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Protocol

A Web-Based Recovery Program (ICUTogether) for Intensive Care Survivors: Protocol for a Randomized Controlled Trial

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Abstract

Background: Those who experience a critical illness or condition requiring admission to an intensive care unit (ICU) frequently experience physical and psychological complications as a direct result of their critical illness or condition and ICU experience. Complications, if left untreated, can affect the quality of life of survivors and impact health care resources. Explorations of potential interventions to reduce the negative impact of an ICU experience have failed to establish an evidence-based intervention.

Objective: The aim of this study is to evaluate the impact of a Web-based intensive care recovery program on the mental well-being of intensive care survivors and to determine if it is a cost-effective approach.

Methods: In total, 162 patients that survived an ICU experience will be recruited and randomized into 1 of 2 groups. The intervention group will receive access to the Web-based intensive care recovery program, ICUTogether, 2 weeks after discharge (n=81), and the control group will receive usual care (n=81). Mental well-being will be measured using the Hospital Anxiety and Depression Scale, The Impact of Events Scale-Revised and the 5-level 5-dimension EuroQoL at 3 time points (2 weeks, 6 months, and 12 months post discharge). Family support will be measured using the Multidimensional Scale of Perceived Social Support at 3 time points. Analysis will be conducted on an intention-to-treat basis using regression modeling. Covariates will include baseline outcome measures, study allocation (intervention or control), age, gender, length of ICU stay, APACHE III score, level of family support, and hospital readmissions. Participants' evaluation of the mobile website will be sought at 12 months postdischarge. A cost utility analysis conducted at 12 months from a societal perspective will consider costs incurred by individuals as well as health care providers.

Results: Participant recruitment is currently underway. Recruitment is anticipated to be completed by December 2020.

Conclusions: This study will evaluate a novel intervention in a group of ICU survivors. The findings from this study will inform a larger study and wider debate about an appropriate intervention in this population.

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KEYWORDS

intensive care; survivorship; survivor; recovery program

Introduction

An intensive care unit (ICU) stay is a stressful, potentially traumatic period for survivors and their families. Admission to an ICU usually means that individuals have suffered a critical illness or condition that is a threat to their lives, and they are among the most critically ill and vulnerable patients in the hospital. It is thought that the complications of a critical illness

or condition are related to not only the severity of the illness but also the ICU experience [1,2]. Intensive care survivors often struggle to return to their previous role in the family and to their preillness state of health owing to prolonged physical and neuropsychological disability [3-5].

Over 172,000 people were admitted to ICUs across Australia during 2014-2015. As survival rates from ICUs have increased over the last 30 years, there has been a concomitant rise in the number of survivors, increasing the number of people who may develop chronic illness as a direct result of their ICU experience [6,7]. It has become increasingly apparent that those who survive an ICU experience and are discharged home suffer myriad physical, cognitive, and mental health impairments as a direct result of their ICU experience and critical condition [8-10]. These impairments can persist over a long period of time [4,11]. Psychological complications have been estimated to be as high as 44% of survivors at hospital discharge [1] and in some populations, they have been noted to increase during the year following hospital discharge [12].

Despite awareness of the high risk of complications post ICU discharge, support to anticipate and address physical and psychological complications is not routinely offered through existing health care services. Many survivors report being unaware of what to expect during recovery and lack knowledge of what is normal and when they need to seek help [13]. The onus to seek help post discharge sits in the hands of the survivor, and it is unknown how many "suffer in silence," unaware if what they are experiencing is a usual part of recovery.

The purpose of this study was to determine if a Web-based intensive care recovery program improves the mental health and well-being of ICU survivors. As a mobile website, availability of the program will be unrestricted, enabling participants to access it at anytime and anywhere via a smart device. The program will enable participants to access support, advice, and guidance during their recovery post discharge from ICU.

Methods

Design

A parallel, prospective randomized controlled study will determine if a Web-based intensive care recovery program improves the mental health and well-being of ICU survivors. The study design for the protocol is outlined in a flow diagram in Figure 1.

Ethical Considerations

Ethical approval was obtained from the participating study site and the university where the researchers are employed.

Study Duration

Recruitment began in November 2018, and data collection will be completed within 2 years.

Participants

Participants will be screened and recruited from a general 10-bed ICU within a 750-bed hospital in Metropolitan Western Australia following discharge from ICU and admission to a general ward. Eligibility criteria for Inclusion are as follows: aged 18 years and over at time of randomization, ventilation in ICU for a minimum period of 24 hours, able to speak and understand English, able to give informed consent, and access to an electronic device. Participants will be informed which group they have been randomized to immediately after providing written informed consent.

Randomization

Permuted block randomization will be conducted in blocks of 20 using a computer random number generator. Allocation concealment will be conducted by an independent researcher using sequentially numbered, opaque, sealed envelopes. The independent researcher will provide the researcher conducting the consent process with the sequentially numbered, sealed, opaque envelopes. Envelopes containing the treatment allocation will only be opened by the recruiting researcher on participant enrollment. Blinding of the participant to allocation status will not be possible owing to the nature of the intervention. The researchers conducting the data analysis will be blinded.

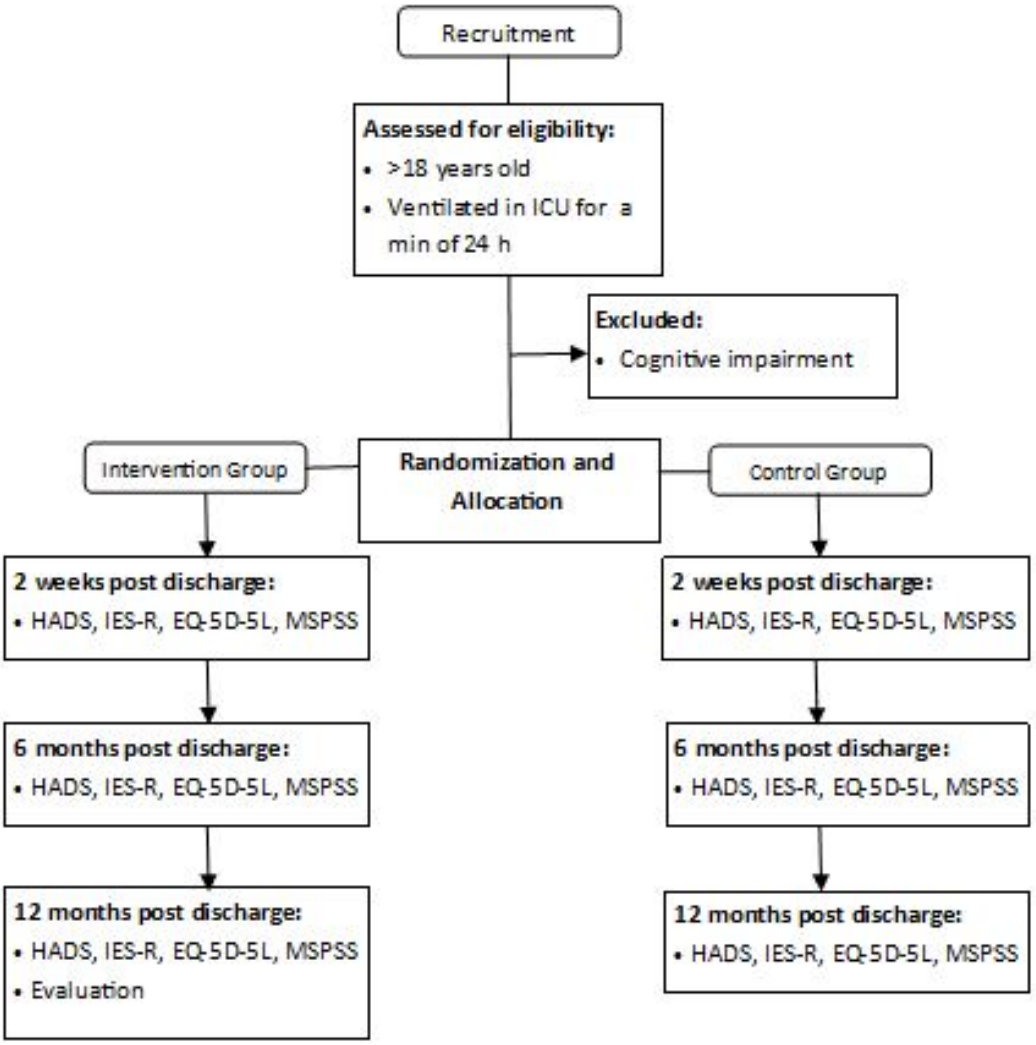
Intervention

Patients in the intervention group will receive access to a Web-based recovery program, ICUTogether that is accessible via smart devices and personal computers. The mobile website will provide information about health and well-being during recovery, including advice about exercise, sleep, and nutrition. Information will be provided on the recovery process, the signs and symptoms of potential complications during recovery, and when and how participants should seek professional help. Participants will be encouraged to keep a journal to promote reflection on progress over time and to explore their thoughts and feelings during their recovery. A chat room will also be available and participants will be able to post items to share with other participants in the study.

Participants will be given access to the mobile website 2 weeks following discharge from the hospital. A hard copy the self-help guide and telephone call will guide participants regarding the use of the site. If the participant is still unable to use the website, a researcher will visit their home and provide direct support with it. A demonstration of the functionality of the mobile website by a researcher will also be given at that time. The frequency of use of the website is at the discretion of the participants who will be encouraged to use the site as frequently as they wish. Each time a participant logs in, they will be prompted to complete a symptom checker that will identify material most useful to the participant at that point in time. The score from the symptom checker will be monitored and an alert notification will be sent to the researchers when the scores reach a certain level and thus gives cause for concern. Participants will receive a weekly email summarizing their participation over the previous 7 days and indicating any days they have not participated along with a prompt to continue participating.

The mobile website was developed by an external provider in collaboration with the researchers. The mobile website is being tested for ease of use and navigation properties by the researchers, clinicians, and a group of ICU survivors prior to commencement of the study.

Figure 1. Study design. ICU: intensive care unit; HADS: Hospital Anxiety and Depression Scale; IES-R: Impact of Event Scale–Revised; EQ-5D-5L: 5-level 5-dimension EuroQoL; MSPSS: Multidimensional Scale of Perceived Social Support.



Control Group

The comparator, the control group, will receive usual care. Usual care is defined as ongoing management by the participants' general practitioner (GP). There is no specific after care provision for ICU survivors offered at the study site. At the time of discharge from the hospital, survivors are discharged back to the care of their GP with additional services provided as necessary. These services do not include any specific ICU aftercare provision, for instance, follow-up by the ICU team. There will be no contact with the control group beyond consent and postal surveys.

Data Collection and Measures

Following the consent process, demographic data will be collected from the participants' health records, which will include the age, gender, admission diagnosis, severity of illness (APACHE III), existing comorbidities, and ICU length of stay. Data will be collected from participants at the following 3 time points: 2 weeks post discharge, 6 months post discharge, and 12 months post discharge (primary timepoint). The following three outcome measures will be used in the study: the Hospital Anxiety and Depression Scale (HADS), the Impact of Events Scale Revised, and the 5-level 5-dimension EuroQoL. All 3 measures will be completed at each of the 3 time points. The level of family support will also be collected at these time points via the Multidimensional Scale of Perceived Support [14]. Table 1 provides a brief description of each of the outcome measures. Participants in both groups will receive the 3 surveys by email 2 weeks post discharge from the hospital to complete the first data collection time point. At the following 2 data collection time points, the 3 surveys will be sent by via email to both groups. All participants will also be contacted by telephone to provide a prompt to complete the surveys at the data collection time points.

Table 1. Summary of outcome measures and description.

Outcome measure	Number of items	Description
Primary outcome		
Hospital Anxiety and Depression Scale	14 on a 4-point scale	• Used to identify the incidence of anxiety and depression in patients with a range of diseases and medical conditions [15].
Secondary outcomes		
Impact of Events Scale Revised	24 on a 5-point scale	• Measure of subjective distress in response to a traumatic event [16]. • It comprises 3 subscales that represent the major symptom clusters of post-traumatic stress disorder: intrusion, avoidance, and hyperarousal [17].
5-level 5-dimension EuroQoL	5 on a 5-point scale and a visual analog scale	• Measure changes to health-related quality of life over time or between or following interventions [18]. • The 5 dimensions within the survey are mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.
Multidimensional Scale of Perceived Social Support	12 on a 7-point Likert scale	• Measures perceptions of support from 3 sources: family, friends, and significant other [14].

For participants in the intervention group at time point 3, 12 months after discharge, an evaluation will be conducted via the website on the acceptability and usability of the website. The evaluation will be conducted through the Web portal and completed online. The evaluation tool will be a modified version of the Mobile App Rating Scale [19] and comprise questions on the acceptability and content of the Web-based recovery program. The website is multidimensional, including recovery resources and an internet-based community, and facilitates journaling. To further understand the contribution each makes to outcomes, we will analyze the website analytics to determine how frequently and for how long the participants interacted with the site and the individual components within it. Participants will also be asked to rate each component of the site in terms of usefulness and perceived impact on their recovery.

Sample Size

Sample size and statistical power were calculated for the primary outcome measure using G*Power 3.1.9.2 [20]. Detecting a 2-point difference (effect size of 0.44) between the 2 groups on HADS with an alpha of .05 and 80% power requires 81 participants in each group for a total sample size of 162 participants. Given the discharge rate of 80 patients per month and a recruitment rate of 30%, it is estimated that it will take 7 months to recruit the required sample size.

Statistical Analysis

Data will be reported in accordance with the Consolidated Standards of Reporting Trial. Data analysis will be conducted using SPSS version 24 (IBM) and Stata SE version 15 (StataCorp). The characteristics of participants in each arm of the study will be summarized using descriptive statistics. Analysis of characteristics to determine similarity between the arms will be conducted using chi-square tests for categorical data and independent *t* tests for continuous data.

Further analysis will include stratifying the APACHE III scores into categories to determine if there is a difference in the level of severity and outcomes. The 3 outcome measures (HADS, IES, and QoL) at follow-up will be analyzed as dependent variables using regression modeling. Covariates will include baseline outcome measures, study allocation (intervention or control), age, gender, length of ICU stay, APACHE III score, and level of family support. Analysis will be conducted on an intention-to-treat basis. A subanalysis of the intervention group based on those who engaged with the mobile website compared with those who did not will also be conducted. The characteristics of people who withdraw from the study will be compared with those who remain in the study. Missing data will be addressed using multiple imputation assuming variables are missing at random. The person who completes the data analysis will be blind to participant allocation status. Summary statistics of frequency of use, time spent using the site, most frequently used elements, and time spent on each screen will be reported.

Economic Outcomes

A cost utility analysis will be conducted at 12 months to determine whether the Web-based recovery program is a cost-effective approach for improving the quality of life of ICU survivors when compared with usual care. The perspective taken for the economic analysis will be a societal perspective and will include costs incurred by individuals as well as health care providers.

Identification of Costs and Benefits

The primary outcome measure for assessing benefits will be quality of life. The identification of costs will be across the following 4 main areas:

1. *Intervention costs* include ongoing mobile website maintenance such as hosting costs as well as the cost of promoting the mobile website to future ICU survivors. The cost for developing the mobile website and implementing the intervention for the study will not be included because these costs will not be incurred in future implementation of the mobile website.
2. *Health care costs* include GP visits; other health practitioner consultations such as counseling services, dieticians, and

physiotherapists; emergency department visits; hospital inpatient stays in acute or mental health settings; mental health outpatient visits; and medication use.

3. *Personal and family costs* include the use of alternative therapies such as massage and reflexology, as well as the use of health promotion resources such as sporting facilities and support groups. Travel costs to attend health services and health promotion activities will also be included. The time cost for using the mobile website will not be included as this will occur during leisure time and is expected to be minimal.
4. *Productivity costs* include time spent absent from work owing to illness.

Measurement of Costs and Benefits

Benefits will be measured using 5-dimension EuroQoL. Intervention costs will be measured through discussions with the mobile website developers about the requirements to maintain the website for a 1-year period. A plan for promoting the mobile website to future ICU survivors will be prepared, detailing the elements that will be included. Health care costs will be measured by a patient diary for GP visits, health practitioner visits, and medication use. Linked data will be used to measure emergency department visits, outpatient visits, and hospital usage. Personal and productivity costs will be measured by a patient diary, which will record the number of times health-related services and health promotion resources are accessed, travel details to access these resources, and time spent absent from paid work.

Valuation of Costs and Benefits

Benefits will be valued by calculating quality adjusted life years from the 5-dimension EuroQoL data using Australian derived utility weights [21]. Intervention costs will be valued by obtaining 3 quotes from service providers. The average of the 3 quotes will be used in the calculations. Health care costs will be valued using the Australian Medicare Benefits Schedule [22], Pharmaceutical Benefits Scheme data [23], and the National Hospital Cost Data Collection [24]. Personal and family costs will be valued by cost prices recorded in the patient diaries. Travel costs will be valued by the number of visits to providers or facilities, the average distance traveled, and the Australian Taxation Office guidelines for car expenses (cents per kilometer method) [25] or the cost of public transport. Productivity costs for time spent absent from paid work will be valued using the human capital approach [26].

Data and Sensitivity Analysis

The incremental cost effectiveness ratio will be calculated by dividing the difference in costs between the intervention and control arms by the difference in quality-adjusted life years.

Probabilistic sensitivity analysis using Monte Carlo simulations will be performed. Uncertainty exists around the estimate of the intervention effect on quality of life and around costs, including the health provider, individual, and productivity costs, and these will be included in the sensitivity analysis with the distributions to be determined from the data. Results will be presented as scatterplots and cost effectiveness acceptability curves for a range of willingness to pay thresholds.

No discounting is required because all costs and benefits will be measured within a 1-year time period. All costs will be valued using Aus $ 2018. No modeling of costs and benefits into the future will be undertaken.

Results

Participant recruitment is currently underway. Recruitment is anticipated to be completed by December 2020 and the first results are expected to be submitted for publication in 2021.

Discussion

ICU survivors face many challenges during their recovery, and many may never achieve a level of recovery that is acceptable to them. Despite the evidence confirming that these individuals have an increased uptake of health care resources and poor outcomes, they are not routinely offered dedicated programs to support them post discharge from ICU.

This research study is an innovative approach to providing an evidence-based recovery program for ICU survivors, a group of individuals who experience significant levels of physical and psychological morbidity. The findings from this study will inform a larger study and wider debate on approaches to engage and support survivors post ICU.

Authors' Contributions

BE, HM, LW, DS, and JH were involved in the conception and organization of the research and the review and critique of the manuscript. KS and BE wrote the first draft of the manuscript.

Conflicts of Interest

None declared.

References

1. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosom Med 2008 May;70(4):512-519. [doi: 10.1097/PSY.0b013e31816aa0dd] [Medline: 18434495]

2. O'Donnell ML, Creamer M, Holmes ACN, Ellen S, McFarlane AC, Judson R, et al. Posttraumatic stress disorder after injury: does admission to intensive care unit increase risk? J Trauma 2010 Sep;69(3):627-632. [doi: 10.1097/TA.0b013e3181bc0923] [Medline: 20118816]
3. Abdalrahim MS, Zeilani RS. Jordanian survivors' experiences of recovery from critical illness: a qualitative study. Int Nurs Rev 2014 Dec;61(4):570-577. [doi: 10.1111/inr.12142] [Medline: 25382166]
4. Granja C, Amaro A, Dias C, Costa-Pereira A. Outcome of ICU survivors: a comprehensive review. The role of patient-reported outcome studies. Acta Anaesthesiol Scand 2012 Oct;56(9):1092-1103. [doi: 10.1111/j.1399-6576.2012.02686.x] [Medline: 22471617]
5. Kelly MA, McKinley S. Patients' recovery after critical illness at early follow-up. J Clin Nurs 2010 Mar;19(5-6):691-700. [doi: 10.1111/j.1365-2702.2009.03117.x] [Medline: 20500311]
6. Secombe PJ, Stewart P. Long-term morbidity and mortality in survivors of critical illness: a 5-year observational follow-up study. Rural Remote Health 2017;17(1):3908 [FREE Full text] [Medline: 28231714]
7. McNelly AS, Rawal J, Shrikrishna D, Hopkinson NS, Moxham J, Harridge SD, et al. An Exploratory Study of Long-Term Outcome Measures in Critical Illness Survivors: Construct Validity of Physical Activity, Frailty, and Health-Related Quality of Life Measures. Crit Care Med 2016 Jun;44(6):e362-e369. [doi: 10.1097/CCM.0000000000001645] [Medline: 26974547]
8. Davydow DS. The burden of adverse mental health outcomes in critical illness survivors. Crit Care 2010;14(1):125 [FREE Full text] [doi: 10.1186/cc8867] [Medline: 20236473]
9. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med 2011 Feb;39(2):371-379. [doi: 10.1097/CCM.0b013e3181fd66e5] [Medline: 20959786]
10. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012 Feb;40(2):502-509. [doi: 10.1097/CCM.0b013e318232da75] [Medline: 21946660]
11. Brummel NE, Jackson JC, Pandharipande PP, Thompson JL, Shintani AK, Dittus RS, et al. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. Crit Care Med 2014 Feb;42(2):369-377 [FREE Full text] [doi: 10.1097/CCM.0b013e3182a645bd] [Medline: 24158172]
12. Myhren H, Ekeberg O, Tøien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. Crit Care 2010;14(1):R14 [FREE Full text] [doi: 10.1186/cc8870] [Medline: 20144193]
13. Ewens BA, Hendricks JM, Sundin D. Never ending stories: visual diarizing to recreate autobiographical memory of intensive care unit survivors. Nurs Crit Care 2017 Jan;22(1):8-18. [doi: 10.1111/nicc.12093] [Medline: 25294316]
14. Zimet G, Dahlem N, Zimet SG, Farley G. The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment 1988 Mar;52(1):30-41. [doi: 10.1207/s15327752jpa5201_2]
15. Montazeri A, Vahdaninia M, Ebrahimi M, Jarvandi S. The Hospital Anxiety and Depression Scale (HADS): translation and validation study of the Iranian version. Health Qual Life Outcomes 2003;1:14 [FREE Full text] [doi: 10.1186/1477-7525-1-14] [Medline: 12816545]
16. Weiss DS, Marmar CR, Metzler TJ, Ronfeldt HM. Predicting symptomatic distress in emergency services personnel. J Consult Clin Psychol 1995 Jun;63(3):361-368. [Medline: 7608348]
17. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. Arlington, VA: American Psychiatric Publishing, Inc; 2013.
18. 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]
19. 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;3(1):e27 [FREE Full text] [doi: 10.2196/mhealth.3422] [Medline: 25760773]
20. 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]
21. Viney R, Norman R, King MT, Cronin P, Street DJ, Knox S, et al. Time trade-off derived EQ-5D weights for Australia. Value Health 2011;14(6):928-936. [doi: 10.1016/j.jval.2011.04.009] [Medline: 21914515]
22. Australian Government Department of Health. 2018. Medicare Benefits Schedule URL: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Downloads-201802 [WebCite Cache ID 6z6ZHc9AX]
23. Australian Government Department of Health. 2018. The Pharmaceutical Benefits Scheme URL: https://www.pbs.gov.au/info/browse/statistics [accessed 2018-05-02] [WebCite Cache ID 6z6ZTpPZ3]
24. Independent Hospital Pricing Authority. 2017. National Hospital Cost Data Collection URL: https://www.ihpa.gov.au/what-we-do/nhcdc [accessed 2018-05-02] [WebCite Cache ID 6z6ZbA1og]
25. Australian Governemnt Australian Taxation Office. 2018. Ride-sourcing and tax URL: https://www.ato.gov.au/General/Ride-sourcing-and-tax/Car-expenses/ [accessed 2018-05-02] [WebCite Cache ID 6z6Zi9Det]
26. Krol M, Brouwer W. How to estimate productivity costs in economic evaluations. Pharmacoeconomics 2014 Apr;32(4):335-344. [doi: 10.1007/s40273-014-0132-3] [Medline: 24504850]

Abbreviations

GP: general practitioner
HADS: Hospital Anxiety and Depression Scale
ICU: intensive care unit

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Protocol

Understanding the Effect of Adding Automated and Human Coaching to a Mobile Health Physical Activity App for Afghanistan and Iraq Veterans: Protocol for a Randomized Controlled Trial of the Stay Strong Intervention

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Abstract

Background: Although maintaining a healthy weight and physical conditioning are requirements of active military duty, many US veterans rapidly gain weight and lose conditioning when they separate from active-duty service. Mobile health (mHealth) interventions that incorporate wearables for activity monitoring have become common, but it is unclear how to optimize engagement over time. Personalized health coaching, either through tailored automated messaging or by individual health coaches, has the potential to increase the efficacy of mHealth programs. In an attempt to preserve conditioning and ward off weight gain, we developed *Stay Strong*, a mobile app that is tailored to veterans of recent conflicts and tracks physical activity monitored by Fitbit Charge 2 devices and weight measured on a Bluetooth-enabled scale.

Objective: The goal of this study is to determine the effect of activity monitoring plus health coaching compared with activity monitoring alone.

Methods: In this randomized controlled trial, with *Stay Strong*, a mobile app designed specifically for veterans, we plan to enroll 350 veterans to engage in an mHealth lifestyle intervention that combines the use of a wearable physical activity tracker and a Bluetooth-enabled weight scale. The *Stay Strong* app displays physical activity and weight data trends over time. Enrolled participants are randomized to receive the *Stay Strong* app (active comparator arm) or *Stay Strong + Coaching*, an enhanced version of the program that adds coaching features (automated tailored messaging with weekly physical activity goals and up to 3 telephone calls with a health coach—intervention arm) for 1 year. Our primary outcome is change in physical activity at 12 months, with weight, pain, patient activation, and depression serving as secondary outcome measures. All processes related to recruitment, eligibility screening, informed consent, Health Insurance Portability and Accountability Act authorization, baseline assessment, randomization, the bulk of intervention delivery, and outcome assessment will be accomplished via the internet or smartphone app.

Results: The study recruitment began in September 2017, and data collection is expected to conclude in 2019. A total of 465 participants consented to participate and 357 (357/465, 77%) provided baseline levels of physical activity and were randomized to 1 of the 2 interventions.

Conclusions: This novel randomized controlled trial will provide much-needed findings about whether the addition of telephone-based human coaching and other automated supportive-coaching features will improve physical activity compared with using a smartphone app linked to a wearable device alone.

Trial Registration: ClinicalTrials.gov NCT02360293; https://clinicaltrials.gov/ct2/show/NCT02360293 (Archived by WebCite at http://www.webcitation.org/75KQeIFwh)

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KEYWORDS

exercise; veterans; cell phones; mobile phone; telemedicine

Introduction

Background and Significance

The type and intensity of physical activities performed by the veteran population changes considerably from active duty to postdeployment. This is often because of the relatively unstructured nature of postdeployment life, as well as service-connected illnesses or injuries [1]. Younger veterans involved in the Afghanistan and Iraq conflicts—Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND; OEF/OIF/OND)—may also have work-life balance issues related to childcare and elder care issues and additional civilian reintegration issues related to high physical and mental health burdens, which may present unique challenges to being more physically active (eg, chronic pain, mental illness, and substance abuse) [2,3]. The transition from being physically fit and active to being more sedentary can lead to rapid weight gain and an increased risk of adverse health outcomes including diabetes, heart disease, joint disorders, and some cancers. This rapid weight gain was documented in a prospective study by Litman et al (2013), where it was found that there is an increased rate of weight gain in veterans around the time of military discharge [4]. In a large cohort of OEF/OIF/OND veterans seen in the Veteran Health Administration (VHA) postdeployment, 65.8% of men and 46.7% of women were overweight or obese at their first visit [5]. Early intervention with individually tailored lifestyle programs targeting physical activity and prevention of weight gain has the potential to sustain the high level of fitness required for military service well past active-duty status and improve mental and physical health.

A potential strategy for increasing access to lifestyle modification programs for OEF/OIF/OND veterans and more technology savvy patients is through the use of mobile health (mHealth), which refers to the use of mobile computing, wearable sensors, and communication devices for the provision of health services and information [6]. Although mHealth apps are still emerging and evolving, there exists a solid foundation demonstrating that internet-mediated interventions [7], particularly when combined with the use of wearable physical activity monitors, tailored motivational messaging, and online coaching, can increase physical activity and have the potential to improve health outcomes [8-10]. Through leveraging the ubiquity of mobile devices, we can easily increase access to these types of interventions [6,11,12]. mHealth interventions have been built on findings from internet-mediated intervention trials and have likewise been shown to be effective in chronic disease self-management and promoting behavior change [13-22]; however, the evidence base for mHealth interventions is largely made up of small trials with short-term follow-up [6,18], and long-term engagement with mHealth programs is not always sustained [23,24]. A potential strategy for improving upon mHealth interventions is through the addition of health coaching, including telephone-based lifestyle coaching delivered by human coaches. Health coaching is a patient-centered, collaborative model grounded in theories of health behavior change, in which coaches work in partnership with patients to identify goals and action plans that maximize personal well-being and overall health. Many coaching interventions use techniques like motivational interviewing, goal setting, and problem-solving as key strategies. Across a wide variety of populations, health coaching has produced positive impacts on lifestyle modifications [25-27]. Adding automated coaching features, such as personalized messaging addressing barriers and motivators, as well as goal setting based on past outcomes gleaned from wearable devices, may further enhance the impact of health coaching [28].

Specific Aims

We aim to evaluate the effect of adding automated (ie, automated tailored messaging and automated goal setting) and human telephone health coaching to *Stay Strong*, an mHealth app that seeks to improve physical activity in OEF/OIF/OND US veterans over 1 year. *Stay Strong* is a mobile app that is tailored to these veterans and tracks physical activity monitored by Fitbit Charge 2 devices and weight measured on a Bluetooth-enabled scale. Captured data are presented visually to participants to facilitate behavior change. We also aim to further assess the impact on the secondary outcomes of weight loss, depression, patient activation, and pain, as well as to test for potential moderating effects of individual characteristics (eg, demographics and familiarity with technology). We hypothesize that our enhanced version of the intervention *Stay Strong + Coaching* will result in greater improvement in physical activity (primary outcome) at 12 months compared with the base *Stay Strong* program.

Methods

Trial Design

This study is a randomized trial to test the effect of adding coaching (ie, automated tailored messaging, automated goal setting, and telephone calls with a health coach) to an mHealth intervention to improve and sustain levels of physical activity among a national sample of US veterans over 12 months. In this study, participants are randomized to receive either the base intervention (*Stay Strong*) or an enhanced intervention that includes coaching features (*Stay Strong + Coaching*). The decision to incorporate an active control group was guided by several considerations. First, there is sufficient evidence in the literature to suggest that this type of technology-mediated intervention for promoting increased physical activity is effective [8-10], even in a veteran population [29,30]. As such, we felt justified in not including a true usual-care control. Furthermore, physical activity tracking devices are highly ubiquitous in the general US adult population. On the one hand, the use of a wearable device by participants assigned to the control group would confound results. On the other hand, we did not believe it would be ethical to ask control-group participants to refrain from using one over the course of a 12-month intervention period. This study was reviewed and approved by the VHA Central institutional review board (IRB)–VHA IRB for multisite studies.

Intervention

Stay Strong is a multicomponent mHealth physical activity intervention for iOS and Android platforms that supports physical activity and weight self-monitoring. Vibrent Health, a digital health company in Fairfax, VA, was engaged to develop the app, online portal, and server platforms necessary to support *Stay Strong* [31] (see Multimedia Appendix 1 for screenshots of the *Stay Strong* interface). The study team defined the functional system requirements to Vibrent, and then the team and Vibrent collaborated on the user-interface design. Feedback on the design was gathered from a convenience group of testers employed at the VA, several of whom were OEF/OIF/OND veterans, and the approach of utilizing a wearable activity tracker was endorsed by the target population in some of our previous work [32].

Theoretical Foundations

Figure 1 shows the theoretical framework underlying the design of the intervention. The theoretical orientation of *Stay Strong* is informed by the information-motivation-behavioral skills (IMB) model and self-regulatory theory [33-36]. Both models have been successfully applied to physical activity and describe processes of behavior change mediated through goal attainment and skill mastery, and both models acknowledge the central role that self-efficacy plays in sustained behavior change [37-42]. The IMB hypothesizes that cognitive and behavioral skills are a prerequisite for any health behavior change like increasing physical activity. However, skills are the product of information that is relevant to health problems and personal and social support for activation to change behavior. Thus, information interacts with activation to enhance self-efficacy and build skill mastery to facilitate sustained behavior change. Informed by the pilot data and the IMB, *Stay Strong + Coaching* will boost the positive reinforcing relationship between self-monitoring and feedback with goal setting and activation through a coaching support component. Human coaches will enhance activation and facilitate goal setting by (1) providing social support, (2) helping to develop specific plans of action, (3) helping with problem solving to avoid or mitigate barriers to goal achievement, and (4) enhancing engagement with the *Stay Strong* app by helping to interpret the individuals' physical activity data and using it to monitor progress toward their goals. Automated coaching will further strengthen these supports by (1) providing personalized, realistic physical activity goals, grounded in the objective physical activity monitoring provided through the Fitbit Charge 2 device, (2) sending personalized messages to help overcome barriers to physical activity, and (3) sending educational and motivational messages via the *Stay Strong* app.

The theory of self-regulation also informs the core components of *Stay Strong + Coaching*. In self-regulation, individuals participate in self-directed behaviors. These self-directed behaviors are hypothesized to be managed through a dynamic feedback loop in which individuals' self-monitoring and feedback about their past behavior are integrated into their goals and activation to change future behaviors [43]. Thus, aligned with IMB, self-regulation involves both cognitive and behavioral processes to facilitate goal setting and attainment. A key strategy of *Stay Strong + Coaching* is to enhance activation and facilitate goal setting though enhanced self-monitoring. The Fitbit Charge 2 device will provide detailed minute-by-minute self-monitoring information through the objective measurement of physical activity. The self-monitoring and feedback loop will act on self-efficacy via 2 pathways: (1) influencing participants' goal setting and activation to adhere to goals and (2) providing data for the human coaches and for automated coaching to customize motivational messages about goal attainment and to set appropriate, realistic future goals. Increased self-efficacy will mediate positive changes in physical activity, which will, in turn, lead to secondary outcomes of weight control and improved overall mental (eg, depression) and physical health (eg, pain) status. This theoretical grounding guided the choice of intervention components, which have each been classified in terms of an established taxonomy of behavior change techniques (BCTs) [44] (see Multimedia Appendix 2 for a complete list of BCTs by group assignment).

Stay Strong and Stay Strong + Coaching Components

The *Stay Strong + Coaching* intervention comprises multiple components that support physical activity and weight self-monitoring. Figure 2 illustrates the components with data flows and Table 1 provides a complete list of intervention components by study arm.

Figure 1. Theoretical framework. PA: physical activity; SS: *Stay Strong*.

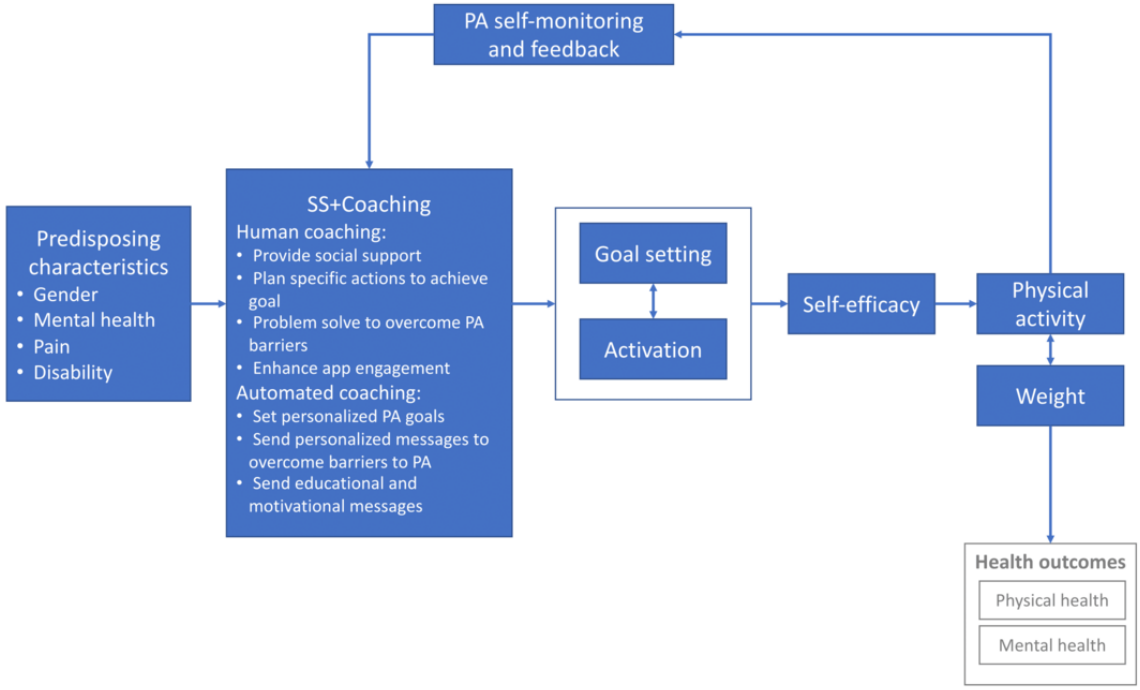


Figure 2. The *Stay Strong* intervention and data flow.

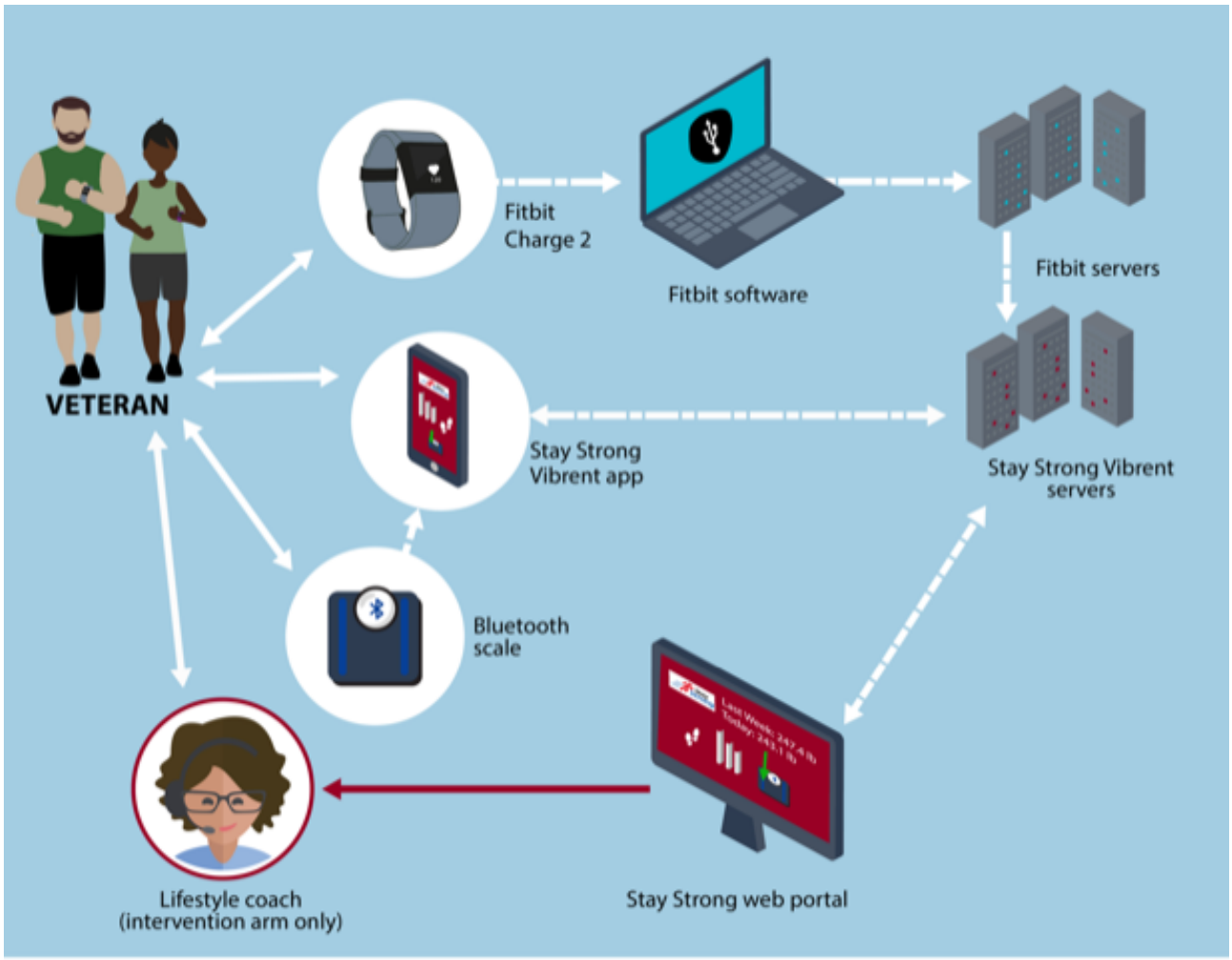


Table 1. *Stay Strong* components by trial arm.

Component	SS[a] Arm	SS + Coaching Arm	Intensity	Duration	Mode
Objective physical activity monitoring (Fitbit Charge 2 and data visualizations within SS)	✓	✓	Fitbit worn daily and data syncing at least once per week	1 year	Fitbit worn on wrist; Data visualizations available within the *SS* app
Weight self-monitoring (scale and weight data visualizations within SS)	✓	✓	Weight measured weekly with data syncing at least once per week	1 year	Data visualizations available within the *SS* app
Administrative message reminders (reminders for syncing, adverse event reporting, and data assessments)	✓	✓	1 message less than 230 characters	As needed over 1 year	Push notification on the smartphone
Automated personalized goal setting	—[b]	✓	Weekly, based on previous week's and physical activity data	1 year	Abbreviated phone push notification plus message with image within the *SS* app
Automated messages: nonpersonalized	—	✓	1 message up to 225 characters, 3 per week	1 year	Abbreviated phone push notification plus a full message with visual image within the SS app
Automated messages: personalized, based on self-reported barriers	—	✓	1 message up to 225 characters, 3 per week	1 year	In-app and smartphone notification with image
Telephone-based lifestyle coaching	—	✓	Up to 30 min	3 calls in the first 9 weeks	Telephone

[a]SS: Stay Strong.

[b]Not applicable.

Stay Strong Components

Physical Activity Self-Monitoring

After enrollment, all the participants were provided with a Fitbit Charge 2 device, which is a wrist worn physical activity monitor that logs different objective measurements of physical activity, including *active minutes*, miles, steps, stairs, and heart rate zone. Data from the Fitbit device sync with the Fitbit platform and are then pulled into the *Stay Strong* app for viewing in table or chart view in 1- to 4-week increments. All the participants were encouraged to wear the Fitbit device during waking hours for the duration of the study period and upload device data at least weekly via the Fitbit Connect (Fitbit, Inc) software on their computer. Fitbit devices were chosen for their relatively low cost as well as their ubiquity in the consumer wearables marketplace, as well as in the research world [45], facilitating a path to implementation if the *Stay Strong* program is proven effective at improving physical activity in this population. Furthermore, previous work has demonstrated that although the Fitbit Charge HR (the previous version of the Charge 2 device) has its limitations compared with other wearable devices [46], it is suitable for research purposes as it provided an accurate measure of heart rate during walking and running activities [47].

Weight Self-Monitoring

After enrollment, all the participants were also provided a Bluetooth-enabled weight scale (A&D Deluxe Connected Weight Scale UC-352BLE). The data from the scale can sync with *Stay Strong* or be manually entered, and the data can be viewed in table or chart view in 1- to 4-week increments. All the participants were asked to use and sync their scale at least once per week during the study.

Automated Administrative Messaging Reminders

During the study period, all participants receive a variety of automated administrative messages, reminders to report any adverse events every 90 days, and reminders to complete 6- and 12-month survey assessments.

Stay Strong + Coaching Components

In addition to *Stay Strong* components, *Stay Strong + Coaching* participants receive the following components.

Automated Personalized Physical Activity Goals

Stay Strong + Coaching participants receive a new, automated and personalized daily physical activity goal, based on their previous physical activity, every Sunday morning at 9:00 am (based on the participants' local time). New goals are calculated based on an average of the most recent 7 consecutive days where at least 5 of the 7 days have valid data (ie, at least 5 min of light activity). Physical activity goals specify the number of *active minutes* participants should seek to obtain every day. *Active minutes* is a proprietary measure that captures the number of minutes of continuous moderate-to-vigorous exercise when this level of activity is sustained for at least 10 min [48]. The minimum goal issued to participants is to average 10 *active minutes* per day. To minimize the risk associated with starting an exercise program and increase the likelihood of sustaining increased physical activity, automated goals guide participants

to gradually increase their physical activity by no more than 5 *active minutes* per week. For safety reasons, no goal may exceed 60 *active minutes* per day, and physical activity goals set each week are never increased by more than 5 *active minutes* over the previous week's goal. In the event participants have not synced physical activity data recently, automated reminders are sent. For participants who do not provide new data (either because of failure to sync data or nonadherence to wearing the Fitbit), the previous week's goal will be reused. For participants who fail to meet their goal, their next goal may decrease or remain the same because goals are based on activity during the previous 7 days. Each week, goals are calculated based on data through Saturday, 11:59 pm local time. Participants are notified of their new goal through push notifications on their phone, and current goals are visually displayed within the *Stay Strong* app.

Automated Personalized Educational and Motivational Messaging

Stay Strong + Coaching participants receive 3 in-app and push notification messages per week. To keep messages fresh throughout the duration of the 12-month intervention and reduce the likelihood of participants ignoring messages sent at predictable times, messages are sent between 9:30 am and 5:30 pm (local time) Monday through Saturday at varying times. All messages are sent during the morning, afternoon, or evening, at a randomly selected time from the following options: morning=9:30 am, 10:30 am, 11:00 am, or 11:15 am; afternoon=1:00 pm, 1:45 pm, 2:40 pm, or 3:00 pm; evening=4:00 pm, 4:30 pm, 4:45 pm, or 5:15 pm. All messages are 225 characters or less including spaces, and they are designed to help the participants stay engaged in healthy lifestyle habits, as well as learn more about a variety of topics, including the following: (1) exercise, (2) healthy eating, (3) initiating behavior change, (4) pain, (5) inspirational quotes, (6) maintaining behavior change, (7) weight loss and weight management, (8) heart rate monitoring, (9) appropriate athletic gear, and (10) tips to overcoming self-identified barriers to physical activity. For messages pertaining to overcoming barriers to physical activity, the participants are asked to endorse up to 4 of a prespecified list of 11 barriers to increasing physical activity (lack of time, social influence, lack of energy, lack of willpower or motivation, fear of injury or pain, lack of resources, family obligations, weather conditions, depression, lack of accountability or external motivation, and disability) during the baseline and 6-month assessment. These barriers include the top 10 most common reasons why people are not more physically active, based on work by Sallis and Hovell (1990), Sallis et al (1992), and highlighted by the Centers for Disease Control and Prevention. In addition, we included 1 additional barrier related to disability [49,50].

Lifestyle Telephone Coaching Calls

Stay Strong + Coaching participants complete up to 3 phone calls with the *Stay Strong* coach within the first 9 weeks of the study. The *Stay Strong* coach has access to the participants' survey responses and synced Fitbit data and works with participants to help them meet physical activity goals. The coach provides information to participants to enhance motivation through (1) assistance in developing goals and action plans to achieve Fitbit-derived physical activity goals, (2) assistance in problem solving barriers to achieving physical activity goals via tailored motivational support, and (3) guidance on features of the *Stay Strong* app, with an emphasis on interpreting Fitbit physical activity data outputs. In the event coaches are not able to reach participants by phone for coaching sessions, we attempt to contact participants via US mail.

Participant Inclusion and Exclusion Criteria

To be eligible to participate in this study, participants had to be an OEF/OIF/OND veteran, identify a VHA medical center and VHA health care provider responsible for his or her care, be interested in starting a physical activity program in the next 30 days, have access to a computer with an internet connection and a working Universal Serial Bus (USB) port, have a smartphone running a compatible iOS or Android operating system, and be younger than the age of 65 years.

The decision to limit our recruitment to individuals under 65 years of age was because of higher risk of cardiac issues in individuals over the age of 65 years. The individuals were excluded if they reported that a health care provider had told them that it was currently unsafe to exercise in an unsupervised or unmonitored setting, they had a history of eating disorders or a body mass index less than 20, they were not competent to consent for themselves to a research study, or have worn a physical activity sensor within the last 30 days.

Recruitment Procedure

Sample Size Calculation

Our sample size estimate is based on the primary hypothesis: OEF/OIF/OND veterans randomized to the *Stay Strong + Coaching* intervention arm will have greater mean daily minutes of *active minutes* (moderate-to-vigorous physical activity) at 12 months than veterans randomized to the *Stay Strong* arm. A 10-min differential improvement at 12 months was set as a minimal clinically important difference. This represents the differential between the intervention and comparison arms at 12 months; therefore, the power and sample size considerations apply even if the comparison arm also improves over the study period. The mean daily minutes at 12 months will be obtained based on an analytic model using weekly averages of activity per day over the 12-month study period with up to 52 weeks of data. Sample size calculations are based on analysis of covariance methods as described in Borm's paper, and are thus conservative [51]. We used data from the Lifestyle Education for Activity and Nutrition study [52] and our earlier unpublished feasibility study to estimate quantities needed for the sample size calculation. Our sample size calculations were based on unpublished data from a pilot study led by members of our team using a Body Media Fit device [32]. Although these calculations are based on a different device, we expect the SD of *active minutes* (our primary outcome) or the clinically meaningful and detectable difference, to be similar for interventions using the Body Media Fit versus the Fitbit Charge 2 device. On the basis of this unpublished pilot data, we anticipated a baseline mean of 53 min, a SD of 28 min in both treatment groups, .46 correlation between baseline and 12 months, and 25% attrition by 12 months based on previous studies. The study is designed to randomize 350 patients (175 per group) to detect with a .05

level 2-sided test, with a 10-min difference in improvement at 12 months with 90% power.

Participants

To recruit participants, we used the OEF/OIF/OND roster from the VHA Corporate Data Warehouse to identify candidate participants who had been seen in VHA primary care in the past year. Using scrambled social security numbers from the OEF/OIF/OND roster, we retrieved current mailing addresses through the VHA Informatics and Computing Infrastructure in batches of 2000. The pool of candidate participants was selected to proportionally represent each of the eligible VHA sites across the continental United States and Puerto Rico. It should be noted that the majority of letters intended for potential participants from Puerto Rico were returned as undeliverable or were intentionally not sent by the study team because of Hurricane Maria in September 2017. We oversampled women to achieve a targeted proportion of 20%. The enrolled individuals were randomly assigned to 1 of 2 groups in a 1:1 ratio: (1) the active control group (*Stay Strong*) or (2) the intervention group (*Stay Strong + Coaching*). The high targeted number of consented individuals (n=750) was because of anticipation that many individuals were likely to drop out because of the number of technical steps that must be completed before randomization including downloading and installing the *Stay Strong* app on their smartphone, pairing their Fitbit device to the app and syncing sufficient valid activity data in a 7-day period to capture baseline activity.

Study Recruitment, Enrollment, Randomization, and Retention

Recruitment packets containing an invitation letter and a brief study overview sheet were sent in batches of approximately 200. First, the candidate participants were provided an individually assigned program code in their invitation letter and directed to a website. Second, the individuals completed a set of screening questions to assess study eligibility. If they were eligible, they were then directed to the online consent and Health Insurance Portability and Accountability Act (HIPAA) authorization processes and the baseline survey. Next, participants were instructed to install and register the *Stay Strong* app through Google Play (Android smartphone users) or Apple (iPhone users) stores. When the participants successfully installed the *Stay Strong* app on their smartphone, the study team was automatically notified via an online portal. At this point, the participants were considered to be fully enrolled if they completed all of these steps. All the participants were reminded to follow-up with their health care provider as needed throughout the study.

The participants who were fully enrolled were then shipped a package that included a welcome letter, devices (Fitbit Charge 2 & Bluetooth weight scale), a Fitbit USB dongle for syncing their Fitbit device, instructions, a frequently asked questions document, a written copy of the Study Information Sheet, and HIPAA authorization. The participants were required to authorize the *Stay Strong* app to sync and access data from Fitbit. When they were fully configured, the participants were instructed to use their devices for up to 2 weeks and to sync their data via the Fitbit Connect software, at least weekly. When 7 consecutive days having at least 5 valid days of data were synced, the individual was randomized to *Stay Strong* or *Stay Strong + Coaching*. A day's worth of data were deemed valid if at least 5 lightly *active minutes* had been recorded. The individuals were instructed to sync data via the Fitbit Connect software only via a Bluetooth-enabled dongle, which required access to a computer using a USB port. This was necessary to comply with VHA data security and confidentiality standards.

If the participant had not met the minimum criteria to be randomized after 2 weeks, the study staff would attempt to call the individual to solve any technical issues that had arisen. A total of 3 attempts were made to contact the individual and receive the physical activity data. Our intent was to randomize the participants who successfully completed all the steps and met all the criteria. Randomization was stratified by gender, physical activity level (high vs low), and smart phone operating system (android vs iOS) into the 2 groups in a 1:1 ratio, with a target of randomizing 175 participants per arm. All the study staff were blinded to the randomization list, which was created by the study statistician using Stata 14.1 (StataCorp LLC) with random block sizes and uploaded into the study tracking database by the programmer. After an individual met the requirements for randomization, a staff member requested the arm assignment using an automated system within the study tracking database. After the assignment was made, the staff updated the mobile app to comply with the assigned arm. The study staff did not have any in-person interactions with the participants during the course of the study and had specific telephone contact protocols to protect against potential bias.

All the study participants will be provided with a US $25 Amazon gift card at 6- and 12-months for completing the study follow-up surveys. The participants will be permitted to keep the Fitbit device and scale that were issued as a part of this study.

Data Collection

Online survey data for this study are collected at baseline, as a part of the enrollment process, and again at 6- and 12-months postrandomization. In the event participants fail to complete the online assessments and are unreachable via phone, we will attempt to contact the participants via US mail. After completing the 12-month data collection survey, as well as a final Fitbit device upload, all participants' study-issued Fitbit accounts are deleted and the participants are able to setup their own personal account at their discretion. The *Stay Strong* app for both groups will remain active for an extra 30 days to ensure that sufficient endpoint physical activity and weight data are synced.

Measures

Within this study, we will collect a variety of outcome measures, which are summarized in Table 2.

Table 2. Outline of measures and data collection points for the *Stay Strong* trial.

Measure	Source	Timepoints assessed	Method of measurement
Demographic measures	Online survey	Baseline	Self-report
Active minutes [48]	Fitbit	Continuous	Wearable sensor
Body weight	Bluetooth scale	Daily or as assessed by user	Synced data from scale or manually entered
Patient activation measure	Online survey	Baseline, 6 and 12 months	Self-report
Motivation to change health behaviors [53]	Online survey	Baseline, 6 and 12 months	Self-report
Social support general (ISEL-12[a]) [54]	Online survey	Baseline, 6 and 12 months	Self-report
Physical activity questions including exercise vital signs [55]	Online survey	Baseline, 6 and 12 months	Self-report
Self-regulation exercise and diet [56]	Online survey	Baseline, 6 and 12 months	Self-report
Self-efficacy and controllability [57]	Online survey	Baseline, 6 and 12 months	Self-report
Social support for diet and exercise [58]	Online survey	Baseline, 6 and 12 months	Self-report
Diet—starting the conversation [59]	Online survey	Baseline, 6 and 12 months	Self-report
Physical activity [60]	Online survey	Baseline, 6 and 12 months	Self-report
Self-perception of weight [61]	Online survey	Baseline, 6 and 12 months	Self-report
General health via SF-12[b] [62]	Online survey	Baseline, 6 and 12 months	Self-report
Depressive symptoms (PHQ-8[c]) [63]	Online survey	Baseline, 6 and 12 months	Self-report
Pain, pain intensity, and pain interference with daily activities [64-67]	Online survey	Baseline, 6 and 12 months	Self-report
Sleep (MOS-6[d]) [68]	Online survey	Baseline, 6 and 12 months	Self-report
Smoking and alcohol use [69,70]	Online survey	Baseline, 6 and 12 months	Self-report
Technology use, comfort, and acceptance [71,72]	Online survey	Baseline, 6 and 12 months	Self-report
Physical Activity devices	Online survey	Baseline, 6 and 12 months	Self-report
Barriers to physical activity [73,74]	App-based survey for Intervention only	Baseline, 6 and 12 months	Self-report

[a]ISEL-12: 12-item Interpersonal Support Evaluation List.

[b]SF-12: 12-Item Short-Form Health Survey.

[c]PHQ-8: 8-item Patient Health Questionnaire.

[d]MOS-6: 6-item Sleep Scale from the Medical Outcomes Study.

Physical Activity

Our primary outcome of interest is physical activity from baseline to 1-year postrandomization, as measured by average daily *active minutes* on the Fitbit device. Specifically, we will compare with groups the *daily active minutes* at 12 months (primary endpoint) and change in daily *active minutes* from baseline to 12 months (slope) based on data measured weekly, averaged over a 1-week period based on availability of at least 5 days of valid data (ie, requiring at least 5 min of light activity within each day). As a secondary measure of physical activity, we will also compare average step counts from baseline to 12 months.

Weight Loss

Weights are objectively assessed using the study-issued Bluetooth-enabled scale (A&D scale) and can be automatically synced with *Stay Strong*. Users also have the option of manually entering their weight within the app. Weekly average weights will be calculated similarly to weekly *active minutes*.

Depression

The presence and severity of depression will be measured by the 8-item Patient Health Questionnaire (PHQ-8) [63]. The PHQ-8 is the same as the widely used 9-item PHQ (PHQ-9), with the removal of 1 item focused on suicidality. The PHQ-9 is a widely used tool for screening, diagnosing, monitoring, and measuring the severity of depression, and it has been shown to be a reliable and valid measure [75].

Patient Activation

Change in patient activation will be assessed using the Patient Activation Measure (PAM) developed by Hibbard et al [76]. The PAM is a 13-item measure that assesses knowledge, skills, beliefs, and confidence for managing an individual's own health. PAM scores have demonstrated high construct validity, and

they are highly correlated with individual's engagement in healthier lifestyle behaviors [77].

Pain

Pain is often a barrier to physical activity, but higher levels of physical activity can help reduce chronic pain [78]. We will utilize the VHA Standard Pain Frequency and Intensity scale to assess pain.

Statistical Analysis Plan

The primary analytic cohort will be intent-to-treat, with the proposed primary and secondary analyses focusing on the effect of *Stay Strong + Coaching* compared with *Stay Strong* alone. The 1 exception is with women who self-report pregnancy at any of the 3 assessment times (baseline, 6-month, and 12-month); they will not be included in the analyses for the primary outcome of physical activity or for weight loss.

Descriptive statistics, including graphical displays, will be used to summarize all study variables overall and by arm. Evidence of between-arm imbalance in baseline characteristics that are potentially related to change in physical activity level (eg, baseline weight and full-time work status) will be noted and sensitivity analyses adjusting for these baseline characteristics will be considered to ensure that an observed intervention effect is not because of this baseline imbalance. Summary statistics will also be reported for primary and all secondary outcomes by arm, including unadjusted changes in daily *active minutes* from baseline to 12 months as means and 95% CIs.

Between-group comparison of *active minutes* will be examined using all longitudinally assessed weekly averages of *active minutes*, including the baseline *active minutes*, based on the longitudinal data mixed-effects model (75) with time (weeks since randomization), treatment group, and interaction of time by treatment group as primary predictors, participants and slopes as random effects, and autoregressive correlation within the person. The model will be adjusted for stratification factors of sex, operating system, and baseline activity level (high vs low). Time may be parameterized appropriately if a nonlinear slope over time is suggested in graphical examination of the outcome measures over time. On the basis of the model, predicted *active minutes* at 12 months will be compared with 2 treatment groups, and a test of significant slope of the interaction term will also be used to test if the change from baseline in *active minutes* differ between treatment groups. Weights will be analyzed similarly. Although assessments will be done only 3 times, the secondary outcomes of depression and pain will be analyzed similarly as for the analyses for *active minutes*. To test for moderation of the coaching effect by gender, the model specified above will be expanded to include the gender by *Stay Strong + Coaching* interaction. We also plan to conduct analyses to examine patterns of intervention utilization and dose-response relationships. All the statistical analysis will be completed by the study team, independent of the funder and vendors involved in the study.

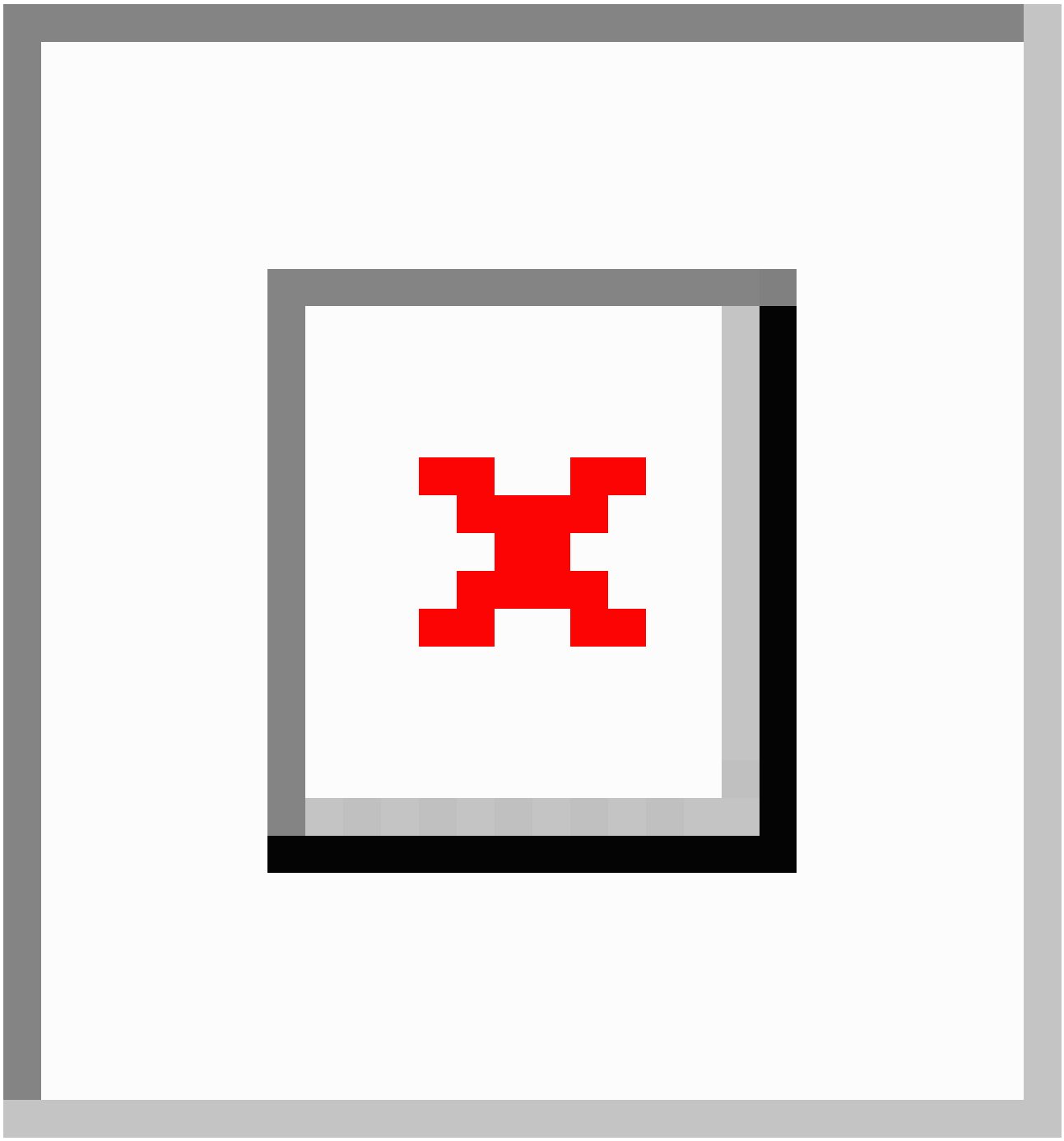
Adverse Event Monitoring

The participants are instructed to report any changes in their medical condition to their primary health care provider first, followed by a report to the study hotline. Moreover, all participants receive automated in-app reminders every 90 days to notify the study staff of health changes. Any reported adverse event will be followed up by the study staff for additional information and will be classified as serious or not serious, related or unrelated, and anticipated or unanticipated, as well as severity, by the study staff and study physicians. Any adverse event that is categorized as serious is subject to IRB required reporting, and medical suspension and reclearance processes will be initiated as required.

Results

The participant recruitment began in September 2017 and concluded in May 2018. Figure 3 shows the flow of patients from initial contact to randomization. In total, 2286 invitation letters were sent, and 540 potential participants completed the eligibility screening, 23.62% (540/2286) response rate. Of those who completed the eligibility screening, 7.4% (40/540) were screened as ineligible based on their survey responses. Of the remaining 500 eligible potential participants, 81.8% (409/500) of the individuals consented to participate in the study, provided HIPAA authorization, and registered the *Stay Strong* app by installing it on their smartphone. Of those, 87.3% (357/409) provided valid baseline physical activity levels and were randomized to *Stay Strong* (n=179) or *Stay Strong + Coaching* trial arms (n=178). Currently, all the participants have completed at least 9 weeks of the trial, and all coaching calls are complete. Data collection is expected to conclude in 2019.

Figure 3. Participant flow through recruitment, enrollment, and randomization. HIPAA: Health Insurance Portability and Accountability Act. Note: a: Unable to sync Fitbit (N=12), did not pair with study account (N=12), unable to setup device due to secure environment (N=1), unable to contact (N=9), unable to setup Fitbit with *Stay Strong* app (N=10), unable to comply or follow study procedures (N=5); b: Changed mind about participating (N=3).



Discussion

Trial Implications

This study marks a significant contribution to the mHealth literature. Despite the increasing ubiquity of wearable physical activity tracking devices among consumers, recent reviews identified the need for randomized trials with a sufficiently large sample size and longer duration (longer than 12 weeks) interventions [6,28]. Moreover, the lack of fully described theoretical frameworks that underlie mHealth-mediated behavior change interventions has been noted [79,80]. *Stay Strong* is a fully powered trial with an active comparator, which follows participants for 12 months [28]. It features a theoretically driven behavior change intervention. Furthermore, most trials using wearables include samples with a minority of men, whereas participants in this trial are predominately male (267/357, 74.8%), which is an especially important contribution to the literature. Also, we seek to assess if coaching provides additional benefits via deeper engagement with wearable activity monitors compared with activity monitoring alone, a unique contribution to the literature.

This study is also significant in its reliance on a national sample of OEF/OIF/OND veterans who were consented and enrolled online with no in-person assessments or interactions. On the whole, OEF/OIF/OND veterans are younger than other veteran cohorts. Publicly available data show that post-9/11 veterans have a median age of 35 years; thus, many are *digital natives* born after 1980, having grown up with computers and other forms of information technology [81]. Recent estimates indicate that 98% of American adults aged 30-49 years have a cell phone, and 89% have a smartphone, suggesting that our smartphone-based intervention is well suited to our targeted population, important for increased adoption and uptake [82].

The response to mailed letters was much higher than anticipated based on our team's past experiences with recruiting for internet-mediated interventions. This has been especially striking, given that it can be challenging to engage veterans in lifestyle interventions as demonstrated by our work and the work of others. The average age of participation in VHA's weight loss program (also known as MOVE!) is 57 years [83], compared with 37 years for *Stay Strong* participants. Thus, mHealth interventions have significant potential for engaging this cohort of veterans to improve lifestyle behaviors like physical activity. The *Stay Strong* trial is the first national trial of an mHealth intervention in the VHA aimed at increasing physical activity.

Limitations

This study has limitations. Our primary outcome measure of physical activity is focused on *active minutes*, as measured by the Fitbit device. As previously mentioned, *active minutes* is a proprietary measure that is not precisely defined, and any potential changes to how *active minutes* are calculated by Fitbit are out of our control. Although this is a limitation to our approach, there is also strength in the fact that our use of this measure allows us to ensure that this nationally-conducted randomized trial can be conducted entirely without bringing participants into a clinic or research setting for data collection. This pragmatic nature opens the door to a more nationally representative sample and reduces the ultimate burden placed on research participants. In this vein, another limitation to our approach is our reliance on self-reported data for some of our collected measures. We have taken steps to gather objectively measured data whenever possible (via study issued devices). Another limitation of our approach centers on the fact that not all coaching features persist after the first 2-3 months of the intervention. Although our automated features continue through the duration of the program, contact with human coaches is focused on in the first several weeks. Future work should seek to determine whether prolonged human-coach contact has an effect on participant engagement and participant outcomes. We also have a methodological limitation because we seek to determine the effectiveness of adding coaching features to the *Stay Strong* intervention and we are predominately focused on quantitative measures. Although we understand the richness that a qualitative or mixed-methods approach would add to this study, budgetary constraints preclude additional measures or qualitative data collection. Additionally, our approach is limited by the fact that participants are instructed to sync their data using a dongle attached to a laptop or desktop computer rather than syncing directly using the Fitbit app on their smartphone. This was necessary in our setting to help ensure privacy of personal data and comply with VA regulations. This decision will likely affect our user engagement and compliance with syncing protocols because of the increased burden in using this approach. The reliance on laptop or desktop syncing reduces generalizability and potentially disproportionally excludes lower-income individuals, who are more likely to rely on cell phones for internet connectivity and are less likely to own desktops or laptops. Lastly, though we intended to block-randomize participants by gender, physical activity level, and smartphone operating system into the 2 groups in a 1:1 ratio, the first 283 participants were randomized without blocks because of a programming error. However, the last 74 participants were block randomized. This led to unequal distributions in a few of the *cells*. However, analyses showed there were no differences in baseline characteristics.

Conclusions

This randomized control trial will provide much-needed findings about whether the addition of telephone-based plus automated coaching and personalized goal setting will improve levels of physical activity compared with using a wearable device and smartphone app alone. This year-long trial will also provide insights on feasibility and acceptability of interventions like *Stay Strong* among OEF/OIF/OND veterans.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Stay Strong + Coaching screenshots.

[PDF File (Adobe PDF File), 386KB - resprot_v8i1e12526_app1.pdf]

Multimedia Appendix 2

Behavior change techniques (BCTs) by *Stay Strong* intervention component.

