune individuals. Protective antibody responses are defined as those of the IgG1 or IgG3 isotype and of greater magnitude or higher affinity in clinically immune individuals than in

patients with severe malaria. Antigens against which such a response is detected are identified by using mass spectrometry (see detailed experimental protocol).

Validation of 2D Western Blot Results

Immunoaffinity chromatography involves the extraction of a specific antigen from an antigen mixture by using antibodies immobilized on a matrix (eg, Sephadex column). Immunoaffinity chromatography has been used to generate purified immunoglobulin subclass fractions from polyclonal human immunoglobulin preparations [45]. This has been achieved by using monoclonal immunoglobulin subclass antibodies immobilized to the Sephadex column through proteins A and G. Antigens bound by immunoglobulins produced by mice with enhanced immunity to *Plasmodium yoelii* have been isolated and identified by immobilizing immunoglobulins from immune mice to a Sephadex column and then passing a blood-stage antigen mixture through the column followed by elution of antigens with sodium deoxycholate and identification of antigens after SDS-PAGE and western blotting with specific antibodies [46,47].

Experimental Protocol

Preparation of P. falciparum Blood-Stage Antigens

Purified parasitophorous vacuolar membrane–enclosed merozoite structures (PEMSs) are initially generated, which contain a highly homogeneous synchronous parasite population at the mature schizont stage, which is essentially free of contaminating host cell proteins [21,48,49]. Parasites are grown using the method of Trager and Jensen [48] (Multimedia Appendix 2).

The procedure is repeated until sufficient protein is generated for all gels required for the project. To ensure that the same protein mixture is used for all gels of this project, the isolated PEMSs are pooled after a sufficient amount is generated for all experiments. To facilitate equal conditions for processing of patient serum samples for cases and controls wherever possible, the serum of one patient with severe malaria is processed at the same time as the serum of an age-matched control with afebrile *P. falciparum* parasitemia. This requires 25 2D-PAGE and western blot processes (amounting to a total of 345 gels), including the generation of 25 2D-PAGE gels for protein identification and micropreparative purposes. For each patient or run of analysis, samples equivalent to 2700 µg of protein are required for nine 2D gels. Sufficient antigens is produced for all 25 runs of analysis. A total of at least 103.5 mg of *P. falciparum* protein is required for the project.

To determine how many PEMSs need to be produced, the protein content of the parasite pellet is determined by a test run of protein extraction. Pellets are pulse sonicated on a sonifier with microtip sonication (6-mm probe; Sonics Vibracell VCX130) on ice for 10 min at 25% amplitude (with pulses of 2 seconds on and 3 seconds off), resulting in a 4-min total pulse-on time [50] (to prevent foaming and carbamylation). Sonication is followed by centrifugation at 40,000 *g* for 60 min at 4°C [51]. The supernatant and pellets are collected and stored at –80°C. Before each analysis, the pellet is solubilized in a solution used as enhanced rehydration and extraction solution and lysis buffer: 8 M urea, 2 M thiourea, 4% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), 2% ASB-14, 40 mM Dithiothreitol (DTT), and 0.5% (v/v) immobilized pH 3-11 gradient buffer by 1 hour of incubation on ice (Multimedia Appendix 3).

The protocol regarding isoelectric focusing (IEF) that follows has essentially been adopted from a study by Goerg et al [52] (Multimedia Appendix 2).

Day 1: IEF

Turn on the cooling system of Multiphor II (usually 15°C) or immobilized pH gradient (IPG)phor (Multimedia Appendix 3).

It is critical to prepare an equilibration buffer, which is used fresh each time; at room temperature, urea takes time to dissolve; therefore, start preparing the buffer before stopping the first-dimension run.

The antigen mixture is subjected to 2D electrophoresis using IEF in the first dimension using a pH gradient of 3 to 11 in the IPG strip (Immobiline DryStrip pH3-11NL24cm, GEHealthcareLiveScience) and polyacrylamide gel electrophoresis using a large-format gel with a 26 cm×20 cm width and length in the second dimension (Multimedia Appendix 2).

Day 2: Preparation of Cup Loading Followed by Overnight Incubation From Day 2 to Day 3

At this time point, the electrode paper strips (wicks) are replaced by fresh ones (Multimedia Appendix 1). Voltage is then increased to 3500 V for 12 hours (Multimedia Appendix 3). The focusing temperature is 20°C until the steady state with constant focusing patterns is obtained

Day 3: 2D Electrophoresis

After completion of IEF, IPG strips are equilibrated for 10 min each in the SDS equilibration buffer (50 mM Tris-HCl; pH 6.8; 6 M urea; 30% v/v glycerol; 2% w/v SDS; 0.002% bromophenol blue containing 2% DT). The equilibrated IPG gel strips are slightly rinsed and blotted to remove the excess equilibration buffer. Finally, the strip is placed in the SDS electrophoresis running buffer (0.25 M Tris-HCl; pH 8.3; 0.1% SDS; 192 mM glycine) for 10 min as a final equilibration step [51]. If not used for IEF, the IPG gel strips are stored between 2 sheets of plastic film at –78°C (for up to several months).

After IEF is completed, it is important to proceed immediately to gel equilibration, unless the IPG strip is being frozen for future analysis. Equilibration is always performed immediately before the second-dimension run, never before the storage of the Immobiline DryStrip gels. The second-dimension gel itself should be prepared and ready to accept the Immobiline DryStrip gel before beginning the equilibration protocol. SDS-PAGE in the second-dimension is performed using the Ettan DALTsix LargeVertical System (GE Healthcare). The preparations mentioned in this paragraph are performed before IEF is completed, followed by the preparation of electrophoresis (Multimedia Appendix 2).

The total running time is approximately 9 hours. Nine gels are generated for each participant. Eight gels are used for

immunoblotting and one preparative gel. After SDS-PAGE, the gel is withdrawn from the cassette and equilibrated in the transfer buffer: Towbin buffer consisting of 192 mM glycine, 25 mM Tris, 20% methanol (v/v), pH of 8.3 for 20 min to remove excess SDS. The membrane and the filter paper used for transfer are equilibrated in the transfer buffer for 10 min.

2D Western Blotting

Antigens from 8 gels are blotted onto the nitrocellulose membranes for each patient. Nitrocellulose is the medium of choice for these techniques because of its very high capacity for protein binding [53]. The Amersham Protran 0.1 membrane with a minimal pore size of 0.1 µm, exhibiting excellent binding affinity for small peptides (molecular weight <10,000) and producing very low background in chemiluminescent western blotting. Nitrocellulose membranes are directly soaked with a transfer buffer without prewetting in methanol. SDS is detrimental to the binding of proteins to membranes, and the general rule is that excess SDS should be removed from the gel before transfer by equilibration for 15 to 30 min in the transfer buffer. However, it may be necessary to include low amounts of SDS (0.02% to 0.1%) in the transfer buffer if the proteins are only partially soluble due to high molecular weight or if they contain a surplus of hydrophobic amino acids.

To process the large gel used in this study, the gel is cut into 2 pieces (high- and low-molecular-weight part) to avoid overheating during the blotting procedure [54]. A sheet of nitrocellulose (Amersham Protran 0.1 membrane with a minimal pore size of 0.1 µm) is briefly wetted with water and laid on a scouring pad (Scotch Brite is a trademark of 3M), which is supported by a stiff plastic grid (a disposable micropipette tray; Medical Laboratory Automation, Inc). The gel to be blotted is placed on the nitrocellulose sheet and care is taken to remove all air bubbles. A second pad and a plastic grid are added, and rubber bands are strung around all layers. The gel is firmly and evenly pressed against the nitrocellulose sheet. The assembly was placed in an electrophoretic destaining chamber with a nitrocellulose sheet facing the cathode. For the high molecular weight part of the gel, the cathode buffer consists of 50 mM boric acid, 10% methanol, 5% SDS, and pH 9.0; the anode buffer consisted of 50 mM boric acid, 20% methanol, and pH 9.0. For the low-molecular-weight part of the gel, the cathode and anode buffers consist of 100 mM boric acid, 20% methanol, and pH 9.0. The blotting time is 2 hours at 1 mA/cm^2 [53-55]. The membrane was then washed with 100% methanol to remove SDS and stained with Ponceau S for 30 seconds to document the number and location of proteins transferred and scanned with the scanner. Ponceau S is easily removed with water (if water is not sufficient, Tris-buffered saline with Tween 20 is used) and is regarded as a *gentle* treatment that does not interfere with the subsequent immunological detection steps (Multimedia Appendix 2).

Overnight From Day 3 to Day 4

To allow binding of the antibodies in the serum to the blotted antigens, the bags are covered with glass plates on a shaker so that solutions are circulated properly within the packages by shaking overnight at 4°C [54]. After incubation with primary antibodies, the membrane is washed 4 times for 15 min in a PBST buffer.

Day 4: Identification of Antigens Against Which a High-Avidity Antibody Response is Detectable

For identification of high-avidity antibodies, the blotted antigen-antibody complexes on 4 of 8 nitrocellulose sheets per participant are subjected to a washing step with a dissociation buffer, including phosphate buffered saline (PBS) with 8 M urea with vigorous shaking for 5 min followed by 2 additional washes with the PBS buffer with vigorous shaking for 5 min. Avidity is quantified by the avidity index, which is the ratio of the optical density of urea-treated spots to the optical density value of untreated spots multiplied by 100, with all values higher than 50% ranked as high avidity. An avidity index of less than 30% is defined as low avidity and that of between 30% and 50% as intermediate avidity [25,56]. Bound immunoglobulin is visualized with a secondary antihuman immunoglobulin conjugated with horseradish peroxidase. The type of antibody hereby is a specific antisubclass antibody for IgG1, IgG2, IgG3, and IgG4 conjugated with horseradish peroxidase for one gel each. The secondary antibody is diluted 1:5000 in 5% milk with the PBST buffer to give a volume of 50 mL and incubated for 1 hour. Membranes are then washed again 4 times for 15 min in the PBST buffer. The immunoblot is developed with tetrazolium—a reagent, which has been reported to increase the sensitivity of the horseradish peroxidase system about three-fold [57]. One set of 2 gels (one with and one without dissociation buffer treatment) is used for each antibody subclass**.** Blot signals are normalized by relating to intensity of blot staining from a DyLight 800–conjugated antibody to a mouse monoclonal antibody of known concentration against the housekeeping antigen ovalbumin added to the PEMS antigens.

The membrane is then exposed to Amersham ECL Select (GE Healthcare) and shaken for 1 min at room temperature. Excess fluid is dripped off the membranes [54]. Subsequently, chemiluminescence is visualized using a charge-coupled device, camera-based imager.

Data generation from spots generated by the peroxidase reaction on the nitrocellulose membrane is performed using the ImageQuant TL (GE Healthcare) or MELANIE, PDQuest, Z3, Z4000, Phoretix, or Progenesis software package [58-61].

Identification of Immunorelevant Antigens

One gel for each of the initial test runs and subsequently participants is subjected to a SYPRO Ruby staining for the localization of antigens identified as immunorelevant on a subsequent analysis of the 4 gels subjected to the analysis of isotype-specific high-affinity antibodies and used for a mass spectrometric analysis of gel sections with immunorelevant antigens (*master gel*).

After the SYPRO Ruby staining (Molecular Probes), images could be generated using a Typhoon 9410 fluorescent imager set at an excitation bandwidth of 510 to 532 nm and an emission filter at 610 nm for matching.

Overnight from Day 4 to Day 5

For mass spectrometry, gels selected for spot excision are incubated overnight in 350 mL of 10% (v/v) ethanol.

Day 5: Mass Spectrometric Identification of Immunorelevant Antigens

Protein spots are cut from gels using a Genomic Solutions ProPic robot, and gel plugs are placed in 96-well plates in 100 mL of 10% ethanol. Proteins can be subjected to tryptic in-gel digestion on a ProGest workstation. To this end, the storage liquid was removed and the gel plugs were washed with ammonium bicarbonate (50 mL; 25 mM) for 10 min and then with acetonitrile (ACN; 50 mL) for 10 min. Washing with ammonium bicarbonate and ACN is repeated. DTT (30 mL) is added to the gel plugs to reduce the proteins, and samples are incubated at 60°C for 10 min before they are allowed to cool to room temperature. The liquid is discarded and proteins are alkylated in iodoacetamide (30 mL; 100 mM) for 45 min. Gel plugs are washed with ammonium bicarbonate and ACN twice before rehydration in 10 mL trypsin solution (20 mg lyophilized trypsin [Promega] is dissolved in 200 mL 0.01% formic acid, and then 1.8 mL of ammonium bicarbonate are added to give a 10 ng/mL solution). After 10 min, ammonium bicarbonate (15 mL; 25 mM) is added and samples are incubated at 37C for 4 hours. The reaction is stopped by the addition of 7 mL of 3% formic acid. A portion of the resulting supernatant is used for a matrix-assisted laser desorption/ionization/mass spectrometry (MALDI/MS) analysis. Samples can be spotted onto a MALDI target robotically (ProMS) using ZipTips. Peptides are eluted from the C18 (ZipTip) material with a matrix (acyano 4-hydroxy cinnamic acid) prepared in 60% ACN and 0.2% trifluoroacetic acid (TFA). MALDI/MS data are acquired on an Applied Biosystems Voyager DE-STR instrument, and the observed *m*/*z* values are submitted to ProFound (Proteometrics software package) for peptide mass fingerprint searching, which queries a locally stored copy of the NCBInr database (version 20041201). Amino acid sequences found by this process can be attributed to proteins using the fully deciphered *P. falciparum* genome. In an alternative protocol, protein spots of interest are carefully excised from the SYPRO Ruby–stained gel, sliced into 1 mm^2 pieces, and washed in 50% (v/v) ACN/25 mM ammonium bicarbonate, pH 7.8, and then dried in a vacuum concentrator. The digestion buffer (4-10 µL; 10 µg/mL modified sequencing grade trypsin; Promega) in 25 mM NH_4HCO_3 is added to the gel slices and incubated overnight at 37°C. The resulting peptides are extracted by the addition of 4 µL of water followed by 7 µL 30% (w/v) ACN/0.1% (v/v) TFA, vortexing, and brief centrifugation. The extracts are concentrated in a vacuum concentrator to approximately 5 µL. The concentrated sample extract is mixed in a ratio of 1:1 with a matrix (10 mg/mL; CHCA [Aldrich] in 50% [v/v] ACN/50% [v/v] ethanol/0.001% [v/v] TFA) containing an internal standard (adrenocorticotrophic hormone; 50 fM/L) and 1 µL of the mixture is loaded onto a 96-position target. Peptide mass fingerprints are obtained semiautomatically on a MALDI mass spectrometer, and the resultant mass lists are searched against a nonredundant protein database (Swiss Prot/TrEMBL) using ProteinLynx V. 3.4 (Micromass) software. Protein identification was confirmed from a statistically significant MOWSE score resulting from fingerprint interrogation using MASCOT [62]. Protein identification is considered valid if more than 2 peptides matched and the MASCOT score is greater than or equal to the significance threshold (P<.05) [63].

Immunoaffinity Chromatographical Purification for the Detection of Potentially Immunorelevant Antigens Using an IgG Concentrate of Malaria Immune Adults

Extraction of Subclass Antibodies From IgG Concentrate Using Protein G Bound to Sepharose

Cross-Linking or Antisubclass Antibodies to Protein G

The columns used for positive purification are modified by cross-linking of the antisubclass antibody to protein G using the Schneider cross-linking technique [64] (reagents by Sigma-Aldrich) to prevent elution of the anti-immunoglobulin subclass antibody bound to the subclass antibody from the Protein G Sepharose matrix (Multimedia Appendix 2).

Negative Purification

Previously published data [65] suggested that positive purification resulted in impure preparations due to nonspecific binding of other IgG subclasses to Sepharose. Therefore, negative purification is required before the use of positive purification. From the IgG preparation of Malawian adults, a solution with physiological IgG concentration is generated. The physiological IgG concentration is about 11 mg/mL with an assumed distribution of immunoglobulin subclass concentrations as follows: 6 mg/mL IgG1, 3 mg/mL IgG2, 0.6 mg/mL IgG3, and 0.24 mg/mL IgG4. Therefore, 308 mg of the lyophilizate is added to 10 mL of distilled water. The amount of suspended lyophilizate to be added to each column is therefore used to capture all immunoglobulin subclasses in the added sample determined by the added amount of IgG1 present in the mixture. Assuming that one antisubclass antibody binds 2 subclass antibodies, the columns prepared above containing anti-IgG1 subclass antibodies will bind 200 g IgG1. About 200 µg of IgG1 are assumed to be present in 33 µL of the suspended lyophilizate. A total of 33 µL of the suspended lyophilizate is diluted in 567 L of distilled water, and the resulting 600 L is added to each column as part of the following procedure (Multimedia Appendix 2).

Generation of Columns With Antiplasmodial IgG Subclass Antibodies

For each immunoglobulin subclass, 2 separate columns are generated (one for the antibody avidity assessment and one for the quantification of the antibody responses) using Protein G High Performance SpinTrap (Sigma-Aldrich; Multimedia Appendix 2).

Cross-Linking of the Subclass Antibodies to Protein G

The columns used for binding of schizont antigens to subclasses are modified by cross-linking of the subclass antibodies to protein G using the Schneider cross-linking technique [64] (reagents by Sigma-Aldrich) to prevent elution of antigens nonspecifically bound to or trapped in Sepharose, which could

cause contamination of antigen specifically bound to the respective subclass of antiplasmodial antibody, and to prevent elution of the subclass antibody bound to the antigen from the Protein G Sepharose matrix, thereby further contaminating the antigen mixture subsequently analyzed by MS.

The bound antibody is cross-linked to the protein G matrix by washing with 10-column volumes of 0.2 M triethanolamine in 0.1 M borate buffer, pH 8.2. Washing is conducted by adding 600 µL aliquots of this solution and centrifugation for 30 seconds at 100 *g*, followed by washing in a 0.2 M triethanolamine in 0.1 M borate buffer solution containing 50 mM dimethyl pimelimidate prepared 1 to 3 hours previously. The pH of this cross-linking solution is readjusted to 8.2 with concentrated NaOH. Washing is conducted by adding 600 µL aliquots of this solution and centrifugation for 30 seconds at 100 *g*.

The gel cross-linking solution mixture is continuously agitated for 45 min, and a further washing step is performed with 20-column volumes of 50 mM ethanolamine, pH 8.2. Washing is conducted by adding 600 µL aliquots of this solution and centrifugation for 30 seconds at 100*g*, followed by washing with 20-column volumes of the same 50 mM ethanolamine buffer for 5 min. Washing is conducted by adding 600 µL aliquots of this solution and centrifugation for 30 seconds at 100*g*. The gel-antibody complex is then poured back into its original column format with PBS containing 0.02% sodium azide.

Loading of the Schizont Antigen Suspension

One milligram of schizont antigen (PEMS) per column suspended in 600 µL of lysis buffer (8 M urea, 2 M thiourea, 4% CHAPS, 2% ASB-14, 40 mM DTT) is loaded onto each pair of immunoglobulin subclass–loaded columns. Ovalbumin (50 µg) is added as a control antigen to all columns. Steps for binding are repeated (see section on purification), including the assessment of binding efficiency in the collection tubes. To assess the binding efficiency, antigen concentration in the collection tubes is measured by mass spectrometry.

Determination of Antibody Affinity

One each of the 2 immunoglobulin subclass columns is then subjected to an elution step with 1 M ammonium thiocyanate solution. The eluted antigen is quantified and identified by high pressure liquid chromatography/mass spectrometry (HPLC/MS).

Determination of Type and Quantity of Antigen Bound by Each Immunoglobulin Subclass

All columns are then subjected to elution with 1% deoxycholate to elute all bound antigens, which are then quantified and identified by HPLC/MS.

Data Analysis

The western blot spot intensities are corrected for exposure of participants to *P. falciparum* infection. This is carried out by calculating the ratio to the level of antibodies to a mixture of all *P. falciparum* antigens and normalized by relating to the intensity of blot staining from a DyLight 800–conjugated antibody to a mouse monoclonal antibody of known concentration against the housekeeping antigen ovalbumin added to the PEMS antigens. If the corrected and normalized spot intensity for the antibody reaction to an antigen reveals a statistically more extensive antibody reaction of protective isotypes IgG1 or IgG3 (at least two-fold) and/or a reaction of higher affinity in clinically immune compared with nonimmune participants, this antigen is deemed to be immune-relevant and a candidate for future vaccine development. Principal component analysis (PCA) is used to visualize natural groupings in data based on similar patterns of variation. The presence of natural clusters in PCA indicates that there is more variation between groups than within groups. The absence of clusters indicates that the variation between groups is of the same order of magnitude as that within groups. This analysis will help identify patterns of antigens against which the immune reaction is protective.

On analysis of the results of the immunoaffinity chromatography, the relative antibody affinity is determined as the ratio of quantity of antigen eluted with and without a history of previous treatment with ammonium thiocyanate after normalization of the quantity relative to ovalbumin control. High affinity is hereby defined as the ratio being >50%, intermediate as 30% to 50%, and low as <30%. The antigens, together with their affinity bound by each IgG subclass, are then identified and registered.

The patterns emerging with this method are related to clinical immunity. A group of 15 comprising at least 10-year-old individuals with clinical immunity is compared with a group of 15 comprising at least 10-year-old age-matched patients from the same ethnic (tribal) group hospitalized with acute malaria. The association with a protective antibody response is derived from the quantitative data analysis of spot intensities. Given the small number of samples analyzed, it is essential to reduce the variability of antibody binding introduced by differences in antigen presence in the 2D gel, protein losses after transfer to the nitrocellulose membrane, differences in antibody binding due to washing steps, and differences in action/presence of chemicals present in different amounts locally denaturing the antibody binding sites on protein. To avoid the differences between cases and controls arising from these sources of variability, a pair of case and matching control is processed together under the same conditions, with the same batch of reagents and equipment under the same condition and at the same temperature. Data analysis is aimed at further reducing the effects of the *noise* introduced by the aforementioned factors and image processing. This will increase the detection power of a statistically significant difference in antibody binding to specific antigens with a small sample size.

Analysis of Errors in 2D Gel Image Analysis

There are two different types of errors in 2D gel image analysis data.

First, there are spots that are not reproducibly observed (where detection or matching has failed) by the software. These are regarded as observation errors and account for a false discovery rate (FDR). Second, there are spots that are reproducibly observed, and their integrated optical density (IOD) has some intrinsic variations between the 2 gels. These are referred to as quantitation errors. To investigate the source and size of these

errors, the errors between multiple scans are compared with the errors measured between multiple gels. The differences between these methods allow us to distinguish errors due to image analysis from errors particular to the gel running and staining system. This is done by comparing the variability of the detected protein load on the preparative gels in the 10 initial test runs as detected by SYPRO Ruby staining, with the variability of IOD on repeatedly running the densitometry scan. The other one is the comparison of western blot stain intensity between the initial run with the identical antibody source and the variability of results from scanning the same blot.

Control for differences in detected quality and quantity of antiplasmodial antibody responses between groups due to different antigen uptake by gels and differences in handling of individual western blots affecting the binding of patient antibodies and secondary antibodies.

Variability of signal due to different antigen uptake between gels, different binding of primary and secondary antibodies, and differences in staining related to methodology between the gels and not related to differences in the patient's antibody responses are taken into account in the data analysis in the following ways.

Variability due to processing between blots of cases and controls of the same run is corrected for by normalization by relating to the intensity of blot staining from a DyLight 800–conjugated antibody to a mouse monoclonal antibody of known concentration against the housekeeping antigen ovalbumin added to the PEMS antigens.

Image Analysis

Consensus western blot spot patterns are generated for clinically immune patients and patients with malaria. The consensus pattern is produced by spot detection on a fused image that essentially contains all spots in the experiments. Image fusion is a method that combines multiple images into a new, synthetic image, where each pixel is a function of the corresponding pixels in the input images. The resulting image looks like a real blot image, and more importantly, all spots from the experiment are represented on it. Thus, spots that are present only on a few of the gels can be located in the fused image and properly separated from those surrounding them. Software packages that can achieve this are used: PDQuest 2D analysis software (BIORAD) and Delta2D software version 4.0 (Decodon). A subgroup analysis is performed for different age groups. Antigens found to be associated with a protective antibody response can be identified by mass spectrometry using sections of the master gel where the antigen was found to be situated, from a comparison of the master gel with the position on the nitrocellulose membrane. To achieve this, the respective protein spots in the SYPRO Ruby–stained mastergel are identified after overlaying the western blot images used. PCA was used to identify potential outlier gels and outlier samples in the datasets. PCA is an excellent methodology for visualizing natural groupings or clusters in data based on similar patterns of variation. The presence of natural clusters in PCA, therefore, indicates that there is more variation between groups than within groups. The absence of clusters indicates that the variation between groups is of the same order of magnitude as that within groups. Two statistical criteria are used to select potential immunorelevant antigens: an FDR of 5% and a fold change of 2 or more. By limiting the FDR to 5%, it is ensured that minimal resources are spent on following up false-positive leads. A two-fold or greater change is chosen over a lower cutoff as it increases the chance that a change will be detectable with independent methods.

Investigation of the Influence of Exposure

One aim of this project is to consider that differences in the presence, quantity, and affinity of any specific antibody response between patients may simply be due to differences in intensity and duration of exposure and not due to the protective properties of such a response. To control for this fact, the antibody response needs to be related to the concentration of all *P. falciparum* antibodies. This is done by including a presentation of all the results as ratios to levels of global antiplasmodial antibodies. To address this, 50 µL of plasma from a patient is analyzed by Captia Malaria Total Antibody EIA (Trinity Biotech) at the Hospital of Tropical Diseases, London.

Results

2D Western Blotting

The first study applying 2D electrophoresis with western blotting to the serum of patients for an analysis of antibody responses to *P. falciparum* was employed by Fontaine et al [66]. The study focused on antibody responses to proteins in membranes of infected red blood cells only. These were studied in French soldiers with brief exposure: *P. falciparum* mature stages (trophozoite and schizont stages) were enriched by Plasmion flotation. Immunoblots were directly digitalized using a Typhoon Trio Image scanner. Images were analyzed with Decyder v6.5 software, allowing accurate spot matching between 2D protein patterns and 2D antigenic patterns from gels and immunoblots, respectively. The sera allowed detection of 42 antigenic spots on the 2D immunoblot. The 42 antigenic spots detected on the immunoblot were excised and subjected to mass spectrometry for identification. The resulting fragment ion spectra were searched against the *Homo sapiens* and *P. falciparum* protein databases (NCBInr). Nineteen protein spots (45%) were successfully identified and corresponded to 13 distinct proteins according to their National Center for Biotechnology Information accession number. Among them, 4 were identified as *P. falciparum* proteins and 9 as *Hsapiens* proteins. This indicated the presence of autoantibodies in *P. falciparum* malaria. This study failed to identify several well-described *P. falciparum* antigenic proteins from the iRBC plasma membrane. The major part of these *P. falciparum* antigens are large hydrophobic proteins (>150 kDa), which are generally underrepresented and can be difficult to detect by 2D electrophoresis such as PfEMP1, Pf332 cytoadherence-linked asexual protein 9 (Clag 9) or EBA-175. The reducing and denaturing conditions used for the immunoblot analysis in this study did not consider conformational epitopes. Proteins with extreme isoelectric points or molecular weight may not have been detectable with the type of 2D electrophoresis applied in this study. 2D electrophoresis of *P. falciparum* schizonts performed with a high-resolution procedure revealed 661 protein

spots in one study using a pH range of 4 to 7 in the first dimension. This indicated a loss of detection of proteins (there are 1036 predicted schizont proteins) at lower and higher pH which is relevant because of the bimodal distribution of isoelectric points of schizont proteins reaching those pH extremes [48].

Immunoaffinity Chromatography

Immunoaffinity chromatography has been used to generate purified immunoglobulin subclass fractions from polyclonal human immunoglobulin preparations [45,46]**.** This has been achieved by the use of monoclonal immunoglobulin subclass antibodies immobilized to Sephadex through proteins A and G. Antigens bound by immunoglobulins produced by mice with enhanced immunity to *P yoelii* have been isolated and identified by immobilizing immunoglobulin from immune mice to a Sephadex column and then passing a blood-stage antigen mixture through the column followed by elution of antigens with sodium deoxycholate and identification of antigens after SDS-PAGE and western blotting using specific antibodies.

Discussion

Strengths and Limitations of 2D Western Blotting and Immunoaffinity Chromatography

The approach to discovery of immunorelevant antigens proposed in this experimental protocol takes into account the complexity of native proteins with their numerous *protein species* [67] for each expressed amino acid sequence, which is generated by posttranslational modification in *P. falciparum* through glycosylation, phosphorylation, and methylation as well as the generation of disulfide bonds, which are all essential in the formation of nonlinear conformational epitopes not generated in recombinant antigens. The 2 methods employed for the identification of immunorelevant antigens have advantages and disadvantages and may thus complement each other.

Advantages of 2D western blotting of native antigens are as follows:

- Potential for identification of antibody responses selective for specific defined isomeric forms of the same protein, including isoforms (*protein species*) generated by posttranscriptional modifications such as phosphorylation, glycosylation, and methylation.
- Highly sensitive detection and preservation of antibody responses in the process of 2D western blotting.

Disadvantages of 2D western blotting of native antigens are as follows:

- Loss of antigens during the blotting process.
- Only semiquantitative determination of antibody responses and inaccurate quantification of antigens.

Advantages of immunoaffinity chromatography are as follows:

- No matching of the 2D western blot image with master gel is required.
- No antigen loss is observed through the blotting process.
- Potential for exact quantification of antigens eluted possible through mass spectrometry. The quantification of eluted antigens allows indirectly quantification of the magnitude of antibody responses to these antigens because the amount of antigens eluted corresponds to the amount of antibodies binding them.

Disadvantages of immunoaffinity chromatography are as follows:

- Loss and denaturation of immunoglobulin subclass antibodies during the purification and immobilization of each immunoglobulin subclass on the Sephadex columns.
- Nonspecific trapping of an unknown quantity of antigen in the Sephadex column.
- Quantity of saturation by antigens of antigen-binding sites of an unknown quantity of immobilized immunoglobulin subclass antibodies specific to each epitope is unknown. If antigen-binding sites are saturated, the quantitation of bound antigens may become unreliable because of the competition for binding sites by identical or similar (isomorphic or isomeric) antigens, which may lead to an underestimation of immune-relevant antigens that are not bound because of this process.

Potential Impact of Identification of Immunorelevant Antigens

The aforementioned methods may be suitable for the identification of hypothetical candidates for vaccine antigens. Only future prospective vaccine trials using the antigens identified could demonstrate that they elicit protective immunity. This proposed project is only geared to help identify candidates for such trials. A difficulty arising from the further use of native proteins or protein complexes as vaccine candidates is mass production. This has been brilliantly put in reference to merozoite protein-containing vaccines:

> *In order to generate an immunogenic protein aggregate, it would be desirable to mimic the quaternary structure of merozoite proteins on the merozoite surface (the reason why many viral vaccines are so effective at inducing neutralizing antibodies is that they deliver capsid antigens in virus-like particles stabilized by native protein-protein interactions). Although there have been recent major advances in our knowledge of the protein-protein interactions of merozoite surface proteins, it is not yet possible to use this information to generate a homo- or heteropolymer to test as a vaccine candidate. Even with a more detailed picture of the ultrastructure of the merozoite surface coat, however, it would be technically difficult to produce a native merozoite surface protein complex for use in a vaccine consisting of recombinant proteins. [68]*

Authors' Contributions

ME conceived the hypothesis and ways to test the hypotheses and wrote the entire manuscript. ME gave the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity or any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Head-to-head comparison of response to immunization by native versus recombinant antigens.
[DOC File , 32 KB - resprot_v9i7e15690_app1.doc]

Multimedia Appendix 2
Details of preparation and conduct of electrophoresis and immunochromatography.
[DOCX File , 49 KB - resprot_v9i7e15690_app2.docx]

Multimedia Appendix 3
Trouble shooting guide.
[DOCX File , 18 KB - resprot_v9i7e15690_app3.docx]