[PDF File (Adobe PDF File), 57KB - resprot_v8i1e12526_app2.pdf]

References

1. Buis LR, Kotagal LV, Porcari CE, Rauch SA, Krein SL, Richardson CR. Physical activity in postdeployment Operation Iraqi Freedom/Operation Enduring Freedom veterans using Department of Veterans Affairs services. J Rehabil Res Dev 2011;48(8):901-911 [FREE Full text] [Medline: 22068369]
2. Haskell SG, Mattocks K, Goulet JL, Krebs EE, Skanderson M, Leslie D, et al. The burden of illness in the first year home: do male and female VA users differ in health conditions and healthcare utilization. Womens Health Issues 2011;21(1):92-97 [FREE Full text] [doi: 10.1016/j.whi.2010.08.001] [Medline: 21185994]
3. Possemato K, Wade M, Andersen J, Ouimette P. The impact of PTSD, depression, and substance use disorders on disease burden and health care utilization among OEF/OIF veterans. Psychol Trauma 2010;2(3):218-223. [doi: 10.1037/a0019236]
4. Littman AJ, Jacobson IG, Boyko EJ, Powell TM, Smith TC, Millennium Cohort Study Team. Weight change following US military service. Int J Obes (Lond) 2013 Feb;37(2):244-253 [FREE Full text] [doi: 10.1038/ijo.2012.46] [Medline: 22491091]
5. Rosenberger PH, Ning Y, Brandt C, Allore H, Haskell S. BMI trajectory groups in veterans of the Iraq and Afghanistan wars. Prev Med 2011 Sep;53(3):149-154 [FREE Full text] [doi: 10.1016/j.ypmed.2011.07.001] [Medline: 21771610]
6. Burke LE, Ma J, Azar KM, Bennett GG, Peterson ED, Zheng Y, American Heart Association Publications Committee of the Council on Epidemiology Prevention, Behavior Change Committee of the Council on Cardiometabolic Health, Council on Cardiovascular Stroke Nursing, Council on Functional Genomics Translational Biology, Council on Quality of Care Outcomes Research, Stroke Council. Current science on consumer use of mobile health for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation 2015 Sep 22;132(12):1157-1213. [doi: 10.1161/CIR.0000000000000232] [Medline: 26271892]
7. Bhardwaj NN, Wodajo B, Gochipathala K, Paul ID, Coustasse A. Can mHealth revolutionize the way we manage adult obesity? Perspect Health Inf Manag 2017 Apr 1;14(Spring):1a [FREE Full text] [Medline: 28566984]
8. Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, et al. Using pedometers to increase physical activity and improve health: a systematic review. JAMA 2007 Nov 21;298(19):2296-2304. [doi: 10.1001/jama.298.19.2296] [Medline: 18029834]
9. Davies CA, Spence JC, Vandelanotte C, Caperchione CM, Mummery WK. Meta-analysis of internet-delivered interventions to increase physical activity levels. Int J Behav Nutr Phys Act 2012 Apr 30;9:52 [FREE Full text] [doi: 10.1186/1479-5868-9-52] [Medline: 22546283]
10. Richardson CR, Newton TL, Abraham JJ, Sen A, Jimbo M, Swartz AM. A meta-analysis of pedometer-based walking interventions and weight loss. Ann Fam Med 2008;6(1):69-77 [FREE Full text] [doi: 10.1370/afm.761] [Medline: 18195317]
11. Lewis BA, Napolitano MA, Buman MP, Williams DM, Nigg CR. Future directions in physical activity intervention research: expanding our focus to sedentary behaviors, technology, and dissemination. J Behav Med 2017 Feb;40(1):112-126 [FREE Full text] [doi: 10.1007/s10865-016-9797-8] [Medline: 27722907]
12. Triantafyllidis A, Filos D, Claes J, Buys R, Cornelissen V, Kouidi E, et al. Computerised decision support in physical activity interventions: a systematic literature review. Int J Med Inform 2018 Mar;111:7-16. [doi: 10.1016/j.ijmedinf.2017.12.012] [Medline: 29425636]
13. Buchholz SW, Wilbur J, Ingram D, Fogg L. Physical activity text messaging interventions in adults: a systematic review. Worldviews Evid Based Nurs 2013 Aug;10(3):163-173. [doi: 10.1111/wvn.12002] [Medline: 23746267]
14. Burke LE, Conroy MB, Sereika SM, Elci OU, Styn MA, Acharya SD, et al. The effect of electronic self-monitoring on weight loss and dietary intake: a randomized behavioral weight loss trial. Obesity (Silver Spring) 2011 Feb;19(2):338-344 [FREE Full text] [doi: 10.1038/oby.2010.208] [Medline: 20847736]
15. Changizi M, Kaveh MH. Effectiveness of the mHealth technology in improvement of healthy behaviors in an elderly population-a systematic review. Mhealth 2017 Nov 27;3:51 [FREE Full text] [doi: 10.21037/mhealth.2017.08.06] [Medline: 29430455]
16. Flores Mateo G, Granado-Font E, Ferré-Grau C, Montaña-Carreras X. Mobile phone apps to promote weight loss and increase physical activity: a systematic review and meta-analysis. J Med Internet Res 2015 Nov 10;17(11):e253 [FREE Full text] [doi: 10.2196/jmir.4836] [Medline: 26554314]
17. Lee JA, Choi M, Lee SA, Jiang N. Effective behavioral intervention strategies using mobile health applications for chronic disease management: a systematic review. BMC Med Inform Decis Mak 2018 Feb 20;18(1):12 [FREE Full text] [doi: 10.1186/s12911-018-0591-0] [Medline: 29458358]

18. Pfaeffli Dale L, Dobson R, Whittaker R, Maddison R. The effectiveness of mobile-health behaviour change interventions for cardiovascular disease self-management: a systematic review. Eur J Prev Cardiol 2016 May;23(8):801-817. [doi: 10.1177/2047487315613462] [Medline: 26490093]
19. Stephens J, Allen J. Mobile phone interventions to increase physical activity and reduce weight: a systematic review. J Cardiovasc Nurs 2013;28(4):320-329 [FREE Full text] [doi: 10.1097/JCN.0b013e318250a3e7] [Medline: 22635061]
20. Wang J, Wang Y, Wei C, Yao NA, Yuan A, Shan Y, et al. Smartphone interventions for long-term health management of chronic diseases: an integrative review. Telemed J E Health 2014 Jun;20(6):570-583. [doi: 10.1089/tmj.2013.0243] [Medline: 24787747]
21. Whitehead L, Seaton P. The effectiveness of self-management mobile phone and tablet apps in long-term condition management: a systematic review. J Med Internet Res 2016 May 16;18(5):e97 [FREE Full text] [doi: 10.2196/jmir.4883] [Medline: 27185295]
22. Zhao J, Freeman B, Li M. Can mobile phone apps influence people?s health behavior change? An evidence review. J Med Internet Res 2016 Dec 31;18(11):e287 [FREE Full text] [doi: 10.2196/jmir.5692] [Medline: 27806926]
23. Birkhoff SD, Smeltzer SC. Perceptions of smartphone user-centered mobile health tracking apps across various chronic illness populations: an integrative review. J Nurs Scholarsh 2017 Jul;49(4):371-378. [doi: 10.1111/jnu.12298] [Medline: 28605151]
24. Buis LR, Hirzel L, Turske SA, Des Jardins TR, Yarandi H, Bondurant P. Use of a text message program to raise type 2 diabetes risk awareness and promote health behavior change (part II): assessment of participants' perceptions on efficacy. J Med Internet Res 2013 Dec 19;15(12):e282 [FREE Full text] [doi: 10.2196/jmir.2929] [Medline: 24356359]
25. Kivelä K, Elo S, Kyngäs H, Kääriäinen M. The effects of health coaching on adult patients with chronic diseases: a systematic review. Patient Educ Couns 2014 Nov;97(2):147-157. [doi: 10.1016/j.pec.2014.07.026] [Medline: 25127667]
26. Oliveira JS, Sherrington C, Amorim AB, Dario AB, Tiedemann A. What is the effect of health coaching on physical activity participation in people aged 60 years and over? A systematic review of randomised controlled trials. Br J Sports Med 2017 Oct;51(19):1425-1432. [doi: 10.1136/bjsports-2016-096943] [Medline: 28320732]
27. Olsen JM, Nesbitt BJ. Health coaching to improve healthy lifestyle behaviors: an integrative review. Am J Health Promot 2010;25(1):e1-e12. [doi: 10.4278/ajhp.090313-LIT-101] [Medline: 20809820]
28. Goode AP, Hall KS, Batch BC, Huffman KM, Hastings SD, Allen KD, et al. The impact of interventions that integrate accelerometers on physical activity and weight loss: a systematic review. Ann Behav Med 2017 Feb;51(1):79-93 [FREE Full text] [doi: 10.1007/s12160-016-9829-1] [Medline: 27565168]
29. Goodrich DE, Larkin AR, Lowery JC, Holleman RG, Richardson CR. Adverse events among high-risk participants in a home-based walking study: a descriptive study. Int J Behav Nutr Phys Act 2007 May 23;4:20 [FREE Full text] [doi: 10.1186/1479-5868-4-20] [Medline: 17521443]
30. Richardson CR, Brown BB, Foley S, Dial KS, Lowery JC. Feasibility of adding enhanced pedometer feedback to nutritional counseling for weight loss. J Med Internet Res 2005 Nov 17;7(5):e56 [FREE Full text] [doi: 10.2196/jmir.7.5.e56] [Medline: 16403720]
31. Vibrent Health. 2018. Vibrent URL: https://www.vibrenthealth.com/ [accessed 2019-01-10] [WebCite Cache ID 75KXfRRaj]
32. Holtz B, Krein SK, Bentley DR, Hughes ME, Giardino ND, Richardson CR. Comparison of veteran experiences of low-cost, home-based diet and exercise interventions. J Rehabil Res Dev 2014;51(1):149-160. [doi: 10.1682/JRRD.2013.04.0088] [Medline: 24805901]
33. Amico KR, Harman JJ, O'Grady MA. Attrition and related trends in scientific rigor: a score card for ART adherence intervention research and recommendations for future directions. Curr HIV/AIDS Rep 2008 Nov;5(4):172-185. [Medline: 18838057]
34. Fisher JD, Amico KR, Fisher WA, Harman JJ. The information-motivation-behavioral skills model of antiretroviral adherence and its applications. Curr HIV/AIDS Rep 2008 Nov;5(4):193-203. [Medline: 18838059]
35. Fisher JD, Fisher WA. Changing AIDS-risk behavior. Psychol Bull 1992 May;111(3):455-474. [Medline: 1594721]
36. Steinhardt MA, Dishman RK. Reliability and validity of expected outcomes and barriers for habitual physical activity. J Occup Med 1989 Jun;31(6):536-546. [Medline: 2786559]
37. Ashford S, Edmunds J, French DP. What is the best way to change self-efficacy to promote lifestyle and recreational physical activity? A systematic review with meta-analysis. Br J Health Psychol 2010 May;15(Pt 2):265-288. [doi: 10.1348/135910709X461752] [Medline: 19586583]
38. DuVall C, Dinger MK, Taylor EL, Bemben D. Minimal-contact physical activity interventions in women: a pilot study. Am J Health Behav 2004;28(3):280-286. [Medline: 15152887]
39. Kelly S, Melnyk BM, Belyea M. Predicting physical activity and fruit and vegetable intake in adolescents: a test of the information, motivation, behavioral skills model. Res Nurs Health 2012 Apr;35(2):146-163. [doi: 10.1002/nur.21462] [Medline: 22262049]
40. Pearson ES. Goal setting as a health behavior change strategy in overweight and obese adults: a systematic literature review examining intervention components. Patient Educ Couns 2012 Apr;87(1):32-42. [doi: 10.1016/j.pec.2011.07.018] [Medline: 21852063]

41. Rhodes RE, Dickau L. Moderators of the intention-behaviour relationship in the physical activity domain: a systematic review. Br J Sports Med 2013 Mar;47(4):215-225. [doi: 10.1136/bjsports-2011-090411] [Medline: 22278998]
42. Williams SL, French DP. What are the most effective intervention techniques for changing physical activity self-efficacy and physical activity behaviour--and are they the same? Health Educ Res 2011 Apr;26(2):308-322 [FREE Full text] [doi: 10.1093/her/cyr005] [Medline: 21321008]
43. Vohs KD, Baumeister RF, editors. Self-regulation of action and affect. In: Handbook Of Self-Regulation: Research, Theory, and Applications. New York, NY: Guilford Press; 2004:3-24.
44. 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]
45. Henriksen A, Haugen Mikalsen M, Woldaregay AZ, Muzny M, Hartvigsen G, Hopstock LA, et al. Using fitness trackers and smartwatches to measure physical activity in research: analysis of consumer wrist-worn wearables. J Med Internet Res 2018 Mar 22;20(3):e110 [FREE Full text] [doi: 10.2196/jmir.9157] [Medline: 29567635]
46. Dooley EE, Golaszewski NM, Bartholomew JB. Estimating accuracy at exercise intensities: a comparative study of self-monitoring heart rate and physical activity wearable devices. JMIR Mhealth Uhealth 2017 Mar 16;5(3):e34 [FREE Full text] [doi: 10.2196/mhealth.7043] [Medline: 28302596]
47. Stahl SE, An HS, Dinkel DM, Noble JM, Lee JM. How accurate are the wrist-based heart rate monitors during walking and running activities? Are they accurate enough? BMJ Open Sport Exerc Med 2016 Apr 25;2(1):e000106 [FREE Full text] [doi: 10.1136/bmjsem-2015-000106] [Medline: 27900173]
48. Fitbit, Inc. 2018. What are active minutes? URL: https://help.fitbit.com/articles/en_US/Help_article/1379 [accessed 2019-01-11] [WebCite Cache ID 75LwPdMwP]
49. Sallis J, Hovell M. Determinants of exercise behavior. Exerc Sport Sci Rev 1990;18:307-330. [Medline: 2192898]
50. Sallis JF, Hovell MF, Hofstetter CR. Predictors of adoption and maintenance of vigorous physical activity in men and women. Prev Med 1992 Mar;21(2):237-251. [Medline: 1579558]
51. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. J Clin Epidemiol 2007 Dec;60(12):1234-1238. [doi: 10.1016/j.jclinepi.2007.02.006] [Medline: 17998077]
52. Shuger SL, Barry VW, Sui X, McClain A, Hand GA, Wilcox S, et al. Electronic feedback in a diet- and physical activity-based lifestyle intervention for weight loss: a randomized controlled trial. Int J Behav Nutr Phys Act 2011 May 18;8:41 [FREE Full text] [doi: 10.1186/1479-5868-8-41] [Medline: 21592351]
53. Williams GC, Grow VM, Freedman ZR, Ryan RM, Deci EL. Motivational predictors of weight loss and weight-loss maintenance. J Pers Soc Psychol 1996 Jan;70(1):115-126. [Medline: 8558405]
54. Cohen S, Mermelstein R, Kamarck T, Hoberman HM. Measuring the functional components of social support. In: Sarason IG, Sarason BR, editors. Social Support: Theory, Research and Applications. Dordrecht: Springer; 1985:73-94.
55. Coleman KJ, Ngor E, Reynolds K, Quinn VP, Koebnick C, Young DR, et al. Initial validation of an exercise "vital sign" in electronic medical records. Med Sci Sports Exerc 2012 Nov;44(11):2071-2076. [doi: 10.1249/MSS.0b013e3182630ec1] [Medline: 22688832]
56. Villejo RE, Humphrey LL, Kirschenbaum DS. Affect and self-regulation in binge eaters: effects of activating family images. Int J Eat Disord 1997 Apr;21(3):237-249. [Medline: 9097197]
57. Ajzen I. Perceived behavioral control, self-efficacy, locus of control, and the theory of planned behavior 1. J Appl Soc Psychol 2002;32(4):665-683. [doi: 10.1111/j.1559-1816.2002.tb00236.x]
58. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. Prev Med 1987 Nov;16(6):825-836. [Medline: 3432232]
59. Paxton AE, Strycker LA, Toobert DJ, Ammerman AS, Glasgow RE. Starting the conversation performance of a brief dietary assessment and intervention tool for health professionals. Am J Prev Med 2011 Jan;40(1):67-71. [doi: 10.1016/j.amepre.2010.10.009] [Medline: 21146770]
60. Macera CA, Ham SA, Yore MM, Jones DA, Ainsworth BE, Kimsey CD, et al. Prevalence of physical activity in the United States: behavioral risk factor surveillance system, 2001. Prev Chronic Dis 2005 Apr;2(2):A17 [FREE Full text] [Medline: 15888228]
61. Kinsinger LS, Jones KR, Kahwati L, Harvey R, Burdick M, Zele V, et al. Design and dissemination of the MOVE! Weight-management program for veterans. Prev Chronic Dis 2009 Jul;6(3):A98 [FREE Full text] [Medline: 19527600]
62. Ware Jr J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [Medline: 8628042]
63. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
64. Centers for Disease Control and Prevention.: CDC; 2013. BRFSS Questionnaires URL: https://www.cdc.gov/brfss/questionnaires/index.htm [accessed 2019-01-11] [WebCite Cache ID 75LyPIfDP]
65. Goulet JL, Brandt C, Crystal S, Fiellin DA, Gibert C, Gordon AJ, et al. Agreement between electronic medical record-based and self-administered pain numeric rating scale: clinical and research implications. Med Care 2013 Mar;51(3):245-250 [FREE Full text] [doi: 10.1097/MLR.0b013e318277f1ad] [Medline: 23222528]

66. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20(5):309-318. [Medline: 15322437]
67. Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Med Care 2007 Mar;45(3):259-263. [doi: 10.1097/01.mlr.0000254515.63841.81] [Medline: 17304084]
68. Stewart AL. In: Ware Jr JE, editor. Measuring functioning and well-being: the medical outcomes study approach. Measuring functioning and well-being: the medical outcomes study approach: Duke University Press; May 27, 1992:456.
69. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998 Sep 14;158(16):1789-1795. [Medline: 9738608]
70. Nelson DH, Holtzman D, Bolen J, Stanwyck CA, Mack KA. Reliability and validity of measures from the Behavioral Risk Factor Surveillance System (BRFSS). Soz Praventivmed 2001;46(Suppl 1):S3-42. [Medline: 11851091]
71. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Q 1989 Sep;13(3):319-340. [doi: 10.2307/249008]
72. Zulman DM, Piette JD, Jenchura EC, Asch SM, Rosland AM. Facilitating out-of-home caregiving through health information technology: survey of informal caregivers' current practices, interests, and perceived barriers. J Med Internet Res 2013 Jul 10;15(7):e123 [FREE Full text] [doi: 10.2196/jmir.2472] [Medline: 23841987]
73. Centers for Disease Control and Prevention. 2018. Barriers to being active quiz what keeps you from being more active? URL: https://www.cdc.gov/diabetes/ndep/pdfs/8-road-to-health-barriers-quiz-508.pdf [accessed 2019-01-11] [WebCite Cache ID 75LzjOnBb]
74. Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition and Physical Activity. Promoting Physical Activity: A Guide for Community Action. Vermont: Human Kinetics; 2018:408.
75. 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] [Medline: 11556941]
76. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res 2005 Dec;40(6 Pt 1):1918-1930 [FREE Full text] [doi: 10.1111/j.1475-6773.2005.00438.x] [Medline: 16336556]
77. Hibbard JH, Mahoney ER, Stock R, Tusler M. Do increases in patient activation result in improved self-management behaviors? Health Serv Res 2007 Aug;42(4):1443-1463 [FREE Full text] [doi: 10.1111/j.1475-6773.2006.00669.x] [Medline: 17610432]
78. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017 Dec 24;4:CD011279 [FREE Full text] [doi: 10.1002/14651858.CD011279.pub3] [Medline: 28436583]
79. 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]
80. Cowan LT, Van Wagenen SA, Brown BA, Hedin RJ, Seino-Stephan Y, Hall PC, et al. Apps of steel: are exercise apps providing consumers with realistic expectations?: a content analysis of exercise apps for presence of behavior change theory. Health Educ Behav 2013 Apr;40(2):133-139. [doi: 10.1177/1090198112452126] [Medline: 22991048]
81. 2016 American Community Survey Public Use Microdata Sample. 2016. Key Statistics by Veteran Status and Period of Service URL: https://www.va.gov/vetdata/docs/SpecialReports/KeyStats.pdf [accessed 2019-01-11] [WebCite Cache ID 75M0G1IUJ]
82. Pew Research Center. 2018 Feb 5. Mobile Fact Sheet URL: http://www.pewinternet.org/fact-sheet/mobile/ [accessed 2019-01-08] [WebCite Cache ID 75M0Nz4UA]
83. Littman AJ, Damschroder LJ, Verchinina L, Lai Z, Kim HM, Hoerster KD, et al. National evaluation of obesity screening and treatment among veterans with and without mental health disorders. Gen Hosp Psychiatry 2015;37(1):7-13. [doi: 10.1016/j.genhosppsych.2014.11.005] [Medline: 25500194]

Abbreviations

BCT: behavior change technique
HIPAA: Health Insurance Portability and Accountability Act
IMB: information-motivation-behavioral skills
IRB: institutional review board
mHealth: mobile health
OEF: Operation Enduring Freedom
OIF: Operation Iraqi Freedom
OND: Operation New Dawn
PAM: Patient Activation Measure

PHQ-8: 8-item Patient Health Questionnaire
PHQ-9: 9-item Patient Health Questionnaire
USB: Universal Serial Bus
VHA: Veterans Health Administration

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Original Paper

Recruitment and Baseline Characteristics of Participants in the Social, Emotional, and Economic Empowerment Through Knowledge of Group Support Psychotherapy Study (SEEK-GSP): Cluster Randomized Controlled Trial

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Abstract

Background: Psychosocial characteristics, including self-esteem, perceived social support, coping skills, stigma, discrimination, and poverty, are strongly correlated with depression symptoms. However, data on the extent of these correlations among persons living with HIV and the associations between psychosocial characteristics and HIV treatment outcomes are limited in sub-Saharan Africa.

Objective: This paper aims to describe the recruitment process and baseline characteristics associated with depression in a sample of HIV-positive people in a cluster randomized trial of group support psychotherapy (GSP) for depression delivered by trained lay health workers (LHWs).

Methods: Thirty eligible primary care health centers across three districts in Uganda were randomly allocated to have their LHWs trained to deliver GSP (intervention arm) or group HIV education and treatment as usual (control arm) to persons living with HIV comorbid with depression. Baseline demographic, socioeconomic, and psychosocial characteristics were collected via interviewer-administered questionnaires. Among eligible participants, differences between those enrolled versus those who refused

enrollment were assessed using chi square for categorical variables and t tests for continuous variables. Spearman rank order correlation analyses were conducted to determine associations between baseline depression symptoms and adherence to antiretroviral therapy (ART), viral load suppression, and other psychosocial variables.

Results: The study screened 1473 people and 1140 were found to be eligible and enrolled over 14 weeks. Participants recruited comprised 95% of the target sample size of 1200. The sample's mean age was 38.5 (SD 10.9) years and both genders were well represented (males: 46.32%, 528/1140). Most participants met the diagnostic criteria for major depressive disorder (96.92%, 1105/1140), had significant posttraumatic stress symptoms (72.46%, 826/1140), reported moderate suicide risk (52.54%, 599/1140), had primary or no formal education (86.22%, 983/1140), and reported no income-generating activity (72.63%, 828/1140) and no food insecurity (81.67%, 931/1140). Among eligible participants, 48 of 1140 (4.21%) refused to participate in the interventions; these participants were more likely to be males (χ^2_1=4.0, *P*=.045) and have significantly lower depression symptoms scores (t_2=2.36, *P*=.01) than those who participated in the interventions. There was a significant positive correlation between viral load and number of traumatic experiences (ρ=.12, *P*=.05). Adherence to ART was positively correlated with perceived social support (ρ=.15, *P*<.001), but negatively correlated with depression symptoms (ρ=–.11, *P*=.05) and stigma (ρ=–.14, *P*<.001).

Conclusions: Men and women with HIV and depression experience multiple social and economic vulnerabilities and disadvantages. Culturally tailored psychological interventions aimed at these individuals should address these socioeconomic disadvantages in addition to addressing their mental health care needs.

Trial Registration: Pan African Clinical Trials Registry PACTR201608001738234; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=1738 (Archived by WebCite at http://www.webcitation.org/74NtMphom)

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KEYWORDS

cluster randomized trial; group support psychotherapy; lay health workers; depression; recruitment; psychosocial stressors; persons living with HIV/AIDS; Uganda

Introduction

Individuals with major depression account for a substantial proportion of antiretroviral therapy (ART) users attending HIV treatment centers in sub-Saharan Africa. Yet they hardly receive any mental health services [1,2]. Several studies in HIV-positive populations both in developed and developing countries have shown that psychosocial stressors, such as a lack of social support and poor coping skills [3,4], low self-esteem [5], lack of financial resources [6], and internalized stigma and discrimination [7,8] are associated with depression. Furthermore, several studies conducted in HIV-positive populations have shown that alcohol use problems and posttraumatic stress are frequent and often complicate depression [9,10]. However, data on the extent of these correlations among persons living with HIV in sub-Saharan Africa are limited.

Past research studies in developed countries have shown that depression and related psychosocial stressors influence progression of HIV disease [11]. For example, there is some evidence that persons living with HIV (PLWH) who report experiencing stigma and discrimination have worse health outcomes [12]. Past research has also shown that lack of social support and poor coping skills [13], poor financial resources [14], and food insecurity [15] among ART users have been associated with poor HIV treatment outcomes. However, most past research on these associations come from high-income countries and from studies with small sample sizes. The correlations between psychosocial characteristics and HIV treatment outcomes in other parts of the world, and especially in sub-Saharan Africa where HIV is highly prevalent, are unknown.

Further, although studies of psychological interventions with depressed PLWH in high-income countries have endeavored to document related psychosocial stressors or HIV treatment outcomes [16], those conducted in low- and middle-income countries have rarely done so [17]. As a result, there is little information on the psychosocial stressors associated with HIV treatment from low- and middle-income countries. This makes it difficult to understand and appreciate the social context of PLWH in these settings. Past research from the United States has highlighted the role of various environmental stressors related to poverty, persistent residential mobility, racial discrimination, and inadequate access to resources on HIV care and outcomes. These findings indicate the importance of attending to social context in addition to clinical factors in planning interventions for PLWH [18].

To attend to the contextual realities of PLWH in sub-Saharan Africa, we developed group support psychotherapy (GSP)—a culturally sensitive cognitive behavioral-based intervention that treats depression by enhancing emotional and social support, positive coping, and livelihood skills [19]. The Social, Emotional, and Economic empowerment through Knowledge of GSP (SEEK-GSP) trial follows a series of pilot studies [20,21] that demonstrated the effectiveness of GSP in treating mild to moderate depression. This trial will provide robust evidence for the change processes and outcomes we observed in these pilot studies.

The PLWH participating in the SEEK-GSP trial were recruited from a postconflict region where there is a heavy burden of depression, posttraumatic stress symptoms, and psychosocial stressors [22]. This sample provides an opportunity to understand the processes and challenges in recruiting this highly vulnerable population, who are rarely recruited into clinical

trials. The purpose of this paper is to summarize the recruitment procedures and baseline results of this trial, and explore associations among depression symptoms, related psychosocial stressors, adherence to ART, and viral suppression.

Methods

Overview of Study Design and Interventions

A detailed description of the study protocol is published elsewhere [23] and is registered in the Pan African Clinical Trials Registry (PACTR201608001738234). Briefly, this is a pragmatic two-arm cluster randomized trial evaluating the effectiveness GSP delivered by trained lay health workers (LHWs) to PLWH presenting with mild to moderate depression in primary care. The study involves 30 primary health centers in three districts in northern Uganda that were randomly assigned (with a 1:1 ratio) to have their LHWs trained in the delivery of GSP (intervention) or group HIV education (control condition) to PLWH with mild to moderate depression. The PLWH treated by the trained LHWs were evaluated at baseline, at the end of intervention, and at intervals of 6 months thereafter for 2 years.

The development of the GSP and group HIV education interventions has been described in detail in previous publications [19,21]. A detailed description of the content of both interventions has also been previously published [24]. The study was submitted to and approved by the Makerere University College of Health Sciences Research Ethics Committee, The AIDS Support Organization Research Ethics Committee, and the Uganda National Council of Science and Technology. All study participants were required to provide written informed consent. Light refreshments were served during all group sessions in both arms, and each participant and group facilitator received a financial incentive amounting to 8000UGX (US $2.16) and 80,000UGX (US $21.62), respectively, at the end of treatment to defray transportation costs. Figure 1 summarizes the trial profile.

Training of Health Workers

Group Support Psychotherapy Training

Over a 4-month period (January to April 2016), Makerere University, in collaboration with the Ministry of Health, designed a GSP training program that consisted of both formal and informal training. This training was delivered using a training-of-trainers model in May and August 2016. Mental health specialists trained primary health center workers who, in turn, trained the LHWs. Formal training consisted of eight training modules delivered in a 5-day training workshop that employed active learning techniques including role plays, brainstorming sessions, and small group discussions. In brief, the first three modules included an overview of the training program, introduction to the GSP model, and an introduction to depression and HIV/AIDS were delivered on the first day. On the second and third days, modules on basic counseling skills and effective coping strategies were delivered, respectively. On the fourth day, participants received training in basic livelihood skills (enterprise selection, basic financial skills, and resource mobilization) required to overcome poverty. The last day of training focused on self-care strategies, posttraining assessments, and training workshop evaluation. Informal training consisted of conducting supervised pilot GSP sessions. Newly trained health workers were supervised by a pool of previously trained health workers who participated in the pilot randomized controlled trial [21]. The competencies targeted by the training have been published elsewhere [24]. Multimedia Appendix 1 shows the health worker supervision checklist used by supervisors.

Group HIV Education Training

In May 2016, Makerere University, in collaboration with The AIDS Support Organization, designed a group HIV education training program that consisted of both formal and informal training. Between May and August 2016, the training-of-trainers model was used to deliver the training, whereby The AIDS Support Organization HIV care providers trained primary health center workers who in turn trained the LHWs. Formal training consisted of five training modules delivered in a lecture format in a 2-day training workshop. In brief, on the first day, three modules including an overview of the training program, introduction to depression and HIV/AIDS, HIV progression, and transmission were delivered. On the second day, modules on mother-to-child transmission and basic facts on ART were delivered. Informal training consisted of conducting supervised pilot group HIV education sessions.

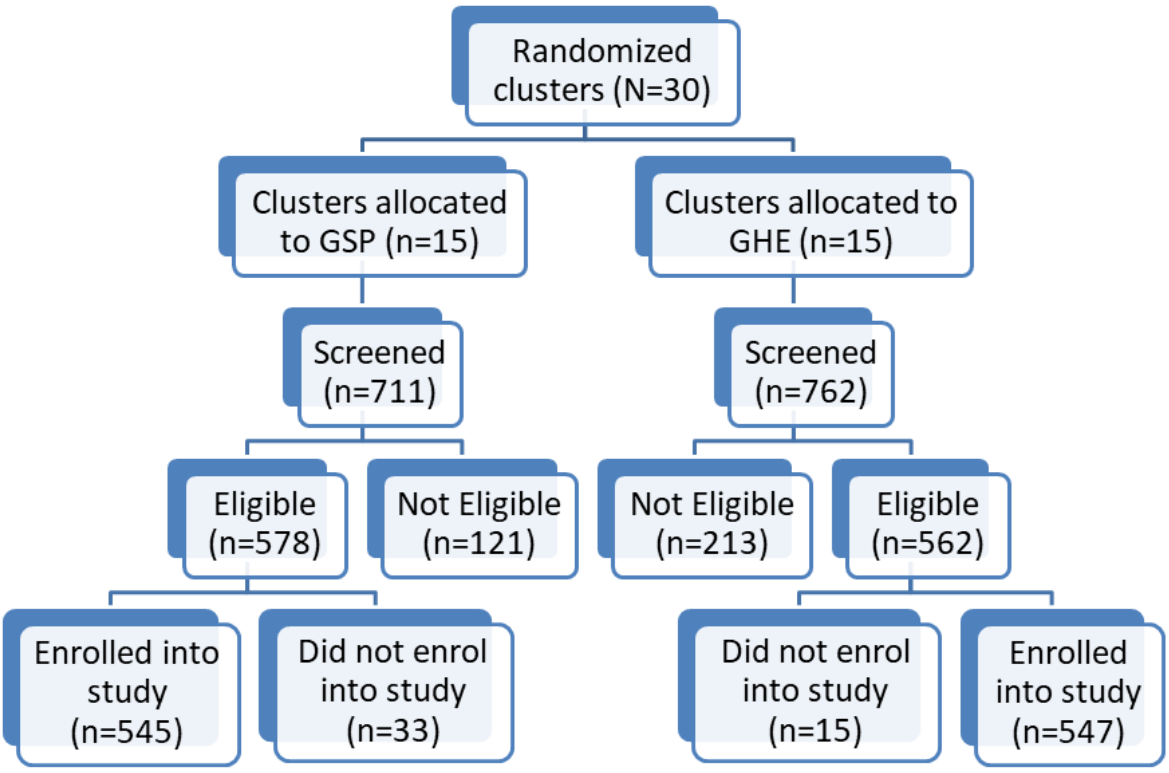
After both trainings, the trained LHWs initiated health education talks on depression in villages where they work and also among PLWH returning for medication refill. The PLWH who identified they had depression symptoms were invited for further evaluation. Those who met diagnostic criteria for mild to moderate depression were invited to attend group sessions of either GSP or group HIV education.

Study Screening and Recruitment

We used study teams that reflected the ethnicity of the target community at each of the participating primary health centers. The study teams worked with the trained LHWs, who are the first level of health care delivery in the country, to spread information about the study by word of mouth in villages within the study region. The LHWs are members of the village health team [25]. They know individuals in the community who are receiving HIV care and could approach them directly with information about the study.

The study team conducted presentations in the community to explain study purpose and procedures to facilitate community understanding of the trial activities. At each participating primary health center, trained LHWs gave health talks on depression to clients in the waiting area. Those who had experienced symptoms of depression described in the health talk were invited for further evaluations using the Luo version of the 20-item Self-Reporting Questionnaire (SRQ-20) and the Mini International Neuropsychiatric Interview (MINI) depression module [26].

Figure 1. Recruitment process. GHE: group HIV education; GSP: group support psychotherapy.



This procedure was repeated until a total of 40 PLWH meeting the MINI criteria of major depression were obtained from each primary health center. Research assistants approached each eligible client and explained study procedures, determined that other eligibility criteria were met and then obtained informed consent. To be recruited in the study, participants had to be HIV positive, aged 19 years or older, meet MINI criteria for major depressive disorder, antidepressant naïve, using ART, and residing in the villages where the trained LHWs lived. Individuals at high suicide risk [27], with a severe medical condition such as pneumonia or active tuberculosis, those with psychotic symptoms, or hearing or visual impairment were excluded from the study. Recruited participants from the same village were assigned to a trained LHW residing in or near their village to receive the intervention they had been trained to deliver (ie, either GSP or group HIV education).

Study Measures

A structured questionnaire administered in the local language was used to collect data on a number of baseline variables in one-on-one, face-to-face interviews.

Baseline Sociodemographic Variables

Sociodemographic variables were assessed using a demographic questionnaire that asked about descriptive information including age, gender, number of children, education, and relationship and employment status. Employment status was categorized into ‘‘unemployed,” “employed,” and “peasant farmer.” Relationship status was categorized into ‘‘never married,” “married/living with a partner,” “divorced/ separated,” or “widowed.” Education status was categorized into “primary/no formal education” and “secondary and above.”

Baseline Psychiatric and Psychosocial Variables

Major Depressive Disorder

Major depressive disorder was diagnosed with the MINI depression module. The MINI is a diagnostic structured interview that was developed for the *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition) of psychiatric disorders [26]. The psychometric properties of the MINI have not been described in Uganda; however, its depression diagnostic section has been translated and locally adapted in Luganda and previously used in this setting [28]. The depression diagnostic section consists of two screening questions, seven additional questions related to depression symptoms, and one question related to functional impairment. The two screening questions ask about the presence of depressed mood and loss of interest in daily activities over a period of 4 weeks in the recent past. If either one or both questions were positively endorsed by a study participant, the clinician asked additional questions to explore current (ie, 4 weeks before the interview) major depressive disorder. A diagnosis of current major depressive disorder was made if a study participant positively endorsed five or more questions related to depression symptoms

and the one question related to functional impairment over a 4-week period.

Depression Symptoms

Depression symptoms were assessed using the SRQ-20 [29]. Cross-cultural adaptation and validation of the SRQ-20 in PLWH in southern Uganda showed that an optimum cut-off point of six or higher had a sensitivity of 84% and a specificity of 93% for current depression [30]. In this study sample, SRQ scores were modeled as a continuous variable with a Cronbach alpha reliability coefficient of .77.

Functioning Level

We assessed functioning levels using a five-item locally developed function assessment method [24]. Items were derived from qualitative interviews with individuals and their caregivers who were attending psychotrauma centers in Kitgum and Gulu [31].

In this population, the measure attained a Cronbach alpha of .86. The scale consisted of five categories of tasks including household (eg, washing clothes, sweeping the yard), work in the field (eg, digging, grazing animals), social interactions (eg, attending social events), and job-related or school-related tasks (eg, participating in income-generating activities, attending school or skills-training courses) and tasks related to personal hygiene (eg, bathing). Study participants were asked to indicate their ability to do a given task on a three-point scale where 0 referred to those who responded ‘‘no, I am not able,” 1 to ‘‘yes, but not like before,” and 2 to ‘‘yes, I am able to.”

Disability Days

We assessed disability days by asking a single question “How many working days have you lost due to depression-related symptoms in the previous 30 days?” Disability days reported were modeled as a continuous variable.

Posttraumatic Stress Symptoms

Posttraumatic stress symptoms were assessed using the locally adapted Harvard Trauma Questionnaire. It has been successfully translated into several languages, with acceptable measures of reliability and validity [32]. In this study population, the measure attained a Cronbach alpha reliability coefficient of .93.

Traumatic Experiences

War-related traumatic experiences were assessed using a locally developed 16-item trauma event checklist. Participants were asked whether they had experienced a given traumatic event or not. The trauma event checklist included items such as ‘‘Has the patient been forced to torture others?” “Has the patient witnessed torture/killing of another person?” “Has the patient been forced to kill?’’ A variable indicating the number of traumatic experiences by an individual was created and modeled as a continuous variable.

Perceived Social Support:

Perceived social support was assessed with the 12-item multidimensional social support scale [33]. The scale has been validated in Uganda and its three-subscale structure (family, friends, and significant other) was confirmed [34]. The Cronbach alpha for this sample was .96. Responses were based on a seven-point Likert scale with higher scores indicating greater support from friends, family, and significant others. We obtained total scores from the scale and modeled the scores as a continuous variable.

Self-Esteem

Self-esteem was measured using the 10-item Rosenberg Self-Esteem Scale, which provides assessment of one’s general feelings about oneself [35]. Responses were based on a four-point scale. This scale has been used in HIV-positive women in South Africa [36]. The scores range from 10 to 40 with higher scores indicating higher self-esteem. We obtained total scores from the scale and modeled the scores as a continuous variable. In this study sample, the measure attained a Cronbach alpha of .93.

Alcohol Use

We assessed alcohol use with the Alcohol Use Disorders Identification Test (AUDIT) [37]. This 10-item scale has been validated in PLWH populations in sub-Saharan Africa [10]. Each of the 10 questions is rated on a four-point scale. The total score ranges from 0 to 40. A total of eight or higher is recommended as an indicator of hazardous drinking behavior and a score of 20 or higher is indicative of alcohol dependence. We report this variable both as categorical using the cut-off point of eight or higher and continuous using total AUDIT scores. In this study population, the measure attained a Cronbach alpha of .95.

Coping Skills

We used the modified coping inventory to assess a broad range of both positive and negative coping responses which establish how the study participants responded when they were confronted with difficult or stressful events in their lives [38]. Each coping strategy is assessed by a set of two questions. Responses were based on a four-point scale. For each coping strategy, the scores range from two to eight, with higher scores indicating frequent use of the coping strategy. Each coping strategy was modeled as a continuous variable.

Stigma and Discrimination

To measure internalized stigma, we used the brief AIDS-related stigma scale [39]. Responses were based on a four-point Likert scale. The scores ranged from 8 to 32 with high scores indicating higher levels of internalized stigma.

To measure discrimination (enacted stigma), we used a total of 13 items adapted from an HIV/AIDS indicator survey previously used by Nyblade and MacQuarrie [40] which described various forms of discriminatory events experienced by PLWH as a result of their HIV status. Both stigma and discrimination were modeled as continuous variables.

Viral Load

Once a year, HIV treatment centers routinely assess the viral load of clients. Measures of viral load were obtained from the medical charts of study participants. Although the name of the assay used to measure viral load in the laboratory was not recorded, all viral load measures were conducted by the same laboratory. If the record in the chart noted undetectable viral copies, that individual was assumed to have achieved viral

suppression. If there was a record of detected viral copies in the chart, these were transcribed to the study questionnaire. Viral load was treated both as a continuous variable and as a categorical variable indicating suppression (coded 1) or nonsuppression of viral load (coded 0).

Adherence to Antiretroviral Therapy

Adherence to ART was assessed by using the missed-dose method, which is simple to implement and straightforward. Participants were asked to report the number of missed doses within a specified time period. We asked a single question: "During the past week, on how many days have you missed taking all your medication doses?" Adherence was calculated as the percent of days in the week the person missed all medications. Adherence "scores" were treated both as a continuous variable in correlation analyses and also converted to a dichotomous variable (eg, adherent/nonadherent) to simplify their interpretation for the descriptive analyses. In previous studies, researchers have used either 80% or 90% or 100% as the cut-off point for adherence [41,42]. In this study, we used 100% as the cut-off point.

Socioeconomic Status Index

To evaluate the baseline socioeconomic status (SES) of study participants, we created an SES index using principal component analysis of the following variables: presence or absence of an income-generating activity, food security, savings, and household assets (land, animals, poultry, radio, television, mobile phone, bicycle, or motorcycle). The index was categorized into quintiles with the first quintile representing low SES, the second to fourth quintiles representing the medium SES, and the fifth quintile representing the high SES group.

Statistical Analyses

Statistical analyses were performed using STATA statistical software version 15. Descriptive statistics were used to describe the demographic, clinical, and psychosocial characteristics of the study population. Among eligible participants, differences between those enrolled versus those who refused enrollment were assessed using chi square tests for categorical variables and *t* tests for continuous variables. Due to violations of normality, nonlinear relationships and the presence of ordinal variables, we opted to use the nonparametric Spearman rank order correlation (ρ coefficient) to examine associations between depression symptoms and other baseline variables. A Bonferroni adjustment was applied to calculated significance levels. Statistical significance was considered at two-tailed $P \leq .05$.

Results

Screening and Recruitment

The study recruitment period was from September to December 2016. After a series of health talks on depression in 30 participating primary health centers, a total of 1473 individuals expressed interest in being screened for depression. Of these, 1140 were eligible and enrolled in the study. On commencement of the interventions, 48 (4.21%) did not attend any group session. Of these, 21 had failed to complete baseline assessments, while 27 had completed baseline assessments. Although these participants appeared to have withdrawn from the study after enrollment, they did not announce their exit. Therefore, we still consider them as part of the study. Figure 1 summarizes the recruitment process.

The study was able to recruit 95% the target sample size of 1200 described in the study protocol. The target of 40 participants in each health center was met by only 14 primary health centers. Only 23 participants were enrolled outside the target enrollment period. Multimedia Appendices 2 and 3 show the geographical distribution of the primary health centers and the actual enrollment versus target enrollment, respectively.

Other protocol deviations reported included the enrollment of 141 of 1140 (12.37%) individuals who did not meet the MINI criteria for major depression. However, of those enrolled, 127 of 1140 (11.14%) were judged to be clinically depressed by the health workers and had attained a score of more than six on the SRQ-20, which indicates a high probability of major depression [30]. In addition, 13 of 1140 (1.14%) did not meet the criteria for depression and 22 of 1140 (2.02%) did not have a record of their depression status. Individuals with high suicide risk were to be excluded from the study; however, for 32 of 1140 (2.80%) individuals with high suicide risk, the health workers insisted that they be included in the study as the group sessions were the only interventions accessible at that time and it would be unethical if they did not receive any form of intervention for their depression. Multimedia Appendix 4 illustrates details of the protocol deviations.

Baseline Characteristics of Study Participants

The sample consisted of slightly more women (612/1140, 53.68%) than men (528/1140, 46.32%). The age of participants ranged from 19 to 80 years, with a mean age of 38.5 (SD 10.9) years. The majority were peasant farmers (622/1140, 54.56%), with primary level education or less (983/1140, 86.22%), without an income-generating activity (828/1140, 72.63%), and without food security (931/1140, 81.67%). Most participants met criteria for major depression (1105/1140, 96.92%) at baseline, as described previously, and reported moderate suicide risk (599/1140, 52.54%). Participants' function scores ranged from 0 to 10, with a mean function score of 4.98 (SD 2.91). In all, 72.46% of study participants (826/1140) met the criteria for probable posttraumatic stress disorder, and 27.46% (313/1140) met the criteria for hazardous alcohol consumption. Tables 1 and 2 provide detailed descriptions of participant baseline sociodemographic and psychosocial characteristics, respectively.

Participants who did not attend any group sessions were significantly more likely to be male than females ($\chi^2_1=4.0$, $P=.045$) and on average had more depression symptoms ($t_2=2.36$, $P=.01$) than participants who attended group sessions. Table 3 provides detailed comparisons of study participants who attended versus those who did not attend any group sessions.

Table 1. Baseline sociodemographic characteristics of the study participants (N=1140).

Variable	Participants
Age (years)	
Mean (SD)	38.5 (10.9)
Range	19-80
Gender, n (%)	
Female	612 (53.68)
Male	528 (46.32)
Educational background, n (%)	
Primary education or lower	983 (86.23)
Secondary education or higher	157 (13.77)
Employment status, n (%)	
Not employed	405 (35.53)
Employed	113 (9.91)
Peasant farmer	622 (54.56)
Relationship status, n (%)	
Never married	151 (13.25)
Married or living with partner	816 (71.58)
Separated or divorced	87 (7.63)
Widowed	86 (754)
Has income-generating activity, n (%)	
Yes	312 (22.37)
No	828 (72.63)
Has savings, n (%)	
Yes	302 (26.49)
No	838 (73.51)
Has a leadership position in the community, n (%)	
Yes	171 (15.00)
No	648 (85.00)
Has food security, n (%)	
Yes	209 (18.33)
No	931 (81.67)
Number of children	
Mean (SD)	4.0 (2.0)
Range	0-16
Disability days in the past month	
Mean (SD)	8.5 (9.2)
Range	0-30
Baseline monthly income (UGX)	
Mean (SD)	7476 (17,651)
Range	0-150,000
Baseline savings(UGX)	
Mean (SD)	13,758 (40,964)
Range	0-400,000

Variable	Participants
Social economic status index	
Low (quintile 1)	342 (38.78)
Medium (quintiles 2-4)	485 (54.99)
High (quintile 5)	55 (6.24)
Missing	258 (22.63)

Table 2. Baseline psychosocial characteristics of the study participants (N=1140).

Variable	Participants
Major depression, n (%)	
Met MINI criteria	978 (85.78)
Clinically depressed	127 (11.14)
Did not meet any criteria	13 (1.14)
Missing data	22 (1.93)
Suicide risk, n (%)	
Low	479 (42.02)
Moderate	599 (52.54)
High	32 (2.80)
Missing	30 (2.63)
Depression score, mean (SD); range	13.6 (4); 0-20
Posttraumatic stress score, mean (SD); range	42.6 (12.5); 16-64
Function score, mean (SD); range	5 (2.9); 0-10
Social support score, mean (SD); range	44 (20); 0-84
Self-esteem score, mean (SD); range	14 (8); 0-32
Internalized stigma score, mean (SD); range	22 (5); 8-32
Alcohol Use(AUDIT) score, mean (SD); range	6 (9.0); 0-40
Positive coping skills, mean (SD); range	
Self-distraction	3.7 (2.0); 2-8
Active coping	4.2 (2.0); 1-8
Use of emotional support	4 (2); 2.0-8
Use of venting	3.9 (2.0); 2-8
Acceptance	4.2 (2.0); 1-8
Use of positive reframing	4 (2.0); 1-8
Use of religion	4.7 (2.0); 0-8
Negative coping skills, mean (SD); range	
Denial	5 (2.0); 0-8
Self-blame	2.8 (1.2); 0-4
Use of alcohol and substances	4.55 (2.6); 0-8
Behavioral disengagement	5.2 (2.0); 0-8
Enacted stigma (discrimination), mean (SD); range	
Isolation	2.8 (3.0); 0-10
Verbal abuse	2.2 (1.4); 0-4
Loss of identity	1.2 (1.2); 0-4
Unable to access community resources	2.6 (3.0); 0-10

Table 3. A comparison of eligible study participants who attended versus those who did not attend any group sessions (N=1140).

Variable	Attended (n=1092)	Did not attend (n=48)	Effect estimate		*P* value
			X^2_1	t_2	
Age (years), mean (SD)	38.5 (10.9)	37 (8.7)		0.81	.20
Gender, n (%)			4.0		.04
Female	593 (54.30)	19 (39.6)			
Male	499 (45.69)	29 (60.4)			
Educational background, n (%)			1.1		.31
Primary education or lower	944 (86.45)	39 (81.3)			
Secondary education or higher	148 (13.55)	9 (18.75)			
Occupational status, n (%)			1.3		.53
Not employed	385 (35.25)	20 (41.7)			
Employed	110 (10.10)	3 (6.3)			
Peasant farmer	597 (54.67)	25 (52.1)			
Relationship status, n (%)			3.9		.27
Never married	149 (13.65)	2 (4.2)			
Married or living with partner	779 (71.16)	37 (77.1)			
Separated or divorced	82 (7.51)	5 (10.4)			
Widowed	82 (7.51)	4 (8.3)			
Depression score, mean (SD)	13.6 (2.4)	11.9 (4.4)		2.36	.01

Correlations Among Depression and Related Psychosocial Variables

There were several significant associations found between depression symptoms and both clinical and psychosocial variables at baseline. Depression symptoms assessed by the MINI were positively correlated with posttraumatic stress symptoms (ρ=.43, *P*<.001), suicide risk (ρ=.32, *P*<.001), stigma (ρ=.30, *P*<.001), number of traumatic experiences (ρ=.25, *P*<.001), and negatively correlated with perceived social support (ρ=–.35, *P*<.001), functioning (ρ=–.22, *P*<.001), self-esteem (ρ=–.39, *P*<.001), and adherence to ART(ρ=–.12, *P*=.05). Suicide risk was positively correlated with posttraumatic stress symptoms (ρ=.28, *P*<.001), number of traumatic experiences (ρ=.21, *P*<.001), stigma (ρ=.2, *P*<.001), and alcohol use (ρ=.21, *P*<.001).

Adherence to ART was positively correlated with social support (ρ=.15, *P*<.001) and negatively correlated with stigma (ρ=–.14, *P*<.001). The number of traumatic experiences was positively correlated with viral load (ρ=.12, *P*=.05). Correlations between viral load and depression symptoms were positive but weak and nonsignificant. See Table 4 for the correlation matrix.

Table 4. Baseline correlations among depression symptoms and related psychosocial variables (N=1140). *P<.001; **P<.05.

Symptoms and variables	Depression	Suicide risk	Function	PTSD[a]	Social support	Self-esteem	Stigma	Viral load	Adherence	Trauma	Alcohol Use	SES[b] Index
Depression												
Suicide risk	.32*											
Function	–.22*	–.17*										
PTSD	.43*	.28*	–.36*									
Social support	–.35*	–.22*	.28*	–.33*								
Self-esteem	–.40*	–.21*	.51*	–.48*	.46*							
Stigma	.30*	.20*	–.26*	.28*	–.33*	–.42*						
Viral load	.02	.05	.07	–.02	.04	.08	–.06					
Adherence	–.11**	–.01	–.00	–.04	.15*	.06	–.14*	.05				
Trauma	.24*	.21*	–.11**	.13*	–.06	–.08	.05	.12**	.05			
Alcohol use	–.08	.22*	.04	–.06	–.01	.09	.06	–.05	.01	.13*	1.00	
SES Index	–.04	.15*	.02	–.03	.09	.07	–.02	.03	–.01	.02	0.02	1.00

[a]PTDS: posttraumatic stress disorder.

[a]SES: socioeconomic status.

Discussion

The SEEK-GSP study tests GSP delivered by trained LHW for treatment of depression in rural areas in postconflict northern Uganda. The recruitment goal for the study was largely achieved, with 95% of the targeted sample size enrolled in the trial in a 14-week period. This finding suggests that participants were easy to recruit for the study and were willing to participate in either study arm. In contrast to previous trials of psychological interventions for depression in sub-Saharan Africa [43-45], 80% of those recruited in the study attended all group sessions. This high attendance, which was also observed in our previous pilot trial [24], indicates keen interest and confirms the acceptability of group interventions in the target population.

Among trials of psychological interventions to treat depression in PLWH in sub-Saharan Africa, this study is the first to enroll a large sample of males. The majority of previous trials of psychological interventions for depression have largely focused on women, including studies by Kaaya and colleagues from Tanzania [44], Chibanda and colleagues from Zimbabwe [45], and Bolton and colleagues from southern Uganda [46]. These studies are important given the dearth of prior studies focused on psychological treatments for depression in sub-Saharan Africa. However, interventions that attract men may be particularly relevant to African communities and may be a promising avenue for engaging them in research and, if e cacious, improving the health of the entire community.

The baseline data from this study indicate that PLWH with depression are vulnerable on multiple levels and disadvantaged across many social and economic determinants of health. The majority have low education, lack an income-generating activity and food security, and on average were unable to work for 10 days in the month prior to enrollment. These findings are not surprising. Such socioeconomic disadvantage has been documented among HIV-positive populations across the African continent [47,48] and is often associated with depression [49,50].

Correlation analyses indicate that there are significant positive and negative correlations between depression symptoms and other baseline variables. The positive correlations between depression and posttraumatic symptoms, internalizing stigma and number of traumatic experiences, are not surprising. Several studies have demonstrated the comorbidity of stigma, depression, and posttraumatic stress symptoms in primary care settings [51-53].

Among the negative correlations, a larger number of depression symptoms were associated with lower levels of functioning, perceived social support, and self-esteem. Previous studies have confirmed that depression impairs functioning [54,55], while social support is the most potent buffer against depression [56-58]. Further, a meta-analysis of 77 longitudinal studies provides consistent support for the fact that low self-esteem contributes to depression [5].

Our study findings further indicate that with a larger number of depression symptoms, there is a lesser degree of adherence to ART, confirming what a myriad of previous studies have shown worldwide [59]. We also found a significant positive correlation between the number of traumatic experiences and viral load. Prior longitudinal studies in high-income countries have found a similar association [60,61]. However, such an association has not been documented among PLWH in sub-Saharan Africa. Overall, our study findings justify the active ingredients of our experimental intervention—GSP which places emphasis on enhancing emotional and social support, coping skills to combat stigma and discrimination, and support economic empowerment.

This study has a number of limitations. Although our data are drawn from multiple HIV clinics across three districts in northern Uganda, the study participants share the same ethnicity.

Given that Uganda is a multiethnic country, our results may not be applicable to other ethnic populations. The study needs to be replicated in other regions of the country. Self-report is not the most reliable measure of ART adherence; therefore, our adherence estimates may represent an overestimate. However, a gold standard for adherence assessment does not exist and different assessment methods have been used in different studies [62].

Despite these limitations, the SEEK-GSP study provides a rich dataset with follow-up of the high number of persons with major depressive disorder and HIV disease in sub-Saharan Africa. The large sample size will allow us to conduct subgroup analyses to assess how some variables, such as gender and psychiatric comorbidities (hazardous alcohol consumption and posttraumatic stress), can modify the effects of GSP on depression. Identifying groups of individuals for whom GSP works best will assist future work toward developing selection criteria to guide referral of patients for GSP. Additionally, variables that mediate the effects of GSP on depression, and subsequently other study outcomes, can thus be identified.

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Authors' Contributions

EN-M, KW, JO, SM, RM, JB, EM, and JN conceptualized the study and EN-M sought and obtained funding. EM and OH conducted statistical analyses. EN-M and JO managed the literature searches. EN-M, RM, EM, and JN wrote the initial manuscript. SM, RM, HM, ME, EM, and JN revised the manuscript critically for important intellectual content. All authors contributed to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Health Worker Supervision Checklist.

[PDF File (Adobe PDF File), 275KB - resprot_v8i1e11560_app1.pdf]

Multimedia Appendix 2

Geographical distribution of primary health care centers in the study.

[PNG File, 601KB - resprot_v8i1e11560_app2.png]

Multimedia Appendix 3

Actual versus expected enrolment of study participants.

[PNG File, 115KB - resprot_v8i1e11560_app3.png]

Multimedia Appendix 4

Study protocol deviations.

[PDF File (Adobe PDF File), 16KB - resprot_v8i1e11560_app4.pdf]

References

1. Nakimuli-Mpungu E, Bass JK, Alexandre P, Mills EJ, Musisi S, Ram M, et al. Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. AIDS Behav 2012 Nov;16(8):2101-2118. [doi: 10.1007/s10461-011-0087-8] [Medline: 22116638]
2. Bernard C, Dabis F, de Rekeneire N. Prevalence and factors associated with depression in people living with HIV in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One 2017;12(8):e0181960 [FREE Full text] [doi: 10.1371/journal.pone.0181960] [Medline: 28783739]
3. Li L, Lin C, Liang L, Ji G. Exploring coping and social support with gender and education among people living with HIV in China. AIDS Behav 2016 Feb;20(2):317-324 [FREE Full text] [doi: 10.1007/s10461-015-1232-6] [Medline: 26494110]

4. Yeji F, Klipstein-Grobusch K, Newell M, Hirschhorn LR, Hosegood V, Bärnighausen T. Are social support and HIV coping strategies associated with lower depression in adults on antiretroviral treatment? Evidence from rural KwaZulu-Natal, South Africa. AIDS Care 2014;26(12):1482-1489. [doi: 10.1080/09540121.2014.931561] [Medline: 24991994]
5. Sowislo JF, Orth U. Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. Psychol Bull 2013 Jan;139(1):213-240. [doi: 10.1037/a0028931] [Medline: 22730921]
6. Familiar I, Murray S, Ruisenor-Escudero H, Sikorskii A, Nakasujja N, Boivin MJ, et al. Socio-demographic correlates of depression and anxiety among female caregivers living with HIV in rural Uganda. AIDS Care 2016 Dec;28(12):1541-1545 [FREE Full text] [doi: 10.1080/09540121.2016.1191609] [Medline: 27240825]
7. Mahajan AP, Sayles JN, Patel VA, Remien RH, Sawires SR, Ortiz DJ, et al. Stigma in the HIV/AIDS epidemic: a review of the literature and recommendations for the way forward. AIDS 2008 Aug;22 Suppl 2:S67-S79 [FREE Full text] [doi: 10.1097/01.aids.0000327438.13291.62] [Medline: 18641472]
8. Lowther K, Selman L, Harding R, Higginson IJ. Experience of persistent psychological symptoms and perceived stigma among people with HIV on antiretroviral therapy (ART): a systematic review. Int J Nurs Stud 2014 Aug;51(8):1171-1189. [doi: 10.1016/j.ijnurstu.2014.01.015] [Medline: 24602830]
9. Olley BO, Zeier MD, Seedat S, Stein DJ. Post-traumatic stress disorder among recently diagnosed patients with HIV/AIDS in South Africa. AIDS Care 2005 Jul;17(5):550-557. [doi: 10.1080/09540120412331319741] [Medline: 16036241]
10. Myer L, Smit J, Roux LL, Parker S, Stein DJ, Seedat S. Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales. AIDS Patient Care STDS 2008 Feb;22(2):147-158. [doi: 10.1089/apc.2007.0102] [Medline: 18260806]
11. Boarts JM, Sledjeski EM, Bogart LM, Delahanty DL. The differential impact of PTSD and depression on HIV disease markers and adherence to HAART in people living with HIV. AIDS Behav 2006 May;10(3):253-261. [doi: 10.1007/s10461-006-9069-7] [Medline: 16482405]
12. Katz IT, Ryu AE, Onuegbu AG, Psaros C, Weiser SD, Bangsberg DR, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. J Int AIDS Soc 2013 Nov 13;16(3 Suppl 2):18640 [FREE Full text] [Medline: 24242258]
13. Ironson G, O'Cleirigh C, Kumar M, Kaplan L, Balbin E, Kelsch CB, et al. Psychosocial and neurohormonal predictors of HIV disease progression (CD4 cells and viral load): a 4 year prospective study. AIDS Behav 2015 Aug;19(8):1388-1397 [FREE Full text] [doi: 10.1007/s10461-014-0877-x] [Medline: 25234251]
14. Delpierre C, Cuzin L, Lauwers-Cances V, Datta GD, Berkman L, Lang T. Unemployment as a risk factor for AIDS and death for HIV-infected patients in the era of highly active antiretroviral therapy. Sex Transm Infect 2008 Jun;84(3):183-186. [doi: 10.1136/sti.2007.027961] [Medline: 18192292]
15. Aibibula W, Cox J, Hamelin A, McLinden T, Klein MB, Brassard P. Association between food insecurity and HIV viral suppression: a systematic review and meta-analysis. AIDS Behav 2017 Mar;21(3):754-765. [doi: 10.1007/s10461-016-1605-5] [Medline: 27837425]
16. van der Heijden I, Abrahams N, Sinclair D. Psychosocial group interventions to improve psychological well-being in adults living with HIV. Cochrane Database Syst Rev 2017 Mar 14;3:CD010806 [FREE Full text] [doi: 10.1002/14651858.CD010806.pub2] [Medline: 28291302]
17. Chibanda D, Cowan FM, Healy JL, Abas M, Lund C. Psychological interventions for common mental disorders for people living with HIV in low- and middle-income countries: systematic review. Trop Med Int Health 2015 Jul;20(7):830-839 [FREE Full text] [doi: 10.1111/tmi.12500] [Medline: 25753741]
18. Murry VM, Brown PA, Brody GH, Cutrona CE, Simons RL. Racial discrimination as a moderator of the links among stress, maternal psychological functioning, and family relationships. J Marriage and Family 2001 Nov;63(4):915-926. [doi: 10.1111/j.1741-3737.2001.00915.x]
19. Nakimuli-Mpungu E, Wamala K, Okello J, Alderman S, Odokonyero R, Musisi S, et al. Developing a culturally sensitive group support intervention for depression among HIV infected and non-infected Ugandan adults: a qualitative study. J Affect Disord 2014 Jul;163:10-17. [doi: 10.1016/j.jad.2014.03.042] [Medline: 24836082]
20. Nakimuli-Mpungu E, Wamala K, Okello J, Alderman S, Odokonyero R, Musisi S, et al. Outcomes, feasibility and acceptability of a group support psychotherapeutic intervention for depressed HIV-affected Ugandan adults: a pilot study. J Affect Disord 2014 Sep;166:144-150. [doi: 10.1016/j.jad.2014.05.005] [Medline: 25012423]
21. Nakimuli-Mpungu E, Wamala K, Okello J, Alderman S, Odokonyero R, Mojtabai R, et al. Group support psychotherapy for depression treatment in people with HIV/AIDS in northern Uganda: a single-centre randomised controlled trial. The Lancet HIV 2015 May;2(5):e190-e199. [doi: 10.1016/S2352-3018(15)00041-7]
22. Roberts B, Ocaka KF, Browne J, Oyok T, Sondorp E. Factors associated with post-traumatic stress disorder and depression amongst internally displaced persons in northern Uganda. BMC Psychiatry 2008 May 19;8:38 [FREE Full text] [doi: 10.1186/1471-244X-8-38] [Medline: 18489768]
23. Nakimuli-Mpungu E, Musisi S, Wamala K, Okello J, Ndyanabangi S, Mojtabai R, et al. The effect of group support psychotherapy delivered by trained lay health workers for depression treatment among people with HIV in Uganda: protocol of a pragmatic, cluster randomized trial. JMIR Res Protoc 2017 Dec 11;6(12):e250 [FREE Full text] [doi: 10.2196/resprot.8925] [Medline: 29229589]

24. Nakimuli-Mpungu E, Wamala K, Okello J, Ndyanabangi S, Kanters S, Mojtabai R, et al. Process evaluation of a randomized controlled trial of group support psychotherapy for depression treatment among people with HIV/AIDS in Northern Uganda. Community Ment Health J 2017 Dec;53(8):991-1004 [FREE Full text] [doi: 10.1007/s10597-017-0129-4] [Medline: 28317086]
25. Baingana F, Mangen PO. Scaling up of mental health and trauma support among war affected communities in northern Uganda. Intervention 2011:1. [doi: 10.1097/WTF.0b013e32834dfcc3]
26. 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;quiz 34 [FREE Full text] [Medline: 9881538]
27. Patterson WM, Dohn HH, Bird J, Patterson GA. Evaluation of suicidal patients: The SAD PERSONS scale. Psychosomatics 1983 Apr;24(4):343-349. [doi: 10.1016/S0033-3182(83)73213-5]
28. Muhwezi WW, Okello ES, Neema S, Musisi S. Caregivers' experiences with major depression concealed by physical illness in patients recruited from central Ugandan Primary Health Care Centers. Qual Health Res 2008 Aug;18(8):1096-1114. [doi: 10.1177/1049732308320038] [Medline: 18650565]
29. Beusenberg M, Orley J, World Health Organization. A User's Guide to the Self-Reporting Questionnaire (SRQ). Geneva: World Health Organization; 1994.
30. Nakimuli-Mpungu E, Mojtabai R, Alexandre PK, Katabira E, Musisi S, Nachega JB, et al. Cross-cultural adaptation and validation of the self-reporting questionnaire among HIV+ individuals in a rural ART program in southern Uganda. HIV AIDS (Auckl) 2012;4:51-60 [FREE Full text] [doi: 10.2147/HIV.S29818] [Medline: 22570575]
31. Nakimuli-Mpungu E, Alderman S, Kinyanda E, Allden K, Betancourt TS, Alderman JS, et al. Implementation and scale-up of psycho-trauma centers in a post-conflict area: a case study of a private-public partnership in northern Uganda. PLoS Med 2013;10(4):e1001427 [FREE Full text] [doi: 10.1371/journal.pmed.1001427] [Medline: 23610562]
32. Mollica R. Harvard Program in Refugee Trauma. 2004. Measuring trauma, measuring torture URL: http://hprt-cambridge.org/screening/measuring-trauma-measuring-torture/ [accessed 2018-12-06] [WebCite Cache ID 74TEwNn7r]
33. 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]
34. Nakigudde J, Musisi S, Ehnvall A, Airaksinen E, Agren H. Adaptation of the multidimensional scale of perceived social support in a Ugandan setting. Afr Health Sci 2009 Aug 01;9 Suppl 1:S35-S41 [FREE Full text] [Medline: 20589159]
35. Rosenberg M. Society and the Adolescent Self-Image. Princeton, NJ: Princeton University Press; 1965.
36. Mundell JP, Visser MJ, Makin JD, Kershaw TS, Forsyth BW, Jeffery B, et al. The impact of structured support groups for pregnant South African women recently diagnosed HIV positive. Women Health 2011 Aug 31;51(6):546-565 [FREE Full text] [doi: 10.1080/03630242.2011.606356] [Medline: 21973110]
37. Nakamura A, Osonoi T, Terauchi Y. Relationship between urinary sodium excretion and pioglitazone-induced edema. J Diabetes Investig 2010 Oct 19;1(5):208-211 [FREE Full text] [doi: 10.1111/j.2040-1124.2010.00046.x] [Medline: 24843434]
38. Carver C, Scheier M, Weintraub J. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol 1989 Feb;56(2):267-283. [Medline: 2926629]
39. Kalichman SC, Simbayi LC, Jooste S, Toefy Y, Cain D, Cherry C, et al. Development of a brief scale to measure AIDS-related stigma in South Africa. AIDS Behav 2005 Jun;9(2):135-143. [doi: 10.1007/s10461-005-3895-x] [Medline: 15933833]
40. Nyblade L, MacQuarrie K. Can We Measure HIV/AIDS-Related Stigma and Discrimination? Current Knowledge About Quantifying Stigma in Developing Countries. Washington: US Agency for International Development; 2017. URL: https://pdf.usaid.gov/pdf_docs/ [accessed 2018-12-07] [WebCite Cache ID 74UDcrepA]
41. Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001 May 15;134(10):968-977. [Medline: 11352698]
42. Golin CE, Liu H, Hays RD, Miller LG, Beck CK, Ickovics J, et al. A prospective study of predictors of adherence to combination antiretroviral medication. J Gen Intern Med 2002 Oct;17(10):756-765 [FREE Full text] [Medline: 12390551]
43. Petersen I, Hanass Hancock J, Bhana A, Govender K. A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: a randomized controlled pilot study. J Affect Disord 2014 Apr;158:78-84. [doi: 10.1016/j.jad.2014.02.013] [Medline: 24655769]
44. Kaaya SF, Blander J, Antelman G, Cyprian F, Emmons KM, Matsumoto K, et al. Randomized controlled trial evaluating the effect of an interactive group counseling intervention for HIV-positive women on prenatal depression and disclosure of HIV status. AIDS Care 2013;25(7):854-862. [doi: 10.1080/09540121.2013.763891] [Medline: 23383726]
45. Chibanda D, Weiss HA, Verhey R, Simms V, Munjoma R, Rusakaniko S, et al. Effect of a primary care-based psychological intervention on symptoms of common mental disorders in Zimbabwe: a randomized clinical trial. JAMA 2016 Dec 27;316(24):2618-2626. [doi: 10.1001/jama.2016.19102] [Medline: 28027368]
46. Bolton P, Bass J, Neugebauer R, Verdeli H, Clougherty KF, Wickramaratne P, et al. Group interpersonal psychotherapy for depression in rural Uganda: a randomized controlled trial. JAMA 2003 Jun 18;289(23):3117-3124. [doi: 10.1001/jama.289.23.3117] [Medline: 12813117]
47. Buvé A, Bishikwabo-Nsarhaza K, Mutangadura G. The spread and effect of HIV-1 infection in sub-Saharan Africa. Lancet 2002 Jun 08;359(9322):2011-2017. [doi: 10.1016/S0140-6736(02)08823-2] [Medline: 12076570]

48. Wojcicki JM. Socioeconomic status as a risk factor for HIV infection in women in East, Central and Southern Africa: a systematic review. J Biosoc Sci 2005 Jan;37(1):1-36. [Medline: 15688569]
49. Lund C, Breen A, Flisher AJ, Kakuma R, Corrigall J, Joska JA, et al. Poverty and common mental disorders in low and middle income countries: a systematic review. Soc Sci Med 2010 Aug;71(3):517-528 [FREE Full text] [doi: 10.1016/j.socscimed.2010.04.027] [Medline: 20621748]
50. Richardson R, Westley T, Gariépy G, Austin N, Nandi A. Neighborhood socioeconomic conditions and depression: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 2015 Nov;50(11):1641-1656. [doi: 10.1007/s00127-015-1092-4] [Medline: 26164028]
51. Bonfils KA, Lysaker PH, Yanos PT, Siegel A, Leonhardt BL, James AV, et al. Self-stigma in PTSD: prevalence and correlates. Psychiatry Res 2018 Jul;265:7-12 [FREE Full text] [doi: 10.1016/j.psychres.2018.04.004] [Medline: 29679793]
52. Greene T, Neria Y, Gross R. Prevalence, detection and correlates of PTSD in the primary care setting: a systematic review. J Clin Psychol Med Settings 2016 Dec;23(2):160-180. [doi: 10.1007/s10880-016-9449-8] [Medline: 26868222]
53. Hernandez D, Kalichman SC, Katner HP, Burnham K, Kalichman MO, Hill M. Psychosocial complications of HIV/AIDS-metabolic disorder comorbidities among patients in a rural area of southeastern United States. J Behav Med 2018 Aug;41(4):441-449 [FREE Full text] [doi: 10.1007/s10865-018-9912-0] [Medline: 29383534]
54. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014 Jul;44(10):2029-2040. [doi: 10.1017/S0033291713002535] [Medline: 24168753]
55. Fried EI, Nesse RM. The impact of individual depressive symptoms on impairment of psychosocial functioning. PLoS One 2014;9(2):e90311 [FREE Full text] [doi: 10.1371/journal.pone.0090311] [Medline: 24587318]
56. Cobb S. Presidential address-1976: social support as a moderator of life stress. Psychosom Med 1976;38(5):300-314. [Medline: 981490]
57. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychol Bull 1985 Sep;98(2):310-357. [Medline: 3901065]
58. Stein ER, Smith BW. Social support attenuates the harmful effects of stress in healthy adult women. Soc Sci Med 2015 Dec;146:129-136. [doi: 10.1016/j.socscimed.2015.10.038] [Medline: 26513122]
59. Uthman OA, Magidson JF, Safren SA, Nachega JB. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. Curr HIV/AIDS Rep 2014 Sep;11(3):291-307 [FREE Full text] [doi: 10.1007/s11904-014-0220-1] [Medline: 25038748]
60. Mugavero MJ, Pence BW, Whetten K, Leserman J, Swartz M, Stangl D, et al. Predictors of AIDS-related morbidity and mortality in a southern US cohort. AIDS Patient Care STDS 2007 Sep;21(9):681-690. [doi: 10.1089/apc.2006.0167] [Medline: 17919095]
61. Ironson G, O'Cleirigh C, Fletcher MA, Laurenceau JP, Balbin E, Klimas N, et al. Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. Psychosom Med 2005;67(6):1013-10121 [FREE Full text] [doi: 10.1097/01.psy.0000188569.58998.c8] [Medline: 16314608]
62. Ammassari A, Trotta MP, Murri R, Castelli F, Narciso P, Noto P, AdICoNA Study Group. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. J Acquir Immune Defic Syndr 2002 Dec 15;31 Suppl 3:S123-S127. [Medline: 12562034]

Abbreviations

ART: antiretroviral therapy
AUDIT: Alcohol Use Disorders Identification Test
GSP: group support psychotherapy
LHW: lay health worker
MINI: Mini International Neuropsychiatric Interview
PLWH: person living with HIV
SEEK-GSP: Social, Emotional, and Economic Empowerment Through Knowledge of Group Support Psychotherapy
WHO: World Health Organization

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Protocol

Treatment of Atopic Dermatitis Using a Full-Body Blue Light Device (AD-Blue): Protocol of a Randomized Controlled Trial

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Abstract

Background: Irradiation with visible blue light (wavelength 400-495 nm) is a promising, effective, and safe new treatment option for chronic inflammatory skin diseases such as psoriasis and atopic dermatitis.

Objective: We will perform a multicenter, placebo-controlled, double-blinded, 3-armed, prospective, randomized controlled trial to investigate the efficacy and safety of full-body blue light devices (wavelengths: 415 nm and 450 nm) compared with that of placebo irradiation for the treatment of atopic dermatitis.

Methods: We are planning to enroll a total of 150 patients at the University hospitals in Göttingen (Germany), Marburg (Germany), and Geneva (Switzerland).

Results: The trial was approved by the lead ethics committee of the medical faculty of the University of Göttingen (21/11/16). Further approvals were obtained from local and federal authorities (ethics committee Marburg, Cantonal Commission for Research Ethics Geneva, Suisse Medic, and Bundesinstitut für Arzneimittel und Medizinprodukte).

Conclusions: We will disseminate the results in a peer-reviewed journal.

Trial Registration: ClinicalTrials.gov NCT03085303; https://clinicaltrials.gov/ct2/show/NCT03085303 (Archived by WebCite at http://www.webcitation.org/73ucqkkA1)

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KEYWORDS

atopic dermatitis; atopic eczema; blue light; irradiation; ultraviolet light

Introduction

Background

Atopic dermatitis is a common chronic inflammatory disease of the skin with a lifetime prevalence of 10%-20% in adults in developed countries [1]. Mutations in the filaggrin gene were shown to play a key role in the etiology of the disease [2]. Patients present with itchy, red, dry or oozing lesions primarily at flexural body areas. Disease severity can be measured using the Eczema Area and Severity Index (EASI), which assesses redness, thickness, scratching, and lichenification on a scale of 0 (none) to 3 (severe) for different body regions [3]. SCORing Atopic Dermatitis (SCORAD) and Patient Oriented-SCORing Atopic Dermatitis (PO-SCORAD) are instruments that additionally consider the subjective symptoms of pruritus and insomnia [4,5]. The Investigator's Global Assessment (IGA) is a score to assess overall disease severity on a scale of 0 (clear) to 4 (severe) [6]. Disease-related impairment of quality of life can be measured using the Dermatology Life Quality Index (DLQI) [7].

As atopic dermatitis is a chronic disease with an unpredictable and often relapsing course, long-term control is necessary [8]. In clinical practice, a stepwise approach is used, starting with active agent-free lipid balancing creams, cortisone-containing topical agents, and conventional ultraviolet (UV) irradiation for mild to moderate disease forms. Immunosuppressive medication is employed in more severely affected patients. Cortisone-containing topical agents effectively reduce inflammation but may also cause infection and skin atrophy in long-term use [9]. Conventional UV irradiation bears the risk of developing skin cancer and promotes accelerated skin aging [8]. Recently, a new treatment modality, UV-free blue light irradiation (wavelengths between 400 and 495 nm), was found to effectively improve inflammatory skin diseases at a favorable risk profile [10-13].

Preliminary Data With Blue Light

Clinical data on blue light in chronic inflammatory skin diseases are scarce. Psoriasis and eczema have been the exclusive indications for comprehensive clinical trials in the past. Regarding eczema, Keemss et al [11] reported on 21 patients with mild to moderate disease who were locally treated with blue light-emitting diode (LED) light (wavelength: 453 nm) for 30 minutes 3 times per week for 4 weeks. No adverse events (AEs) occurred. The local Eczema Severity Index, which rates erythema, infiltration, lichenification, and crusts on a scale of 0 to 3, decreased on average by 1.9 (SD 2.02) in treated areas compared with that by 1.3 (SD 2.24) in untreated areas. Becker et al [10] investigated the treatment of 36 patients with severe atopic dermatitis with a full-body blue (FBB) light irradiation device (wavelengths between 400 and 500 nm accounted for 66% of the emission spectrum of the light source). Treatment consisted of 1 cycle of consecutive, daily blue light irradiations over 5 days. Each side of the body was irradiated for 24 minutes. Cycles were repeated in case of disease exacerbation, triggered by the patient's demand. The EASI score in the treated patients improved by 41% and 54% after 3 and 6 months, respectively. The following transitory mild AEs were reported: local redness, warmth, and itching of the skin.

Other smaller studies investigated the effect of blue light on patients with psoriasis. Pfaff et al [12] used a localized blue light device (wavelength: 453 nm) to treat 49 patients with mild psoriasis for 30 minutes daily or almost daily for 12 weeks with 4 weeks of follow-up. After 78-90 days, the Local Psoriasis Severity Index significantly decreased compared to an untreated area (mean 0.92 [SD 1.10]). No treatment-related AEs occurred. Weinstabl et al [13] reported on localized irradiation of 40 patients with mild to moderate psoriasis with blue light. Group 1 (n=20) received treatment at home with blue light (LED, emission maximum: 420 nm) for 15 minutes once daily for 4 weeks (2 weeks follow-up). Group 2 (n=20) received treatment with another blue light device (LED emission maximum: 453 nm). The contralateral control plaques remained untreated in both groups. In both groups, the Local Psoriasis Severity Index significantly decreased in treated areas compared with that in untreated areas. No severe AEs occurred. Slight transient hyperpigmentation was noted after 3 weeks in both groups (59% and 50%, respectively). However, an FBB light device has not been clinically tested outside the mentioned studies.

Methods

Study Design

AD-Blue trial is a multicenter, placebo-controlled, double-blinded, 3-armed, prospective, randomized controlled trial (European Database on Medical Devices #CIV-16-11-017565 and ClinicalTrials.gov NCT03085303). We designed the clinical study following the Standard Protocol Items: Recommendations for Interventional Trials guidelines (see Multimedia Appendix 1).

Objectives

The primary objective is to estimate the efficacy of irradiation with blue light (415 nm and 450 nm) compared with placebo irradiation in adult patients with atopic dermatitis, determined using multiple clinical scores, such as EASI and SCORAD. Secondary objectives comprise the assessment of safety, tolerability, and satisfaction with irradiation with blue light as well as the time until treatment response under therapy and the duration of response after the last irradiation.

Endpoints

The primary endpoint is to determine the change from baseline in EASI in a comparison between treatment arms and placebo arm at the end of treatment. Secondary endpoints include the change from baseline in SCORAD, PO-SCORAD, visual analog scale of itch, DLQI, and IGA scores; the proportion of patients achieving 50% reduction from baseline EASI score (response); the so far mentioned endpoints at follow-up; and time until treatment response. The following safety endpoints will be addressed: change from baseline in hyperpigmentation of treated skin exposed to blue light and control as well as AEs (serious and nonserious), adverse device events (serious and nonserious), and device deficiencies.

Study Population

A total of 150 patients with atopic dermatitis will be recruited at 3 sites: Geneva, Marburg, and Göttingen. The recruitment

will be independent of the severity of disease and is limited to 50.0% (75/150) at each site. A sample size of 50 patients per group will have 84% power to detect a mean effect size of 0.6.

Recruitment and Status of the Study

The first enrollment took place in March 2017. The study duration per patient is 13 weeks (1 week of screening, 8 weeks of irradiation, and 4 weeks of follow-up), and the estimated total time frame for recruitment of 150 patients is 14 months (last visit of the last patient estimated to be in August 2018). During July to September, no irradiations will take place due to the possible improvement of disease severity linked to the increased natural sun exposure.

Inclusion and Exclusion Criteria

Patients aged 18-75 years with atopic dermatitis according to the UK criteria of atopic dermatitis [14] and a body mass index between 18 and 35 kg/m^2 who are willing to abstain from excessive sun or UV exposure and have given written informed consent will be eligible. Patients with a severe past or present disease that may affect the outcome of the study, including HIV or hepatitis B or C; patients with a risk of noncompliance with study procedures; pregnant or nursing women; patients with alcohol or drug abuse within 12 months prior to screening; patients with photodermatosis, photosensitivity, immunodeficiency, or genetic deficiencies with increased sensitivity to light; and patients who have been diagnosed with invasive skin cancer at any time or with severe actinic damage present at baseline visit will be excluded from the trial.

We will prohibit the following concomitant medication within a certain timeframe before and during the study: systemic immunosuppression treatment such as glucocorticoids, cyclosporine, azathioprine, and mycophenolate mofetil (within 8 weeks prior to baseline visit); UV irradiation treatment (within 4 weeks prior to baseline visit); topical steroids or calcineurin inhibitors (within 2 weeks prior to baseline visit); and photosensitizing medication and colors on the patient's skin (within 3 days prior to baseline visit). Active agent-free lipid balancing creams (Unguentum leniens) will be allowed during the trial and handed out on request.

Investigational Devices

We will investigate FBB-CT01 devices (Philips; Aachen, Germany; not Conformité Européene, CE, marked) with LEDs emitting blue light (Figure 1). This will be done by using the following three different parameter settings:

1. 415 nm device: Device equipped with 415 nm wavelength LEDs. Light output=40 mW/cm^2. Light module equipped with fans.
2. 450 nm device: Device equipped with 450 nm wavelength LEDs. Light output=40 mW/cm^2. Light module equipped with fans.
3. Placebo device: Device equipped with 450 nm wavelength LEDs. Light output=0.2 mW/cm^2. Light module without fans.

The devices are on lock wheels for easy transportation. We will administer phototherapeutic light for 15 minutes to each side of the body of the patient (30 minutes in total for both sides) who will lie flat on a treatment table. We will provide specific protective goggles to filter the blue color of the light. Once the user presses the ON button to switch on the device, all treatment LEDs will be on. If the user needs to stop the treatment, he or she will either press the OFF button or, in case of an emergency, the "emergency stop" button.

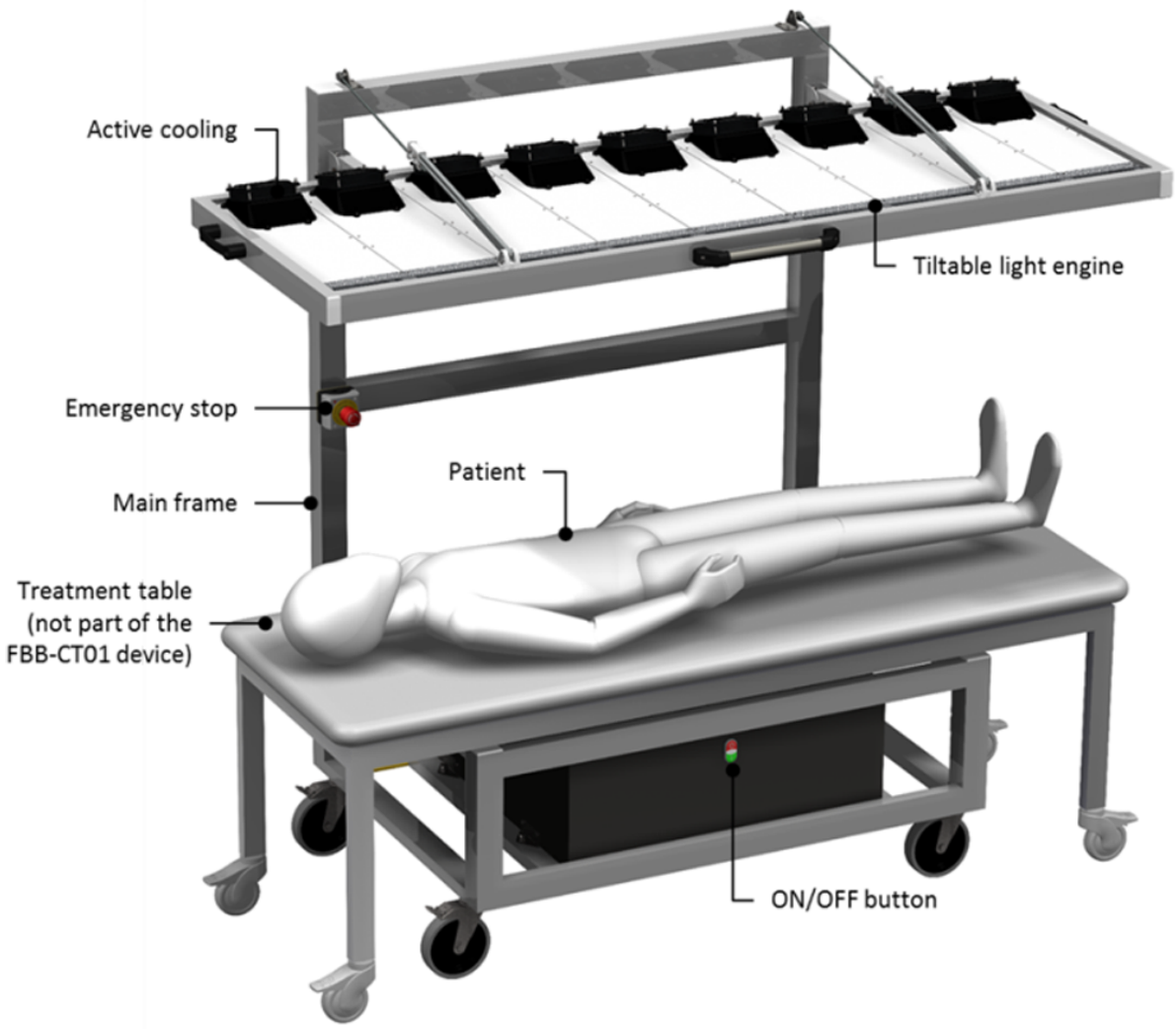
Methodology

We will randomize 150 patients diagnosed with atopic dermatitis 1:1:1 to arm 1 (irradiation for 30 minutes at 415 nm wavelength), arm 2 (irradiation for 30 minutes at 450 nm wavelength), and arm 3 (irradiation for 30 minutes at low-dose, placebo). We will stratify randomization by study site and initial EASI score (assessed during screening visit) with permuted and variable block sizes. For each strata combination, a list of separate randomization sequences will be generated using SAS 9.3 (Cary, NC). Irradiation will be scheduled 3 times a week for 8 weeks. Participants will be followed up for 4 weeks after the last irradiation. Patients will be blinded by wearing tinted protective goggles that disenable the distinction of different wavelengths of light. Medical doctors will examine patients in rooms other than those equipped with the investigational medical devices. These examiners are blinded and are, therefore, not involved in the preparation and process of irradiation. If the safety of an enrolled patient is potentially jeopardized, the investigator can break the blinding of the treatment. According to the predefined study schedule, we will measure skin pigmentation with a mexameter; take photos and blood samples; measure blood pressure; and gather data on Fitzpatrick skin type, DLQI, itch on visual analog scale, SCORAD, IGA, EASI, and PO-SCORAD scores. Detailed information on assessments is depicted in the study schedule (Multimedia Appendix 2). If the EASI score increases by 50% or more compared to baseline after at least 4 weeks of treatment (earliest: day 28=visit 13), a rescue scheme can be applied that allows the use of topical steroids or antihistamines. The investigator will decide whether to prescribe these medications, in what doses, and for how long. The respective patient will not drop out, but the rescue medication as well as the day of rescue will be documented. The study database will be provided by the Universitätsmedizin Göttingen, Ressort Forschung und Lehre, Referat Klinisches Studien Management using secuTrial, which is a browser-based electronic data capture system compliant with Good Clinical Practice (audit trail, role-rights concept). The database will be accessible via the internet.