References

1. McGregor IA. Gamma-globulin and acquired immunity to human malaria. Nature 1961 Nov 25;192:733-737. [doi: 10.1038/192733a0] [Medline: 13880318]
2. Perrin LH, Dayal R, Rieder H. Characterization of antigens from erythrocytic stages of plasmodium falciparum reacting with human immune sera. Trans R Soc Trop Med Hyg 1981;75(1):163-165. [doi: 10.1016/0035-9203(81)90055-9] [Medline: 7022789]
3. Brown GV, Anders RF, Mitchell GF, Heywood PF. Target antigens of purified human immunoglobulins which inhibit growth of plasmodium falciparum in vitro. Nature 1982 Jun 17;297(5867):591-593. [doi: 10.1038/297591a0] [Medline: 7045680]
4. Johnson DM, Cohen S. Immunological detection of plasmodium knowlesi antigens after electrophoretic transfer from SDS-polyacrylamide gels to diazophenylthioether paper. Parasite Immunol 1984 Jan;6(1):83-93. [doi: 10.1111/j.1365-3024.1984.tb00783.x] [Medline: 6199719]
5. Eisenhut M. The evidence for a role of vasospasm in the pathogenesis of cerebral malaria. Malar J 2015 Oct 13;14:405 [FREE Full text] [doi: 10.1186/s12936-015-0928-4] [Medline: 26463364]
6. Brière F, Servet-Delprat C, Bridon JM, Saint-Remy JM, Banchereau J. Human interleukin 10 induces naive surface immunoglobulin D+ (sIgD+) B cells to secrete IgG1 and IgG3. J Exp Med 1994 Feb 1;179(2):757-762 [FREE Full text] [doi: 10.1084/jem.179.2.757] [Medline: 8294883]
7. Carrayanopoulos L, Capra JD. Immunoglobulins: structure and functions. In: Paul WE, editor. Fundamental Immunology. Third Edition. New York, USA: Raven Press; 1993:283-314.
8. Bouharoun-Tayoun H, Druilhe P. Plasmodium falciparum malaria: evidence for an isotype imbalance which may be responsible for delayed acquisition of protective immunity. Infect Immun 1992 Apr;60(4):1473-1481 [FREE Full text] [Medline: 1548071]
9. Theander TG, Andersen BJ, Pedersen BK, Jepsen S, Bygbjerg IC, Hviid L, et al. Cell-mediated immunity to plasmodium falciparum infection: evidence against the involvement of cytotoxic lymphocytes. Scand J Immunol 1988 Jul;28(1):105-111. [doi: 10.1111/j.1365-3083.1988.tb02421.x] [Medline: 3041559]
10. Celada A, Cruchaud A, Perrin LH. Opsonic activity of human immune serum on in vitro phagocytosis of plasmodium falciparum infected red blood cells by monocytes. Clin Exp Immunol 1982 Mar;47(3):635-644. [Medline: 7044626]
11. Groux H, Gysin J. Opsonization as an effector mechanism in human protection against asexual blood stages of Plasmodium falciparum: functional role of IgG subclasses. Res Immunol 1990;141(6):529-542. [doi: 10.1016/0923-2494(90)90021-p] [Medline: 1704637]
12. Bouharoun-Tayoun H, Druilhe P. Antibodies in falciparum malaria: what matters most, quantity or quality? Mem Inst Oswaldo Cruz 1992;87(Suppl 3):229-234 [FREE Full text] [doi: 10.1590/s0074-02761992000700038] [Medline: 1343695]
13. Aribot G, Rogier C, Sarthou JL, Trape JF, Balde AT, Druilhe P, et al. Pattern of immunoglobulin isotype response to plasmodium falciparum blood-stage antigens in individuals living in a holoendemic area of Senegal (Dielmo, West Africa). Am J Trop Med Hyg 1996 May;54(5):449-457. [doi: 10.4269/ajtmh.1996.54.449] [Medline: 8644897]

14. Sarthou JL, Angel G, Aribot G, Rogier C, Dieye A, Balde AT, et al. Prognostic value of anti-plasmodium falciparum-specific immunoglobulin G3, cytokines, and their soluble receptors in West African patients with severe malaria. Infect Immun 1997 Aug;65(8):3271-3276 [FREE Full text] [Medline: 9234786]
15. Troye-Blomberg M, Perlmann H, Patarroyo ME, Perlmann P. Regulation of the immune response in plasmodium falciparum malaria. II. Antigen specific proliferative responses in vitro. Clin Exp Immunol 1983 Aug;53(2):345-353. [Medline: 6192953]
16. Tangteerawatana P, Montgomery SM, Perlmann H, Looareesuwan S, Troye-Blomberg M, Khusmith S. Differential regulation of IgG subclasses and IgE antimalarial antibody responses in complicated and uncomplicated Plasmodium falciparum malaria. Parasite Immunol 2007 Sep;29(9):475-483 [FREE Full text] [doi: 10.1111/j.1365-3024.2007.00965.x] [Medline: 17727571]
17. Taylor RR, Allen SJ, Greenwood BM, Riley EM. IgG3 antibodies to Plasmodium falciparum merozoite surface protein 2 (MSP2): increasing prevalence with age and association with clinical immunity to malaria. Am J Trop Med Hyg 1998 Apr;58(4):406-413. [doi: 10.4269/ajtmh.1998.58.406] [Medline: 9574783]
18. Metzger WG, Okenu DM, Cavanagh DR, Robinson JV, Bojang KA, Weiss HA, et al. Serum IgG3 to the Plasmodium falciparum merozoite surface protein 2 is strongly associated with a reduced prospective risk of malaria. Parasite Immunol 2003 Jun;25(6):307-312 [FREE Full text] [doi: 10.1046/j.1365-3024.2003.00636.x] [Medline: 14507328]
19. Soe S, Theisen M, Roussilhon C, Aye K, Druilhe P. Association between protection against clinical malaria and antibodies to merozoite surface antigens in an area of hyperendemicity in Myanmar: complementarity between responses to merozoite surface protein 3 and the 220-kilodalton glutamate-rich protein. Infect Immun 2004 Jan;72(1):247-252 [FREE Full text] [doi: 10.1128/iai.72.1.247-252.2004] [Medline: 14688102]
20. Fowkes FJ, Richards JS, Simpson JA, Beeson JG. The relationship between anti-merozoite antibodies and incidence of Plasmodium falciparum malaria: a systematic review and meta-analysis. PLoS Med 2010 Jan 19;7(1):e1000218 [FREE Full text] [doi: 10.1371/journal.pmed.1000218] [Medline: 20098724]
21. Olesen CH, Brahimi K, Vandahl B, Lousada-Dietrich S, Jogdand PS, Vestergaard LS, et al. Distinct patterns of blood-stage parasite antigens detected by plasma IgG subclasses from individuals with different level of exposure to Plasmodium falciparum infections. Malar J 2010 Oct 26;9:296 [FREE Full text] [doi: 10.1186/1475-2875-9-296] [Medline: 20977761]
22. Ferreira MU, Kimura EA, de Souza JM, Katzin AM. The isotype composition and avidity of naturally acquired anti-Plasmodium falciparum antibodies: differential patterns in clinically immune Africans and Amazonian patients. Am J Trop Med Hyg 1996 Sep;55(3):315-323. [doi: 10.4269/ajtmh.1996.55.315] [Medline: 8842122]
23. Pullen GR, Fitzgerald MG, Hosking CS. Antibody avidity determination by ELISA using thiocyanate elution. J Immunol Methods 1986 Jan 22;86(1):83-87. [doi: 10.1016/0022-1759(86)90268-1] [Medline: 3944471]
24. Macdonald RA, Hosking CS, Jones CL. The measurement of relative antibody affinity by ELISA using thiocyanate elution. J Immunol Methods 1988 Feb 10;106(2):191-194. [doi: 10.1016/0022-1759(88)90196-2] [Medline: 3339255]
25. Leoratti FM, Durlacher RR, Lacerda MV, Alecrim MG, Ferreira AW, Sanchez MC, et al. Pattern of humoral immune response to Plasmodium falciparum blood stages in individuals presenting different clinical expressions of malaria. Malar J 2008 Sep 24;7:186 [FREE Full text] [doi: 10.1186/1475-2875-7-186] [Medline: 18816374]
26. Reddy SB, Anders RF, Beeson JG, Färnert A, Kironde F, Berenzon SK, et al. High affinity antibodies to Plasmodium falciparum merozoite antigens are associated with protection from malaria. PLoS One 2012;7(2):e32242 [FREE Full text] [doi: 10.1371/journal.pone.0032242] [Medline: 22363818]
27. Herrera R, Anderson C, Kumar K, Molina-Cruz A, Nguyen V, Burkhardt M, et al. Reversible conformational change in the plasmodium falciparum circumsporozoite protein masks its adhesion domains. Infect Immun 2015 Oct;83(10):3771-3780 [FREE Full text] [doi: 10.1128/IAI.02676-14] [Medline: 26169272]
28. Guy AJ, Irani V, Beeson JG, Webb B, Sali A, Richards JS, et al. Proteome-wide mapping of immune features onto Plasmodium protein three-dimensional structures. Sci Rep 2018 Mar 12;8(1):4355 [FREE Full text] [doi: 10.1038/s41598-018-22592-3] [Medline: 29531293]
29. Doolan DL. Plasmodium immunomics. Int J Parasitol 2011 Jan;41(1):3-20 [FREE Full text] [doi: 10.1016/j.ijpara.2010.08.002] [Medline: 20816843]
30. Gray JC, Corran PH, Mangia E, Gaunt MW, Li Q, Tetteh KK, et al. Profiling the antibody immune response against blood stage malaria vaccine candidates. Clin Chem 2007 Jul;53(7):1244-1253. [doi: 10.1373/clinchem.2006.081695] [Medline: 17510307]
31. Doolan DL, Mu Y, Unal B, Sundaresh S, Hirst S, Valdez C, et al. Profiling humoral immune responses to P falciparum infection with protein microarrays. Proteomics 2008 Nov;8(22):4680-4694 [FREE Full text] [doi: 10.1002/pmic.200800194] [Medline: 18937256]
32. Baum E, Badu K, Molina DM, Liang X, Felgner PL, Yan G. Protein microarray analysis of antibody responses to Plasmodium falciparum in western Kenyan highland sites with differing transmission levels. PLoS One 2013;8(12):e82246 [FREE Full text] [doi: 10.1371/journal.pone.0082246] [Medline: 24312649]
33. Crompton PD, Kayala MA, Traore B, Kayentao K, Ongoiba A, Weiss GE, et al. A prospective analysis of the Ab response to Plasmodium falciparum before and after a malaria season by protein microarray. Proc Natl Acad Sci U S A 2010 Apr 13;107(15):6958-6963 [FREE Full text] [doi: 10.1073/pnas.1001323107] [Medline: 20351286]

34. Nnedu ON, O'Leary MP, Mutua D, Mutai B, Kalantari-Dehaghi M, Jasinskas A, et al. Humoral immune responses to Plasmodium falciparum among HIV-1-infected Kenyan adults. Proteomics Clin Appl 2011 Dec;5(11-12):613-623 [FREE Full text] [doi: 10.1002/prca.201100021] [Medline: 21956928]
35. Costa RM, Nogueira F, de Sousa KP, Vitorino R, Silva MS. Immunoproteomic analysis of Plasmodium falciparum antigens using sera from patients with clinical history of imported malaria. Malar J 2013 Mar 18;12:100 [FREE Full text] [doi: 10.1186/1475-2875-12-100] [Medline: 23506095]
36. Trieu A, Kayala MA, Burk C, Molina DM, Freilich DA, Richie TL, et al. Sterile protective immunity to malaria is associated with a panel of novel P falciparum antigens. Mol Cell Proteomics 2011 Sep;10(9):M111.007948 [FREE Full text] [doi: 10.1074/mcp.M111.007948] [Medline: 21628511]
37. González-Hernández A, Borloo J, Peelaers I, Casaert S, Leclercq G, Claerebout E, et al. Comparative analysis of the immune responses induced by native versus recombinant versions of the ASP-based vaccine against the bovine intestinal parasite Cooperia oncophora. Int J Parasitol 2018 Jan;48(1):41-49 [FREE Full text] [doi: 10.1016/j.ijpara.2017.07.002] [Medline: 28859849]
38. Etlinger HM, Caspers P, Matile H, Schoenfeld HJ, Stueber D, Takacs B. Ability of recombinant or native proteins to protect monkeys against heterologous challenge with Plasmodium falciparum. Infect Immun 1991 Oct;59(10):3498-3503 [FREE Full text] [Medline: 1894356]
39. El-Faham MH, Wheatcroft-Francklow KJ, Price HP, Sayers JR, Doenhoff MJ. Schistosoma mansoni cercarial elastase (SmCE): differences in immunogenic properties of native and recombinant forms. Parasitology 2017 Sep;144(10):1356-1364. [doi: 10.1017/S0031182017000658] [Medline: 28777067]
40. Vercauteren I, Geldhof P, Vercruysse J, Peelaers I, van den Broeck W, Gevaert K, et al. Vaccination with an ostertagia ostertagi polyprotein allergen protects calves against homologous challenge infection. Infect Immun 2004 May;72(5):2995-3001 [FREE Full text] [doi: 10.1128/iai.72.5.2995-3001.2004] [Medline: 15102812]
41. Geldhof P, de Maere V, Vercruysse J, Claerebout E. Recombinant expression systems: the obstacle to helminth vaccines? Trends Parasitol 2007 Nov;23(11):527-532. [doi: 10.1016/j.pt.2007.08.012] [Medline: 17945533]
42. Mattow J, Jungblut PR, Schaible UE, Mollenkopf HJ, Lamer S, Zimny-Arndt U, et al. Identification of proteins from Mycobacterium tuberculosis missing in attenuated Mycobacterium bovis BCG strains. Electrophoresis 2001 Aug;22(14):2936-2946. [doi: 10.1002/1522-2683(200108)22:14<2936::AID-ELPS2936>3.0.CO;2-S] [Medline: 11565788]
43. Nirmalan N, Sims PF, Hyde JE. Quantitative proteomics of the human malaria parasite Plasmodium falciparum and its application to studies of development and inhibition. Mol Microbiol 2004 May;52(4):1187-1199 [FREE Full text] [doi: 10.1111/j.1365-2958.2004.04049.x] [Medline: 15130134]
44. Laishram DD, Sutton PL, Nanda N, Sharma VL, Sobti RC, Carlton JM, et al. The complexities of malaria disease manifestations with a focus on asymptomatic malaria. Malar J 2012 Jan 31;11:29 [FREE Full text] [doi: 10.1186/1475-2875-11-29] [Medline: 22289302]
45. Bird P, Lowe J, Stokes RP, Bird AG, Ling NR, Jefferis R. The separation of human serum IgG into subclass fractions by immunoaffinity chromatography and assessment of specific antibody activity. J Immunol Methods 1984 Jun 8;71(1):97-105. [doi: 10.1016/0022-1759(84)90209-6] [Medline: 6327828]
46. Kamali AN, Marín-García P, Azcárate IG, Diez A, Puyet A, Bautista JM. Plasmodium yoelii blood-stage antigens newly identified by immunoaffinity using purified IgG antibodies from malaria-resistant mice. Immunobiology 2012 Aug;217(8):823-830. [doi: 10.1016/j.imbio.2012.05.002] [Medline: 22658767]
47. Kamali AN, Marín-García P, Azcárate IG, Puyet A, Diez A, Bautista JM. Experimental immunization based on plasmodium antigens isolated by antibody affinity. J Immunol Res 2015;2015:723946 [FREE Full text] [doi: 10.1155/2015/723946] [Medline: 26539558]
48. Gelhaus C, Fritsch J, Krause E, Leippe M. Fractionation and identification of proteins by 2-DE and MS: towards a proteomic analysis of Plasmodium falciparum. Proteomics 2005 Nov;5(16):4213-4222. [doi: 10.1002/pmic.200401285] [Medline: 16196089]
49. Salmon BL, Oksman A, Goldberg DE. Malaria parasite exit from the host erythrocyte: a two-step process requiring extraerythrocytic proteolysis. Proc Natl Acad Sci U S A 2001 Jan 2;98(1):271-276 [FREE Full text] [doi: 10.1073/pnas.011413198] [Medline: 11114161]
50. Foth BJ, Zhang N, Mok S, Preiser PR, Bozdech Z. Quantitative protein expression profiling reveals extensive post-transcriptional regulation and post-translational modifications in schizont-stage malaria parasites. Genome Biol 2008;9(12):R177 [FREE Full text] [doi: 10.1186/gb-2008-9-12-r177] [Medline: 19091060]
51. Smit S, Stoychev S, Louw AI, Birkholtz L. Proteomic profiling of Plasmodium falciparum through improved, semiquantitative two-dimensional gel electrophoresis. J Proteome Res 2010 May 7;9(5):2170-2181. [doi: 10.1021/pr9009244] [Medline: 20218691]
52. Weiss W, Görg A. Two-Dimensional Electrophoresis with Immobilized pH Gradients. In: Proteome Research: Two-Dimensional Gel Electrophoresis and Identification Methods. Berlin, Heidelberg: Springer; 2000:57-106.
53. Bolt MW, Mahoney PA. High-efficiency blotting of proteins of diverse sizes following sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Anal Biochem 1997 May 1;247(2):185-192. [doi: 10.1006/abio.1997.2061] [Medline: 9177676]

54. Krah A, Miehlke S, Pleissner K, Zimny-Arndt U, Kirsch C, Lehn N, et al. Identification of candidate antigens for serologic detection of Helicobacter pylori-infected patients with gastric carcinoma. Int J Cancer 2004 Jan 20;108(3):456-463 [FREE Full text] [doi: 10.1002/ijc.11557] [Medline: 14648714]
55. Towbin H, Staehelin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. Proc Natl Acad Sci U S A 1979 Sep;76(9):4350-4354 [FREE Full text] [doi: 10.1073/pnas.76.9.4350] [Medline: 388439]
56. Mehrizi AA, Zakeri S, Salmanian A, Sanati MH, Djadid ND. IgG subclasses pattern and high-avidity antibody to the C-terminal region of merozoite surface protein 1 of Plasmodium vivax in an unstable hypoendemic region in Iran. Acta Trop 2009 Oct;112(1):1-7. [doi: 10.1016/j.actatropica.2009.05.016] [Medline: 19481997]
57. Taketa K, Ichikawa E, Hanada T. A tetrazolium method for staining peroxidase labels in blotting assays. J Immunol Methods 1986 Dec 4;95(1):71-77. [doi: 10.1016/0022-1759(86)90319-4] [Medline: 2431066]
58. Western Blotting. Principles and Methods. Research & Biopharmaceutical Manufacturing: Cytiva. URL: http://www.gelifesciences.com/handbooks [accessed 2020-06-05]
59. Appel RD, Hochstrasser DF, Funk M, Vargas JR, Pellegrini C, Muller AF, et al. The MELANIE project: from a biopsy to automatic protein map interpretation by computer. Electrophoresis 1991 Oct;12(10):722-735. [doi: 10.1002/elps.1150121006] [Medline: 1802690]
60. Appel RD, Vargas JR, Palagi PM, Walther D, Hochstrasser DF. Melanie II--a third-generation software package for analysis of two-dimensional electrophoresis images: II. Algorithms. Electrophoresis 1997 Dec;18(15):2735-2748. [doi: 10.1002/elps.1150181507] [Medline: 9504805]
61. Marengo E, Robotti E, Antonucci F, Cecconi D, Campostrini N, Righetti PG. Numerical approaches for quantitative analysis of two-dimensional maps: a review of commercial software and home-made systems. Proteomics 2005 Feb;5(3):654-666. [doi: 10.1002/pmic.200401015] [Medline: 15669000]
62. Makanga M, Bray PG, Horrocks P, Ward SA. Towards a proteomic definition of CoArtem action in Plasmodium falciparum malaria. Proteomics 2005 May;5(7):1849-1858. [doi: 10.1002/pmic.200401076] [Medline: 15832369]
63. Henzel WJ, Billeci TM, Stults JT, Wong SC, Grimley C, Watanabe C. Identifying proteins from two-dimensional gels by molecular mass searching of peptide fragments in protein sequence databases. Proc Natl Acad Sci U S A 1993 Jun 1;90(11):5011-5015 [FREE Full text] [doi: 10.1073/pnas.90.11.5011] [Medline: 8506346]
64. Schneider C, Newman RA, Sutherland DR, Asser U, Greaves MF. A one-step purification of membrane proteins using a high efficiency immunomatrix. J Biol Chem 1982 Sep 25;257(18):10766-10769 [FREE Full text] [Medline: 6955305]
65. Lowe J, Bird P, Hardie D, Jefferis R, Ling NR. Monoclonal antibodies (McAbs) to determinants on human gamma chains: properties of antibodies showing subclass restriction or subclass specificity. Immunology 1982 Oct;47(2):329-336. [Medline: 6180976]
66. Fontaine A, Pophillat M, Bourdon S, Villard C, Belghazi M, Fourquet P, et al. Specific antibody responses against membrane proteins of erythrocytes infected by Plasmodium falciparum of individuals briefly exposed to malaria. Malar J 2010 Oct 11;9:276 [FREE Full text] [doi: 10.1186/1475-2875-9-276] [Medline: 20932351]
67. Jungblut P, Thiede B, Zimny-Arndt U, Müller EC, Scheler C, Wittmann-Liebold B, et al. Resolution power of two-dimensional electrophoresis and identification of proteins from gels. Electrophoresis 1996 May;17(5):839-847. [doi: 10.1002/elps.1150170505] [Medline: 8783010]
68. Anders RF, Adda CG, Foley M, Norton RS. Recombinant protein vaccines against the asexual blood stages of Plasmodium falciparum. Hum Vaccin 2010 Jan;6(1):39-53. [doi: 10.4161/hv.6.1.10712] [Medline: 20061790]

Abbreviations

2D: two-dimensional
ACN: acetonitrile
CHAPS: 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate
DTT: dithiothreitol
EBA: erythrocyte-binding antigen 175
FDR: false discovery rate
GLURP: glutamate-rich protein
HPLC/MS: high pressure liquid chromatography/mass spectrometry
IEF: isoelectric focusing
IgG: immunoglobulin G
IOD: integrated optical density
IPG: immobilized pH gradient
MSP-2: merozoite surface protein-2
PAGE: polyacrylamide gel electrophoresis
PBS: phosphate buffered saline
PCA: principal component analysis

PEMS: parasitophorous vacuole membrane–enclosed merozoite structure
TFA: trifluoroacetic acid

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Protocol

Using Application Programming Interfaces to Access Google Data for Health Research: Protocol for a Methodological Framework

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Abstract

Background: Individuals are increasingly turning to search engines like Google to obtain health information and access resources. Analysis of Google search queries offers a novel approach, which is part of the methodological toolkit for infodemiology or infoveillance researchers, to understanding population health concerns and needs in real time or near-real time. While searches predominantly have been examined with the Google Trends website tool, newer application programming interfaces (APIs) are now available to academics to draw a richer landscape of searches. These APIs allow users to write code in languages like Python to retrieve sample data directly from Google servers.

Objective: The purpose of this paper is to describe a novel protocol to determine the top queries, volume of queries, and the top sites reached by a population searching on the web for a specific health term. The protocol retrieves Google search data obtained from three Google APIs: Google Trends, Google Health Trends (also referred to as Flu Trends), and Google Custom Search.

Methods: Our protocol consisted of four steps: (1) developing a master list of top search queries for an initial search term using Google Trends, (2) gathering information on relative search volume using Google Health Trends, (3) determining the most popular sites using Google Custom Search, and (4) calculating estimated total search volume. We tested the protocol following key procedures at each step and verified its usefulness by examining search traffic on *birth control* in 2017 in the United States. Two separate programmers working independently achieved similar results with insignificant variation due to sample variability.

Results: We successfully tested the methodology on the initial search term *birth control*. We identified top search queries for *birth control*, of which *birth control pill* was the most popular and obtained the relative and estimated total search volume for the top queries: relative search volume was 0.54 for the pill, corresponding to an estimated 9.3-10.7 million searches. We used the estimates of the proportion of search activity for the top queries to arrive at a generated list of the most popular websites: for the pill, the Planned Parenthood website was the top site.

Conclusions: The proposed methodological framework demonstrates how to retrieve Google query data from multiple Google APIs and provides thorough documentation required to systematically identify search queries and websites, as well as estimate relative and total search volume of queries in real time or near-real time in specific locations and time periods. Although the protocol needs further testing, it allows researchers to replicate the steps and shows promise in advancing our understanding of population-level health concerns.

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KEYWORDS

Google; search data; infodemiology; infoveillance; infodemic; reproductive health; abortion; birth control; Google Trends; APIs

Introduction

Individuals in the United States seeking health information online turn to search engines first. According to a 2012 Pew Internet & American Life survey, 83% of users identified Google as their main search engine [1]. Health questions and concerns are frequently of a sensitive nature, so queries people type privately into a search engine can provide insight about their true health concerns, especially those that they may not be comfortable sharing with their clinician or a research survey. Stephens-Davidowitz has found that these types of searches often capture what people actually "do, think, or want" because people reveal "some very personal things" in constructing their Google queries [2].

The most popular tool for analyzing and aggregating patterns of search data is Google Trends, a public website that has provided real-time and archived data on Google queries by users since 2004 [3]. It has been used to study online behavior on diverse health topics, such as early detection of influenza epidemics [4-6], pertussis outbreak monitoring [7], asthma monitoring [8], and cancer detection [9,10]. The tool has also been used to study public interest in cancer [11,12], suicide assessment [13,14], depression-related information seeking [15], lifestyle-disease surveillance [16], bariatric surgery [17], herpes zoster vaccinations [18], searches for walk-in clinics and emergency departments [19], obesity-related behavior [20], and reproductive health [21-26]. Research using this tool has increased over 20-fold between 2009 and 2018 [27].

From a methodological standpoint, Google Trends has been used to measure web-based interest and variations of this interest over time [7,18,21,28], assess correlations between search queries with other data sources to inform public health and policy [9,26], and to forecast disease occurrence and outbreaks [4,6,29-31]. These applications fall within the emerging field of infodemiology. As first described by Eysenbach, infodemiology is "the science of distribution and determinants of information in an electronic medium, specifically the internet, or in a population, with the ultimate aim to inform public health and public policy" [32]. A related term, infoveillance, has been used where infodemiology methods are employed for surveillance.

While infodemiology was first used to analyze the quality of information on websites (ie, supply side), the scope has expanded to include what people need and their health-seeking behavior (ie, demand side). According to Eysenbach, analyses of information supply and demand both require new methods to measure the epidemiology of information and to examine the relationships between information supply and/or demand and population health [33].

Although Google Trends is an easily accessible tool for analyzing large population search queries, there is no consensus on how to retrieve, organize, and code queries. Researchers have applied inconsistent methodologies when using this tool and interpreting search data, which sometimes has led to questionable or invalid findings and problems with replicability and comparability across studies [34,35]. In response to these shortcomings, Mavragani and Ochoa [35] recently proposed a concise step-by-step methodological framework that describes how to select the appropriate keyword, region, time period, and category for analysis of search queries to ensure the validity of health assessments with the web-based Google Trends tool. This framework, if used appropriately by researchers, should prove useful to ascertain more uniformity and comparability across studies and further our insight into human behavior.

Less noted is that Google data is also available through Google application programming interfaces (APIs). Multimedia Appendix 1 compares the Google Trends website and the API and illustrates their similarities and differences through an example. The Google Trends API can be used as a first step to identify top queries or search terms, and the API can be used in combination with two other Google APIs—Google Health Trends API and the Custom Search API—to extend the researcher's understanding of search behaviors. The reason to combine APIs is that although the Google Trends website gives insight into search query volume, the additional APIs are needed to relate search intent to individual websites. All three APIs allow users to write code in a programming language such as Python to retrieve sample data directly from Google servers. However, access to the Google Trends API and Health Trends API is restricted to researchers and requires an application to Google.

This article aims at documenting and illustrating a novel protocol for the use of three Google APIs to determine search query volume and individual websites reached by a given population searching using a health-related search term. This protocol is not the only one enabled by these APIs but is appropriate for the stated aim. We draw on examples from our study, which seeks to examine insights obtained from aggregated search queries related to the prevention of pregnancy. Analyses of queries related to birth control are relevant for policy and programmatic efforts because public funding and access to birth control are increasingly under attack in the United States [36]. As access becomes more restrictive, use of the web may become more important in decision making about family planning.

Since there are no accepted methodological standards for the use of Google APIs in academic research, our paper contributes to the systematization of an approach to combining APIs. The proposed methodology allows for a fuller picture of the volume and content of searches we are exploring through the examination of top topics and queries, relative search volume (RSV), top websites visited when searching for these top queries, and estimated volume of searches. The use of multiple APIs also provides multiple methods to estimate key values, ensuring the data obtained are accurate and reliable.

Methods

Overview

We obtain key pieces of Google search data by using three Google APIs. Google Trends provides the top search topics and top search queries given an initial search term for a specified time period and location. Google Health Trends generates the RSV for a list of top queries in a specific region and time period. Finally, Google Custom Search provides the list of top websites that people who search using a given initial search term are shown when using the Google search engine. Custom Search gives results at the time of accessing the API, and these results can be specified at the national level.

The Google Health Trends API, previously known as Google Flu Trends, gives normalized RSV across a set of search queries, allowing for more in-depth analysis of the relationships between queries. This RSV refers to the proportion of searches for a specific query as compared to the sum total of searches for a set of queries, and thus differs from the relative search index given by Google Trends, which gives search interest relative to all searches during the specified period of time. Although this proprietary tool is not available via the Google Trends website, it offers benefits to the researcher by providing a clearly defined metric to understand and interpret RSV.

We show that the RSV provided by Google Health Trends can be combined with another trusted data source to estimate total search volume. RSV can also inform estimates of proportions of searches to a given site. To gather information on the top websites displayed on the Google search engine for a specific search term or topic of interest, we can access data through the Custom Search API. Because Custom Search gives results at the time of API access, researchers should plan accordingly and prepare to take regular samples of top sites during the time period of interest. This list of top sites is for the entire country. Evidence shows that the selection, sorting, and ranking criteria of search engines influence online health-information seeking [37]. Custom Search data allow for analysis of content and quality of information that people get online. Thus, while the Google Trends website can determine what information people search for, it cannot determine what information they find. Hence, working with the three APIs enables a more comprehensive analysis than could be completed by using only the Google Trends website.

We developed a simulation protocol that consisted of four steps: identifying a list of search queries for the topics of interest, obtaining RSV, determining top sites for top search queries, and calculating estimated total search volume. We describe these fully in Tables 1-5. We tested the protocol to examine the top queries for *birth control* in the United States in 2017 and created visualizations for each step. We used Python, version 2.7.13 (Python Software Foundation), for all of the API calls. Examples of the Python commands used are shown in Figures MA2-1 to MA2-7 in Multimedia Appendix 2. Multimedia Appendix 3 contains the documentation of the Python package Graphviz [38] and the APIs used.

Step 1: Developing a List of Search Queries

In the first step, we used the *getTopQueries* function to get the queries most associated with the initial topic of interest during a researcher-specified time period in a researcher-specified geographic region. The *getTopQueries* function can also gather the queries most associated with the previously obtained top queries, referred to as follow-up queries. Top queries are displayed in a graph that illustrates the relationship between queries. More details of the step-by-step procedures carried out are shown in Table 1. Figures 1 and 2 show intermediary Steps 1.3 and 1.5 of the protocol.

Table 1. Developing a list of top search queries.

Step	Description
1.1	Begin with a list of regions to explore and a single, broad, initial search term, such as *birth control*.
1.2	For each region, make a request to Google Trends' *getTopTopics* function to obtain the most searched-for topics for a specific initial search term. The function will return a list of topics that term is most closely related to as well as a value from 0 to 100 that denotes how strongly linked the topic is to the initial term: 100 is the most closely associated and 0 is the least. This list of top topics serves only to validate the top queries by examining similarities between the top topics and top queries.
1.3	Next, make a call to Google Trends' *getTopQueries* function to get a list of the search queries most related to the initial search term in Step 1.1 for a given region, such as the United States. Each response from the *getTopQueries* method contains a *title*, or query, and a *value* attribute, which is a number from 0 to 100 and represents how related the query is to the provided initial search term in the United States: 100 is the most associated and 0 is the least. The data are presented in the form of a JSON (JavaScript Object Notation)-encoded mapping (see Figure MA2-1 in Multimedia Appendix 2), which can easily be converted into a graph via Python or exported to a CSV (Comma-Separated Values) file. If there are other regions of interest (eg, US states), this step must be repeated for all other regions. Each region will have a *final list* variable that stores all the top queries for that region. Once all final lists are generated for all regions of interest, they will be combined to create a *master list* that includes the top queries for every region of interest (Figure 1 shows an example). Figure MA2-2 in Multimedia Appendix 2 shows a snippet of the Python code.
1.4	For every query generated in Step 1.3, send a request to *getTopQueries* to obtain *follow-up terms*. Only queries with a *value* attribute greater than or equal to 70, as this indicates a high level of correlation between the terms, is added to our *follow-up queries* list. Irrelevant searches relating to pop culture should be manually filtered from results. Step 1.4 should be recursively executed—the *follow-up queries* become the base set at each iteration—until no new queries can be added to the base set. During this step, how each query is related to each other (ie, how a query ended up in our set of queries) should be recorded. This step is terminated when requests to *getTopQueries* do not return unique queries that have not already been received in the simulation for this region.
1.5	Then, generate a graph using the Graphviz package for Python 2.7 [38] that illustrates how the search queries in the *final list* and the *follow-up queries* list are related to one another. As shown in Figure 2, every node in the graph is a search query, and those in the first level will be included in the final list of search queries for the simulation. If a node is encapsulated by a double circle, then this represents an overarching topic coded for internal organizational purposes within the Google application programming interface (API) and is not included in the *final list* or *follow-up queries*. Every direct edge (arrow) in the graph represents a relationship between two search queries (nodes) in the graph. Note that with the current cutoff value of 70 in Step 1.4, there may be other intermediate terms in the graph not captured. Figure MA2-3 in Multimedia Appendix 2 shows the Python function used.

Figure 1. Creation of a master list as visualized in Python for *birth control* in the United States, Mississippi, and Louisiana in 2017.