Patient and Public Involvement

No patients or public were involved in the design of this study.

Figure 1. Design of the FBB-CT01 device (415 nm and 450 nm). The patient lies on the treatment table and receives treatment from the light engine above.



Statistical Considerations

The primary analysis will be performed based on the full analysis set following the intention-to-treat principle. Dropouts during first 4 weeks of treatment will be replaced. Patients missing more than 5 irradiation appointments in total until day 25 (inclusive) or more than 3 consecutive irradiation appointments until day 25 (inclusive) will be considered dropouts and will be replaced. Dropouts after day 25 of the study protocol will not be replaced and will be analyzed in the intention-to-treat population. Sensitivity analysis will be done on the per-protocol population. The difference between the end of treatment after 8 weeks and baseline in primary effectiveness endpoint EASI will be analyzed using pairwise 2-sample *t* tests between each of both active treatments against placebo. As sensitivity analysis, an analysis of covariance will be used with study site, gender, and the hand out of topical emollient as additional factors and the EASI baseline value, age, and Fitzpatrick skin type as covariates. Other continuous secondary endpoints will be analyzed analogously. The EASI response will be analyzed primarily using chi-square test and as a sensitivity analysis with logistic regression. Time until treatment response will be analyzed using Kaplan-Meier estimator and log-rank test. In a further sensitivity analysis, if both wavelengths show better effectiveness than placebo, a pooled comparison against placebo will be done to increase the sample size.

The two comparisons, namely, 415 nm versus placebo and 450 nm versus placebo will be evaluated equally. To address the multiplicity, a success will be declared if both comparisons are statistically significant at an alpha level of .05 or if one of these two is statistically significant with respect to half of alpha at .025.

The two risk differences between one of each blue light irradiation treatments against placebo of the rates of patients with at least one device-related adverse event (rated as possible, probable, or certain) will be compared using asymptotic Wald test of noninferiority for the risk difference. Missing values for the primary and secondary endpoints will be replaced using proper single regression methods (IVEware; University of Michigan, Ann Arbor, MI). Besides the scores (such as EASI scores), the study site, study visits with the documented EASI score, treatment group, gender, age, hand out of topical emollient, and Fitzpatrick skin type will be included in the regression models. In safety analysis, per-protocol analysis, and explorative analysis, missing values will not be replaced.

After the completion of the treatment phase of about 75 patients, first, the EASI score difference between the end of treatment and baseline and, second, the rates of device-related AEs will be analyzed descriptively using *t* test and Fisher's exact test, as appropriate (interim analysis). Based on the estimates, it will be evaluated whether a total of 150 patients will be sufficient to show superiority against placebo at the end of the study.

Ethics and Dissemination

This investigation will be performed according to the Declaration of Helsinki [15], International Organization for Standardization (ISO) 14155, European Medical Device Vigilance System (MEDDEV) 2.3/7 serious adverse event reporting, and other applicable regional and national regulations (eg, for Europe, the Medical Device Directive, Active Implant Medical Device Directive, MEDDEV, and other ISO norms for specific medical devices). The sponsor has taken out an insurance policy for the total duration of the study. This insurance policy covers the patients in respect of the risks involved in this study. Before initiation of the study, the protocol, the patient information sheet, and the consent form were presented to and approved by the independent ethics committee of the medical faculty of the University of Göttingen (lead ethics committee; 21/11/16). Further approvals were obtained from local and federal authorities (EC Marburg, Cantonal Commission for Research Ethics Geneva, Suisse Medic, and Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]). The names of patients and all confidential data are subject to professional discretion and the Bundesdatenschutzgesetz. Processing of medical data will only take place in pseudonymous form.

During the screening visit and preceding any study-mandated procedure, the patient will receive a copy of the written patient information sheet containing a complete and comprehensive explanation of the significance, nature, extent, and possible risks of the study and the statement that the patient is free to withdraw from the study at any time without any negative consequences. In addition, a physician will conduct an oral information session during which the patient will be given sufficient time and opportunity to clarify any questions. After this, a written informed consent will be given to the patients for a dated signature. After signature, the patient will receive a copy of the signed consent form. In addition, the patients will be asked to grant consent for taking blood and skin samples for additional investigations outside the current clinical trial. This is not mandatory and does not affect clinical trial participation in general.

Safety and Risk to Benefit Rationale

Foreseeable AEs include thermal discomfort during the irradiation and increased skin pigmentation, which we expect to be of a very mild nature as experienced in previous trials. Due to the absence of UV light in our devices, we do not expect dermatitis solaris (sunburn) or an increased risk for melanoma or nonmelanoma skin cancer.

Unexpected physical accidents during the irradiation procedure itself (eg, the patient falling off the examination bed or a deficient device harming participants' physical integrity) are possible out of general considerations. The non-CE mark investigational medical devices are classified as Class IIa according to Annex IX of the Directive 93/42/EEC and as Risk Group 2 devices according to EN 60601-2-57. They have been approved by competent federal authorities (BfArM, Suisse Medic). Precautions have been taken by means of risk management, testing, and protocol design to protect the health and safety of the patients and personnel participating in the clinical study. All AEs will be recorded and documented. Serious AEs will be reported in accordance with the appropriate legal regulations (Medizinprodukte-Sicherheitsplanverordnung). Due to the well-documented efficacy of blue light treatment in psoriasis and eczema, clinical benefits include an improvement in objective disease severity and quality of life (less itching or less insomnia expected).

In summary, blue light has the potential to improve inflammatory skin diseases. Associated risks are rare, mild, and transitory. After re-evaluation of the risks, the overall residual risk has been concluded to be satisfactory. As an overall result, we conclude that the benefits for the patients outweigh residual risk, thereby justifying the introduction of the device.

Results

The project was funded by Philips Light & Health, and enrollment was completed in May 2018. Data analysis is currently underway, and the first results are expected to be submitted for publication in January 2019.

Discussion

This is the first international, multicenter, randomized controlled trial investigating the effect of treatment with FBB light devices in patients with atopic dermatitis. A broad range of validated outcome measures has been applied to account for objective and subjective symptoms. This is an investigator-initiated trial with the design developed at the academic institutions. However, clinical heterogeneity and placebo effects may dilute the intervention's effects.

Acknowledgments

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This study is fully sponsored by Philips Light & Health, High Tech Campus 5, 5656AE Eindhoven, The Netherlands. The irradiation devices were developed and built by the sponsor. Since the sponsor's team does not include any physicians, the study

design was developed by the academic physicians. The technical details of the irradiation devices were amended by the sponsor. The study protocol was finally discussed and approved by all authors of this manuscript including employees of the sponsor.

Authors' Contributions

All authors were involved in planning of this study. MPS is the lead investigator. CK, MPS, and TB wrote the first draft of this manuscript. CK, VPN, SP, HJL, WHB, WP, MPS, and TB were involved in data collection, manuscript review and critique, and final approval of the manuscript. JL and MB were involved in the manuscript review, critique, and final approval.

Conflicts of Interest

MB and JL are employees of Philips Light & Health.

Multimedia Appendix 1

SPIRIT Checklist.

[PDF File (Adobe PDF File), 130KB - resprot_v8i1e11911_app1.pdf]

Multimedia Appendix 2

Study schedule of assessments.

[PDF File (Adobe PDF File), 250KB - resprot_v8i1e11911_app2.pdf]

References

1. Weidinger S, Novak N. Atopic dermatitis. Lancet 2016 Mar 12;387(10023):1109-1122. [doi: 10.1016/S0140-6736(15)00149-X] [Medline: 26377142]
2. Irvine AD, McLean WHI, Leung DYM. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 2011 Oct 06;365(14):1315-1327. [doi: 10.1056/NEJMra1011040] [Medline: 21991953]
3. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001 Feb;10(1):11-18. [Medline: 11168575]
4. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997;195(1):10-19. [doi: 10.1159/000245677] [Medline: 9267730]
5. Stalder J, Barbarot S, Wollenberg A, Holm EA, De Raeve L, Seidenari S, PO-SCORAD Investigators Group. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. Allergy 2011 Aug;66(8):1114-1121. [doi: 10.1111/j.1398-9995.2011.02577.x] [Medline: 21414011]
6. Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. J Am Acad Dermatol 2016 Feb;74(2):288-294. [doi: 10.1016/j.jaad.2015.09.062] [Medline: 26685719]
7. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994 May;19(3):210-216. [Medline: 8033378]
8. Werfel T, Heratizadeh A, Aberer W, Ahrens F, Augustin M, Biedermann T, et al. S2k guideline on diagnosis and treatment of atopic dermatitis--short version. J Dtsch Dermatol Ges 2016 Jan;14(1):92-106. [doi: 10.1111/ddg.12871] [Medline: 26713654]
9. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess 2000;4(37):1-191 [FREE Full text] [Medline: 11134919]
10. Becker D, Langer E, Seemann M, Seemann G, Fell I, Saloga J, et al. Clinical efficacy of blue light full body irradiation as treatment option for severe atopic dermatitis. PLoS One 2011;6(6):e20566 [FREE Full text] [doi: 10.1371/journal.pone.0020566] [Medline: 21687679]
11. Keemss K, Pfaff SC, Born M, Liebmann J, Merk HF, von Felbert V. Prospective, Randomized Study on the Efficacy and Safety of Local UV-Free Blue Light Treatment of Eczema. Dermatology 2016;232(4):496-502 [FREE Full text] [doi: 10.1159/000448000] [Medline: 27537360]
12. Pfaff S, Liebmann J, Born M, Merk HF, von Felbert V. Prospective Randomized Long-Term Study on the Efficacy and Safety of UV-Free Blue Light for Treating Mild Psoriasis Vulgaris. Dermatology 2015;231(1):24-34. [doi: 10.1159/000430495] [Medline: 26044167]
13. Weinstabl A, Hoff-Lesch S, Merk HF, von Felbert V. Prospective randomized study on the efficacy of blue light in the treatment of psoriasis vulgaris. Dermatology 2011;223(3):251-259. [doi: 10.1159/000333364] [Medline: 22105015]
14. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014 Feb;70(2):338-351 [FREE Full text] [doi: 10.1016/j.jaad.2013.10.010] [Medline: 24290431]

15. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent 2014;81(3):14-18. [Medline: 25951678]

Abbreviations

AE: adverse event
BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index
FBB: full-body blue
IGA: Investigator's Global Assessment
ISO: International Organization for Standardization
LED: light-emitting diode
MEDDEV: European Medical Device Vigilance System
PO-SCORAD: Patient-Oriented-SCORing Atopic Dermatitis
SCORAD: SCORing Atopic Dermatitis
UV: ultraviolet

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Protocol

Rehabilitation for Children With Dystonic Cerebral Palsy Using Haptic Feedback in Virtual Reality: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cerebral palsy (CP) is the most common developmental motor disorder in children. Individuals with CP demonstrate abnormal muscle tone and motor control. Within the population of children with CP, between 4% and 17% present dystonic symptoms that may manifest as large errors in movement tasks, high variability in movement trajectories, and undesired movements at rest. These symptoms of dystonia typically worsen with physical intervention exercises.

Objective: The aim of this study is to establish the effect of haptic feedback in a virtual reality (VR) game intervention on movement outcomes of children with dystonic CP.

Methods: The protocol describes a randomized controlled trial that uses a VR game-based intervention incorporating fully automated robotic haptic feedback. The study consists of face-to-face assessments of movement before, after, and 1 month following the completion of the 6-session game-based intervention. Children with dystonic CP, aged between 7 and 17 years, will be recruited for this study through posted fliers and laboratory websites along with a group of typically developing (TD) children in the same age range. We anticipate to recruit a total of 68 participants, 34 each with CP and TD. Both groups of children will be randomly allocated into an intervention or control group using a blocked randomization method. The primary outcome measure will be the smoothness index of the interaction force with the robot and of the accelerometry signals of sensors placed on the upper limb segments. Secondary outcomes include a battery of clinical tests and a quantitative measure of spasticity. Assessors administering clinical measures will be blinded. All sessions will be administered on-site by research personnel.

Results: The trial has not started and is pending local institutional review board approval.

Conclusions: Movement outcomes will be examined for changes in muscle activation and clinical measures in children with dystonic CP and TD children. Paired *t* tests will be conducted on movement outcomes for both groups of children independently. Positive and negative results will be reported and addressed.

Trial Registration: ClinicalTrials.gov NCT03744884; https://clinicaltrials.gov/ct2/show/NCT03744884 (Archived by WebCite at http://www.webcitation.org/74RSvmbZP)

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KEYWORDS

cerebral palsy; child; dystonia; motor skills; muscle spasticity; randomized controlled trial; rehabilitation; robotics; sensory feedback; virtual reality

Introduction

Background

Cerebral palsy (CP) is the most common developmental motor disorder in children, present in 3.6 of every 1000 live births in the United States [1]. Individuals with CP demonstrate abnormal muscle tone and motor control that contribute to impaired postural control and movement coordination that compromise health [2,3]. CP is considered a static encephalopathy; there is no known cure, and the physical impairments present at early age tend to worsen with time [4].

Between 4% and 17% of children with CP present dystonic symptoms as the predominant motor impairment [5]. Dystonia is typically characterized by involuntary muscle activity that may be sustained or intermittent, thereby causing abnormal postures or movements that can be described as trembling, writhing, or contouring [6-8]. These abnormal movements are often present during attempted voluntary movement and can worsen when this movement is sustained [7].

Approximately 70% of children with CP present spastic symptoms. Spasticity manifests as (1) increased resistance to external muscle stretch that varies with flexion or extension and/or (2) resistance that quickly rises past a certain joint angle position or velocity [6,7]. Dystonia and spasticity often manifest in the same child with CP [5,7,9].

The main goals of rehabilitation in CP include promoting function while decreasing the risk for skeletal deformity and muscular atrophy later in life [10-14]. Rehabilitative therapies for CP most commonly include orthopedic surgery, botulinum toxin injections, and physical therapy (PT). PT interventions consist of intensive stretching and strengthening exercises and, more recently, high dosage robotic training [10-14]. However, dystonia worsens with PT and is often “refractory to treatment” [15]. Management of dystonia typically involves oral medication that produces little improvement and may have adverse side effects [16]. It has been recently shown that deep brain stimulation provides only moderate benefits in some patients with dystonia and none in others [16-21]. In individuals with combined spasticity and dystonia, physical interventions that improve spastic symptoms cause worsening of dystonic symptoms [7].

This worsening of dystonic symptoms is thought to be caused by abnormal signal-dependent noise modulated by the central nervous system [15]. With this in mind, we consider a low-magnitude (30% ± 10% maximum voluntary contraction) isometric force task intervention to limit signal-dependent noise that is characteristic of dystonia while minimizing movement-related sensory feedback. In addition, the intervention is designed as a virtual reality (VR) game aiming to stimulate motivation and attention as part of the rehabilitation strategy. Motivation and attention have been recognized by the National Institutes of Health Taskforce on Neuroplasticity for Clinical Applications as key for neuroplasticity during rehabilitation [8].

We hypothesize that training children with dystonic CP to match force direction targets at low magnitudes of isometric force with real-time feedback in a low dimensional space rendered in VR will improve quantitative and clinical movement outcome measures.

Choice of Comparator

Children aged 7 to 17 years with dystonic CP and a group of typically developing (TD) children in the same age range will be recruited for the study. The CP and TD groups will be randomly assigned to an intervention or no-intervention (control) group. The control groups will be assessed in the same schedule as the intervention groups. Participants will continue with their regular PT schedule and continue their typical exercise regimen as applicable.

Trial Design

We will conduct paired *t* tests on movement outcomes for the CP and TD groups independently. In case of non-normality, nonparametric techniques will be used. Differences before and after as well as before and follow-up will be obtained on the primary outcome measure: smoothness of movement. Differences will also be calculated on secondary outcomes for exploratory purposes. The primary outcome measure will be the smoothness index of the accelerometry signals of sensors placed on the upper limb segments. Secondary outcomes include the interaction force with the robot and a battery of clinical tests and a quantitative measure of spasticity. The study is powered for the main outcome. The desired allocation will be 1:1, with 1 participant in the control group for every participant in the intervention group for both CP and TD participants.

In the application presented here, the VR environment follows a prescribed remapping based on principal component analysis of force data generated from people with typical movement control [22,23]. Participants will, therefore, be asked to produce efforts in directions of high variance that are associated with performance of typically developed adults.

This intervention will not be incorporated into a broader health care program at this time.

Objective

The primary objective was to establish the effect of a VR game-based force-direction training intervention on movement outcomes of children with dystonic CP using robotic feedback.

Methods

Study Setting

All procedures will take place at 2 sites: the Neuroscience of Dance in Health and Disability laboratory located at the University of Illinois at Urbana-Champaign (UIUC) or the Children's Hospital of Illinois/OSF Saint Francis Medical Center. Both sites are located in Illinois, United States and are in the urban counties of Champaign and Peoria, respectively. The ethno-racial composition of the state of Illinois for the population younger than 18 years is approximately 66% white, 24% Hispanic, 16% black, 13% other, and 5% Asian. Expected total recruitment is 68 participants (Table 1) [24].

Eligibility Criteria

The inclusion criteria are shown in Textbox 1. The exclusion criteria included not meeting all inclusion criteria.

Interventions

All potential participants will be assessed to verify that inclusion and exclusion criteria are met during baseline assessments before being allocated into an intervention or control group. Participants in the control group will be assessed at a study site approximately 6 times, each lasting a maximum of 1.5 hours. The assessments will take place over the course of 6 to 7 weeks; there will be baseline assessments, postassessments, and 1-month follow-up assessments. Participants will attend a total of approximately 9 hours for the assessments involved in the study. All participants will be asked to continue typical PT or exercise routines outside of the study. A parent or guardian will be requested to stay in the research room at all times to further ensure participant safety and comfort.

Participants randomly allocated into the game-like intervention will participate in 6 training sessions, of up to 1 hour in duration, in addition to assessments for a total of 12 sessions. The intervention will occur over a 1- to 2-week period depending on schedule accommodations. Total participation time for intervention groups is estimated at 15 hours. Participants will play the VR game in which they will produce isometric efforts against the robot-force transducer unit that is programmed to resist their effort with a static torque control mode. The active game play time will be anywhere between 10 and 30 min depending on user preference. The source code and VR game will be available upon request.

Table 1. Allocation by performance site. It is expected that most participants will be tested at the Peoria location.

Performance site	Male (n=34), n (%)	Female (n=34), n (%)	Total (N=68), n (%)
Neuroscience of Dance in Health and Disability Laboratory, Kinesiology and Community Health, and UIUC[a]	12 (35)	12 (35)	24 (35)
Children's Hospital of Illinois/OSF Saint Francis Medical Center, Peoria, Illinois	22 (65)	22 (65)	44 (65)

[a]UIUC: University of Illinois at Urbana-Champaign.

Textbox 1. Inclusion criteria.

1. Aged between 7 and 17 years
2. Diagnosis with dystonic cerebral palsy (CP), for participants with CP, or have no neuromuscular conditions, for typically developing participants
3. Mild to no difficulty understanding conversations compared with others of the same age
4. Communicate age appropriately or with some difficulty, but a new listener can understand
5. No uncorrected vision
6. Hearing without the need of a hearing aid
7. No other neural, neuromuscular, or musculoskeletal conditions
8. No history of surgical procedures within 6 months before enrollment in the study
9. Participation in stable school and/or private physical or occupational therapy with a frequency no greater than 2 sessions per week for cerebral palsy groups
10. No changes in medication for the 6 months before enrollment in the study
11. Medically stable
12. No other concurrent illness
13. Received no Botox treatment within 3 months previous to the initiation of the study
14. No use of cardiac pacemakers, hearing aids, or another electronic implanted device
15. Absence of allergy to silver or skin adhesives
16. No history of seizures
17. Manual Ability Classification System score I-III

Figure 1. Projection into virtual reality (VR) space. The vector x in VR space is the projection of the signal vector b of n=6 force and torque signals, by the principal components matrix A.

$$\begin{bmatrix} x_1 \\ x_2 \\ \dots \\ x_n \end{bmatrix} = \begin{bmatrix} a_{1,1}\ a_{1,2} \dots a_{1,6} \\ a_{2,1}\ a_{2,2} \dots a_{2,6} \\ \dots \\ a_{n,1}\ a_{n,2} \dots a_{n,6} \end{bmatrix} \begin{bmatrix} b_1 \\ b_2 \\ \dots \\ b_6 \end{bmatrix}$$

The robot-force transducer unit consists of a 6-dimensional force and torque transducer (ATI-Nano 25, ATI Industrial Automation, North Carolina) mounted onto the end-effector of a 5 degree of freedom robotic arm (KUKA Roboter gmbh, Augsburg, Germany) that is fixed to a table. The end of the robotic arm is positioned in 5 points within the reach space of the upper limb in a vertical plane by custom software (Microsoft Visual Studio Professional 2015, Redmond, Washington). Participants will apply force to the sensor via a comfortable gripper and will receive real-time feedback on the forces and torques exerted by the hand against the robot. Feedback will be mapped onto a space displayed on a flat monitor (refresh rate: 60 Hz) or VR head mounted display (Oculus Rift ConsumerVersion1, refresh rate: 90 Hz, Oculus, Menlo Park, California).

The force and torque signals will be remapped into the VR game using the principal component analysis matrix of the average set forces and torques generated against the robot from pre-existing data of healthy adults, such that if b is the vector of n=6 force and torque signals and A is the principal components matrix then x is the projection in the VR space as shown in Figure 1. In the simplest level of the game, only the first row of the principal components matrix (n=1) is projected into the game. Following levels increase in difficulty as rows of the matrix are incorporated in the mapping (n=2, 3, …, 6).

Participants will be allowed to rest as desired between efforts that will be at 30% ± 10% of the maximal voluntary contraction for each participant. The custom game (Unity, Unity Technologies SF, San Francisco, California) requires the participants to match remapped lower-dimensional force targets that are displayed as ships in a space exploration game. A total of 14 force and torque coordinates will need to be matched, 5 times, at the 5 robot positions, in spaces of reduced dimensions ranging from 1 to 6. The game increases in difficulty (number of matching dimensions) as the participant matches the targets successfully. Participants may choose to use a screen or VR headset to play the game according to their preference. VR sessions will be limited to 30 min for each session; the remainder of the hour will be used for setup purposes and administration of the maximum voluntary muscle contractions if surface electromyography (sEMG) will be used during the session. Muscle activity will be recorded with up to 16 wireless sEMG sensors (Trigno, Delsys, Massachusetts) that are placed bilaterally on the following muscles: middle deltoid, pectoralis major, anterior deltoid, latissimus dorsi, biceps brachii, triceps brachii lateralis, flexor carpi radialis, and extensor carpi radialis.

Participants will be able to stop participating at any time without consequence. If a child has a first seizure during the study, the inclusion and exclusion criteria will no longer be met, and participation in the study will be terminated. A procedural checklist will be followed during experiments.

Outcomes

All participants will be assessed for outcome measures at a site using sEMG sensors embedded with inertial measurement units (ATI-Nano 25, ATI Industrial Automation, North Carolina) and the robot-force transducer unit. All assessments and measurements are noninvasive and involve minimum risk to the participants. The accelerometry data will be used to assess smoothness of movement during the execution of a prescribed movement and measures muscle activation patterns during assessments involving the robot-force transducer unit used to measure force and torque outputs within the reachable space of the upper limbs of the participant. In addition, the robot is programmed to produce a path of zero resistance, within the reachable space, that provides haptic feedback perpendicular to the path. For assessing children with CP, we will collect clinical and quantitative measures of upper limb range of motion, motor function, dystonia, and spasticity. The outcome measures will be obtained before, after the intervention, and at 1-month follow-up (Textbox 2).

Assessments 1 to 4 are standard clinical questionnaires and tests. Assessment 5 is a quantitative test of spasticity based on sEMG recordings and angle velocity of a joint by manual manipulation.

Assessment 6 involves the robot, force sensor, and sEMG. A predetermined zero-force path has been programmed by the research team to allow the robot to move through straight lines connected to 5 points on a vertical plane. These positions coincide with the 5 positions of the training intervention, resting in a reachable rhombus-like configuration. The participants will attempt to find and move along a zero-force path. The force transducer will measure the forces exerted by the participant as they do so. This task will be limited to a 7-min period or until the task is complete.

Textbox 2. Measured outcomes. Measures for all participants (ie, listed from 6 to 10 will be done for all participants). The remaining articles are outcome measures for participants with cerebral palsy, that is, these will be specific to participants with cerebral palsy.

1. Dyskinesia Impairment Scale
2. Selective Control of the Upper Extremity Scale
3. Quality of Upper Extremity Skills Test
4. Tardieu Test
5. Montreal Spasticity Rating Test
6. Zero-Force Channel Assessment
7. Surface electromyography and accelerometry
8. Forces and torques against force sensor
9. World Health Organization Disability Assessment Schedule 2 Children and Youth
10. Qualitative Feedback Module

Assessment 7 will be used as necessary during assessments and on the first and last day of gameplay. Accelerometry and sEMG data will be collected during the execution of a first *port de bras*. The first *port de bras* will follow the format from the Royal Academy of Dance as demonstrated (Figure 2). Accelerometry data will be integrated to calculate the smoothness index on the velocity profile of the trajectories [25]. Data will be analyzed for changes in muscle activity patterns and smoothness of movement. The sEMG data will also be acquired for maximum voluntary efforts.

Assessment 8 measures force and torque inputs using the force and torque sensor that is mounted on the end-effector of the robot. A maximum voluntary effort will be made by the participant's dominant arm; the sensor will be mounted to a sturdy table for this task. The subject will be asked to push and pull along cardinal directions to determine the maximum force output that will be used to customize sensitivity subsequent efforts for each participant. Participants will also be assessed with the force sensor in 14 different directions at 30% ± 10% of the maximal force.

Assessment 9 is the World Health Organization Disability Assessment Schedule II-Children and Youth (WHODAS II-CY) that characterizes the children's level of disability. This measure will only be used for population demographic purposes.

Assessment 10 will be the qualitative feedback module, which will provide qualitative feedback on participants' experiences.

Participant Timeline

The full study timeline is approximated to take 20 weeks (Table 2). Possible schedules for participation will vary per participant; however, assessments will be within ± 1 week from the suggested dates for accommodations (Tables 3 and 4).

Sample Size

No previous sample data exist for this type of study that would enable sample size calculations. Data from a study on finger muscle control in children with dystonic CP with a mean difference effect size for within-subjects designs of dz=2.98, alpha=.05, and power=0.8 yields a required sample size of n=4 in each comparison group [26]. Given the wide age range and motor impairment characteristics in the eligibility criteria for this study, we propose a sample size of n=17 with a total number of 68 participants. We expect a 25% attrition rate that will approximately yield a total of 13 participants per group. We consider that this number is a conservative estimate for a randomized controlled trial in the pilot phase.

Recruitment

The participants will be neither students nor employees of the research team personnel. We intend to recruit participants from the Central Illinois community. Physicians involved in the experiment from the Children's Hospital of Illinois/OSF Saint Francis Medical Center will assist in referring participants and may distribute flyers with contact information regarding the study. In addition, participants will be recruited through posted flyers, advertisement in the Daily Illini, E-week, local newspapers, and laboratory websites. Once participants' parent or guardian receives information about the study, they will have the option to contact the principal investigator as indicated in the study information flyer. We are not accessing patient records for recruitment or Illinois schools. The final decision on inclusion will be made by the principal investigator in accordance to the inclusion and exclusion criteria of the experiment.

During the initial contact interview, research assistants will read a script describing the study and, if interested, parents or guardians will be provided with the participant medical form, to be completed by the parent or guardian and physician, and the consent form. A model consent form is provided in the Multimedia Appendix 1. Screening materials will be kept for participants that enroll in the study and destroyed for those that do not meet the criteria or decide not to enroll. A schematic diagram is included (Figure 3).

Figure 2. Royal Academy of Dance first port de bras. From left to right: en bas, first position, second position, and en bas. Participants will be asked to move through these positions during assessment 7 to measure muscle activity patterns and smoothness of movement.

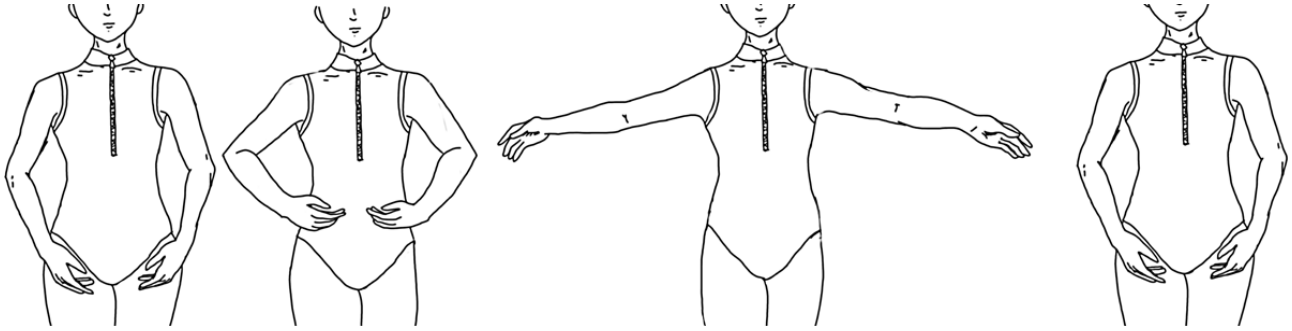

Table 2. Full study timeline. Experiment tasks are divided into weeks.

Time (weeks)	1	2	3	4	5	6	7	8	9 to 14	15 to 20
Recruitment and enrollment	✓[a]	✓	—[b]	—	—	—	—	—	—	—
Baseline assessments	✓	✓	—	—	—	—	—	—	—	—
Intervention period	—	✓	✓	—	—	—	—	—	—	—
Postassessments	—	✓	✓	—	—	—	—	—	—	—
1-month follow-up	—	—	—	—	—	✓	✓	—	—	—
Data processing	—	—	✓	✓	✓	✓	✓	✓	✓	—
Data analysis	—	—	✓	✓	✓	✓	✓	✓	✓	✓

[a]✓ corresponds to times when activity occurs.

[b]Empty cells indicate times when activity is not expected to occur.

Table 3. Possible schedule 1. Interventions in this schedule will take place over a period of 2 weeks with days between. Assessments will take place over 2 days. This schedule is subject to change based on the participants' availability.

Time (weeks)	1	2	3	4	5	6	7
Saturday	Assess	—[a]	Assess	—	—	—	Assess
Sunday	Assess	—	Assess	—	—	—	—
Monday	Game	Game	—	—	—	—	—
Tuesday	—	—	—	—	—	—	—
Wednesday	Game	Game	—	—	—	—	—
Thursday	—	—	—	—	—	—	—
Friday	Game	Game	—	—	—	Assess	—

[a]Empty cells indicate no activity.

Table 4. Possible schedule 2. Interventions in this schedule will have no days between sessions. Assessments will take place over 2 days. This schedule is subject to change based on the participants' availability.

Time (weeks)	1	2	3	4	5	6	7
Saturday	Assess	Game	—[a]	—	—	Assess	—
Sunday	Assess	Assess	—	—	—	Assess	—
Monday	Game	Assess	—	—	—	—	—
Tuesday	Game	—	—	—	—	—	—
Wednesday	Game	—	—	—	—	—	—
Thursday	Game	—	—	—	—	—	—
Friday	Game	—	—	—	—	—	—

[a]Empty cells indicate no activity.

Figure 3. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flow diagram of participants. CP: cerebral palsy; DIS: Dyskinesia Impairment Scale; MSRT: Montreal Spasticity Rating Test; PT: physical therapy; QUEST: Quality of Upper Extremity Skills Test; sEMG: surface electromyography; SCUES: Selective Control of the Upper Extremity Scale; WHODAS 2-CY:World Health Organization Disability Assessment Schedule II-Children and Youth.

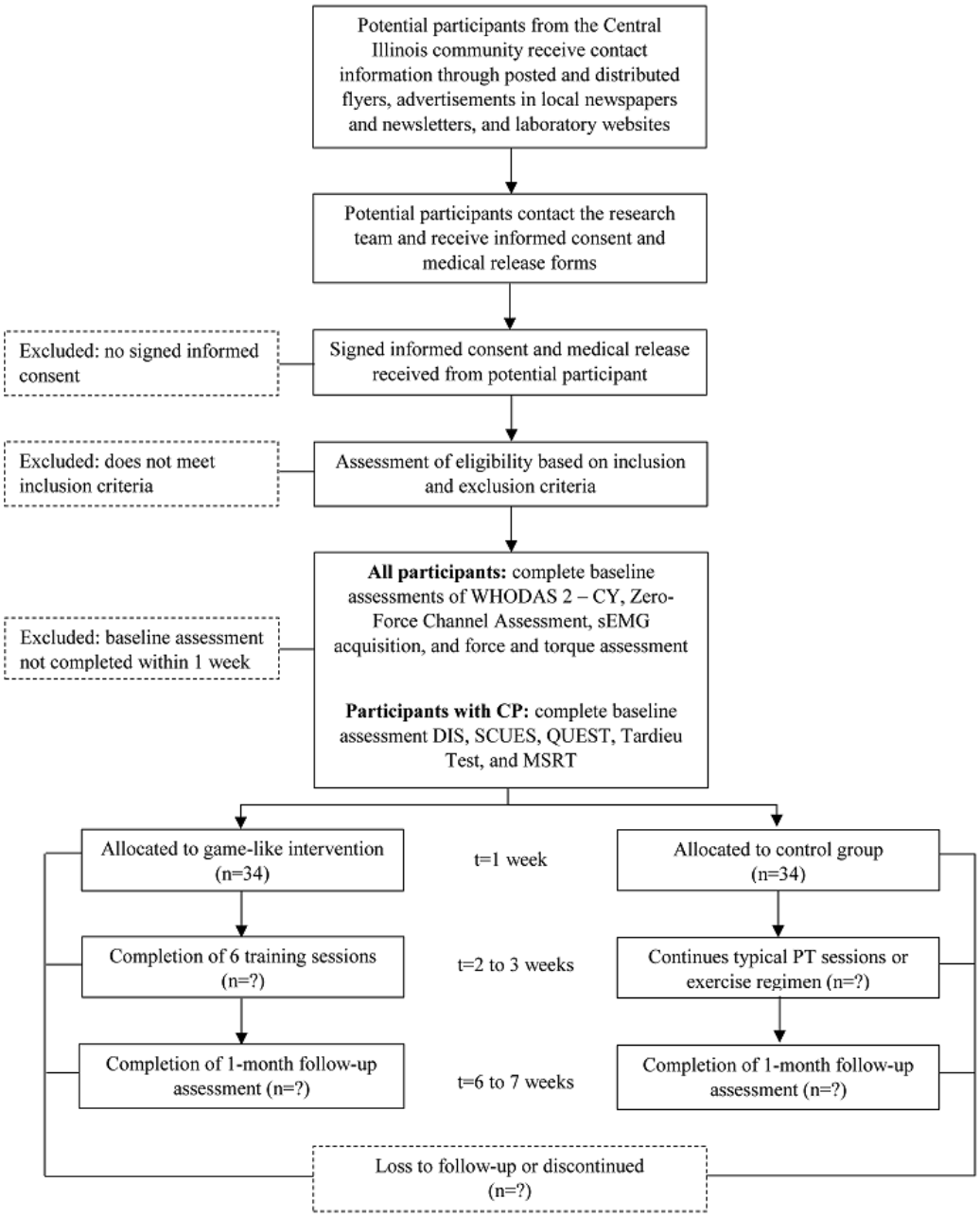

Table 5. Participant group allocation. All participants will be divided into intervention and control groups.

Participants	Intervention (n=34), n (%)	No intervention (control; n=34), n (%)	Total (N=68), n (%)
Children with cerebral palsy	17 (50)	17 (50)	34 (50)
Typically developing children	17 (50)	17 (50)	34 (50)

Allocation

After the initial contact interview, assessment of inclusion and exclusion criteria, and completion of the consent and assent forms, the participant will be allocated to a control or intervention group using a blocked randomization method (Table 5). The block sizes and randomized sequences will be hidden from those who enroll or allocate participants to prevent predictability of the next assignment. Allocation will be concealed by using sequentially numbered, opaque, sealed envelopes. Different members of the research team will allocate the sequence, enroll participants, and assign them to groups.

Blinding

Research team members administering clinical assessments will be blinded from participant allocation. Participant's allocation will not be revealed during the course of the study.

Data Collection Methods

All assessors are trained to conduct the assessments for children with and without CP. Outcome data will be collected at assessments.

The Dyskinesia Impairment Scale measures the severity of dystonia and choreoathetosis when an individual is at rest or conducting movement. It was found to show good to excellent reliability and validity [27]. It is also notable that in a 2012 systematic review of measures of dystonia and choreoathetosis, this scale is listed as the only clinical tool that examines choreoathetosis and dystonia in the same scale [28].

The Selective Control of the Upper Extremity Scale is a video-based tool to measure selective control of upper limb tasks. Psychometric analysis shows "comparable validity to other accepted video-based clinical assessment tools for the upper extremity in children with CP" with content validity ratio values indicating substantial agreement for most items [29].

The Quality of Upper Extremity Skills Test is 36 items in length and measures upper limb movement, hand function, and cooperativeness in children with CP. It has been found to be reliable to assess children with CP in the age range of 18 months and 8 years, with increased reliability in children aged up to 12 years [30]. It has also been found to show adequate to excellent validity [31,32].

The Tardieu scale examines spasticity with quantified measures of the responses to stretch reflexes of discrete velocity. This scale shows high test retest and poor to moderate inter-rater reliability; the Tardieu scale performs better than other similar measures, however, indicating it may be more reliable [33].

The Montreal Spasticity Rating Test is a quantitative measure of spasticity that identifies resistance to external forces of stretch tasks. This test identifies the point at which the stretch reflex is activated in a muscle. Documentation on the reliability and validity of this test is unavailable.

The WHODAS II-CY is a self-administered 36-item document that assesses daily issues surrounding health conditions such as illnesses, injuries, and problems with mental health. In a validity study, it was found to show good reliability; however, limitations regarding options for those without significant disabilities were present [34].

Plans to promote participant retention include payment at the end of, or separation from, the study.

Data Management

All data will be deidentified. Paper medical records will be brought by participants to the testing site or sent by US mail to the principal investigator's university address; they will be stored under double lock. All consent and assent forms will be completed at a testing site. Clinical test results performed during the experiment will be paper-recorded, and deidentified data will be inputted electronically for data analysis. Input of electronic records will be verified by 2 different members of the research team. Tests that record data electronically, such as sEMG, will be kept electronically. Data collected from source documents will be inputted into an encrypted and password-protected computer that is secured by the campus firewalls.

Paper records will be locked in a double-locked cabinet. All electronic data will be stored on password-protected computer that is secured by the campus firewalls. The computer designated for data collection and experimentation will not be connected to the internet for heightened security. All deidentified data will be submitted to an online repository as required for publication of randomized clinical trials.

Statistical Methods

The assessment and training protocols target improvements in selective motor control and amelioration of dystonia. We will conduct paired *t* tests on movement primary and secondary outcomes for the CP and TD groups independently. In case of non-normality, nonparametric techniques will be used. Differences before and after as well as before and follow-up will be obtained on the primary outcome measure: smoothness of movement. Tests on secondary outcomes are for exploratory purposes only. Bonferroni corrections will be applied as needed.

Missing values will be omitted from calculations or corrected for according to standard statistical techniques.

Monitoring

Data Monitoring

A data monitoring committee will not be needed as this will be a minimal risk trial.

Risks Related to the Intervention

Physical discomfort caused by the weight of the VR headset or simulation sickness may arise with extended VR use. Muscle soreness because of repetitive use of muscle groups may occur, and skin irritation from adhesives is possible. There is a risk of seizure using the VR headset estimated to be 1 in 4000 in the general population.

Safety Measures

To avoid simulation sickness, the programed VR images are slow, soothing, and were created following Oculus Best Practices Version 310-30000-02 as provided by Oculus VR, LLC. In addition, any health risks associated with VR headset use in children will be mitigated by referencing the Health and Safety Warnings provided by Oculus VR, LLC; children younger than 13 years will not be permitted to use the virtual headset. The participant has the option to play the game on a flat monitor or using a VR headset according to their preference. If simulation sickness arises, no medication will be administered as it is not a severe side effect of VR. Grounding exercises may be done if needed or the participant may decide to stop for the day or continue without the headset. Headset use will be limited to 30-min intervals.

Aside from maximum voluntary efforts, most efforts that participants produce will be 30% ± 10% of their maximum voluntary effort. The experiment will also be conducted in a seated position, reducing risk of injury because of falls, and ample care will be taken to ensure the participants' comfort as needed including provision of seat cushions. Trained research personnel will use gait belts, when needed, to transport participants from their wheelchair to the chair used for the experiment and back to their wheelchair as necessary. If their wheelchair allows for interaction with the robot, no transfer will take place. Surfaces that come in contact with participants are wiped down with hospital grade antiviral and antibacterial wipes before and after use.

Potential participants with a history of seizures will not be included in the study. Research personnel are trained to manage the rare event of a first seizure and follow the guidelines of the British Epilepsy Association: (1) remove objects nearby and cushion the head, (2) note the time when jerking starts, (3) place the person on one side of their body in recovery position after any jerking stops, and (4) stay with the person. In addition, (5) movement will not be restrained, (6) no objects will be put in the mouth, (7) the person will not be moved, and (8) no food or drink will be given until full recovery [35]. If the person is seated in a wheelchair, the brakes will be put on, and the person will be gently supported to prevent falling out of the chair if necessary. Research personnel will call for an ambulance, as it would be the person's first seizure. The experiment will be stopped, and the participants' guardian will be advised to seek immediate medical attention. The guardian will be asked to stay present during each session. If a seizure were to occur, the participant will not be allowed to continue with the study as the inclusion and exclusion criteria will no longer be met.

The robot (KUKA Roboter gmbh, Augsburg, Germany) is approved for human-robot collaborative mode and is assured to perform as instructed. A trained researcher will be next to the participant and robot at all times and will be prepared to unplug the robot if any unexpected movement of the robot occurs. The participant is not secured to the robot as well, which allows the participant to release the end effector if necessary. In addition, if a large force is applied to the robot, the uppermost link will turn off. The gripper mounted on the sensing surface of the force and torque transducer is rounded with no sharp edges.

Additional safeguards are included in the inclusion and exclusion criteria, in the consent and assent forms, and in the protocol design. In addition, the assent forms have extensive language describing the study and allow for the termination of participation by the participant at any time and for any reason.

We have tested the system extensively and do not expect any major changes or bugs. In case of any unexpected event, including situations of power failure in which testing has proven to cause no harm to the participant, the experiment will be stopped, and the research team will test the system to ensure functionality. Participants will be asked to return to the site on another day and will be reimbursed for the additional time.

Benefits

The participants may not receive any direct benefit beyond the satisfaction of participating in research, playing a VR game, and advancing the knowledge of motor control and coordination in humans. However, participants may notice improved control of movement of the upper limbs. The benefit to society rests on the advancement of our understanding of motor control and coordination in humans as well as improving diagnostic specificity in CP and providing a possible therapy modality. This information may be used to train future physicians.

Harms

All communications will be sent to both the Peoria and UIUC institutional review boards (IRBs).

Auditing

Auditing will be done as per the policies of the sponsor and the bodies that have sponsor oversight.

Ethics and Dissemination

Approval from the study sites institutional review boards will be sought. All protocol modifications will be communicated to both IRBs.

Potential participants and a parent or guardian will have the option to sign an assent and consent form, respectively, for participation in the study.

Identifiable elements including names, phone numbers, street addresses, city or state, zip code, email addresses, date of birth, grade level in school, and photos and videos (no close-up footage) will be collected. Screening materials will be kept for the participants that enroll in the study and destroyed for those that do not meet the criteria or decide not to enroll. Authorization for use and disclosure of the participants' personal health information for this specific study does not expire. The data will be kept for 5 years after publication, as required by

the American Psychological Association. Identifiers will be destroyed 5 years after the completion of the study.

Personal contact information will be used for the study team to contact participants during the study. Health information and results of tests and procedures are being collected as part of this research study for fulfillment of inclusion criteria and for the advancement of clinical care. By signing assent and consent forms, permission is given to the principal investigator and the research team to use the protected health information for the purposes of the study. Permission is also granted to the OSF Healthcare System and the University of Illinois College of Medicine at Peoria to disclose or release the participants' protected health information for this study.

If suspected abuse, neglect, or exploitation of a child or a disabled or elderly adult is disclosed, the researcher or members of the study staff will report the information to Child Protective Services, Adult Protective Services, or a law enforcement agency.

Images and videos will be stored without personal identifiers associated with the files apart from the image or video itself. If permission is given, these photos could be included in scholarly publications in print and electronic form, which will allow participants' faces to potentially be visible and recognizable by anyone reading the publications. Photos and videos may also be presented at meetings or conferences without any personal identifiers attached to the photos and videos other than the content itself. Data will be kept with coding and will only be viewable by lab personnel who are associated directly with the maintenance of data for this study.

Video footage with audio will be recorded at all sessions to ensure safety and adhesion to study protocols as well as to record the study. The footage is being taken to ensure the rights of participants and for the researchers alike. By signing the consent and assent forms, authorization is given for the principal investigator and research team to record the participant during participation of the study and to share the footage with the following items if emergencies arise or the research protocol is not properly followed:

- The IRBs
- The Office of Human Research Oversight
- Authorized members of the University of Illinois College of Medicine Peoria workforce
- Representatives of the university committee and office that reviews and approves research studies
- Office for Protection of Research Subjects
- Other representatives of the state and university responsible for ethical, regulatory, or financial oversight of research
- Federal government regulatory agencies such as the Office of Human Research Protections in the Department of Health and Human Services

Results

The trial has not started and is in queue for local IRB approval. We expect end results to be available by May 2019.

Discussion

Research Team

The members of the research team have diverse backgrounds: kinesiology, neuroscience, pediatric surgery, mechanical and electrical engineering, game design and development, and dance. This allows for a novel rehabilitation paradigm incorporating haptic feedback in VR targeting dystonia. In a routine application setting, similar levels of human involvement may be necessary to run the training sessions.

Limitations

A limitation of this study may be the limited intervention timeline. A total of 6 sessions may not be enough time for changes to occur; however, a similar study for the treatment of spasticity did demonstrate improvements in this timeline [23]. The small sample size and limited geographic area preclude absolute generalization of the results. Larger clinical trials would be necessary for generalization. In addition, as a characteristic of any rehabilitation intervention trials, participant blinding to the intervention or having a true placebo group is impossible.

Comparison With Prior Work

No prior work has been completed.

Conclusions

This study aims to examine movement outcomes of children with and without dystonic CP after a VR rehabilitation intervention using haptic feedback. We anticipate improvements in smoothness of movement after the intervention as well as in clinical movement tests.

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The study sponsor and funder are not involved in study design, data collection, management, analysis, interpretation of data, writing of the report, decision to submit for publication, nor will have ultimate authority over any of these. All activities will be completed by the principal investigator (CLO) and the research team (PC, RNM, NCS, and JJL).

Authors' Contributions

CLO is the principal investigator and grant holder. CLO and PC conceived of the study and study design. RNM and NCS assisted with implementation. CLO and RNM provided statistical expertise in clinical trial design. NCS and PC contributed to systems

integration, and RNM created the virtual reality game. All authors contributed to refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Model Consent Form.

[PDF File (Adobe PDF File), 226KB - resprot_v8i1e11470_app1.pdf]

References

1. Christensen D, Van Naarden Braun K, Doernberg NS, Maenner MJ, Arneson CL, Durkin MS, et al. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning - Autism and Developmental Disabilities Monitoring Network, USA, 2008. Dev Med Child Neurol 2014 Jan;56(1):59-65 [FREE Full text] [doi: 10.1111/dmcn.12268] [Medline: 24117446]
2. Paneth N. Establishing the diagnosis of cerebral palsy. Clin Obstet Gynecol 2008 Dec;51(4):742-748. [doi: 10.1097/GRF.0b013e318187081a] [Medline: 18981799]
3. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007 Feb;109:8-14. [Medline: 17370477]
4. Liptak GS. Health and well being of adults with cerebral palsy. Curr Opin Neurol 2008 Apr;21(2):136-142. [doi: 10.1097/WCO.0b013e3282f6a499] [Medline: 18317270]
5. Rice J, Skuza P, Baker F, Russo R, Fehlings D. Identification and measurement of dystonia in cerebral palsy. Dev Med Child Neurol 2017 Dec;59(12):1249-1255. [doi: 10.1111/dmcn.13502] [Medline: 28786476]
6. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin J, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers 2016 Jan 07;2:15082. [doi: 10.1038/nrdp.2015.82] [Medline: 27188686]
7. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW, Task Force on Childhood Motor Disorders. Classification and definition of disorders causing hypertonia in childhood. Pediatrics 2003 Jan;111(1):e89-e97. [Medline: 12509602]
8. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. Brain 2011 Jun;134(Pt 6):1591-1609 [FREE Full text] [doi: 10.1093/brain/awr039] [Medline: 21482550]
9. Sanger TD. Arm trajectories in dyskinetic cerebral palsy have increased random variability. J Child Neurol 2006 Jul;21(7):551-557. [doi: 10.1177/08830738060210070201] [Medline: 16970842]
10. Sukal-Moulton T, Clancy T, Zhang LQ, Gaebler-Spira D. Clinical application of a robotic ankle training program for cerebral palsy compared to the research laboratory application: does it translate to practice? Arch Phys Med Rehabil 2014 Aug;95(8):1433-1440 [FREE Full text] [doi: 10.1016/j.apmr.2014.04.010] [Medline: 24792141]
11. Beveridge B, Feltracco D, Struyf J, Strauss E, Dang S, Phelan S, et al. "You gotta try it all": parents' experiences with robotic gait training for their children with cerebral palsy. Phys Occup Ther Pediatr 2015;35(4):327-341. [doi: 10.3109/01942638.2014.990547] [Medline: 25529412]
12. Chen K, Ren Y, Gaebler-Spira D, Zhang LQ. Home-based tele-assisted robotic rehabilitation of joint impairments in children with cerebral palsy. Conf Proc IEEE Eng Med Biol Soc 2014;2014:5288-5291. [doi: 10.1109/EMBC.2014.6944819] [Medline: 25571187]
13. Krebs HI, Fasoli SE, Dipietro L, Fragala-Pinkham M, Hughes R, Stein J, et al. Motor learning characterizes habilitation of children with hemiplegic cerebral palsy. Neurorehabil Neural Repair 2012 Sep;26(7):855-860 [FREE Full text] [doi: 10.1177/1545968311433427] [Medline: 22331211]
14. Fasoli SE, Fragala-Pinkham M, Hughes R, Krebs HI, Hogan N, Stein J. Robotic therapy and botulinum toxin type A: a novel intervention approach for cerebral palsy. Am J Phys Med Rehabil 2008 Dec;87(12):1022-1025. [doi: 10.1097/PHM.0b013e31817fb346] [Medline: 18617860]
15. Sanger TD, Kaiser J, Placek B. Reaching movements in childhood dystonia contain signal-dependent noise. J Child Neurol 2005 Jun;20(6):489-496. [doi: 10.1177/088307380502000604] [Medline: 15996397]
16. Vidailhet M. Treatment of movement disorders in dystonia-choreoathtosis cerebral palsy. Handb Clin Neurol 2013;111:197-202. [doi: 10.1016/B978-0-444-52891-9.00019-1] [Medline: 23622164]
17. Olaya JE, Christian E, Ferman D, Luc Q, Krieger MD, Sanger TD, et al. Deep brain stimulation in children and young adults with secondary dystonia: the Children's Hospital Los Angeles experience. Neurosurg Focus 2013 Nov;35(5):E7. [doi: 10.3171/2013.8.FOCUS13300] [Medline: 24175867]
18. Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: experience and technical pearls. J Neurosurg Pediatr 2011 Dec;8(6):566-574. [doi: 10.3171/2011.8.PEDS11153] [Medline: 22132914]

19. Lin JP, Lumsden DE, Gimeno H, Kaminska M. The impact and prognosis for dystonia in childhood including dystonic cerebral palsy: a clinical and demographic tertiary cohort study. J Neurol Neurosurg Psychiatry 2014 Nov;85(11):1239-1244. [doi: 10.1136/jnnp-2013-307041] [Medline: 24591458]
20. Koy A, Pauls KA, Flossdorf P, Becker J, Schönau E, Maarouf M, et al. Young adults with dyskinetic cerebral palsy improve subjectively on pallidal stimulation, but not in formal dystonia, gait, speech and swallowing testing. Eur Neurol 2014;72(5-6):340-348. [doi: 10.1159/000360984] [Medline: 25322688]
21. Koy A, Hellmich M, Pauls KA, Marks W, Lin J, Fricke O, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. Mov Disord 2013 May;28(5):647-654. [doi: 10.1002/mds.25339] [Medline: 23408442]
22. López-Ortiz C, Gladden K, Deon L, Schmidt J, Girolami G, Gaebler-Spira D. Dance program for physical rehabilitation and participation in children with cerebral palsy. Arts Health 2012 Feb 01;4(1):39-54 [FREE Full text] [doi: 10.1080/17533015.2011.564193] [Medline: 25431617]
23. Lopez-Ortiz C, Simkowski J, Gomez W, Stoykov N, Gaebler-Spira D. Motor learning in children with cerebral palsy with feedback of principal component space of reduced dimension. In: Pons J, Torricelli D, Pajaro M, editors. Converging Clinical and Engineering Research on Neurorehabilitation. Heidelberg: Springer Berlin Heidelberg; 2013:311-315.
24. United States Censor Bureau. 2018. Annual estimates of the resident population by sex, age, race alone or in combination, and Hispanic origin for the United States and States: April 1, 2010 to July 1, 2017 URL: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2017_PEPASR5H&prodType=table [WebCite Cache ID 70cPLQgJf]
25. Balasubramanian S, Melendez-Calderon A, Roby-Brami A, Burdet E. On the analysis of movement smoothness. J Neuroeng Rehabil 2015 Dec 09;12:112 [FREE Full text] [doi: 10.1186/s12984-015-0090-9] [Medline: 26651329]
26. Young SJ, van Doornik J, Sanger TD. Finger muscle control in children with dystonia. Mov Disord 2011 Jun;26(7):1290-1296 [FREE Full text] [doi: 10.1002/mds.23534] [Medline: 21449015]
27. Monbaliu E, Ortibus E, De Cat J, Dan B, Heyrman L, Prinzie P, et al. The Dyskinesia Impairment Scale: a new instrument to measure dystonia and choreoathetosis in dyskinetic cerebral palsy. Dev Med Child Neurol 2012 Mar;54(3):278-283. [Medline: 22428172]
28. Stewart K, Harvey A, Johnston LM. A systematic review of scales to measure dystonia and choreoathetosis in children with dyskinetic cerebral palsy. Dev Med Child Neurol 2017 Aug;59(8):786-795. [doi: 10.1111/dmcn.13452] [Medline: 28485494]
29. Wagner LV, Davids JR, Hardin JW. Selective control of the Upper Extremity Scale: validation of a clinical assessment tool for children with hemiplegic cerebral palsy. Dev Med Child Neurol 2016 Jun;58(6):612-617 [FREE Full text] [doi: 10.1111/dmcn.12949] [Medline: 26526592]
30. Thorley M, Lannin N, Cusick A, Novak I, Boyd R. Reliability of the quality of upper extremity skills test for children with cerebral palsy aged 2 to 12 years. Phys Occup Ther Pediatr 2012 Feb;32(1):4-21. [doi: 10.3109/01942638.2011.602389] [Medline: 21838618]
31. Law M, Cadman D, Rosenbaum P, Walter S, Russell D, DeMatteo C. Neurodevelopmental therapy and upper-extremity inhibitive casting for children with cerebral palsy. Dev Med Child Neurol 1991 May;33(5):379-387. [Medline: 2065824]
32. Klingels K, De Cock P, Desloovere K, Huenaerts C, Molenaers G, Van Nuland I, et al. Comparison of the Melbourne Assessment of Unilateral Upper Limb Function and the quality of Upper Extremity Skills Test in hemiplegic CP. Dev Med Child Neurol 2008 Dec;50(12):904-909 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03123.x] [Medline: 18811701]
33. Mehrholz J, Wagner K, Meissner D, Grundmann K, Zange C, Koch R, et al. Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. Clin Rehabil 2005 Oct;19(7):751-759. [doi: 10.1191/0269215505cr889oa] [Medline: 16250194]
34. Wolf AC, Tate RL, Lannin NA, Middleton J, Lane-Brown A, Cameron ID. The World Health Organization Disability Assessment Scale, WHODAS II: reliability and validity in the measurement of activity and participation in a spinal cord injury population. J Rehabil Med 2012 Sep;44(9):747-755 [FREE Full text] [doi: 10.2340/16501977-1016] [Medline: 22854805]
35. Epilepsy Action. What to do when someone has a seizure URL: https://www.epilepsy.org.uk/info/firstaid/what-to-do [accessed 2018-07-02] [WebCite Cache ID 70cQeVFfn]

Abbreviations

CP: cerebral palsy
IRB: institutional review board
PT: physical therapy
sEMG: surface electromyography
TD: typically developing
UIUC: University of Illinois at Urbana-Champaign
VR: virtual reality
WHODAS II-CY: World Health Organization Disability Assessment Schedule II-Children and Youth

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Protocol

TheraSphere Yttrium-90 Glass Microspheres Combined With Chemotherapy Versus Chemotherapy Alone in Second-Line Treatment of Patients With Metastatic Colorectal Carcinoma of the Liver: Protocol for the EPOCH Phase 3 Randomized Clinical Trial

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Abstract

Background: Colorectal cancer is one of the most common cancers and causes of cancer-related death. Up to approximately 70% of patients with metastatic colorectal cancer (mCRC) have metastases to the liver at initial diagnosis. Second-line systemic treatment in mCRC can prolong survival after development of disease progression during or after first-line treatment and in those who are intolerant to first-line treatment.

Objective: The objective of this study is to evaluate the efficacy and safety of transarterial radioembolization (TARE) with TheraSphere yttrium-90 (^{90}Y) glass microspheres combined with second-line therapy in patients with mCRC of the liver who had disease progression during or after first-line chemotherapy.

Methods: EPOCH is an open-label, prospective, multicenter, randomized, phase 3 trial being conducted at up to 100 sites in the United States, Canada, Europe, and Asia. Eligible patients have mCRC of the liver and disease progression after first-line chemotherapy with either an oxaliplatin-based or irinotecan-based regimen and are eligible for second-line chemotherapy with the alternate regimen. Patients were randomized 1:1 to the TARE group (chemotherapy with TARE in place of the second chemotherapy infusion and subsequent resumption of chemotherapy) or the control group (chemotherapy alone). The addition of targeted agents is permitted. The primary end points are progression-free survival and hepatic progression-free survival. The study objective will be considered achieved if at least one primary end point is statistically significant. Secondary end points are overall survival, time to symptomatic progression defined as Eastern Cooperative Oncology Group Performance Status score of 2 or higher, objective response rate, disease control rate, quality-of-life assessment by the Functional Assessment of Cancer Therapy-Colorectal Cancer questionnaire, and adverse events. The study is an adaptive trial, comprising a group sequential design with 2 interim analyses with a planned maximum of 420 patients. The study is designed to detect a 2.5-month increase in median progression-free survival, from 6 months in the control group to 8.5 months in the TARE group (hazard ratio [HR] 0.71), and a 3.5-month increase in median hepatic progression-free survival time, from 6.5 months in the control group to 10 months in the TARE group (HR 0.65). On the basis of simulations, the power to detect the target difference in either progression-free survival or hepatic progression-free survival is >90%, and the power to detect the target difference in each end point alone is >80%.

Results: Patient enrollment ended in October 2018. The first interim analysis in June 2018 resulted in continuation of the study without any changes.

Conclusions: The EPOCH study may contribute toward the establishment of the role of combination therapy with TARE and oxaliplatin- or irinotecan-based chemotherapy in the second-line treatment of mCRC of the liver.

Trial Registration: ClinicalTrials.gov NCT01483027; https://clinicaltrials.gov/ct2/show/NCT01483027 (Archived by WebCite at http://www.webcitation.org/734A6PAYW)

International Registered Report Identifier (IRRID): RR1-10.2196/11545

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KEYWORDS

colorectal neoplasms; neoplasm metastasis; microspheres; yttrium radioisotopes; research design; clinical trial, phase III; randomized controlled trial; metastatic colorectal cancer; mCRC

Introduction

Colorectal cancer is the third most common newly diagnosed cancer and the fourth most common cause of cancer death globally [1]. Metastatic disease is observed at first diagnosis in an estimated 25% of new patients (synchronous distant metastasis) [2] and eventually develops in a further estimated 60% of patients (metachronous metastasis) [2-4]. The prognosis for metastatic colorectal cancer (mCRC) remains poor, with a 5-year survival rate around 14% [5]; the 5-year relative survival is worse for patients with metachronous metastasis than for those with synchronous metastasis (17.6% vs 7.2%) [6]. The liver is the most common site of metastasis because the blood that drains from the bowel and colon goes through the portal vein, and the circulating tumor cells are deposited in the liver [7,8]. Up to approximately 70% of metastatic patients present with mCRC to the liver at the initial diagnosis [7].

Although the outcome for patients with mCRC has improved with the rapid progress in diagnostic techniques and treatments, for most patients with mCRC, treatment is palliative rather than curative because the majority of patients are not candidates for surgical resection [9]. In mCRC patients for whom cure is not possible, potential goals of treatment are to prolong progression-free intervals, prolong life, improve quality of life, palliate symptoms, shrink tumor size, and protect the normal liver parenchyma. Patients with mCRC to the liver can achieve a median overall survival of approximately 30 months [10,11].

Most patients with mCRC receive systemic chemotherapy with or without targeted biological agents. First- and second-line systemic therapies typically include a fluoropyrimidine combined with either irinotecan (FOLFIRI regimen) or oxaliplatin (FOLFOX regimen). Biologically targeted agents include vascular endothelial growth factor inhibitors and epidermal growth factor receptor inhibitors [12]. Liver-directed therapies, that is, transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), are well established in the armamentarium for treatment of metastatic disease, mostly in the salvage setting. The delivery of chemotherapy or radioactive-labeled yttrium-90 (^{90}Y) microspheres via the hepatic arteries is selective to liver tumors because liver tumors are mostly perfused via the hepatic arteries, whereas normal hepatic parenchyma receives blood from the portal venous system [13].

Most mCRC patients who receive standard first-line treatment with combination regimens and treatment with targeted biological agents eventually develop either intolerance, recurrence, or progression and require second-line treatment. TARE is a treatment option that could be considered for patients with unresectable colorectal cancer and liver-dominant metastases who are refractory to chemotherapy. In such patients, prospective and retrospective studies have demonstrated that TARE is feasible and may compare favorably with standard-of-care treatment [14-16]. A rationale for the combination of TARE and systemic therapy is that liver-directed treatment with TARE will better control liver disease and

systemic therapy will control extrahepatic progression and micrometastatic disease.

Here, we report the design of the EPOCH study: A Phase 3 Randomized Clinical Trial Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver Who Have Failed First-line Chemotherapy (trial registration: clinicaltrials.gov NCT01483027). The EPOCH study is being conducted to evaluate progression-free survival and hepatic progression-free survival in patients with mCRC when TheraSphere is added to second-line standard-of-care chemotherapy. In the second-line mCRC treatment setting, the EPOCH study is expected to be the largest study of the comparison of locoregional therapy with TARE in combination with standard-of-care systemic therapy versus standard-of-care systemic therapy alone.

Methods

Overview of Design

The study is being conducted in accordance with the Declaration of Helsinki. Participating institutions obtained institutional review board approval of the protocol and informed consent form and are responsible for obtaining written informed consent from patients at screening (Multimedia Appendix 1).

EPOCH is an ongoing, open-label, prospective, multicenter, randomized, phase 3 clinical trial. The objective is to evaluate the efficacy and safety of TARE with TheraSphere in patients with mCRC of the liver who have disease progression on first-line chemotherapy with either an oxaliplatin-based regimen or an irinotecan-based regimen and who are eligible for second-line chemotherapy with the alternate regimen. All patients receive chemotherapy; however, in the TARE group, TheraSphere is administered in place of the second cycle of chemotherapy, with chemotherapy subsequently resuming. A maximum of 420 patients are planned to be randomized at up to 100 sites in the United States, Canada, Europe, and Asia. The 2 primary end points are progression-free survival and hepatic progression-free survival. The study objective will be considered achieved if at least one primary end point is statistically significant. All patients are to be followed prospectively from randomization to death until the predefined number of progression-free survival events, to allow the final analysis to be conducted, have occurred.

The study commenced enrollment with a single primary end point of progression-free survival, with hepatic progression-free survival as a secondary end point. Progression-free survival is a valid surrogate end point for overall survival for mCRC patients receiving first- and second-line systemic chemotherapy with or without the inclusion of systemic targeted therapies [17,18]. The expected benefit for patients receiving a liver-directed therapy is an increased duration of liver disease control. Accordingly, the efficacy of a liver-directed treatment can be evaluated and measured by hepatic progression-free survival. A survival benefit of liver-directed treatment could occur via improvement of hepatic progression-free survival. Other liver-directed therapies, such as intra-arterial chemotherapy infusion, radiofrequency ablation, or TACE with drug-eluting beads, have demonstrated improvement of overall survival through improved control of hepatic disease [19,20]; thus, the efficacy of a liver-directed treatment may be evaluated and measured by hepatic progression-free survival [21]. To demonstrate the clinical benefit of TARE in mCRC patients with liver metastases, hepatic progression-free survival was subsequently included as a second primary end point. Progression-free survival and hepatic progression-free survival will evaluate the 2 major determinants of progression (extrahepatic factors and intrahepatic factors).

Trained clinical research associates performed a site initiation visit with investigators and their teams before the start of patient screening. Patient medical records are reviewed in a timely manner to confirm eligibility and compliance with the study protocol. Data entries on the electronic case report forms are reviewed by the clinical research associate and compared with the medical records and study protocol on an ongoing basis. An independent data monitoring committee (IDMC) was established to oversee the conduct of the study. The IDMC met periodically to review enrollment, protocol deviations, and safety events. In addition, the IDMC conducted and reviewed an initial feasibility safety analysis and will evaluate the progression-free survival data at interim analyses for consideration of stopping the study early for efficacy. The IDMC was tasked to make formal recommendations to the study sponsor based on decision rules in the IDMC charter.

Screening and Eligibility

Screening and baseline evaluations occur from day −14 to day 0, where day 0 is the day of randomization. Demographics, medical history, medications, prior treatment history, and Eastern Cooperative Oncology Group (ECOG) Performance Status score were documented. Patients undergo physical examination and have baseline clinical laboratory tests including blood chemistry, hematology, coagulation tests, and colorectal cancer tumor marker (serum carcinoembryonic antigen). Kirsten retrovirus-associated DNA sequence (KRAS) oncogene status is determined if it is not already known. Serum pregnancy tests were conducted for women of childbearing potential. Patients must have baseline images for disease evaluation (spiral computerized tomography [CT] or magnetic resonance imaging [MRI] of the abdomen, pelvis, and chest) taken within 28 days before day 0 (randomization) when first-line chemotherapy is completed or after, and images must show measurable target tumors in the liver according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [22]. Tumor burden was estimated from CT scans (visual or volumetric assessment). Inclusion and exclusion criteria are shown in Textbox 1.

Eligible patients must discontinue first-line chemotherapy and biologic agents during screening for a washout period of at least 14 days. The intended second-line chemotherapy regimen, including any biological agents, and dosages are decided. Patients complete the Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C) quality-of-life questionnaire during the screening period.

Textbox 1. Inclusion and exclusion criteria for the EPOCH study.

Inclusion criteria

- Age at least 18 years.
- Colorectal cancer with unresectable metastatic unilobar or bilobar liver disease and disease progression in the liver with either (1) oxaliplatin-based or (2) irinotecan-based first-line chemotherapy; patient must be eligible to receive second-line standard-of-care chemotherapy with the alternate regimen. The determination of unresectable was based on local consideration, provided that the treatment decision was made by a multidisciplinary team that included a surgeon.
- Primary tumor either resected or clinically stable.
- Baseline images with measurable target tumors in the liver according to Response Evaluation Criteria in Solid Tumors version 1.1 using standard imaging techniques taken within 28 days before randomization. Images must be taken at completion of first-line chemotherapy or after.
- Tumor replacement less than 50% of total liver volume.
- Eastern Cooperative Oncology Group Performance Status score of 0 to 1 from screening to first treatment on study.
- Laboratory parameters: serum creatinine up to 2.0 mg/dL, serum bilirubin up to 1.2× upper limit of normal, albumin at least 3.0 g/dL, and neutrophil count more than 1200/mm^3 (1.2×10^9/L).

Exclusion criteria

- Prior external beam radiation treatment to the liver and prior intra-arterial liver-directed therapy (including transarterial chemoembolization or TheraSphere yttrium-90 microspheres therapy).
- Planned nonstudy liver-directed therapy or radiation therapy. Planned treatment with biological agents within 28 days before receiving TheraSphere.
- Confirmed extrahepatic metastases. Limited, indeterminate extrahepatic lesions in the lung and/or lymph nodes are permitted (up to 5 lesions in the lung, with each individual lesion smaller than 1 cm; any number of lymph nodes with each individual node smaller than 1.5 cm).
- History of hepatic encephalopathy; history of severe peripheral allergy or intolerance to contrast agents, narcotics, sedatives, or atropine that cannot be managed medically.
- Contraindications to angiography and selective visceral catheterization, such as bleeding diathesis or coagulopathy that is not correctable by usual therapy with hemostatic agents; contraindications to the planned second-line chemotherapy regimen.
- Pulmonary insufficiency or clinically evident chronic obstructive pulmonary disease.
- Cirrhosis or portal hypertension.
- Receipt of intervention for the Ampulla of Vater or compromise thereof.
- Clinically evident ascites aside from trace ascites on imaging.
- Unresolved toxicities related to cancer therapy that the investigator determines will continue and compromise patient safety.
- Significant life-threatening extrahepatic disease, for example, unresolved diarrhea or serious unresolved infections, such as human immunodeficiency virus, acute hepatitis B virus, or hepatitis C virus.

Randomization and Stratification

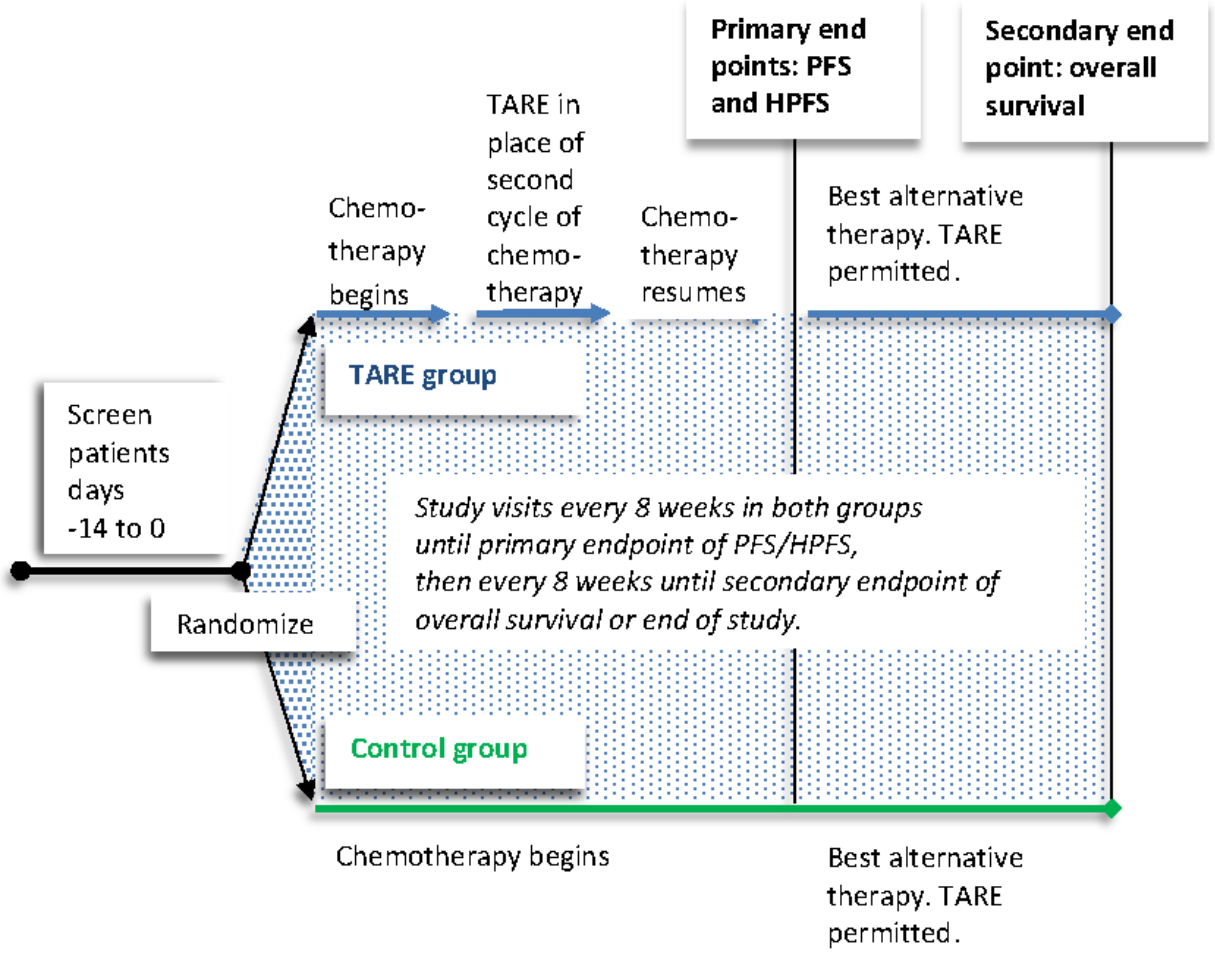
Eligible patients are randomized on day 0 in a 1:1 ratio to either the control group or the TARE group. If the study is not stopped early for efficacy, approximately 210 patients will be randomized to each group. To randomize eligible patients, the study site contacts the central randomization office where randomization will be determined using assignment by a computer-generated randomization scheme. Upon randomization, each patient is assigned an identity code. To ensure that treatment groups are balanced, patients are stratified at randomization based on the extent of liver involvement (unilobar vs bilobar disease), type of first-line chemotherapy (oxaliplatin-based vs irinotecan-based), and KRAS status (wild type vs mutant). Additional factors permitting covariate analysis are captured at randomization but are not stratification criteria. These factors have been defined based on the planned covariate analyses. Patients randomized to either the control or the TARE group who are unable to receive their planned study treatment continue to be followed under their assigned study group for the purpose of the intent-to-treat analysis.

Chemotherapy

The treatment schema is shown in Figure 1.

For both groups, second-line chemotherapy started within 21 days of randomization. If during the first-line chemotherapy, patients had received an oxaliplatin-based regimen, then during the EPOCH study, they receive a standard-of-care irinotecan-based chemotherapy. Those who received an irinotecan-based regimen as first-line therapy receive a standard-of-care oxaliplatin-based regimen in this study. Generally, second-line chemotherapy is given every 2 weeks for 6 to 12 cycles; chemotherapy is continued at the investigator's discretion.

Figure 1. Clinical trial schema for the TheraSphere microspheres EPOCH study. Eligible patients have a washout period of at least 14 days from previous chemotherapy and biologic agents. Second-line chemotherapy is started within 21 days of randomization. Control group: biologic agents are permitted starting at the first cycle of second-line chemotherapy. TARE group: biological agents are discontinued at least 28 days before TARE and are not permitted until the first cycle of second-line chemotherapy that occurs after TARE. HPFS: hepatic progression-free survival; PFS: progression-free survival; TARE: transarterial radioembolization with TheraSpheres™ microspheres.



Control group patients can receive biological agents starting with the first cycle of second-line chemotherapy. For the TARE group, one cycle of chemotherapy is administered before the TheraSphere treatment, and biological agents may only be added to the first cycle of chemotherapy regimen that occurs after the TheraSphere administration.

Transarterial Radioembolization

In the TARE group, TheraSphere microspheres are administered in place of the second cycle of chemotherapy. The treatment approach for TheraSphere can be lobar or selective. Patients with unilobar disease receive TARE to the diseased lobe. Patients with bilobar disease receive treatment to both lobes via successive lobar infusions during the same treatment session. Biological agents must be discontinued for at least 28 days before TARE. Chemotherapy resumes 2 weeks after TARE, at which time treatment with biologic agents may be started.

Eligibility for TARE with TheraSphere microspheres is determined by evaluations that include a pretreatment angiography with technetium-99m macroaggregated albumin (^{99m}Tc-MAA), followed by a ^{99m}Tc-MAA single-photon emission computed tomography (SPECT) or SPECT-CT scan to assess the potential for shunting microspheres to the lungs as well as the potential for the deposition of microspheres to the gastrointestinal tract. Repeat ^{99m}Tc-MAA may be needed for subsequent treatments to estimate cumulative lung shunt or to reassess gastrointestinal shunting. Patients are ineligible for TARE if radiation exposure to the lungs exceeds 30 Gy (or 50 Gy cumulative across all planned infusions, estimated during the dose calculation) or embolization cannot be performed to effectively block gastrointestinal blood flow from the hepatic arterial system. Randomized patients deemed ineligible for TARE continue with the planned second-line chemotherapy.