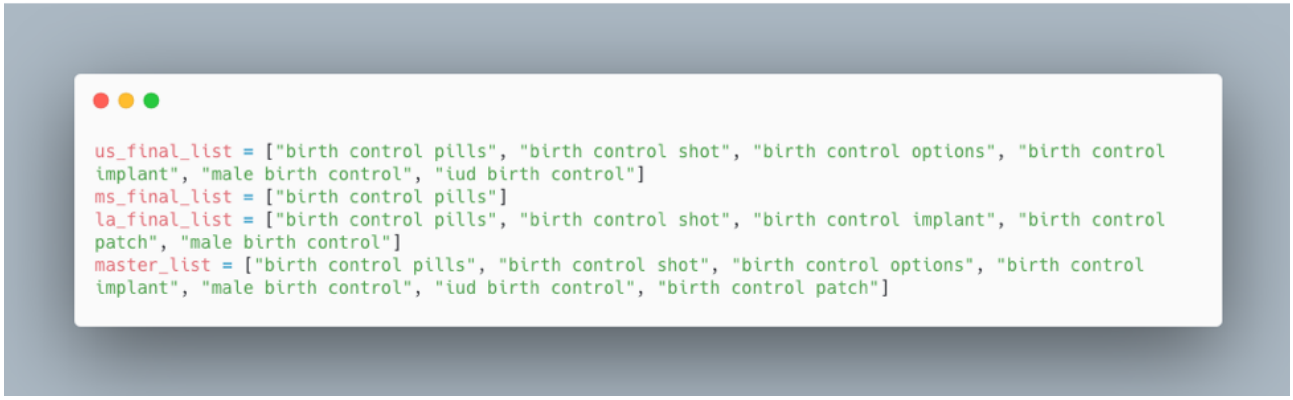
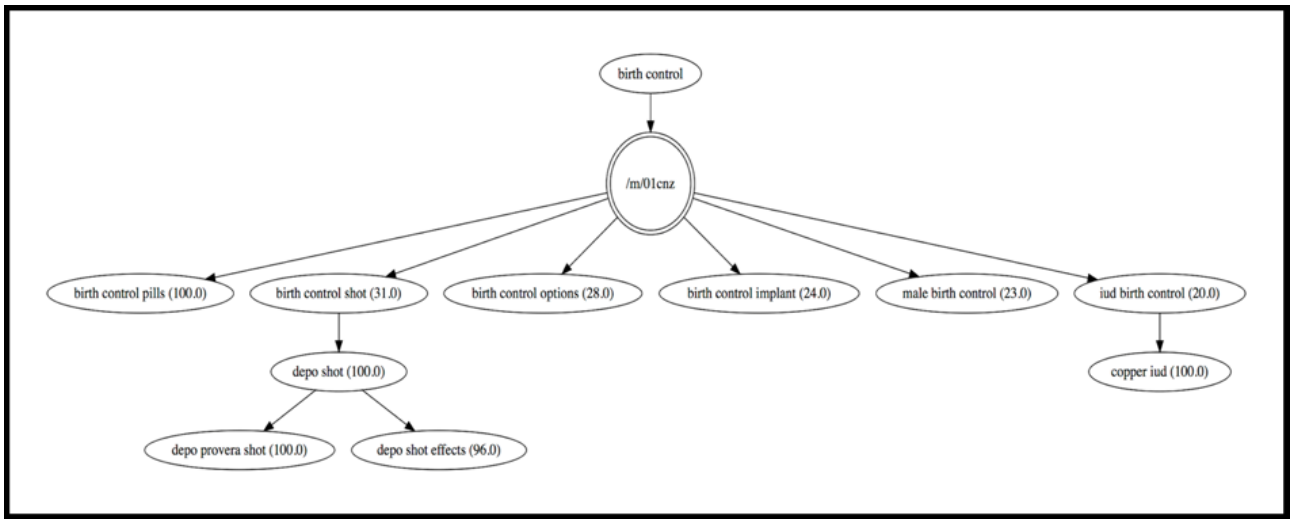


Figure 2. Top queries for *birth control* in the United States in 2017. Single circles in the graph represent search queries, whereas a double circle indicates an overarching topic coded for internal organizational purposes within the Google application programming interface (API) and is not included in the list of top queries. Numbers in parentheses indicate how relation of query to the provided initial search term. iud: intrauterine device.



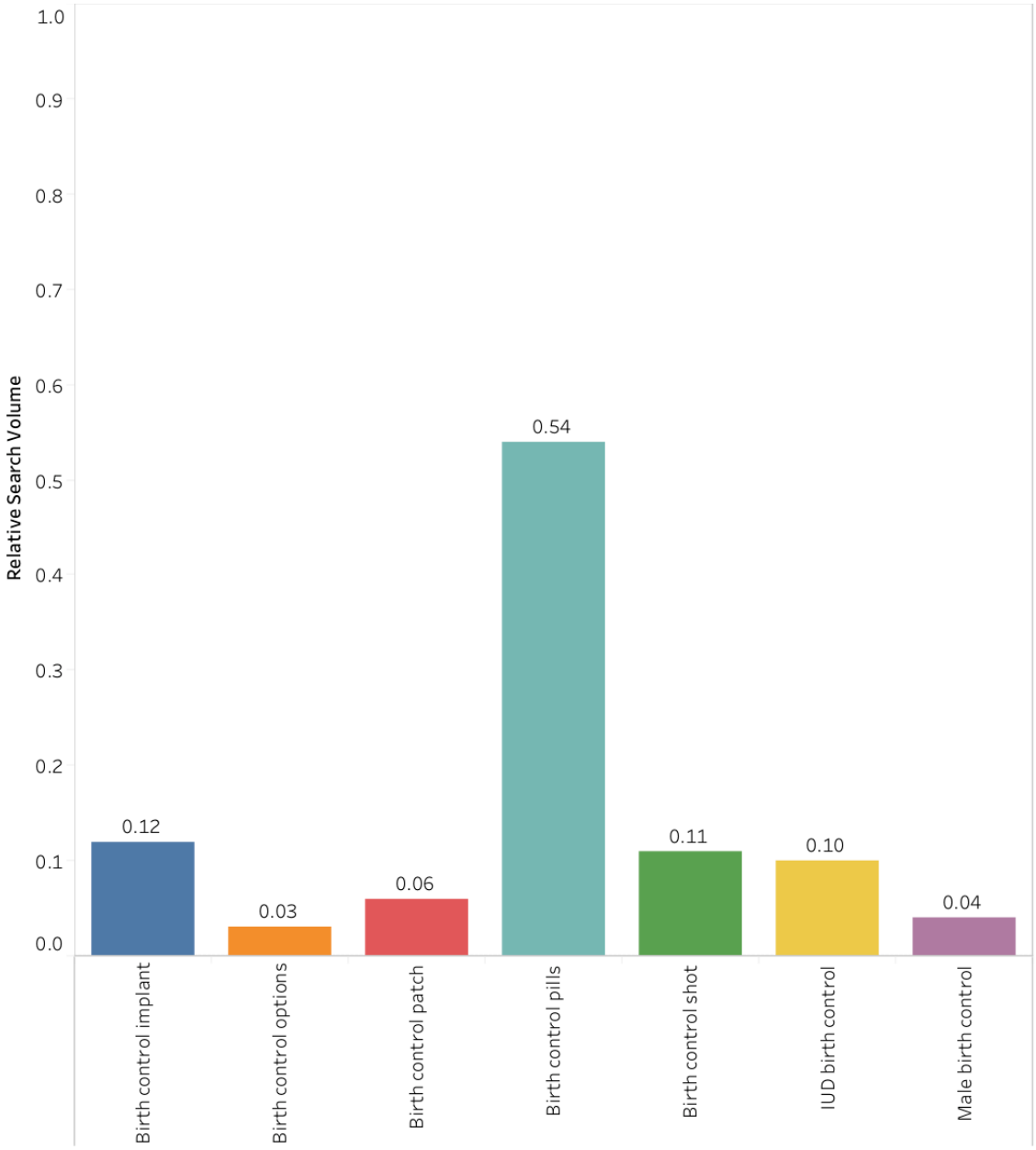
Step 2: Gathering Information on Search Volume

In the second step, the *getTimelinesForHealth* function in the Google Health Trends API gives the RSV for the top search queries generated in the previous step. All values generated are relative: the API gives the relative frequency of a specific term as compared to the other terms in the *master list* for a specific region during a specified period of time. More step-by-step details are shown in Table 2. Figure 3 illustrates the normalized RSV as described in the intermediary Step 2.3.

Table 2. Gathering information on search volume.

Step	Description
2.1	For each region, for every term in the master list, send a request to the *getTimelinesForHealth* function from the Google Health Trends application programming interface (API) to obtain relative search volume. Figure MA2-4 in Multimedia Appendix 2 shows an example of the API call in Python.
2.2	The process in Step 2.1 should be repeated 30 times to minimize error. We take the average of the 30 samples of relative search volumes, which represents the estimated search volume for a given term with the date and location restrictions provided. Figure MA2-5 in Multimedia Appendix 2 shows a sample response of relative search volumes given by the *getTimelinesForHealth* function in the United States.
2.3	To compare across regions, normalize the values for each region by dividing each term's value with the aggregate search volume for the region. Before normalization, the value returned is skewed and does not take into account parameters such as geographical size differences. The normalized value will range from 0 to 1. The total sum of all values of the set of queries is 1 after normalization. The value from 0 to 1 allows for understanding of the relative search frequency within search queries. These data can then be used to define search frequencies for each term (see Figure 3). The normalization function used in this study is found in Figure MA2-6 in Multimedia Appendix 2.

Figure 3. Relative search volume for *birth control* in the United States in 2017. IUD: intrauterine device.



Step 3: Determining the Most Popular Sites

In the third step, we send a request to the Google Custom Search API for each query in the master list to obtain a list of ranked top websites as they appear on the Google search engine results (see Table 3). A study from Chitika [39] demonstrated that the first 10 sites in the search results receive about 95% of the traffic or more, prompting us to only consider the first page of sites returned in the search results. According to the Chitika study, the probabilities of someone clicking on the first, second, and third sites are 0.35, 0.20, and 0.15, respectively; the probabilities of someone clicking on the fourth and fifth sites are 0.08 and 0.07, respectively. The probabilities keep decreasing, such that the probability of someone clicking on any site following the ninth site is 0.01. The Chitika frequencies for site rankings, the Custom Search API rankings, and the RSV for the query can be used to calculate the estimated proportion of site visits at the time of API access. The call to the Custom Search API is outlined in Figure MA2-7 in Multimedia Appendix 2. An example of this step, involving the term *birth control pills* and the top five sites visited [40-44], is illustrated in Table 4 in the Results section.

Table 3. Determining the most popular sites.

Step	Description
3.1	Use the master list generated in *Step 1: Developing a List of Search Queries* and send a request to the Google Custom Search application programming interface (API) for every term in the master list. This API returns a list of ranked top websites as they appear on the Google search engine results.
3.2	Use the frequencies for site rankings, the Custom Search API rankings, and the relative search volume for the query to calculate the estimated proportion of site visits. For example, as shown in Table 4, the top site for the term *birth control pills* in the United States is the *birth control pill* webpage on the Planned Parenthood website [40]. The relative search volume for *birth control pills* in the United States in 2017 is 0.54, and the probability of someone clicking on the first site returned on the Google search engine is 0.35. Thus, the estimated proportion of site visits to Planned Parenthood is 0.19.

Table 4. Top five sites visited for birth control pill searches in the United States in August 2018.

Site ranking	Website	Webpage
1	Planned Parenthood [40]	Birth control pill
2	WebMD [41]	Birth control pills
3	Wikipedia [42]	Combined oral contraceptive pill
4	BirthControl.com [43]	Birth control pills
5	Healthline [44]	Birth control pills: Are they right for you?

Step 4: Calculating Estimated Total Search Volume

Google does not provide total search volumes. We overcome this limitation by using actual volume on searches to a concrete website as the baseline for calculating estimated total search volume corresponding to the RSV for the top search queries obtained from the Health Trends API. We worked with Planned Parenthood Federation of America (PPFA) to obtain the number of searches that led to their website, as this is the most popular website for reproductive health information that people access in the United States. PPFA works with Vector Media to collect analytics on the number of visitors to their site. A search is defined as a user typing in a query in a search engine and then being directed to the search engine's results [45]. All of the data on searches that we obtained are, thus, the result of a user entering in a query regarding a particular initial search term in the Google search engine, which then leads them to the Planned Parenthood website. Slightly different processes must be used when the search query that directly relates to the site that the search data comes from is not present in the list of top queries. Estimated total search volume should be presented as a range that includes an upper bound determined by the lowest association of the top queries obtained. This assumes that there may be queries with lower associations that are not returned by the API. We show an example in the Results section.

Results

Step 1: Developing a List of Search Queries

We follow Step 1 of our procedure to gain information on the top queries for *birth control* in the United States in 2017. As shown in Figure 2, the most popular query was for birth control pills, followed in order of popularity by the shot, often searched for by its medical term Depo Provera and its effects; the implant; male birth control; and the intrauterine device (IUD). Queries for the IUD were predominantly for the copper IUD.

Step 2: Gathering Information on Search Volume

We then use our findings in Step 1 to complete Step 2 of the protocol: determining the RSV of the top queries. Figure 3 shows, for instance, that in the United States in 2017, the pill (RSV=0.54) was searched for 4.5 times more than the implant (RSV=0.12) and 5.4 times more than male birth control (RSV=0.04).

Step 3: Determining the Most Popular Sites

We follow Step 3 of the protocol to obtain information on top sites. We chose one top query, *birth control pills*, as an example to demonstrate; however, to gain a full picture of top sites viewed, it is important to carry out this step for all top queries (see Table 4).

Step 4: Calculating the Estimated Total Search Volume

We estimate that the total number of searches for birth control in 2017 fell within the following ranges for the United States: 17,171,784-19,747,552 searches. These values were calculated using the formula outlined in Table 5. *Planned Parenthood* is not a top search query for the term *birth control*, but as we found out, it is a top search query for *abortion*. By obtaining the RSV of *birth control* as compared to *abortion*, we were able to obtain the estimated total search volume for *birth control* and then applied the RSV weights to obtain estimated total search volume for the top queries. Because the top queries do not account for all queries searched for—evidenced by the association values presented in Figure 3—we calculated an upper bound of 15% that we include in our estimates. Figure 4 shows the estimated total search volume for each of the top search queries for *birth control* in the United States in 2017 based on the RSV weights for the top birth control methods.

Table 5. Calculations for estimated total search volume for birth control in the United States.

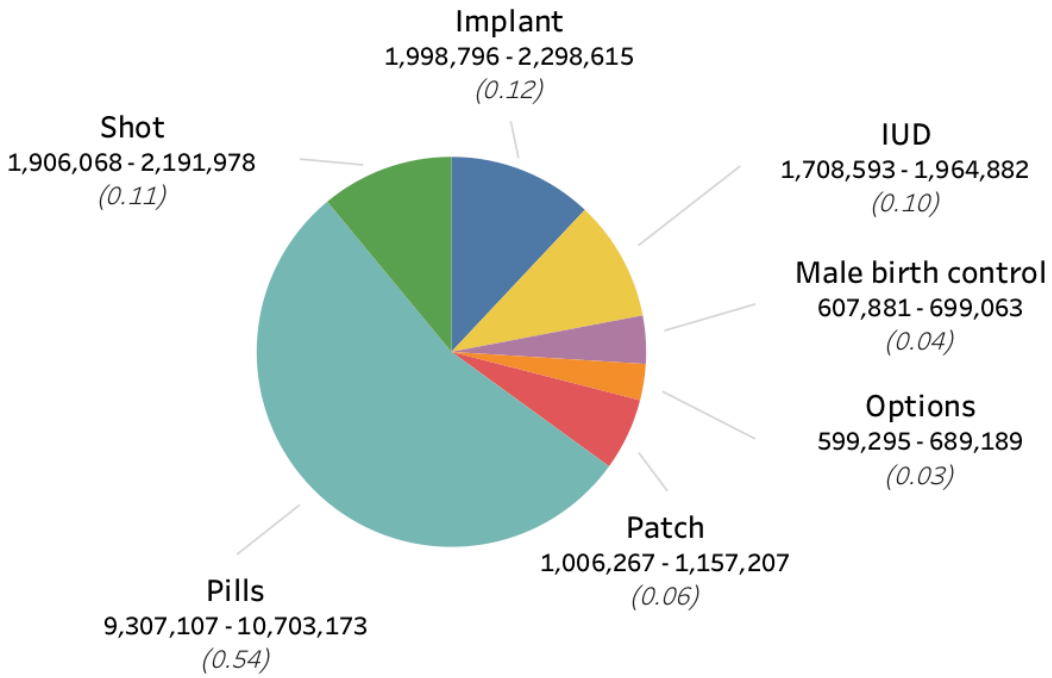
Search item measure	Value
Total number of searches for *abortion* from Planned Parenthood	12,393,960
RSV[a] for *abortion*	0.4192
RSV for *birth control*	0.5808
Estimated total number of searches overall	29,565,744[b]
Estimated total number of searches for *birth control*	17,171,784[c]

[a]RSV: relative search volume.

[b]0.4192 (*RSV for abortion*)x = 12,393,960 (total number of searches for *abortion* from Planned Parenthood); x = 29,565,744.

[c]0.5808 (RSV for *birth control*) × 29,565,744 (estimated total number of searches overall) = 17,171,784.

Figure 4. Estimated total search volume (range) and relative search volume (within parentheses) for *birth control* in the United States in 2017. IUD: intrauterine device.



Discussion

Principal Findings

Google Trends has become a popular tool for analyzing search traffic on health. It has been used by researchers to measure general web-based interest, examine policy-related issues, get insights into health behavior, and to monitor and predict health-related events [27,29]. However, it has been used inconsistently due to a lack of consensus on how to document Google search engine queries in academic research. This leaves room for methodological development. In this article, we show that Google Trends data, when retrieved from the Google Trends API, offers more versatile analytic capabilities than the data from the Google Trends website and offers the benefit of incorporating other APIs to extend insight into search-traffic behavior.