Radioembolization can be performed via a segmental or lobar approach, depending on operator preference and angiographic anatomy. The targeted administered dose is 120±10% Gy to the target volume, based on a single-compartment Medical Internal Radiation Dose model [23].

TheraSphere should be administered by appropriately trained or designated personnel from the departments of radiology, nuclear medicine, and/or interventional radiology. Before the activation of trial sites with the appropriate approvals to administer TheraSphere, the health care professionals directly involved in the planning and administration of TheraSphere are required to attend a center of excellence training in which expert

speakers lecture on topics related to patient selection and TheraSphere dosimetry and administration. Investigational teams must then accomplish at least three (or five) patient treatment cases with TheraSphere. The minimum number of cases is determined by a trained team of study sponsor proctors who review the treatment planning and perform on-site review of treatment administration. Upon completion of the training program, investigators are trained on the study protocol.

Treatment for Disease Progression

After disease progression is observed and confirmed, patients in either group may receive the best alternative therapy or care that the investigator considers appropriate. Patients in the TARE group who have hepatic progression with hepatic lesions that are still amenable to TheraSphere are eligible for repeat treatment with TheraSphere. In these patients, TheraSphere may be administered at the investigator's discretion on separate treatment days. Although this is not a cross-over study, patients in the control group who have hepatic progression with hepatic lesions that are amenable to liver-directed therapy can receive TheraSphere or any other liver-directed therapies according to the investigator's decision. As with the initial administration of TheraSphere, biological agents must be discontinued for at least 28 days before any additional TheraSphere administration.

Follow-Up Evaluations

The schedule of postrandomization evaluations is shown in Table 1.

Efficacy assessment scans are taken according to standard-of-care clinical management guidelines every 8 weeks (±1 week) after randomization until either death, withdrawal from study follow-up, or end of the study. The imaging modality used at baseline must be used throughout the study. Image assessment must follow study imaging guidelines. Tumor response is evaluated locally according to RECIST version 1.1. In case of progression, a confirmatory scan is requested. If the first progression occurs outside the liver, efforts must be made to continue the scheduled follow-up until hepatic progression occurs; no confirmatory scan is requested. Imaging performed for disease assessment must be submitted to the sponsor or designate for centralized review. Adverse events, serious adverse events, and unanticipated adverse device effects, as defined by the study protocol, will be collected throughout the study.

Independent review of the CT and MRI images is performed by a central imaging review organization. Central image review interpretation (independent reads by 2 radiologists with adjudication, if required, by a third radiologist) is performed in a blinded fashion on the full set of patient images and captured on an electronic case report form. The results of the primary study end points will be based on the central image review findings.

Efficacy End Points and Definitions

The primary efficacy end points of the EPOCH study are progression-free survival and hepatic progression-free survival. The secondary efficacy end points are overall survival, time to symptomatic progression, objective response rate, disease control rate, quality of life assessment by FACT-C questionnaire, and adverse events. Definitions of these outcomes are as follows:

1. Progression-free survival is the time from the randomization date to the date of radiological progression or death from any cause, whichever occurs first. Radiological progression is determined by blinded central image review according to RECIST version 1.1.
2. Hepatic progression-free survival is the time from randomization to the date of radiological progression in the liver or death from any cause, whichever occurs first. Radiological progression is determined by blinded central image review according to RECIST version 1.1.
3. Overall survival is the time from the randomization date to death from any cause.
4. Time to symptomatic progression is the time from randomization to ECOG Performance Status score greater than 2 points. Such deterioration in performance score is to be confirmed at one subsequent evaluation at least 8 weeks later.
5. Objective response rate is the proportion of patients achieving a best tumor response of either complete response or partial response during the study, as assessed by blinded central image review according to RECIST version 1.1.
6. Disease control rate is the proportion of patients achieving a best tumor response of either complete response, partial response, or stable disease during the study, as assessed by blinded central image review according to RECIST version 1.1.
7. Quality-of-life assessment is based on the patient-reported FACT-C questionnaire. Deterioration in quality of life is a decline of at least seven points in the total FACT-C score or death, whichever occurs first. The time to deterioration in quality of life is calculated as the time from randomization to deterioration in quality of life.

TARE can cause tumor inflammation (edema) early after treatment; therefore, any tumor assessments performed within six weeks of randomization will not be included in the analysis of imaging-related efficacy end points to rule out the risk of false progression.

Table 1. Schedule of events after randomization on day 0.

Interventions and assessments	Chemotherapy	First TARE[a] workup and administration in TARE group	Study visits to progression	Additional TARE workup and administration[b]	Study visits until death or end of study
Description	Every 2 weeks	Replaces second cycle of chemotherapy	Every 8 weeks from day 0 (±1 week)	After hepatic progression, TARE replaces a cycle of chemotherapy	Every 8 weeks (±1 week)
Interventions					
Hepatic angiogram,[99m]Tc-MAA[c] scan,[d] calculate liver volume and mass,[d] calculate TheraSphere dose,[d] order and administer TheraSphere	—[e]	✓	—	✓	—
Administer second-line chemotherapy	✓	—	—	—	—
Assessments					
ECOG[f] Performance Status	✓[g]	✓	✓	✓	✓[g]
Hematology[h], chemistry panel, liver function tests	✓	—	✓	✓	—
Coagulation tests[i]	✓[j]	—	—	✓	—
Serum pregnancy[k]	—	✓	—	✓	—
Tumor markers for colorectal cancer (serum carcinoembryonic antigen)	—	—	✓	—	—
Record and administer any chemotherapy following second-line chemotherapy[l]	—	—	—	—	✓
Quality-of-life questionnaire	—	—	✓	—	✓[g]
Spiral CT[m] or MRI[n] of the abdomen, pelvis, or chest[o]	—	—	✓	✓	—
Assess and report adverse events	✓	✓	✓	✓	✓
Review and record concurrent medication	✓	✓	✓	✓	✓
Final end point, efficacy and safety documentation, and exit patient	—	—	—	—	✓

[a]TARE: transarterial radioembolization.

[b]In lesions amenable to further TARE.

[c][99m]Tc-MAA: technetium-99m macroaggregated albumin.

[d]Before TARE administration.

[e]Assessment or intervention was not conducted at that time.

[f]ECOG: Eastern Cooperative Oncology Group.

[g]Can be done remotely if patient is not coming in for clinic visit.

[h]Hematology tests: white blood cells with differential, hemoglobin, hematocrit, and platelets.

[i]Coagulation tests: prothrombin time, partial thromboplastin time, and international normalized ratio.

[j]Only required at chemotherapy visits as clinically indicated, that is, if patient is being followed for coagulopathy.

[k]Required for female patients of childbearing potential.

[l]All randomized patients must receive chemotherapy within 21 days of randomization.

[m]CT: computed tomography.

[n]MRI: magnetic resonance imaging.

[o]All attempts should be made to obtain imaging every 8 weeks until hepatic progression, plus confirmatory scan.

The following additional efficacy variables will be assessed:

- Progression-free survival and hepatic progression-free survival by investigator assessment, with progression determined by the investigator according to RECIST version 1.1.
- Objective response rate, determined by the investigator, defined as the proportion of randomized patients achieving a best overall response of complete response or partial response, as defined by RECIST version 1.1.
- Duration of objective response will be determined for patients who had a best response of complete response or partial response. Duration of objective response is defined as the time from the first date of complete response or partial response to date of progression or death from any cause, whichever occurs first. Duration of response will be assessed separately for response determined by blinded central image review and by investigator assessment.
- Disease control rate, as determined by the investigator, defined as the proportion of randomized patients achieving a best overall response of complete response, partial response, or stable disease as defined by RECIST version 1.1.
- Duration of disease control will be determined for patients who had a best response of complete response, partial response, or stable disease. Duration of disease control is defined as the time from the first date of complete response, partial response, or stable disease until the date of progression or death from any cause, whichever occurred first. Duration of disease control will be assessed separately for response determined by blinded central image review and by investigator assessment.
- Depth of response, defined as the percentage change from baseline to the nadir in the sum of the longest diameters of target lesions.
- Posttreatment tumor shrinkage, defined as the proportion of patients achieving a decrease of at least 20% in the sum of the longest diameters of target lesions.
- Change from baseline in tumor marker for colorectal cancer (carcinoembryonic antigen).

Planned Statistical Analysis

Sample Size Estimate

The study is a phase 3 adaptive trial, comprising a group sequential design with 2 interim analyses. The study could be stopped early for efficacy at an interim analysis based on superiority in progression-free survival but not hepatic progression-free survival.

The study is designed to detect a 2.5-month increase in median progression-free survival, from 6 months in the control group to 8.5 months in the TARE group (hazard ratio [HR] 0.71), and a 3.5-month increase in median hepatic progression-free survival time, from 6.5 months in the control group to 10 months in the TARE group (HR 0.65). On the basis of simulations, the power to detect the target difference in either progression-free survival or hepatic progression-free survival is >90%, and the power to detect the target difference in each end point alone is >80%, using log-rank tests.

The analysis of progression-free survival will be based on a group sequential design with 2 interim analyses at 50% and 70% of the required total number of 344 progression-free survival events with a stopping boundary defined by the rho family error spending function with $\rho=1.5$ [24]. It is estimated that a maximum of 420 patients will need to be recruited over 36 months, with a 1-year additional follow-up period, allowing for 10% of patients lost to follow-up and for whom a date of progression or death is not recorded. Although the forecasted accrual period has been increased to 60 months, this does not increase the number of patients required or affect the statistical power of the study because both the power and the timing of the interim and final analyses are based on the number of progression-free survival events rather than the number of patients. The Hochberg procedure will be used to control type 1 error for the 2 primary end points at the final analysis [25].

A simulation study, assuming that progression-free survival and hepatic progression-free survival have a correlation between 0.3 and 0.8, showed that the power to detect the target difference in either median progression-free survival (ie, HR 0.71) or median hepatic progression-free survival (ie, HR 0.65) is >90%, and the power to detect the target difference in progression-free survival or hepatic progression-free survival alone is >80%. The simulation study also demonstrated control of type 1 error at the nominal one-sided level of 0.025.

Populations

The intent-to-treat population will comprise all randomized patients. The per-protocol population will be analyzed according to the treatment actually received, excluding patients with major protocol deviations that may affect the efficacy evaluation. The safety analysis population will comprise all randomized patients who received study treatments at least once.

Primary Efficacy End Points

Analysis of Primary End Points

Progression-free survival and hepatic progression-free survival will be compared between the control and TARE groups using log-rank tests. The HR and 2-sided 95% CI will be computed. Kaplan-Meier curves will also be produced.

Interim Analyses of Primary End Point of Progression-Free Survival

The first interim analysis is planned at 172 progression-free survival events. Progression-free survival will be compared between treatment groups using a log-rank test converted to a z-score and compared with the nominal critical value of 2.372 based on the rho family error spending function corresponding to a one-sided $P \leq .0088$, allowing the study to be stopped early for efficacy, in which case hepatic progression-free survival will be tested at the same boundary as progression-free survival using a log-rank test converted to a z-score.

A second interim analysis is planned at 241 progression-free survival events, where progression-free survival will be compared between treatment groups using a log-rank test converted to a z-score and compared with the nominal critical value of 2.330 based on the rho family error spending function corresponding to a one-sided $P \leq .0099$, allowing the study to

be stopped early for efficacy. If the study is stopped early for progression-free survival at the second interim analysis, hepatic progression-free survival will be tested using the boundary derived based on an incremental alpha of .0057. This boundary will account for the correlation between the z-score for progression-free survival at the first interim analysis and the z-score for hepatic progression-free survival at the second interim analysis, which is determined by the observed number of hepatic progression-free survival events at the first interim analysis and the cumulative number of hepatic progression-free survival events observed at the second interim analysis.

Final Analysis of Primary End Points of Progression-Free Survival and Hepatic Progression-Free Survival

The final analysis is planned at 344 progression-free survival events. The Hochberg procedure will be used to control type 1 error for the 2 primary end points [25]. Whichever of progression-free survival or hepatic progression-free survival that has the larger *P* value will be compared between treatment groups using a log-rank test converted to a z-score and compared with the nominal critical value of 2.312 with a corresponding one-sided $P \leq .0104$ required to declare a statistically significant improvement in hazard rate for this end point. To ensure that type 1 error is controlled for both primary end points, this boundary is based on the incremental alpha of .0104 instead of the *P* value scale boundary of .0168, using the rho family error spending function with $\rho=1.5$.

According to the Hochberg procedure, if the primary end point with the larger *P* value is statistically significant, then the other primary end point is also statistically significant. However, if the primary end point with the larger *P* value is not statistically significant, then the other primary end point will be compared between treatment arms using a log-rank test converted to a z-score and compared with the nominal critical value of 2.562 based on the rho family error spending function, with a corresponding one-sided $P \leq .0104/2=.0052$ required to declare a statistically significant improvement in hazard rate for this end point.

Analysis of Secondary Efficacy End Points

Comparison between treatment groups for all secondary end points will be conducted at the final analysis at one-sided alpha of .025.

Time-to-event end points (ie, overall survival, time to symptomatic progression, and time to deterioration in quality of life) will be compared between treatment groups using a log-rank test. Disease control rates and objective response rate will be compared between treatment groups using the continuity-adjusted Newcombe-Wilson test. The FACT-C score will be compared between treatment arms using a mixed linear model with baseline score and the relative time from baseline as covariates.

Poolability and Other Analyses

Univariable Cox regression analyses of the primary efficacy end points and all other time-to-event end points (ie, overall survival, time to symptomatic progression, and time to deterioration in quality of life) will be conducted with the following baseline factors, one at a time, together with randomized group: age group, race, ethnicity, gender, unilobar versus bilobar disease, oxaliplatin or irinotecan first-line chemotherapy, KRAS status, ECOG performance status, region, duration of time from date of diagnosis of mCRC to randomization, duration of time from the start of first-line chemotherapy to date of progression on first-line therapy, duration of time from date of progression on first-line therapy to date of start of second-line chemotherapy, synchronous versus metachronous metastases, location of primary tumor at the time of first diagnosis of primary colorectal cancer (right-sided vs left-sided), tumor burden, and presence of lung or lymph node lesions. Receipt of oxaliplatin- or irinotecan-based second-line chemotherapy and the receipt of biological agents during the study will also be assessed one at a time. This will allow an assessment of each of these factors on the study outcomes.

To assess the poolability of data across study sites, multivariable Cox regression analyses of the time-to-event end points will be conducted, including factors of randomized group, study site, randomized group by study site interaction, and the factors from the univariable analyses that have a one-sided $P<.075$. Similarly, to assess the poolability of data across regions, Cox regression analysis will be conducted with study site replaced by region.

Logistic regression analyses of the binary end points (ie, objective response rate and disease control rate) will be conducted in the same way as the Cox regression analyses described above.

Results

After the first 20 patients in the TARE group received TheraSphere microspheres followed by at least two cycles of chemotherapy, a feasibility safety assessment was conducted. The IDMC reviewed the safety results of both groups in an unblinded fashion. A consideration for adjusting the dose of cytotoxic agents, other safety recommendations, or stopping further enrollment could have been made if there was either an unanticipated patient death definitely or probably related to the sequential administration of TARE with oxaliplatin-based or irinotecan-based chemotherapy or there was a pattern of serious toxicity clearly related to the sequential administration of TARE with oxaliplatin-based or irinotecan-based chemotherapy. However, the IDMC did not recommend any changes to the study.

Enrollment for the study completed in October 2018. Results of the first interim analysis were reviewed by the IDMC, and their recommendation was to continue the study without any changes.

Discussion

Overview

First-line chemotherapy regimens for unresectable mCRC are well established [10]. Second-line therapy using the combination of chemotherapy and targeted therapies has demonstrated efficacy with improved overall survival, progression-free survival, and overall response rate in comparison with chemotherapy alone [26,27]. However, the choice of the optimal treatment strategy remains challenging and is mostly driven by

the type of and response to the first-line treatment administered, the type of retrovirus-associated DNA sequence mutation (KRAS, NRAS, and HRAS), microsatellite stability, tumor burden, patient performance status, and comorbidities.

The EPOCH study was designed to account for known prognostic and predictive factors [10]. Patients in the EPOCH study are stratified at randomization according to key factors that could influence the primary or secondary study end points: (1) tumor load (unilobar vs bilobar), (2) KRAS status (wild type vs mutant), and (3) prior first-line chemotherapy (oxaliplatin-based or irinotecan-based) to ensure balance between groups.

High tumor load is a known factor of chemotherapy failure [28]. KRAS mutation is a predictive factor of nonresponse to epidermal growth factor receptor inhibitor treatment [29,30]. Whether KRAS mutation is a prognostic factor is widely debated. KRAS mutant patients may have different sensitivity to treatment compared with KRAS wild-type patients [31-35], and KRAS mutational status will drive the postprogression treatment received. Second-line treatment with irinotecan-based regimens has been associated with shorter median progression-free survival [36]. Tumor sidedness is currently undergoing intense study, given the recognition that tumor location is prognostic and predictive [37-39]. Tumor sidedness is not a stratification factor in the EPOCH study because when the study was designed, the importance of this prognostic factor was less understood; however, a preplanned analysis to assess the impact of this factor will be performed. In addition, the impact of important covariates, such as asynchronous or metachronous metastases, location of primary tumors (right vs left), presence of lung or lymph node lesions at baseline, and biological agents received, will be assessed. This study was designed before well-established data on the prognostic significance of BRAF mutations were available, and thus, BRAF mutation status was not collected on the electronic case report forms. However, because BRAF mutant tumors are often right sided, the preplanned analysis to assess the impact of right-sided vs left-sided primary tumor location should provide an indirect assessment of BRAF mutation status.

TARE treatment for patients with liver or liver-dominant disease has been outlined in prospective and retrospective studies that have demonstrated that this option was manageable in this patient population and compared favorably with standard-of-care treatment [14-16,40,41]. The relevancy of TARE in the first-line setting was extensively explored in the pooled analyses of the randomized studies FOXFIRE, SIRFLOX, and FOXFIRE-Global [42,43]. This analysis demonstrated that TARE (with ^{90}Y resin microspheres) in association with an oxaliplatin- and fluorouracil-based chemotherapy regimen failed to improve overall survival and progression-free survival compared with chemotherapy alone. However, the combination of TARE with first-line oxaliplatin-based chemotherapy significantly improved response rate and liver-specific progression-free survival in comparison with chemotherapy alone. In spite of an increased toxicity in the TARE group, the quality of life was not significantly different between the 2 treatment groups [42-44]. Factors that may have contributed to the failure of the previous ^{90}Y resin microspheres trials are a long delay between randomization to starting TARE treatment, the percentage of patients with extrahepatic metastatic disease at baseline (40% of patients enrolled), the lower percentage of patients in the TARE group who received postprogression therapies, and inferior chemotherapy dose intensity in the TARE group.

In the EPOCH study, the patient population and treatment schedule were selected to avoid these factors that may have contributed to the failure of the previous first-line trials. Patients with rapid and diffuse progression of disease and those with extrahepatic metastasis are not eligible to participate, thus limiting the risk of the trial not reaching a primary progression-free survival end point because of extrahepatic progression. In addition, to avoid a discrepancy between the 2 treatment groups regarding chemotherapy intensity and the delay to start the attributed treatment, the 2 groups must start the first study treatment, that is, chemotherapy, within 21 days after randomization. Both groups also receive an optimal dose of chemotherapy based on oncologist determination. No dose reduction was preplanned in the TARE group. The safety of the treatment schedule was evaluated after the treatment of 20 patients, and the schedule was considered safe by the IDMC. Limitations of the study include the unblinded design, which is required for such a complex treatment intervention when it would be unethical to consider a *sham* procedure for the control group.

Conclusion

It is important to establish an effective and tolerable treatment to improve patient outcome for unresectable liver metastases from colorectal cancer. One challenge in the treatment of mCRC patients with liver-dominant disease is providing an efficient treatment of the cancer without impairing liver function and allowing systemic treatment to continue with minimal interruption. TARE has a limited toxicity profile when used appropriately and, consequently, a low impact on the dose intensity and duration of systemic treatment. Enrollment for the EPOCH study completed in October 2018. Data from this trial will enhance the knowledge base regarding optimal treatment options for patients with unresectable mCRC.

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Conflicts of Interest

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Multimedia Appendix 1

IRB approval letter for the principal investigator of the multicenter study.

[PDF File (Adobe PDF File), 593KB - resprot_v8i1e11545_app1.pdf]

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015 Mar 1;136(5):E359-E386. [doi: 10.1002/ijc.29210] [Medline: 25220842]
2. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014 Sep;25(Suppl 3):iii1-iii9. [doi: 10.1093/annonc/mdu260] [Medline: 25190710]
3. American Cancer Society. Atlanta: American Cancer Society; 2017. Cancer Facts & Figures URL: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf [accessed 2018-10-08] [WebCite Cache ID 731C6RaGJ]
4. Salvatore L, Aprile G, Arnoldi E, Aschele C, Carnaghi C, Cosimelli M, et al. Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM). ESMO Open 2017;2(1):e000147 [FREE Full text] [doi: 10.1136/esmoopen-2016-000147] [Medline: 28761730]
5. American Cancer Society. Atlanta: American Cancer Society; 2018. Survival rates for colorectal cancer, by stage URL: https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html [accessed 2018-10-08] [WebCite Cache ID 731Bez3Yx]
6. Ghiringhelli F, Hennequin A, Drouillard A, Lepage C, Faivre J, Bouvier A. Epidemiology and prognosis of synchronous and metachronous colon cancer metastases: a French population-based study. Dig Liver Dis 2014 Sep;46(9):854-858. [doi: 10.1016/j.dld.2014.05.011] [Medline: 24908575]
7. Holch JW, Demmer M, Lamersdorf C, Michl M, Schulz C, von Einem JC, et al. Pattern and dynamics of distant metastases in metastatic colorectal cancer. Visc Med 2017 Mar;33(1):70-75 [FREE Full text] [doi: 10.1159/000454687] [Medline: 28612020]

8. Kaifi JT, Kunkel M, Zhu J, Dicker DT, Gusani N, Yang Z, et al. Circulating tumor cells are associated with diffuse spread in stage IV colorectal cancer patients. Cancer Biol Ther 2013 Dec;14(12):1174-1181 [FREE Full text] [doi: 10.4161/cbt.26884] [Medline: 24153154]
9. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer 2018 Dec 15;18(1):78 [FREE Full text] [doi: 10.1186/s12885-017-3925-x] [Medline: 29334918]
10. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016 Dec;27(8):1386-1422. [doi: 10.1093/annonc/mdw235] [Medline: 27380959]
11. Venook AP, Niedzwiecki D, Lenz H, Innocenti F, Fruth B, Meyerhardt JA, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. J Am Med Assoc 2017 Dec 20;317(23):2392-2401 [FREE Full text] [doi: 10.1001/jama.2017.7105] [Medline: 28632865]
12. Martini G, Troiani T, Cardone C, Vitiello P, Sforza V, Ciardiello D, et al. Present and future of metastatic colorectal cancer treatment: a review of new candidate targets. World J Gastroenterol 2017 Jul 14;23(26):4675-4688 [FREE Full text] [doi: 10.3748/wjg.v23.i26.4675] [Medline: 28765689]
13. Nicolay NH, Berry DP, Sharma RA. Liver metastases from colorectal cancer: radioembolization with systemic therapy. Nat Rev Clin Oncol 2009 Dec;6(12):687-697. [doi: 10.1038/nrclinonc.2009.165] [Medline: 19884901]
14. Jakobs TF, Paprottka KJ, Raeßler F, Strobl F, Lehner S, Ilhan H, et al. Robust evidence for long-term survival with Y radioembolization in chemorefractory liver-predominant metastatic colorectal cancer. Eur Radiol 2017 Jan;27(1):113-119. [doi: 10.1007/s00330-016-4345-z] [Medline: 27059858]
15. Kennedy A, Cohn M, Coldwell DM, Drooz A, Ehrenwald E, Kaiser A, et al. Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. J Gastrointest Oncol 2017 Aug;8(4):614-624 [FREE Full text] [doi: 10.21037/jgo.2017.03.10] [Medline: 28890810]
16. Marsala A, Lee EW, Padia SA. Yttrium-90 radioembolization for metastatic colorectal cancer: outcomes by number of lines of therapy. Semin Intervent Radiol 2017 Jun;34(2):116-120 [FREE Full text] [doi: 10.1055/s-0037-1602711] [Medline: 28579679]
17. Shi Q, de Gramont A, Grothey A, Zalcberg J, Chibaudel B, Schmoll H, et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. J Clin Oncol 2015 Jan 01;33(1):22-28 [FREE Full text] [doi: 10.1200/JCO.2014.56.5887] [Medline: 25385741]
18. Sidhu R, Rong A, Dahlberg S. Evaluation of progression-free survival as a surrogate endpoint for survival in chemotherapy and targeted agent metastatic colorectal cancer trials. Clin Cancer Res 2013 Mar 01;19(5):969-976 [FREE Full text] [doi: 10.1158/1078-0432.CCR-12-2502] [Medline: 23303214]
19. de Baere T, Tselikas L, Boige V, Ducreux M, Malka D, Goéré D, et al. Intra-arterial therapies for colorectal cancer liver metastases (radioembolization excluded). Bull Cancer 2017 May;104(5):402-406. [doi: 10.1016/j.bulcan.2016.10.025] [Medline: 27993355]
20. Ruers T, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, European Organisation for Research and Treatment of Cancer (EORTC), Gastro-Intestinal Tract Cancer Group, Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst 2017 Dec 01;109(9) [FREE Full text] [doi: 10.1093/jnci/djx015] [Medline: 28376151]
21. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res 2012 Apr;32(4):1387-1395. [Medline: 22493375]
22. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009 Jan;45(2):228-247. [doi: 10.1016/j.ejca.2008.10.026] [Medline: 19097774]
23. Kennedy A, Coldwell D, Sangro B, Wasan H, Salem R. Radioembolization for the treatment of liver tumors general principles. Am J Clin Oncol 2012 Feb;35(1):91-99. [Medline: 22363944]
24. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. New York: Chapman & Hall; 2000.
25. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75(4):800-802. [doi: 10.1093/biomet/75.4.800]
26. Shitara K, Yamanaka T, Denda T, Tsuji Y, Shinozaki K, Komatsu Y, et al. Reverce: randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan. J Clin Oncol 2018;36(4):557 [FREE Full text] [doi: 10.1200/JCO.2018.36.4_suppl.557]

27. Sobrero A, Damiani A. Maintenance therapy in advanced colorectal cancer, yes or no? Ask the laboratory. Ann Oncol 2017 Dec 01;28(9):2043-2044. [doi: 10.1093/annonc/mdx395] [Medline: 28911090]
28. Massacesi C, Pistilli B, Valeri M, Lippe P, Rocchi MB, Cellerino R, et al. Predictors of short-term survival and progression to chemotherapy in patients with advanced colorectal cancer treated with 5-fluorouracil-based regimens. Am J Clin Oncol 2002 Apr;25(2):140-148. [Medline: 11943891]
29. Porru M, Pompili L, Caruso C, Biroccio A, Leonetti C. Targeting KRAS in metastatic colorectal cancer: current strategies and emerging opportunities. J Exp Clin Cancer Res 2018 Mar 13;37(1):57 [FREE Full text] [doi: 10.1186/s13046-018-0719-1] [Medline: 29534749]
30. Yokota T. Are KRAS/BRAF mutations potent prognostic and/or predictive biomarkers in colorectal cancers? Anticancer Agents Med Chem 2012 Feb;12(2):163-171 [FREE Full text] [Medline: 22043994]
31. Cabart M, Frénel J, Campion L, Ramée J, Dupuis O, Senellart H, et al. [KRAS mutation does not influence oxaliplatin or irinotecan efficacy, in association with bevacizumab, in first line treatment of metastatic colorectal cancer]. Bull Cancer 2016 Jun;103(6):541-551. [doi: 10.1016/j.bulcan.2016.03.007] [Medline: 27155924]
32. Clarke CN, Kopetz ES. BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: clinical characteristics, clinical behavior, and response to targeted therapies. J Gastrointest Oncol 2015 Dec;6(6):660-667 [FREE Full text] [doi: 10.3978/j.issn.2078-6891.2015.077] [Medline: 26697199]
33. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015 Oct;16(13):1306-1315. [doi: 10.1016/S1470-2045(15)00122-9] [Medline: 26338525]
34. Passot G, Kim BJ, Glehen O, Mehran RJ, Kopetz SE, Goere D, BIG-RENAPE Working Group. Impact of RAS mutations in metastatic colorectal cancer after potentially curative resection: does site of metastases matter? Ann Surg Oncol 2018 Jan;25(1):179-187. [doi: 10.1245/s10434-017-6141-7] [Medline: 29071660]
35. Serna-Blasco R, Sanz-Álvarez M, Aguilera Ó, García-Foncillas J. Targeting the RAS-dependent chemoresistance: the Warburg connection. Semin Cancer Biol 2018 Feb 09 Epub ahead of print(forthcoming). [doi: 10.1016/j.semcancer.2018.01.016] [Medline: 29432815]
36. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004 Jan 15;22(2):229-237. [doi: 10.1200/JCO.2004.05.113] [Medline: 14657227]
37. Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, et al. Effect of Primary Tumor Location on Second- or Later-line Treatment Outcomes in Patients With RAS Wild-type Metastatic Colorectal Cancer and All Treatment Lines in Patients With RAS Mutations in Four Randomized Panitumumab Studies. Clin Colorectal Cancer 2018 Dec;17(3):170-178.e3 [FREE Full text] [doi: 10.1016/j.clcc.2018.03.005] [Medline: 29627309]
38. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. Eur J Cancer 2017 Dec;70:87-98. [doi: 10.1016/j.ejca.2016.10.007] [Medline: 27907852]
39. Wasan H, Sharma R, Heinemann V, Sharma N, Taieb J, Ricke J, et al. FOXFIRE-SIRFLOX-FOXFIRE global prospective randomised studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer: KRAS mutation and tumour site analysis. Ann Oncol 2017;28(suppl 5):mdx440.018. [doi: 10.1093/annonc/mdx440.018]
40. Hickey R, Lewandowski RJ, Prudhomme T, Ehrenwald E, Baigorri B, Critchfield J, et al. 90Y radioembolization of colorectal hepatic metastases using glass microspheres: safety and survival outcomes from a 531-patient multicenter study. J Nucl Med 2016 May;57(5):665-671 [FREE Full text] [doi: 10.2967/jnumed.115.166082] [Medline: 26635340]
41. Lewandowski RJ, Memon K, Mulcahy MF, Hickey R, Marshall K, Williams M, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. Eur J Nucl Med Mol Imaging 2014 Oct;41(10):1861-1869. [doi: 10.1007/s00259-014-2799-2] [Medline: 24906565]
42. Sharma RA, Wasan HS, Van Hazel GA, Heinemann V, Sharma NK, Taieb J, et al. Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer. J Clin Oncol 2017 May 20;35(15_suppl):3507-3507. [doi: 10.1200/JCO.2017.35.15_suppl.3507]
43. Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, FOXFIRE trial investigators, SIRFLOX trial investigators, FOXFIRE-Global trial investigators, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol 2017 Dec;18(9):1159-1171 [FREE Full text] [doi: 10.1016/S1470-2045(17)30457-6] [Medline: 28781171]
44. Sangha BS, Nimeiri H, Hickey R, Salem R, Lewandowski RJ. Radioembolization as a treatment strategy for metastatic colorectal cancer to the liver: what can we learn from the SIRFLOX Trial? Curr Treat Options Oncol 2016 Dec;17(6):26. [doi: 10.1007/s11864-016-0402-8] [Medline: 27098532]

Abbreviations

^{90}Y: yttrium-90
^{99m}Tc-MAA: technetium-99m macroaggregated albumin
CT: computerized tomography
ECOG: Eastern Cooperative Oncology Group
EPOCH: A Phase 3 Clinical Trial Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver who have Failed First Line Chemotherapy
FACT-C: Functional Assessment of Cancer Therapy-Colorectal Cancer
HR: hazard ratio
IDMC: independent data monitoring committee
KRAS: Kirsten retrovirus–associated DNA sequence
mCRC: metastatic colorectal cancer
MRI: magnetic resonance imaging
RECIST: Response Evaluation Criteria in Solid Tumors
SPECT: single-photon emission computed tomography
TACE: transarterial chemoembolization
TARE: transarterial radioembolization

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Protocol

Delivery of Peer Support Through a Self-Management mHealth Intervention (Healing Circles) in Patients With Cardiovascular Disease: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cardiovascular disease (CVD) is a leading cause of hospitalization and death around the world. The prevalence of CVD is increasing and, therefore, development and investigation of effective programs to help people better self-manage their CVD and prevent secondary complications are needed.

Objective: In this paper, we report on a protocol to evaluate Healing Circles—an evidence-based and patient-informed peer support mobile health program designed to facilitate self-management and support patients in their recovery from and management of CVD. We hypothesize that individuals with CVD who use Healing Circles will experience greater improvements to their self-management ability than individuals receiving usual care.

Methods: In this single-blinded (assessor) randomized controlled trial, 250 community-living individuals with CVD will be randomized on a 1:1 basis to either Healing Circles or Usual Care. The primary outcome of self-management will be measured using the Health Education Impact Questionnaire version 3.0. Secondary outcomes include self-efficacy with chronic disease management, health-related quality of life, health resource use and costs, and electronic health literacy. Measurements will be taken at the baseline and every 6 months for 24 months.

Results: The study started recruitment in September 2017. Individuals are currently being recruited for participation, and existing participants are currently on follow-up. Measurements will be taken every 6 months until the study end, which is anticipated in December 2019.

Conclusions: Healing Circles is a novel program aimed toward improving self-management through peer support. Given our real-world study design, our findings will be readily translatable into practice. If the results support our hypothesis, it will indicate that Healing Circles is an effective intervention for improving self-management and reducing health care use.

Trial Registration: ClinicalTrials.gov NCT03159325; https://clinicaltrials.gov/ct2/show/NCT03159325 (Archived by WebCite at http://www.webcitation.org/74DvxVKUd)

International Registered Report Identifier (IRRID): DERR1-10.2196/12322

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KEYWORDS

cardiovascular disease; eHealth; mhealth; mobile phone; peer support; self-management

Introduction

Cardiovascular disease (CVD) is a leading cause of hospitalization and death around the world [1]. In 2015, 17.7 million people died from a CVD (7.4 million due to coronary artery disease), representing 31% of all deaths worldwide [1]. In the United States, >90 million people are reported to have a CVD, with total direct costs of medical care exceeding US$396 billion in 2012 [2]. Owing to population aging and the rising epidemics of obesity and type 2 diabetes, it is anticipated that the CVD number will continue to grow, along with annual costs that are estimated to reach US$918 billion by 2030 [2].

Patient self-management, defined as an individual's ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with one or more chronic conditions [3], is a cornerstone of treatment for CVD [4]. At present, it is estimated that half of the CVD-related hospital readmissions are due to patients not effectively self-managing their CVD [5,6]. Enhancing patient self-management, therefore, can help prevent patient deterioration and downstream hospitalizations for CVD, as well as reduce health care costs and premature mortality [7-9]. Importantly, patients who adopt self-management practices are empowered with the skills and knowledge necessary to manage their condition for long-term health benefits [7,10]. A key element of effective self-management support includes access to social and peer support networks [10-12]. Patients with CVD who report poor social support have higher readmission rates [13-15] and increased risk of mortality [16-18]. Social support programs that facilitate patients sharing information can reduce depression, provide comfort, restore confidence, improve functional status, and offer practical solutions for self-management [19], which, in turn, can result in lower rates of premature mortality [20] and fewer subsequent CVD events [21].

Despite benefits from self-management programs, questions remain as to how these programs can be implemented. Much discussion has centered on integrating self-management within the health care systems in Canada and the United States [12,22,23]. However, the integration of support for self-management practices into these health care systems has been slow, primarily due to the inherent challenges of systems that have traditionally emphasized the management of acute and episodic conditions rather than the chronic and continuous care patients with CVD require [12,22]. Without the development and testing of accessible and effective self-management programs to help people better manage their CVD and prevent secondary complications, the burden of the disease is likely to reach insurmountable levels.

In this study, we report the protocol of a real-world randomized controlled trial to evaluate Healing Circles—a mobile health (mHealth) self-management and social support program designed to bring peers with CVD together to learn from and support each other in the recovery and daily management of their disease. The primary hypothesis of this study is that individuals with CVD who participate in Healing Circles will experience improvements in their self-management ability, which are significantly greater than individuals receiving usual care. We are also investigating the effects of Healing Circles on the health-related quality of life, self-efficacy with chronic disease management, electronic health (eHealth) literacy, and health care resource use as part of our economic evaluation.

Methods

Study Design

This multisite study uses a randomized, controlled, parallel-group, single-blinded (assessor) study design, which has been guided by our Healthcare Innovation Community advisory group of researchers, clinicians, patients, and decision makers. This study has been registered on ClinicalTrials.gov (#NCT03159325). The reporting of this protocol follows the Standard Protocol Items: Recommendations for Intervention Trials [24] guidelines. Figure 1 presents an overview of trial procedures.

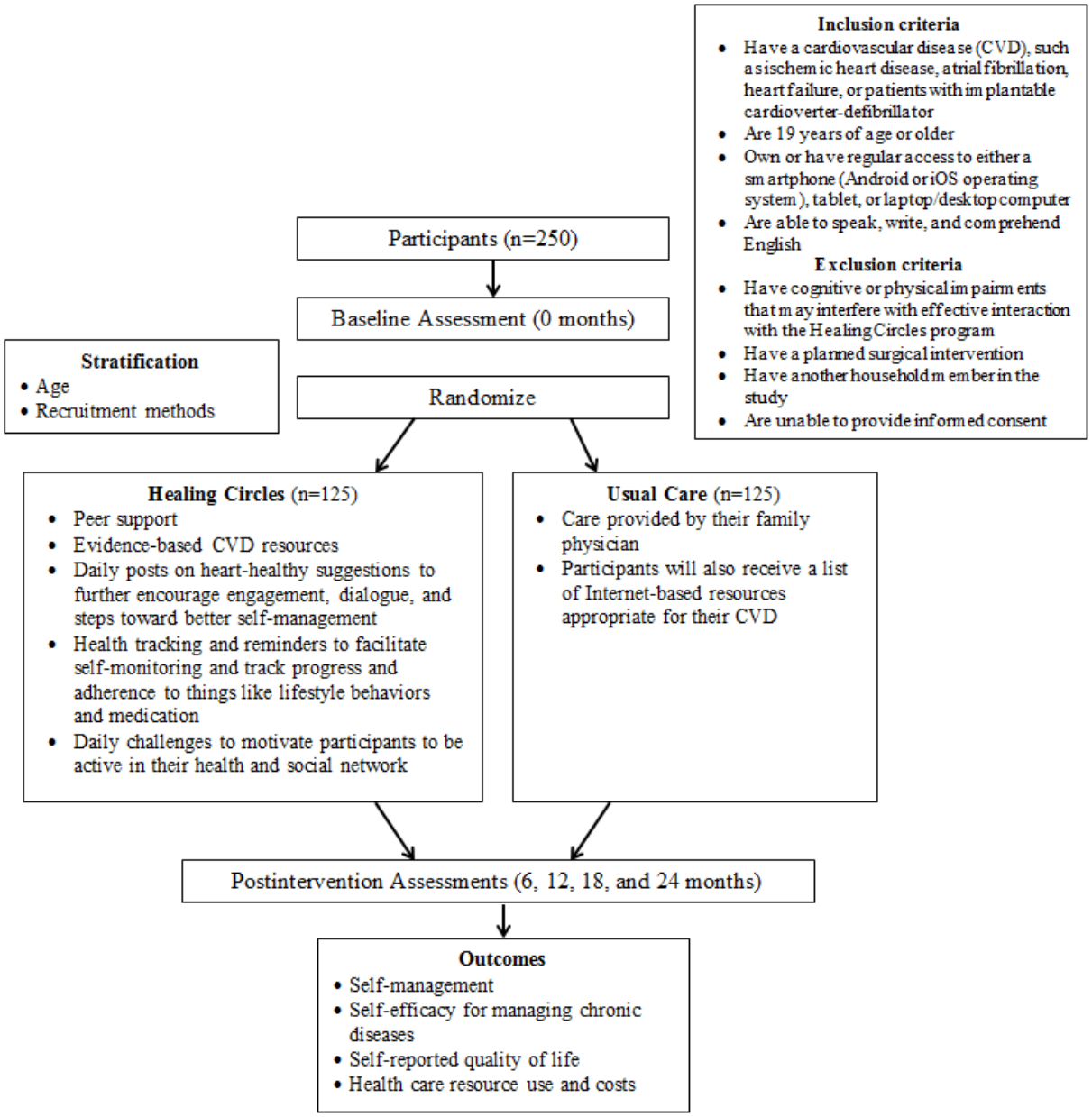
Patient Population

Volunteers from British Columbia, Canada, will be recruited from cardiac outpatient clinics and community-based CVD support groups. Individuals will be included for study if they (1) have a CVD (ischemic heart disease, atrial fibrillation, heart failure, or patients with implantable cardioverter-defibrillator; together these are nearly 80% of patients with CVD); (2) are aged ≥19 years; (3) own or have regular access to either a smartphone (Android or iOS operating system), tablet, or laptop or desktop computer; and (4) can speak, write, and comprehend English. Individuals will be excluded if they (1) have cognitive or physical impairments that may interfere with effective interaction with the Healing Circles program; (2) have a known planned surgical intervention; (3) have another household member in the study; or (4) are unable to provide informed consent.

Sample Size Estimate

Data from our single-group, pre-post pilot study that examined the proof-of-concept of the Healing Circles program [25] indicated an expected effect size of 0.58 in our primary outcome, the difference in the change in the social integration and support subscale of the Health Education Impact Questionnaire (HeiQ) Version 3 [26]. For this study, we selected a more conservative effect size of 0.33 that is, a mid-to-large effect based on Cohen *f* mid effect (0.25) plus large effect (0.40) divided by 2 [27] to account for comparison between the 2 groups (of note, this estimate may increase slightly in the Usual Care group) and the fact that the parameter estimates from our small pilot study may be highly variable. With an alpha of.05, we calculated a sample size of 198 to have 90% power. To adjust for an expected loss to follow-up rate of ~20%, over the duration of the study, we will recruit a sample size of 250 (125 per group) to retain 198 participants at the study end.

Figure 1. Overview of trial procedures.



Randomization and Interventions

After the baseline assessment, participants will be stratified by sex and recruitment site, and randomized using Web-based, computer-generated, random block sizes of 4 and 6 in a 1:1 manner to either the Usual Care or the Healing Circles group. A member of the research team who is not involved with recruitment, assessments, or study intervention will perform the randomization procedures.

Usual Care Group

Participants randomized to the usual care group will receive a list of internet-based resources appropriate for their specific CVD. For many participants, usual care will comprise the care provided by their family physician. By virtue of our recruitment, some participants will be attending cardiac outpatient clinics and may receive some self-management education as a result. However, participants are unlikely to have access to formalized peer support programs or regular access to expert input or advice. There will be no contact between the study personnel and Usual Care participants for the study duration or any attempt to influence any aspect of patient care.

Experimental (Healing Circles) Group

In addition to receiving care as usual, participants randomized to the intervention group will receive access to and instruction on how to use (ie, provision of an on-boarding document) the Healing Circles program. Healing Circles is a novel, evidence-based, and patient-informed self-management platform designed to support patients with CVD. It uses a private, secure social network that helps connect participants and provides functions to assist participants in self-management through evidence-based principles of behavioral change (eg, social support [11] and self-monitoring [28]).

Healing Circles has 3 following layers: (1) the participant; (2) the participant's circle, and (3) the broader Healing Circles community. The participant's circle is the private group that consists of other Healing Circle users that a participant chooses to support him or her (ie, an online support group). These private circles are used for private group or one-on-one chat and communication, peer support, challenges, and sharing. The broader community comprises all Healing Circles users, where participants can see public posts from others not in their circle.

Participants access Healing Circles by downloading or installing, at no cost, the platform onto their personal device (smartphone or tablet). Upon initiating Healing Circles, participants are asked to enter optional information about themselves such as gender, age, cardiac condition, region of residence, types of treatments, and personal interests and hobbies. This information allows the platform to customize and personalize the user experience, from suggesting peers with whom to connect with and add to their support circle, to personalizing content and customizing management tracking tools. However, entering this information is optional and is kept private and secure in accordance with Canadian and American data privacy laws (ie, Personal Information Protection and Electronic Documents Act in Canada and the Health Insurance Portability and Accountability Act in the United States). The participants' next step is to form their own circle of 8-10 "friends". Social support is strongest when coming from peers who have similar characteristics and who possess knowledge that is pragmatic and derived from similar lived experiences [19], so Healing Circles offers participants a matching algorithm that can be used to identify similar users to invite to their Circle. The proprietary algorithm is capable of matching from one to several users that help participants develop their Circle. In addition, participants can be invited into other Circles by other users (participants can be in more than one Circle). Similarly, this matching algorithm also matches participants to relevant evidence-based content on Healing Circles, thereby providing a personalized experience. While we will advise participants to use Healing Circles at their own convenience, we will encourage them to create their Circles within 1 week to minimize the time from the baseline assessment and first use. Participants will be instructed to contact the program developers if they experience issues using the program.

Participants also have access to evidence-based educational materials on CVD as well as several functions such as *self-initiated reminders*, which participants can sign themselves up for. These simple reminders are push notifications to prompt participants to enter data. For example, participants can sign up for daily reminders to take their medication and, when prompted, can indicate if they have taken their medication. Furthermore, Healing Circles allows participants to track their progress and adherence to things like lifestyle behaviors and medication (*health tracking*) and to pose *daily challenges* to individuals in their Circle, their entire Circle, or the entire community; these challenges can serve to motivate participants to be active in their health and social network.

Study Outcome Measures

The primary outcome is the difference in the change in the social integration and support subscale of the HeiQ Version 3 [26] between the Healing Circles and Usual Care groups. HeiQ is a self-management measure developed using Item Response Theory, comprising 8 self-management subscales as follows: health directed activity (4 items); positive and active engagement in life (5 items); emotional distress (6 items); self-monitoring and insight (6 items); constructive attitudes and approaches (5 items); skill and technique acquisition (4 items); social integration and support (5 items); and health service navigation (5 items). Each item is scored using a 4-point response scale (1=strongly disagree; 2=disagree; 3=agree; 4=strongly agree). A mean score is derived for each subscale with higher scores indicating better self-management ability, with the exception of the emotional well-being subscale where a higher mean score is indicative of lower self-management ability.

We selected the 5-item social integration and support subscale as our primary outcome because the items align closely with the Healing Circles intervention, and results from our pilot study suggested that this subscale is most responsive to changes as a result of the Healing Circles program [25]. Moreover, this subscale has been shown to have high internal consistency reliability (Cronbach alpha=.86) [26].

Secondary outcomes include the 7 other subscales within the HeiQ as well as several other variables as follows. *Self-efficacy* will be measured using the 6-item Self-efficacy for Managing Chronic Disease Scale [29]. This 6-item scale covers several domains that are common across many chronic diseases, including symptom control, role functioning, emotional functioning, and communicating with physicians and has high internal consistency reliability (Cronbach alpha=.91) [29]. Responses for each item range from 1 (not at all confident) to 10 (totally confident). Higher mean scores indicate higher self-efficacy.

Generic preference-based measures of *health-related quality of life* and *capability well-being* will be collected using the EuroQoL-5 dimension 5-level version (EQ-5D-5L) [30] and ICEpop CAPability measure for Adults (ICECAP-A) [31], respectively. These two measures will be used in the economic analysis (see below). The EQ-5D-5L is a widely used outcome measure for the estimation of quality-adjusted life years (QALYs). Developed by the EuroQol Group, the EQ-5D-5L was introduced to improve the sensitivity as compared with the EQ-5D 3-level version [32]. The ICECAP-A is based on Amartya Sen's capability approach, which distinguishes between capabilities and achieved functioning [31]. It accounts for the fact that a person's capabilities (what a person can do) may differ from their functioning (what a person actually does), and goes beyond health-related aspects of the quality of life. Both EQ-5D-5L and ICECAP-A have been validated in a range of clinical contexts [33-36].

Health care resource use data will be collected from a combination of medical records and self-report questionnaires. The self-report questionnaires will be variants of versions that have been used in previous trial-based economic evaluations [37-39]. Data collection will focus on key cost drivers, such as hospital attendances (inpatient stays, outpatient appointments, and any other hospital visits to health care practitioners), consultations with primary health care providers (eg, family

doctors and nurse practitioners), and prescribed medications. Details of nonhealth care costs will be collected, including out-of-pocket expenses, periods of work absence, as well as an assessment of the use of other mHealth -based applications. The dollar value of all resources will be estimated from a number of sources, including local health authority accounts data, Canadian Institute for Health Information patient cost estimator for acute sector admissions [40], and self-reported costs.

Usage of Healing Circles will be assessed by tracking the frequency of using Healing Circles features (eg, log-ins and the frequency of use of various platform features) using program metrics. Furthermore, we will assess what devices participants used to access the platform, as well as engagement and communication with other Healing Circles users.

Finally, *participants' perceptions, attitudes, and satisfaction* with Healing Circles will be assessed using qualitative interview methodologies at the end of the study. A subgroup of 20-30 participants in the Healing Circles group will be recruited and taken through semistructured, open-ended interviews to explore their experiences and the factors that influence acceptance and the use of the Healing Circles program. Potential interview participants will be identified by stratified purposeful sampling, with representation from both sexes, type of CVD, urban or rural residence, and highly active and less-active Circles. A 3-stage analysis of interview transcripts (open-coding, axial coding, and selective coding) will be guided by an inductive iterative approach [41,42]. The interviews will be conducted by phone and recorded and transcribed with personal identifiers removed.

Statistical Analyses

Descriptive statistics will be used to characterize the sample. For the analysis of the primary outcome, the social integration, and support subscale of the HeiQ, we will evaluate the difference in change scores between groups using a mixed-effects model that takes into account the repeated measures of the outcome. The model will incorporate the strata of sex and method of recruitment, as well as control for sociodemographic covariates such as age and sex.

With the exception of the data collected for the economic analysis, all other continuous outcomes (our secondary outcomes), including the other 7 subscales of the HeiQ, will also be assessed using a mixed-effects model. In addition, we will investigate whether there are associations of the primary and secondary outcomes with sex, urban or rural residence, disease status, and eHealth literacy. Nonnormally distributed continuous variables will be transformed prior to analyses. All analyses will be tested using an alpha of.05.

Economic Analyses

The primary framework for the economic analysis will be a cost-consequence analysis, where resource use, costs, and outcomes of the 2 treatment groups are listed separately in a disaggregated format (eg, hospital costs, out-of-pocket expenses, self-management outcomes, health-related quality of life, and capability well-being). The time horizon for the cost-consequence analysis will complement the study's design for the follow-up to maximize the use of available data (ie, 0-6, 0-12, 0-18, and 0-24 months).

We will also perform a cost-utility analysis from the perspective of the publicly funded health care payer, in line with recommendations from the Canadian Agency for Drugs and Technologies in Health [43]. Health outcomes will be expressed as QALYs, with QALY estimates generated from EQ-5D-5L responses using a Canadian value set [44]. The time horizon for the cost-utility analysis will be dependent on the sample sizes observed at 12-, 18-, and 24-month follow-up. In addition, differences between groups in costs and QALYs will be expressed using the cost-per-QALY ratio, which provides an estimate of the additional cost required to gain each additional unit of outcome.

Results

Assessments

Baseline

Baseline will consist of the collection of our primary and secondary outcomes that require pre and post measurements, as well as social demographic data, medical history, and eHealth literacy using the eHealth Literacy Scale (eHEALS) [45], to assess the participants' use of technology to access and evaluate health information. The eHEALS is used to assess the combined knowledge, comfort, and perceived skills at finding, evaluating, and applying electronic health information to health problems.

Follow-Up

Every 6 months between randomization and the study's end (anticipated in December 2019), participants will undergo an assessment of outcomes only. Those recruited at the end and beginning of recruitment will experience follow-up periods ranging from 6 to 24 months (2 years), respectively. We expect an average of 18 months of follow-up. In addition, we anticipate that the main effects on self-management will occur early after randomization; however, extended follow-up will allow us to investigate the sustainability of any observed effect, Healing Circles' use over time, and health care use for an extended period. Participants may complete data collection either in-person with a blinded assessor, self-report through mailed responses, or on the Web. The study started recruitment in September 2017. Individuals are still currently being recruited for participation, and existing participants are currently on follow-up.

Study Organization and Funding

This study is funded by the Canadian Institutes of Health Research eHealth Innovations Partnership Program and the Michael Smith Foundation for Health Research. Ethical approval has been obtained, all study staff have been hired and trained, and recruitment is currently under way.

Discussion

Healing Circles is a novel program aimed at improving self-management through peer support, as well as recovery from and management of CVD. Given our real-world study design

and the participatory aspects of engaging end users, our findings could be readily translated into practice. If the results support our hypotheses, it will indicate that Healing Circles is an effective intervention for improving self-management and reducing health care use. If so, this robust assessment of the implementation and use of Healing Circles could be used to inform future design of the program and inform plans for scale-up.

Acknowledgments

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Conflicts of Interest

SAL reports being the Chief Scientific Officer for Curatio, the mHealth company that developed the Healing Circles program.

Multimedia Appendix 1

Peer-reviewer report from the Canadian Institutes of Health Research.

[PDF File (Adobe PDF File), 157KB - resprot_v8i1e12322_app1.pdf]

References

1. World Health Organization. 2017. Cardiovascular diseases (CVD): Key facts URL: http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [accessed 2018-11-20] [WebCite Cache ID 743vuc5Kj]
2. Benjamin E, Blaha M, Chiuve S, Cushman M, Das S, Deo R, American Heart Association Statistics CommitteeStroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017 Mar 07;135(10):e146-e603 [FREE Full text] [doi: 10.1161/CIR.0000000000000485] [Medline: 28122885]
3. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Educ Couns 2002;48(2):177-187. [Medline: 12401421]
4. Riegel B, Moser D, Buck H, Dickson V, Dunbar S, Lee C, American Heart Association Council on Cardiovascular Stroke Nursing; Council on Peripheral Vascular Disease; Council on Quality of Care Outcomes Research. Self-Care for the Prevention and Management of Cardiovascular Disease and Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association. J Am Heart Assoc 2017 Aug 31;6(9) [FREE Full text] [doi: 10.1161/JAHA.117.006997] [Medline: 28860232]
5. Horowitz C, Rein S, Leventhal H. A story of maladies, misconceptions and mishaps: effective management of heart failure. Soc Sci Med 2004 Feb;58(3):631-643 [FREE Full text] [Medline: 14652059]
6. Sethares KA, Elliott K. The effect of a tailored message intervention on heart failure readmission rates, quality of life, and benefit and barrier beliefs in persons with heart failure. Heart Lung 2004;33(4):249-260. [Medline: 15252415]
7. Jovicic A, Holroyd-Leduc J, Straus S. Effects of self-management intervention on health outcomes of patients with heart failure: a systematic review of randomized controlled trials. BMC Cardiovasc Disord 2006 Nov 02;6:43 [FREE Full text] [doi: 10.1186/1471-2261-6-43] [Medline: 17081306]
8. Wheeler JRC, Janz NK, Dodge JA. Can a disease self-management program reduce health care costs? The case of older women with heart disease. Med Care 2003 Jun;41(6):706-715. [doi: 10.1097/01.MLR.0000065128.72148.D7] [Medline: 12773836]
9. Panagioti M, Richardson G, Small N, Murray E, Rogers A, Kennedy A, et al. Self-management support interventions to reduce health care utilisation without compromising outcomes: a systematic review and meta-analysis. BMC Health Serv Res 2014 Aug 27;14:356 [FREE Full text] [doi: 10.1186/1472-6963-14-356] [Medline: 25164529]
10. Lorig K, Holman H. Self-management education: history, definition, outcomes, and mechanisms. Ann Behav Med 2003 Aug;26(1):1-7. [doi: 10.1207/S15324796ABM2601_01] [Medline: 12867348]
11. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
12. Health Council of Canada. 2012 May 01. Self-management support for Canadians with chronic health conditions: A focus for primary health care URL: https://healthcouncilcanada.ca/372/ [accessed 2018-11-22] [WebCite Cache ID 747kz9u36]
13. Chin MH, Goldman L. Correlates of early hospital readmission or death in patients with congestive heart failure. Am J Cardiol 1997 Jun 15;79(12):1640-1644. [Medline: 9202355]
14. Krumholz HM, Butler J, Miller J, Vaccarino V, Williams CS, Mendes de Leon CF, et al. Prognostic importance of emotional support for elderly patients hospitalized with heart failure. Circulation 1998 Mar 17;97(10):958-964. [Medline: 9529263]
15. Schwarz KA, Elman CS. Identification of factors predictive of hospital readmissions for patients with heart failure. Heart Lung 2003;32(2):88-99. [doi: 10.1067/mhl.2003.15] [Medline: 12734531]

16. Berkman LF, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. Ann Intern Med 1992 Dec 15;117(12):1003-1009. [Medline: 1443968]
17. Case RB, Moss AJ, Case N, McDermott M, Eberly S. Living alone after myocardial infarction. Impact on prognosis. JAMA 1992;267(4):515-519. [Medline: 1729573]
18. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med 1984 Aug 30;311(9):552-559. [doi: 10.1056/NEJM198408303110902] [Medline: 6749228]
19. Lockhart E, Foreman J, Mase R, Heisler M. Heart failure patients' experiences of a self-management peer support program: a qualitative study. Heart Lung 2014;43(4):292-298 [FREE Full text] [doi: 10.1016/j.hrtlng.2014.04.008] [Medline: 24863072]
20. Berkman LF. The role of social relations in health promotion. Psychosom Med 1995;57(3):245-254. [Medline: 7652125]
21. Reifman A. Social relationships, recovery from illness, and survival: a literature review. Ann Behav Med 1995;17(2):124-131. [doi: 10.1007/BF02895061] [Medline: 18425663]
22. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff (Millwood) 2001;20(6):64-78. [doi: 10.1377/hlthaff.20.6.64] [Medline: 11816692]
23. Battersby M, Von Korff M, Schaefer J, Davis C, Ludman E, Greene SM, et al. Twelve evidence-based principles for implementing self-management support in primary care. Jt Comm J Qual Patient Saf 2010 Dec;36(12):561-570. [Medline: 21222358]
24. Chan A, Tetzlaff J, Altman D, Laupacis A, Gotzsche P, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of Internal Medicine 2013;158(3):200-207. [Medline: 23295957]
25. Sakakibara B, Ross E, Arthur G, Brown-Ganzert L, Petrin S, Sedlak T, et al. Using Mobile-Health to Connect Women with Cardiovascular Disease and Improve Self-Management. Telemed J E Health 2017 Dec;23(3):233-239. [doi: 10.1089/tmj.2016.0133] [Medline: 27623231]
26. Osborne R, Elsworth G, 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]
27. Cohen J. Statistical power analysis for the behavioural sciences. New York: Academic Press; 1969.
28. 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]
29. Lorig K, Sobel D, Ritter P, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. Eff Clin Pract 2001;4(6):256-262. [Medline: 11769298]
30. 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]
31. Al-Janabi H, Flynn T, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. Qual Life Res 2012 Feb;21(1):167-176 [FREE Full text] [doi: 10.1007/s11136-011-9927-2] [Medline: 21598064]
32. Buchholz I, Janssen MF, Kohlmann T, Feng Y. A Systematic Review of Studies Comparing the Measurement Properties of the Three-Level and Five-Level Versions of the EQ-5D. Pharmacoeconomics 2018 Jun;36(6):645-661 [FREE Full text] [doi: 10.1007/s40273-018-0642-5] [Medline: 29572719]
33. Mitchell PM, Al-Janabi H, Byford S, Kuyken W, Richardson J, Iezzi A, et al. Assessing the validity of the ICECAP-A capability measure for adults with depression. BMC Psychiatry 2017 Dec 02;17(1):46 [FREE Full text] [doi: 10.1186/s12888-017-1211-8] [Medline: 28148234]
34. Goranitis I, Coast J, Al-Janabi H, Latthe P, Roberts T. The validity and responsiveness of the ICECAP-A capability-well-being measure in women with irritative lower urinary tract symptoms. Qual Life Res 2016 Dec;25(8):2063-2075 [FREE Full text] [doi: 10.1007/s11136-015-1225-y] [Medline: 26754141]
35. Fermont JM, Blazeby JM, Rogers CA, Wordsworth S, By-Band-Sleeve Study Management Group. The EQ-5D-5L is a valid approach to measure health related quality of life in patients undergoing bariatric surgery. PLoS One 2017;12(12):e0189190 [FREE Full text] [doi: 10.1371/journal.pone.0189190] [Medline: 29252996]
36. Golicki D, Niewada M, Buczek J, KarliÅ„ska A, Kobayashi A, Janssen M, et al. Validity of EQ-5D-5L in stroke. Qual Life Res 2015 Apr;24(4):845-850 [FREE Full text] [doi: 10.1007/s11136-014-0834-1] [Medline: 25347978]
37. Ross ES, Sakakibara BM, Mackay MH, Whitehurst DG, Singer J, Toma M, et al. The Use of Text Messaging to Improve the Hospital-to-Community Transition in Acute Coronary Syndrome Patients (Txt2Prevent): Intervention Development and Pilot Randomized Controlled Trial Protocol. JMIR Res Protoc 2017 May 23;6(5):e91 [FREE Full text] [doi: 10.2196/resprot.6968] [Medline: 28536088]
38. Whitehurst DGT, Bryan S, Lewis M, Hay EM, Mullis R, Foster NE. Implementing stratified primary care management for low back pain: cost-utility analysis alongside a prospective, population-based, sequential comparison study. Spine (Phila Pa 1976) 2015 Mar 15;40(6):405-414. [doi: 10.1097/BRS.0000000000000770] [Medline: 25599287]
39. Whitehurst DGT, Bryan S, Lewis M, Hill J, Hay EM. Exploring the cost-utility of stratified primary care management for low back pain compared with current best practice within risk-defined subgroups. Ann Rheum Dis 2012 Nov;71(11):1796-1802 [FREE Full text] [doi: 10.1136/annrheumdis-2011-200731] [Medline: 22492783]

40. Canadian Institutes for Health Information. Patient Cost Estimator URL: http://www.cihi.ca/cihi-extportal/internet/en/documentfull/spending+and+health+workforce/spending/pce_application [accessed 2018-11-20] [WebCite Cache ID 743wLBSgB]
41. Srivastava P, Hopwood N. A Practical Iterative Framework for Qualitative Data Analysis. International Journal of Qualitative Methods 2009 Mar;8(1):76-84. [doi: 10.1177/160940690900800107]
42. Thomas DR. A General Inductive Approach for Analyzing Qualitative Evaluation Data. American Journal of Evaluation 2016 Jun 30;27(2):237-246. [doi: 10.1177/1098214005283748]
43. Canadian Agency for Drugs Technologies in Health. Guidelines for the Econmic Evaluation of Health Technologies, 4th ed. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2017.
44. Xie F, Pullenayegum E, Gaebel K, Bansback N, Bryan S, Ohinmaa A, Canadian EQ-5D-5L Valuation Study Group. A Time Trade-off-derived Value Set of the EQ-5D-5L for Canada. Med Care 2016 Jan;54(1):98-105 [FREE Full text] [doi: 10.1097/MLR.0000000000000447] [Medline: 26492214]
45. Norman C, Skinner H. eHEALS: The eHealth Literacy Scale. J Med Internet Res 2006 Nov 14;8(4):e27 [FREE Full text] [doi: 10.2196/jmir.8.4.e27] [Medline: 17213046]

Abbreviations

CVD: cardiovascular disease
eHealth: electronic health
EQ-5D-5L: EuroQoL-5 dimension 5-level version
HeiQ: Health Education Impact Questionnaire
ICECAP-A: ICEpop CAPability measure for Adults
mHealth: mobile health
QALY: quality-adjusted life year

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Protocol

The Impact of the mKidney mHealth System on Live Donor Follow-Up Compliance: Protocol for a Randomized Controlled Trial

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Abstract

Background: Every year, more than 5500 healthy people in the United States donate a kidney for the medical benefit of another person. The Organ Procurement and Transplantation Network (OPTN) requires transplant hospitals to monitor living kidney donors (LKDs) for 2 years postdonation. However, the majority (115/202, 57%) of transplant hospitals in the United States continue to fail to meet nationally mandated requirements for LKD follow-up. A novel method for collecting LKD follow-up is needed to ease both the transplant hospital-level and patient-level burden. We built mKidney—a mobile health (mHealth) system designed specifically to facilitate the collection and reporting of OPTN-required LKD follow-up data. The mKidney mobile app was developed on the basis of input elicited from LKDs, transplant providers, and thought leaders.

Objective: The primary objective of this study is to evaluate the impact of the mKidney smartphone app on LKD follow-up rates.

Methods: We will conduct a two-arm randomized controlled trial (RCT) with LKDs who undergo LKD transplantation at Methodist Specialty and Transplant Hospital in San Antonio, Texas. Eligible participants will be recruited in-person by a study team member at their 1-week postdonation clinical visit and randomly assigned to the intervention or control arm (1:1). Participants in the intervention arm will receive the mHealth intervention (mKidney), and participants in the control arm will receive the current standard of follow-up care. Our primary outcome will be policy-defined complete (all components addressed) and timely (60 days before or after the expected visit date) submission of LKD follow-up data at required 6-month, 1-year, and 2-year visits. Our secondary outcome will be hospital-level compliance with OPTN reporting requirements at each visit. Data analysis will follow the intention-to-treat principle. Additionally, we will collect quantitative and qualitative process data regarding the implementation of the mKidney system.

Results: We began recruitment for this RCT in May 2018. We plan to enroll 400 LKDs over 2 years and follow participants for the 2-year mandated follow-up period.

Conclusions: This pilot RCT will evaluate the impact of the mKidney system on rates of LKD and hospital compliance with OPTN-mandated LKD follow-up at a large LKD transplant hospital. It will provide valuable information on strategies for implementing such a system in a clinical setting and inform effect sizes for future RCT sample size calculations.

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KEYWORDS

app; follow-up; health care; kidney transplantation; mHealth; mobile phone; randomized controlled trial; protocol

Introduction

Need for Living Donor Kidney Transplantation

Almost 100,000 patients with end-stage renal disease (ESRD) are currently on the waitlist for a deceased donor kidney transplant (DDKT) in the United States. An additional 30,000 are added to the waitlist each year. In 2017, only 14,038 received a DDKT. Most patients who are listed for a kidney transplant today (who do not have a living donor) will have to wait 3-7 years to get an organ offer. Live donor kidney transplantation (LDKT) offers patients with ESRD a timely and therapeutic modality that has superior outcomes to DDKT and dialysis [1]. LDKT has been recognized and promoted as the best treatment option for patients with kidney failure by the American Society of Transplantation Living Donor Community of Practice in a consensus statement [2].

Sequelae of Living Kidney Donation

Living kidney donors (LKDs) experience 50% nephron loss (ie, one kidney) following donor nephrectomy, with the immediate consequence of 25%-40% loss of renal reserve as measured by the glomerular filtration rate (GFR). The health risks of this loss of GFR at nephrectomy appear to be minimal for most LKDs, with an estimated lifetime risk of ESRD of 90 per 10,000 LKDs [3-5]. However, further GFR loss might be consequential for some LKDs in the long term, especially in the event of *de novo* disease [5,6]. Diabetes mellitus (DM), hypertension (HTN), and glomerulonephritis account for over 60% of documented cases of ESRD in the LKD population [7].

Moreover, there are racial disparities in postdonation outcomes. In a national study linking Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) registry data with administrative data of a private US health insurer, Lentine et al found that African American LKDs have a 1.5-fold higher risk of HTN, a 2.3-fold higher risk of DM, and a 2.3-fold higher risk of chronic kidney disease (CKD) compared with Caucasian LKDs at 7 years postdonation [8]. Using the same linkage, Lentine et al found that this disparity persisted across age, sex, and biological relationship to the recipient. The adjusted incidence of any renal diagnosis was higher among African American LKDs compared with Caucasian LKDs (14.9% vs 9.0%; adjusted hazard ratio [aHR] 1.72; *P*=.002), including CKD (12.6% vs 5.5%; aHR 2.32), proteinuria (5.7% vs 2.5%; aHR 2.27), and nephrotic syndrome (1.3% vs 0.1%; aHR 15.7) [9]. Within 15 years, African American LKDs have a higher absolute risk of ESRD (74.7 cases per 10,000 LKDs) than Caucasian (22.7 per 10,000) or Hispanic LKDs (32.6 per 10,000) [4]. While the overall risk of developing a renal disease is low [4], follow-up and self-care management are important.

Importance of Living Kidney Donor Follow-Up to Reduce Progression to Late-Stage Renal Disease

Long before *de novo* diseases cause CKD and ESRD, they manifest as hyperglycemia, elevated blood pressure, proteinuria, and hematuria. Routine laboratory tests can screen for these subclinical entities. Appropriate LKD follow-up might present an opportunity for early detection and control of DM, HTN, glomerulonephritis, and CKD, thus slowing CKD or ESRD progression. Routine screening is especially important for young donors who face many decades with reduced renal reserve and, thus, a higher lifetime risk of ESRD.

Current Landscape of Living Kidney Donor Follow-Up

OPTN/UNOS has collected postdonation follow-up data on LKDs since 1999. However, LKD follow-up has remained consistently poor. This prompted a national policy that began requiring centers to collect these data beginning in 2013 [10,11]. OPTN/UNOS now requires transplant hospitals to collect and submit clinical data (the presence of HTN, diabetes, dialysis, kidney-related complications, recent hospitalizations, medical insurance status, income, and vital status) for 80% and laboratory data (serum creatinine and urine protein) for 70% of LKDs for 2 years postdonation (Multimedia Appendix 1). Transplant hospitals are required to collect these data from each LKD within a 120-day period (60 days before or after the 6-month, 1-year, or 2-year postdonation date) for each follow-up visit [10]. Implementation of this requirement has shown limited improvement. In a national study, we found that only 43% (87/202) of transplant hospitals met OPTN/UNOS-mandated 6-month, 1-year, and 2-year thresholds for LKDs who donated in 2013 [12]. In the face of barriers, such as cost, LKD inconvenience, and the burden of data collection [13,14], transplant hospitals lack the tools to improve LKD engagement.

Appropriate Living Kidney Donor Follow-Up Might Improve Our Ability to Understand Long-Term Sequelae of Donation

Given the limitations of the current system of LKD follow-up, alternative approaches are of utmost urgency to enable the medical community to uphold its obligation to care for living organ donors. To date, knowledge of postoperative health outcomes has largely been limited to perioperative mortality, long-term survival, and ESRD risk prediction, accounting for differences among racial and ethnic minorities [8,15-19]. Because of the lack of national follow-up and long-term data, inferences on long-term donor morbidity have been limited primarily to risks of cardiovascular disease, CKD, and ESRD [5,20,21]. In addition, only limited pilot data are available on the effect of donation on the pathophysiology of cardiovascular disease; hence, more research is needed to better define the effects of donation on cardiovascular disease surrogates and clinical events [22].

Benefits of mHealth Technology to Patients and Providers

As mobile phone use has changed the way providers communicate with patients and each other, there is a need to develop the science of mobile health (mHealth) [23,24]. mHealth apps designed for smartphones are perceived to offer considerable potential as tools to engage patients in chronic disease management [25]. mHealth technologies have been implemented in several chronic disease settings with promising results. Users of an mHealth system to promote self-management among patients with type-2 diabetes (mDAWN) experienced improved disease biomarkers and decreased health distress after using the app for a 3-month period [26]. Delivery of an mHealth intervention for the prevention of weight gain (TXT2BFiT) resulted in modest but sustained weight loss after 9 months [27]. Furthermore, mHealth technologies have shown promise in facilitating behavioral interventions to reduce cardiovascular risk factors such as smoking, physical inactivity, and suboptimal nutrition [28].

Benefits of Patient Engagement

Growing evidence suggests that health care is more efficient and effective when patients are actively engaged in their treatment [29]. Engaged patients collaborate with their providers, are better treated with respect and dignity, receive information related to their care, and are involved in decision making [30]. LKDs who are better engaged and informed may be able to keep better track of their postdonation health and may benefit from being able to visualize and summarize their health information, receive guidance on preventive care, and communicate with health care providers and the transplant system.

Preliminary Data

In formative research conducted at the Johns Hopkins Hospital, 95 of 100 LKDs reported owning a smartphone [31], which is consistent with Pew Research Center findings that 92% of adults in the United States owned a mobile phone in 2015 [32]. Among participants, 80% (80/100) thought that mHealth technology would be useful in completing follow-up [31]. A pilot study of 69 LKDs found that engagement through short message service (SMS) text messages exceeded 80% at 2 years postdonation, compared with only 20% using traditional follow-up engagement strategies (ie, telephone; electronic medical record, EMR; or patient portal). Most LKDs (97%) selected electronic communication (email or SMS text message) as their preferred method of postdonation communication with the study team, with no significant differences by sex or race [33]. These findings demonstrate the feasibility of using electronic communications, like mHealth, to improve existing methods of postdonation communication with LKDs.

Innovation

Design and Development of a New Technology

An effective method of follow-up communication with LKDs that does not place an undue burden on either patients or providers, allows for the monitoring and tracking of surgical recovery milestones, and can detect the development of *de novo* kidney disease to intervene when possible is needed. We designed an mHealth platform to capitalize on the available computing power and technologies that can transform the reach of medical care and research [34].

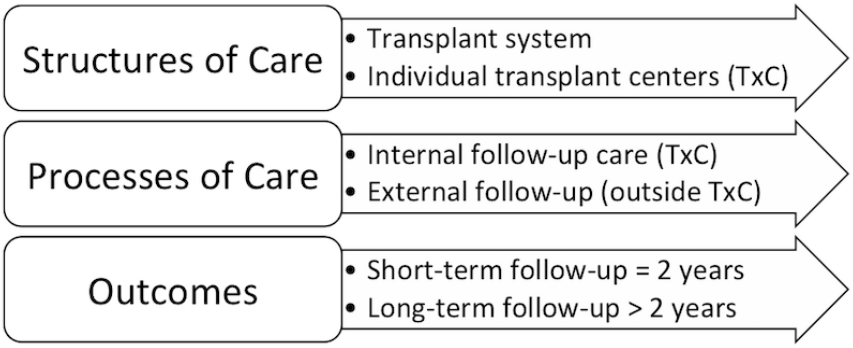
Novel Approach to Improve a Health System Failure

SMS text messages, emails, and mHealth are promising new approaches to rectify the striking gap in regular postdonation medical care for LKDs. mHealth interventions have been evaluated in clinical trials for self-management support, weight management, and prevention and management of cardiovascular disease and diabetes in other populations [26-28,35-38]. An mHealth system to engage LKDs in postdonation follow-up care might improve transplant hospitals' ability to achieve compliance with OPTN/UNOS-mandated reporting requirements and provide a link to critical preventive care for LKDs.

Benefit and Innovation of mHealth for Living Kidney Donor Follow-Up

Despite the recent proliferation of mHealth technologies, few are currently used in research studies [39]. The National Institutes of Health (NIH) strategic plan supports contributing to the mHealth evidence base because everyone can use this technology [40]. With donors from the UNOS Living Donor Committee and among informal conversations with LKDs on Facebook, we identified the following 5 primary benefits to an mHealth system for LKD engagement and follow-up: (1) *portability*: mHealth goes beyond point-of-care clinical diagnostics, thus following the LKD past transplant hospital visits; (2) *scalability*: mHealth platforms have been shown to be economical to scale [41], and with no current mechanism for reimbursement for required follow-up, transplant hospitals absorb the cost; (3) *rich data input through continuous data sampling*: devices and wearables are meant to integrate with daily functions making data collection convenient, which could make LKD follow-up automatic and seamless; (4) *personalization capacity*, and (5) *real-time data and feedback with the ability for automated analyses*. An mHealth system could provide LKDs with an opportunity to medically engage with the hospital where they donated a kidney, ask for medical record review, and have a built-in system to alert primary care health care providers when laboratory tests or blood pressure measurements become worrisome. Novel applications of inexpensive and automated electronic communication technologies, such as mHealth, could enhance patient follow-up and be applied to other patient populations. In an environment of spiraling health care costs where paperwork is administratively expensive and burdensome, this technology could find broad application.

Figure 1. Adapted conceptual framework for living kidney donor follow-up.



Overview and Theoretical Framework

This research is based on the Donabedian 3-factor conceptual framework of care quality, adapted to LKD follow-up (Figure 1) [42,43]. In the adapted conceptual framework, structures of care include the national organ transplant system and the transplant hospitals performing the living donor transplant surgery, which are responsible for reporting follow-up to OPTN/UNOS. Processes of care include LKD follow-up care that takes place both internal and external to the transplant hospital responsible for reporting. Outcomes include short-term (2-year) and long-term (>2-year) follow-up and vary in measures based on policy requirements and principles of prevention. The development of our mHealth system for LKD engagement and follow-up care sought to address all aspects of this framework.

Objective

This study aims to pilot-test an mHealth system (mKidney) and design a future large-scale multicenter randomized controlled trial (RCT) of this intervention. We will recruit 400 participants (200 per year for 2 years) to pilot-test the intervention. We will compare rates of follow-up between LKDs in the intervention (mKidney system) and control arms (standard of care) at 6, 12, and 24 months to help estimate potential effect sizes of the intervention (to inform subsequent RCT design and power calculations).

Methods

Study Design

We are conducting an exploratory pilot RCT with parallel-group design to evaluate the impact of the mKidney system on rates of postdonation follow-up among LKDs, in preparation for a fully powered clinical trial (NCT03400085). Participants will be randomized to the intervention (mKidney system) or control arm (standard of care) and will be followed for the mandated 2-year LKD follow-up period (Figure 2).

Study Population

We plan to enroll 400 LKDs who have donated a kidney at Methodist Specialty and Transplant Hospital in San Antonio, Texas, during the study period. LKDs randomized to the intervention arm (approximate n=200) will receive the mKidney system, whereas LKDs randomized to the control arm (approximate n=200) will receive the current standard of follow-up care.

Inclusion and Exclusion Criteria

For the pilot RCT, LKDs who have donated a kidney at the Methodist Specialty and Transplant Hospital during the study period will be eligible for study participation. We will exclude LKDs who do not speak English or own a smartphone device; by national policy, all donors are ≥18 years of age.

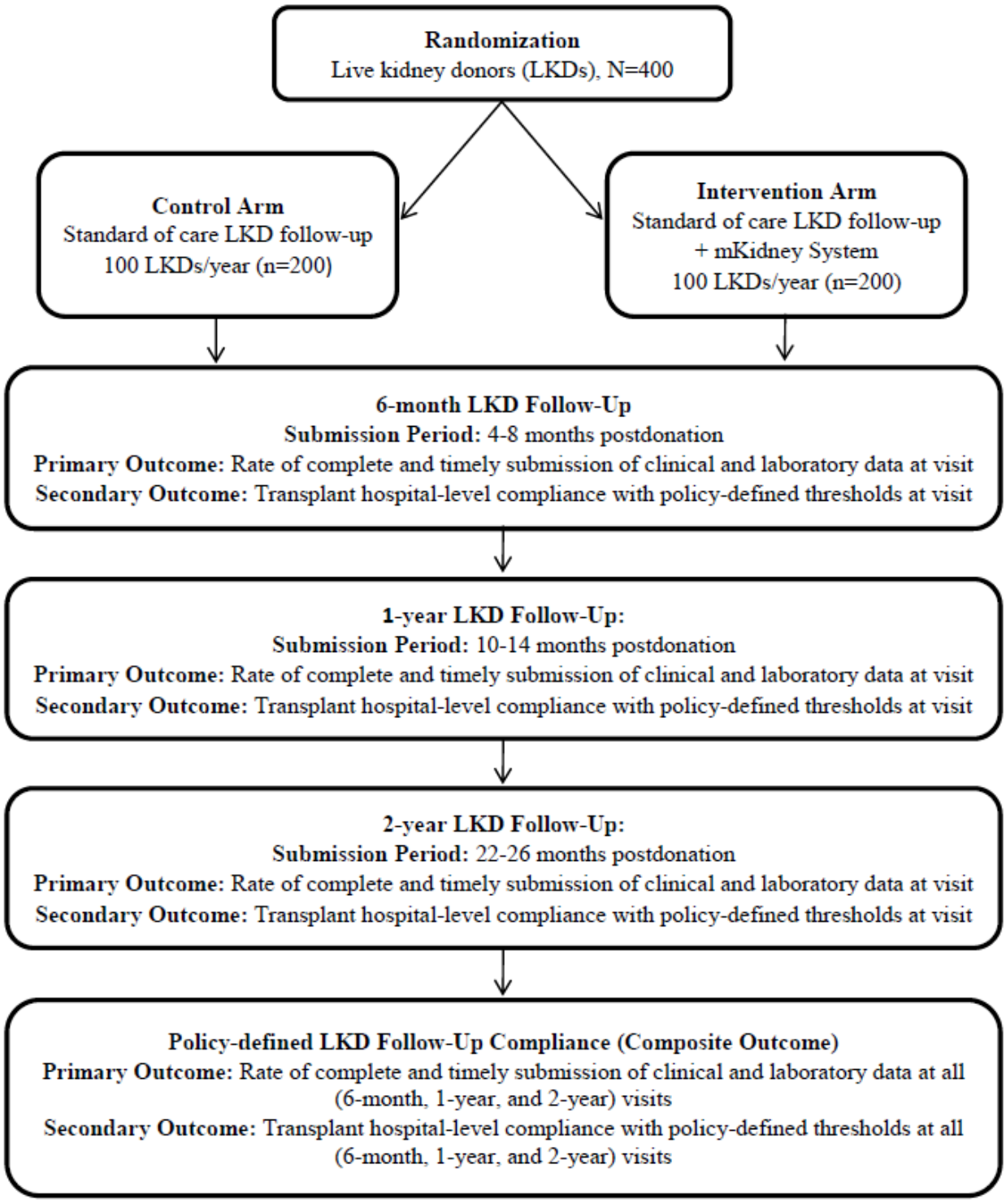
mKidney System Description

The mKidney system includes 2 components—an LKD-facing smartphone app and a transplant provider-facing Web portal. Using the Health Insurance Portability and Accountability Act (HIPAA)-compliant mKidney app, LKDs can enter their responses to required questionnaires, record lab values, and submit a photo of their lab work at each 6-month, 1-year, and 2-year follow-up time point. The questionnaire for each follow-up time point will become available at the beginning of the 120-day submission period (Multimedia Appendix 1). LKDs will receive an automated SMS text message, email, and push notifications throughout the open submission period to prompt follow-up completion. If needed, transplant providers may contact LKDs using traditional engagement strategies (eg, telephone and EMR patient portal) in addition to automated mKidney app notifications. In addition, LKDs can access Web resources through the mKidney app, including the transplant hospital website and locations of laboratory testing sites. Using the secure, HIPAA-compliant mKidney Web portal, transplant providers can monitor patients' compliance with follow-up, log additional contact attempts, view questionnaire responses, and export data for reporting purposes.

Study Procedure

LKDs will undergo consent and randomization at their medically required 1-week postdonation clinical visit. Study personnel who have undergone Human Subjects Training will use a written consent form to document consent (Multimedia Appendix 2). Surgeon and clinician members of the study team will not participate in recruitment activities to avoid the potential for coercion and appearance of a conflict of interest. Paradata will be collected on the number of acceptances, eligible enrollments, and refusals.

Figure 2. Schematic of the study design. LKD: living kidney donor.



We will assign participants either to the intervention (mKidney system) or the control arm (standard of care) using block randomization with block sizes ranging from 2 to 8. Block randomization will improve the probability of balanced groups over the course of the study. A statistician on the Johns Hopkins study team, blind to group allocations, will use this method to generate a list of sequential group assignments using Stata 15 for Linux (StataCorp Inc). The list will be used to create sequentially numbered, sealed envelopes that will be used to allocate consenting participants to the control or intervention arms of our study. Each patient will have a 50% chance of being assigned to the intervention arm of the study. Patients, health care workers on the study team, and study team members responsible for data collection and analysis will be aware of which arm participants are randomized to. Therefore, this study will not be blinded to providers, patients, or study personnel.

Study personnel will assist participants assigned to the mHealth intervention arm with downloading the mKidney app and explain its functioning. After enrollment in the study, participants in the intervention arm will receive notifications

and have the ability to complete a questionnaire documenting their remote standard-of-care visit and enter the required laboratory values at 6 months, 1 year, and 2 years postdonation using the mKidney app. Participants in the control arm will be instructed to complete the required follow-up as is standard of care but will not use the mKidney app to do so (Figure 2).

The primary outcome of interest will be the rate of policy-defined complete (all components addressed) and timely (60 days before or after the expected visit date) submission of data at all 6-month, 1-year, and 2-year follow-up visits, compared between study arms. The secondary outcome will be the transplant hospital-level compliance with OPTN reporting requirements at each visit. Outcomes will be assessed independently for each follow-up time point and as a composite outcome over the study period, as well as will be compared between study arms following the intention-to-treat principle. To understand logistical or demographic barriers to implementation, we will also collect process data and utilize routinely collected data on LKDs in the study. These data include age, sex, race, ethnicity, and educational level of LKDs.

There will not be study-specific efforts to retain participants or promote the use of the mKidney app for LKD follow-up data submission, as this would be a form of intervention that might impact outcomes. However, transplant providers at Methodist Specialty and Transplant Hospital may contact LKDs for obtaining complete and timely LKD follow-up data to comply with nationally mandated follow-up requirements. Participants may withdraw from the RCT at any time without penalty. Withdrawal from the RCT would not preclude participants from obtaining regular medical care or follow-up care related to their kidney donation. If participants choose to withdraw, the study team will use the data collected prior to withdrawal and mark the remaining data as censored. Other than interventions that might impact the rates of LKD follow-up compliance, no concomitant care or interventions will be prohibited during the trial.

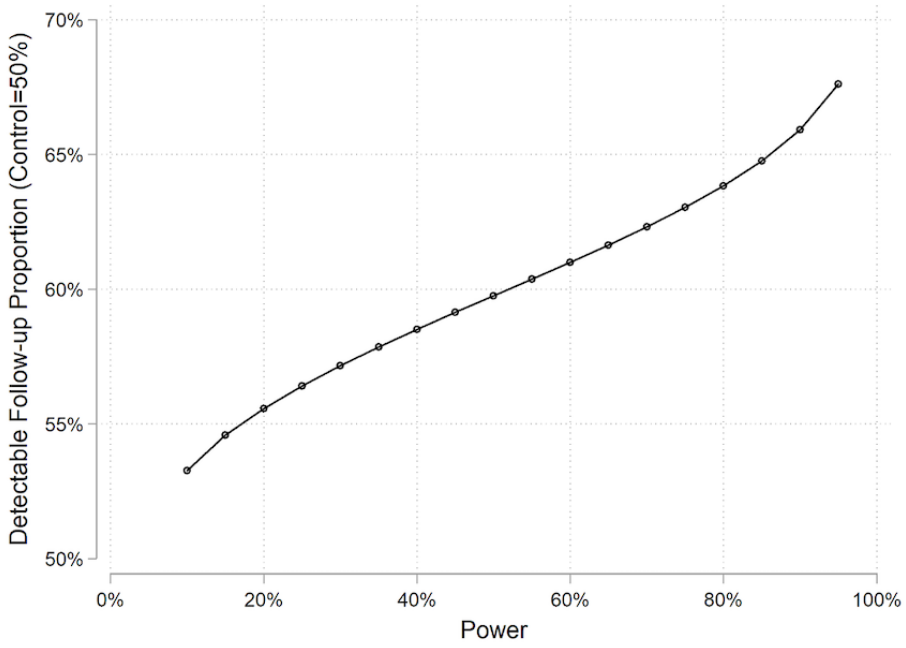
Sample Size and Power Calculation

If we recruit a total of 400 LKDs over a 2-year period and the proportion of control arm LKDs with compliant follow-up is 50%, we will have 80% power to detect a difference of 13.8% and 90% power to detect a difference of 15.9% (Table 1). If the projected follow-up rate of donors in the intervention arm is 67% (the minimum threshold for policy compliance), this study will have 79% power to detect a difference. If the follow-up rate in the intervention arm is 70%, this study will have 95% power to detect a difference (Figure 3). There is a possibility that we might face low levels of recruitment or high levels of dropout. If we are only able to recruit 300 LKDs over 2 years, then we will have 80% power to detect a difference of 15.9% and 90% power to detect a difference of 18.3%. If we are only able to recruit 200 LKDs over 2 years, we will have 80% power to detect a difference of 19.3% and 90% power to detect a difference of 22.1%.

Table 1. Power size calculations.

Number of recruited live kidney donors	Control proportion	Intervention proportion (80% power)	Delta (80% power)	Intervention proportion (90% power)	Delta (90% power)
200	0.50	0.693	0.193	0.721	0.221
300	0.50	0.659	0.159	0.683	0.183
400	0.50	0.638	0.138	0.659	0.159

Figure 3. Power calculation of piloting mKidney with 200 donors per year.



Analysis

Research team members at Johns Hopkins will conduct all analyses for this pilot RCT. Descriptive statistical methods will be used to analyze the frequency of key variables, including chi-square and rank-sum tests. Rates of the follow-up compliance among participants in the intervention and control arms will be compared using generalized linear regression. We will perform subgroup analyses for younger donors (age at donation<40 years), older donors (age ≥40 years), men, and women. In addition, the impact of the mKidney system on LKD follow-up compliance will be compared with historical follow-up with a difference-in-difference framework. All analyses will follow an intention-to-treat principle. Data will be analyzed with Stata 15 for Linux (StataCorp Inc).

Ethics and Protection of Human Subjects

Ethical Standard

Participants are followed up for their compliance with standard-of-care recommendations, including a clinical visit (evaluating the vital status, income, medical insurance, recent hospitalizations, kidney-related complications, dialysis, HTN, and diabetes) and laboratory measurements (serum creatinine and urine protein levels). No additional care or procedures will be administered to study participants.

Institutional Review Board Approval

This study was reviewed and approved by both the Johns Hopkins School of Medicine Institutional Review Board (IRB) (IRB00162212) and Methodist Specialty and Transplant Hospital IRB (IRB12091661). Protocol amendments will be submitted to the Johns Hopkins School of Medicine and Methodist Specialty and Transplant Hospital IRBs.

Participant and Data Confidentiality

Only requisite study personnel at Methodist Specialty and Transplant Hospital will have access to identifying patient information in the EMR for extraction purposes. Johns Hopkins study team members will only be involved with data analysis and will have no direct patient contact in this study. Research team members at Johns Hopkins will receive data about whether patients enrolled in the pilot RCT at Methodist Specialty and Transplant Hospital completed their required 6-month, 1-year, and 2-year follow-up visits. All study personnel have received requisite training in data confidentiality and human subjects research.

LKD follow-up data will be stored on the emocha Mobile Health server for a minimum of 7 years according to HIPAA requirements. Research team members at Johns Hopkins will have access to the raw data submitted using the mKidney app and the system's audit logs. All emocha platforms comply with HIPAA regulations on handling protected health information, including secure encryption of data, access controls, and industry-standard best practices. A robust role-based permission system limits system access to only authorized, authenticated users to ensure the need-to-know basis of protected health information.

Data Safety and Trial Monitoring

The Johns Hopkins School of Medicine IRB determined that a data monitoring committee was not necessary for this RCT due to minimal participant risk. Data monitoring will be conducted and reported by the Principal Investigator (PI) as projected by the data safety monitoring plan. The PI will immediately report any unanticipated adverse events or study deviations to the Johns Hopkins School of Medicine IRB. Trial conduct will be monitored through the mKidney system. Any viewing or modification of the system, or patient data, is logged in a persistent and unmodified database. Audit trail records include, but are not limited to, the action being taken, the date and time, and, in the case of modifications, both the old and new values. In addition, no data are ever deleted in the system; data are "soft-deleted" by marking with a flag that will hide the record during normal operations, but leaves it easily recoverable if needed.

Results

We began recruitment for this pilot RCT in May 2018 at Methodist Specialty and Transplant Hospital in San Antonio, Texas. We plan to recruit for 2 years and to follow up participants for the 2-year mandated follow-up period. Pilot findings will inform the development of a larger, multisite proposal and will provide process measures, an initial comparison to standard or care, and will inform effect size estimation for a fully powered RCT.

Discussion

Potential Limitations and Proposed Solutions

Insufficient Recruitment

A potential challenge may be participant recruitment. While we anticipate high levels of participation, even with low recruitment, we believe the study will be feasible, given an expected living donor volume of approximately 800-1000 LKD transplants during the study period. The recruitment period can be extended if needed. If the living donor volume at the pilot transplant hospital is insufficient, we will leverage the existing study population, experienced research team, and resources associated with an ongoing NIH-funded cohort study of LKDs. These resources will help to ensure timeliness, feasibility, and a high likelihood of success. It is also possible that the effect size will be larger than the estimate in the power calculations and that a smaller sample might provide adequate power.

Special Populations

LKDs at Methodist Specialty and Transplant Hospital have historically been predominantly Caucasian and Hispanic; thus, recruitment of African Americans and Asian LKDs might be limited. We will consider age-related issues to technology adaptation and use, which could be a limitation to the implementation of the mKidney system. Based on recent trends at our pilot site, we anticipate approaching patients with a wide distribution of age.

Technical Infrastructure and Connectivity

We will leverage the robust resources of emocha Mobile Health Inc. and the Johns Hopkins University to limit possible challenges to the interoperability and functionality. Future updates to mobile operating systems or related software might affect the function of mKidney. We will continuously monitor the function of mKidney and provide updates as necessary with the developer, emocha Mobile Health.

Need for Tailoring for Differences in Adoption Among Different Racial and Ethnic Groups

Should we receive feedback that differs based on factors, such as sex, age, race or ethnicity, and health literacy, it might be necessary to tailor the mKidney system or design a different mHealth system to mitigate the potential for health disparities. The UNOS Living Donor Committee has expertise in the design, development, and cultural tailoring of transplant education materials and tools should the need arise to develop different versions.

Dissemination Policy

Summary results of this pilot RCT will be reported to ClinicalTrials.gov no later than 1 year after the study completion date, as per the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information [44]. We also anticipate submitting the findings of this pilot RCT for peer-reviewed publication. Authorship eligibility will be determined using the International Committee of Medical Journal Editors guidelines [45].

Acknowledgments

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Conflicts of Interest

Under a license agreement with emocha Mobile Health Inc, the Johns Hopkins University is entitled to fees and royalty distributions related to technology used in the study described in this publication. In addition, the University owns equity in emocha. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. MLH is a member of the OPTN/UNOS Board of Directors, Executive Committee, and Living Donor Committee. MAL serves as the Director of Information Technology Operations for the United Network for Organ Sharing. MLH, DLS, and AGT are the inventors of mKidney.

Authors' Contributions

MLH is the PI. AWB is the Site PI; DLS and AGT are coinvestigators; JB is involved in transplant administration; ABM is a trialist and offers analytical support; AKE and MMW are involved in data acquisition and management; MAL is technology and implementation advisor

Multimedia Appendix 1

OPTN/UNOS Living Donor Follow-Up Worksheet.

[PDF File (Adobe PDF File), 224KB - resprot_v8i1e11000_app1.pdf]

Multimedia Appendix 2

Informed Consent Form.

[PDF File (Adobe PDF File), 58KB - resprot_v8i1e11000_app2.pdf]

References

1. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Schnitzler MA, et al. OPTN/SRTR 2012 Annual Data Report: kidney. Am J Transplant 2014 Jan;14 Suppl 1:11-44 [FREE Full text] [doi: 10.1111/ajt.12579] [Medline: 24373166]
2. LaPointe Rudow D, Hays R, Baliga P, Cohen DJ, Cooper M, Danovitch GM, et al. Consensus conference on best practices in live kidney donation: recommendations to optimize education, access, and care. Am J Transplant 2015 Apr;15(4):914-922 [FREE Full text] [doi: 10.1111/ajt.13173] [Medline: 25648884]
3. Massie AB, Muzaale AD, Luo X, Chow EKH, Locke JE, Nguyen AQ, et al. Quantifying Postdonation Risk of ESRD in Living Kidney Donors. J Am Soc Nephrol 2017 Sep;28(9):2749-2755 [FREE Full text] [doi: 10.1681/ASN.2016101084] [Medline: 28450534]
4. Muzaale AD, Massie AB, Wang M, Montgomery RA, McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014 Feb 12;311(6):579-586 [FREE Full text] [doi: 10.1001/jama.2013.285141] [Medline: 24519297]

5. Maggiore U, Budde K, Heemann U, Hilbrands L, Oberbauer R, Oniscu GC, ERA-EDTA DESCARTES working group. Long-term risks of kidney living donation: review and position paper by the ERA-EDTA DESCARTES working group. Nephrol Dial Transplant 2017 Dec 01;32(2):216-223. [doi: 10.1093/ndt/gfw429] [Medline: 28186535]
6. Steiner RW, Ix JH, Rifkin DE, Gert B. Estimating risks of de novo kidney diseases after living kidney donation. Am J Transplant 2014 Mar;14(3):538-544 [FREE Full text] [doi: 10.1111/ajt.12625] [Medline: 24612746]
7. Anjum S, Muzaale AD, Massie AB, Bae S, Luo X, Grams ME, et al. Patterns of End-Stage Renal Disease Caused by Diabetes, Hypertension, and Glomerulonephritis in Live Kidney Donors. Am J Transplant 2016 Dec;16(12):3540-3547 [FREE Full text] [doi: 10.1111/ajt.13917] [Medline: 27287605]
8. Lentine KL, Schnitzler MA, Xiao H, Saab G, Salvalaggio PR, Axelrod D, et al. Racial variation in medical outcomes among living kidney donors. N Engl J Med 2010 Aug 19;363(8):724-732 [FREE Full text] [doi: 10.1056/NEJMoa1000950] [Medline: 20818874]
9. Lentine K, Schnitzler M, Garg A, Xiao H, Axelrod D, Tuttle-Newhall J, et al. Race, Relationship and Renal Diagnoses After Living Kidney Donation. Transplantation 2015 Aug;99(8):1723-1729 [FREE Full text] [doi: 10.1097/TP.0000000000000733] [Medline: 25905980]
10. OPTN. Policy 18. 5.A Reporting Requirements After Living Kidney Donation January 21 ed 2016:2013.
11. OPTN. Policy 14 Living Donation. January 21 ed 2016:2016.
12. Henderson ML, Thomas AG, Shaffer A, Massie AB, Luo X, Holscher CM, et al. The National Landscape of Living Kidney Donor Follow-Up in the United States. Am J Transplant 2017 Dec;17(12):3131-3140. [doi: 10.1111/ajt.14356] [Medline: 28510355]
13. Waterman AD, Dew MA, Davis CL, McCabe M, Wainright JL, Forland CL, et al. Living-donor follow-up attitudes and practices in U.S. kidney and liver donor programs. Transplantation 2013 Mar 27;95(6):883-888. [doi: 10.1097/TP.0b013e31828279fd] [Medline: 23388736]
14. Mandelbrot DA, Pavlakis M, Karp SJ, Johnson SR, Hanto DW, Rodrigue JR. Practices and barriers in long-term living kidney donor follow-up: a survey of U.S. transplant centers. Transplantation 2009 Oct 15;88(7):855-860. [doi: 10.1097/TP.0b013e3181b6dfb9] [Medline: 19935453]
15. Segev DL, Muzaale AD, Caffo BS, Mehta SH, Singer AL, Taranto SE, et al. Perioperative mortality and long-term survival following live kidney donation. JAMA 2010 Mar 10;303(10):959-966. [doi: 10.1001/jama.2010.237] [Medline: 20215610]
16. Muzaale AD, Massie AB, Wang M, Montgomery RA, McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014 Feb 12;311(6):579-586 [FREE Full text] [doi: 10.1001/jama.2013.285141] [Medline: 24519297]
17. Muzaale AD, Massie AB, Kucirka LM, Luo X, Kumar K, Brown RS, et al. Outcomes of Live Kidney Donors Who Develop End-Stage Renal Disease. Transplantation 2016 Dec;100(6):1306-1312 [FREE Full text] [doi: 10.1097/TP.0000000000000920] [Medline: 26457599]
18. Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR, Chronic Kidney Disease Prognosis Consortium. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med 2016 Feb 04;374(5):411-421 [FREE Full text] [doi: 10.1056/NEJMoa1510491] [Medline: 26544982]
19. Cherikh WS, Young CJ, Kramer BF, Taranto SE, Randall HB, Fan P. Ethnic and gender related differences in the risk of end-stage renal disease after living kidney donation. Am J Transplant 2011 Aug;11(8):1650-1655 [FREE Full text] [doi: 10.1111/j.1600-6143.2011.03609.x] [Medline: 21672160]
20. Mjøen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Øyen O, et al. Long-term risks for kidney donors. Kidney Int 2014 Jul;86(1):162-167 [FREE Full text] [doi: 10.1038/ki.2013.460] [Medline: 24284516]
21. O'Keeffe LM, Ramond A, Oliver-Williams C, Willeit P, Paige E, Trotter P, et al. Mid- and Long-Term Health Risks in Living Kidney Donors: A Systematic Review and Meta-analysis. Ann Intern Med 2018 Feb 20;168(4):276-284. [doi: 10.7326/M17-1235] [Medline: 29379948]
22. Lentine KL, Segev DL. Understanding and Communicating Medical Risks for Living Kidney Donors: A Matter of Perspective. J Am Soc Nephrol 2017 Jan;28(1):12-24 [FREE Full text] [doi: 10.1681/ASN.2016050571] [Medline: 27591246]
23. Patrick K, Griswold WG, Raab F, Intille SS. Health and the mobile phone. Am J Prev Med 2008 Aug;35(2):177-181 [FREE Full text] [doi: 10.1016/j.amepre.2008.05.001] [Medline: 18550322]
24. Nilsen W, Kumar S, Shar A, Varoquiers C, Wiley T, Riley WT, et al. Advancing the science of mHealth. J Health Commun 2012;17 Suppl 1:5-10. [doi: 10.1080/10810730.2012.677394] [Medline: 22548593]
25. Broderick A, Haque F. Mobile health and patient engagement in the safety net: a survey of community health centers and clinics. Issue Brief (Commonw Fund) 2015 May;9:1-9. [Medline: 26040018]
26. Ho K, Newton L, Boothe A, Novak-Lauscher H. mobile Digital Access to a Web-enhanced Network (mDAWN): Assessing the Feasibility of Mobile Health Tools for Self-Management of Type-2 Diabetes. AMIA Annu Symp Proc 2015;2015:621-629 [FREE Full text] [Medline: 26958197]
27. Allman-Farinelli M, Partridge SR, McGeechan K, Balestracci K, Hebden L, Wong A, et al. A Mobile Health Lifestyle Program for Prevention of Weight Gain in Young Adults (TXT2BFiT): Nine-Month Outcomes of a Randomized Controlled Trial. JMIR Mhealth Uhealth 2016 Jun 22;4(2):e78 [FREE Full text] [doi: 10.2196/mhealth.5768] [Medline: 27335237]

28. Urrea B, Misra S, Plante TB, Kelli HM, Misra S, Blaha MJ, et al. Mobile Health Initiatives to Improve Outcomes in Primary Prevention of Cardiovascular Disease. Curr Treat Options Cardiovasc Med 2015 Dec;17(12):59. [doi: 10.1007/s11936-015-0417-7] [Medline: 26474892]
29. Greene J, Hibbard JH, Sacks R, Overton V, Parrotta CD. When patient activation levels change, health outcomes and costs change, too. Health Aff (Millwood) 2015 Mar;34(3):431-437. [doi: 10.1377/hlthaff.2014.0452] [Medline: 25732493]
30. Singh K, Drouin K, Newmark LP, Rozenblum R, Lee J, Landman A, et al. Developing a Framework for Evaluating the Patient Engagement, Quality, and Safety of Mobile Health Applications. Issue Brief (Commonw Fund) 2016 Feb;5:1-11. [Medline: 26934758]
31. Eno AK, Thomas AG, Ruck JM, Van Pilsum Rasmussen SE, Halpern SE, Waldram MM, et al. Assessing the Attitudes and Perceptions Regarding the Use of Mobile Health Technologies for Living Kidney Donor Follow-Up: Survey Study. JMIR Mhealth Uhealth 2018 Oct 09;6(10):e11192 [FREE Full text] [doi: 10.2196/11192] [Medline: 30305260]
32. Anderson M. Technology Devie Ownership. Pew Research Center October Report No 2015:2015.
33. Ruck JM, Zhou S, Thomas AG, Cramm SL, Massie AB, Montgomery JR, et al. Electronic messaging and communication with living kidney donors. Clin Transplant 2018 Feb;32(2). [doi: 10.1111/ctr.13184] [Medline: 29281129]
34. Steinhubl SR, Muse ED, Topol EJ. The emerging field of mobile health. Sci Transl Med 2015 Apr 15;7(283):283rv3 [FREE Full text] [doi: 10.1126/scitranslmed.aaa3487] [Medline: 25877894]
35. Kaufman N, Khurana I. Using Digital Health Technology to Prevent and Treat Diabetes. Diabetes Technol Ther 2016 Feb;18 Suppl 1:S56-S68 [FREE Full text] [doi: 10.1089/dia.2016.2506] [Medline: 26836430]
36. Sieverdes JC, Raynor PA, Armstrong T, Jenkins CH, Sox LR, Treiber FA. Attitudes and perceptions of patients on the kidney transplant waiting list toward mobile health-delivered physical activity programs. Prog Transplant 2015 Mar;25(1):26-34 [FREE Full text] [doi: 10.7182/pit2015884] [Medline: 25758797]
37. Piette JD, Farris KB, Newman S, An L, Sussman J, Singh S. The potential impact of intelligent systems for mobile health self-management support: Monte Carlo simulations of text message support for medication adherence. Ann Behav Med 2015 Feb;49(1):84-94 [FREE Full text] [doi: 10.1007/s12160-014-9634-7] [Medline: 25082177]
38. Karhula T, Vuorinen A, Rääpysjärvi K, Pakanen M, Itkonen P, Tepponen M, et al. Telemonitoring and Mobile Phone-Based Health Coaching Among Finnish Diabetic and Heart Disease Patients: Randomized Controlled Trial. J Med Internet Res 2015 Jun 17;17(6):e153 [FREE Full text] [doi: 10.2196/jmir.4059] [Medline: 26084979]
39. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, et al. Mobile health technology evaluation: the mHealth evidence workshop. Am J Prev Med 2013 Aug;45(2):228-236 [FREE Full text] [doi: 10.1016/j.amepre.2013.03.017] [Medline: 23867031]
40. National Institutes of Health. NIH-Wide Strategic Plan: Fiscal Years 2016-2020. Bethesda, MD: The National Institutes of Health (NIH) 2015.
41. Schweitzer J, Synowiec C. The economics of eHealth and mHealth. J Health Commun 2012;17 Suppl 1:73-81. [doi: 10.1080/10810730.2011.649158] [Medline: 22548602]
42. Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q 1966 Jul;44(3):Suppl:166-Suppl:206. [Medline: 5338568]
43. Donabedian A. The quality of care. How can it be assessed? JAMA 1988;260(12):1743-1748. [Medline: 3045356]
44. National Institutes of Health. NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information in NIH Guide Notice. National Institutes of Health Notice Number NOT-OD-16-149 2016.
45. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. International Committee of Medical Journal Editors 2017 Dec.

Abbreviations

CKD: chronic kidney disease
DDKT: deceased donor kidney transplant
DM: diabetes mellitus
EMR: electronic medical record
ESRD: end-stage renal disease
GFR: glomerular filtration rate
HTN: hypertension
IRB: Institutional Review Board
LKD: living kidney donor
mHealth: mobile health
NIH: National Institutes of Health
OPTN/UNOS: Organ Procurement and Transplantation Network/United Network for Organ Sharing
PI: Principal Investigator
RCT: randomized controlled trial
SMS: short service message

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Protocol

Effect of a Mobile App on Preoperative Patient Preparation for Major Ambulatory Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Background: Inadequate preoperative patient preparation causes organizational, economic, and emotional problems to patients and professionals. In Spain, no current evidence is available on either the rate of compliance or the impact of good compliance with preoperative recommendations by patients in the ambulatory setting. However, it is known that around 25% of surgical cancellations in the major ambulatory surgery (MAS) are due to poor compliance with these recommendations and, therefore, avoidable. Introducing innovative tools based on mobile health (mHealth) apps may help patients meet the preoperative recommendations and, consequently, reduce the rate of cancellations in the ambulatory setting.

Objective: The objective of this study was to evaluate the effectiveness of the Listeo+ mHealth app as a tool for improving compliance with preoperative recommendations in MAS versus standard of care (SOC).

Methods: A multicenter, randomized, open-label clinical trial that compares SOC with the additional use of Listeo+, a specific mHealth app for MAS preoperative patient monitoring, is being conducted. The study will include patients aged ≥18 years with surgical indication for MAS who meet the necessary technological and connectivity requirements. Patients in the control group will receive written preoperative recommendations, while those in the intervention group will additionally use the Listeo+ mHealth app. There will be a competitive recruitment of 790 patients during 6 months in 4 hospitals in Andalusia (Spain) that belong to the National Health System. The primary efficacy outcome is the level of compliance with preoperative recommendations. Secondary outcomes include the rate of cancellations, associated resource consumption, and perceived usability and utility with Listeo+ by participants of the intervention group. Simple randomization 1:1 procedure will be used to allocate patients to each study group.

Results: The technological development of Listeo+ and the integration and interoperability of information systems was completed in September 2017. Subsequently, simulation tests were performed with Listeo+, and a pilot study was initiated with real patients that concluded successfully in October 2017. Patient recruitment began in December 2017 in the 4 participating centers. After an intermediate analysis performed 10 months after the start of the recruitment phase, the data collection and cleaning phases are estimated to be completed in April 2019, and the analysis with the final results will be conducted in July 2019.

Conclusions: Progress in the integration and interoperability of information systems represents a major step forward in the field of mHealth. The app will allow health professionals to monitor in real-time patients' preparation and critical preoperative recommendations fulfillment. We expect a reduction in avoidable preoperative cancellations due to a lack of or a poor patient preparation. Self-assessed Web-based questionnaires and focus group will provide important information about the perceived usability and utility of Listeo+ app among patients and health care professionals.

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KEYWORDS

ambulatory surgical procedures; cost-benefit analysis; mobile phone; patient compliance; patient safety; preoperative care; telemedicine

Introduction

Providing quality care in different phases of the surgical process has become an important challenge for health systems because of the increase in the care burden, the increase in the complexity of surgical procedures, and increasingly demanding attention focused on patients' preferences [1]. Throughout the surgical process, different factors (organizational, relative to patients' clinical condition, or medical) can lead to surgery cancellations or surgical delay [2-4]. The implications of surgery cancellations can be analyzed from the perspectives of health management and patient safety, as their effects on health resource consumption can be considered adverse events (AEs) that require control and monitoring [5-7]. One major cause is the inadequate preoperative patient preparation because the safety guarantees for the intervention are not met [8,9]; this affects both the quality of the surgical procedure and the consumption of hospital resources as a result of the increase in hospital stay and consumption of medicines [1].

Major ambulatory surgery (MAS) is characterized by short-term postoperative care and does not require hospital admission; it has greatly increased in developed countries in recent decades [10]. In Spain, it represents 62.5% of the total number of surgeries performed by the National Health System (NHS) [11], which is one of the highest rates among Organisation for Economic Co-Operation and Development member countries [12]. Although the rate of cancellations in MAS is approximately 4% [13,14], lower than that reported in other countries where cancellations on the day of surgery oscillate between 5% and 40% [10,15], a quarter (27%) of those cancellations are because of poor compliance with preoperative recommendations and are, therefore, avoidable [13,16]. Conversely, inadequate preoperative patient preparation for MAS is also considered one of the main causes of patient no-shows on the day of surgery [17], which is likely due to patient anxiety before surgery [18].

There are tools such as preassessment clinics (PACs) and the surgical safety checklist (SSC) that help minimize risks in the preoperative process by assessing patients' anesthetic risk [19] or verifying compliance with essential surgical aspects from the beginning to the end of surgery [20]. Regarding these two elements, one of the initiatives to ensure that the requirements established in the preoperative assessment are met is to provide recommendations to patients so they can participate in their own care in aspects such as the use of medications (eg, anticoagulants and biologicals) and hygienic and dietetic measures. In this way, we hypothesize that involving patients in the preoperative care and promoting them to meet the specific recommendations can lead to avoiding risky situations and, consequently, surgery cancellations.

Currently, there is evidence of the benefits of PACs and the SSC on the reduction of postoperative complications in the ambulatory setting [21], preoperative anxiety [18], and cancellations for medical reasons (eg, inappropriate use of medication before surgery) [22,23].

Some experiences based on information and communication technologies, such as incorporating the SSC in digital form to the electronic health record (EHR) or sending short message service text messages as a reminder of health appointments, have made it possible to increase compliance to treatment and surgical recommendations, reduce cancellations, and avoid no-shows [1,24-27]. Currently, mobile devices (tablet, mobile phone, and wearable devices) have a very high degree of penetration in Spain [28], Andalusia in particular, with 70.9% of the population (some 4.8 million inhabitants) connecting to the internet through these devices [29]. Because of its characteristics, (eg, mobility, instant access, connectivity, and variety of functionalities), mobile health (mHealth) can influence patients' attitudes and behaviors and facilitate the asynchronous information exchange between patients and health professionals [30]. Some mHealth-based interventions such as the use of mHealth apps, have proven effective in the management of chronic diseases (eg, diabetes, asthma, and hypertension) by improving clinical parameters, compliance, and reducing disease costs [31]. Despite their great potential, the few initiatives undertaken thus far in the ambulatory surgical setting have been limited to postoperative patient monitoring [32,33]. Thus, there is no available evidence of the effect of mHealth apps on compliance with preoperative recommendations and, consequently, on the reduction of surgical cancellations.

Listeo+ is a multifunctional mobile app that provides personalized information to surgical patients (date and time of surgery), adjusted to their clinical condition. In addition to sending reminders on critical aspects of the operation at different times, Listeo+ monitors compliance with preoperative recommendations by establishing a communication channel between patients and health care professionals, which facilitates intervention in the case of possible AEs.

The aim of this study is to evaluate the impact of Listeo+ as a complement to standard of care (SOC) in patient compliance

with preoperative recommendations, surgery cancellations, and associated resource consumption in the ambulatory surgical setting, in a clinical context of real-world evidence, and to evaluate the user experience with the app (perceived usability and utility).

Methods

Study Design

A multicenter, randomized, and open-label controlled trial was planned to evaluate the Listeo+ mHealth app as a complement to SOC in patients undergoing MAS. The study protocol has two arms: patients who receive preoperative written recommendations (control group) and patients who use the Listeo+ mHealth app as a multifunctional tool to monitor personal recommendations from health professionals (intervention group). The study considers guidelines and recommendations of the Standard Protocol Items: Recommendations for Interventional Trials [34] and Consolidated Standards of Reporting Trials statements [35].

The study protocol has been approved in a peer-review process by the Spanish Ministry of Economy and Competitiveness in its Technological Projects in Health call on July 14, 2015 (application identification DTS15/00228) and by the Andalusian Regional Ministry of Health in its Health Research Projects call on July 15, 2015 (application identification PI-0447-2014).

Study Setting

Four High-Resolution Hospital Centers belonging to the Public Health System of Andalusia as a part of the NHS hospital network are recruiting patients for this study (Multimedia Appendix 1). High-Resolution Hospital Centers encourage ambulatory surgery and short-term hospitalization using MAS; thus, they were considered suitable centers to evaluate the initiative. Participating Hospital reference population is about 187,957 inhabitants.

Eligibility Criteria

Characteristics and Selection Criteria of Patients Undergoing Major Ambulatory Surgery

Patients participating in this study will be adults aged ≥18 years at the start of the study who will undergo MAS in the specialties of traumatology, orthopedic surgery, ophthalmology, or general surgery.

Inclusion Criteria

To participate in this study, participants should be autonomous or dependent on one or more caregivers to perform their preoperative preparation, with the necessary technological and connectivity resources (ie, to dispose a smartphone or tablet mobile device with an Android or iOS operating system with an internet connection and familiarity with mobile technologies).

Patients who are autonomous to perform their preoperative preparation and lack the technological requirements but have caregivers with the necessary technological and connectivity resources who can supervise their preoperative preparation may also be included in the study.

Exclusion Criteria

Patients with two scheduled operations during the same clinical episode or time period will be excluded from the study. Nonautonomous patients, whose caregivers cannot be located when personal preoperative recommendations (Multimedia Appendix 2) are provided, and patients of the intervention group who have not downloaded and registered on Listeo+ will also be excluded. To avoid the loss of patients, a rescue procedure will be used with patients who, within 7-14 days, have not registered on the Listeo+ app. A telephone call will be made urging them to register on the Listeo+ app. If a patient has not registered within 72 hours (3 days) after the rescue call has been made, he or she will be excluded from the study.

Study Outcomes

Primary Outcomes

The primary outcome will be measured as the average percentage of patient compliance with preoperative recommendations (the number of recommendations met by surgical intervention). Compliance with type 2 recommendations will be checked at the point of anesthesia consultation, whereas types 1 and 3 at the point of patient reception and preparation the day of surgery.

Secondary Outcomes

The secondary outcomes include the rate of surgery cancellations (the absolute number of cancellations compared with the number of scheduled operations for each study group in the study period) and the associated consumption of hospital resources assessed by a cost analysis between the control and intervention groups, so only direct costs will be considered. To evaluate the user experience with the Listeo+ app in the intervention group, the perceived usability and utility of mHealth apps will be analyzed. The level of usability, defined as the extent to which Listeo+ is utilized by users to achieve specific objectives of mHealth apps [36], will be evaluated exclusively in patients, whereas the perceived utility of Listeo+ will be evaluated in health professionals using qualitative techniques.

Then, the absolute change (numerical difference over the two study groups) and relative change (percentage of variation among the intervention group over the SOC) will be determined to assess the impact of the intervention for the primary and secondary outcomes (except for variables related to user experience and the level of usability).

Participants

Figure 1 presents the patient flow from the MAS assessment appointment to hospital discharge. This includes a first visit to surgery consultation, a second face-to-face anesthesia consultation (all patients except for ophthalmological patients with indication for topical anesthesia), and a third hospitalization visit to undergo MAS. Patients in the control group will follow the existing MAS patient assistance route in the centers, which consists of providing written recommendations. Participants are not going to pay for the app.

Intervention

Patients included in the intervention group will be provided with personal recommendations through the Listeo+ mobile app (Figures 2 and 3). These personal recommendations will also be printed and provided to the intervention group. Furthermore, the intervention group patients will be given access to download the mobile app through their mobile apps market (Google Play and Apple Store) using a link and quick response (QR)code.

Figure 1. Patient flowchart. MAS: major ambulatory surgery.

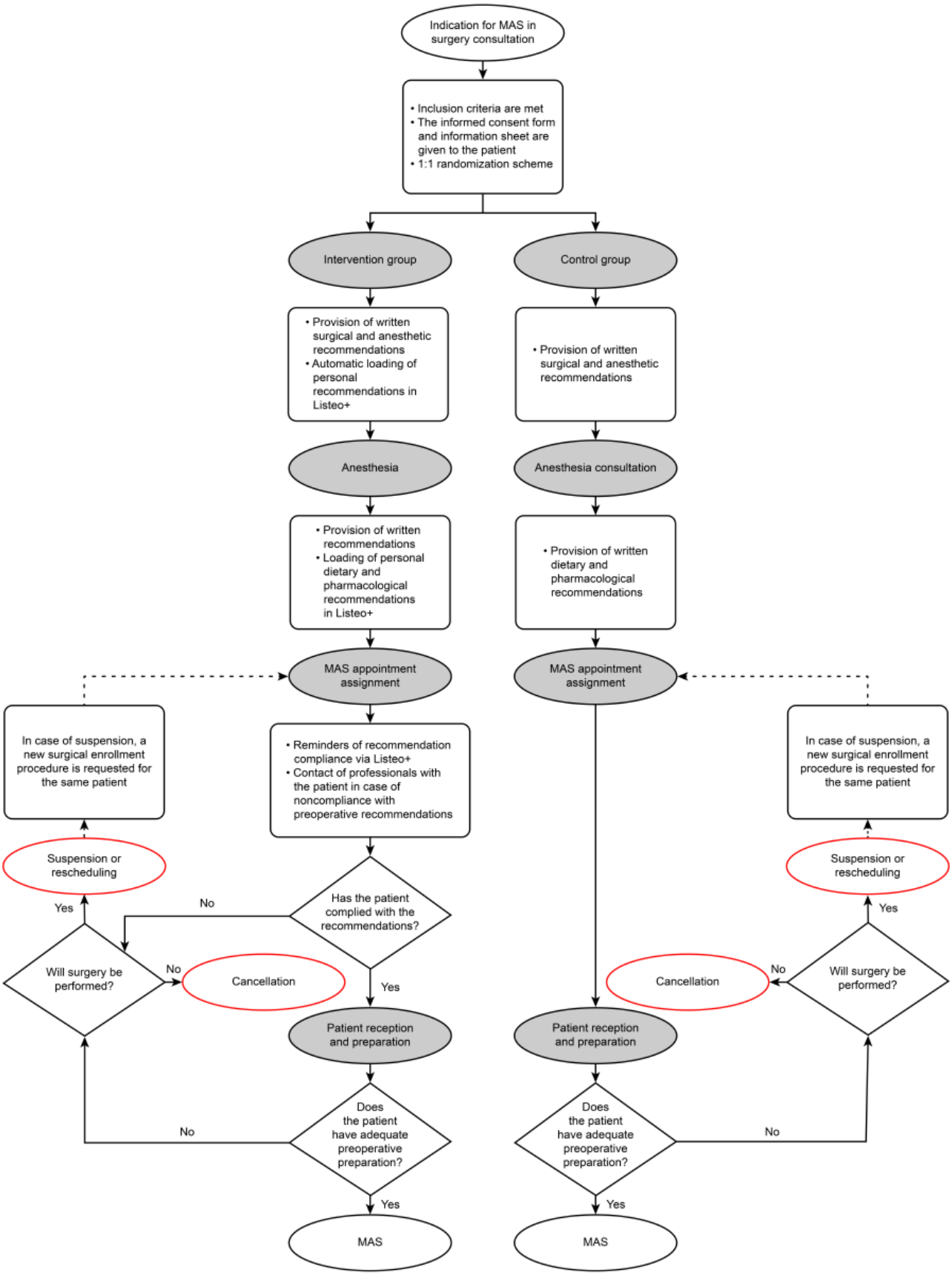
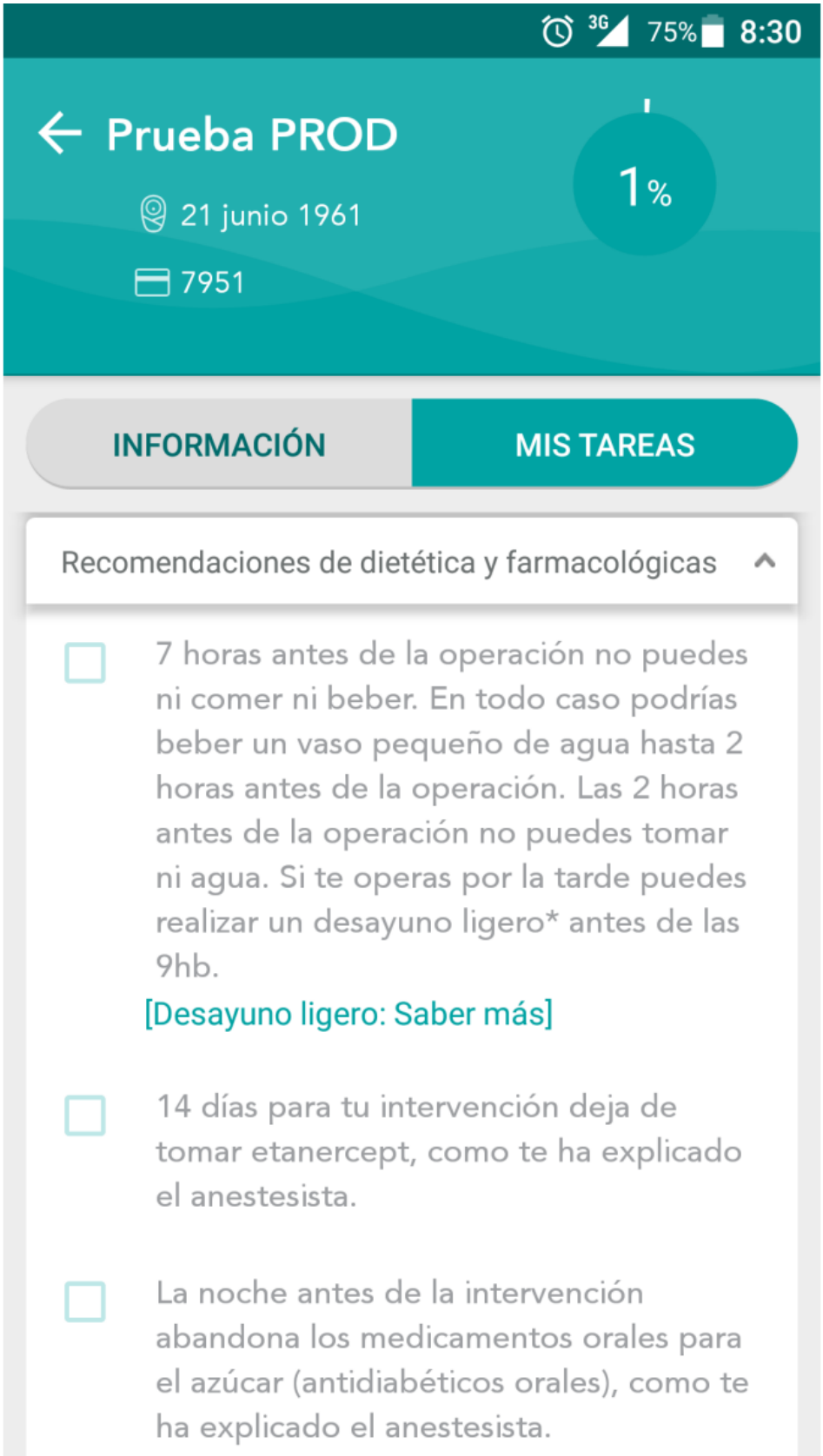


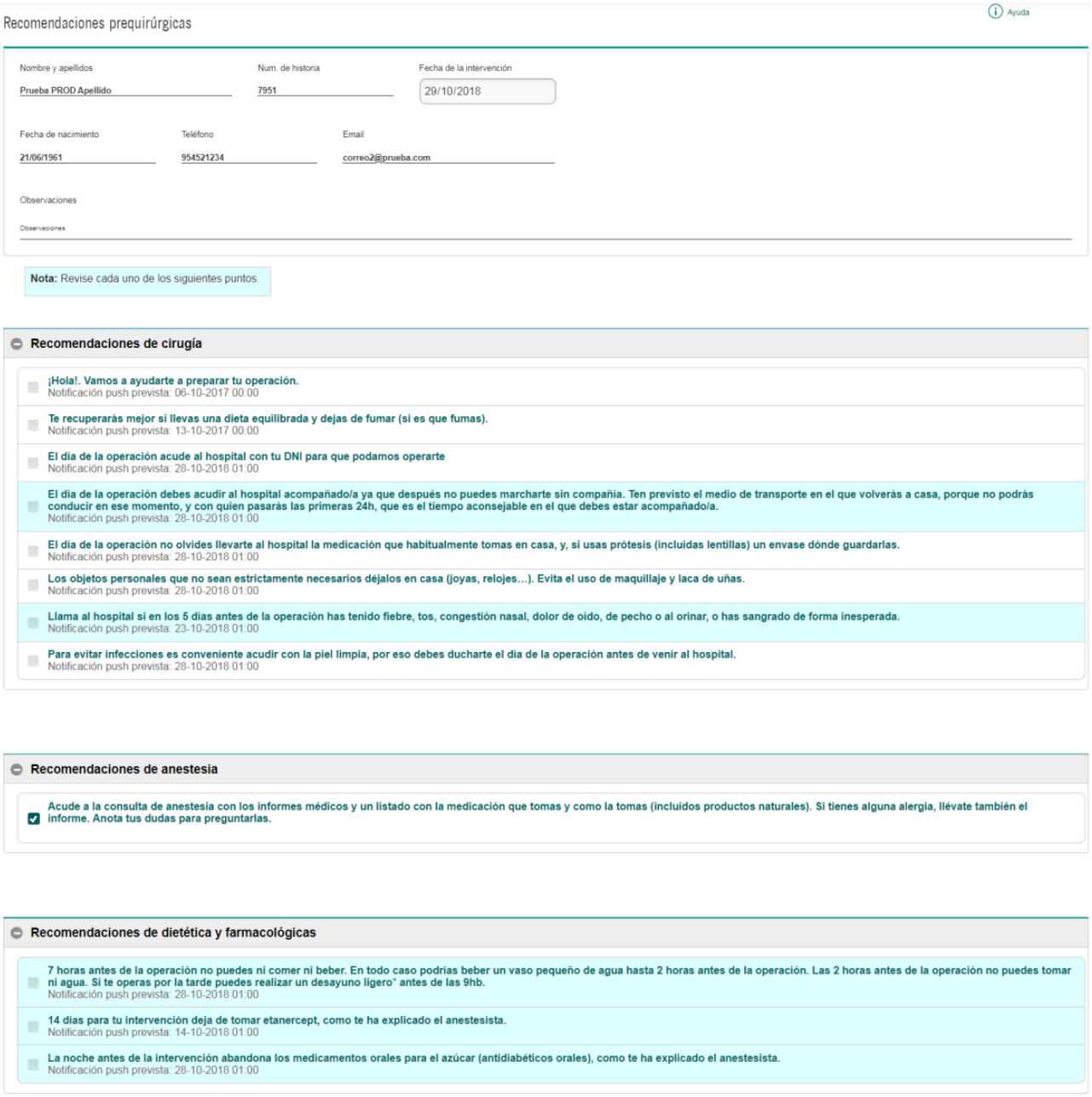
Figure 2. Screenshots of Listeo+ app.

Figure 3. Screenshot of the to-do list for patients in the Listeo+ app.



Once the app is downloaded, patients will be able to use a personalized QR code included in their printed recommendations that will allow them to access their episode identification data and their personalized recommendations already set up by their anesthesiologist in the Web-based Listeo+ module integrated into the EHR platform of the Hospitals (Figure 4). Simultaneously, the EHR also sends all the necessary data for the app via Web service establishing the communication between the EHR and the app for the very first time.

Figure 4. Screenshot of health care professionals' Listeo+ module within the electronic health record platform.



Any interaction between app users and individualized recommendations will be immediately notified to the Listeo+ module and visualized in the EHR platform, which will automatically send notifications to the mobile app as well as emails to the designated health care professional of the participating center in case a critical recommendation (recommendations that may pose a risk to the patient or in which patient noncompliance may lead to the suspension, cancellation, or rescheduling of surgery as stated in Multimedia Appendix 2) is not marked. Additionally, health care professionals will be able to contact by phone to encourage patients to meet the recommendation or solve any potential problem. Notably, the nature of the incident will always be registered.

Sample Size and Statistical Plan

The sample size required to estimate the main objective of this study was calculated as 395 patients per group for a total of 790 patients. This estimate was made assuming an alpha risk of .05, a beta risk of .2, and a difference in proportions between the groups of 10%. The analysis will be performed considering per intention-to-treat (ITT) and per protocol populations. The ITT population will include all randomized patients, whereas the per protocol population will include randomized patients who finally obtain an appointment to undergo MAS.

In addition, statistical analyses will be performed using the R software version 3.3.2 (R Foundation for Statistical Computing). For all analyses, an alpha risk of .05 will be assumed; therefore, to consider a statistically significant difference, the *P* value of the contrast statistic should be ≤.05. The statistical analysis planned *a priori* will consist of a descriptive analysis of the demographic and clinical characteristics of patients. For quantitative variables, the mean, SD, 95% CIs, variance, SE, 5% trimmed mean, median, minimum, and maximum will be

calculated. For qualitative variables, frequency distributions with their respective percentages will be calculated. To determine whether there are differences in the level of compliance with surgical recommendations between the group with written recommendations and the group with written recommendations plus the app, Fisher's exact test will be performed.

To assess the influence of sociodemographic and clinical characteristics of patients in the level of compliance with preoperative recommendations, multivariate logistic regression will be performed. Furthermore, the reasons for the exclusion of the ITT population will be included.

Allocation

Patients who meet the inclusion criteria and sign informed consent will be provided with an information sheet about the project and evaluated before participating in the study. To allocate patients to study groups, simple randomization 1:1 procedure will be used. To include patients in the study, each center will be provided with one randomization scheme generated by computer. Given the characteristics of the study, it is not possible to blind patients and professionals. Subsequently, we will collect sociodemographic data (age, sex, area of residence of patients, level of education of patients or caregivers using the app or patient or caregiver of the control group, occupation, marital status, and knowledge or handling of apps), clinical data (type of surgery, medical diagnosis [International Classification of Diseases, Ninth Revision], anesthetic evaluation, and medications taken), and functional situation by measuring disability (Barthel index).

Data Collection

All the study data will be collected through an electronic case report form (eCRF). To facilitate the completion of the eCRF, a specific module has been created and integrated into the EHR of the participating centers. The information that the researchers include in the eCRF will be exported to an anonymized database (without identifying patient data to ensure data confidentiality) for further analysis of the study data. The researchers will be responsible for creating a system that relates the numbers of the EHR (containing the eCRF data) with the anonymized code in the database where the data are exported and for maintaining the list of identification codes.

Instruments

The Barthel index will be used to assess physical dependence and loss of autonomy of patients at the point of patient reception and preparation. Health care professionals will score patients based on whether they did or did not require physical assistance to perform daily activities, ranging from 0 (patient is dependent in all assessed activities) to 100 (patient is independent to perform the reflected activities) [37,38].

The criteria of the *American Society of Anesthesiologists* (ASA) will be used to evaluate the anesthetic risk and identify the clinical outcomes in patients at the point of anesthesia consultation. It scores patient's overall health to describe 6 different levels (level I describes a normal healthy patient, whereas level VI describes a declared brain-dead patient whose organs are being removed for donor purposes) [39]. Only low-risk (ASA I and ASA II) patients are a candidate for MAS. Eventually, ASA III patients could benefit from MAS, after undergoing evaluation on individual basis for the risk-benefit balance of the ambulatory care (ie, ASA III without decompensation in the last 3 months) [10].

The information about mobile app usability by the intervention group will be collected through a modified version of the self-assessed mobile-based *Computer System Usability Questionnaire* [40]. Four focus groups—with 6-8 participants each—will be organized to collect qualitative data about the utility perceived by health professionals as well as intervention group patients' experience with the app.

Both research tools will provide very insightful information that will eventually lead to changes in the Listeo+ functionality or content. In the event an incident occurs involving the cancellation, suspension, or rescheduling of surgery, the consumption of hospital resources will be recorded (consumption of medications, hospital stay, consumption of laboratory tests, diagnostic imaging, etc).

Data Monitoring and Validation

Electronic monitoring of the completion of the eCRFs will be performed to detect missing information and possible data inconsistencies, thus, ensuring their quality. For this purpose, the researchers will be contacted during the patient recruitment phase, 3 and 6 months after the start of the project, using confidential information access codes. The inclusion of patients according to the established criteria (inclusion or exclusion criteria), the correct completion of the eCRFs, the signing and filing of the informed consent form of participating patients, and any other aspects required by the research team will be reviewed. The monitor will communicate to the corresponding research team the variables that must be reviewed in cases of lost or inconsistent data.

Technological Development, Integration, and Interoperability

To ensure proper communication between mHealth app users (patients and health professionals), a process of integration of information systems and interoperability between Listeo+ and EHR has been developed. This process was planned in 4 phases: (1) codesign of the system and pilot; (2) integration and technical tests; (3) simulation and pilot testing; and (4) real environment testing.

Ethical Aspects of the Study, Confidentiality, and Privacy

The study protocol has been evaluated and approved by the Regional Ethics Committee of Andalusia through the Biomedical Research Ethics Portal of Andalucía (PEIBA, for its acronym in Spanish). This study will be conducted in accordance with the principles of the latest version of the Declaration of Helsinki and will follow the Good Clinical Practice guidelines of Spain.

Written informed consent duly signed by all patients, legal representatives, or caregivers participating in this study will be collected before patient allocation to study groups. Data confidentiality will be protected under the Spanish law that

ensures the protection of personal data (Organic Law on Protection of Personal Data, 15/1999, December 13). The researcher of each center will be responsible for keeping a study file containing patient identification and information, including the informed consent form signed by patients. Throughout the study, all related documents will be located in a secure area of the participating center. Any analysis derived from the study will be performed from an anonymized database; it will not contain any identification of patients or caregivers but only a numeric code, through which it will not be possible to reveal their identities. At the end of the study, the researcher will be responsible for preserving the necessary documentation for at least 5 years.

Results

Currently, this study is in the recruitment phase, which will end once 790 patients are included (395 for each arm). The data collection and cleaning phases are estimated to be completed in April 2019, and the analysis with the final results will be conducted in July 2019.

Previously, the technical aspects of interoperability between the hospital and the Listeo+ app backend (set of system components accessible only to the developers or platform administrators) were resolved successfully, defining an application programming interface for Web services. In December 2016, an eCRF was created that was fully integrated into the EHR of the participating centers.

Prior to the recruitment of patients, a pilot phase was conducted in January 2017 with the aim of identifying complications in the subsequent phases of recruitment and data analysis. During the pilot phase, face-to-face sessions were held in the hospitals with both health professionals and specialized information and communication technologies personnel. In these sessions, test runs were performed with several patients, verifying the effective communication between the systems and the usability of the new functionality integrated into the EHR. As a result, a telephone call was included in the protocol, at 7 and 14 days after the provision of recommendations during the anesthesiologist appointment, for the patients of the intervention group who had not downloaded their personal preoperative recommendations using the QR code. In addition, two new recommendations were added (see Multimedia Appendix 2: R1_18 and R3_24), and the wording of the recommendations was modified to facilitate patient understanding. Simultaneously, improvements were made in the design and functionality of Listeo+.

Discussion

Principal Findings

The introduction of new multifunctional technologies allows achieving different objectives in patient preparation, providing personalized information, and establishing an effective communication channel that facilitates patient monitoring by health professionals [30]. The evaluation of initiatives based on new technologies in the health sector is a fundamental element because of its subsequent adoption by the different stakeholders (patients, health professionals, and decision makers). According to the World Health Organization (WHO), the lack of evidence on the effectiveness and economic impact of mHealth-based interventions is one of the most important barriers for implementing these programs within the framework of the European Union [41]. In this sense, it is necessary to perform initiatives aimed at generating evidence on the effect of compliance with preoperative recommendations and their economic impact in MAS using mHealth apps, which evaluate their utility and efficiency in critical areas such as surgical patient safety. Taking into account the increasingly important role of citizens and patients in health systems, the possibility of having information about user experience (perceived usability and utility) makes it possible to evaluate the suitability of these tools in a real clinical setting.

Relevance of the Study

Improvements in systems integration and interoperability could have great relevance. Currently, it has been possible to incorporate into the EHR of the participating centers a generator of preoperative recommendation lists that allows selecting the information according to individual patient characteristics. In addition, the structure of information systems for data exchange has been modified from the users' mobile device using Listeo+ and the EHR in these centers. The learning process and the improvement in systems integration and interoperability can be used for other initiatives within the framework of mHealth apps in Andalusia, a region with a favorable environment for the development of initiatives based on new technologies and, by extension, to the rest of the NHS.

Furthermore, the interest of the study lies in the increase in MAS and the adoption of mobile devices and acceptance of mHealth apps by the population. Thus, the number of MAS operations in developed countries has continued to increase in recent years. In 2015, in Spain, 1,632,824 MAS operations were performed, corresponding to an increase of 4.2% from the period of 2010-2015 [11]. In addition, it highlights that the penetration level of smartphones is also increasing, even among the elderly, reducing the generation gap [42]. Finally, data from a local survey on the use of mHealth apps show that 73.8% of patients would use them if recommended by their doctor, which suggests a high level of acceptance of mHealth apps by the population [43].

Limitations

This study has some limitations related to the design of the intervention and the methodology used. First, it is a randomized clinical trial with an *open-label* design. Although not blinding patients and professionals could lead to potential bias in the interpretation of results, this type of design is widely accepted in complex nonpharmacological interventions (eg, surgery and medical devices) [44] in which masking cannot be applied. Second, Listeo+ has been evaluated as a complement to SOC (written recommendations). In this sense, other published clinical trials based on MAS and Patient Support Programs also use this methodological approach where intervention is assumed as a complement to SOC [45,46].

Conclusions

In line with WHO guidelines, mHealth apps help search for new formulas that support patient safety by involving them in the care process and making them responsible for their own safety. Listeo+ mobile app will allow health professionals to monitor in real-time patients' preparation and critical preoperative recommendation fulfillment. The achievements obtained in the integration and interoperability of information systems prior to recruitment are considered a fundamental advancement in the development of strategies for mHealth app-based solutions. As a result, a reduction in avoidable preoperative cancellations due to a lack of or a poor patient preparation is expected, and self-assessed Web-based questionnaires and focus group will provide important information about the perceived usability and utility of Listeo+ app among patients and health care professionals.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Listeo+ promotional video.

[MOV File, 21MB - resprot_v8i1e10938_app1.mov]

Multimedia Appendix 2

MAS preoperative recommendations in Listeo+.

[PDF File (Adobe PDF File), 70KB - resprot_v8i1e10938_app2.pdf]

Multimedia Appendix 3

CONSORT-EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 2MB - resprot_v8i1e10938_app3.pdf]

Multimedia Appendix 4

Peer-review report and trial registration from the national funding agency.

[PDF File (Adobe PDF File), 33KB - resprot_v8i1e10938_app4.pdf]

Multimedia Appendix 5

Peer-review report and trial registration from the regional funding agency.

[PDF File (Adobe PDF File), 38KB - resprot_v8i1e10938_app5.pdf]

References

1. Waller A, Forshaw K, Carey M, Robinson S, Kerridge R, Proietto A, et al. Optimizing Patient Preparation and Surgical Experience Using eHealth Technology. JMIR Med Inform 2015 Sep 01;3(3):e29 [FREE Full text] [doi: 10.2196/medinform.4286] [Medline: 26330206]
2. Souzdalnitski D, Narouze S. Evidence-based approaches toward reducing cancellations on the day of surgery. Saudi J Anaesth 2014 Nov;8(Suppl 1):S6-S7 [FREE Full text] [doi: 10.4103/1658-354X.143921] [Medline: 25538524]
3. Mesmar M, Shatnawi NJ, Faori I, Khader YS. Reasons for cancellation of elective operations at a major teaching referral hospital in Jordan. East Mediterr Health J 2011 Aug;17(8):651-655. [Medline: 21977567]
4. Tung A, Dexter F, Jakubczyk S, Glick DB. The limited value of sequencing cases based on their probability of cancellation. Anesth Analg 2010 Sep;111(3):749-756. [doi: 10.1213/ANE.0b013e3181e661e8] [Medline: 20581163]
5. Kumar R, Gandhi R. Reasons for cancellation of operation on the day of intended surgery in a multidisciplinary 500 bedded hospital. J Anaesthesiol Clin Pharmacol 2012 Jan;28(1):66-69 [FREE Full text] [doi: 10.4103/0970-9185.92442] [Medline: 22345949]

6. Ezike H, Ajuzieogu V, Amucheazi A. Reasons for elective surgery cancellation in a referral hospital. Ann Med Health Sci Res 2011 Jul;1(2):197-202 [FREE Full text] [Medline: 23209975]
7. Garg R, Bhalotra AR, Bhadoria P, Gupta N, Anand R. Reasons for cancellation of cases on the day of surgery-a prospective study. Indian J Anaesth 2009 Feb;53(1):35-39 [FREE Full text] [Medline: 20640075]
8. González-Arévalo A, Gómez-Arnau JI, delaCruz FJ, Marzal JM, Ramírez S, Corral EM, et al. Causes for cancellation of elective surgical procedures in a Spanish general hospital. Anaesthesia 2009 May;64(5):487-493 [FREE Full text] [doi: 10.1111/j.1365-2044.2008.05852.x] [Medline: 19413817]
9. Martínez RF, Codina GJ, Deulofeu QP, Garrido CJ, Blasco CF, Gibanel GX, et al. [Indicators of healthcare quality in day surgery (2010-2012)]. Rev Calid Asist 2014;29(3):172-179. [doi: 10.1016/j.cali.2014.01.006] [Medline: 24636148]
10. Terol-García E, Palanca-Sanchez I. Manual Unidad de Cirugía Mayor Ambulatoria. Estándares y recomendaciones. [Major Ambulatory Surgery Unit Manual: Standards and recommendations.]. Madrid: Ministerio de Sanidad y Consumo. Gobierno de España. Centro de Publicaciones; 2008. URL: http://www.mscbs.gob.es/organizacion/sns/planCalidadSNS/docs/guiaCMA.pdf [accessed 2018-11-16] [WebCite Cache ID 71LgQ8cGM]
11. Ministry of Health, Social Services and Equality. [Statistics on Specialized Care Centers]. 2017. URL: http://www.mspsi.gob.es/estadEstudios/estadisticas/estHospiInternado/inforAnual/documentos/Indicadores_hospitalarios_Evolucion_2010-2015.pdf [accessed 2018-11-19] [WebCite Cache ID 71LkPvBEw]
12. OECDiLibrary. Paris: OECD Publishing; 2015 Nov 4. Health at a Glance 2015: OECD Indicators URL: https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2015_health_glance-2015-en [WebCite Cache ID 71MoZSOPx]
13. Guillén JM, Bernadó AJ, Solanas JAG, Guedea ME, Villahoz ER, Díez MM. [Cancellation in CMA: incidence and causes]. Cir Esp 2012;90(7):429-433. [doi: 10.1016/j.ciresp.2011.05.007] [Medline: 21835396]
14. Bernadó AJ, Artigas C, Elia M, Casamayor C, Gracia JA, Martinez M. Cancellations in ambulatory day surgery: Ten years observational study. Ambulatory Surgery 2006 Jan;12(3):119-123. [doi: 10.1016/j.ambsur.2005.09.002]
15. Dimitriadis PA, Iyer S, Evgeniou E. The challenge of cancellations on the day of surgery. Int J Surg 2013;11(10):1126-1130 [FREE Full text] [doi: 10.1016/j.ijsu.2013.09.002] [Medline: 24035905]
16. Lee CM, Rodgers C, Oh AK, Muckler VC. Reducing Surgery Cancellations at a Pediatric Ambulatory Surgery Center. AORN J 2017 Apr;105(4):384-391. [doi: 10.1016/j.aorn.2017.01.011] [Medline: 28336027]
17. Xue W, Yan Z, Barnett R, Fleisher L, Liu R. Dynamics of Elective Case Cancellation for Inpatient and Outpatient in an Academic Center. J Anesth Clin Res 2013 May 01;4(5):314 [FREE Full text] [Medline: 24286019]
18. Davidson S, McKendrick D, French T. Preassessment clinic interview and patient anxiety. Saudi J Anaesth 2016;10(4):402-408 [FREE Full text] [doi: 10.4103/1658-354X.177339] [Medline: 27833482]
19. Committee on Standards and Practice Parameters, Apfelbaum JL, Connis RT, Nickinovich DG, American Society of Anesthesiologists Task Force on Preanesthesia Evaluation, Pasternak LR, et al. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology 2012 Mar;116(3):522-538. [doi: 10.1097/ALN.0b013e31823c1067] [Medline: 22273990]
20. World Health Organization. WHO Guidelines for Safe Surgery 2009 Safe Surgery Saves Lives. Geneva: World Health Organization; 2009.
21. Grau M. [Utility of surgical checklists: effect on the relationships and communication in the work team, morbidity, mortality and patient safety]. Barcelona: Agència de Qualitat i Avaluació Sanitàries de Catalunya; 2015. URL: https://www.seguridaddelpaciente.es/resources/documentos/2016/seguridad-bloque-quirurgico/Listados_verificacion_quirurgica_AQuAS_2015_RedAgencias_MinisterioSanidad.pdf [accessed 2018-11-19] [WebCite Cache ID 71LlAWvNr]
22. Knox M, Myers E, Hurley M. The impact of pre-operative assessment clinics on elective surgical case cancellations. Surgeon 2009 Apr;7(2):76-78. [Medline: 19408797]
23. McKendrick DRA, Cumming GP, Lee AJ. A 5-year observational study of cancellations in the operating room: Does the introduction of preoperative preparation have an impact? Saudi J Anaesth 2014 Nov;8(Suppl 1):S8-S14 [FREE Full text] [doi: 10.4103/1658-354X.144053] [Medline: 25538529]
24. Gitelis ME, Kaczynski A, Shear T, Deshur M, Beig M, Sefa M, et al. Increasing compliance with the World Health Organization Surgical Safety Checklist-A regional health system's experience. Am J Surg 2017 Jul;214(1):7-13. [doi: 10.1016/j.amjsurg.2016.07.024] [Medline: 27692671]
25. Robotham D, Satkunanathan S, Reynolds J, Stahl D, Wykes T. Using digital notifications to improve attendance in clinic: systematic review and meta-analysis. BMJ Open 2016 Dec 24;6(10):e012116 [FREE Full text] [doi: 10.1136/bmjopen-2016-012116] [Medline: 27798006]
26. Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Atun R, Car J. Mobile phone messaging reminders for attendance at healthcare appointments. Cochrane Database Syst Rev 2013 Dec 05(12):CD007458. [doi: 10.1002/14651858.CD007458.pub3] [Medline: 24310741]
27. DeKoekkoek T, Given B, Given CW, Ridenour K, Schueller M, Spoelstra SL. mHealth SMS text messaging interventions and to promote medication adherence: an integrative review. J Clin Nurs 2015 Oct;24(19-20):2722-2735. [doi: 10.1111/jocn.12918] [Medline: 26216256]

28. National Institute of Statistics. [Survey on Equipment and Use of Information and Communication Technologies in Homes]. 2017 Oct 05. URL: https://www.ine.es/prensa/tich_2017.pdf [accessed 2018-11-19] [WebCite Cache ID 71MohD5cF]
29. Sotillos-González B, Buiza-Camacho B, Herrera-Usagre M, Escobar-Ubreva A, Fernández-Bermejo MC, Santana-López V, et al. [Citizen perspectives on doctor-prescribed mobile health apps and information and communication technology usage within the Andalusian Healthcare System]. Journal of Healthcare Quality Research 2018 Jul;33(4):225-233 [FREE Full text] [doi: 10.1016/j.jhqr.2018.04.004]
30. Iribarren SJ, Cato K, Falzon L, Stone PW. What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. PLoS One 2017;12(2):e0170581 [FREE Full text] [doi: 10.1371/journal.pone.0170581] [Medline: 28152012]
31. Marcolino MS, Oliveira JAQ, D'Agostino M, Ribeiro AL, Alkmim MBM, Novillo-Ortiz D. The Impact of mHealth Interventions: Systematic Review of Systematic Reviews. JMIR Mhealth Uhealth 2018 Jan 17;6(1):e23 [FREE Full text] [doi: 10.2196/mhealth.8873] [Medline: 29343463]
32. Armstrong KA, Coyte PC, Bhatia RS, Semple JL. The effect of mobile app home monitoring on number of in-person visits following ambulatory surgery: protocol for a randomized controlled trial. JMIR Res Protoc 2015 Jun 03;4(2):e65 [FREE Full text] [doi: 10.2196/resprot.4352] [Medline: 26040252]
33. Semple JL, Sharpe S, Murnaghan ML, Theodoropoulos J, Metcalfe KA. Using a mobile app for monitoring post-operative quality of recovery of patients at home: a feasibility study. JMIR Mhealth Uhealth 2015 Feb 12;3(1):e18 [FREE Full text] [doi: 10.2196/mhealth.3929] [Medline: 25679749]
34. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, KrleÅ¾a-JeriÄ‡ 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]
35. 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]
36. International Organization for Standardization. International Organization for Standardization. 1998. ISO 9241-11:1998. Ergonomic requirements for office work with visual display terminals (VDTs) Part 11 Guidance on usability URL: https://www.iso.org/standard/16883.html [accessed 2018-11-29] [WebCite Cache ID 74HtTKVxl]
37. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;10(2):61-63. [Medline: 3403500]
38. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J 1965 Feb;14:61-65. [Medline: 14258950]
39. American Society of Anesthesiologisths (ASA). ASA Physical Status Classification System. 2014 Oct 15. URL: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system [accessed 2018-11-19] [WebCite Cache ID 71MqqSIh5]
40. English LL, Dunsmuir D, Kumbakumba E, Ansermino JM, Larson CP, Lester R, et al. The PAediatric Risk Assessment (PARA) Mobile App to Reduce Postdischarge Child Mortality: Design, Usability, and Feasibility for Health Care Workers in Uganda. JMIR Mhealth Uhealth 2016 Feb 15;4(1):e16 [FREE Full text] [doi: 10.2196/mhealth.5167] [Medline: 26879041]
41. World Health Organization. Geneva: WHO Regional Office for Europe; 2016. From innovation to implementation:eHealth in the WHO European Region URL: http://www.euro.who.int/__data/assets/pdf_file/0012/302331/From-Innovation-to-Implementation-eHealth-Report-EU.pdf [accessed 2018-11-29] [WebCite Cache ID 74HtlyGUl]
42. Telefónica Fundación. Madrid: Editorial Ariel; 2016 Feb 22. [The Information Society in Spain 2015] URL: https://www.fundaciontelefonica.com/arte_cultura/publicaciones-listado/pagina-item-publicaciones/itempubli/483/ [accessed 2018-08-02] [WebCite Cache ID 71MrCcaew]
43. Herrera-Usagre M, Buiza B, Reyes-Alcázar V, Escobar A. ISQUA18-2423 Willingness to Pay for Government-Approved Mobile Health Applications and mHealth Social Acceptability In Spain. International Journal for Quality in Health Care 2018 Sep 18;30(Issue suppl_2):32-33 [FREE Full text] [doi: 10.1093/intqhc/mzy167.46]
44. Kahan BC, Cro S, Doré CJ, Bratton DJ, Rehal S, Maskell NA, et al. Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomised trials. Trials 2014 Nov 21;15:456 [FREE Full text] [doi: 10.1186/1745-6215-15-456] [Medline: 25416527]
45. Yu K, Zhou Y, Liu G, Li B, He P, Zhang H, et al. A prospective, multicenter, controlled, observational study to evaluate the efficacy of a patient support program in improving patients' persistence to adjuvant aromatase inhibitor medication for postmenopausal, early stage breast cancer. Breast Cancer Res Treat 2012 Jul;134(1):307-313. [doi: 10.1007/s10549-012-2059-8] [Medline: 22527106]
46. Oliveira-Ciabati L, Vieira CS, Franzon ACA, Alves D, Zaratini FS, Braga GC, et al. PRENACEL - a mHealth messaging system to complement antenatal care: a cluster randomized trial. Reprod Health 2017 Dec 07;14(1):146 [FREE Full text] [doi: 10.1186/s12978-017-0407-1] [Medline: 29116028]

Abbreviations

ASA: American Society of Anesthesiologists
HER: electronic health record
ITT: intention-to-treat
MAS: major ambulatory surgery
NHS: National Health System
QR: quick response
SOC: standard of care
SSC: surgical safety checklist
WHO: World Health Organization

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Protocol

Evaluating the Effectiveness of an App-Based Nurse-Moderated Program for New Mothers With Depression and Parenting Problems (eMums Plus): Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Postnatal depression adversely affects many mothers and infants with good evidence that caregiving difficulties associated with depressive symptoms play a key role in later adverse childhood outcomes. In many countries, there is only limited support available for women who experience symptoms of depression during the postnatal period, particularly those experiencing subthreshold symptom levels. Furthermore, mental health services and community family health services in many countries tend to focus primarily on providing help for depressive symptoms or maternal caregiving, respectively, despite these problems commonly being comorbid. Group-based nurse-led interventions delivered over the Web through mobile phone "apps" have the potential to be a cost-effective method of providing a large number of mothers with easy access to integrated support for both maternal depressive symptoms and caregiving difficulties.

Objective: This paper describes the protocol for a pragmatic randomized controlled trial of a 4-month group-based nurse-led intervention delivered over the Web when infants were 2-6 months. The primary aims of the trial are to determine whether the intervention (1) reduces levels of maternal depressive symptoms and (2) improves the quality of maternal caregiving when infants are 8-12 months of age.

Methods: The trial aimed to recruit and randomize 160 mothers of infants aged 2-8 weeks to either the intervention (eMums plus) or standard care. Assessments were completed when infants were aged 1-2 (preintervention), 8, and 12 months. The primary outcomes were the level of maternal depressive symptoms and the quality of maternal caregiving assessed when infants were aged 12 months. The intervention provided specific support for problems with mood and problems with caregiving. The intervention was delivered by community health nurses as a part of routine service delivery to mothers via a mobile phone app.

Results: Participant recruitment was carried out from March to July 2017. Follow-up data collection was completed in mid-2018. Data analysis has commenced.

Conclusions: In the past, many mothers participated in nurse-led face-to-face groups postnatally. However, mothers' groups held in clinics can be difficult for busy mothers to attend. The eMums intervention was delivered over the Web by nurses, allowing easy access by mothers early in an infant's life. The intervention was evaluated while delivered as part of the routine service practice by community child health nurses. The advantage of evaluating the effectiveness of the intervention in the routine service practice is that if it is found to be effective, it can be more easily adopted by the service provider than if it had been assessed in an efficacy trial.