The proposed protocol—empirically tested with *birth control* as the key initial search term—is capable of addressing important questions about Google search traffic and search interest. By following four distinct steps using three Google APIs, we are able to identify top search queries and websites as well as estimate relative and total search volume of queries in real time or near-real time in specified locations and time periods. The use of multiple APIs also provides multiple methods to obtain key values, ensuring the data obtained are accurate and reliable.

Our methodology is robust insofar as it is well documented and avoids inserting any personal bias into the process of determining top search queries, since all top queries are given by the API. In addition, we are able to provide a novel solution to the current limitation of Google data, which, for privacy concerns, does not provide the absolute volume of searches. Prior studies proposed an approach to calculating total estimated search volume [25], but this approach is no longer replicable given the constant updates Google makes to its technologies.

The thorough documentation provided to apply the proposed protocol will allow researchers to replicate the methods used to further the understanding of population interest in health issues. The protocol can be applied to compare state-level searches to those at the national level and to explore changes

in search traffic over time. It can easily be applied to other initial search terms; in our own exploration, we found that in the United States, people who searched for *family planning* instead of *birth control* were searching for traditional or *natural family planning* methods based on fertility awareness. Additionally, our protocol can be utilized at the zip code–based Nielsen Demographic Marketing Area (DMA) level, which is the smallest geolocation level that Google reports on and is available for each state. However, to protect user privacy, Google does not report data below a certain unknown threshold, so data may be unavailable for some DMAs.

Google data can provide essential context to administrators, health care professionals, and academics. Top queries show varying interest in health topics as well as products and services by location, thus allowing health care providers to tailor services and information available at clinics and local practices to the questions people are asking. RSV provides context on how search interest compares by location, thus allowing one to focus on what resources are most desired or sought out. Top websites are crucial information for researchers, as they give a direct picture of what searchers are finding when they seek information. This data can provide insight as to why misinformation may spread or what organizations are having the greatest influence in sharing their beliefs, products, and services with potential patients and/or consumers. Finally, estimated total search volume allows professionals to know the amount of the population that may be seeking access to resources or information on the resources in question. More broadly speaking, this data gives interested stakeholders understanding of the changing health care landscape and identifies key concerns of potential patients and clients. Trends in search data over time may reveal the impact of administrative revisions and/or decisions made at the state or national level.

Limitations

The results that our protocol can achieve must be tempered by the limitations of the data and the data sources. Google Trends reports on the top related and rising queries, as well as the top related and rising topics, but does not provide a list of all queries searched for. Thus, although the list of top queries is a comprehensive list of the most popular queries that users search for, it does not include every single query searched for relating to a particular initial search term. Similarly, the RSV is only relative to the other queries in our final list and does not include other queries that were not a part of the list of top queries. Furthermore, we are not able to identify the number of unique users or their individual characteristics.

For most popular sites, we were unable to identify the key websites at the state level or request a specified time period. To overcome this limitation, one could import another source of data, such as a Google Consumer Survey (GCS) run at the state level. GCS is a tool that allows for online, customized market research and can be used to survey internet users about their preferred websites that they seek for specific queries [46]. The values obtained from these responses could additionally be used as anchor points for calculating total volume of searches.

Clearly, we require more studies to assess the value and validity of the proposed methodology. Temporal changes in the interface and capabilities of Google data pose challenges to the research community because researchers cannot build on nonspecific, nonreplicable, and discontinued methodologies. Hence, the proposed methodology will necessarily evolve as Google continues to make changes. In June 2019, Google made additional changes to the Google Trends API that had an effect on the *getTopQueries* function, resulting in a broader list of top queries than when our study data were retrieved. Future studies may integrate Google searches and other sources of online big data with machine learning models to track health topics [47].

Conclusions

The combination of Google APIs suggested in the proposed methodological framework offers a novel approach to analysis of Google health queries, expanding the tools available to gain insight into health assessments.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Google Trends website and Google Trends application programming interface (API) comparison.
[DOCX File , 845 KB - resprot_v9i7e16543_app1.docx]

Multimedia Appendix 2
Python code appendix.
[DOCX File , 1764 KB - resprot_v9i7e16543_app2.docx]

Multimedia Appendix 3
Details of packages used within code and documentation for application programming interfaces (APIs).
[DOCX File , 13 KB - resprot_v9i7e16543_app3.docx]

References

1. Purcell K, Brenner J, Rainie L. Search Engine Use 2012. Washington, DC: Pew Internet & American Life Project; 2012 Mar 09. URL: https://www.pewinternet.org/wp-content/uploads/sites/9/media/Files/Reports/2012/PIP_Search_Engine_Use_2012.pdf [accessed 2019-08-15]
2. Stephens-Davidowitz S. Everybody Lies: Big Data, New Data, and What the Internet Can Tell Us About Who We Really Are. New York, NY: HarperCollins Publishers; 2017.
3. Google Trends. URL: https://trends.google.com/trends/ [accessed 2020-01-27]
4. Ginsberg J, Mohebbi MH, Patel RS, Brammer L, Smolinski MS, Brilliant L. Detecting influenza epidemics using search engine query data. Nature 2009 Feb 19;457(7232):1012-1014. [doi: 10.1038/nature07634] [Medline: 19020500]
5. Klembczyk JJ, Jalalpour M, Levin S, Washington RE, Pines JM, Rothman RE, et al. Google Flu Trends spatial variability validated against emergency department influenza-related visits. J Med Internet Res 2016 Jun 28;18(6):e175 [FREE Full text] [doi: 10.2196/jmir.5585] [Medline: 27354313]
6. Kandula S, Hsu D, Shaman J. Subregional nowcasts of seasonal influenza using search trends. J Med Internet Res 2017 Nov 06;19(11):e370 [FREE Full text] [doi: 10.2196/jmir.7486] [Medline: 29109069]
7. Gianfredi V, Bragazzi N, Mahamid M, Bisharat B, Mahroum N, Amital H, et al. Monitoring public interest toward pertussis outbreaks: An extensive Google Trends-based analysis. Public Health 2018 Dec;165:9-15. [doi: 10.1016/j.puhe.2018.09.001] [Medline: 30342281]
8. Mavragani A, Sampri A, Sypsa K, Tsagarakis KP. Integrating smart health in the US health care system: Infodemiology study of asthma monitoring in the Google era. JMIR Public Health Surveill 2018 Mar 12;4(1):e24 [FREE Full text] [doi: 10.2196/publichealth.8726] [Medline: 29530839]
9. Phillips CA, Barz Leahy A, Li Y, Schapira MM, Bailey LC, Merchant RM. Relationship between state-level Google online search volume and cancer incidence in the United States: Retrospective study. J Med Internet Res 2018 Jan 08;20(1):e6 [FREE Full text] [doi: 10.2196/jmir.8870] [Medline: 29311051]
10. Xu C, Wang Y, Yang H, Hou J, Sun L, Zhang X, et al. Association between cancer incidence and mortality in web-based data in China: Infodemiology study. J Med Internet Res 2019 Jan 29;21(1):e10677 [FREE Full text] [doi: 10.2196/10677] [Medline: 30694203]
11. Mukhija D, Venkatraman A, Nagpal SJ. Effectivity of awareness months in increasing internet search activity for top malignancies among women. JMIR Public Health Surveill 2017 Aug 21;3(3):e55 [FREE Full text] [doi: 10.2196/publichealth.7714] [Medline: 28827213]
12. Vasconcellos-Silva PR, Carvalho DB, Trajano V, de La Rocque LR, Sawada AC, Juvanhol LL. Using Google Trends data to study public interest in breast cancer screening in Brazil: Why not a pink February? JMIR Public Health Surveill 2017 Apr 06;3(2):e17 [FREE Full text] [doi: 10.2196/publichealth.7015] [Medline: 28385679]
13. Arora V, Stuckler D, McKee M. Tracking search engine queries for suicide in the United Kingdom, 2004-2013. Public Health 2016 Aug;137:147-153. [doi: 10.1016/j.puhe.2015.10.015] [Medline: 26976489]
14. Lee D, Lee H, Choi M. Examining the relationship between past orientation and US suicide rates: An analysis using big data-driven Google search queries. J Med Internet Res 2016 Feb 11;18(2):e35 [FREE Full text] [doi: 10.2196/jmir.4981] [Medline: 26868917]
15. Tana JC, Kettunen J, Eirola E, Paakkonen H. Diurnal variations of depression-related health information seeking: Case study in Finland using Google Trends data. JMIR Ment Health 2018 May 23;5(2):e43 [FREE Full text] [doi: 10.2196/mental.9152] [Medline: 29792291]
16. Memon SA, Razak S, Weber I. Lifestyle disease surveillance using population search behavior: Feasibility study. J Med Internet Res 2020 Jan 27;22(1):e13347 [FREE Full text] [doi: 10.2196/13347] [Medline: 32012050]
17. Rahiri J, Barazanchi A, Furukawa S, MacCormick AD, Harwood M, Hill AG. Using Google Trends to explore the New Zealand public's interest in bariatric surgery. ANZ J Surg 2018 Dec;88(12):1274-1278. [doi: 10.1111/ans.14772] [Medline: 30173419]
18. Berlinberg EJ, Deiner MS, Porco TC, Acharya NR. Monitoring interest in herpes zoster vaccination: Analysis of Google search data. JMIR Public Health Surveill 2018 May 02;4(2):e10180 [FREE Full text] [doi: 10.2196/10180] [Medline: 29720364]
19. Ssendikaddiwa J, Lavergne R. Access to primary care and internet searches for walk-in clinics and emergency departments in Canada: Observational study using Google Trends and population health survey data. JMIR Public Health Surveill 2019 Nov 18;5(4):e13130 [FREE Full text] [doi: 10.2196/13130] [Medline: 31738175]
20. Wang H, Chen D. Economic recession and obesity-related internet search behavior in Taiwan: Analysis of Google Trends data. JMIR Public Health Surveill 2018 Apr 06;4(2):e37 [FREE Full text] [doi: 10.2196/publichealth.7314] [Medline: 29625958]

21. Nobles AL, Dredze M, Ayers JW. "Repeal and replace": Increased demand for intrauterine devices following the 2016 presidential election. Contraception 2019 May;99(5):293-295. [doi: 10.1016/j.contraception.2018.10.012] [Medline: 30878137]
22. Wood LN, Jamnagerwalla J, Markowitz MA, Thum DJ, McCarty P, Medendorp AR, et al. Public awareness of uterine power morcellation through US Food and Drug Administration communications: Analysis of Google Trends search term patterns. JMIR Public Health Surveill 2018 Apr 26;4(2):e47 [FREE Full text] [doi: 10.2196/publichealth.9913] [Medline: 29699965]
23. Cartwright AF, Karunaratne M, Barr-Walker J, Johns NE, Upadhyay UD. Identifying national availability of abortion care and distance from major US cities: Systematic online search. J Med Internet Res 2018 May 14;20(5):e186 [FREE Full text] [doi: 10.2196/jmir.9717] [Medline: 29759954]
24. Reidpath DD, Allotey P. Predicting US state teenage birth rate using search engine query data on pregnancy termination and prevention. J Glob Health Rep 2018 Mar 01;2:1-4 [FREE Full text] [doi: 10.29392//001c.11938]
25. Stephens-Davidowitz S. The New York Times. 2016 Mar 05. The return of the D.I.Y. abortion URL: https://www.nytimes.com/2016/03/06/opinion/sunday/the-return-of-the-diy-abortion.html [accessed 2019-08-18]
26. Reis BY, Brownstein JS. Measuring the impact of health policies using internet search patterns: The case of abortion. BMC Public Health 2010 Aug 25;10:514 [FREE Full text] [doi: 10.1186/1471-2458-10-514] [Medline: 20738850]
27. Arora V, McKee M, Stuckler D. Google Trends: Opportunities and limitations in health and health policy research. Health Policy 2019 Mar;123(3):338-341. [doi: 10.1016/j.healthpol.2019.01.001] [Medline: 30660346]
28. Foroughi F, Lam AK, Lim MS, Saremi N, Ahmadvand A. "Googling" for Cancer: An infodemiological assessment of online search interests in Australia, Canada, New Zealand, the United Kingdom, and the United States. JMIR Cancer 2016 May 04;2(1):e5 [FREE Full text] [doi: 10.2196/cancer.5212] [Medline: 28410185]
29. Mavragani A, Ochoa G. Forecasting AIDS prevalence in the United States using online search traffic data. J Big Data 2018 May 19;5(17):1-21 [FREE Full text] [doi: 10.1186/s40537-018-0126-7]
30. Parker J, Cuthbertson C, Loveridge S, Skidmore M, Dyar W. Forecasting state-level premature deaths from alcohol, drugs, and suicides using Google Trends data. J Affect Disord 2017 Apr 15;213:9-15. [doi: 10.1016/j.jad.2016.10.038] [Medline: 28171770]
31. Young SD, Torrone EA, Urata J, Aral SO. Using search engine data as a tool to predict syphilis. Epidemiology 2018;29(4):574-578. [doi: 10.1097/ede.0000000000000836]
32. Eysenbach G. Infodemiology and infoveillance tracking online health information and cyberbehavior for public health. Am J Prev Med 2011 May;40(5 Suppl 2):S154-S158. [doi: 10.1016/j.amepre.2011.02.006] [Medline: 21521589]
33. Eysenbach G. Infodemiology and infoveillance: Framework for an emerging set of public health informatics methods to analyze search, communication and publication behavior on the internet. J Med Internet Res 2009 Mar 27;11(1):e11 [FREE Full text] [doi: 10.2196/jmir.1157] [Medline: 19329408]
34. Nuti SV, Wayda B, Ranasinghe I, Wang S, Dreyer RP, Chen SI, et al. The use of Google Trends in health care research: A systematic review. PLoS One 2014;9(10):e109583 [FREE Full text] [doi: 10.1371/journal.pone.0109583] [Medline: 25337815]
35. Mavragani A, Ochoa G. Google Trends in infodemiology and infoveillance: Methodology framework. JMIR Public Health Surveill 2019 May 29;5(2):e13439 [FREE Full text] [doi: 10.2196/13439] [Medline: 31144671]
36. Public Policy Office, Guttmacher Institute. Guttmacher Institute. Washington, DC: Guttmacher Institute; 2020 May 01. Insurance coverage of contraceptives URL: https://www.guttmacher.org/state-policy/explore/insurance-coverage-contraceptives [accessed 2019-08-17]
37. Allam A, Schulz PJ, Nakamoto K. The impact of search engine selection and sorting criteria on vaccination beliefs and attitudes: Two experiments manipulating Google output. J Med Internet Res 2014 Apr 02;16(4):e100 [FREE Full text] [doi: 10.2196/jmir.2642] [Medline: 24694866]
38. Python Package Index (PyPI). Simple Python interface for Graphviz: Project description URL: https://pypi.org/project/graphviz/ [accessed 2019-08-17]
39. Donnini G. Search Engine Journal. 2013 Jul 22. The value of Google result positioning URL: https://www.searchenginejournal.com/the-value-of-google-result-positioning/65176/ [accessed 2019-08-17]
40. Planned Parenthood. Birth control pill URL: https://www.plannedparenthood.org/learn/birth-control/birth-control-pill [accessed 2020-05-12]
41. WebMD. Birth control pills URL: https://www.webmd.com/sex/birth-control/birth-control-pills#1 [accessed 2020-05-12]
42. Wikipedia. Combined oral contraceptive pill URL: https://en.wikipedia.org/wiki/Combined_oral_contraceptive_pill [accessed 2020-05-12]
43. BirthControl.com. Birth control pills URL: https://birthcontrol.com/options/birth-control-pills/ [accessed 2020-05-12]
44. Healthline. Birth control pills: Are they right for you? URL: https://www.healthline.com/health/birth-control-pills [accessed 2020-05-12]
45. Google Analytics Help. 2019. How a web session is defined in Analytics URL: https://support.google.com/analytics/answer/2731565?hl=en [accessed 2019-08-17]

46. Google Surveys Help. 2019. How it works URL: https://support.google.com/surveys/topic/6194669?hl=en&ref_topic=7156628 [accessed 2019-08-17]
47. Sadilek A, Caty S, DiPrete L, Mansour R, Schenk T, Bergtholdt M, et al. Machine-learned epidemiology: Real-time detection of foodborne illness at scale. NPJ Digit Med 2018 Nov;1:36 [FREE Full text] [doi: 10.1038/s41746-018-0045-1] [Medline: 31304318]

Abbreviations

API: application programming interface
CSV: Comma-Separated Values
DMA: Demographic Marketing Area
GCS: Google Consumer Survey
IUD: intrauterine device
JSON: JavaScript Object Notation
PPFA: Planned Parenthood Federation of America
RSV: relative search volume

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Protocol

Improving Understanding of Participation and Attrition Phenomena in European Cohort Studies: Protocol for a Multi-Situated Qualitative Study

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Abstract

Background: Cohort studies represent a strong methodology for increasing one's understanding of human life-course development and etiological mechanisms. Retention of participants, especially during long follow-up periods, is, however, a major challenge. A better understanding of the motives for participation and attrition in cohort studies in diverse sociogeographic and cultural settings is needed, as this information is most useful in developing effective retention strategies.