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KEYWORDS

app; infant; mobile phone; mother-child relations; mother-child nursing; postnatal depression; protocol; randomized controlled trial

Introduction

Background

Postnatal depression is associated with a range of adverse child outcomes [1-3]. Furthermore, there is good evidence that caregiving difficulties associated with depressive symptoms play a key role mediating the association between maternal depression and adverse child outcomes [4-6]. A range of important caregiving practices are adversely affected by postnatal depression, including breastfeeding, sleep routines, health check attendances, and vaccinations [4]. Problems in all of these areas can adversely affect children's longer-term growth and development. The United Kingdom's National Institute of Clinical Excellence guidelines for ante- and postnatal care highlight that even subthreshold depressive symptoms can adversely affect mothers' general functioning and infant development [7]. This has led many countries, including Australia, to initiate universal screening programs to identify mothers with depressive symptoms [8]. However, a major ongoing challenge is the very limited availability of support services for mothers who screen positive and difficulty engaging busy new mothers with clinic-based treatment programs [8].

In 2014, a new National Institute of Clinical Excellence guideline specifically advocated for randomized controlled trials (RCTs) focused on mothers experiencing subthreshold depressive symptoms to test the effectiveness of interventions designed to improve mother-baby relationships in this large group of mothers [7]. In the Australian national postnatal depression screening program, 7.5% of women scored >12 on the Edinburgh Postnatal Depression Scale (EPDS), suggesting the presence of postnatal depression, and 8.0% scored in the range of 10-12 on EPDS [9]. The latter is important as subthreshold levels of postnatal depression symptoms in the early postnatal period are a risk factor for the development of postnatal depression and also have the potential to interfere with optimal mother-infant development [6,10,11]. The aim of this trial is to evaluate a new app-based intervention designed to help mothers experiencing postnatal depressive symptoms and parenting problems. The intervention employed mobile phone technology to provide easy access for a large number of new mothers to both nurse and peer support during the immediate postnatal period.

Two broad approaches have been used to help mothers with symptoms of depression and parenting problems. Commonly, these approaches are delivered in separate services and provide support for either depression or parenting problems. First, community child and family health services provide help that focuses on (1) improving maternal parenting skills and self-efficacy; (2) reducing mother-infant problems; and (3) supporting maternal health and well-being. A significant strength of community services is that they have direct contact with a very high proportion of all mothers during the immediate postnatal period. As such, they are well placed to screen mothers for the presence of problems and help a large number of mothers with difficulties in these areas. However, the help provided by these services is limited and largely focuses on caregiving problems rather than maternal depressive symptoms. Additionally, nurse training and confidence needed to manage maternal postnatal depression is often limited. The second approach, which is widely used in mental health services, typically employs psychosocial programs based on the cognitive behavioral therapy or interpersonal psychotherapy [7]. However, an important limitation of these programs is that, in contrast to child and family services, they largely focus on maternal depressive symptoms rather than caregiving problems [6]. Furthermore, mental health services often lack the resources to provide help to those with subthreshold levels of depressive symptoms, reserving treatment for those with serious mental illness. As a result, mothers with subthreshold depressive symptoms can have little or no access to professional services. Postnatal depressive symptoms also have unique triggers, such as the challenges of the transition to a parenting role, time demands required to care for new infants, and the potential for social isolation during this period. Given this, it is not surprising that there is little evidence that current mental health programs have a positive effect on mother-infant problems or longer-term child outcomes [12].

The intervention tested in this trial was based on the evidence that maternal self-efficacy and social support are two key mechanisms influencing the onset, maintenance, and impact of maternal postnatal depressive symptoms [13,14]. Perceptions of self-efficacy influence the extent to which individuals feel that they can cope with demanding life situations, and this, in turn, can shape affective responses to stressful role changes such as becoming a new mother [15]. For example, mothers who lack confidence in their ability to settle their distressed

infant are more likely to give up quickly, leading to a sense of failure and depressed mood [14]. They are then more likely to experience persistent infant problems, such as feeding and sleeping difficulties, placing them at greater risk for elevated depressive symptoms. Additionally, social support appears to play a protective function in the postnatal period by reducing the stress associated with the transition to motherhood [14]. However, greater family mobility, changes to female participation in the labor market, and increasing time pressures on young families have made access to traditional sources of family and professional support more difficult. These increase the risk that new mothers will become socially isolated and lack daily support [16]. As such, app-based interventions that facilitate easy access to social and professional support may be particularly important for new mothers experiencing depressive symptoms and struggling with parenting demands [17].

In order to support a large number of women who experience subthreshold levels of depression, new approaches are needed that can help a larger number of mothers than it is possible to support using traditional face-to-face programs. Web-based interventions are one way through which this can be achieved. Internet access among women of child-bearing age in Australia is now ubiquitous, with new mothers making extensive use of the internet to obtain child-raising information and social support. This has encouraged the development of numerous websites and "phone apps" by commercial, professional, and government organizations. However, health-related information on the internet can often be misleading and, occasionally, "utterly wrong" [16]. As well, there is a marked absence of evaluations assessing the extent to which Web-based information and support is utilized by mothers and improves maternal and child outcomes.

The intervention tested in this trial was based on our previous evaluation of "eMums," an innovative group-based nurse-led intervention delivered over the Web that provided support for common parenting difficulties for the general population of mothers [18,19]. The intervention tested in this trial "eMums plus" builds on this work, with the addition of integrated support for depression as well as parenting difficulties. The eMums plus intervention was based on 4 core principles. First, it was designed to provide both peer and professional support as there are a number of Web-based interventions that provide information alone without peer or professional support but when tested have very low usage rates [20,21]. Second, it was designed as an app-based intervention to enable easy access very early after birth without requiring travel or attendance at clinics at specific appointment times. Third, it was designed to have the capacity to support a larger number of mothers than is possible with face-to-face care. Finally, it was designed and tested in a pragmatic RCT in collaboration with a statewide Child and Family Health Service (CaFHS). This was done to ensure that the intervention was readily translatable into standard clinical practice in contrast to efficacy trials where interventions are generally developed and tested by researchers in academic settings and then have to be adapted to the demands of routine clinical service. To the best of our knowledge, no previous study has evaluated the effectiveness of a group-based nurse-led intervention delivered over the Web through routine services and designed to reduce maternal depressive symptoms and parenting problems.

Objectives and Hypotheses

The protocol for the study utilized an RCT to determine whether a 4-month group-based nurse-led intervention delivered over the Web through a mobile phone app when infants were 2-6 months reduced levels of maternal depressive symptoms and improved the quality of maternal caregiving when infants were aged 8-12 months.

We hypothesized that when their infants are aged 12 months, questionnaire scores and direct observation assessments would indicate that mothers who received the app-based intervention would be functioning better than comparison mothers with (1) lower scores on the EPDS [22] assessing the level of maternal depressive symptoms; (2) higher scores on the Parenting Sense of Competence Scale (PSCS) score assessing mothers' perception of their maternal caregiving competence [23,24] and lower scores on the Parenting Stress Index (PSI) [25] Competence subscale indicating the improved sense of competence in caregiving; and (3) higher scores on the Nursing Child Assessment Satellite Training (NCAST) Parent-Child Interaction Teaching Total Scale scores [26], assessing the quality of mother–child interactions, and lower scores of the PSI Attachment subscale indicating the improved parent-child relationship quality.

Methods

Study Design

The study was a pragmatic RCT of a group-based nurse-led intervention delivered over the Web versus "standard care." The trial was embedded into the routine service practice in the statewide CaFHS. This enabled the trial to examine whether the intervention was effective when delivered as a part of the routine service delivery [27,28].

Setting

Participants were recruited from 14 CaFHS sites located in major urban areas and a large regional center in South Australia. CaFHS is the key community health service in the State, providing a range of services for mothers and infants, including infant health checks and home-based maternal support.

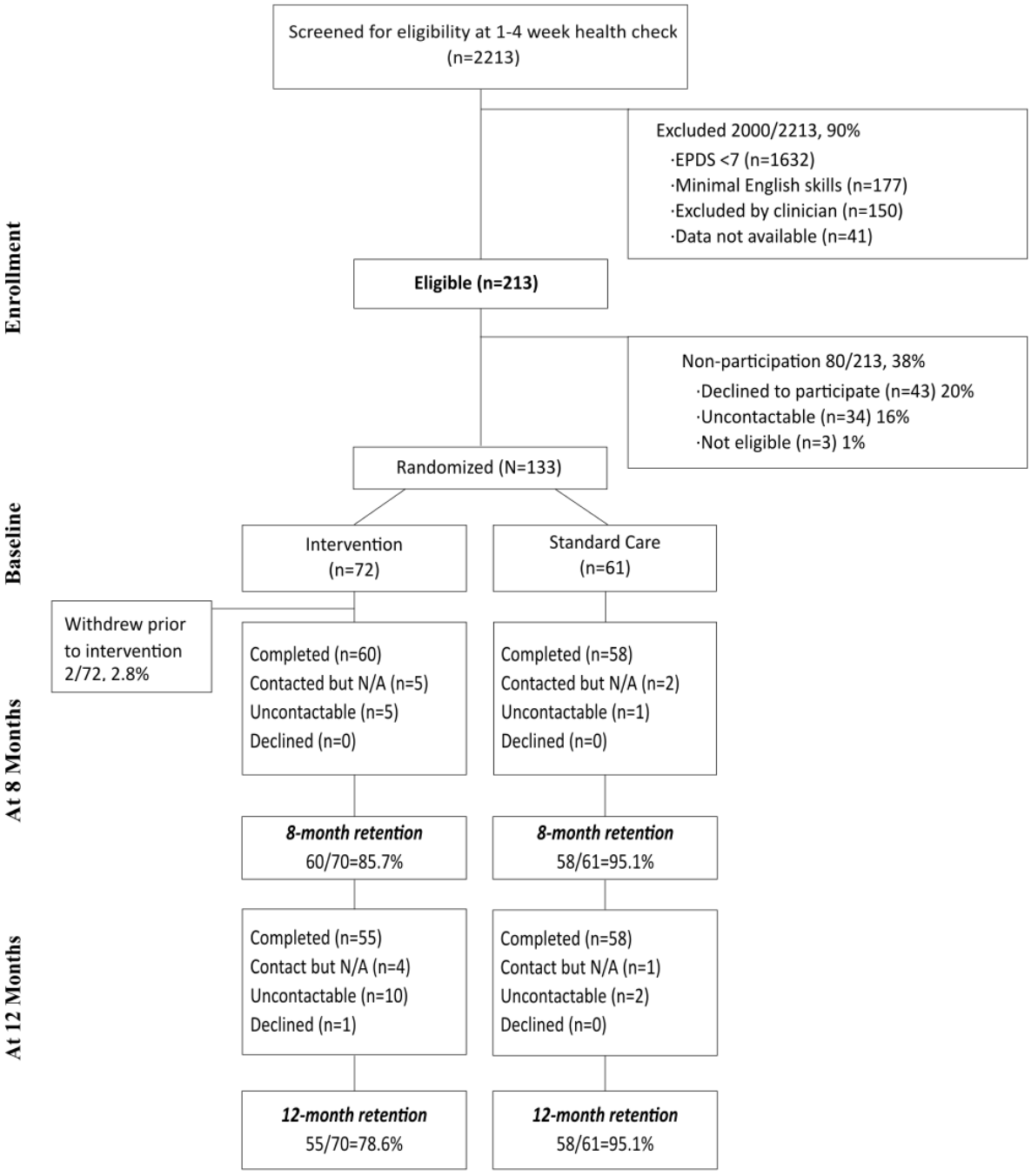
Participants and Recruitment

We aimed to enroll 160 mothers of infants aged 2-8 weeks at the time that they completed their 1-4-week postnatal health check with CaFHS (Figure 1). At the time CaFHS administration staff routinely made contact with mothers to organize their postnatal health check, potential participants were asked whether they were willing to consider participating in the research project should they prove to be eligible for the study. Mothers who indicated that they were willing to consider participation were asked to consent to allow their phone contact details to be passed on to the research team, if they were eligible for the study. During the postnatal health check, these mothers completed a questionnaire comprising a 4-item parenting problems scale and the EPDS [22]. Mothers who scored >7 on the EPDS and reported, at least, 1 problem on the 4-item parenting problems

questionnaire were eligible to participate. Following their postnatal health check, eligible mothers were contacted by telephone by the research team. The research team explained the study to the mother, sought verbal consent for a home visit by a member of the study's field-worker team, and randomized mothers to either the intervention arm or the comparison ("standard care") arm of the study. Field workers contacted mothers who had given their consent and arranged a time to visit them to complete the "formal" consent process and, where written consent was given, complete the baseline research assessment.

The exclusion criteria included mothers (1) with an EPDS score >13 and who were judged by their screening nurse to have a level of depressive symptoms that precluded their participation in the study; (2) those judged by their screening nurse to be experiencing domestic violence, illicit drug use, or other major distress that precluded their participation in the study; or (3) those who lacked sufficient English skills to complete the self-report questionnaires. Mothers with an EPDS score >13 whose nurses judged they would be able to participate in the trial were included provided they also had access to support from a family doctor or other health professional. All mothers identified as experiencing high levels of depressive symptoms (ie, >13 on the EPDS) were referred to other services, most frequently general practitioners. Such referrals occurred in both the intervention and comparison groups in this study.

Figure 1. Flow chart of participants. EPDS: Edinburgh Postnatal Depression Scale; N/A: not available.



Following randomization, mothers in the intervention arm were assigned to a group over the Web supported by a CaFHS nurse comprising approximately 20 mothers of similar-aged infants; they were also able to access standard care services as required. The intervention was delivered when infants were aged 2-6 months because this is (1) a key developmental period for infants; (2) a time when mothers are most vulnerable to depressive symptoms; and (3) as previously shown, it is the time when mothers most actively seek information from nurses and want to share and exchange ideas with each other [18].

Randomization

The trial used group randomization with blocks of 20 eligible mothers consecutively identified and then randomized to either the intervention or comparison arms of the study. A group randomization sequence was used to determine the arm to which each group was assigned. This approach ensured that mothers' groups in the intervention arm contained no more than 20 mothers per group. The randomization schedule was generated by a statistician who was independent of the study team. The research team was blind to group allocation at the time of recruitment and assignment of mothers to the study groups. However, due to the nature of the intervention, after the intervention commenced, it was not possible to keep research staff or field workers blind to the groups to which mothers had been allocated. The exception to this was research staff members coding the NCAST Parent-Child Interaction scale, who were blind to the group allocation while completing coding.

Intervention Delivery

The intervention comprised a 4-month group-based nurse-led program delivered over the Web by community health nurses to mothers via a mobile phone app when their infants were 2-6 months of age. A key premise of the intervention was that to be effective, help for new mothers experiencing problems with their mood and caregiving role must be closely integrated. To achieve this, the intervention was designed to (1) reduce maternal depressive symptoms; (2) support mothers to gain competence and self-efficacy in caring for their infants and solving caregiving difficulties; and (3) support mothers to achieve healthy lifestyles for themselves and their infants.

Nurses who delivered the intervention received training in the use and management of the app from the lead nurse who was extensively involved in the delivery of our original eMums program and from the research team. Nurses also received an additional 3 days of training in the delivery of the mental health components of the eMums plus intervention and general training in responding to those experiencing mental health problems (outlined below).

The "mother's view" of the app comprises 4 components, each of which is explained in an "Orientation" given at the beginning of the program (see Figure 2).

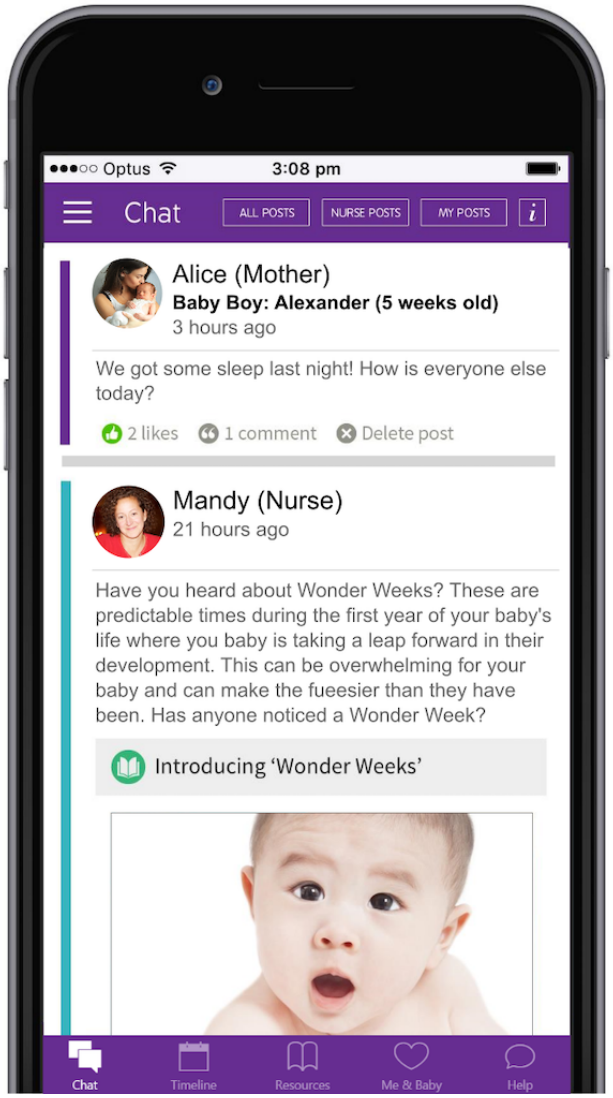
The components are highlighted in a "site-map" available with the app. The 4 components for mothers are as follows:

1. *Chat:* It contains a chat room where mothers post questions and nurses can reply with posts and comments visible to all group members in a similar format to Facebook. Mothers can also reply and answer each other's questions. The parenting and emotional health curriculum is posted on the chat room 2 times a week for mothers. Furthermore, the nurse posts additional content depending on the needs of her group.
1. *Timeline:* It provides a list of child development milestones and health reminders that provides guidance to mothers appropriate to their baby's age during the intervention. Mothers can record these items as "completed" on the eMums plus app. Nurses can also view the timeline to assess whether children have completed health checks and are meeting developmental milestones. Mothers can also access a maternal and infant "mood-rater" that allows mothers to monitor their own mood and nurses to track mothers' and infants' moods over time. It also contains an events calendar displaying topics that nurses discuss and other material relevant to the functioning of the group.
2. *Resources:* It contains short articles and activities on parenting and emotional health that make up the eMums plus curriculum, as well as additional information about other topics that may be useful for mothers. This is available for mothers to search as required if they are looking for accurate CaFHS-endorsed information on a particular topic. Mothers are able to post topics from the resources section into the chat page if they want to share information with the group.
3. *Contacts and Assistance:* It contains useful contact numbers and a portal through which mothers can privately message their group's nurse. Nurses are able to respond to mothers privately and send messages and notifications about upcoming discussions to all the mothers in their group.

The "nurses' view" of the app comprises 3 main elements as follows:

1. *Group Dashboard:* It displays information about individual groups such as group activities, notes maintained by nurses, and responses to mood ratings completed by mothers.
2. *Parent Dashboard:* It displays information about individual mothers, including parent case notes, individual website log-in activities (eg, when mothers view material, such as a depression module or the content of the chat room, mothers' latest ratings of their mood, and their babies' mood), and notifications that mothers have added information about children's milestones.
3. *Nurse Home Group:* It enables nurses to access their group's chat room and contains additional resources that nurses utilize (eg, information inserted into the group chat room such as messages, reminders, and curriculum topics). In addition to accessing the program on their computer, nurses also have a nurse-app installed on their mobile phones. This app contains all the features of the mothers' app, with additional capabilities that allow them to send messages and notifications about upcoming discussions to all the mothers in their group. At the beginning of the program, nurses welcome mothers to their group and outline the goals of the program. They explain how to make the best use of the app and its various features (eg, the use of notifications to mothers about when the nurse will be online and topics scheduled for discussion).

Figure 2. The eMums plus mobile phone app. (Source: image taken from eMums plus intervention).



Intervention Content

The intervention has 2 main curriculum components and a training component for nurses delivering the intervention. The curriculum consists of information provided to support mothers with parenting problems and a modulized program designed to reduce symptoms of depression.

Maternal Parenting Problems

For the eMums plus program, we have adapted existing CaFHS parenting resources to create an app-based intervention designed to help mothers with parenting during their infants' first months of life. The curriculum focuses on improving maternal caregiving through anticipatory guidance about infant development, problem solving, common parenting difficulties, promoting maternal sensitivity and responsiveness, and providing social support. The parenting content includes steps that mothers can take (1) to resolve common practical problems experienced by mothers of young children (eg, feeding, sleeping, and "settling") and (2) to look after their own health and well-being. It also shows mothers' activities that they can use to promote the health and development of their infants (eg, improving parent-infant attachment and stimulating infant language development). The curriculum is comprised of weekly modules containing information and links to further information in the "Resources" section of the website. This section can be accessed independently by mothers. While the curriculum has a schedule for delivery, nurses use their experience of child development and maternal psychosocial role adjustment, as well as the content of mothers' discussions and questions on the Web, to tailor the curriculum to each group's particular needs. This "just-in-time" approach is used because clinical experience suggests that new mothers primarily want information relevant to their specific situation and the age of their infant, rather than more broadly based anticipatory advice about what might occur in the future.

Maternal Depressive Symptoms

The curriculum addressing maternal depressive symptoms is adapted from the *Mothers and Babies Course*, a manualized group treatment program for postnatal depression [29,30]. The *Mothers and Babies Course* is an evidence-based program that has been demonstrated to reduce maternal depressive symptoms in efficacy trials [29,30]. Our adaptation of the *Mothers and Babies Course* makes it appropriate for delivery in combination with the parenting intervention content. The program is based

on the cognitive behavioral theory and attachment theory and targets the unique needs and stressors mothers face during the postnatal period. It has achieved promising results in initial trials delivered alone and in combination with a home-visiting program provided to low-income mothers. In the app, module content is presented in the form of text and video or audio messages. Each module provides mothers with a task to complete (eg, behavioral activation), with the aim of prompting group discussion and problem solving around the task, and engaging mothers in managing mood and the stressors of parenthood. The timing of the presentation of depression modules is based on children's ages, and they are largely "self-help" rather than requiring nurse assistance for their completion. The primary role of nurses is to encourage the use of the modules. Nurses receive training in the use of their content from a clinical psychologist trained in the delivery of the *Mothers and Babies Course*.

Mental Health First Aid

All nurses delivering the intervention completed the *Mental Health First Aid* [31,32] training program with the aim of improving their ability to identify depressive symptoms and provide support for mothers experiencing symptoms of postnatal depression. This training program was designed to help lay individuals and professionals develop skills in working with individuals developing mental health problems or in a mental health crisis. A meta-analysis of trials evaluating *Mental Health First Aid* has shown that this training increases participants' knowledge regarding mental health, decreases their negative attitudes, and increases supportive behaviors for individuals with mental health problems [33].

The use of these curriculum and training components ensured that the intervention appropriately addressed both maternal depressive symptoms and problems with parenting.

Standard Care

Only mothers in the intervention arm had access to the internet intervention. However, mothers in both intervention and comparison groups had access to standard care arrangements.

For the vast majority of mothers, standard care comprised a single home visit by a CaFHS nurse who checks the health of mothers and infants, provides advice about issues relevant to infant care, and offers information about other relevant community services available for mothers and infants.

Outcome Measures

All measures were completed when infants were aged 1-2 (preintervention), 8, and 12 months. Measures were completed during home visits conducted by trained field workers to ensure high-quality data. The primary outcomes for the trial were the level of maternal depressive symptoms and observed the quality of maternal caregiving assessed when infants were aged 8 and 12 months.

Maternal Depressive Symptoms

The EPDS is a 10-item self-report questionnaire that assesses the level of depressive symptoms experienced by mothers during the postnatal period [22]. Questions assess symptomatology during the previous 7 days and utilize a 4-point response scale and include items such as *"I have blamed myself unnecessarily when things went wrong "* and "*Things have been getting on top of me*." Scores on all items are summed and recommended cutoff points are available to identify mothers who would benefit from additional support [34]. Scores range from 0 to 30, with higher scores indicating higher levels of depression symptoms.

Maternal Caregiving

The Parenting Sense of Competence Scale

PSCS is a 16-item self-report questionnaire designed to measure the parental efficacy and satisfaction in the parenting role. Items are rated on a 6-point response scale and include "*Being a parent is manageable, and any problems are easily solved "* and "*Being a parent makes me tense and anxious*." Scores range from 16 to 96, with higher scores indicating higher levels of parenting competence. The scale has been successfully used with Australian mothers and has satisfactory psychometric properties [23,24].

Nursing Child Assessment Satellite Training Scales

NCAST scales are designed to assess the quality of mother–child interactions, including the sensitivity to cues, response to distress, fostering social–emotional functioning, and fostering cognitive growth [26]. For the purpose of this study, we used the Teaching Scale suitable for use with 0-36-month olds. The scale utilizes 3-5-minute video-recordings of mothers teaching their child a skill appropriate to the age of their child, selected from a list in the NCAST training manual. Field workers recorded mothers completing the teaching interaction during home visits. Subsequently, research assistants who have completed the NCAST training program coded the video-recordings to generate a total score and subscale scores [26]. Items were coded as "Yes" or "No" and include "*Child attempts to engage caregiver in eye-to-eye contact "* and "*Caregiver praises child's successes or partial successes*." Scores range from 0 to 73, with higher scores indicating higher levels of positive mother–child interaction quality. The NCAST scale has been found to have satisfactory psychometric properties [26].

Parenting Stress Index

PSI is a widely used self-report questionnaire designed to assess parent and child characteristics relevant to "parent-child systems" with acceptable psychometric properties [25]. Items consist of statements such as "*I often have doubts about my ability to handle being a parent "* and "*I expected to have closer and warmer feelings for my child than I do and this bothers me "* and are rated on a 5-point response scale. Relevant subscales assess maternal perceptions of parenting competence, the quality of parent-child relationships, and the impact of parenting responsibilities on autonomy and self-identity. Higher scores indicate worse functioning with scores for parenting competence (11 items, excluding 2 items assessing parental education) and the quality of parent-child relationships (7 items) with range 11-55 and 7-35, respectively.

Other Measures

Service Utilization

Service utilization was included as a secondary outcome for this study, as it is possible that mothers who received eMums plus required less support from other services. This information is routinely recorded by CaFHS, including the number of clinic visits and the number of health checks. Maternal self-report questionnaires identified other services (eg, general practitioners) used by mothers and infants.

Intervention Quality

Mothers' perceptions about the quality of the support provided by the intervention were assessed using a 40-item questionnaire after 8 months, which we have developed for this purpose. Items asked about the intervention effectiveness and usability of the mobile phone app. After 12 months, mothers were asked to answer 10 questions about what had been the most useful elements of the intervention.

App Usage

The extent to which mothers used the app was recorded. Data were automatically collected on a number of indices, including the number of log-ins, comments, and replies that mothers post, as well as the amount of time spent in different sections of the app.

Analysis Plan

Analyses will be by intention-to-treat and focus on intervention effects on maternal depression (EPDS) [22], mother–child interactions (NCAST) [26], and maternal caregiving competence (PSI and PSCS) [23,25] at 8 and 12 months. General linear modeling techniques will be used when the scores are continuous outcomes, including log-binomial regression for dichotomous outcomes (eg, the percentage of mothers scoring above recommended EPDS cutoff scores). Data collected at baseline will be used to control for any imbalances between the trial arms. Multiple imputations will be used to address missing data where this approach is appropriate.

Sample Size

The sample size target for this study was 160 (80 in each trial arm). This sample size would provide 0.80 power to detect an effect size of Cohen d=0.4 at an alpha of .05.

Ethics

Ethics approval was received from the Women's and Children's Health Network Human Research Ethics Committee (approval numbers SSA/16/WCHN/016, HREC/16/WCHN/014).

Results

Participant recruitment was carried out from March to July 2017. Follow-up data collection was completed in June 2018. Data analysis has commenced.

Discussion

The broad aim of this study was to assess whether a 4-month group-based, nurse-led intervention delivered through a mobile phone app when infants were aged 2-6 months reduced levels of maternal depressive symptoms and improved the quality of maternal caregiving when infants were aged 8-12 months. The intervention was assessed in a pragmatic RCT with the intervention delivered as part of the routine service practice by community child health nurses. The advantage of this methodology is that when an intervention is found to improve child and maternal outcomes services, it can be more readily taken up and continue providing this service using staff already experienced in delivering the intervention. It has been widely recognized in the medical and public health literature that results from such trials are more likely to be translated into practice than results from trials conducted in academic or research settings [27,28].

A large number of mothers experience subthreshold levels of postnatal depression, and it has been recognized that even subthreshold levels of depression can adversely affect maternal functioning and infant development. If the results from the trial demonstrate a positive effect, it will have established the basis for a new app-based approach that can help a large number of mothers experiencing depressive symptoms and caregiving difficulties early in their infant's life, including mothers in rural communities who frequently have limited access to clinic-based services.

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Conflicts of Interest

None declared.

References

1. Murray L. The impact of postnatal depression on infant development. J Child Psychol Psychiatry 1992 Mar;33(3):543-561. [Medline: 1577898]
2. Murray L, Arteche A, Fearon P, Halligan S, Goodyer I, Cooper P. Maternal postnatal depression and the development of depression in offspring up to 16 years of age. J Am Acad Child Adolesc Psychiatry 2011 May;50(5):460-470. [doi: 10.1016/j.jaac.2011.02.001] [Medline: 21515195]
3. Stein A, Gath DH, Bucher J, Bond A, Day A, Cooper PJ. The relationship between post-natal depression and mother-child interaction. Br J Psychiatry 1991 Jan;158:46-52. [Medline: 2015451]
4. Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. Infant Behav Dev 2010 Feb;33(1):1-6 [FREE Full text] [doi: 10.1016/j.infbeh.2009.10.005] [Medline: 19962196]
5. Field T. Infants of depressed mothers. Infant Behavior and Development 1995 Jan;18(1):1-13. [doi: 10.1016/0163-6383(95)90003-9]
6. Murray L, Cooper P, Fearon P. Parenting difficulties and postnatal depression: implications for primary healthcare assessment and intervention. Community Pract 2014 Nov;87(11):34-38. [Medline: 25612413]
7. National Institute for Health and Care Excellence. 2014. Antenatal and postnatal mental health: clinical management and service guidance URL: https://www.nice.org.uk/guidance/cg192 [accessed 2018-04-19] [WebCite Cache ID 73wOUddCF]
8. Buist A, Bilszta J, Milgrom J. beyondblue. 2005. The beyondblue National Postnatal Depression Program Prevention and Early Intervention 2001 – 2005 Final Report URL: https://www.beyondblue.org.au/docs/default-source/8.-perinatal-documents/bw0075-report-beyondblue-national-research-program-vol2.pdf?sfvrsn=2 [accessed 2018-04-19] [WebCite Cache ID 73wQyJWFB]
9. Buist AE, Austin MV, Hayes BA, Speelman C, Bilszta JLC, Gemmill AW, et al. Postnatal mental health of women giving birth in Australia 2002-2004: findings from the beyondblue National Postnatal Depression Program. Aust N Z J Psychiatry 2008 Jan;42(1):66-73. [doi: 10.1080/00048670701732749] [Medline: 18058446]
10. Henshaw C, Foreman D, Cox J. Postnatal blues: a risk factor for postnatal depression. J Psychosom Obstet Gynaecol 2004;25(3-4):267-272. [Medline: 15715025]
11. Dennis C. Can we identify mothers at risk for postpartum depression in the immediate postpartum period using the Edinburgh Postnatal Depression Scale? J Affect Disord 2004 Feb;78(2):163-169. [Medline: 14706728]
12. Murray L, Cooper PJ, Wilson A, Romaniuk H. Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression: 2. Impact on the mother-child relationship and child outcome. Br J Psychiatry 2003 May;182:420-427. [Medline: 12724245]
13. Cutrona CE, Troutman BR. Social support, infant temperament, and parenting self-efficacy: a mediational model of postpartum depression. Child Dev 1986 Dec;57(6):1507-1518. [Medline: 3802975]
14. Haslam DM, Pakenham KI, Smith A. Social support and postpartum depressive symptomatology: The mediating role of maternal self-efficacy. Infant Ment Health J 2006 May;27(3):276-291. [doi: 10.1002/imhj.20092] [Medline: 28640472]
15. Bandura A, Pastorelli C, Barbaranelli C, Caprara GV. Self-efficacy pathways to childhood depression. J Pers Soc Psychol 1999 Feb;76(2):258-269. [Medline: 10074708]
16. Plantin L, Daneback K. Parenthood, information and support on the internet. A literature review of research on parents and professionals online. BMC Fam Pract 2009 May 18;10:34 [FREE Full text] [doi: 10.1186/1471-2296-10-34] [Medline: 19450251]
17. National Institute for Health and Care Excellence. 2015 Feb. Postnatal care up to 8 weeks after birth URL: https://www.nice.org.uk/guidance/cg37 [accessed 2018-04-19] [WebCite Cache ID 73wQMIZ5F]
18. Sawyer MG, Reece CE, Bowering K, Jeffs D, Sawyer ACP, Mittinty M, et al. Nurse-Moderated Internet-Based Support for New Mothers: Non-Inferiority, Randomized Controlled Trial. J Med Internet Res 2017 Jul 24;19(7):e258 [FREE Full text] [doi: 10.2196/jmir.6839] [Medline: 28739559]
19. Sawyer M, Reece C, Bowering K, Jeffs D, Sawyer ACP, Peters JD, et al. Usage, adherence and attrition: how new mothers engage with a nurse-moderated web-based intervention to support maternal and infant health. A 9-month observational study. BMJ Open 2016 Dec 05;6(8):e009967 [FREE Full text] [doi: 10.1136/bmjopen-2015-009967] [Medline: 27496227]
20. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res 2009 Apr 24;11(2):e13 [FREE Full text] [doi: 10.2196/jmir.1194] [Medline: 19403466]
21. Waller R, Gilbody S. Barriers to the uptake of computerized cognitive behavioural therapy: a systematic review of the quantitative and qualitative evidence. Psychol Med 2009 May;39(5):705-712. [doi: 10.1017/S0033291708004224] [Medline: 18812006]
22. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987 Jun;150:782-786. [Medline: 3651732]
23. Johnston C, Mash E. A Measure of Parenting Satisfaction and Efficacy. Journal of Clinical Child Psychology 1989 Jun;18(2):167-175. [doi: 10.1207/s15374424jccp1802_8]
24. Rogers H, Matthews J. The parenting sense of competence scale: Investigation of the factor structure, reliability, and validity for an Australian sample. Aust Psychol 2004;39(1):88-96. [doi: 10.1080/00050060410001660380]
25. Abidin R. Parenting Stress Index™ 4th ed. Odessa, Florida: PAR; 2012.

26. Sumners G, Spietz A, editors. NCAST Caregiver/Parent-Child Interaction Teaching Manual. 2nd ed. In: NCAST Programs, University of Washington, School of Nursing. Seattle, WA: NCAST Programs; 2013.
27. Karanicolas PJ, Montori VM, Devereaux PJ, Schünemann H, Guyatt GH. A new 'mechanistic-practical“ framework for designing and interpreting randomized trials. J Clin Epidemiol 2009 May;62(5):479-484. [doi: 10.1016/j.jclinepi.2008.02.009] [Medline: 18468856]
28. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. CMAJ 2009 May 12;180(10):E47-E57 [FREE Full text] [doi: 10.1503/cmaj.090523] [Medline: 19372436]
29. Le H, Muñoz R. The Mothers and Babies Course: Instructor's Manual. Washington, DC: George Washington University; 2011.
30. Le H, Perry DF, Mendelson T, Tandon SD, Muñoz RF. Preventing Perinatal Depression in High Risk Women: Moving the Mothers and Babies Course from Clinical Trials to Community Implementation. Matern Child Health J 2015 Oct;19(10):2102-2110. [doi: 10.1007/s10995-015-1729-7] [Medline: 25673369]
31. Kitchener B, Jorm A, Kelly C. Mental Health First Aid Manual 2nd ed. Melbourne: Orygen Youth Health Research Centre; 2010.
32. Jorm AF, Kitchener BA. Noting a landmark achievement: Mental Health First Aid training reaches 1% of Australian adults. Aust N Z J Psychiatry 2011 Oct;45(10):808-813. [doi: 10.3109/00048674.2011.594785] [Medline: 21827342]
33. Hadlaczky G, Hökby S, Mkrtchian A, Carli V, Wasserman D. Mental Health First Aid is an effective public health intervention for improving knowledge, attitudes, and behaviour: a meta-analysis. Int Rev Psychiatry 2014 Aug;26(4):467-475. [doi: 10.3109/09540261.2014.924910] [Medline: 25137113]
34. beyondblue. Clinical practice guidelines for depression and related disorders - anxiety, bipolar disorder and puerperal psychosis - in the perinatal period. A guideline for primary care health professionals. Melbourne: beyondblue: the national depression initiative; 2011.

Abbreviations

CaFHS: Child and Family Health Service
EPDS: Edinburgh Postnatal Depression Scale
NCAST: Nursing Child Assessment Satellite Training
PSCS: Parenting Sense of Competence Scale
PSI: Parenting Stress Index
RCT: randomized controlled trial

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Protocol

Collecting Symptoms and Sensor Data With Consumer Smartwatches (the Knee OsteoArthritis, Linking Activity and Pain Study): Protocol for a Longitudinal, Observational Feasibility Study

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Abstract

Background: The Knee OsteoArthritis, Linking Activity and Pain (KOALAP) study is the first to test the feasibility of using consumer-grade cellular smartwatches for health care research.

Objective: The overall aim was to investigate the feasibility of using consumer-grade cellular smartwatches as a novel tool to capture data on pain (multiple times a day) and physical activity (continuously) in patients with knee osteoarthritis. Additionally, KOALAP aimed to investigate smartwatch sensor data quality and assess whether engagement, acceptability, and user experience are sufficient for future large-scale observational and interventional studies.

Methods: A total of 26 participants with self-diagnosed knee osteoarthritis were recruited in September 2017. All participants were aged 50 years or over and either lived in or were willing to travel to the Greater Manchester area. Participants received a smartwatch (Huawei Watch 2) with a bespoke app that collected patient-reported outcomes via questionnaires and continuous watch sensor data. All data were collected daily for 90 days. Additional data were collected through interviews (at baseline and follow-up) and baseline and end-of-study questionnaires. This study underwent full review by the University of Manchester Research Ethics Committee (#0165) and University Information Governance (#IGRR000060). For qualitative data analysis, a

system-level security policy was developed in collaboration with the University Information Governance Office. Additionally, the project underwent an internal review process at Google, including separate reviews of accessibility, product engineering, privacy, security, legal, and protection regulation compliance.

Results: Participants were recruited in September 2017. Data collection via the watches was completed in January 2018. Collection of qualitative data through patient interviews is still ongoing. Data analysis will commence when all data are collected; results are expected in 2019.

Conclusions: KOALAP is the first health study to use consumer cellular smartwatches to collect self-reported symptoms alongside sensor data for musculoskeletal disorders. The results of this study will be used to inform the design of future mobile health studies. Results for feasibility and participant motivations will inform future researchers whether or under which conditions cellular smartwatches are a useful tool to collect patient-reported outcomes alongside passively measured patient behavior. The exploration of associations between self-reported symptoms at different moments will contribute to our understanding of whether it may be valuable to collect symptom data more frequently. Sensor data–quality measurements will indicate whether cellular smartwatch usage is feasible for obtaining sensor data. Methods for data-quality assessment and data-processing methods may be reusable, although generalizability to other clinical areas should be further investigated.

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KEYWORDS

medical informatics computing; mHealth; patient-reported outcomes; musculoskeletal diseases; mobile phone

Introduction

The increasing uptake of consumer wearable devices provides an opportunity for health data collection in people's natural environments. Wearable devices permit frequent collection of patient-reported outcomes via touchscreen questionnaires alongside passively collected measures of behavior via sensors (eg, physical activity). This may help develop novel insights into conditions with symptoms that are otherwise difficult to track. Osteoarthritis is an example of such a condition. It is a prevalent, degenerative condition [1,2] where fluctuating pain and loss of mobility are the major symptoms. In knee osteoarthritis, increased physical activity may exacerbate knee pain. Conversely, certain forms of exercise are known to have a beneficial effect on pain symptoms [3,4]. Characterizing the relationship between pain and activity could help in the development of targeted interventions. However, in the past, it has been challenging to capture self-reported pain symptoms alongside objective measurements of physical activity. Typically, patients are asked to summarize or recall pain over large time periods (eg, "in the last week" or "generally this month") in paper-based questionnaires and self-report activity. Having continuous activity data alongside frequent pain reports would improve data quality and reduce recall bias.

Wearable consumer devices are increasingly popular as fitness tools [5]. Recently, consumer-grade cellular smartwatches (eg, Apple Watch, Huawei Sawshank, and LG Urbane) have been introduced to the market. These watches have similar functionalities as a mobile phone. Users can use them to make phone calls, navigate using global positioning system (GPS), or check emails. Like mobile phones, they have full-color touch screens, and like activity trackers (eg, Fitbit), they have a wide range of sensors that can measure users' behavior. Smartwatches could potentially be used to capture health-related data for research or clinical practice. Although the devices and accompanying software are well developed, various questions remain unanswered. Would participants wear the devices and self-report outcomes for a longer period of time? How can missing sensor data be handled? Is sensor data quality from smartwatch sensors sufficient? How can researchers or clinicians convert high volumes of sample-rate sensor data to meaningful outcomes? These questions need to be answered before consumer wearables can be used as novel interventions or to improve outcome assessment in clinical trials.

In this study, we developed a smartwatch app to collect patient-reported outcomes alongside sensor data using an Android Wear cellular smartwatch (Figure 1). The app was developed in collaboration with the Google Fit & Android Wear groups at Google UK.

The overall aim of this study was to investigate the feasibility of using consumer smartwatches as a novel tool to capture data on pain (multiple times a day) and activity (continuously) for 3 months in patients with knee osteoarthritis.

Specific study objectives were to test the feasibility, acceptability, and ongoing engagement with smartwatch data collection for research; to explore motivations, health behavior, and perceived impact of sensor data collection and frequent symptom reporting; to examine the association between twice-daily symptoms and weekly/monthly validated osteoarthritis questionnaires; and to explore the relationship between self-reported pain and activity levels. In addition, the analysis of exploratory observational data gathered in this study may serve as the first step toward the development of new outcome measures for remote monitoring of disease severity for use in clinical practice and research that incorporate both physical activity and pain.

Figure 1. Images of the Knee OsteoArthritis, Linking Activity and Pain app user interface; left: notification of an active survey and start screen of questionnaire; middle: data entry screen for survey "level of knee pain"; right: data are entered by swiping the numeric rating scale icon.

Methods

Overview

For this study, data were collected in three ways: via consumer cellular smartwatches (all participants), participant interviews at the beginning and end of the study (subset of participants), and via a baseline and end-of-study questionnaire (all participants). In this section, we first provide an overview of participants and the study process and then specify the data-collection methods.

Study Design

Participants and Recruitment

Eligibility criteria for participants were the presence of knee osteoarthritis (self-reported), age of 50 years or above, living in the Greater Manchester area or willing to travel to Manchester, owning a smartphone, and willing to participate in the *Cloudy with a Chance of Pain* study.

In July 2017, the study was advertised in local newspapers and magazines and via social media channels. Interested participants were invited to contact the study team, after which they were sent a patient information sheet and invitation to one of four enrollment events in September 2017.

Study Duration

The study was designed as a feasibility study in which people with knee osteoarthritis were asked to wear a consumer cellular smartwatch for 90 days. Additionally, participants were invited for voluntary participation in interviews at baseline and after completion of the study. The study was nested within an existing mobile phone study—*Cloudy with a Chance of Pain*—that examined the relationship between weather and pain among people with long-term pain conditions [6,7].

Smartwatches

The Huawei Watch 2 was used for the study. Google UK provided these cellular smartwatches with subscriber-identity module cards (enabling data collection and direct transmission, independent from a mobile phone). The watches were preinstalled with the Knee OsteoArthritis, Linking Activity and Pain (KOALAP) app developed by the Google Android Wear team in collaboration with the researchers (Figure 1). This app passively collected raw sensor data and launched various questionnaires to collect patient-reported outcomes (see Data Collection section). Patients wore the watch on the wrist that they found most comfortable.

Enrolment Event

At the enrolment event, participants provided written consent, completed the baseline questionnaire, and received the study smartwatch and user guide. Participants were asked whether they were willing to be considered as potential participants for two additional interviews (one at baseline and one at follow-up). Staff from Google attended the enrolment events to address any technical questions that arose. After setting up the smartwatch, participants downloaded the *Cloudy with a Chance of Pain* app on their mobile phone. During the setup of their *Cloudy* account, participants entered their unique KOALAP identifier for later pairing of data from both sources.

Study End

Participants returned their smartwatch in January 2018 (during the follow-up interview or by prepaid postage). They were each sent a link to an electronic end-of-study questionnaire about their experiences with the watch. Participants were given a £10 shopping voucher for completing the feedback questionnaire and for each interview they participated in, and they were reimbursed reasonable travel costs.

Data Collection

Smartwatch Use

Participants were asked to wear the smartwatch shortly after waking until going to bed. They were asked to respond to all symptom questionnaire notifications they received via the watch (maximum of 6 on Sundays, 5 on Wednesdays, and 4 on other days). Participants charged their smartwatches overnight. During charging of the watch, participants' activity and questionnaire data were uploaded to the servers (see Data Storage and Transfer section). Self-reported symptom data and passively collected sensor data were collected from participants via the smartwatch.

Self-Reported Symptom Data

During the smartwatch setup on Day 1, participants answered questions A1 to A4 displayed in Table 1. The answers to

question A2 to A4 were used in the recurring watch questions during the main study.

Four to five times a day, the watch app activated questions B1 to B5 (Table 2; Figure 2). These questions asked patients to record on 0-10 numeric rating scales the level of knee pain (twice daily), to what extent the knee pain affected their daily activities (daily), the level of knee pain after the important activity specified upon enrolment (daily), to what extent knee pain had prevented them from doing their painful activity specified upon enrolment (weekly), and their quality of life (weekly). An animated version of the user interface for answering questions is available in Multimedia Appendix 1.

In addition to the daily and weekly questions B1 to B5 (Table 2), participants were asked to answer 26 questions on their pain and function (monthly, on Days 14, 44, and 74 from the start point). These were taken from the standard Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire [8] (pain domain: Q1 to Q9, activities of daily life domain: Q1 to Q17) and rated on a 5-point Likert scale. We used only two KOOS subscales from the full KOOS questionnaire (42 items) to reduce the burden of data entry for participants.

Participants were alerted to the twice-daily and daily questions with watch buzzer vibrations. Questions opened on touching the notification. The watch vibrated when the survey was triggered and, if the questionnaire was not answered, every 2 hours until expiry of the question window. This time window comprised 4 hours for the twice-daily questionnaire, 7 hours for the daily questionnaire, 12 hours for the weekly questionnaire, and 7 days for the monthly questionnaire (Table 2). If participants did not answer a questionnaire within a fixed time period, the questionnaire was automatically dismissed. The watch did not vibrate after 9 PM. To avoid alert fatigue, the weekly and monthly questionnaires did not generate additional vibrations.

Sensor Data

The KOALAP app collected sensor data on the inertial measurement unit (accelerometer, gyroscope, and magnetometer) at 50 Hz, estimated pulse rate at 1 Hz, and barometer once per minute. These sampling frequencies balanced the battery life and data-collection frequency. Although the smartwatch was capable of collecting GPS data, this function was not used in order to achieve a battery life of 10-12 hours. To further preserve battery life, all smartwatch apps apart from the study app were disabled, and the watch was permanently prevented from data transmission (in “airplane mode”) until docked to a charger at night. Apart from the study app, participants could see a home screen that included the time, their daily step count, their last-measured pulse rate (with an option to see data from the complete day), and battery status. Figure 3 shows the home screen at 4:57 AM for a participant who has taken 0 steps, a heart rate of 66 beats per minute, a remaining battery life of 78%, and no outstanding questionnaires (or surveys) to complete.

Table 1. Baseline data items.

Item	Questions	Multiple choice answers
A1	In which of the following sites do you have OA[a]? (max 5)	Hand(s), Shoulder(s), Hip(s), Ankle(s), Foot/ feet
A2	In which knee is your OA typically more troublesome? (max 1)	Left, Right
A3	Thinking about your (A2: right/left) knee, what is the one activity, or action, that consistently causes you the most knee *pain*? (max 1)	Standing, Walking, Turning/twisting, Sitting for long periods, Sitting to standing, Squatting/bending/kneeling, Walking up stairs/inclines
A4	Thinking about your (A2: right/left) knee, what is the one activity, or action, most *important* for you to be able to do with minimal pain and difficulty? (max 1)	Socialise, Walk, Play sport, Do household tasks, Work effectively, Get washed and dressed

[a]OA: osteoarthritis.

Table 2. Questionnaire timings—vibrating notification trigger and completion window times.

Item	Frequency	Trigger time	Window	Question
B1	Twice daily	12:22 PM and 6:22 PM	12:22 PM-4 PM and 6:22 PM-10 PM	Level of knee pain
B2	Daily	5 PM	5 PM-12 AM	Knee pain affecting daily activities
B3	Daily	5 PM	5 PM-12 AM	Knee pain after (important activity A4)
B4	Weekly	Wednesday 12 PM	Wednesday 12 PM-12 AM	Knee pain preventing (painful activity A3)
B5	Weekly	Sunday 12 PM	Sunday 12 PM-12 AM	Quality of life
KOOS[a]	Monthly	Days 14, 44, 74 from start point	1 week	26 questions from KOOS questionnaire

[a]KOOS: Knee injury and Osteoarthritis Outcome Score.

Figure 2. Example of the input screen for the numerical rating scale in the Knee OsteoArthritis, Linking Activity and Pain app.

Figure 3. Watch homescreen of the Knee OsteoArthritis, Linking Activity and Pain app.

Data Collection via Mobile Phone

Via the *Cloudy with a Chance of Pain* mobile phone app, participants received a notification every day (default time 6:24 PM) to rate 10 aspects of their symptoms in the app on a five-point ordinal scale [6,7]. Optionally, participants could answer (any of) the 10 aspects additional times in a day, for example, in the case of changing pain. In parallel, the mobile phone's location services passively recorded geolocation hourly to enable collection of local weather data.

Data Collection via Participant Interviews

Participant interviews were conducted to explore motivations, health behavior, and perceived impact of activity monitoring for self-management and health behavior. All participants were invited to participate in two interviews (at baseline and end of study), and 19 participants (73%) agreed to participate. Sixty-minute interviews were conducted by a university researcher (KH) at the on-boarding/off-boarding events or the participant's home. Interviews were semistructured and guided by an interview schedule. Participants were asked about their general health and their experiences of living with osteoarthritis. Their motivations, expectations of the study, and previous use of electronic Health (eHealth) technologies were also explored. The interviews were analyzed using a grounded theory approach. Transcripts were coded using NVIVO by the research team, who met monthly to discuss emerging themes. Audio recordings from the interviews will be archived for a period of 10 years. Google will be provided with a copy of the summary report analysis of interview and questionnaire responses, but will not have access to interview audio recordings or transcripts.

Sample Size

A minimum sample size of 20 participants was required based on expected attrition. In a previous study assessing feasibility and acceptability of data collection via mobile phones in a population with arthritis, 30% of participants withdrew from the study [6].

Data Storage and Transfer

Smartwatch data were stored temporarily on the smartwatch in its SQLite database. When participants charged the watch, the watch stopped collecting data, disabled the airplane mode, uploaded all data to the server over 4G, and erased data from the watch. If the internal memory of the smartwatch was full, the watch stopped collecting data until it was charged again, and data were then successfully uploaded to the servers. This only happened if data were not uploaded to the servers for several days, because 4G connectivity was poor at the location of charging or because participants were abroad (no 4G connectivity).

The anonymized data were transferred in encrypted form over HTTPS to a remote server hosted by Google, where they were stored encrypted at rest in Spanner (Google LLC), Google's globally distributed NewSQL database. At no point were the data linked or will be linked to personally identifiable information such as name or email address. Details of Google's data center security are provided [9].

The decryption key to participants' anonymized data was stored securely on two separate university servers. At no time was the key shared with Google. Google will not have access to participants' names and will not therefore be able to personally identify any study participant. Google will only access the data for quality-control purposes and will not use the data for any other purpose. At the end of the study, once the university research team has indicated it is satisfied that all data have been received, Google will delete the data collected and provide written confirmation of data destruction.

Analysis

In this section, we present the analysis methods per the study objectives described in the Introduction.

Feasibility, Acceptability, and Ongoing Engagement

To assess feasibility, we will examine data completeness. For the sensor data, we will examine whether actual sampling frequencies are at least as high as that specified during app design. For the questionnaire data, we will examine the percentage of questions answered per day and per participant per day. To assess acceptability, answers to the relevant questions of the end-of-study questionnaire will be summarized as a percentage of participants selecting a multiple-choice option/giving a similar open answer. Patterns of engagement through time will be described with descriptive statistics per participant, such as percentage of questions answered (per day or per participant per day), hours of wearing the watch, and time in study.

Motivations, Perceived Impact of Continuous Passive Monitoring, Symptom Reporting, and Health Behavior

Thematic analysis (drawing on techniques of a grounded theory approach) will be used to identify initial themes and explore relations between themes and across cases (using constant comparison). In addition, relevant questions from the end-of-study questionnaire will be summarized as a percentage of participants selecting a multiple-choice option/giving a similar open answer.

Association Between Twice-Daily Symptoms and Weekly and Monthly Symptoms

We will examine the association between twice-daily and weekly symptom reports, including the variability in the twice-daily responses within the week. This analysis will have an exploratory nature and focus on generating hypotheses for future research. Panel linear regression and latent growth models will be used to assess how pain varies over the repeated observations (as reported in up to 4680 twice-daily questions, 2340 of each of the daily questions, 364 weekly questions, and 78 monthly surveys of 17 KOOS questions). Further exploratory work may investigate whether the variation in pain is homogenous throughout the sample (eg, with multilevel models) or whether some factors moderate/mediate these trajectories.

Relationship Between Self-Reported Pain and Activity Levels

Significant sensor data signal processing will be required to translate the raw sensor output into clinically meaningful variables. The physical activity outcomes we aim to create from the sensor data include amount of physical activity, characteristics of painful walking, and activity patterns that may aggravate pain.

Approaches to examine the relationship between symptom data and sensor data will likely include several processing steps such as extracting gravitational orientation vectors, computing dynamic body acceleration vectors, extracting properties of these vectors such as magnitude and direction, segmenting magnitude and direction vectors into behaviorally contiguous

time regions, extracting a range of features from these regions, and identifying regions that are most likely to correspond to gait or other behaviors implicated in pain aggravation. For these regions, measures of patterns of behavior relevant to patients with osteoarthritis can be estimated (eg, step count, time spent in sedentary behaviors, and time spent in motorized or other transport activities). These measures will then be compared to the self-reported measures using appropriate techniques (eg, prediction errors for interval self-report scales or classification errors for nominal scales). Self-reported scales will be interpolated to make such comparisons against continuous sensor data measures meaningful. Based on the processing of sensor data described above, we will explore patterns of physical activity-related behavior in participants. The metrics of physical activity derived from the sensor data will be summarized for all participants.

Results

Here, we specify the user interface of the KOALAP smartwatch application, the timelines for the study, and the review processes the study has undergone.

User Interface

Figures 1-3 show the user interface of the KOALAP smartwatch app. Multimedia Appendix 1 presents an animated version of Figure 2 that shows how data are entered in the user interface.

Timelines

Participants have been recruited in September 2017. Data collection via the watches was completed in January 2018. Collection of qualitative data through patient interviews is still ongoing. Data analysis will commence when all data are collected; results are expected in 2019.

Ethics

This study underwent full review by the University of Manchester Research Ethics Committee (#0165) and University Information Governance (#IGRR000060). For the qualitative data analysis, a system-level security policy was developed in collaboration with the University Information Governance Office. The project also underwent an internal review process at Google, including separate reviews of accessibility, product engineering, privacy, security, legal, and protection regulation compliance.

The results from this study will be disseminated at national and international conferences as well as in peer-reviewed journals and, where possible and appropriate, at public engagement events.

Discussion

KOALAP is the first health study to use consumer cellular smartwatches to collect self-reported symptoms alongside sensor data for musculoskeletal disorders. This feasibility study will assess the practicalities of recruitment and acceptability of using smartwatches to collect symptom and sensor data. In addition, the study will examine the relationship between passively recorded physical activity and patient-reported knee osteoarthritis symptom reports.

Although statistical power will be limited in this feasibility study, it will be the first step toward new methods for collecting health data and possibly generating novel outcomes.

The results of the feasibility study will be used to inform the design of future mobile health studies. Results for the first two objectives (feasibility and participant motivations) will inform future researchers whether or under which conditions cellular smartwatches are a useful tool to collect patient-reported outcomes alongside passively measured patient behavior. The third objective (exploration of associations between self-reported symptoms at different moments) will contribute to our understanding of whether it may be valuable to collect symptom data more frequently. Sensor data–quality measurements will indicate whether cellular smartwatch usage is feasible for obtaining sensor data. Methods for data-quality assessment and data-processing methods may be reusable, although generalizability to other clinical areas should be further investigated.

Acknowledgments

WGD led the conception of the protocol. ALB and MJP wrote the first draft of the protocol manuscript. All authors critically reviewed the protocol manuscript and approved the final version of the document. This project has been possible through collaboration with the Google Fit & Android Wear groups at Google UK. The Google team has collaboratively built the KOALAP app for self-reported data collection and the system for collecting and transmitting sensor data. This work was supported by Arthritis Research UK as part of the *Cloudy with a Chance of Pain* study (grant number: 21225). The work was further supported by the Arthritis Research UK Centre for Epidemiology (grant number: 20380). MP and TON receive salary support from the National Institute for Health Research as part of the Manchester Musculoskeletal NIHR Biomedical Research Centre Grant. ALB is supported by a Medical Research Council doctoral training partnership (grant number MR/N013751/1).

Conflicts of Interest

WGD has provided consultations for Google.

Multimedia Appendix 1

Animated version of the symptom-input screen of the Knee OsteoArthritis, Linking Activity and Pain App with the numerical rating scale.

[MP4 File (MP4 Video), 1MB - resprot_v8i1e10238_app1.mp4]

Multimedia Appendix 2

Electronic feedback questionnaire.

[PDF File (Adobe PDF File), 144KB - resprot_v8i1e10238_app2.pdf]

Multimedia Appendix 3

Peer-reviewer report from Arthritis Research UK.

[PDF File (Adobe PDF File), 104KB - resprot_v8i1e10238_app3.pdf]

References

1. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013 Sep;21(9):1145-1153 [FREE Full text] [doi: 10.1016/j.joca.2013.03.018] [Medline: 23973124]
2. Hunter DJ, Felson DT. Osteoarthritis. BMJ 2006 Mar 18;332(7542):639-642 [FREE Full text] [doi: 10.1136/bmj.332.7542.639] [Medline: 16543327]
3. Fransen M, McConnell S, Harmer A, Van der Esch M, Simic M, Bennell K. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015 Jan 09;1:CD004376. [doi: 10.1002/14651858.CD004376.pub3] [Medline: 25569281]
4. Uthman O, van der Windt DA, Jordan J, Dziedzic KS, Healey EL, Peat GM, et al. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. Br J Sports Med 2014 Nov;48(21):1579. [doi: 10.1136/bjsports-2014-5555rep] [Medline: 25313133]
5. Standing M, Hampson E. Digital health in the UK: An industry study for the Office of Life Sciences. 2015. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/461479/BIS-15-544-digital-health-in-the-uk-an-industry-study-for-the-Office-of-Life-Sciences.pdf [accessed 2019-01-10] [WebCite Cache ID 75KO5oHcu]
6. Reade S, Spencer K, Sergeant J, Sperrin M, Schultz DM, Ainsworth J, et al. Cloudy with a Chance of Pain: Engagement and Subsequent Attrition of Daily Data Entry in a Smartphone Pilot Study Tracking Weather, Disease Severity, and Physical Activity in Patients With Rheumatoid Arthritis. JMIR Mhealth Uhealth 2017 Mar 24;5(3):e37 [FREE Full text] [doi: 10.2196/mhealth.6496] [Medline: 28341616]
7. Druce K, McBeth J, van der Veer SN, Selby DA, Vidgen B, Georgatzis K, et al. Recruitment and Ongoing Engagement in a UK Smartphone Study Examining the Association Between Weather and Pain: Cohort Study. JMIR Mhealth Uhealth 2017 Nov 01;5(11):e168 [FREE Full text] [doi: 10.2196/mhealth.8162] [Medline: 29092810]
8. Roos E, Lohmander L. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003 Nov 03;1:64 [FREE Full text] [doi: 10.1186/1477-7525-1-64] [Medline: 14613558]
9. Google Data Centers. Data and security URL: https://www.google.com/about/datacenters/inside/data-security/ [accessed 2019-01-09] [WebCite Cache ID 75IpJzNrO]

Abbreviations

eHealth: electronic Health
GPS: global positioning system
KOALAP: Knee OsteoArthritis, Linking Activity and Pain
OA: osteoarthritis
KOOS: Knee injury and Osteoarthritis Outcome Score

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Protocol

Improving Blood Pressure Among African Americans With Hypertension Using a Mobile Health Approach (the MI-BP App): Protocol for a Randomized Controlled Trial

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Abstract

Background: African Americans shoulder significant disparities related to hypertension (HTN), which is a serious public health problem in the city of Detroit, Michigan, where more than 80% of the population is African American. Connectivity through smartphones, use of home blood pressure (BP) monitoring, and newly developed mobile health (mHealth) interventions can facilitate behavioral changes and may improve long-term self-care for chronic conditions, but implementation of a combined approach utilizing these methods has not been tested among African American patients with uncontrolled HTN. Since African Americans are more likely than other racial or ethnic subgroups to utilize the emergency department (ED) for ambulatory care, this presents an opportunity to intervene on a population that is otherwise difficult to reach.

Objective: The MI-BP app aims to reduce health disparities related to HTN in the community by employing a user-centered intervention focused on self-BP monitoring, physical activity, reduced sodium intake, and medication adherence. We seek to test the efficacy of MI-BP, an mHealth app for HTN self-management, on BP control (primary aim), physical activity, sodium intake, and medication adherence (secondary aim) in African Americans with HTN. This study also seeks to evaluate the cost-effectiveness of MI-BP when compared with usual care methods.

Methods: This is a 1-year randomized controlled trial that will recruit individuals who have uncontrolled HTN from 2 EDs in the city of Detroit, with a planned sample size of 396 randomized participants. To be eligible for inclusion, potential participants must be African American, 25 to 70 years old, previously diagnosed with HTN, have a smartphone compatible with MI-BP, and have uncontrolled BP at triage and on repeat measurement at least 1-hour post triage vitals. Once a participant is deemed eligible, all study procedures and subsequent follow-up visits (8 in total) are conducted at the Wayne State University Clinical Research Service Center. We seek to determine the effect of MI-BP on BP for 1 year (using BP control and mean systolic BP as coprimary outcomes and physical activity, sodium intake, and medication adherence as secondary outcomes) compared with usual care controls.

Results: Recruitment for this study began in January 2018. The study will continue through 2021.

Conclusions: As the first of its kind conducted in an ED setting, MI-BP was designed to document the efficacy and acceptability of a multicomponent mHealth approach to help African Americans with uncontrolled BP modify their lifestyle to better manage

their HTN. We expect to lay the foundation to sustainably reduce HTN-related health disparities through better integration of multiple behavior self-monitoring and improve outcomes for those who traditionally rely on the ED for chronic disease care.

Trial Registration: ClinicalTrials.gov NCT02360293; http://clinicaltrials.gov/ct2/show/NCT02360293

International Registered Report Identifier (IRRID): RR1-10.2196/12601

(JMIR Res Protoc 2019;8(1):e12601) doi:10.2196/12601

KEYWORDS

hypertension; mHealth; blood pressure; smartphone; mobile phone

Introduction

Background

Hypertension (HTN) is one of the most important cardiovascular disease risk factors affecting more than 100 million Americans under the new American College of Cardiology/American Heart Association (AHA) guidelines [1,2]. However, only about half of those with HTN achieve blood pressure (BP) control, and about 15.9% remain unaware of their condition [3]. Compared with whites, African Americans are more likely to develop HTN and have uncontrolled BP [4], increasing the risk of premature cardiovascular morbidity and mortality. African Americans are also more likely to utilize the emergency department (ED) for ambulatory care of chronic conditions such as HTN [5], a factor strongly linked with adverse cardiovascular events and diminished awareness of HTN [6], as well as lower BP control [7]. Although there are many reasons for such patterns of ED utilization, including poor access to primary care, and the ability to receive care at all hours regardless of the ability to pay, it serves to highlight the challenges certain populations face, which may have downstream effects on self-management.

Recommendations for improving HTN-related outcomes have been consistent for decades: maintain a healthy weight, reduce daily sodium intake, increase physical activity, and comply with antihypertensive therapy, as prescribed [8]. Despite strong evidence supporting these recommendations, facilitating the necessary behavior changes in patients with HTN remains difficult. African Americans, in particular, are less likely than whites to report adherence with such lifestyle and behavioral changes [3]. Moreover, existing interventions for improving BP typically focus on targeting 1 behavior, which may not be sufficient for improving BP control [9-12]. However, comprehensive evaluations of multiple health behavior change interventions, especially as they relate to BP control among African Americans, are lacking from the literature.

Accordingly, we sought to develop and test a mobile health (mHealth) approach to deliver a multiple behavior change intervention targeting BP reduction in African American ED patients with uncontrolled HTN. About 95% of American adults own some form of a mobile phone, and smartphone adoption is about the same in white and African American populations (77% and 75%, respectively) [13], yet African Americans are more dependent on smartphones for internet access than whites (24% vs 14%, respectively) [14], suggesting that an mHealth approach may be particularly useful in this population. Since BP is routinely measured in EDs, visits to the ED provide a unique opportunity to both identify patients with uncontrolled HTN and intercede, particularly in African American communities where regular interaction with the health care system may be lacking.

Study Objective

The purpose of this study is to establish the efficacy of MI-BP, a multiple behavior change intervention delivered via mHealth that supports achieving and maintaining BP control in African Americans who have uncontrolled HTN and are recruited from 2 urban EDs. This study also seeks to evaluate the cost-effectiveness of MI-BP compared with enhanced usual care methods.

Our primary study aim is to determine the effect of MI-BP on BP for 1 year (using BP control and mean systolic blood pressure [SBP] as coprimary outcomes) compared with usual care controls, in a 1-year randomized controlled trial (RCT) (NCT02955537). We hypothesize that at 1 year, BP control rates will be significantly greater in the MI-BP arm than in usual care. We also hypothesize that at 1 year, mean SBP will be significantly lower in the MI-BP arm than in usual care. Our second aim is to determine the effect of MI-BP on secondary outcomes (physical activity, sodium intake, and medication adherence) compared with usual care controls, in a 1-year RCT. We hypothesize that at 1 year, measures of physical activity, sodium intake, and medication adherence will be significantly better in the MI-BP arm than in usual care. Our third aim is to evaluate the cost-effectiveness of MI-BP compared with usual care methods. We hypothesize that the MI-BP approach will provide good value for money, both within-trial and long term. Here we describe the MI-BP approach that was developed for this study.

Methods

Overview

This is a 1-year, 2-arm, RCT of MI-BP versus enhanced usual care plus follow-up. The methods for this study have been approved by Wayne State University's (WSU) Institutional Review Board (IRB#: 040416M1F) and the University of Michigan IRBMED (HUM00114202).

MI-BP Intervention Description

MI-BP is a comprehensive, user-centered, multicomponent intervention that targets multiple behavior changes for managing HTN. The MI-BP intervention was developed building on our previous work with the BPMED text message intervention to improve HTN medication adherence in the same population [15]. Our design process incorporated target end user feedback

from the Hypertension Community Advisory Board in Detroit, Michigan.

The MI-BP intervention includes a smartphone-based app that incorporates the following components, which users are encouraged but not required to use. Vibrent Health (Fairfax, VA), a digital health company, was engaged to develop the app, online portal, and server platforms necessary to support this project.

Home Blood Pressure Monitoring and Tracking

MI-BP allows users to revicew both 1- and 4-week graphs of BP readings, collected via study-issued home BP cuffs. In addition to graphs, numerical logs of 1- and 4-week BP data are also available for review (see Figure 1 for screenshots of the MI-BP app). BP data can be either digitally synced, or manually entered into the MI-BP app. Participants with arm circumferences of 23 to 45 cm, which represents the majority of users, will receive a Bluetooth-enabled digital BP monitor (A&D UA-651BLE) that can store up to 30 BP measurements. With a touch of a button, this cuff can automatically sync collected measurements with the MI-BP app. For the participants who have an arm circumference between 42 and 60 cm, we will provide an extra-large arm monitor (LifeSource A&D UA-789). These cuffs are not Bluetooth-enabled and require manual data entry.

Users are instructed to measure and sync (or manually enter) their BP to the MI-BP app, at home, for a minimum of at least 3 days per week; however, daily self-monitoring and syncing are encouraged. When taking BP at home, users are instructed to take 3 consecutive readings and adhere to the following guidelines:

- Relieve yourself in the bathroom before taking BP, if needed.
- Keep arm at heart level by resting it on a table during monitoring.
- Sit in a chair with a back and with feet flat on the floor for at least 5 min before taking BP.
- Avoid tobacco, caffeine, or alcohol for 30 min before taking BP.
- Avoid taking BP right after exercise, when emotionally upset, or in pain.
- Avoid talking while taking BP.

In the event that a participant records a BP with systolic reading of greater than 180 mmHg or less than 100 mmHg, or a diastolic reading of greater than 110 mmHg, the MI-BP users are then instructed by the study staff at baseline, as well as by automated notifications within the app at the time of the elevated reading, to do the following:

- Wait for 5 min and then check BP again.
- If the SBP is still above 180 mmHg or less than 100 mmHg, or if the diastolic BP is still above 110 mmHg for 3 days in a row, call the research staff.
- Report to the ED and follow up after with a call to the research staff if experiencing symptoms of dizziness, chest pain, severe headache, visual changes, or numbness or weakness in face or extremities.

Physical Activity Monitoring and Tracking

MI-BP also allows users to view numerical logs, as well as 1- and 4-week graphs of physical activity data, such as steps counts and miles collected via study-issued Fitbit Zip pedometers (see Figure 1 for screenshots of the MI-BP app). These devices can store up to 30 days of step-count data. Recent work by Tully et al found the Fitbit Zip to be a valid measure of physical activity in free-living adults [16]. Users are instructed to wear their Fitbit daily and to sync the device at least once per week.

Sodium Intake Monitoring and Tracking

In addition to BP and physical activity, MI-BP allows users to track their daily intake of high-sodium foods using a checklist approach and monitor their intake over time with 1- and 4-week graphs. Rather than asking users to self-report all of the food they eat in a day, we take a more adaptive approach to estimate sodium intake. The MI-BP users are asked to self-monitor their intake of high-sodium foods, using a checklist-type log available within MI-BP. Our checklist comprises 7 categories, with 3 to 8 items per category. The categories and items included within were based on resources from the University of California, San Francisco [17], Centers for Disease Control and Prevention [18], and work by Smith et al [19], and they were refined based on our own team's expertise working within this target population. Each time an MI-BP user eats one of the foods on the checklist (regardless of portion size), we ask the participants to indicate this within the sodium log. At the end of the day, users should have a count of the number of times a high-sodium food was consumed in the day. Although we encourage users to track their intake of high-sodium foods daily, this is not required (see Figure 1 for screenshots of the MI-BP app).

Goal Setting

Physical activity goal setting is conducted weekly and step-count goals are displayed within the MI-BP app, as well as sent to users via push notification. Step-count goals are gradually incremented based on previous work from our team [20-24] and are calculated based on an average of 7 consecutive days of data, during which at least 5 of the days must be valid (ie, more than 200 steps per day). Calculated goals are never more than 600 steps more than the previous goal, which allows goals to be gradually incremented in order to reduce adverse events.

Figure 1. Screenshots from the MI-BP app.

Sodium intake goal setting is conducted every 2 to 4 weeks, and sodium intake goals are displayed within the MI-BP app, as well as sent to users via push notification (see Figure 1 for screenshots of the MI-BP app). MI-BP users are instructed to intensively self-monitor their diet every day for the first week of their intervention period. This 1-week period serves 2 purposes: (1) as an acclimation period in which the participants become familiar with the act of tracking daily sodium intake and (2) for use as a baseline assessment from which an average daily sodium intake measure is calculated and the first daily sodium goal is issued. After this baseline monitoring period, users are asked to log their intake of high-sodium foods for a 3-day period approximately 2 weeks later. If the user meets their sodium goal (defined as submitting log data for all 3 logging days where all 3 values are less than or equal to the goal), then the user will be issued a new, lower goal based on the submitted data and will be asked to again intensively monitor their food intake 4 weeks later. Failure to meet the sodium goal during the logging period will prompt the system to ask the user to complete another 3-day logging period 2 weeks later. The sodium goals are calculated using the following algorithm:

- For those who log an average of 2 to 6 items per day during their logging period, their new goal is 1 item less than the average.
- For those who log an average of 7 to 12 items per day during their logging period, their new goal is 2 items less than the average.

- For those who log an average of 13+ items per day during their logging period, their new goal is 3 items less than the average.

Messaging

MI-BP provides users with 4 different types of messages, which are sent via push notification and in-app messaging. These messages include educational messaging, motivational messaging, tailored messaging, and daily medication reminders. In addition to the daily medication reminders, MI-BP sends about 7 messages per week. To enhance long-term engagement with the intervention from participants, message content, frequency, and timing are varied and tailored wherever possible, to maximize user engagement (see Multimedia Appendix 1 for sample messages and Figure 1 for screenshots of the MI-BP app).

Educational Messaging

MI-BP provides users with educational messaging via push notification and in-app messages. Educational messaging topics include tips pertaining to tracking BP, physical activity, and sodium; tips pertaining to increasing physical activity, improving diet, increasing medication adherence, lowering BP, and making or maintaining behavior changes; and tips pertaining to overcoming barriers to behavior changes.

Motivational Messaging

In addition to educational messaging, motivational messaging and words of encouragement to meet goals are also provided to MI-BP users.

Tailored Messaging Relevant to Individual Participants

MI-BP also provides tailored messaging to users, including tips for overcoming specific, self-reported barriers to behavior changes (assessed at baseline and repeated at 6 months) and previous history of app usage (eg, reminders to sync or log data), along with reminders about self-monitoring protocols, and support for goal attainment, where applicable. For example, positive reinforcement messages are sent to the participants when goals are met, and action-oriented messages promoting behavior changes are sent when goals are not met.

Medication Reminders

MI-BP also enables users to set up daily medication adherence reminders (see Figure 1 for screenshots of the MI-BP app). The number of messages and the timing of those messages are customizable by the user to account for multiple antihypertensive medications and multiple doses per day. Although the study staff help users set up reminders at the time of randomization, users are free to modify these reminders at any time.

Clinical Setting

Participant recruitment occurs at the Detroit Medical Center (DMC) in the EDs of Detroit Receiving Hospital (DRH) and Sinai-Grace Hospital (SGH), both located in Detroit, Michigan. In Detroit, where 59% of the population lives in a medically underserved area, and an equal number (32.5% of individuals and 27% of families) live in poverty [25], reliance on the ED for primary care of chronic conditions such as HTN is commonplace. Once enrolled, the study participants complete all subsequent visits on the campus of WSU, in the Clinical Research Service Center (CRSC).

Recruitment

Recruitment occurs on site in the 2 EDs with active screening 24 hours per day, 7 days per week, 365 days per year. All patients that enter the ED are screened by trained research staff through the DMC electronic medical records system (Citrix Systems, Inc). Once a patient is deemed eligible, a research staff member approaches the patient's treating physician and asks if this study will benefit the patient's medical needs. Upon agreeance of the physician, the patient is then approached and educated on the study. If the patient is interested and agrees to participate in the study, an informed consent form is signed by the patient before any study procedure is done. Participants recruited to the MI-BP study are also approached during their baseline appointment to participate in an optional biorepository of blood samples collected during the trial. The biorepository has a separate consent process, which states that the participants' data from MI-BP are associated with their blood sample.

Eligibility Criteria

Inclusion Criteria

To be enrolled, potential participants must be African American and between the ages of 25 to 70 years, have been previously diagnosed with HTN, have a smartphone compatible with the mobile intervention, and have uncontrolled BP (SBP>135 mmHg) at triage and on repeat measurement using the BpTRU (Smiths Medical PM Inc, Waukesha, WI) device at least 1-hour post triage vitals.

Exclusion Criteria

Individuals who are pregnant; have serious existing medical conditions that may make BP control difficult or necessitate frequent hospitalization (ie, previous diagnosis of resistant HTN, steroid-dependent asthma or emphysema, cirrhosis or hepatic failure, stage C or D chronic heart failure, stage IV or V chronic kidney disease, and terminal cancer or ongoing active chemotherapeutic or radiation therapy); have a history of other serious medical conditions (eg, stroke, dementia, myocardial infarction or known coronary artery disease); or have a history of alcohol or drug abuse as determined by the CAGE-AID-Cut down, Annoyed, Guilty, Eye-opener Adapted to Include Drugs questionnaire (excluded if 2 or more) [26] are excluded.

Those who meet the eligibility criteria are enrolled in the ED and given a subsequent appointment for follow-up 1 to 2 weeks later at the WSU CRSC where BP is remeasured using the BpTRU device. To ensure that we are indeed including a sample with uncontrolled HTN, the participants who have a SBP<130 mmHg at that time are deemed ineligible and excluded from the study.

Sample Size

On the basis of data from our previous studies, we estimate that 30% of usual-care participants will achieve BP control (BP<130/80 mmHg) by 1 year. We consider at least 17.5% higher control rates for the intervention arm to be clinically meaningful. On the basis of a 2-sided chi-square test of

comparing 2 proportions at a 5% level of significance, the power for detecting the difference between MI-BP self-monitoring arm and usual care is 90%, with 161 participants per arm. Allowing for 19% attrition based on our previous work in similar patient populations, we plan to recruit 198 participants per arm, for a total of 396 participants. It is anticipated that at the end of trial, both groups will improve on average SBP. We estimate a 10- and 17- point drop in the usual care and MI-BP arms, respectively, at 1 year. Further, a constant between-subject SD of 10 mmHg is assumed, along with an intra-subject correlation of 0.5. With 161 subjects per arm, we can detect a group-by-time interaction with power >95% at 5% level of significance.

Procedures

Once enrolled and consented in the ED (weeks −1 to −2), participants are scheduled for a return visit in 1 to 2 weeks for their baseline appointment (week 0) at the WSU CRSC. As noted above, only those individuals with persistent uncontrolled HTN at this visit are eligible to remain in the study. Baseline data collection also occurs at week 0, and participants are given a prescription for antihypertensive therapy, and referrals to primary care are made by study physicians. For the participants already taking antihypertensive medications and who have an existing relationship with a primary care provider (PCP), we contact their PCP to inform them of our algorithm-based approach to antihypertensive therapy and work to coordinate any medication adjustments. In week 2, participants undergo medication titration, the process of adjusting antihypertensive medication dosages to ensure appropriate and optimal treatment, and are then randomized into 1 of the 2 study arms. Please see Multimedia Appendix 2 for the medication algorithm used in this trial for titration. From our previous unpublished work, we have determined that attrition is greatest between ED recruitment and the first follow-up visit. Thus, by delaying randomization until after this run-in period, we anticipate fewer participants will be lost to follow-up. Moreover, to reduce attrition, at baseline, we collect contact information for up to 3 alternate contacts, who we may call if we are unable to locate the participant to schedule data collection visits. Our staff also heavily rely on telephone calls and text messaging to participant smartphones to communicate as needed to coordinate scheduling, which tend to be the preferred modes of communication among participants. If needed and requested by participants, we also provide transportation to data collection visits. The MI-BP study staff take a participant-centered approach to trial management and are available daily to meet participant needs. Participants are encouraged to call the staff for any questions pertaining to their medications, their BP, technical issues with the intervention, or other issues that arise (see Figure 2 for a flow diagram of trial procedures). Peer-review report from the Center for Scientific Review has been provided in Multimedia Appendix 3.

Randomization is stratified by sex in blocks of equal size, allowing us to investigate sex as an effect-modifying biological variable. To control response fatigue, we created 6 different permutations of the baseline survey, each with a different order of instruments, which are also balanced within blocks. The research assistants responsible for arm allocation are blinded to block size to prevent contamination.

After randomization, all study materials, including any equipment and/or materials, are distributed to the participants according to the treatment arm. Medication titration occurs again at week 8, and at subsequent follow-up visits at weeks 13, 26, 39, and 52 to ensure optimal treatment. Data collection follow-up visits take place at weeks 13, 26, 39, and 52, where a consistent set of study measures is collected—BP, health status, weight, adherence to BP measurements, physical activity, sodium intake, and medication adherence self-monitoring. Technology acceptance measures, including perceived ease of use and perceived usefulness, are also collected.

For medication titration and follow-up visits, patients are instructed to bring their HTN medications with them so pill counts can be conducted. Pill counts are used to avoid prescribing potentially harmful up-titration in antihypertensive therapy for patients with elevated BP at follow-up visits that may be because of medication noncompliance. For patients who self-report not filling prescriptions between visits, or when the expected number of pills found in the participant's medication bottles (based on dosage and dispense date) suggests a less than 80% medication adherence, we continue with the same regimen without adjustment. We also monitor for any potentially harmful renal or metabolic issues at weeks 0, 26, and 52 and adjust medications accordingly. In addition to the medications, participants are instructed to bring study-dispensed devices so data can be downloaded, and adherence to self-monitoring behaviors can be ascertained.

Finally, to measure sodium intake, at weeks 0, 26, and 52, participants are given supplies to collect 24-hour urine for sodium measurement. This test reveals the amount of sodium ingested in the previous 24 hours and may identify whether sodium intake has been reduced. Study staff collect these specimens directly from the participants at their home to ensure compliance. All medication titration and study follow-up visits are free; however, participants are responsible for the cost of medications, PCP visits, or copays, as applicable.

All the participants are encouraged to contact the study staff for any assistance needed for the study, including assistance for technical and nontechnical matters. This is accomplished through in-app messaging (intervention arm only), as well as through handouts given at randomization and in person at each data collection visit.

Trial Arm Description

Participants are randomized equally to the 2 treatment arms, which include an enhanced usual care control arm as well as the MI-BP intervention arm.

Comparison Group: Enhanced Usual Care

The usual-care participants are given a prescription for antihypertensive medications, printed educational materials on HTN, and a home BP monitor for daily use, but they receive no further intervention (see Table 1); however, the participants take part in all study-specific follow-up visits. Although not all patients with HTN consistently utilize home BP monitoring, it is widely accepted as a guideline-based standard of care, making it appropriate to include in the usual care arm.

Figure 2. Trial procedure flow diagram.

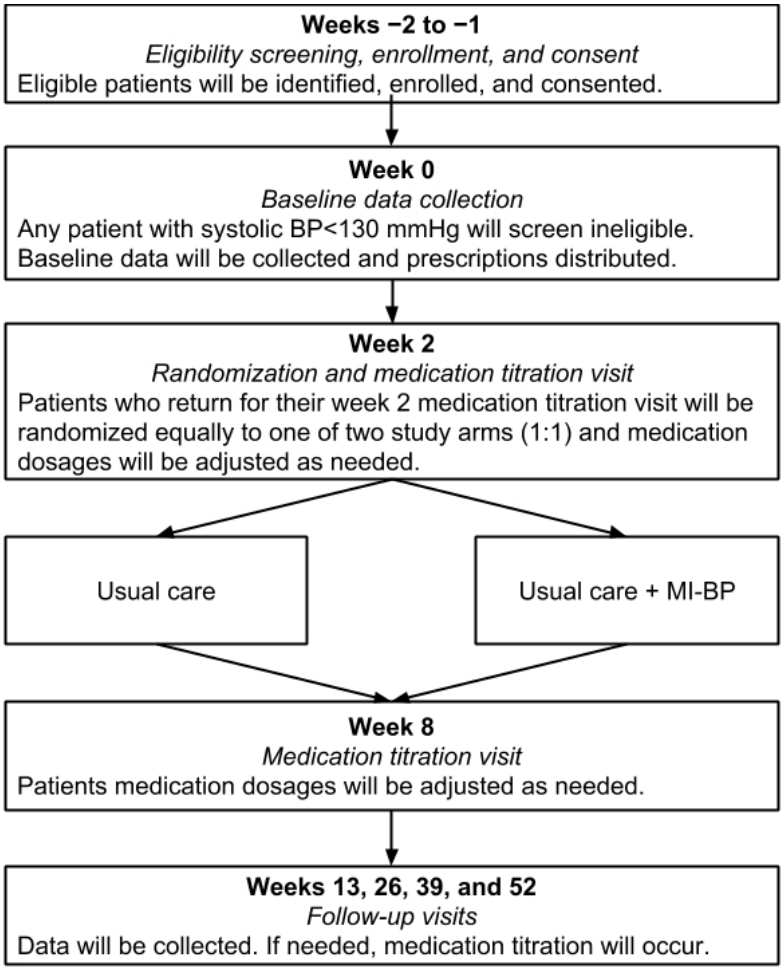


Table 1. Trial arms.

Components: intervention component	Trial arm	
	Usual care	Usual care + MI-BP
Prescription for hypertension medication	Yes	Yes
Referral to primary care if needed	Yes	Yes
Home blood pressure monitoring	Yes, but no digital tracking tools	Yes, with digital tracking tools via MI-BP app
Physical activity monitoring	No	Yes, with Fitbit or MI-BP app
Sodium intake self-monitoring	No	Yes, with MI-BP app
Medication reminders	No	Yes, with MI-BP app
Patient education materials	Yes, via pamphlet	Yes, with pamphlet or MI-BP app
Goal setting and motivational messages	No	Yes, with MI-BP app
Medication titration and data collection visits at weeks 2, 8, 13, 26, 39, and 52	Yes	Yes

Intervention Group: MI-BP, Technology-Enhanced Self-Monitoring

MI-BP participants receive an antihypertensive medication prescription and are asked to use the MI-BP intervention described above for 12 months.

Measures

Throughout this study, we are collecting a variety of different measures to help determine the feasibility and efficacy of MI-BP including BP, physical activity, sodium intake, and medication adherence. Given the number of measures we are assessing in this trial, our primary data collection visits at baseline and weeks 13, 26, 39, and 52 are lengthy and take about 90 min to complete. To reduce the effect of potential response fatigue because of participant burden, we have divided our surveys into

sections focused on measures pertaining to BP, physical activity, and sodium intake, and block orders are randomized among participants. The remaining data collection visits are 30 min or less in duration. While we are collecting a range of measures to ascertain intervention efficacy, our main outcome is differential BP change over time. Other measures will be included as covariates in the modeling of our main outcome and analyzed independently as exploratory end points. In this way, we will be able to capture information on the mediators of our main outcome along with independent effects on specific aspects of self-management.

Blood Pressure

We are collecting 2 types of BP data in this trial: in-clinic and home BPs. In-clinic BPs are assessed for every patient, regardless of trial arm, at every study visit by a trained study staff member using a BpTRU BP monitoring device. Home BP data are also collected from the intervention-group participants as a part of their use of the MI-BP app.

Physical Activity

A total of 2 different types of physical activity data are collected in this trial. All the participants, regardless of treatment arm, complete the International Physical Activity Questionnaire at baseline and weeks 13, 26, 39, and 52 [27]. In addition, the participants randomized to the MI-BP intervention group are instructed to wear their Fitbit Zip pedometer daily and asked to sync their Fitbit Zip using the Fitbit app at least once per week, which allows the MI-BP app to obtain their physical activity data.

Sodium Intake

Sodium intake is measured by 3 different ways. All the participants, regardless of treatment arm, are asked to complete the Block Sodium Screener at weeks 0, 13, 26, 39, and 52 [28], as well as a 24-hour urine sodium test at baseline and weeks 26 and 52. The latter provides an objective measure of the actual total daily sodium intake load. To complete the 24-hour sodium assessment, participants are provided collection materials during study visits and instructed to start their urine collection the following morning. The participants are instructed to start the 24-hour collection time immediately after the first-morning urination, which is discarded and not included in the collection. Participants collect all voided urine for the remainder of the day and night. The next morning, at the same time as day 1, participants collect the first-morning urine and add this to the total, so that a full 24-hour urine has been collected. Participants are instructed to store their specimen in the refrigerator during and after the collection process. Finally, the intervention-group participants are asked to periodically self-monitor their intake of high-sodium foods using a checklist approach, as previously described.

Medication Adherence

Medication adherence is measured by 3 different methods to gain a highly comprehensive approach to assess medication adherence, offsetting the weakness of each individual measure in the process.

Pill Counts

Participants are asked to bring all HTN medications to follow-up visits at weeks 2, 8, 13, 26, 39, and 52 so that pill counts can be conducted. Participants will be considered adherent if the number of pills remaining in the bottle is within 20% of the expected amount.

Self-Reported Adherence

Self-reported medication adherence will be assessed at baseline and weeks 2, 8, 13, 26, 39, and 52, with the Adherence to Refills and Medication Scale, a validated and widely used self-report measure [29].

Medication Adherence Assay

Blood samples are drawn at baseline and follow-up visits at weeks 13, 26, 39, and 52, and a liquid chromatography mass spectrometry (LC-MS) assay developed by Precera Bioscience, Inc (Brentwood, TN) is used to detect several hundred prescription medications, over-the-counter medications, and medication metabolites in each patient sample received (including all drugs incorporated into our treatment algorithm) in participant blood samples. This serves as a direct, objective assessment of medication presence and levels to measure medication adherence. This assessment will be compared with other measures of medication adherence. The assay imparts limited burden on participants, as it requires only 100 microliters of serum or plasma. Unpublished data from our previous work have shown that there is a negative relationship between assay adherence and change in SBP among patients prescribed less than or equal to 3 antihypertensive medications (Figure 3) [30].

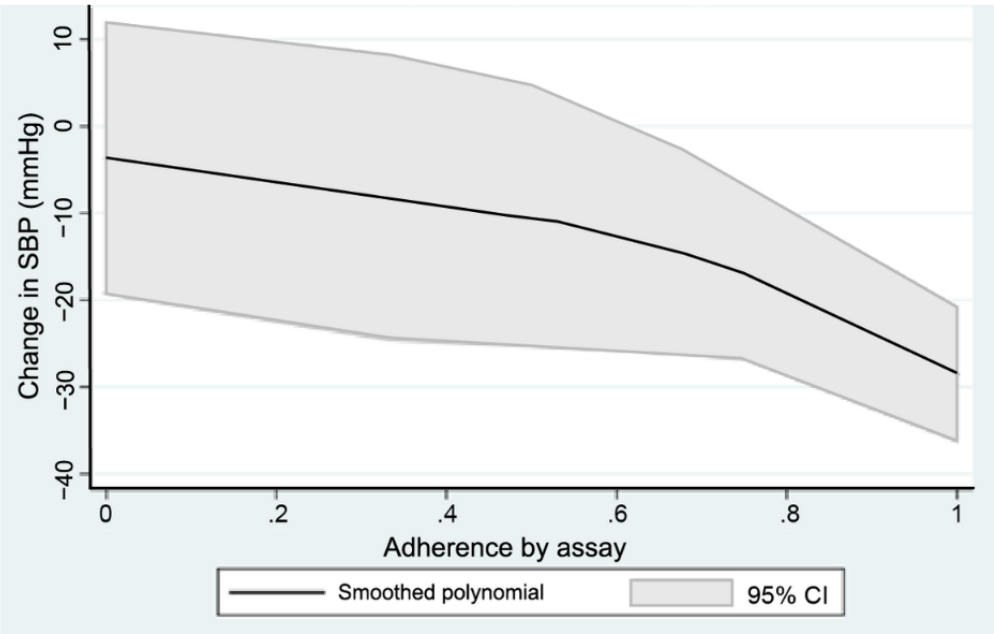
Self-Efficacies for Behavior Change

We collect various measures of self-efficacy for our target behavior changes at baseline and weeks 13, 26, 39, and 52, including physical activity via the Exercise Self-Efficacy Scale [31], medication adherence via the Medication Adherence Self-Efficacy Scale [32], and diet using an investigator-developed 11-item instrument assessing confidence in reducing sodium consumption, avoiding high-fat foods, avoiding sugar-sweetened beverages, and improving vegetable and legume intake.

Additional Health Measures

In addition to measures focused on specific behavior changes, we will also measure patient activation with the Patient Activation Measure [33], HTN knowledge with the 14-item Hypertension Evaluation of Lifestyle and Management Knowledge Scale [34], and functional status using the 12-Item Short-Form Health Survey (SF-12) at baseline and weeks 13, 26, 39, and 52 [35]. Additionally, we will measure health literacy via the 7-item Rapid Estimate of Adult Literacy in Medicine-Short Form at baseline [36], a modified Sugar-Sweetened Beverages measure at baseline and weeks 26 and 52 [37], and patient perceptions of the LC-MS assay for medication adherence, using investigator-developed questions, at week 52.

Figure 3. Association between assay adherence and change in systolic blood pressure (unpublished data from previous work). SBP: systolic blood pressure.



Technology-Related Measures (MI-BP Group Only)

To help put into context the intervention-group outcomes, we will assess several different technology-related measures, including technology acceptance (among the MI-BP participants only) via measures adapted from the Technology Acceptance Model by Davis that looks at participant perceptions of the perceived ease of use and perceived usefulness of MI-BP at weeks 13, 26, 39, and 52 [38]. We will also assess participant perceptions of the MI-BP intervention. Finally, MI-BP utilization will be assessed through usage log analysis at the end of the study.

Statistical Analysis Plan

Analysis of Blood Pressure Control

To determine the effect of MI-BP on BP at 1 year (aim 1) and to determine whether BP control is better in intervention-group participants compared with controls (hypotheses 1a), we will conduct a comparative analysis using a logistic regression with BP control as the outcome and study arm as the primary factor, controlling for demographic characteristics such as age, gender, medical history, baseline levels of functional status, health literacy, HTN knowledge, self-efficacy, and baseline BP at randomization. To determine whether mean SBP is better in the intervention group, compared with controls (hypothesis 1b), differential reduction in the coprimary outcome of SBP will be assessed in a linear mixed-effects regression framework, with time (baseline and end-of-trial), group, and time-by-group interaction as the primary independent variables. The subject-level characteristics used in the analysis of the primary outcome will be controlled in the regression model.

To determine the effect of MI-BP on secondary outcomes (aim 2), we will also use linear mixed-effects regression models with the secondary outcomes of interest as the dependent variables and week (as a continuous variable), study group, and week-by-group interaction as the primary independent variables. All appropriate model diagnostics will be carried out.

During data analysis, we will statistically address missing data resulting from incomplete data collection or participant attrition using the multiple imputation technique. Missing values will be imputed by repeatedly and iteratively fitting a sequence of regression models; it is a technique that is flexible in allowing different types of variables (categorical and continuous) to be imputed together without requiring any multivariate joint distributional assumption. Missing values are sequentially updated using bootstrap or Markov Chain Monte Carlo based on multiple regression models with other variables as covariates. This procedure will be conducted for 10 repetitions or cycles, a number considered adequate for most applications, thereby constructing an *imputed* dataset. Results from the 10 regressions will be combined with the imputed data using Rubin's formula [39].

Analysis of Cost-Effectiveness Data

Cost-effectiveness studies focused on mHealth interventions, specifically within the context of HTN, are lacking from the literature [40]. We will evaluate the cost-effectiveness of MI-BP using data from within the trial (aim 3); however, since HTN is a long-term chronic disease, the observed outcomes for the patients may not capture the entire benefit of the intervention. As such, we will also use a modeling approach to simulate patient lifetime outcomes, given their health status and trajectories at the end of the trial. We hypothesize that MI-BP will be cost-effective compared with usual care.

Costs will be prospectively collected from DMC, which serves most of the health needs of enrolled individuals. For the within-trial cost-effectiveness analysis, we will use ED, pharmacy, outpatient, estimated patient costs, and hospital cost data. Quarterly SF-12 assessments will be converted into utility measures using the methods of Brazier et al [41] and aggregated

over the year to calculate quality adjusted life years (QALYs), a standard health-economic measure to compare across interventions. Total costs and total QALYs will be calculated for both arms. The MI-BP arm will be compared with usual care using an Incremental Cost-Effectiveness Ratio, a measure that compares health value for money. Bootstrapping will be used to assess uncertainty around the mean estimates, and it will be used to create cost-effectiveness acceptability curves [42].

For the long-term cost-effectiveness analysis, we will create a mathematical model of long-term quality of life and mortality because of HTN, which will be based upon other models in the literature, such as the approach used by Smith-Spangler et al [43], which modeled the relationship between SBP and long-term heart attack and stroke using a logistic risk function based on the Framingham data. Costs of disease states such as heart attacks and strokes will be taken from extant literature and databases such as the Medical Expenditure Panel Survey and Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality. Health utilities will be taken both from the utilities collected and the medical literature (particularly for heart attacks and strokes). The models will begin with the health state of the participants at the end of the trial and will model health outcomes into the future. We will explore various assumptions about the durability of BP changes (eg, continuing improvement, stable BP, regression to prestudy BP levels). These cost-effectiveness analyses will follow standard guidelines for a *reference case* analysis, while the modeling approach and analysis will follow recent guidelines [44-46].

In addition to analyses for our stated aims, we also intend to conduct analyses to look at the patterns of MI-BP use that are associated with improved outcomes. For each of our self-monitoring behaviors (BP, physical activity, sodium intake, and medication adherence), we will calculate an overall utilization rate by dividing the number of logged data points by the total number of expected data points. Adherence to behavioral self-monitoring uptake for each activity will be compared within the MI-BP arm by means of count regression with the number of adherence instances (among the repeated observations) as outcome. Models will be controlled for variables similar to those in aim 1. To investigate whether better adherence to the self-monitoring uptake corresponds to an improvement in BP, we shall use a mixed-model analysis similar to that in aim 1 with BP measure as outcome and adherence as time-dependent binary covariates. Different self-monitoring behavioral components will simultaneously be used in the same model.

Results

The recruitment period for the study began in January 2018 and was met with challenges because of overly restrictive inclusion criteria. Please see our section on Limitations for further discussion. After amending our protocol, recruitment efforts have become more fruitful, and this study is expected to conclude in 2021.

Discussion

Principal Findings

At the conclusion of this study, we expect to be able to demonstrate the efficacy of using a novel and innovative multicomponent mHealth approach for supporting HTN management in a community that has exceedingly high prevalence of untreated chronic diseases. By incorporating mobile devices in a population that has high smartphone adoption rates, mHealth interventions may be superior compared with usual care methods. We anticipate that by focusing on multiple health behaviors, such as diet and exercise, along with promoting self-monitoring, we will reduce HTN-related disparities in African Americans with uncontrolled BP. We will be able to document the efficacy of MI-BP and learn from our participants how to overcome barriers to BP control, ultimately reducing deaths from HTN-related cardiovascular disease.

Comparison With Previous Work

Although mHealth approaches for targeting HTN have been previously reported, most are focused on single behavior interventions that utilize simple platforms such as text messaging [40]. Moreover, despite the promise of mHealth for HTN, a recent scientific statement of the AHA on the use of mHealth for cardiovascular disease prevention found only 13 RCTs of sufficient quality focused on mHealth to promote BP control, of which only 4 utilized smartphones for intervention delivery. Furthermore, of the 69 total studies identified for cardiovascular disease prevention, it was noted that most relied on short message service text message and internet-mediated delivery modalities, and few used more advanced mHealth approaches, such as those incorporated into MI-BP. Although the AHA scientific statement acknowledged promise for mHealth approaches to reduce SBP, several limitations of the available research were noted, including a lack of understanding about which intervention components led to behavior changes, a lack of understanding of factors that contribute to technology use, and short-term (less than 6 months) follow-up [47].

This study builds upon our previous work with BPMED, a single-behavior change intervention, delivered via text messaging, to target medication adherence in this same population [15]. Our work with BPMED demonstrated the feasibility and acceptability of using a mobile approach within this target population. This MI-BP trial extends our previous work by using a more robust platform that targets many of the recommended self-care behaviors for managing HTN, and it is in line with the more sophisticated mHealth interventions for HTN that are missing from the literature [40]. There has been some acknowledgement in the literature that more sophisticated apps, with more comprehensive feature sets, may be more effective in lowering BP [48]. Furthermore, although this MI-BP trial is just 1 of several ongoing trials targeting HTN with mobile approaches, to the best of our knowledge, this is the only study that seeks to understand how such an intervention may affect African Americans in urban environments, where HTN-related health disparities are common.

Limitations

Perhaps the largest limitation of this study is the risk of loss of participants after initial enrollment. To address this, a staged screening method is used to identify truly interested participants, and we will oversample by 19%. Moreover, we use a distributed incentive system, rewarding study visit completion. Additional retention strategies include obtaining contact information for the participant and up to 3 friends or relatives who can help locate the participant. The other main limitation relates to our plan for relatively aggressive participant recruitment. Quickly after launching recruitment, and before the publication of this protocol, our study team saw that we were not accruing participants at the rate that we had hoped for. After reviewing our screen-fail logs, we identified that our biggest barriers for enrollment were BP criteria and age. As such, with the support of our Data Safety Monitoring Board we submitted protocol amendments with our IRBs, as well as with Clinicaltrials.gov, to relax eligibility age criteria (from 25-55 years to 25-70 years) and SBP criteria (from >160 mmHg to ≥135 mmHg at screening, and from >140 mmHg to >130 mmHg at baseline) and to add a recruitment site. In addition to helping spur recruitment, these changes were also made to better reflect the new AHA BP guidelines for detecting and managing HTN [1]. Finally, generalizability will be limited by virtue of our target population; however, our primary goal is to improve BP control and limit the consequences of HTN on a disproportionate risk population.

Conclusions

As the first of its kind, MI-BP was designed to test the efficacy and acceptability of a multicomponent mHealth approach to help African Americans with uncontrolled BP modify their lifestyle to better manage their HTN. We expect to lay the foundation to sustainably reduce HTN-related health disparities through better integration of multiple behavior self-monitoring. If the MI-BP trial is effective at reducing BP in our target population, it would provide solid evidence to support the development of similar mHealth-based interventions aimed at improving HTN control among vulnerable patients. While our cohort is exclusively African American and replication of findings would be needed in a broader patient population before widespread implementation, data from MI-BP would be among the first to be obtained from the ED, supporting the viability of this often-overlooked setting as a delivery point for chronic disease management. Finally, the success of MI-BP would support future efforts to create health policies that seek expanded coverage and reimbursement for mHealth initiatives focused on bolstering self-monitoring for HTN and other chronic conditions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample messages.

[PDF File (Adobe PDF File), 39KB - resprot_v8i1e12601_app1.pdf]

Multimedia Appendix 2

Titration algorithm.

[PDF File (Adobe PDF File), 101KB - resprot_v8i1e12601_app2.pdf]

Multimedia Appendix 3

Peer-reviewer report from the Center for Scientific Review.

[PDF File (Adobe PDF File), 134KB - resprot_v8i1e12601_app3.pdf]

References

1. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright Jr JT, et al. Potential U.S. population impact of the 2017 ACC/AHA high blood pressure guideline. J Am Coll Cardiol 2018 Jan 16;71(2):109-118. [doi: 10.1016/j.jacc.2017.10.073] [Medline: 29146532]
2. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2018 May 15;71(19):e127-e248. [doi: 10.1016/j.jacc.2017.11.006] [Medline: 29146535]
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, American Heart Association Council on EpidemiologyPrevention Statistics CommitteeStroke Statistics Subcommittee. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018 Mar 20;137(12):e67-e492. [doi: 10.1161/CIR.0000000000000558] [Medline: 29386200]
4. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015-2016. NCHS Data Brief 2017 Oct(289):1-8 [FREE Full text] [Medline: 29155682]
5. Niska R, Bhuiya F, Xu J. National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. Natl Health Stat Report 2010 Aug 6(26):1-31 [FREE Full text] [Medline: 20726217]
6. Ndumele CD, Baer HJ, Shaykevich S, Lipsitz SR, Hicks LS. Cardiovascular disease and risk in primary care settings in the United States. Am J Cardiol 2012 Feb 15;109(4):521-526 [FREE Full text] [doi: 10.1016/j.amjcard.2011.09.047] [Medline: 22112741]
7. Niska RW. Blood pressure measurements at emergency department visits by adults: United States, 2007-2008. NCHS Data Brief 2011 Aug(72):1-8 [FREE Full text] [Medline: 22617045]
8. National Institute of Health: National Heart, Lung, and Blood Institute. 2003. Your Guide to Lowering Blood Pressure URL: https://www.nhlbi.nih.gov/files/docs/public/heart/hbp_low.pdf [accessed 2019-01-10] [WebCite Cache ID 75KB9jIum]
9. Avenell A, Brown TJ, McGee MA, Campbell MK, Grant AM, Broom J, et al. What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. J Hum Nutr Diet 2004 Aug;17(4):293-316. [doi: 10.1111/j.1365-277X.2004.00530.x] [Medline: 15250841]
10. Curioni CC, Lourenço PM. Long-term weight loss after diet and exercise: a systematic review. Int J Obes (Lond) 2005 Oct;29(10):1168-1174. [doi: 10.1038/sj.ijo.0803015] [Medline: 15925949]
11. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc 2007 Oct;107(10):1755-1767. [doi: 10.1016/j.jada.2007.07.017] [Medline: 17904936]
12. Sweet SN, Fortier MS. Improving physical activity and dietary behaviours with single or multiple health behaviour interventions? A synthesis of meta-analyses and reviews. Int J Environ Res Public Health 2010 Apr;7(4):1720-1743 [FREE Full text] [doi: 10.3390/ijerph7041720] [Medline: 20617056]
13. Pew Research Center. 2018 Feb 5. Mobile Fact Sheet URL: http://www.pewinternet.org/fact-sheet/mobile/ [accessed 2019-01-10] [WebCite Cache ID 75KBSpfzb]
14. Pew Research Center. 2018 Feb 5. Internet/Broadband Fact Sheet URL: http://www.pewinternet.org/fact-sheet/internet-broadband/ [accessed 2018-10-19] [WebCite Cache ID 73I95diZk]
15. Buis L, Hirzel L, Dawood RM, Dawood KL, Nichols LP, Artinian NT, et al. Text messaging to improve hypertension medication adherence in African Americans from primary care and emergency department settings: results from two randomized feasibility studies. JMIR Mhealth Uhealth 2017 Feb 1;5(2):e9 [FREE Full text] [doi: 10.2196/mhealth.6630] [Medline: 28148474]
16. Tully MA, McBride C, Heron L, Hunter RF. The validation of Fibit Zip™ physical activity monitor as a measure of free-living physical activity. BMC Res Notes 2014 Dec 23;7:952. [doi: 10.1186/1756-0500-7-952] [Medline: 25539733]
17. Patient E. University of California San Francisco. Patient Education: Guidelines for a Low Sodium Diet URL: https://www.ucsfhealth.org/education/guidelines_for_a_low_sodium_diet/ [accessed 2019-01-10] [WebCite Cache ID 75KBu6OUF]
18. Centers for Disease Control Prevention, US Department of Health and Human Services. Salt URL: https://www.cdc.gov/salt/index.htm [accessed 2019-01-10] [WebCite Cache ID 75KC84LGn]
19. Smith KW, Hoelscher DM, Lytle LA, Dwyer JT, Nicklas TA, Zive MM, et al. Reliability and validity of the Child and Adolescent Trial for Cardiovascular Health (CATCH) Food Checklist: a self-report instrument to measure fat and sodium intake by middle school students. J Am Diet Assoc 2001 Jun;101(6):635-647. [doi: 10.1016/S0002-8223(01)00161-4] [Medline: 11424542]
20. Richardson CR, Buis LR, Janney AW, Goodrich DE, Sen A, Hess ML, et al. An online community improves adherence in an internet-mediated walking program. Part 1: results of a randomized controlled trial. J Med Internet Res 2010 Dec 17;12(4):e71 [FREE Full text] [doi: 10.2196/jmir.1338] [Medline: 21169160]
21. Richardson CR, Mehari KS, McIntyre LG, Janney AW, Fortlage LA, Sen A, et al. A randomized trial comparing structured and lifestyle goals in an internet-mediated walking program for people with type 2 diabetes. Int J Behav Nutr Phys Act 2007 Nov 16;4:59 [FREE Full text] [doi: 10.1186/1479-5868-4-59] [Medline: 18021411]

22. Krein SL, Kadri R, Hughes M, Kerr EA, Piette JD, Holleman R, et al. Pedometer-based internet-mediated intervention for adults with chronic low back pain: randomized controlled trial. J Med Internet Res 2013 Aug 19;15(8):e181 [FREE Full text] [doi: 10.2196/jmir.2605] [Medline: 23969029]
23. Martinez CH, Moy ML, Nguyen HQ, Cohen M, Kadri R, Roman P, et al. Taking Healthy Steps: rationale, design and baseline characteristics of a randomized trial of a pedometer-based Internet-mediated walking program in veterans with chronic obstructive pulmonary disease. BMC Pulm Med 2014 Feb 3;14:12 [FREE Full text] [doi: 10.1186/1471-2466-14-12] [Medline: 24491137]
24. Moy ML, Weston NA, Wilson EJ, Hess ML, Richardson CR. A pilot study of an internet walking program and pedometer in COPD. Respir Med 2012 Sep;106(9):1342-1350 [FREE Full text] [doi: 10.1016/j.rmed.2012.06.013] [Medline: 22795984]
25. Detroit Healthcare Stabilization Group Issues Recommendations. 2003 Jul 8. Strengthening the Safety Net in Detroit and Wayne County URL: https://www.michigan.gov/documents/ReportofDetroitHealthCareStabilizationWorkgroup_1_70764_7.pdf [accessed 2019-01-10] [WebCite Cache ID 75KCUBXoB]
26. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J 1995;94(3):135-140. [Medline: 7778330]
27. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
28. Norris J, Block T, Block G. Development of a Brief Screening Tool for Sodium Intake. San Fransisco; 2012 Oct 30 Presented at: 140th APHA Annual Meeting and Exposition; October 27-31, 2012; San Francisco, CA URL: https://apha.confex.com/apha/140am/webprogram/Paper270258.html
29. Kripalani S, Risser J, Gatti ME, Jacobson TA. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. Value Health 2009;12(1):118-123 [FREE Full text] [doi: 10.1111/j.1524-4733.2008.00400.x] [Medline: 19911444]
30. McNaughton CD, Brown NJ, Rothman RL, Liu D, Kabagambe EK, Levy PD, et al. Systolic blood pressure and biochemical assessment of adherence: a cross-sectional analysis in the emergency department. Hypertension 2017 Aug;70(2):307-314 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.117.09659] [Medline: 28652467]
31. Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. Res Q Exerc Sport 1992 Mar;63(1):60-66. [doi: 10.1080/02701367.1992.10607557] [Medline: 1574662]
32. Ogedegbe G, Mancuso CA, Allegrante JP, Charlson ME. Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients. J Clin Epidemiol 2003 Jun;56(6):520-529. [Medline: 12873646]
33. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res 2005 Dec;40(6 Pt 1):1918-1930 [FREE Full text] [doi: 10.1111/j.1475-6773.2005.00438.x] [Medline: 16336556]
34. Schapira MM, Fletcher KE, Hayes A, Eastwood D, Patterson L, Ertl K, et al. The development and validation of the hypertension evaluation of lifestyle and management knowledge scale. J Clin Hypertens (Greenwich) 2012 Jul;14(7):461-466 [FREE Full text] [doi: 10.1111/j.1751-7176.2012.00619.x] [Medline: 22747619]
35. Ware Jr J, Kosinski M, Keller S. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [Medline: 8628042]
36. Arozullah AM, Yarnold PR, Bennett CL, Soltysik RC, Wolf MS, Ferreira RM, et al. Development and validation of a short-form, rapid estimate of adult literacy in medicine. Med Care 2007 Nov;45(11):1026-1033. [doi: 10.1097/MLR.0b013e3180616c1b] [Medline: 18049342]
37. Center for Disease Control and Prevention. Behavioral Risk Factor Surveillance System Survey Questionnaire 2011-2013 URL: https://www.cdc.gov/brfss/index.html [accessed 2018-10-19] [WebCite Cache ID 73ICpzIbg]
38. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Q 1989 Sep;13(3):319-340 [FREE Full text] [doi: 10.2307/249008]
39. Mislevy RJ, Little RJ, Rubin DB. Statistical analysis with missing data. J Educ Stat 1991;16(2):150-155 [FREE Full text] [doi: 10.2307/1165119]
40. Rehman H, Kamal AK, Morris PB, Sayani S, Merchant AT, Virani SS. Mobile health (mHealth) technology for the management of hypertension and hyperlipidemia: slow start but loads of potential. Curr Atheroscler Rep 2017 Mar;19(3):12. [doi: 10.1007/s11883-017-0649-y] [Medline: 28210974]
41. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care 2004 Sep;42(9):851-859. [Medline: 15319610]
42. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 2002;23:377-401. [doi: 10.1146/annurev.publhealth.23.100901.140534] [Medline: 11910068]
43. Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. Ann Intern Med 2010 Apr 20;152(8):481-487. [doi: 10.7326/0003-4819-152-8-201004200-00212] [Medline: 20194225]

44. Caro JJ, Briggs AH, Siebert U, Kuntz KM, ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Med Decis Making 2012;32(5):667-677. [doi: 10.1177/0272989X12454577] [Medline: 22990082]
45. Neumann PJ, Russell LB, Siegel JE, Ganiats TG, Sanders GD. Cost-Effectiveness in Health Medicine. New York, NY: Oxford University Press; 2016.
46. Drummond MF, Sculpher MJ, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. UK: Oxford University Press; Jun 10, 2005:400.
47. Burke LE, Ma J, Azar KM, Bennett GG, Peterson ED, Zheng Y, American Heart Association Publications Committee of the Council on Epidemiology Prevention, Behavior Change Committee of the Council on Cardiometabolic Health, Council on Cardiovascular Stroke Nursing, Council on Functional Genomics Translational Biology, Council on Quality of Care Outcomes Research, Stroke Council. Current science on consumer use of mobile health for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation 2015 Sep 22;132(12):1157-1213. [doi: 10.1161/CIR.0000000000000232] [Medline: 26271892]
48. Alessa T, Abdi S, Hawley MS, de Witte L. Mobile apps to support the self-management of hypertension: systematic review of effectiveness, usability, and user satisfaction. JMIR Mhealth Uhealth 2018 Jul 23;6(7):e10723 [FREE Full text] [doi: 10.2196/10723] [Medline: 30037787]

Abbreviations

AHA: American Heart Association
BP: blood pressure
CRSC: Clinical Research Service Center
DMC: Detroit Medical Center
DRH: Detroit Receiving Hospital
ED: emergency department
HTN: hypertension
IRB: institutional review board
LC-MS: liquid chromatography mass spectrometry
mHealth: mobile health
PCP: primary care provider
QALY: quality adjusted life year
RCT: randomized controlled trial
SBP: systolic blood pressure
SF-12: 12-Item Short-Form Health Survey
SGH: Sinai-Grace Hospital
WSU: Wayne State University

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Original Paper

The Feasibility of Examining the Effects of Gastric Bypass Surgery on Intestinal Metabolism: Prospective, Longitudinal Mechanistic Clinical Trial

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Abstract

Background: Bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), is the best treatment for severe obesity and its complications including type 2 diabetes mellitus (T2DM). Understanding the mechanisms responsible for the beneficial metabolic effects will help to engineer ways to improve the procedure or produce these effects without surgery.

Objective: The aim is to present data on recruitment and feasibility of a translational study designed to collect intestinal samples before and after bariatric surgery. The goal of biobanking is to allow future studies to test the hypothesis that the mechanism of action of RYGB involves specific changes in the postsurgical short- and long-term metabolism and morphology of the jejunum (Roux limb). Specifically, to test whether the intestine enhances its metabolism and activity after RYGB and increases its fuel utilization, we designed a prospective, longitudinal study, which involved the recruitment of candidates for RYGB with and without T2DM. We describe the tissue bank that we have generated, and our experience, hoping to further facilitate the performance of longitudinal mechanistic studies in human patients undergoing bariatric surgery and especially those involving post-RYGB intestinal biology.

Methods: We conducted a trial to characterize the effects of RYGB on intestinal metabolism. Intestinal tissue samples were collected from the jejunum at surgery, 1, 6, and 12 months postoperatively for the analysis of intestinal gene expression and metabolomic and morphologic changes. The target number of patients who completed at least the 6-month follow-up was 26, and we included a 20% attrition rate, increasing the total number to 32.

Results: To enroll 26 patients, we had to approach 79 potential participants. A total of 37 agreed to participate and started the study; 33, 30, and 26 active participants completed their 1-month, 6-month, and 12-month studies, respectively. Three participants withdrew, and 30 participants are still active. Altruism and interest in research were the most common reasons for participation. Important factors for feasibility and successful retention included (1) large volume case flow, (2) inclusion and exclusion criteria broad enough to capture a large segment of the patient population but narrow enough to ensure the completion of study aims and protection of safety concerns, (3) accurate assessment of willingness and motivation to participate in a study, (4) seamless integration of the recruitment process into normal clinical flow, (5) financial reimbursement and nonfinancial rewards and gestures of appreciation, and (6) nonburdensome follow-up visits and measures and reasonable time allotted.

Conclusions: Human translational studies of the intestinal mechanisms of metabolic and weight changes after bariatric surgery are important and feasible. A tissue bank with unique samples has been established that could be used by investigators in many research fields, further enabling mechanistic studies on the effects of bariatric surgery.

Trial Registration: ClinicalTrials.gov NCT02710370; https://clinicaltrials.gov/ct2/show/NCT02710370 (Archived by WebCite at http://www.webcitation.org/75HrQT8Dl)

(JMIR Res Protoc 2019;8(1):e12459) doi:10.2196/12459

KEYWORDS

bariatric surgery; obesity; diabetes mellitus; metabolism; gastric bypass; intestine; research subject recruitment; feasibility studies

Introduction

Background

Several recent studies have concluded that bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), is the best current treatment option for obesity and obesity-related comorbid conditions, including type 2 diabetes mellitus (T2DM) [1-3]. Although controversial, many investigators have advocated, based on many clinical observations as well as on findings of preclinical studies in animal models, that the effectiveness of RYGB does not depend upon body weight loss. Unraveling the mechanisms underlying the metabolic effects of weight loss surgery will help to engineer ways to improve the surgical procedures or to produce these effects without surgery. To this end, human translational studies will be required; however, a challenge hindering progress is the lack of knowledge about the feasibility of and strategy for recruiting participants for mechanistic studies that require potentially invasive methods.

Objectives

The focus of this study is to present data on recruitment and feasibility of a translational study designed to collect intestinal samples before and after bariatric surgery. The goal of biobanking is to allow future studies to test the hypothesis that the mechanism of action of RYGB involves specific changes in the postsurgical short- and long-term metabolism and morphology of the jejunum (Roux limb) [4]. Specifically, the intestine enhances its metabolism and activity after gastric bypass, resulting in an increase in fuel utilization. This is manifested as augmented intestinal utilization of glucose, cholesterol, and amino acids, which might in turn improve whole-body metabolism and T2DM. To investigate this hypothesis in humans, studies had to be designed to recruit bariatric bypass surgery candidates with and without T2DM to participate in a longitudinal study protocol, which involved collection of intestinal tissue at the time of surgery and at later time points during the first year following surgery. We describe the tissue bank that we have generated, and we discuss in detail our experience, hoping to further facilitate the performance of longitudinal mechanistic studies in human patients undergoing bariatric surgery and especially those involving methods examining the postbypass intestinal biology.

Methods

Screening Strategy, Data Collection, and Outcome Measures

The inclusion and exclusion criteria of the study are shown in Textboxes 1 and 2 and were intentionally broad with respect to age and body mass index.

Textbox 1. Study inclusion criteria.

Inclusion criteria

- Age ≥18 years who are to undergo Roux-en-Y gastric bypass
- Moderate to severe obesity: 35 > body mass index (BMI) ≤ 40 kg/m^2 (with an obesity-related comorbidity) or BMI ≥ 40 kg/m^2
- In total, 2 groups based on type 2 diabetes mellitus (T2DM) status:
  - No T2DM
  - T2DM confirmed by either a documented fasting blood glucose greater than 126 mg/dL, or hemoglobin A1c greater than or equal to 6.5, or treatment with an antidiabetic medication

Textbox 2. Study exclusion criteria.

Exclusion criteria

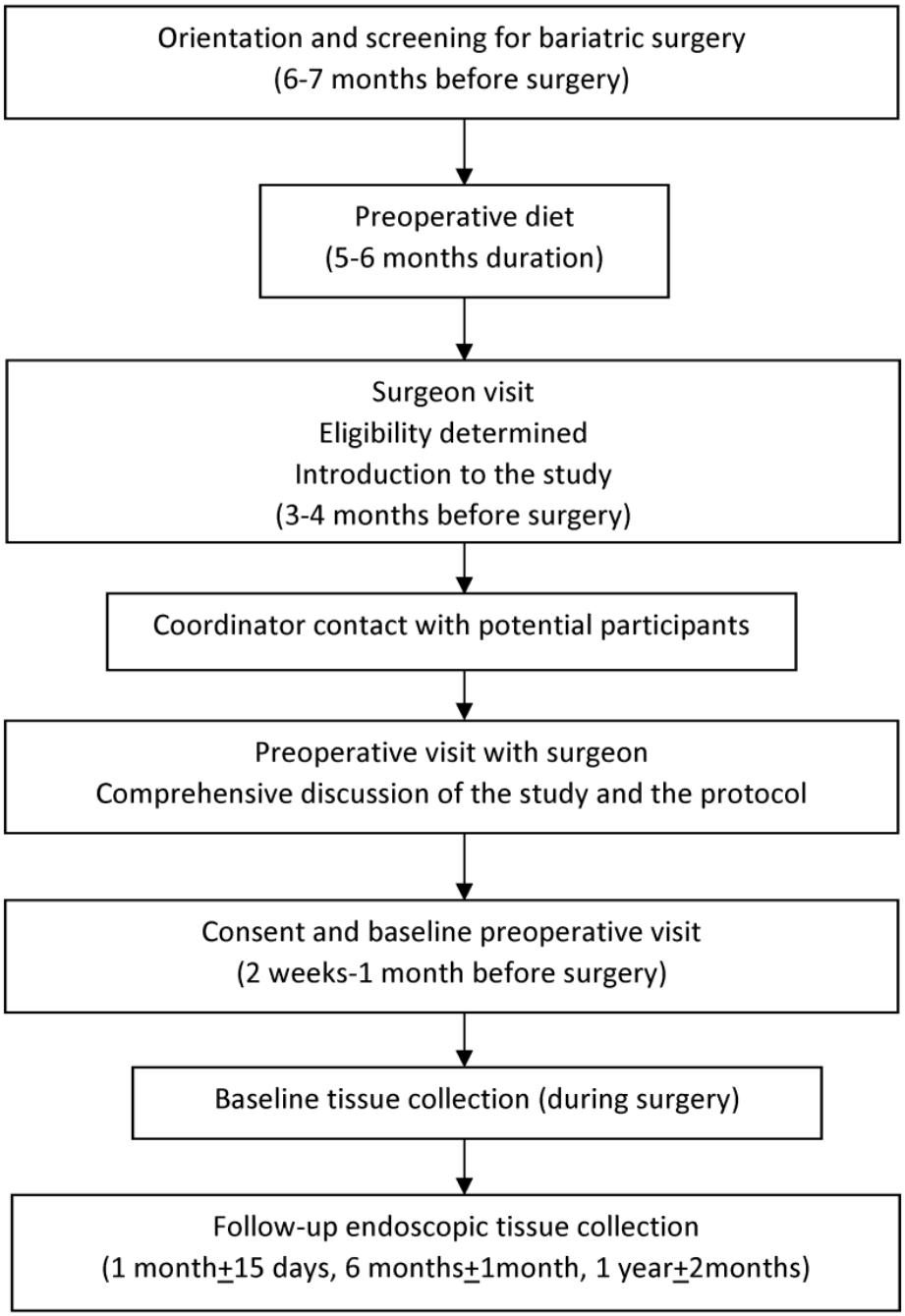
- Prior bariatric or foregut surgery
- Unlikely to comply with follow-up protocol (eg, travel time from home to clinic too long to make visits feasible, unwilling to return for follow-up visits)
- Unable to communicate with local study staff (eg, foreign-language speaking persons who are unable to read, speak, or understand English well enough to participate)
- Known type 1 diabetes mellitus per the medical history
- Impaired mental status
- Drug and/or alcohol addiction
- Current smoking
- Portal hypertension and/or cirrhosis
- Coagulopathy
- Currently pregnant or plan to become pregnant in the next year

The complete study timeline is shown in Figure 1. Potential bariatric surgery candidates per standard of clinical care attended an orientation session and completed a screening information form for bariatric surgery. They engaged in an insurance-required 5- to 6-month diet either through the bariatric group or with their family physician, nutritional evaluation by a dietitian, psychological evaluation that includes screening for substance abuse, and preoperative medical evaluation. Those with T2DM were referred for cardiac evaluation by a cardiologist. At 2 to 3 months into the diet, a one-on-one clinical visit with the surgeon and principal investigator (PI) was scheduled. The PI introduced and explained the research study and protocol to prospective patients if they met the inclusion criteria and did not meet the exclusion criteria (Textboxes 1 and 2). Written materials about the study were provided, and the study coordinator then contacted potential participants by phone to further discuss the study. After completing the required diet and obtaining insurance approval for their surgery, a preoperative visit was scheduled with the PI where a comprehensive review of the study protocol and participation was discussed. If the patient desired to be enrolled in the study, the consent process was completed and a baseline research visit was scheduled before the scheduled bariatric surgery. Baseline assessments were conducted within 30 days before the scheduled surgery, and baseline intestinal tissue samples were collected at the time of surgery. Follow-up assessments were conducted, and tissue samples were collected at 1, 6, and 12 months after bariatric surgery. The tissue samples were obtained via endoscopic biopsy performed by the surgeon of record from the RYGB. Additional baseline and follow-up assessments included laboratory tests (complete metabolic panel, complete blood count, hemoglobin A1c [HbA1c], and prothrombin time/international normalized ratio), physical measures (weight, percent body fat, neck, waist and hip circumference, blood pressure, and pulse), interviewer-administered forms (comorbidities, medication, and the Sigstad clinical diagnostic index), and self-report forms (demographic, eating and weight history, diabetes history, 36-item Short Form Health Survey [SF-36], additional treatments, glycemic symptoms, and the gastrointestinal and neurologic symptom forms). Comorbid conditions in addition to T2DM were determined using a combination of laboratory values, physical measures, patient reported medication use, and medical records review using standard definitions. As metformin is known to increase intestinal glucose utilization, patients on this medication were instructed not to take it 24 hours before their surgery and endoscopy. In addition, they were specifically asked about the exact time the last dose was taken before the operation or the endoscopy, and their response was documented. Health-related quality of life was measured using the Medical Outcomes Study SF-36.

The cost of all research-related activity including the endoscopies and biopsies and anesthesia care was funded by a research grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): grant R01DK108642. Emergency care for procedural complications would be paid by the study.

Study visits were completed in a Clinical and Translational Research Center located close to the outpatient clinic with on-site phlebotomy. Participants were provided parking (a voucher worth US $8) and remuneration for the baseline research visit (US $150) and an ascending remuneration for the 3 subsequent research visits, each of which included an endoscopy and biopsy (US $450, US $500, and US $600). Participants were also provided their anthropometric data and laboratory results at each visit, which graphically displayed their progress. Phone calls were made between in-person visits to foster study relationship and retention.

Figure 1. Study timeline.



Sample Size, Power, and Detectable Effects

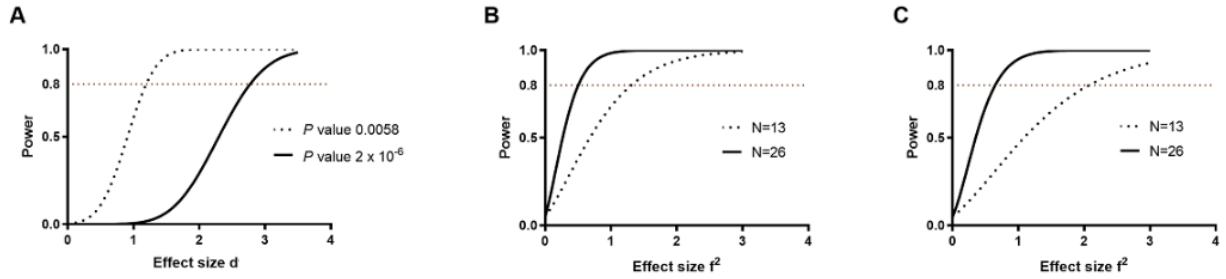
Sample size calculations were performed using STATA/SE 15.0 (StataCorp LLC, College Station, TX) and G*Power (Heinrich-Heine-Universität Düsseldorf, Dusseldorf Germany) software, and it was determined that 26 individuals would need to be recruited within a 5-year period and complete at least the 1-month and the 6-month tissue collection. For the primary analyses, the main outcome measure will be the paired difference in gene expression levels in the same subject (before and each time point after RYGB; two-tailed, paired samples *t* tests). This is a design that maximizes power and minimizes variability. Overall, 1 published study that examined proliferation (measured as Ki-67 positive cells) in intestinal samples collected at the time of surgery and 8 months after RYGB [5] showed that the effect of RYGB on proliferation was so profound that statistically significant differences could be detected with a sample size of 8 participants. Our study involved more and different outcomes. We ran several scenarios for many genes based on the following input data: (1) significance level of .05, (2) power at least 80%, and (3) estimates of the expected mean and SD of the differences in gene expression levels. The estimates of the expected mean difference and the SD of the differences in expression levels were based on an initial pilot microarray study, which determined the gene expression levels in available samples from patients with RYGB and controls. For the sample size calculations, we first corrected for multiple hypothesis testing. The significance level cutoff was determined after controlling the false discovery rate (FDR). Specifically, if we choose a level of FDR α= 5% and we suppose that the

proportion of the genes that will not be differentially expressed is π_0= 90%, the adjusted *P* value cutoff Λ could be estimated by the formula: $\Lambda = (a/1-a) * (1-\pi_0/\pi_0)$ [6]. On the basis of these assumptions, the adjusted cutoff would be .0058.

We then can construct the curves of Cohen effect size *d* (mean/SD) against power (Figure 2). To this end, we use a cutoff of 33% as a meaningful change (increase or decrease) of the expression levels of a gene. On the basis of our pilot dataset, for all these genes that changed over 33%, the mean difference (in Log_2[Fold change]) was 61%, and the SD of the differences was 41%. To determine the sample size to achieve 80% power, the following values were considered: significance level 0.0058, power 0.8, mean of differences for null hypothesis 0, mean of differences for alternative hypothesis 0.61 and SD of differences 0.41. On the basis of these estimates, we concluded that these analyses can generate meaningful results with 13 subjects. As we would like to study the effects of RYGB in patients with and without T2DM, we would need to double this estimate and recruit approximately 26 patients for this study. We also included a 20% attrition rate and thus the maximum number of patients for this study was increased to 32. The second and more stringent approach we explored was to calculate the cutoff for the type I error (ie, the *P* value) that should be accepted if we wanted to keep the familywise error rate (FWER) lower than 5%. For n=24,000 different comparisons (number of probes tested), the adjusted *P* value β can be calculated by the equation: $\beta=1-(1- FWER)^{1/n}$ [7]. Thus, for our chosen FWER cutoff, differences in gene expression levels with a *P* value lower than 2×10^{-6} could be considered statistically significant. The curves of Cohen effect size *d* (mean/SD) against power while controlling for this value are shown in Figure 2.

Repeated measures analysis of variance could be used to evaluate changes among the 3 postoperative time points. To determine the power, we could achieve by including a single group of 13 patients in the analysis, we used GLIMMPSE software [8]. Assumptions used a significance level of .05 and the base case scenario was a parameter (gene expression levels) change of 33% at the 1-month time point and 50% at the 12-month time point post-RYGB. We varied the correlation between the measurements, and many scenarios were evaluated with the basic assumption being that the correlation is higher between the 1-month time point and 6-month time point than the 1-month time point and 12-month time point after RYGBS; the correlation is even higher between the 6-month time point and 12-month time point after RYGBS. We used the Hotelling-Lawley Trace test, which showed that power would be over 0.8 for the base assumptions. We also found that this sample size would provide adequate power to allow us to determine whether the 6-month time point and 12-month time point measurements are different from the 1-month time point measurements and whether the changes follow polynomial trends. For the power analysis of multiple linear regression models, we used 2 sample sizes (N=13 and N=26), and the power calculations are summarized in Figure 2.

Figure 2. Power analysis. A. Curves of effect size (Cohen d), against power for paired samples t test. The effect size is the ratio between the mean of a difference divided by the SD of the difference in a study variable between the 2 groups (eg, here we used the Log2(fold change) in the expression levels of a gene). The power analysis was based on two adjusted P values: *P*=.0058 when controlling for FDR at 5% and *P*=2x10−6 when controlling for familywise error rate at 5%. B and C. Power analysis for regression modeling with 3 predictors (B) and 5 predictors (C). The effect size f2 is given by the ratio R2/(1−R2). R2 is the coefficient of determination. The following conventional values for the effect size f2 have been proposed: small f2=0.02, medium f2=0.15, large f2=0.35. We calculated the power for 2 sample sizes to determine the power of models that are based only on patients with or without diabetes (N=13) or the entire group (N=26). In all panels, the generally accepted cutoff of 80% for the power is shown.

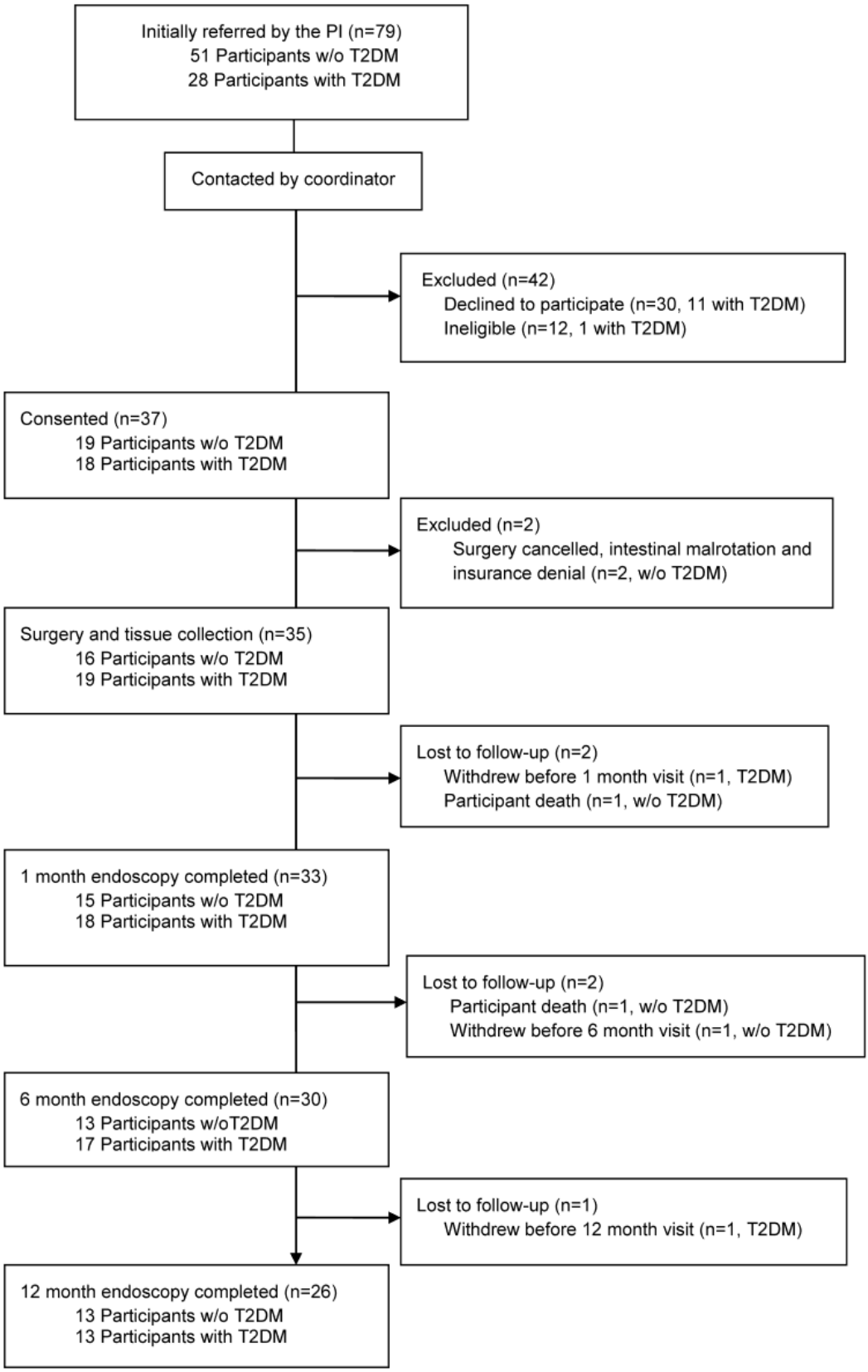


Results

Recruitment and Retention Results

The 26 participants who were required for this study were recruited and completed the assessments within 2 years and 8 months (from February 2016 to October 2018). In this period, 79 patients were determined to meet the criteria and were invited to participate in the study. Of the 79 potential participants, 30 declined to participate and 12 were found to be ineligible. Of these, 1 was subsequently found to be ineligible because of current smoking, 1 participant's lab results did not document diabetes, and 10 did not complete the presurgical process before the recruitment had ended. Of the 30 candidates who declined participation, 11 decided not to undergo bariatric surgery at all, 3 chose to undergo sleeve gastrectomy rather than gastric bypass, 7 were concerned about missing additional work days, 3 felt travel time to the hospital would be burdensome, 2 were concerned about arranging for child care during their study visits, 2 were concerned about anesthesia and undergoing the endoscopic procedures, and 2 did not indicate a specific reason (Figure 3).

Figure 3. Consort diagram. 1 participant was reassigned to group T2DM based on her baseline blood work. PI: principal investigator; T2DM: type 2 diabetes mellitus; w/o: without.



After the consent, 1 participant's surgical procedure was aborted because of intestinal malrotation, and the participant was inactivated. Another participant's surgery was cancelled, as her insurance did not authorize her procedure. There were 3 withdrawals during the study follow-up. One of the participants with T2DM chose to withdraw after her surgery, before her 1-month assessment. A participant without T2DM chose to withdraw before her 6-month visit, and a participant with T2DM

chose to withdraw before his 12-month visit. There were 2 participant deaths (both without T2DM, 1 before the 1-month follow-up from a cardiac event, and 1 before 6-months from possible substance use). When the consented participants were asked on the 9-item self-report survey to choose the reasons that contributed to their participating in the study, 36 participants (97%, 36/37) chose the "ability to help others in the future," 25 participants (67%, 25/37) chose that "research is interesting to me," 23 (62%, 23/37) chose the "personalized feedback of study results," 18 (48%, 18/37) chose they "made a commitment/agreed to participate," and 16 (43%, 16/37) chose the "compensation/reimbursement." (Figure 4) A list of the comorbidities and medications used by the participants at the time of their surgery are listed in Tables 1 and 2.

Recruitment ended after 26 patients completed the 12-month follow-up. At that time, a total of 35 patients had been recruited and had their initial tissue collection during the RYGB surgery. In terms of study retention, 33 active participants have completed their 1-month visit and endoscopic tissue collection (15 controls and 18 participants with T2DM) or 100% of the cohort (Figure 3); 30 participants completed a 6-month visit and 26 (the study target) of the 12-month visits were completed. The attrition at 12 months was 5 of 31 visits or 16.1 % (2 participants who did not have a surgical procedure and 4 participants who have not yet completed their 12-month visit were excluded from this total). The typical clinical attrition in our bariatric surgical program at 12 months for RYGB patients is higher at 25%.

A first analysis using samples from this study has been published recently [9]. The tissue samples or biopsies that were collected will be used for intestinal gene and protein expression, metabolite profile, and assessment of morphologic changes. Plasma and serum samples are also analyzed in parallel. Blood metabolomic signatures can contextualize intestinal tissue metabolomic data to enhance the understanding of intestinal energy utilization after RYGB. These signatures can also be correlated with clinical outcomes such as HbA1c, fasting glucose levels, or body weight loss.

The power and sample size calculations have been presented above in detail. Adjustment for multiple comparisons will be based on the FDR procedure by Benjamini and Yekutieli, allowing for between-metabolite correlations [10]. We will verify the Benjamini and Yekutieli FDR by comparing it with the empirical FDR using the permutation-based approach [11].

For the analysis of the relationship between clinical outcomes and the gene expression or metabolomic signatures, the number of covariates that can be included in the models will need to be limited to preserve degrees of freedom and avoid overfitting (Figure 2). One approach will be to decrease the dimensionality of the data by performing a principal component analysis, as correlation between gene or metabolite levels is expected, given that many of these reside in overlapping pathways. Another analytical approach will be to use Bayesian statistical methods that do not depend on sample size.

Figure 4. Participants' reasons for study enrollment. N=37: 36 endorsed helping others, 25 reported that research is interesting, 23 reported that personalized feedback was helpful, 18 reported that they had made a commitment, and 16 reported that compensation influenced their decision to enroll in the study.

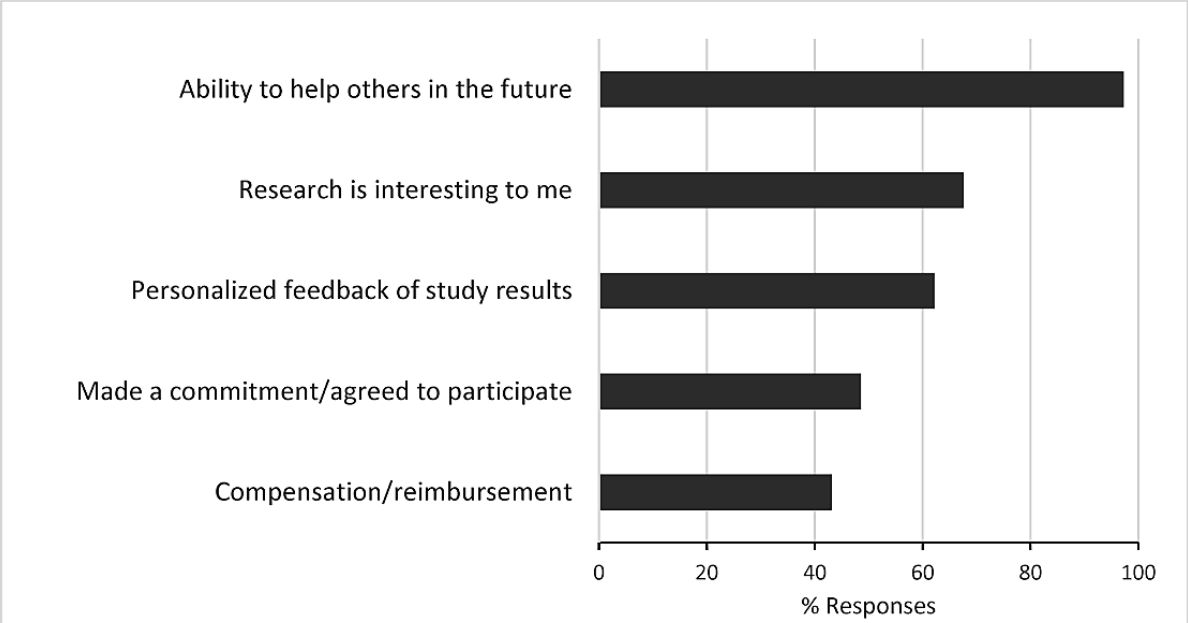


Table 1. Patient comorbidities (N=26).

Comorbidity	Patients, n
Hypertension	
Borderline no medications	5
Treatment with 1 medication	2
Treatment with multiple medication	6
Peripheral vascular disease	
Stroke, loss of tissue because of ischemia	1
Lower extremity edema	
Intermittent lower extremity edema, not requiring treatment	3
Symptoms requiring treatment, diuretics, elevation, or hose	3
Deep vein thrombosis (DVT)/Pulmonary embolism (PE)	
History of DVT resolved with anticoagulation	1
Previous PE	1
Glucose metabolism	
Elevated fasting glucose	2
Diabetes, controlled with oral medication	4
Diabetes, controlled with insulin and oral medication	4
Diabetes, with severe complications (retinopathy, neuropathy, renal failure, and blindness)	3
Lipids (dyslipidemia or hyperlipidemia)	
Present, no treatment required	3
Controlled with single medication	12
Obstructive sleep apnea syndrome	
Sleep apnea symptoms (negative sleep study or not done)	3
Sleep apnea diagnosis by sleep study (no oral appliance)	2
Sleep apnea requiring oral appliance such as continuous positive airway pressure machine	14
Asthma	
Intermittent mild symptoms, no medication	2
Symptoms controlled with oral inhaler	3
Gastroesophageal reflux disease	
Intermittent or variable symptoms, no medication	3
Intermittent medication	1
Histamine H2-receptor antagonists-H2 blockers or low-dose proton pump inhibitors (PPIs)	6
High-dose PPI	3
Cholelithiasis	
Gallstones with no symptoms	1
Gallstones with severe symptoms or history of cholecystectomy	10
Liver disease	
Modest or greater hepatomegaly liver function test alteration, fatty change category 2	4
Back pain	
Intermittent symptoms not requiring medical treatment	6
Symptoms requiring non-narcotic treatment	2
Degenerative changes or positive objective findings, symptoms requiring narcotic treatment	2
Musculoskeletal disease	

Comorbidity	Patients, n
Pain with community ambulation	2
Non-narcotic analgesia required	6
Pain with household ambulation	1
Awaiting or past joint replacement or other disability	1
Fibromyalgia	
Treatment with non-narcotic medications	4
Polycystic ovary syndrome (PCOS)	
Symptoms of PCOS, no treatment	5
Oral contraceptive pills or antiandrogen prescription (Rx)	1
Metformin or Thiazolidinediones	1
Menstrual irregularities	
Irregular periods or oligomenorrhea	6
Prior total abdominal hysterectomy	3
Mental health diagnosis	
Bipolar disorder	1
Anxiety and panic disorder	12
Psychosocial impairment	
Mild impairment in psychosocial functioning but able to perform all primary tasks	5
Moderate impairment in psychosocial functioning but able to perform most primary tasks	1
Moderate impairment in psychosocial functioning and unable to perform some primary tasks	1
Depression	
Mild and episodic not requiring treatment	1
Moderate, accompanied by some impairment, may require treatment	6
Moderate, with significant impairment, treatment indicated	9
Stress Urinary Incontinence	
Minimal and intermittent	3
Abdominal hernia	
Asymptomatic hernia, no prior operation	1
Abdominal skin pannus	
Intertriginous irritation	1
Smoking status	
Current smoker	1
Former smoker (average 15.3 pack-years)	10

Table 2. List of medications used by the study participants at the time of their surgery (N=26).

Medication	Patients, n
Antidiabetic	
Metformin	11
Insulin	6
Glipizide	2
Repaglinide	2
Liraglutide	2
Dulaglutide	1
Linagliptin	1
Sitagliptin	1
Empagliflozine	1
Insulin glargine	1
Nonsteroidal anti-inflammatory drugs	
Acetylsalicylic acid	5
Ibuprofen	3
Meloxicam	2
Indomethacin	1
Diphenhydramine and acetaminophen	1
Antihypertensive	
Amlodipine	5
Hydrochlorothiazide	4
Lisinopril	3
Atenolol	2
Diltiazem	2
Ramipril	1
Losartan	1
Irbesartan	1
Valsartan	1
Labetalol	1
Prazosin	1
Furosemide	1
Hydrochlorothiazide/triamterene	1
Oral birth control	
Norgestimate	3
Levonorgestrel	1
Medroxyprogesterone	1
Statins and fibrates	
Atorvastatin	5
Simvastatin	2
Rosuvastatin	2
Gemfibrozil	2
Fenofibrate	1
Ezetimibe	1

Medication	Patients, n
Proton pump inhibitors and Histamine H2-receptor antagonists -H2 antagonists	
Omeprazole	5
Pantoprazole	3
Ranitidine	2
Lansoprazole	2
Loratadine	1
Antidepressants and central nervous system-acting	
Gabapentin	6
Sertaline	4
Clonazepam	3
Citalopram	2
Topiramate	2
Amytriptiline	2
Paroxetine	1
Escitalopram	1
Fluoxetine	1
Desvenlafaxine	1
Quetiapine	1
Trazodone	1
Olanzepine	1
Ziprasidone	1
Risperidone	1
Prochlorperazine	1
Lorazepam	1
Buproprion	1
Buspirone	1
Zolpidem	1
Melatonin	1
Venlafaxine	1
Duloxetine	2
Mirtazapine	1
Oxycodone	1
Antiallergic	
Fluticasone	3
Hydroxyzine	1
Diphenydramine	1
Promethazine	1
Other	
Levothyroxine	7
Albuterol	3
Cyclobenzaprine	3
Pramipexole	1
Iodine	1

Medication	Patients, n
Linaclotide	1
Sulfasalazine	1
Infliximab	1
Cyclosporine	1
Vardenafil	1
Rivaroxaban	1
Docusate	1
Erythromycin	1
Botox	1
Valacyclovir	1
Nystatin	1
Vitamins and supplements	
Multivitamin	6
B and B12	6
Omega-3 fatty acids	2
D3	2
Folic acid	1
Biotin	1
C	1
Ferrous	1
Calcium	1
Potassium	1
Chromium	1
Turmeric curcumin	1
Glucosamine chondroitin	1
Fish oil	1
Calcium carbonate	1
Magnesium oxide	1
Probiotic	1

Lessons Learned and Important Factors for Feasibility and Successful Retention

We approached patient recruitment in a systematic way using a published conceptual framework for study feasibility, which comprises determining, operationalizing, and adequately resolving a series of essential factors. [12] The first factor was the number of potentially eligible participants who needed to be considered. For bariatric surgery, the presurgical work-up and insurance approval steps are both rigorous and time-consuming, so the potential candidates will often discontinue the process. Many candidates had to be considered and approached at a time in the process where their certainty of ultimately undergoing surgery was relatively high. Typically, for bariatric surgery patients, this time frame was around 3 months into a commonly required 5- to 6-month presurgical preparation period. Therefore, it was essential to target a practice large enough to ensure a large volume or flow of patients who met the eligibility criteria and could be approached for recruitment. The second factor was that the inclusion and exclusion criteria had to be broad enough to capture a large segment of the patient population to approach but narrow enough to ensure the completion of study aims and protection of safety concerns. The third factor was an accurate assessment of the willingness and motivation of people to participate in a study. We conducted an informal pilot project before engaging in the final study and surveyed gastric bypass candidates in person at their clinic evaluation about their potential willingness to participate in a study such as this one. We found that most candidates were agreeable to the idea, motivated by altruism, and interested in understanding the mechanism of diabetes improvement. In the actual study recruitment process, those with T2DM or a family history of T2DM were particularly motivated to contribute to understanding the underlying

mechanisms to help potentially affect a less invasive treatment or cure. Therefore, explaining in lay terms, the scientific basis and hypotheses was an important contributing factor to successful recruitment. The fourth factor was the actual recruitment process whereby and how participants were engaged into the study. Our experience suggests this should be incorporated into the normal clinical flow and integrated into the candidate's experience so that it becomes a seamless part of a whole evaluation and participation scheme for an individual. This is also consistent with recruitment in pragmatic clinical trials where the conduct of research is integrated into the delivery of health care. [13] The fifth factor was that participants were pleased with any financial reimbursement for their expenses that included travel, parking, missed work, child care, and others. Nonfinancial rewards such as gestures of appreciation, reports of their progress, and between-visit calls were also very helpful and meaningful to participants. Finally, for a longitudinal study to be successful, complete retention of participants over time was needed. For this study, this meant that the study and clinic visits needed to be conducted efficiently, and at times, both research and clinical visits were done during the same encounter. Attention was also paid to the protocol design so that the visits and measures were nonburdensome and the time allotted was reasonable (maximum of 3-4 hours).

There were 3 additional factors specific to bariatric surgery that also might have played a role in the successful recruitment and retention into this study. The first important factor was that the surgeon of record for the original gastric bypass surgery carried out both the follow-up visits and the endoscopic tissue biopsies. Participants were comforted by the idea that their surgeon, who knew their anatomy, would be performing biopsies and simultaneously checking for anatomical problems. Participants had voiced, when asked, that being referred to another provider to gather the tissue samples was much less ideal because of their unfamiliarity and discomfort, especially at the early time points following surgery. The second factor was that for bariatric surgery clinical practice, completeness of follow-up in the first 12 months after surgery is typically high (83%-100%) [14]. Therefore, a longitudinal study that is completed within the first 12 months postoperatively for follow-up has a higher chance of success, as study retention rates decline dramatically after the first year, as does clinical follow-up [14]. The third factor was that preoperative bariatric surgery candidates expect and are very compliant with a lengthy and complex work-up process for the surgery itself, so they perhaps tend to be more willing to undertake extra research visits and testing than other types of surgery patients.

Discussion

Unanswered Questions and Future Research

Though many bariatric surgery candidates exhibit a willingness to participate in research, this willingness decreases when the research includes either invasive activities or longitudinal follow-ups [15]. Despite these limitations, the Longitudinal Assessment of Bariatric Surgery study, a prospective observational study, recruited 5108 participants over a 2-year time period for 30-day safety outcomes, and 2458 participants over 3 years for a more extensive study protocol, which was conducted during annual, in-person visits and included measurements, phlebotomy, a corridor walk, physical activity monitoring, and an extensive set of questionnaires [16-18]. Randomized controlled trials in bariatric surgery, particularly those that compare surgical with nonsurgical treatments, also pose recruitment challenges because of several issues: the existence of genuine clinical equipoise between the alternatives, participants not agreeing to a nonsurgical arm after spending a lifetime in the "nonintervention arm," payers not funding the surgical procedures under study, and ethical issues with informed and voluntary consent [19,20]. Prospective clinical trials have been performed that include invasive procedures such as tissue biopsies at the time of the initial bariatric surgery (Table 1). Some of these studies have also obtained longitudinal samples over time, but these were typically collected at convenient time points, when other surgical procedures were done for a clinical indication (eg, for management of surgical complications and cholecystectomy) and not at protocol-specified intervals. Moreover, most studies have utilized tissue sampled from adipose tissue, skeletal muscle, and liver, which is readily available via percutaneous biopsy (Multimedia Appendix 1 [5,21-59]). Prospective, longitudinal studies that seek to explore mechanistic goals by collecting and analyzing tissue from intra-abdominal tissues and organs are virtually absent in the literature.

A review of the Gene Expression Omnibus database revealed only a few datasets that include gene expression profiles of tissues after weight loss surgery [21,22,60-62]. In addition, there are only a few studies that use invasive means to interrogate the metabolic perturbations of weight loss surgery. An exception is the use of hyperinsulinemic-euglycemic clamping. However, although this method is considered the gold standard for estimation of insulin sensitivity, many studies disagree on the role of hepatic and peripheral insulin sensitivity in contributing to diabetes remission after surgery. Although some studies suggest an early role for improved hepatic [63] or peripheral [64,65] insulin sensitivity in contributing to glycemic improvement in the first weeks after surgery, others do not report this effect [66-69].

Conclusions

As this exciting research field of bariatric surgery mechanisms continues to grow, the need for further invasive studies in humans will continue to grow as well. We demonstrate that translational longitudinal clinical trials on intestinal mechanisms are both important and feasible, and we share lessons learned regarding participant recruitment and retention. Factors for successful recruitment and retention included large volume case flow, broad inclusion criteria, integrating study and clinical procedures, participant reimbursement or remuneration, sharing test or measurement data, and minimizing study burden. We believe that the established biobank could further facilitate studies examining the effects of bariatric surgery on intestinal biology and we hope that the factors discussed in this study appear to inform and support successful recruitment and retention into these unique types of trials.

Conflicts of Interest

APC reports grants from the Allurion Corp, outside the submitted work. MAS reports a National Institutes of Health (NIH)-NIDDK grant supporting the submitted work. ES declares no conflict of interest. WFG reports grants from the NIH-NIDDK and Covidien/Ethicon, outside the submitted work. NS reports an NIH-NIDDK grant supporting the submitted work.

Multimedia Appendix 1

Bariatric surgery studies involving analyses of tissue biopsies.