Objective: This study aims to improve our understanding of participation and attrition phenomena in a European cohort study of very preterm/very-low-birth-weight (VPT/VLBW) infants from various sociogeographic and cultural settings to better understand variability and ultimately contribute to developing novel and more "in-context" strategies to improve retention.

Methods: This study uses a triangulation of multisituated methods to collect data on various cohorts in the Research on European Children and Adults Born Preterm (RECAP) network, which include focus group discussions, individual semidriven interviews, and a collaborative, reflexive visual methodology (participant-generated VideoStories) with relevant key actors involved with these cohort studies such as adult participants, parents (caregivers), cohort staff, health care professionals, and academic researchers. The methodological strategy aims to provide a shared flexible framework of various qualitatively driven methods to collect data

on VPT/VLBW adult and child cohorts, from which research partners may choose and combine those most pertinent to apply in their own specific contexts. Data from all sources and sites will be submitted to a triangulation of phenomenological thematic analysis with discourse analysis.

Results: As of January 2020, in this study, we enrolled 92 participants variously involved with child and adult RECAP partnering cohorts from six countries. Multisite enrollment and data collection are expected to be completed in all seven study settings by June 2020. Findings will be reported in future publications.

Conclusions: Qualitative research methods are a useful complement for enriching and illuminating quantitative results. We expect that opting for a multisituated study approach addressing the interplay of the lived experience of individuals in both researcher and researched stances of particular cohort study settings will contribute to filling some gaps in the understanding of participation variability and effectiveness of different implemented strategies in context. Moreover, health research subjects have traditionally been positioned as passive objects of study rather than active participants, even though they have the greatest stake in improving health care policies and practices. Including collaborative methods allows us to counteract the "top-down" model by handing over some research control to the very people who are providing the data on which research findings will be based while also acknowledging the value of their involvement.

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KEYWORDS

European cohorts; VPT; VLBW; preterm; participation; attrition; multi-situated qualitative study; collaborative visual methods; triangulation

Introduction

Background and Rationale

The Horizon 2020 Project Research on European Children and Adults Born Preterm (RECAP), funded by the European Union (under grant agreement no. 733280; January 2017- March 2021), brings together 20 population-based cohorts from 13 European countries, with individuals born very preterm (VPT: <32 weeks of gestation) or with very low birth weight (VLBW: <1500 g), who were followed up since birth. The network includes cohorts assembled over a period of 4 decades, presently covering a large age span, from childhood (>7 years old) to early adulthood (<40 years old). The overall aim of RECAP is to improve health, development, and quality of life of children and adults born VPT/VLBW, by developing collaborative multidisciplinary research on these geographically and temporal diverse cohorts and optimize their use for innovation in practice and policy.

Cohort studies are a strong methodological approach to understand human life-course development and causal mechanisms. A major issue in long-term follow-up studies, however, is that response decreases with a lapse of time between recruitment and follow-up assessments. It is not clear how this attrition influences the results of follow-up studies, different research cases point to distinct outcomes [1], it is certain that they become prone to considerable selection biases with losses to follow-up and dropouts as little as 20% [2]. Cohorts are complex research structures that require sustained involvement of participants, professionals, funding, and supporting infrastructure to ensure continued attention to timeliness, attrition, and quality of collected information. Those requirements are indispensable to meet high scientific standards and allow appropriate translation of findings into clinical practice and policy action. Retention of participants is a major concern and a well-known challenge, and due to international specificities in research regulation and contextual differences, approaches to these issues will also necessarily vary.

Available evidence suggests that investigators should consider using multiple strategies to maximize the retention of participants and that the use of incentives is associated with an increase in retention, which improves with greater incentive value [3-5]. In 2011, the widely quoted systematic review of Booker, Harding, and Benzeval [6] concluded that the use of financial incentives was associated with an increase in retention rates (we note that the expression "rate" is kept here as used in referred sources). Whether cash was the most effective incentive was not clear from studies that compared cash and gifts of similar value. Relevant increases in retention were also found for posting repeat questionnaires, using reminders as well as offering alternative locations and modes of data collection [6]. Other studies also point out that the use of targeted strategies, such as incentives to nonresponders from previous waves of the study, is a cost-effective approach to retain participants at high risk of dropping out and that regular contact between participants and investigators enhances bonding and helps ensure enduring identification with the study [7,8].

These are useful insights about how retention can be enhanced by combining a number of strategies and bonding tools. It should be noted, however, that most available sources on more generalizable results, such as systematic reviews, are yet constrained by the small number, geographical concentration, scarce details, and inconsistent description of published studies reporting implemented strategies. Inferential leaps or generalization to other contexts and, subsequently, usefulness of retention strategies investigated may differ. Further primary research is needed to expand the population assessed and diversity of study settings, especially in Europe. Moreover, there is a paucity of literature regarding expectations and motives for participation and for participants' reluctance to

continue in cohort studies, although such information is essential to enhance recruitment and improve retention [9-11].

To improve understanding of the context of behaviors, survey research, broadly referring to questionnaires and structured interviews to obtain quantifiable aggregated data, provides estimates of many variables. However, survey results are only as good as the questions asked [12] and the potential of the data generated is limited to the assumptions framing the response options. A qualitative research approach is therefore a useful complement for enriching and enlivening quantitative results. Some of the distinctive features of this kind of approach are the use of open, exploratory research questions and meaning-based rather than statistical forms of data analysis, which tend to potentiate the emergence of something new [13-16]. We expect that opting for a triangulation of qualitative methods to garner feedback from various parties involved with diverse cohorts' settings will contribute toward filling some gaps in the understanding of participation and attrition phenomena.

Overall Aim and Objectives

The overall aim of this study is to provide an insight into participation and attrition phenomena in VPT/VLBW cohort studies in various sociogeographic, linguistic, and cultural settings in order to increase our understanding of variability and to ultimately contribute to developing novel and more "in-context" strategies to improve retention. It is a direct response to RECAP's concerns toward improving data collection, follow-up, and participant involvement in cohort studies.

Following the epistemological principle of valuing "in-context" and nuanced inside knowledge from various parties, multisite data collected for this study will contribute to the following objectives:

- To explore perceptions, feelings, and expectations of parents (caregivers) of children and adults born VPT/VLBW who participate in European cohorts studies about enrollment and continuity of participation.
- To explore the experiences and practices of diverse key actors involved with cohort studies with regard to the activities, procedures, and difficulties faced that may affect participants' attendance and commitment continuity to the study.
- To investigate the interplay between lived experience and expectations of cohort participants and the manifested responses obtained by the professionals in follow-up enquiries in different European studies.

Methods

Setting and Sampling

The study proposes a triangulation of multisituated methods to collect data on RECAP's cohorts in various European countries, which include focus group interview, individual semidriven interview, and a collaborative reflexive visual methodology. Our methodological strategy provides a shared framework of various qualitatively driven methods to collect data, from which research partners may choose and combine those most appropriate to their own particular contexts. A multisituated approach not only comprises the concept of multisites or multilocations [17], but also assumes the significance of situated knowledge. It stresses the material, social, and political conditions that contribute to gaining (multiple, partial, diverse) knowledge, and the responsibility to consider them just as valuable [18,19]. Given the framework constraints and nature of the phenomena under study (eg, variety of cohort studies and settings), we find it the most promising strategy to produce rich multimodal and original data, which include diverse subjects' voices, perceptions, and experiences.

As the study is focused on garnering feedback from various parties involved in cohorts of RECAP's network, potential participants of this study will be found, contacted, and enrolled with the collaboration of partnering cohort teams. The range of participating cohorts will achieve a wide sociogeographic heterogeneous sample inclusive of parents of children cohorts and of cohort participants aged 18 years and over; health care professionals; and other relevant key actors such as current and former staff cohort members, representatives of parent organizations, and academic researchers involved with VPT/VLBW cohort studies in various European countries. The sample should be varied enough to obtain feedback for most experiences and perceptions in both research stances. In order to satisfy the saturation criterion, a purposive (selective) nonprobability sampling strategy will be used. The intended total sample size is 120-130 participants to be recruited through a range of multisituated methods from 7 to 8 different cohort settings and countries. Accordingly, local protocols, setting, methods, and sample determination in all sites will be discussed and finalized with the study coordinator.

Data Collection

To be eligble, RECAP's partnering cohorts have to identify a researcher/translator, who can translate content into English, with experience in qualitative research and methods to carry out data collection locally and meet the requirements to conduct one or more of the following proposed methodologies within the cohort of its scope:

1. One or two focus groups with professionals or other relevant key actors involved with the cohort, for a 1- to 1.5-hour discussion. These discussions are conducted either in the native speakers' language or English (in case all potential participants are proficient English speakers and the local researcher finds it appropriate).
2. One or two focus groups with parents (caregivers) of children or focus groups with adults who participate in the cohort, for a 1- to 1.5-hour discussion. These discussions are conducted in the native speakers' language. In case of groups comprising foreign are, immigrants, or languages' participants speaking different languages, the local researcher will choose the most inclusive language to conduct the meeting.

   When the approach to nonresponders from previous waves of the study is available, particular effort will be placed in inviting them to participate, stressing that this initiative has the specific purpose of hearing from them about their difficulties, constraints, and suggestions in order to find more adequate strategies to meet their expectations. Partners

may implement further incentive strategies to foster participation, in case they find it appropriate.

Focus groups will attempt to include 5-7 participants, a number large enough to generate a variety of perspectives and small enough to allow every participant to engage in the exploratory discussion in greater depth [20-22]. Focus group discussions will be driven by 6-8 key issues commonly defined to approach the phenomena under study while including some in-context subtopics of discussion elected by local partners as relevant to the specificities of the cohort study and their particular participants (see Multimedia Appendix 1). The exploratory approach chosen by this study aims to potentiate the emergence of something new from the discussions, and therefore, the moderator will be as nondirective as possible and make use of the guide of key issues to approach only as discussion triggers and if not spontaneously approached by participants. These discussions will also be used to explore the "territory" and map key issues for further group or individual semidriven interviews.

In cases where the cohort participants live far apart or are more responsive to novel digital tools, online focus groups on a secured forum can be considered. Participants in the forum can either express an unlimited number of comments on each of the defined 6-8 key issues to approach over the course of a week or react to one key issue under discussion per day. The advantage is that participants can express themselves at their own convenience while incorporating and reacting to the opinions of others. This often results in less spontaneous interaction among participants, but more focused output. For the particularities of this mediator, in order to balance the variety of perspectives and engagements generated in the discussion, the number of participants suggested is 15-20 [23].

In cases where focus group discussions were considered not feasible, or failed to reach saturation for one or more key issues, or where a willing participant is only available to be interviewed separately, individual semidriven interviews may be conducted face-to-face, through videoconference or teleconference.

3. Individual semidriven interviews are conducted in the native speakers' language for no more than 1 hour. These interviews will be driven by the same 6-8 key issues commonly defined to approach the phenomena under study while including some in-context subtopics of discussion selected by local partners as relevant to the specificities of the cohort study and their particular participants.
4. Participant-generated VideoStories, a collaborative visual methodology, with 4-7 cohort participants aged 18 years and over or with 4-7 parents (caregivers) of children participating in the cohort.

Photo and video elicitation are qualitative methods of investigation in which images are used to facilitate meaningful responses. Still images or video can be taken by the researcher, pulled from a third-party source, or generated by the research participants. In participant-generated visual methodologies, the participant is the one who generates the (audio)visual images that will be further analyzed. These are used to elicit ethnographic data and less-driven personal views while maximizing the alternatives for individual expression and representation.

The collaborative methodology chosen for this study is derived from photo/video voice process [24,25]. It is a methodology well suited for a phenomenological analysis focused on the meaning of behavior, narrative, and "lived personal experience" [26]. Using collaborative techniques that combine video-generated images and critical dialogue, participants are expected to reflect in-depth on the phenomena under study and communicate their concerns to represent their personal experience and acquired knowledge, as research participants expose individual and social problems and ignite changes in behavior. Both the researcher and the participants benefit. On one hand, participants are encouraged to use their critical, confessional, and authoritative/pedagogical voices to clearly establish themselves as legitimate partners in the study [27,28]. On other hand, through reflexivity, they come to new understandings of their practices and behaviors, prompting some to change or develop new strategies [29-31], potentially increasing their identification with the cohort studies and retention. It is also particularly advantageous to prompt recall from multiple subjects concerning their life events that the researcher cannot join as a participant observer.

The VideoStories methodological process involves two steps:

I. "VideoStories assignment": In order to collect audiovisual data that can be compared and contrasted across participants, the participants will be given a standardized assignment to record during a similar visual narrative period. Each participant will agree to generate a set goal of 3-4 videos, each with a maximum length of 10 minutes (4-6 minutes ideally), shot on different days, within a 1-week period. This will encourage the participant to reflect in advance on what, how, and when to shoot each video.
II. "VideoStories debriefing conversation": During week 2, participants handover their photographs/videos to the researcher. Copies of video files will be transferred to the researcher and secured in a protected dedicated storage. Each participant will meet with the researcher at a mutually convenient place for the VideoStories debriefing conversation. This is a semidriven interview or image-elicitation interview [32-34], about the videos, one by one, which should take no more than 1-1.5 hours.

In the European context, the mobile phone has replaced other digital recording devices in the daily lives of a large proportion of the population, crossing economic classes and age groups, which converts this technology into one of the most suitable tools for self-expression and documentation. In addition to being familiar daily tools, mobile phones are also easier to manipulate than video cameras for basic video production. Since participant-generated images in this study are only intended for elicitation and will not be published or disseminated in any form, no further training in video editing will be needed. For these reasons, and anticipating that most of the willing

participants will have their own mobile phones capable of producing video images (minimizing the investment in equipment acquisitions and training), we propose to use this technology to generate VideoStories. In case a willing participant does not have his/her own device, he/she will be given access to video equipment.

Data Analysis

Data collected from multiple sites through a variety of proposed methods will enable triangulation of data, comparing and contrasting data from a range of sources and perspectives, thus enhancing a more nuanced understanding of the phenomena under study.

Interview data from all sources will be audio recorded, transcribed, and translated into English by multisite partnering researchers. It will then be used for triangulation of phenomenological thematic analysis with discourse analysis. Phenomenological analysis is an approach to qualitative research with an idiographic (representational) focus, which means that it aims to offer insights into how a given person, in a given context, makes sense of a given phenomenon. As mentioned earlier, it is focused on the whys; the meaning of behavior, narrative, and "lived personal experience," and has its theoretical origins in phenomenology and hermeneutics. Following Edmund Husserl and Wilhelm Dilthey's hermeneutics, the concept of "lived personal experience," in which experience constitutes the primary reality, includes not only behavior, acts, and sentiments but also reflection of these on the inner, personal experience [26,35].

Both visual and verbal depictions will be treated as narratives and the focus is on a deep understanding of the meaning of description. The meanings, usually implicit, need to be made explicit with thematic analysis. The research team performing the analysis will look then for recurrent themes and repetitions (discursive formations) to determine if any patterns (or representational axes) emerged. Usually, there are two types of themes, collective themes that occur across contexts and groups of participants having a similar experience, and individual themes that are unique to a particular context or a few individuals. Final interpretative analysis will emerge by the generic application of the mode of contents contingency. Contingency derives from Foucault's definition of discursive formation. It is the process of finding the regularity in discourse dispersion.

Data will be sorted ("coded") and then categorized by hand by the research team performing the analysis and verified by the local researchers involved with collection and translation of multisite data. As the study will generate a large body of data, NVivo2011 (a computer-assisted qualitative data analysis software) may be used to handle and help highlighting similarities and differences across the subsets of data for some specific circumstances. However, the first principle of analysis of phenomenological data is to use an emergent strategy, to allow the method to follow the nature of the data itself, which may emerge or change in the course of analysis. In phenomenological thematic analysis and discourse analysis, we abstract themes, discursive formations, and representational axes, and we do not use "a priori coding" instrumentation. For that reason, computer analysis support may only take a marginal role.

Ethics and Dissemination

Despite some variation in the ways ethical approval practices work across diverse social sciences research sectors, the issues assessed by the ethics committees are common concerns to all researchers and include items such as avoidance of harm, researcher integrity, honesty, voluntary informed consent, confidentiality of information provided by participants, and anonymity. However, the general nature of these professional codes and guidelines means that the ethical issues relating to visual methods are not specifically addressed within most codes. Concerns have been expressed among researchers that study designs with a visual element may sometimes be seen with distrust by ethical reviewers based only on unfamiliarity with the methodology [36,37]. Yet, most ethical issues raised by visual research are, arguably, the ones that are relevant to all research. It is mainly the specific issue of dissemination of identifiable images of individuals (and places) that presents the most significant specific ethical challenge to manage in visual research.

For visual research methods, it is important to consider consent as pertaining to not just to the collection of images but also processing and analysis, presentation, and dissemination of images. In the light of this, it is advisable to request that interviewees give consent to the fair handling of records to the researcher. In the case of study participant—generated audio-visual data, copyright rests with the respondents. The researcher may only use the data as agreed with the author, while the author may use and reuse them at his/her wish. While legally the video or photograph taker owns the image and can assign copyright or partial rights of use to the researcher if they wish to do so, other people depicted in the images have not necessarily given their consent to the image. Participants are therefore encouraged to avoid the depiction of other persons in their photographs/videos. In case they include other persons (eg, their children or other family members), they are reminded to always ask their permission, not shoot images that could be embarrassing or troubling, and obtain their assent/written consent for appearance release. Without fulfilling that requirement, those images would not be processed by the researcher.

For this study, neither researcher-generated nor participant-generated audio and visual images will be released for publication or dissemination. Therefore, consent will be sought to participate in the research study and for the use and processing of any generated audio or image records for elicitation of information only within the research team for analysis purposes. Publications and presentations from the study will display findings anonymously (names, recorded utterances, and other personally identifiable information will not be used). Study participants will be given information about the project orally as well as in written form. The methodological design used in this study ensures that all prospective participants will have the opportunity to discuss with the researchers confidentiality and data security procedures as well as who will see their information, before signing the informed consent. We

also believe that creating processes of ongoing consent offers a useful way of respecting the participants' wishes. It safeguards the notion that if participants want it, they can withdraw or propose changes to the limits of their given consent at any time. If a participant decides to withdraw from the study, from that date, the researchers will not use the information already provided by the participant for any further analysis or publications.

All researchers are also subject to legislation on data protection, which demands that data are stored securely and do not lead to any breach of confidentiality and anonymity. All generated data within this study will be secured in a protected dedicated storage and kept for a period of 5 years after the completion of the RECAP Project. As data will be collected from different European countries and handled by members of the research team located in those countries, a secured access policy based on a need-to-know basis principles and password protection for electronic data will be implemented (ie, only the users who need to access the data will be allowed to do so). Any assisting nonresearcher interpreters-translators and transcribers to this study will also sign a confidentially agreement. When research records are to be destroyed, participants' confidentiality will be kept throughout the process.

In all fieldwork sites, approval by ethics committees, data-protection authorities, and signed informed consents by responders in their spoken languages will be sought according to national rules. Additional measures to protect privacy may be applied by the regions according to national rules and requirements by local ethics committees.

Results

This paper focuses on the methodological research approach used for this study and, therefore, the findings will be reported in future publications.

The implementation of this study protocol involves multiple resources for data collection from various cohort structures, research institutions, and countries, requiring collaboration between many involved parties. Due to international differences in the regulation of research, diversity of cohorts, and particular constraints of local research teams involved, it was defined a flexible schedule for the multi-situated implementation of the study.

As of January 2020, ethical clearance was obtained for seven sites, three cohort studies of children in Denmark, Italy, and Portugal and four cohort studies with participants aged 18 years and over in Belgium, Finland, the Netherlands, and Norway. A total of 92 participants variously involved with partnering cohorts of children and adults born VPT/VLBW from six countries were already enrolled to this study. To date, the total sample comprises 29 professionals variously involved with cohorts in five countries (including former and current cohort staff members, health care professionals, and researchers involved with these and other cohort studies), 26 parents of children participating in cohorts are from three countries (of which nine had failed to respond in one or more waves of the studies), and 37 adult participants in cohorts from two countries.

Multisite enrollment and data collection are expected to be completed in all seven study settings by June 2020. Although subsets of data will be handed over for analysis at a different pace, results are expected to be published by the end of 2020.

As described earlier, following the epistemological principle of valuing situated knowledge, decision on data collection methods was enabled by partnering researchers' understanding of their own particular contexts. By way of example, in the Netherlands, adult participants in the Project on Preterm and Small for Gestational Age Infants cohort were able to choose to be interviewed by telephone, videoconference, or taking part in online focus groups on a secured forum; whereas in Portugal, all proposed methodologies were implemented face-to-face and the researchers traveled to alternative locations to meet parents of children participating in the Effective Perinatal Intensive Care in Europe/Screening to Improve Health in Very Preterm Infants in Europe cohort studies.

Discussion

In spite of the knowledge gained on participation and attrition phenomena from systematic reviews, in-depth examination of retention strategies, of how these were modified and adapted over the cohorts' follow-up, and potentially seeking other strategic procedures that may have been effective toward retention in existing research is needed. Published manuscripts often do not reflect the varied strategies employed through the duration of study and, moreover, do not test retention strategies within their study. In fact, as concluded in a recent study via survey and in-depth semistructured interviews, longitudinal studies with high retention rates commonly used personalized approaches and frequently tailored and revised retention strategies specific to participants in their study cohorts [38]. This tailoring is enabled by an understanding of social, cultural, and environmental contexts particular to the population studied.

The research approach chosen by this study has as particular strengths its focus and design. The study focuses on motives for participation and for participants' reluctance to continue in cohort studies in diverse sociogeographic and cultural settings, while addressing the interplay of the points of view and lived experience of individuals in both researcher and researched stances. Considering both standpoints will allow us to better understand the costs and benefits of different implemented approaches and ultimately contribute to develop novel and more "in-context" strategies to improve retention. The study design resorts to a flexible shared framework for triangulation of various qualitative methods to collect more in-context and nuanced data from diverse sites and involved parties, including a collaborative visual methodology. The potential of collaborative methods and nontextual tools in social science research (and namely in public health and related disciplines) is now also widely recognized and well documented in its ability to evoke more nuanced understanding of the ways in which people experience and perceive their worlds [27,39-42].

As demonstrated by several follow-up studies, preterm birth is associated with neuromotor and cognitive impairments, psychiatric morbidity, and, among others, increased anxiety, social rejection, and reduced self-esteem. When working in

settings with communication barriers or with subjects who are more introverted or cannot verbally express themselves because of physical or language difficulties, collaborative visual methods are invaluable additions to researchers' methodological tools. Another well-documented advantage is their transformative impact on participants. For both researchers and research subjects, they are a powerful and significant means of communicating and discussing ideas while opening up ways of seeing and knowing. Combined with others, collaborative methods can be used to consider the vantage points of different social actors and display complexity and heterogeneity that are critical for understanding social issues. They do not necessarily guarantee a better instrument, yet they do have the potential to provide a larger pool of concepts to be considered in subsequent research development or in interpreting already existing data while building a more participatory relationship.

The study's main challenge is the use of a situated approach with multiple methods for data collection. It entails increased effort and time while increasing the complexity of analysis. Although not common in health-related research, as mentioned in previous sections, an analysis of multimodal data collected from different sources is established in social sciences as well as the analytical strategy chosen [43]. Data collection and analysis will be thus performed by a multidisciplinary team led by social science researchers experienced in both.

Conclusions

The culturally sensitive, inclusive, and collaborative approach to public health research on which this study is based expects to inform future research through sharing knowledge about the research process as well as its findings. This study argues for collaboration as a means to empower participants to represent themselves in the research process and in its findings in ways that meet both researchers' and their own expectations and objectives. We find it the most promising strategy to produce rich multimodal original data, which is inclusive of diverse voices, perceptions, and experiences. We believe that handing over some control to the very people who are providing the data on which findings will be based and acknowledging the value of their participation and involvement will not only enrich the results but also potentiate their engagement and enduring identification with cohort studies.

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Authors' Contributions

SCSM conceptualized, designed, coordinated, and implemented the study protocol and drafted the protocol and this manuscript. JD, AB, MC, EK, JL, SvdP, and PP contributed to all phases of the development and multi-site implementation of the protocol. ESD contributed to the development of the protocol. HB coordinated the study. He contributed to the conceptualization and development of the study. All authors critically reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interviewing guide of key issues to approach.
[PDF File (Adobe PDF File), 343 KB - resprot_v9i7e14997_app1.pdf]

References

1. Hille ETM, den Ouden AL, Stuifbergen MC, Verrips GHW, Vogels AGC, Brand R, et al. Is attrition bias a problem in neonatal follow-up? Early Hum Dev 2005;81(11):901-908 [FREE Full text] [doi: 10.1016/j.earlhumdev.2005.07.006] [Medline: 16150560]
2. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: How much is too much? Eur J Epidemiol 2004;19(8):751-760 [FREE Full text] [doi: 10.1023/B:EJEP.0000036568.02655.f8] [Medline: 15469032]
3. Hunt JR, White E. Retaining and tracking cohort study members. Epidemiol Rev 1998;20(1):57-70 [FREE Full text] [doi: 10.1093/oxfordjournals.epirev.a017972] [Medline: 9762509]

4. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007;17(9):643-653 [FREE Full text] [doi: 10.1016/j.annepidem.2007.03.013] [Medline: 17553702]
5. Robinson KA, Dennison CR, Wayman DM, Pronovost PJ, Needham DM. Systematic review identifies number of strategies important for retaining study participants. J Clin Epidemiol 2007;60(8):757-765 [FREE Full text] [doi: 10.1016/j.jclinepi.2006.11.023] [Medline: 17606170]
6. Booker CL, Harding S, Benzeval M. A systematic review of the effect of retention methods in population-based cohort studies. BMC Public Health 2011;11(1):e249 [FREE Full text] [doi: 10.1186/1471-2458-11-249] [Medline: 21504610]
7. Olsen RJ. The problem of respondent attrition: survey methodology is key. Monthly Lab Rev 2005;128(2):63-70 [FREE Full text]
8. Funkhouser E, Wammack J, Roche C, Reis J, Sidney S, Schreiner P. Where are they now? Retention strategies over 25 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Contemp Clin Trials Commun 2018;9:64-70 [FREE Full text] [doi: 10.1016/j.conctc.2017.12.003] [Medline: 29696226]
9. Méjean C, Szabo de Edelenyi F, Touvier M, Kesse-Guyot E, Julia C, Andreeva VA, et al. Motives for participating in a web-based nutrition cohort according to sociodemographic, lifestyle, and health characteristics: the NutriNet-Santé cohort study. J Med Internet Res 2014;16(8):e189 [FREE Full text] [doi: 10.2196/jmir.3161] [Medline: 25135800]
10. Markanday S, Brennan SL, Gould H, Pasco JA. Sex-differences in reasons for non-participation at recruitment: Geelong Osteoporosis study. BMC Res. Notes 2013;6(1):e104 [FREE Full text] [doi: 10.1186/1756-0500-6-104] [Medline: 23506528]
11. Williams B, Entwistle V, Haddow G, Wells M. Promoting research participation: Why not advertise altruism? Soc Sci Med 2008;66(7):1451-1456 [FREE Full text] [doi: 10.1016/j.socscimed.2007.12.013] [Medline: 18222579]
12. Newman I, Kanjanawong S. Using photography to cross generational, linguistic, and cultural barriers to develop useful survey instruments. Health Promot Pract 2005;6(1):53-56 [FREE Full text] [doi: 10.1177/1524839903259307] [Medline: 15574528]
13. Elliot R, Timulak L. Descriptive and interpretive approaches to qualitative research. In: Miles J, Gilbert P, editors. A Handbook of Research Methods for Clinical and Health Psychology New York: Oxford University Press; 2015.
14. Mack N, Woodsong C, Macqueen K, Guest G, Namey E. Qualitative Research Methods: A Data Collector's Field Guide. Research Triangle Park: FHI; 2005.
15. Elliott R. Editor's introduction to special issue on qualitative psychotherapy research: definitions, themes and discoveries. Psychother Res 1999;9(3):251-257 [FREE Full text] [doi: 10.1080/10503309912331332741]
16. Sofaer S. Qualitative methods: What are they and why use them? Health Serv Res 1999;34(5 Pt 2):1101-1118. [Medline: 10591275]
17. Marcus G. Ethnography Through Thick and Thin. Princeton: Princeton University Press; 1998.
18. Haraway D. Situated knowledges: the science question in feminism and the privilege of partial perspective. Fem Stud 1988;14(3):575-599 [FREE Full text] [doi: 10.2307/3178066]
19. Haraway D. When Species Meet. Minneapolis: University of Minnesota Press; 2007.
20. Morgan DL. Focus Groups as Qualitative Research. Thousand Oaks: Sage; 1997.
21. Doyle J. Introduction to interviewing techniques. In: Wood DW, editor. Handbook for IQP Advisors and Students Worcester: WPI; 2004.
22. Gubrium J, Holstein J. Handbook of Interview Research: Context and Method. Thousand Oaks: Sage; 2002.
23. van der Pal SM, Alpay LL, van Steenbrugge GJ, Detmar SB. An exploration of parents' experiences and empowerment in the care for preterm born children. J Child Family Stud 2014;23(6):1081-1089 [FREE Full text] [doi: 10.1007/s10826-013-9765-7]
24. Wang C, Burris MA. Empowerment through photo novella: portraits of participation. Health Educ Quart 1994;21(2):171-186 [FREE Full text] [doi: 10.1177/109019819402100204] [Medline: 8021146]
25. Catalani CECV, Veneziale A, Campbell L, Herbst S, Butler B, Springgate B, et al. Videovoice: community assessment in post-Katrina New Orleans. Health Prom Pract 2012;13(1):18-28 [FREE Full text] [doi: 10.1177/1524839910369070] [Medline: 21914833]
26. Dilthey W. Selected Works, I: Introduction to Human Sciences. Princeton: Princeton University Press; 1989.
27. Chalfen R, Sherman L, Rich M. VIA's visual voices: the awareness of a dedicated audience for voices in patient video narratives. Vis Stud 2010;25(3):201-209 [FREE Full text] [doi: 10.1080/1472586X.2010.523271]
28. Rich M, Patashnick J, Chalfen R. Visual illness narratives of asthma: explanatory models and health related behaviour. Am J Health Behav 2002;26(6):442-453 [FREE Full text] [doi: 10.5993/AJHB.26.6.5] [Medline: 12437019]
29. Collier A, Wyer M. Researching reflexively with patients and families: two studies using video-reflexive ethnography to collaborate with patients and families in patient safety research. Qual Health Res 2015;26(7):979-993 [FREE Full text] [doi: 10.1177/1049732315618937] [Medline: 26658233]
30. D'Amico M, Denov M, Khan F, Linds W, Akesson B. Research as intervention? Exploring the health and well-being of children and youth facing global adversity through participatory visual methods. Glob Public Health 2016;11(5–6):528-545 [FREE Full text] [doi: 10.1080/17441692.2016.1165719]

31. Mitchell C, Chege F, Maina L, Rothman M. Beyond engagement in working with children in eight Nairobi slums to address safety, security, and housing: digital tools for policy and community dialogue. Glob Public Health 2016;11(5–6):651-665 [FREE Full text] [doi: 10.1080/17441692.2016.1165720] [Medline: 27132645]
32. Rose G. Visual Methodologies: An Introduction to Researching with Visual Materials. London: Sage; 2012.
33. Gubrium A, Harper K. Participatory Visual and Digital Methods. Walnut Creek: Left Coast Press; 2013.
34. Pink S. Visual methods. In: Seale C, Gobo G, Gubrium J, Silverman D, editors. Qualitative Research Practice London: Sage; 2006 p. 361-376.
35. Merleau-Ponty M. The Phenomenology of Perception. London: Routledge; 2002.
36. Wiles R, Coffey A, Robison J, Prosser J. Ethical regulation and visual methods: making visual research impossible or developing good practice? Sociol Res Online 2012;17(1):1-17 [FREE Full text] [doi: 10.5153/sro.2274]
37. Clark A, Prosser J, Wiles R. Ethical issues in image-based research. Arts Health 2010;2(1):81-93 [FREE Full text] [doi: 10.1080/17533010903495298]
38. Abshire M, Dinglas VD, Cajita MIA, Eakin MN, Needham DM, Himmelfarb CD. Participant retention practices in longitudinal clinical research studies with high retention rates. BMC Med Res Methodol 2017;17(1):e1 [FREE Full text] [doi: 10.1186/s12874-017-0310-z] [Medline: 28219336]
39. Banks M. Visual Methods in Social Research. London: Sage; 2001.
40. Marques SCS. Research on images and tourism in Kolkata, India: doing fieldwork with participatory visual methodologies. In: Martins H, Mendes P, editors. Trabalho de Campo: Envolvimento e Experiências em Antropologia Lisboa: Imprensa de Ciências Sociais; 2016 p. 241-261.
41. Catalani C, Minckler M. Photovoice: a review of the literature in health and public health. Health Educ Behav 2010;37(3):424-451 [FREE Full text] [doi: 10.1177/1090198109342084] [Medline: 19797541]
42. Mitchell CM, Sommer M. Participatory visual methodologies in public health. Glob Public Health 2016;11(5–6):521-527 [FREE Full text] [doi: 10.1080/17441692.2016.1170184] [Medline: 27105078]
43. Norris S. Systematically Working with Multimodal Data: Research Methods in Multimodal Discourse Analysis. Hoboken: John Wiley & Sons; 2019.

Abbreviations

RECAP: Research on European Children and Adults Born Preterm
VPT/VLBW: very preterm/very-low-birth-weight

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