[DOCX File, 131KB - resprot_v8i1e12459_app1.pdf]

References

1. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016 Jun;39(6):861-877. [doi: 10.2337/dc16-0236] [Medline: 27222544]
2. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017 Feb 16;376(7):641-651. [Medline: 28199805]
3. Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. J Am Med Assoc 2014 Jun 11;311(22):2297-2304. [doi: 10.1001/jama.2014.5988] [Medline: 24915261]
4. Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, et al. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. Science 2013 Jul 26;341(6144):406-410 [FREE Full text] [doi: 10.1126/science.1235103] [Medline: 23888041]
5. Spak E, Björklund P, Helander HF, Vieth M, Olbers T, Casselbrant A, et al. Changes in the mucosa of the Roux-limb after gastric bypass surgery. Histopathology 2010 Nov;57(5):680-688. [doi: 10.1111/j.1365-2559.2010.03677.x] [Medline: 21054493]
6. Liu P, Hwang JT. Quick calculation for sample size while controlling false discovery rate with application to microarray analysis. Bioinformatics 2007 Mar 15;23(6):739-746. [doi: 10.1093/bioinformatics/btl664] [Medline: 17237060]
7. Lee ML, Whitmore GA. Power and sample size for DNA microarray studies. Stat Med 2002 Dec 15;21(23):3543-3570. [doi: 10.1002/sim.1335] [Medline: 12436455]
8. Kreidler S, Muller KE, Grunwald GK, Ringham BM, Coker-Dukowitz ZT, Sakhadeo UR, et al. GLIMMPSE: online power computation for linear models with and without a baseline covariate. J Stat Softw 2013 Sep;54(10):i10 [FREE Full text] [Medline: 24403868]
9. Ben-Zvi D, Meoli L, Abidi WM, Nestoridi E, Panciotti C, Castillo E, et al. Time-dependent molecular responses differ between gastric bypass and dieting but are conserved across species. Cell Metab 2018 Aug 7;28(2):310-23.e6. [doi: 10.1016/j.cmet.2018.06.004] [Medline: 30043755]
10. Yekutieli D, Benjamini Y. The control of the false discover rate in multiple testing under dependency. Ann Stat 2001 Aug;29(4):1165-1188 [FREE Full text] [doi: 10.1214/aos/1013699998]
11. Dudbridge F. A note on permutation tests in multistage association scans. Am J hum genet 2006 Jun;78(6):1094-1095 [FREE Full text] [doi: 10.1086/504527] [Medline: 16685665]
12. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. PLoS One 2016 Mar 15;11(3):e0150205 [FREE Full text] [doi: 10.1371/journal.pone.0150205] [Medline: 26978655]
13. Oude Rengerink K, Kalkman S, Collier S, Ciaglia A, Worsley SD, Lightbourne A, Work Package 3 of the GetReal consortium. Series: pragmatic trials and real world evidence: paper 3. Patient selection challenges and consequences. J Clin Epidemiol 2017 Sep;89:173-180 [FREE Full text] [doi: 10.1016/j.jclinepi.2016.12.021] [Medline: 28502808]
14. Garb J, Welch G, Zagarins S, Kuhn J, Romanelli J. Bariatric surgery for the treatment of morbid obesity: a meta-analysis of weight loss outcomes for laparoscopic adjustable gastric banding and laparoscopic gastric bypass. Obes Surg 2009 Oct;19(10):1447-1455. [doi: 10.1007/s11695-009-9927-2] [Medline: 19655209]
15. Tichansky DS, Madan AK, Ternovits CA, Fain JN, Kitabchi AE. Laparoscopic bariatric patients' will to help: the foundation of research. Surg Obes Relat Dis 2007;3(2):180-183. [doi: 10.1016/j.soard.2006.10.006] [Medline: 17324633]
16. Belle SH, Berk PD, Chapman WH, Christian NJ, Courcoulas AP, Dakin GF, LABS Consortium. Baseline characteristics of participants in the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study. Surg Obes Relat Dis 2013;9(6):926-935 [FREE Full text] [doi: 10.1016/j.soard.2013.01.023] [Medline: 23602493]

17. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, Flum DR, Belle SH, King WC, Wahed AS, Berk P, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 2009 Jul 30;361(5):445-454 [FREE Full text] [doi: 10.1056/NEJMoa0901836] [Medline: 19641201]
18. Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L, Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. J Am Med Assoc 2013 Dec 11;310(22):2416-2425 [FREE Full text] [doi: 10.1001/jama.2013.280928] [Medline: 24189773]
19. Courcoulas AP, Goodpaster BH, Eagleton JK, Belle SH, Kalarchian MA, Lang W, et al. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. JAMA Surg 2014 Jul;149(7):707-715 [FREE Full text] [doi: 10.1001/jamasurg.2014.467] [Medline: 24899268]
20. Paramasivan S, Rogers CA, Welbourn R, Byrne JP, Salter N, Mahon D, et al. Enabling recruitment success in bariatric surgical trials: pilot phase of the By-Band-Sleeve study. Int J Obes (Lond) 2017 Dec;41(11):1654-1661 [FREE Full text] [doi: 10.1038/ijo.2017.153] [Medline: 28669987]
21. Ahrens M, Ammerpohl O, von Schönfels W, Kolarova J, Bens S, Itzel T, et al. DNA methylation analysis in nonalcoholic fatty liver disease suggests distinct disease-specific and remodeling signatures after bariatric surgery. Cell Metab 2013 Aug 6;18(2):296-302 [FREE Full text] [doi: 10.1016/j.cmet.2013.07.004] [Medline: 23931760]
22. Park JJ, Berggren JR, Hulver MW, Houmard JA, Hoffman EP. GRB14, GPD1, and GDF8 as potential network collaborators in weight loss-induced improvements in insulin action in human skeletal muscle. Physiol Genomics 2006 Oct 11;27(2):114-121. [doi: 10.1152/physiolgenomics.00045.2006] [Medline: 16849634]
23. Ranløv I, Hardt F. Regression of liver steatosis following gastroplasty or gastric bypass for morbid obesity. Digestion 1990;47(4):208-214. [doi: 10.1159/000200499] [Medline: 2100271]
24. Friedman JE, Dohm GL, Leggett-Frazier N, Elton CW, Tapscott EB, Pories WP, et al. Restoration of insulin responsiveness in skeletal muscle of morbidly obese patients after weight loss. Effect on muscle glucose transport and glucose transporter GLUT4. J Clin Invest 1992 Feb;89(2):701-705 [FREE Full text] [doi: 10.1172/JCI115638] [Medline: 1737857]
25. de Almeida SR, Rocha PR, Sanches MD, Leite VH, da Silva RA, Diniz MT, et al. Roux-en-Y gastric bypass improves the nonalcoholic steatohepatitis (NASH) of morbid obesity. Obes Surg 2006 Mar;16(3):270-278. [doi: 10.1381/096089206776116462] [Medline: 16545157]
26. Klein S, Mittendorfer B, Eagon JC, Patterson B, Grant L, Feirt N, et al. Gastric bypass surgery improves metabolic and hepatic abnormalities associated with nonalcoholic fatty liver disease. Gastroenterology 2006 May;130(6):1564-1572. [doi: 10.1053/j.gastro.2006.01.042] [Medline: 16697719]
27. Furuya Jr CK, de Oliveira CP, de Mello ES, Faintuch J, Raskovski A, Matsuda M, et al. Effects of bariatric surgery on nonalcoholic fatty liver disease: preliminary findings after 2 years. J Gastroenterol Hepatol 2007 Apr;22(4):510-514. [doi: 10.1111/j.1440-1746.2007.04833.x] [Medline: 17376042]
28. Gastaldi G, Russell A, Golay A, Giacobino JP, Habicht F, Barthassat V, et al. Upregulation of peroxisome proliferator-activated receptor gamma coactivator gene (PGC1A) during weight loss is related to insulin sensitivity but not to energy expenditure. Diabetologia 2007 Nov;50(11):2348-2355. [doi: 10.1007/s00125-007-0782-1] [Medline: 17828388]
29. Sainsbury A, Goodlad RA, Perry SL, Pollard SG, Robins GG, Hull MA. Increased colorectal epithelial cell proliferation and crypt fission associated with obesity and Roux-en-Y gastric bypass. Cancer Epidemiol Biomarkers Prev 2008 Jun;17(6):1401-1410 [FREE Full text] [doi: 10.1158/1055-9965.EPI-07-2874] [Medline: 18559555]
30. Gregor MF, Yang L, Fabbrini E, Mohammed BS, Eagon JC, Hotamisligil GS, et al. Endoplasmic reticulum stress is reduced in tissues of obese subjects after weight loss. Diabetes 2009 Mar;58(3):693-700 [FREE Full text] [doi: 10.2337/db08-1220] [Medline: 19066313]
31. Savu MK, Phillips SA, Oh DK, Park K, Gerlan C, Ciaraldi TP, et al. Response of adiponectin and its receptors to changes in metabolic state after gastric bypass surgery: dissociation between adipose tissue expression and circulating levels. Surg Obes Relat Dis 2009;5(2):172-180. [doi: 10.1016/j.soard.2008.08.013] [Medline: 18996753]
32. Kant P, Sainsbury A, Reed KR, Pollard SG, Scott N, Clarke AR, et al. Rectal epithelial cell mitosis and expression of macrophage migration inhibitory factor are increased 3 years after Roux-en-Y gastric bypass (RYGB) for morbid obesity: implications for long-term neoplastic risk following RYGB. Gut 2011 Jul;60(7):893-901. [doi: 10.1136/gut.2010.230755] [Medline: 21303912]
33. Tamboli RA, Hajri T, Jiang A, Marks-Shulman PA, Williams DB, Clements RH, et al. Reduction in inflammatory gene expression in skeletal muscle from Roux-en-Y gastric bypass patients randomized to omentectomy. PLoS One 2011;6(12):e28577 [FREE Full text] [doi: 10.1371/journal.pone.0028577] [Medline: 22194858]
34. Bradley D, Conte C, Mittendorfer B, Eagon JC, Varela JE, Fabbrini E, et al. Gastric bypass and banding equally improve insulin sensitivity and β cell function. J Clin Invest 2012 Dec;122(12):4667-4674 [FREE Full text] [doi: 10.1172/JCI64895] [Medline: 23187122]
35. Barres R, Kirchner H, Rasmussen M, Yan J, Kantor FR, Krook A, et al. Weight loss after gastric bypass surgery in human obesity remodels promoter methylation. Cell Rep 2013 Apr 25;3(4):1020-1027 [FREE Full text] [doi: 10.1016/j.celrep.2013.03.018] [Medline: 23583180]

36. Kong LC, Tap J, Aron-Wisnewsky J, Pelloux V, Basdevant A, Bouillot JL, et al. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. Am J Clin Nutr 2013 Jul;98(1):16-24. [doi: 10.3945/ajcn.113.058743] [Medline: 23719559]
37. Andersson DP, Eriksson Hogling D, Thorell A, Toft E, Qvisth V, Näslund E, et al. Changes in subcutaneous fat cell volume and insulin sensitivity after weight loss. Diabetes Care 2014 Jul;37(7):1831-1836. [doi: 10.2337/dc13-2395] [Medline: 24760260]
38. Ferrer R, Pardina E, Rossell J, Baena-Fustegueras JA, Lecube A, Balibrea JM, et al. Decreased lipases and fatty acid and glycerol transporter could explain reduced fat in diabetic morbidly obese. Obesity (Silver Spring) 2014 Nov;22(11):2379-2387 [FREE Full text] [doi: 10.1002/oby.20861] [Medline: 25132069]
39. Marambio A, Watkins G, Castro F, Riffo A, Zúñiga R, Jans J, et al. Changes in iron transporter divalent metal transporter 1 in proximal jejunum after gastric bypass. World J Gastroenterol 2014 Jun 7;20(21):6534-6540 [FREE Full text] [doi: 10.3748/wjg.v20.i21.6534] [Medline: 24914374]
40. Albers PH, Bojsen-Møller KN, Dirksen C, Serup AK, Kristensen DE, Frystyk J, et al. Enhanced insulin signaling in human skeletal muscle and adipose tissue following gastric bypass surgery. Am J Physiol Regul Integr Comp Physiol 2015 Sep;309(5):R510-R524 [FREE Full text] [doi: 10.1152/ajpregu.00228.2014] [Medline: 26062634]
41. Casselbrant A, Elias E, Fändriks L, Wallenius V. Expression of tight-junction proteins in human proximal small intestinal mucosa before and after Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2015;11(1):45-53. [doi: 10.1016/j.soard.2014.05.009] [Medline: 25264329]
42. Chen MZ, Hudson CA, Vincent EE, de Berker DA, May MT, Hers I, et al. Bariatric surgery in morbidly obese insulin resistant humans normalises insulin signalling but not insulin-stimulated glucose disposal. PLoS One 2015 Apr 13;10(4):e0120084 [FREE Full text] [doi: 10.1371/journal.pone.0120084] [Medline: 25876175]
43. Coen PM, Menshikova EV, Distefano G, Zheng D, Tanner CJ, Standley RA, et al. Exercise and weight loss improve muscle mitochondrial respiration, lipid partitioning, and insulin sensitivity after gastric bypass surgery. Diabetes 2015 Nov;64(11):3737-3750 [FREE Full text] [doi: 10.2337/db15-0809] [Medline: 26293505]
44. Nascimento EB, Riedl I, Jiang LQ, Kulkarni SS, Näslund E, Krook A. Enhanced glucose metabolism in cultured human skeletal muscle after Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2015;11(3):592-601. [doi: 10.1016/j.soard.2014.11.001] [Medline: 25862179]
45. Nergård BJ, Lindqvist A, Gislason HG, Groop L, Ekelund M, Wierup N, et al. Mucosal glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide cell numbers in the super-obese human foregut after gastric bypass. Surg Obes Relat Dis 2015;11(6):1237-1246. [doi: 10.1016/j.soard.2015.03.021] [Medline: 26143297]
46. Su X, Magkos F, Zhou D, Eagon JC, Fabbrini E, Okunade AL, et al. Adipose tissue monomethyl branched-chain fatty acids and insulin sensitivity: effects of obesity and weight loss. Obesity (Silver Spring) 2015 Feb;23(2):329-334 [FREE Full text] [doi: 10.1002/oby.20923] [Medline: 25328153]
47. Campbell LE, Langlais PR, Day SE, Coletta RL, Benjamin TR, De Filippis EA, et al. Identification of novel changes in human skeletal muscle proteome after Roux-en-Y gastric bypass surgery. Diabetes 2016 Dec;65(9):2724-2731 [FREE Full text] [doi: 10.2337/db16-0004] [Medline: 27207528]
48. González-Plaza JJ, Gutiérrez-Repiso C, García-Serrano S, Rodriguez-Pacheco F, Garrido-Sánchez L, Santiago-Fernández C, et al. Effect of Roux-en-Y gastric bypass-induced weight loss on the transcriptomic profiling of subcutaneous adipose tissue. Surg Obes Relat Dis 2016 Feb;12(2):257-263. [doi: 10.1016/j.soard.2015.07.007] [Medline: 26615868]
49. Severino A, Castagneto-Gissey L, Raffaelli M, Gastaldelli A, Capristo E, Iaconelli A, et al. Early effect of Roux-en-Y gastric bypass on insulin sensitivity and signaling. Surg Obes Relat Dis 2016 Jan;12(1):42-47. [doi: 10.1016/j.soard.2015.06.005] [Medline: 26483070]
50. Hoffstedt J, Andersson DP, Eriksson Hogling D, Theorell J, Näslund E, Thorell A, et al. Long-term protective changes in adipose tissue after gastric bypass. Diabetes Care 2017 Jan;40(1):77-84. [doi: 10.2337/dc16-1072] [Medline: 27852664]
51. Sala P, Torrinhas RS, Fonseca DC, Heymsfield S, Giannella-Neto D, Waitzberg DL. Type 2 diabetes remission after Roux-en-Y gastric bypass: evidence for increased expression of jejunal genes encoding regenerating pancreatic islet-derived proteins as a potential mechanism. Obes Surg 2017 Apr;27(4):1123-1127. [doi: 10.1007/s11695-017-2602-0] [Medline: 28213664]
52. Hinkley JM, Zou K, Park S, Turner K, Zheng D, Houmard JA. Roux-en-Y gastric bypass surgery enhances contraction-mediated glucose metabolism in primary human myotubes. Am J Physiol Endocrinol Metab 2017 Aug 1;313(2):E195-E202 [FREE Full text] [doi: 10.1152/ajpendo.00413.2016] [Medline: 28487439]
53. Hinkley JM, Zou K, Park S, Zheng D, Dohm GL, Houmard JA. Differential acute and chronic responses in insulin action in cultured myotubes following from nondiabetic severely obese humans following gastric bypass surgery. Surg Obes Relat Dis 2017 Nov;13(11):1853-1862. [doi: 10.1016/j.soard.2017.05.019] [Medline: 28673470]
54. Day SE, Garcia LA, Coletta RL, Campbell LE, Benjamin TR, De Filippis EA, et al. Alterations of sorbin and SH3 domain containing 3 (SORBS3) in human skeletal muscle following Roux-en-Y gastric bypass surgery. Clin Epigenetics 2017 Sep 2;9:96 [FREE Full text] [doi: 10.1186/s13148-017-0396-5] [Medline: 28883895]

55. Parker BM, Wu J, You J, Barnes DS, Yerian L, Kirwan JP, et al. Reversal of fibrosis in patients with nonalcoholic steatohepatosis after gastric bypass surgery. BMC Obes 2017 Sep 12;4:32 [FREE Full text] [doi: 10.1186/s40608-017-0168-y] [Medline: 28919979]
56. Afshar S, Malcomson F, Kelly SB, Seymour K, Woodcock S, Mathers JC. Biomarkers of colorectal cancer risk decrease 6 months after Roux-en-Y gastric bypass surgery. Obes Surg 2018 Apr;28(4):945-954 [FREE Full text] [doi: 10.1007/s11695-017-2953-6] [Medline: 28990150]
57. Fonseca DC, Sala P, Singer J, Singer P, Torrinhas RS, Waitzberg DL. Upregulation of ghrelin gene expression in the excluded stomach of obese women with type 2 diabetes after Roux-en-Y gastric bypass in the SURMetaGIT study. Obes Surg 2018 Mar;28(3):877-880. [doi: 10.1007/s11695-017-3098-3] [Medline: 29307107]
58. Schwenger KJ, Fischer SE, Jackson T, Okrainec A, Allard JP. In nonalcoholic fatty liver disease, Roux-en-Y gastric bypass improves liver histology while persistent disease is associated with lower improvements in waist circumference and glycemic control. Surg Obes Relat Dis 2018 Sep;14(9):1233-1239. [doi: 10.1016/j.soard.2018.06.007] [Medline: 30049593]
59. von Schönfels W, Beckmann JH, Ahrens M, Hendricks A, Röcken C, Szymczak S, et al. Histologic improvement of NAFLD in patients with obesity after bariatric surgery based on standardized NAS (NAFLD activity score). Surg Obes Relat Dis 2018 Oct;14(10):1607-1616. [doi: 10.1016/j.soard.2018.07.012] [Medline: 30146425]
60. Berisha SZ, Serre D, Schauer P, Kashyap SR, Smith JD. Changes in whole blood gene expression in obese subjects with type 2 diabetes following bariatric surgery: a pilot study. PLoS One 2011 Mar 10;6(3):e16729 [FREE Full text] [doi: 10.1371/journal.pone.0016729] [Medline: 21423737]
61. Hulsmans M, Geeraert B, De Keyzer D, Mertens A, Lannoo M, Vanaudenaerde B, et al. Interleukin-1 receptor-associated kinase-3 is a key inhibitor of inflammation in obesity and metabolic syndrome. PLoS One 2012;7(1):e30414 [FREE Full text] [doi: 10.1371/journal.pone.0030414] [Medline: 22272346]
62. Ortega FJ, Mercader JM, Moreno-Navarrete JM, Nonell L, Puigdecanet E, Rodriquez-Hermosa JI, et al. Surgery-induced weight loss is associated with the downregulation of genes targeted by microRNAs in adipose tissue. J Clin Endocrinol Metab 2015 Nov;100(11):E1467-E1476. [doi: 10.1210/jc.2015-2357] [Medline: 26252355]
63. Promintzer-Schifferl M, Prager G, Anderwald C, Mandl M, Esterbauer H, Shakeri-Leidenmühler S, et al. Effects of gastric bypass surgery on insulin resistance and insulin secretion in nondiabetic obese patients. Obesity (Silver Spring) 2011 Jul;19(7):1420-1426 [FREE Full text] [doi: 10.1038/oby.2011.92] [Medline: 21494227]
64. Salinari S, Bertuzzi A, Guidone C, Previti E, Rubino F, Mingrone G. Insulin sensitivity and secretion changes after gastric bypass in normotolerant and diabetic obese subjects. Ann Surg 2013 Mar;257(3):462-468. [doi: 10.1097/SLA.0b013e318269cf5c] [Medline: 23388352]
65. Bojsen-Møller KN, Dirksen C, Jørgensen NB, Jacobsen SH, Serup AK, Albers PH, et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes 2014 May;63(5):1725-1737 [FREE Full text] [doi: 10.2337/db13-1307] [Medline: 24241533]
66. Campos GM, Rabl C, Peeva S, Ciovica R, Rao M, Schwarz JM, et al. Improvement in peripheral glucose uptake after gastric bypass surgery is observed only after substantial weight loss has occurred and correlates with the magnitude of weight lost. J Gastrointest Surg 2010 Jan;14(1):15-23 [FREE Full text] [doi: 10.1007/s11605-009-1060-y] [Medline: 19838759]
67. Lima MM, Pareja JC, Alegre SM, Geloneze SR, Kahn SE, Astiarraga BD, et al. Acute effect of roux-en-y gastric bypass on whole-body insulin sensitivity: a study with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab 2010 Aug;95(8):3871-3875. [doi: 10.1210/jc.2010-0085] [Medline: 20484482]
68. Camastra S, Gastaldelli A, Mari A, Bonuccelli S, Scartabelli G, Frascerra S, et al. Early and longer term effects of gastric bypass surgery on tissue-specific insulin sensitivity and beta cell function in morbidly obese patients with and without type 2 diabetes. Diabetologia 2011 Aug;54(8):2093-2102. [doi: 10.1007/s00125-011-2193-6] [Medline: 21614570]
69. Dunn JP, Abumrad NN, Breitman I, Marks-Shulman PA, Flynn CR, Jabbour K, et al. Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. Diabetes Care 2012 Jan;35(1):137-142 [FREE Full text] [doi: 10.2337/dc11-1383] [Medline: 22040841]

Abbreviations

BMI: body mass index
DVT: deep vein thrombosis
FDR: false discovery rate
FWER: familywise error rate
HbA1c: hemoglobin A1c
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIH: National Institutes of Health
PCOS: polycystic ovary syndrome
PE: pulmonary embolism

PI: principal investigator
PPIs: proton pump inhibitors
RYGB: Roux-en-Y gastric bypass
SF-36: 36-item Short Form Health Survey
T2DM: type 2 diabetes mellitus

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Protocol

Magnesium for the Management of Chronic Noncancer Pain in Adults: Protocol for a Systematic Review

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Abstract

Background: Chronic pain is a highly prevalent and complex health problem that is associated with a severe symptom burden, as well as substantial economic and social impact. Many patients with chronic pain still suffer from unrelieved or undertreated pain due to the incomplete efficacy and dose-limiting adverse effects of current therapies. Long-term and high-dose opioid use has considerably increased in the past 20 years despite limited evidence supporting its effectiveness in several chronic pain conditions, and serious concerns have emerged regarding adverse effects and potential misuse. Until recently, the steady increase in opioid prescribing rates has been associated with rising opioid-related mortality and other serious problems, emphasizing the need for better nonopioid therapies. Emerging evidence supports the safe use of magnesium in controlling chronic pain, but its overall efficacy and safety is still unclear.

Objective: This paper aims to assess the efficacy and safety of magnesium compared with a placebo for the treatment of chronic noncancer pain.

Methods: We will conduct a detailed search on Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE from their inception until the date the searches are run to identify relevant randomized controlled trials. The reference lists of retrieved studies as well as Web-based trial registries will also be searched. We will include randomized double-blind trials comparing magnesium (at any dose, frequency, or route of administration) with placebo using participant-reported pain assessment. Two reviewers will independently evaluate studies for eligibility, extract data, and assess trial quality and potential bias. Risk of bias will be assessed using criteria outlined in the Cochrane Handbook for Systematic Review of Interventions. Primary outcomes for this review will include any validated measure of pain intensity or pain relief. Dichotomous data will be used to calculate the risk ratio and number needed to treat or harm. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: This protocol is grant-funded and has undergone a peer-review process through the Queen's University Department of Anesthesiology and Perioperative Medicine Vandewater Endowed Studentship. This project is also supported, in part, by the Chronic Pain Network of the Canadian Institutes of Health Research Strategy for Patient-Oriented Research. The electronic database search strategies are currently being developed and modified. The entire review is expected to be completed by January 1, 2019.

Conclusions: The completion of this review is expected to identify available high-quality evidence describing the efficacy and safety of magnesium for the treatment of chronic noncancer pain.

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KEYWORDS

chronic pain; magnesium; noncancer pain; pain management; placebo

Introduction

Description of the Condition

Chronic pain is a significant health problem given its prevalence, impact on quality of life, economic burden, and difficult management. Chronic pain is defined as pain that persists for over 3 months or past the normal time for tissue healing [1]. However, in most cases the duration of the pain is much longer [2,3]. For example, one Canadian study found that over 65% of people with chronic pain have experienced pain for over 5 years [2]. Chronic pain is associated with increased mortality and has major negative impacts on daily living activities and work-related outcomes, such as employment status, days missed from work, and productivity [4]. Depression and anxiety are highly prevalent in the chronic pain population [5]. Individuals living with chronic pain have double the risk of suicide compared with those who do not [6]. Chronic pain is one of the most common reasons for medical visits and is estimated to affect 1.5 billion people worldwide [7-9]. Approximately 30% of adults in the United States and up to 19% of adults in Canada experience chronic pain [10,11]. The direct health care and productivity costs of chronic pain are as high as US $635 billion per year in the United States and Can $43 billion per year in Canada, which exceed the annual costs from cancer and heart disease [11,12]. Pharmacological agents such as antidepressants, anticonvulsants, opioids, nonsteroidal inflammatory drugs, and muscle relaxants are frequently used for pain management [13,14]. Despite the variety of treatments available, they have limited efficacy and dose-limiting adverse effects, leaving a significant unmet need for sufferers [13]. Increases in opioid prescriptions for chronic pain have been associated with increases in opioid-related mortality due to accidental overdose and in the number of individuals requiring treatment for opioid-misuse disorders [15].

Description of the Intervention

Magnesium is the fourth most abundant cation in the human body and plays a fundamental role in a variety of physiological processes [16,17]. Magnesium serves as a cofactor in over 300 enzyme systems necessary for regulating blood pressure, protein synthesis, muscle contraction, and blood glucose [18,19]. In the nervous system, magnesium is important for neurotransmission and neuromuscular coordination [20]. There is evidence supporting the use of magnesium supplementation in a variety of health problems, including preeclampsia or eclampsia, cardiac arrhythmias, migraine headaches, metabolic syndrome, diabetes, hyperlipidemia, asthma, and premenstrual syndrome [19,20]. Treatment with magnesium is inexpensive and has relatively few, usually mild, side effects [17,21]. Magnesium supplementation can be given orally or parenterally and is available in a variety of formulations [17]. This review will consider all magnesium formulations and dosing regimens when used in the treatment of chronic pain.

How the Intervention Might Work

N- methyl-d-aspartate (NMDA) receptors are active contributors to pain transmission [22,23]. NMDA receptors are found on postsynaptic spinal neurons in the dorsal horn of the spinal cord [24]. Under normal conditions, the NMDA receptor ion channel is blocked by magnesium ions found in nervous tissues [20,25]. However, if there is sustained depolarization of the postsynaptic membrane, such as that from high-frequency pain stimulation or nerve trauma causing abnormal impulse propagation toward the spinal cord, the magnesium plug is removed and calcium enters the cell [13,24]. Increases in intracellular calcium lead to an increase in the intensity of pain through a process termed wind-up [13,24]. In wind-up, the spinal dorsal horn neurons have an amplified and prolonged response to subsequent inputs [23,24]. The influx of calcium can also activate various effector molecules and cause downstream changes [24]. These effector molecules can promote mechanisms of synaptic plasticity, such as long-term potentiation, which can result in elevated sensitivity and activity of dorsal horn neurons [24]. This phenomenon is known as central sensitization and manifests as a heightened response to noxious (hyperalgesia) and normally nonnoxious (allodynia) stimuli [22,24]. Both wind-up and central sensitization are plausible mechanisms for chronic pain states [13]. Magnesium administration modulates NMDA receptor-driven activity by acting as a physiological blocker of the NMDA receptor ion channel [16,26-28]. It is expected that through this mechanism, magnesium administration may prevent wind-up and central sensitization and dampen the activity of the dorsal horn neurons, ultimately reducing the pain experience.

Why It Is Important to Do This Review

Chronic pain is a common and complex health problem that has a marked negative impact on patients' quality of life, physical and mental health, family relationships, employment, and economic well-being [29,30]. In North America, clinicians have increasingly prescribed opioids for chronic pain in efforts to improve pain management, despite the relatively modest evidence base and lack of rigorous research demonstrating its long-term effectiveness [31-33]. The high prescribing rates have been accompanied by significant consequences. Deaths from prescription opioid overdoses quadrupled in the last 15 years in the United States, with >200,000 prescription opioid-related deaths since 1999 [31,34]. Although the opioid crisis has been receiving heavy attention from the government and regulatory bodies, which resulted in a decrease in opioid prescriptions

since 2013, the prescribing rates still remain very high in various areas across North America [34]. Additionally, continuing efforts to curb the opioid crisis is unlikely to be an effective long-term solution to the chronic pain crisis [35]. The nature of attention given to the opioid crisis may worsen the stigma associated with proper use of prescription opioids, as well as the stigma of those who are successfully finding pain relief from appropriate prescription opioid use, and result in patients being aggressively tapered off prescription opioids without other nonopioid strategies to help control their pain [35,36]. Therefore, the chronic pain crisis should be viewed and dealt with in a larger context in addition to the opioid crisis. This may involve improving public education on chronic pain, reducing stigma of those living with chronic pain, and increasing accessibility of services [35]. Due to the side effects and uncertain benefits associated with opioid use, alongside the limited accessibility of nonopioid therapies, our review will specifically focus on better understanding chronic pain clinically in terms of what nonopioid strategies are effective in the management of chronic pain.

However, finding an alternative treatment for chronic pain remains a major challenge. Many patients with chronic pain are still in pain despite treatment [37]. Growth in chronic pain research in recent decades has led to the advent of some novel agents, but we have yet to address the problem fully [13,37]. Emerging evidence supports the safe use of magnesium in controlling chronic pain, but there is no consensus regarding its clinical effects [17,38]. The findings of this systematic review will help elucidate magnesium's efficacy and safety as an alternative for controlling pain. This study seeks to improve the quality of life of patients with chronic pain and inform future management strategies for chronic pain.

Objectives

This paper aims to assess the efficacy and safety of magnesium compared with placebo for the treatment of chronic noncancer pain.

Methods

We have prepared this protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol guidelines [39]. The systematic review will also be carried out in accordance with recommendations specified in the PRISMA statement [40].

Criteria for Considering Studies for This Review

Types of Studies

The review will include randomized, double-blind, placebo-controlled trials that evaluate the efficacy or safety of magnesium in the treatment of chronic noncancer pain. We will exclude studies that are nonrandomized or nonblinded, studies of experimental pain, case reports, and clinical observations.

Types of Participants

We will include studies with adults aged 18 years and over reporting any type of chronic noncancer pain for at least 3 months (12 weeks). Chronic noncancer pain can include persistent (eg, chronic low back pain, fibromyalgia) and intermittent (eg, migraine) pain. Patients with terminal cancer or other terminal illnesses will be excluded.

Types of Interventions

We will focus on magnesium at any dose or frequency, by any route, administered for the relief of chronic pain.

Comparison

The intervention will be compared to placebo. Studies with other active controls will be included only if they also have a placebo control.

Types of Outcome Measures

We will assess participant-reported measures of pain intensity or pain relief using validated methods.

Primary Outcomes

The primary outcomes for this review will include any validated measure of pain intensity or pain relief. We will focus on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials definitions for benefit in chronic pain studies [41].

Secondary Outcomes

Secondary outcomes include (1) any pain-related outcome indicating some improvement (eg, improved function); (2) withdrawals due to lack of efficacy, adverse events, and for any cause; (3) participants experiencing any adverse event; (4) participants experiencing any serious adverse event; and (5) specific adverse events (eg, sedation).

Search Methods for Identification of Studies

Electronic Searches

We will conduct a detailed search on Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE from their inception until the date the searches are run. The search will be limited to studies published in English. The search will include terms relating to the magnesium and chronic noncancer pain. The search strategy for Ovid MEDLINE was developed in consultation with a librarian with expertise in literature searches (Multimedia Appendix 1).

Searching Other Resources

We will also review the bibliographies of any randomized controlled trials identified for relevance, as well as search clinical trial databases (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform to identify additional published or unpublished data.

Data Collection and Analysis

Selection of Studies

We will export search results to EndNote and remove duplicates. Two reviewers will independently evaluate studies for eligibility. Screening will be performed on titles and abstracts, and full text screening will be performed on citations felt to be potentially eligible. We will exclude studies that clearly do not satisfy the inclusion criteria. Disagreements between the reviewers will be resolved by discussion and consensus. If necessary, a third reviewer will be consulted. The screening and selection process

will be presented using a PRISMA flowchart and reasons for exclusion will be reported.

Data Extraction and Management

Data from selected studies will be independently extracted by 2 reviewers using standardized data extraction forms. The forms will capture information about the chronic pain condition; number of participants treated; participant characteristics; inclusion and exclusion criteria; type of magnesium used; magnesium levels before and throughout the treatment period; other study drugs used; dose, frequency, and route of administration of magnesium and other study drugs; study duration and follow-up; study design; primary and secondary outcome measures; and results.

Assessment of Risk of Bias in Included Studies

Risk of bias for each study will be independently assessed by 2 reviewers using criteria outlined in the Cochrane Handbook for Systematic Review of Interventions [42]. Disagreements between reviewers will be resolved with discussion and consensus. If necessary, a third reviewer will be consulted.

Measures of Treatment Effect

We will use dichotomous data to calculate the risk ratio with 95% CIs. A fixed-effect model will be used unless significant statistical heterogeneity is found.

We will calculate the number needed to treat by taking the reciprocal of the absolute risk reduction. We will calculate the number needed to harm in the same manner for unwanted effects.

Dealing With Missing Data

For missing data, we will utilize the intention-to-treat analysis. The intention-to-treat population will include participants who were randomized, received at least 1 dose of the assigned study intervention, and provided at least 1 postbaseline assessment. Missing participants will be assigned zero improvement.

Assessment of Heterogeneity

Only studies evaluating similar conditions will be combined for analysis to avoid clinical heterogeneity. Clinical heterogeneity will also be assessed visually and by using the I^2 statistic. When the I^2 value is higher than 50%, we will consider possible explanations for this.

Assessment of Reporting Bias

This review will extract dichotomous data and will not depend on what the authors of the original studies chose to report or not.

We will assess for publication bias using a method that looks for the amount of unpublished data with a null effect needed to make any result clinically irrelevant (usually taken to mean a number needed to treat of ≥10) [43].

Data Synthesis and Analysis of Outcomes

Extracted data will be compiled in Microsoft Excel for analysis. Analysis will be carried out using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

We plan to use a fixed-effect model for meta-analysis. We will use a random-effects model for meta-analysis if it is deemed appropriate to combine heterogeneous studies.

Quality of Evidence

The quality of evidence will be rated using the Grading of Recommendations Assessment, Development and Evaluation approach through a ‘summary of findings’ table.

Subgroup Analysis and Investigation of Heterogeneity

If sufficient data are available, we plan on conducting a subgroup analysis according to the dose of magnesium, duration of study, different types of pain conditions, and quality of included studies.

Results

This protocol is grant-funded and has undergone a peer-review process through the Queen’s University Department of Anesthesiology and Perioperative Medicine Vandewater Endowed Studentship. This project is also supported, in part, by the Chronic Pain Network of the Canadian Institutes of Health Research Strategy for Patient-Oriented Research. The protocol was submitted to PROSPERO on July 4, 2018 and is currently being assessed. The electronic database search strategies are currently being developed and modified. The entire review is expected to be completed by January 1, 2019.

Discussion

Management of chronic pain is ineffective in many individuals, and the increased prescribing of opioids for alleviating chronic pain has been associated with significant consequences. In attempts to curb the opioid crisis, some patients who appropriately use prescription opioids and find relief are being tapered off this treatment and left with limited access to other nonopioid therapies. This review aims to address these issues by better understanding chronic pain clinically, and investigating whether magnesium can serve as a safe alternative for patients who find limited relief from current therapies or have been aggressively tapered off opioids. The completion of this review is expected to identify available high-quality evidence describing the efficacy and safety of magnesium for the treatment of chronic noncancer pain. The results of this review may guide future research in this area and contribute to the development of evidence-based treatment guidelines for the management of chronic noncancer pain.

Acknowledgments

The authors wish to thank Sandra Halliday for her assistance in building the search strategy. The authors also thank the Queen's University Department of Anesthesiology and Perioperative Medicine. This project is also supported, in part, by the Chronic Pain Network of the Canadian Institutes of Health Research Strategy for Patient-Oriented Research.

Authors' Contributions

RP led the writing of this manuscript and the development of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strategy developed for Ovid MEDLINE.

[PDF File (Adobe PDF File), 37KB - resprot_v8i1e11654_app1.pdf]

Multimedia Appendix 2

Peer-reviewer report from the Queen's University Department of Anesthesiology and Perioperative Medicine Vandewater Endowed Studentship.

[PDF File (Adobe PDF File), 246KB - resprot_v8i1e11654_app2.pdf]

References

1. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015 Feb 17;162(4):276-286. [doi: 10.7326/M14-2559] [Medline: 25581257]
2. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag 2011;16(6):445-450 [FREE Full text] [Medline: 22184555]
3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006 May;10(4):287-333. [doi: 10.1016/j.ejpain.2005.06.009] [Medline: 16095934]
4. Andrew R, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. Pain Pract 2014 Jan;14(1):79-94. [doi: 10.1111/papr.12050] [Medline: 23464879]
5. Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. Psychosom Med 2015 Apr;77(3):333-341. [doi: 10.1097/PSY.0000000000000158] [Medline: 25849129]
6. Tang NKY, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. Psychol Med 2006 May;36(5):575-586. [doi: 10.1017/S0033291705006859] [Medline: 16420727]
7. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. Pain 2004 Jun;109(3):514-519. [doi: 10.1016/j.pain.2004.03.006] [Medline: 15157714]
8. Cherry DK, Woodwell DA, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2005 summary. Adv Data 2007 Jun 29(387):1-39. [Medline: 17703793]
9. Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012 May;2012:7 [FREE Full text] [Medline: 23447793]
10. Reitsma ML, Tranmer JE, Buchanan DM, Vandenkerkhof EG. The prevalence of chronic pain and pain-related interference in the Canadian population from 1994 to 2008. Chronic Dis Inj Can 2011 Sep;31(4):157-164 [FREE Full text] [Medline: 21978639]
11. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012 Aug;13(8):715-724. [doi: 10.1016/j.jpain.2012.03.009] [Medline: 22607834]
12. Lynch ME. The need for a Canadian pain strategy. Pain Res Manag 2011;16(2):77-80 [FREE Full text] [Medline: 21499581]
13. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013 Nov;12(11):1084-1095. [doi: 10.1016/S1474-4422(13)70193-5] [Medline: 24074723]
14. Finnerup NB, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. Nat Clin Pract Neurol 2006 Feb;2(2):107-115. [doi: 10.1038/ncpneuro0118] [Medline: 16932532]
15. Alford DP. Opioid Prescribing for Chronic Pain--Achieving the Right Balance through Education. N Engl J Med 2016 Jan 28;374(4):301-303. [doi: 10.1056/NEJMp1512932] [Medline: 26816007]

16. Do SH. Magnesium: a versatile drug for anesthesiologists. Korean J Anesthesiol 2013 Jul;65(1):4-8 [FREE Full text] [doi: 10.4097/kjae.2013.65.1.4] [Medline: 23904932]
17. Herroeder S, Schönherr ME, De Hert SG, Hollmann MW. Magnesium--essentials for anesthesiologists. Anesthesiology 2011 Apr;114(4):971-993. [doi: 10.1097/ALN.0b013e318210483d] [Medline: 21364460]
18. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. Br J Anaesth 1999 Aug;83(2):302-320 [FREE Full text] [Medline: 10618948]
19. Schwalfenberg GK, Genuis SJ. The Importance of Magnesium in Clinical Healthcare. Scientifica (Cairo) 2017;2017:4179326 [FREE Full text] [doi: 10.1155/2017/4179326] [Medline: 29093983]
20. Kirkland AE, Sarlo GL, Holton KF. The Role of Magnesium in Neurological Disorders. Nutrients 2018 Jun 06;10(6) [FREE Full text] [doi: 10.3390/nu10060730] [Medline: 29882776]
21. Parazzini F, Di Martino M, Pellegrino P. Magnesium in the gynecological practice: a literature review. Magnes Res 2017 Feb 01;30(1):1-7. [doi: 10.1684/mrh.2017.0419] [Medline: 28392498]
22. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg 2003 Oct;97(4):1108-1116. [Medline: 14500166]
23. Na HS, Ryu JH, Do SH. The role of magnesium in pain. In: Vink R, Nechifor M, editors. Magnesium in the Central Nervous System. Adelaide: University of Adelaide Press; 2011.
24. D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. Br J Anaesth 2008 Jul;101(1):8-16 [FREE Full text] [doi: 10.1093/bja/aen088] [Medline: 18417503]
25. Hewitt DJ. The use of NMDA-receptor antagonists in the treatment of chronic pain. Clin J Pain 2000 Jun;16(2 Suppl):S73-S79. [Medline: 10870744]
26. Begon S, Pickering G, Eschalier A, Dubray C. Magnesium increases morphine analgesic effect in different experimental models of pain. Anesthesiology 2002 Mar;96(3):627-632. [Medline: 11873038]
27. Begon S, Pickering G, Eschalier A, Dubray C. Magnesium and MK-801 have a similar effect in two experimental models of neuropathic pain. Brain Res 2000 Dec 29;887(2):436-439. [Medline: 11134637]
28. Begon S, Pickering G, Eschalier A, Mazur A, Rayssiguier Y, Dubray C. Role of spinal NMDA receptors, protein kinase C and nitric oxide synthase in the hyperalgesia induced by magnesium deficiency in rats. Br J Pharmacol 2001 Nov;134(6):1227-1236 [FREE Full text] [doi: 10.1038/sj.bjp.0704354] [Medline: 11704642]
29. Abu-Saad HH. Chronic pain: a review. J Med Liban 2010;58(1):21-27. [Medline: 20358856]
30. Ataoğlu E, Tiftik T, Kara M, Tunç H, Ersöz M, Akkuş S. Effects of chronic pain on quality of life and depression in patients with spinal cord injury. Spinal Cord 2013 Jan;51(1):23-26. [doi: 10.1038/sc.2012.51] [Medline: 22547044]
31. Frieden TR, Houry D. Reducing the Risks of Relief--The CDC Opioid-Prescribing Guideline. N Engl J Med 2016 Apr 21;374(16):1501-1504 [FREE Full text] [doi: 10.1056/NEJMp1515917] [Medline: 26977701]
32. Eccleston C, Fisher E, Thomas KH, Hearn L, Derry S, Stannard C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Database Syst Rev 2017 Dec 13;11:CD010323. [doi: 10.1002/14651858.CD010323.pub3] [Medline: 29130474]
33. Cheung CW, Qiu Q, Choi S, Moore B, Goucke R, Irwin M. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. Pain Physician 2014;17(5):401-414 [FREE Full text] [Medline: 25247898]
34. Centers for Disease Control and Prevention. Opioid Overdose. 2018. Prescription Opioid Data URL: https://www.cdc.gov/drugoverdose/data/overdose.html [accessed 2018-07-01] [WebCite Cache ID 715JMCpcn]
35. Waddell K, Moat K, Lavis J. Evidence brief: Developing a national pain strategy for Canada. Hamilton, Canada: McMaster Health Forum; 2017. URL: https://www.mcmasterforum.org/docs/default-source/product-documents/evidence-briefs/pain-strategy-eb.pdf?sfvrsn=2 [accessed 2018-07-21] [WebCite Cache ID 715KXbCQp]
36. De Ruddere L, Craig KD. Understanding stigma and chronic pain: a-state-of-the-art review. Pain 2016 Dec;157(8):1607-1610. [doi: 10.1097/j.pain.0000000000000512] [Medline: 26859821]
37. Lynch ME, Watson CPN. The pharmacotherapy of chronic pain: a review. Pain Res Manag 2006;11(1):11-38 [FREE Full text] [Medline: 16511612]
38. Nechifor M. Magnesium involvement in pain. Magnes Res 2011 Dec;24(4):220-222 [FREE Full text] [doi: 10.1684/mrh.2011.0296] [Medline: 22061718]
39. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
40. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009 Aug 18;151(4):264-9, W64. [Medline: 19622511]
41. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008 Feb;9(2):105-121. [doi: 10.1016/j.jpain.2007.09.005] [Medline: 18055266]
42. Higgins J, Green S. Chapter 8: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons; 2008.

43. Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA, editors. Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press; 2008:15-24.

Abbreviations

NMDA: N-methyl-d-aspartate
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Adherence to Consolidated Standards of Reporting Trials (CONSORT) Guidelines for Reporting Safety Outcomes in Trials of Cannabinoids for Chronic Pain: Protocol for a Systematic Review

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Abstract

Background: Chronic pain affects a significant proportion of the population and presents a major challenge to clinicians and pain specialists. Despite the availability of pharmacologic treatment options such as opioids, many patients continue to experience persistent pain. Cannabinoids present an alternative option with some data on efficacy; however, to date, a systematic review of adverse events (AEs) assessment and reporting in randomized clinical trials (RCTs) involving cannabinoids has not been performed. As a result, it is unclear whether a clear profile of cannabinoid-associated AEs has been accurately detailed in the literature. As cannabinoids are likely to become readily available for patients in the near future, it is important to study how well AEs have been reported in trials so that the safety profile of cannabinoids can be better understood.

Objective: With a potentially enormous shift toward cannabinoid use for managing chronic pain and spasticity, this study aims to reveal the adequacy of AE reporting and cannabinoid-specific AEs in this setting. Spasticity is a major contributor to chronic pain in patients with multiple sclerosis (MS), with a comorbidity of 75%. Many cannabinoid studies have been performed in MS-related painful spasticity with relevant pain outcomes, and these studies will be included in this review for comprehensiveness. The primary outcome will be the quality of AE assessment and reporting by adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Secondary outcomes will include the type of AE, method of AE reporting, severity of AE, frequency of AEs, patient withdrawals, and reasons for withdrawals.

Methods: We will perform a systematic review by searching for primary reports of double-blind, randomized controlled trials of cannabinoids compared with placebo and any active comparator treatments for chronic pain, with a primary outcome directly related to pain (eg, pain intensity, pain relief, and pain-related interference). We will search the following databases: MEDLINE, Embase, Cochrane Library, and PsycINFO. RevMan software will be used for meta-analysis.

Results: The protocol has been registered on the International Prospective Register of Systematic Reviews (CRD42018100401). The project was funded in 2018 and screening has been completed. Data extraction is under way and the first results are expected to be submitted for publication in January or February 2019.

Conclusions: This review will better elucidate the safety of cannabinoids for the treatment of chronic pain and spasticity through identifying gaps in the literature for AE reporting. Like in any new therapy, it is essential that accurate information surrounding the safety and efficacy of cannabinoids be clearly outlined and identified to balance the benefit and harm described for patients.

Trial Registration: PROSPERO CRD42018100401; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=100401

International Registered Report Identifier (IRRID): DERR1-10.2196/11637

(JMIR Res Protoc 2019;8(1):e11637) doi:10.2196/11637

KEYWORDS

adverse events; adverse event reporting; cannabis; cannabinoids; cannabidiol; chronic pain; clinical trial; systematic review; marijuana; safety; tetrahydrocannabinol

Introduction

Chronic pain affects a significant proportion of the population and presents a major challenge to clinicians and pain specialists. Chronic pain can be defined as ongoing pain lasting longer than 3-6 months and negatively affecting a patient's well-being [1]. Market research suggests that up to 1.5 billion people globally suffer from some form of chronic pain [2]. A World Health Organization study of developed countries conducted in 1998 found chronic pain was reported in 22% of patients coming in for primary care [3]. Recent studies of chronic pain have found prevalence rates ranging from 18% to 50% [4-6]. Interference in activities due to chronic pain included self-care, work, sexual life, and sleep quality. With limited access to evidence-based physical and psychological chronic pain interventions [7,8], medications remain the mainstay of treatment. The socioeconomic burden of chronic pain is also substantial, costing just the US economy alone anywhere from US $560 to US $635 billion per year when direct and indirect costs are factored in [3]. Numerous classes of therapeutic agents have been studied and used to treat chronic pain, such as opioids, anticonvulsants, and antidepressants [3]. Despite the availability of these treatment options, chronic pain persists in patients, perhaps because of a lack of analgesic efficacy or poor tolerability due to adverse effects [9,10]. Additionally, patients with chronic pain report poorer health and increased symptoms of anxiety and depression [11,12], which can be disabling and impede their ability to carry out a functional, productive lifestyle. While opioids are currently used to treat various forms of chronic pain, they are sometimes associated with significant risks, including opioid addictions and opioid-related deaths [13], that make them an unfavorable form of treatment.

Cannabis has been used for centuries for several indications including the treatment of pain. Following research on cannabinoids and their mechanism of action in the late 20th century [14], the endocannabinoid system (ECS) was discovered. The ECS, composed of endogenous cannabinoids, their associated enzymes, and cannabinoid receptors [15], plays a significant role in regulating neuropathic pain through neuromodulation and immunomodulation [14]. Currently, there are three main categories of cannabinoids identified in the literature: phytocannabinoids from the cannabis plant, synthetic cannabinoids, and ECSs [14]. *Cannabis sativa* contains over 400 different chemical compounds, 61 of which are cannabinoids acting on the ECS [16]. There are two main cannabinoid receptors that have been identified in the central and peripheral nervous system: the G-protein-coupled cannabinoid receptor type 1 and type 2 (Table 1). Delta 9-tetrahydrocannabinol and cannabidiol are two cannabinoids found in the resin [17] of the cannabis plant that interact with cannabinoid receptor type 1 and cannabinoid receptor type 2 (Table 2) [18].

With the legalization and subsequent increased availability of cannabis emerging in various parts of the world, it is expected that more individuals will seek cannabinoids as a means of relieving various forms of pain [19], including chronic neuropathic pain. Indeed, some research has shown that the wider use of cannabinoids has resulted in a decrease of opioid-related deaths [20]. It is important to note that there are very little data describing the dose-response effect of various cannabinoids to treat chronic pain. However, studies of cannabis smoking in humans suggest a therapeutic window for analgesia, whereby going above the window may increase pain and adverse effects such as nausea, drowsiness, vomiting, headaches, and memory impairment [21-23]. Thus, it is vital for health care and policy decisions that adverse events (AEs) associated with cannabis use for chronic pain management are clearly outlined and identified to balance the benefit and harm described for patients. The Consolidated Standards of Reporting Trials (CONSORT) guidelines [24], with a harms extension [25], were established to improve the AE assessment and reporting in clinical trials. Recent systematic reviews have studied the adherence of randomized clinical trials (RCTs) to CONSORT guidelines [26-28]. Studies of analgesic RCTs in 3 major pain journals (European Journal of Pain, Journal of Pain, and PAIN) found that approximately 4 out of the 10 recommendations of the CONSORT guidelines were not being met [26-28]. This is of significant clinical concern, as it suggests there is a gap in our understanding of the safety of treatments for chronic pain. If a similar gap in safety assessment and reporting exists in trials for cannabinoids treating chronic pain, then it is vital that clinicians and patients alike are made aware of the harms. This may also promote an improvement in the methodology of AE collection and reporting in clinical trials so that there is an emphasis on safety data along with efficacy.

To date, a systematic review of AE assessment and reporting in RCTs involving cannabinoids for chronic pain has not been performed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses harms checklist [29] was established to improve harms reporting in systematic reviews.

Table 1. The cannabinoid receptors of the endocannabinoid system and their mechanism of action.

Cannabinoid receptor	Expression in the body	Mechanism of action
CB_1 R[a]	Presynaptic terminals of peripheral nociceptors and neurons in the dorsal root ganglion and spinal cord [12,13].	Presynaptic activation of CB_1 R results in the reduction of nociceptive transmission by reducing a release of neurotransmitters such as gamma-aminobutyric acid and glutamate [13].
CB_2 R[b]	Cells such as astrocytes, microglia, and macrophages along with lymphoid tissues in the spleen and lungs.	Activation of CB_2 R decreases the release of proinflammatory cytokines such as interleukins, interferon gamma, and tumor necrosis factor alpha, ultimately resulting in reduced inflammation, nociception, and hyperalgesia.

[a]CB_1 R: cannabinoid receptor type 1.

[b]CB_2 R: cannabinoid receptor type 2.

Table 2. The active metabolites of cannabis and their interactions with the endocannabinoid system.

Active compound	Interacting receptor	Mechanism of action
Delta 9-THC[a]	CB_1 R[b] and CB_2 R[c]	Delta 9-THC acts as a partial agonist on CB_1 R and CB_2 R, resulting in effects such as reduction in pain, increased appetite, and changes in emotional and cognitive processes [13].
CBD[d]	CB_1 R, 5-HT1A[e] serotonergic and TYPV1-2[f] vanilloid receptors	CBD acts as a negative allosteric modulator of CB_1 R and numerous other receptors such as 5-HT1A serotonergic and TYPV1-2 vanilloid receptors. CBD has various pharmacological effects, such as being anxiolytic, anti-inflammatory, antiemetic, and antipsychotic. It has also been shown to have antioxidative, anti-inflammatory, and neuroprotective effects at lower doses [14].

[a]THC: tetrahydrocannabinol.

[b]CB_1 R: cannabinoid receptor type 1.

[c]CB_2 R: cannabinoid receptor type 2.

[d]CBD: cannabidiol.

[e]5HT1A: 5-hydroxytryptamine 1A.

[f]TYPV1-2: transient receptor potential vanilloid 1-2.

An analysis of the adherence of systematic reviews to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses harms checklist has not been performed, and our review seeks to advance the goals of this checklist. Within the scope of patients experiencing chronic pain are those suffering from painful spasticity in multiple sclerosis (MS), which is known to be highly associated with pain, with comorbidity of 75% and treatment frequently using cannabinoids [30]. Many cannabinoid studies have been performed in MS-related painful spasticity with relevant pain outcomes, and these studies will be included in this review. With a potentially enormous shift toward cannabinoid use for managing chronic pain, it is essential that accurate information surrounding both the harms as well as the efficacy of cannabinoids be clearly outlined.

The use of medical cannabis is becoming increasingly legalized across developed nations, such as in Canada (2018), allowing for many members of the population to obtain this substance from dispensaries with ease. This legalization may also result in clinicians prescribing cannabis more frequently than before. It is critical that both the safety and efficacy of medications be well established before prescribing to patients. The findings of this project will help elucidate the AEs associated with cannabinoid use for treating chronic pain and, importantly, reveal the appropriateness and accuracy of AE reporting. This will help to form a clearer picture of the risk-benefit profile of cannabinoids. Furthermore, the findings from this project may help inform both clinicians and the public on the nature of cannabis in a clinical context, helping to ensure it is not used inappropriately. These results may also inform politicians and commissioning bodies who may make changes on relevant policies based on research findings. Ultimately, this project seeks to promote the safety of patients in whom cannabinoids reduce chronic pain. The primary outcome will be the quality of AE assessment and reporting by adherence to CONSORT guidelines. Secondary outcomes will include the type of AE, method of AE reporting, AE severity, frequency of AEs, patient withdrawals, and reasons for withdrawals.

Methods

Eligibility Criteria

We will perform a systematic review by searching for primary reports of double-blind, randomized controlled trials of cannabinoids compared with a placebo and any active comparator treatments studied for chronic noncancer pain, with a primary outcome directly related to pain (eg, pain intensity, pain relief, pain-related interference, other analgesic consumption, etc). Chronic pain has been defined as persistent or recurrent pain lasting longer than 3 months [31]. We will include RCTs with parallel and crossover design published in English peer-reviewed journals from all years until 2018. RCTs

involving patients with any type of chronic noncancer pain and patients with spasticity in multiple sclerosis will be included, with no restrictions with regards to setting, age, or country. RCTs involving patients with terminal cancer or other terminal illness will be excluded. The intervention will be cannabinoid-based medicines, which include phytocannabinoids (herbal cannabis, hashish, and marijuana), plant-derived cannabinoids (nabiximols and delta 9-tetrahydrocannabivarin), synthetic cannabinoids (cannabinoid analogs, levonantradol, and nabilone), and synthetic drugs interacting with the ECS.

We will include drugs administered at any dose or by any route, such as smoking, vaporizing, transdermal applications, and ingesting, as well as RCTs comparing cannabinoids to any active comparator or placebo. Examples of active comparators include nonsteroidal anti-inflammatory drugs, antidepressant medications, anticonvulsant medications, and opioids.

Information Sources and Search Strategy

We will search the following electronic bibliographic databases: MEDLINE, Embase, PsycINFO, and Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Cochrane Methodology Register). Additionally, RCTs registered on clinicaltrials.gov will also be searched. All publication years until 2018 will be included, and other gray literature sources will be excluded.

Search Strategy

An experienced librarian from the Faculty of Health Sciences at Queen's University will be involved in creating the search strategy and conducting the search. A sample strategy for MEDLINE is included here. We will apply the following Medical Subject Headings (MeSH) when retrieving articles: Cannabis, Cannabinoids, Cannabidiol, Marijuana Smoking, Tetrahydrocannabinol, and tetrahydrocannabinol-cannabidiol [25]. Any articles with the keywords, cannabis, cannabinoid, cannabidiol, marijuana, marihuana, dronabinol, tetrahydrocannabinol, or tetrahydrocannabinol will also be retrieved. From this set of articles, we will pass the Medical Subject Heading "Pain," or title keyword "pain" through the "Clinical Queries: therapy/narrow" filter to render the final set of articles [32]. From this, the phrases "chronic pain," "neuropathic pain," "neuropathy," and "painful neuropathy," along with "pain" will be utilized to obtain the relevant literature.

The search strategy will include only terms relating to or describing the intervention. We will combine the terms with the Cochrane MEDLINE filter for controlled trials of interventions. Where available, the search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials.

We will only select studies published in English and those published since the inception of each bibliographic database. We will record the date the searches are run and will rerun them just before the final analyses to retrieve any further studies for inclusion.

Data Extraction, Sorting, and Selection

The selection process will involve two independent reviewers on the research team who will work in pairs for screening, eligibility, and inclusion in the meta-analysis through each phase of the review, so that the work is duplicated. We will screen potential titles across all databases included in the search. The abstracts will then be assessed to ensure the correct treatment in the appropriate setting is being studied. The full report for each abstract will then be screened to ensure that the criteria of the review protocol are met. If there are any disagreements between reviewers, this will be resolved by consulting with a third reviewer from the team. Data that are missing or not reported in trials will be reported in the analysis. The data collection process will involve creating an electronic data extraction form to be used to obtain the relevant data forms. Each reviewer will perform this independently, so that the extraction is done in duplicate. We will resolve any discrepancies through discussion with the review authors and the principal investigator when necessary.

We will extract the following variables for each trial: year of publication, country, type of cannabinoid, design, pain condition, number of treatment groups, comparators, frequency of drug administration, study duration, appropriateness of masking, route of drug delivery, dose administered, primary outcome, number of participants randomized, number of study sites, study sponsor, and journal impact factor from the year in which the article was published.

As the CONSORT Extension for Harms was published in 2004, we will collect data from all published studies but do a comparison from pre-2004 articles to post-2004 in order to assess any difference in AE reporting after the published guidelines.

We will define AEs as all adverse treatment effects occurring during a trial, following the definition in the CONSORT Extension for Harms statement [25]. This definition will range from tolerability to safety issues. Studies will be evaluated for the quality of AE reporting by their adherence to the CONSORT Extension for Harms, each being coded using the descriptors. We will consider partial fulfillment of a recommendation as satisfactory in order to facilitate comparing trials. The studies will be analyzed for their assessment method, categorized as "spontaneous reporting from patient," "asked an open-ended question by investigator to report any AEs," "patient diary," "specific AEs assessed by the patient," "specific AEs assessed by direct questioning by an investigator," "multiple methods of AE assessment," or "not specified." We will also review the timing of AE assessments in addition to the time frame in which the drug was administered. The specific time periods, and reporting of the severity of the AEs will also be recorded. Data will be extracted on study patient withdrawals, whether studies outline reasons for withdrawals, and numbers of withdrawals per study. We will also extract the specific reported AE outcomes from each study and outline the most frequently reported AEs in both the drug and placebo groups.

Outcomes and Prioritization

The primary outcome will be the quality of AE assessment and reporting as evaluated by the adherence of included RCTs to each of the 10 CONSORT Extension for Harms recommendations. We selected this primary outcome as these are well-established guidelines for RCTs to follow with respect to safety assessment and reporting. Additionally, it allows for a standardized, quantitative assessment of studies and comparison across studies.

Secondary outcomes will include the type, method, reporting, severity, and frequency of the AE; the timing of AE reporting [33]; patient withdrawals; and reasons for patient withdrawals. We chose these secondary outcomes because they allow for a comprehensive assessment of the specific AEs experienced by patients in these trials and any potential biases in reporting.

Risk of Bias in Individual Studies

In order to assess internal validity, the Cochrane risk of bias tool will be employed [34]. The risk of bias in the included studies will be independently assessed by two review authors by considering the following characteristics: (1) randomization sequence generation: was the allocation sequence adequately generated?; (2) treatment allocation concealment: was the allocated treatment adequately concealed from study participants and clinicians and other health care or research staff at the enrollment stage?; (3) blinding: were the personnel assessing outcomes and analyzing data sufficiently blinded to the intervention allocation throughout the trial?; (4) completeness of outcome data: were participant exclusions, attrition, and incomplete outcome data adequately addressed in the published report?; (5) selective outcome reporting: is there evidence of selective outcome reporting and might this have affected the study results?; and (6) other sources of bias: was the trial apparently free of any other problems that could produce a high risk of bias?

Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with the involvement of a third review author where necessary.

Data Integration and Synthesis

A descriptive approach to data analysis and reporting will be used. Each item of the CONSORT recommendations will be assigned equal weight in the analysis. The percentage of trials fulfilling each CONSORT Extension for Harms recommendation, and the number of recommendations fulfilled by each trial will be recorded.

We will present adherence to the CONSORT Extension for Harms guidelines as an overall score out of 10. These imputation methods are acceptable, but we will record what method each study used to accommodate for missing data. Careful discussion with the principal investigator will be had to ensure accuracy in analysis for these cases. A narrative synthesis of the findings will be provided from the included studies, structured around the type of intervention, target population characteristics, type of outcome, and intervention content. The review will also present summaries of the intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). The heterogeneity of studies will also be assessed using the Higgins I^2 [35]. For statistical analysis, this review will use RevMan software version 5 (Cochrane Collaboration). Finally, the quality of evidence will be assessed according to the GRADE system [36].

Where studies have used the same type of intervention and comparator with the same outcome measure, we will pool results using a random-effects meta-analysis, with standardized mean differences for continuous outcomes and risk ratios for binary outcomes, and calculate 95% CIs and 2-sided *P* values for each outcome. We will also assess evidence of publication bias.

Results

We have received funding from the Queen's University Anesthesiology Vandewater Studentship, allowing for the project to begin. The PROSPERO registration number is CRD42018100401. The project was funded in 2018 and screening has been completed. Data extraction is under way and the first results are expected to be submitted for publication in January or February 2019.

Discussion

Currently, there is an opioid crisis affecting society, resulting in a reduction in health-related quality of life, increased rates of substance use disorder, and loss of life. Chronic pain is experienced by a significant proportion of the population and, currently, clinicians face challenges in creating a holistic and effective pain management plan for patients that does not revolve around opioids. With limited access to evidence-based physical and psychological chronic pain interventions, medications remain the mainstay of treatment. Current pharmaceutical agents, including opioids, are at best moderately effective in the treatment of chronic pain and are commonly associated with significant harms. The findings of this project can ultimately aid clinicians and the general population in making evidence-based decisions for their care, in the context of a chronic and sometimes debilitating condition.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from Queen's University.

[PDF File (Adobe PDF File), 240KB - resprot_v8i1e11637_app1.pdf]

References

1. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain 1998 Sep;77(3):231-239. [Medline: 9808348]
2. PRWeb. Global Pain Management Market to Reach US$60 Billion by 2015, According to a New Report by Global Industry Analysts, Inc URL: http://www.prweb.com/pdfdownload/8052240.pdf [accessed 2018-07-04] [WebCite Cache ID 70fHkMhQt]
3. Moskowitz MA. Advances in understanding chronic pain: Mechanisms of pain modulation and relationship to treatment. Neurology 2002 Sep 10;59(Issue 5, Supplement 2):S1-S1. [doi: 10.1212/WNL.59.5_suppl_2.S1]
4. de Souza JB, Grossmann E, Perissinotti DMN, de Oliveira Junior JO, da Fonseca PRB, Posso IDP. Prevalence of Chronic Pain, Treatments, Perception, and Interference on Life Activities: Brazilian Population-Based Survey. Pain Res Manag 2017;2017:4643830 [FREE Full text] [doi: 10.1155/2017/4643830] [Medline: 29081680]
5. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016 Jun 20;6(6):e010364 [FREE Full text] [doi: 10.1136/bmjopen-2015-010364] [Medline: 27324708]
6. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag 2011;16(6):445-450 [FREE Full text] [Medline: 22184555]
7. Eccleston C, Palermo TM, Williams ACDC, Lewandowski HA, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2014 May 05(5):CD003968 [FREE Full text] [doi: 10.1002/14651858.CD003968.pub4] [Medline: 24796681]
8. Eccleston C, Hearn L, Williams ACDC. Psychological therapies for the management of chronic neuropathic pain in adults. Cochrane Database Syst Rev 2015 Oct 29(10):CD011259. [doi: 10.1002/14651858.CD011259.pub2] [Medline: 26513427]
9. Reinecke H, Weber C, Lange K, Simon M, Stein C, Sorgatz H. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. Br J Pharmacol 2015 Jan;172(2):324-333 [FREE Full text] [doi: 10.1111/bph.12634] [Medline: 24640991]
10. Goodwin JLR, Kraemer JJ, Bajwa ZH. The use of opioids in the treatment of osteoarthritis: when, why, and how? Curr Rheumatol Rep 2009 Feb;11(1):5-14. [Medline: 19171106]
11. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA 1998 Jul 8;280(2):147-151. [Medline: 9669787]
12. Skevington SM. Investigating the relationship between pain and discomfort and quality of life, using the WHOQOL. Pain 1998 Jun;76(3):395-406. [Medline: 9718258]
13. Coyle DT, Pratt C, Ocran-Appiah J, Secora A, Kornegay C, Staffa J. Opioid analgesic dose and the risk of misuse, overdose, and death: A narrative review. Pharmacoepidemiol Drug Saf 2018 May;27(5):464-472. [doi: 10.1002/pds.4366] [Medline: 29243305]
14. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992 Dec 18;258(5090):1946-1949. [Medline: 1470919]
15. Scotter EL, Abood ME, Glass M. The endocannabinoid system as a target for the treatment of neurodegenerative disease. Br J Pharmacol 2010 Jun;160(3):480-498 [FREE Full text] [doi: 10.1111/j.1476-5381.2010.00735.x] [Medline: 20590559]
16. Sharma P, Murthy P, Bharath MMS. Chemistry, metabolism, and toxicology of cannabis: clinical implications. Iran J Psychiatry 2012;7(4):149-156 [FREE Full text] [Medline: 23408483]
17. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci 2005 Dec 22;78(5):539-548. [doi: 10.1016/j.lfs.2005.09.011] [Medline: 16199061]
18. Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res 2017;2(1):139-154 [FREE Full text] [doi: 10.1089/can.2016.0034] [Medline: 28861514]
19. Woolf CJ, American College of Physicians, American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004 Mar 16;140(6):441-451. [Medline: 15023710]
20. Braida D, Pozzi M, Cavallini R, Sala M. Conditioned place preference induced by the cannabinoid agonist CP 55,940: interaction with the opioid system. Neuroscience 2001;104(4):923-926. [Medline: 11457579]
21. Reilly D, Didcott P, Swift W, Hall W. Long-term cannabis use: characteristics of users in an Australian rural area. Addiction 1998 Jun;93(6):837-846. [Medline: 9744119]
22. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 2007 Nov;107(5):785-796. [doi: 10.1097/01.anes.0000286986.92475.b7] [Medline: 18073554]

23. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012 May;13(5):438-449. [doi: 10.1016/j.jpain.2012.01.003] [Medline: 22483680]
24. 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]
25. Ioannidis JPA, Evans SJW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004 Nov 16;141(10):781-788. [Medline: 15545678]
26. Smith SM, Chang RD, Pereira A, Shah N, Gilron I, Katz NP, et al. Adherence to CONSORT harms-reporting recommendations in publications of recent analgesic clinical trials: an ACTTION systematic review. Pain 2012 Dec;153(12):2415-2421. [doi: 10.1016/j.pain.2012.08.009] [Medline: 22985899]
27. Williams MR, McKeown A, Pressman Z, Hunsinger M, Lee K, Coplan P, et al. Adverse Event Reporting in Clinical Trials of Intravenous and Invasive Pain Treatments: An ACTTION Systematic Review. J Pain 2016 Dec;17(11):1137-1149. [doi: 10.1016/j.jpain.2016.07.006] [Medline: 27522950]
28. Smith SM, Wang AT, Katz NP, McDermott MP, Burke LB, Coplan P, et al. Adverse event assessment, analysis, and reporting in recent published analgesic clinical trials: ACTTION systematic review and recommendations. Pain 2013 Jul;154(7):997-1008. [doi: 10.1016/j.pain.2013.03.003] [Medline: 23602344]
29. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, PRISMA Harms Group. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016 Feb 01;352:i157. [doi: 10.1136/bmj.i157] [Medline: 26830668]
30. Solaro C, Trabucco E, Messmer Uccelli M. Pain and multiple sclerosis: pathophysiology and treatment. Curr Neurol Neurosci Rep 2013 Jan;13(1):320. [doi: 10.1007/s11910-012-0320-5] [Medline: 23250765]
31. Treede R, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain 2015 Jun;156(6):1003-1007 [FREE Full text] [doi: 10.1097/j.pain.0000000000000160] [Medline: 25844555]
32. Hoffer D, Smith SM, Parlow J, Allard R, Gilron I. Adverse event assessment and reporting in trials of newer treatments for post-operative pain. Acta Anaesthesiol Scand 2016 Aug;60(7):842-851. [doi: 10.1111/aas.12721] [Medline: 26991481]
33. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011 Nov;72(5):735-744 [FREE Full text] [doi: 10.1111/j.1365-2125.2011.03970.x] [Medline: 21426373]
34. 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]
35. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-560 [FREE Full text] [doi: 10.1136/bmj.327.7414.557] [Medline: 12958120]
36. Brugnolli A, Cavada L, Saiani L. [The GRADE system]. Assist Inferm Ric 2014;33(4):219-226. [doi: 10.1702/1702.18564] [Medline: 25532928]

Abbreviations

AE: adverse event
CONSORT: Consolidated Standards of Reporting Trials
ECS: endocannabinoid system
MS: multiple sclerosis
RCT: randomized clinical trial

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Protocol

The Integration of Interlinkages Between Nature and Human Health in Primary Health Care: Protocol for a Scoping Review

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Abstract

Background: International overview reports and the majority of scientific publications on interlinkages between nature and human health (NHI) do not seem to focus on the role of the health care sector. Primary health care (PHC) is often the first point of contact people have with the health care system and provides comprehensive, accessible, and community-based care that meets the health needs of individuals throughout their life. PHC is a vital backbone for linking knowledge and practice within the organization of health care. This scoping review aims to focus on the potential role of PHC in relation to NHI.

Objective: The objective of this protocol is to present the method used to scope international overview reports and scientific publications on what is mentioned on the integration of NHI in PHC.

Methods: The international overview reports have been screened for keywords relating to PHC. We developed a specific search strategy to scope scientific literature on NHI in relation to PHC. The scientific literature search ran in Web of Science (WOS) and PubMed from inception to May 2017. The scientific publications are screened by 2 independent reviewers, which will result in a list of relevant publications that meet eligibility and inclusion criteria.

Results: On the basis of a first screen on the title of the first 200 results in both search engines, we decided to restrict to WOS. First insights in the international overview reports and the quantitative overview of the results in WOS give a first impression of a missing link between NHI and PHC. The findings are expected to identify knowledge gaps in the translation of evidence on NHI in PHC practices and the role of PHC regarding the application of that evidence in health care practice.

Conclusions: This is, to our knowledge, the first study that seeks to relate existing knowledge on NHI to PHC. The presentation of our method through this protocol allows researchers to build upon and improve our work in future research on the practical implementation of NIH. The findings of the scoping review are expected to guide future scientific research, international policy directives, and PHC workers to fill the gaps in the integration of NHI in PHC.

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KEYWORDS

primary health care; nature; health; human microbiome; infectious diseases; natural disasters; medicinal plants; nutrition; nature-based care

Introduction

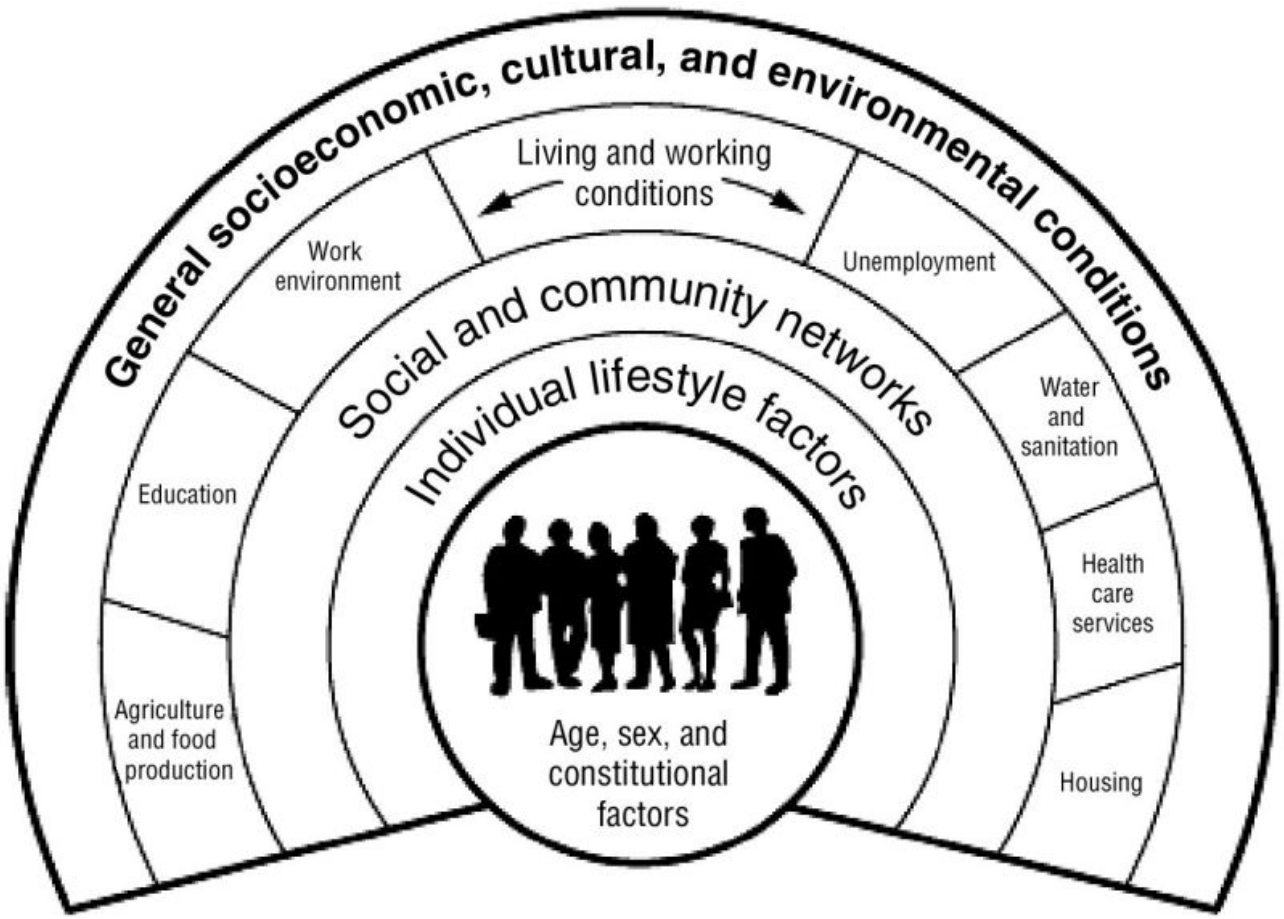
Background

The interlinkages between nature and human health (NHI) have been approached differently by health care over time and space. Where nature is considered a threat to health due to the cause of diseases associated with mass mortalities, nature simultaneously provides the medicinal resources to heal from diseases. This contrary view on NHI is still present, though the research field has expanded with changes in representing health being more than only related to morbidity and mortality and nature being more than a cause of diseases and a resource of medication [1]. Where the biomedical model still dominates in Western countries and gains interest in developing countries, new health approaches complement the central biomedical idea that health improvement mainly requires an understanding of biological causation by adding other determining factors [2]. The Dahlgren-Whitehead model portrays health as determined by a multilevel interaction running from individual to family to community to living and working social status to external forces of society, economy, culture, and environment [2] (Figure 1). This approach of human health reflects the increased attention for preventive health care complementing curative health care.

The generalist perspective makes the PHC setting an ideal partner for integrated approaches covering the multifaceted linkages between nature and human health. PHC is often the first point of contact people have with the health care system and provides comprehensive, accessible, and community-based care that meets the health needs of individuals throughout their life. This scoping review aims to focus on the potential role of PHC in relation to NHI.

Several determinants represented in Figure 1, for example, agriculture and food production and water and sanitation, coincide with the ecosystem approach of nature. Ecosystem services representing all the benefits and functions of natural ecosystems to people cannot be disentangled from health as people cannot remain healthy without clean air, clean water, food, and other resources provided [1]. However, these positive benefits should not ignore the remaining threat of natural ecosystems, such as spreading infectious diseases and contributing to toxicities and natural disasters that again have a major health impact. These new approaches of health and nature and the linkage between both have increased the interdisciplinary character of the research field. The number of scientific publications on NHI has vastly increased in recent years [1], but the majority does not seem to focus on the role of the health care sector. The World Health Organization (WHO) report titled “Ecosystems and Human Well-Being: Health Synthesis” did not specify the role of PHC in applying this knowledge [3].

Figure 1. The Dahlgren-Whitehead model that revises the determinants of health.



Objectives

The objective of this protocol is to perform a scoping review aimed at recent international overview reports and scientific publications on the use of knowledge on NHI in PHC. To scope the available knowledge, the following research question was developed: What does the literature mention on the integration of NHI in PHC? To do so, this scoping review screens the literature for arguments, practice supporting tools and methods, management approaches, and challenges and constraints characterizing the integration of NHI in PHC.

Methods

Strategy

Search Strategy

We searched in the grey literature for international overview reports. The protocol presents a list of international overview reports on NHI obtained through a snowballing search starting from the personal knowledge of the coauthor (HK) through his involvement in international networks and expert communities working on the theme of NHI. The international overview reports are complemented by a search in the scientific literature.

Sources of Knowledge

Table 1 gives an overview of the selection of recent international overview reports on NHI. The WHO contribution to the Millennium Ecosystem Assessment [3] is included to have a historical perspective. Moreover, 1 international overview report lead by the WHO and the Convention on Biological Diversity (CBD) is included in this review as it illustrates the commitment of international governmental organizations in collaboration with the scientific community. This report results from the joint initiative by the WHO and the CBD for a state-of-knowledge review on biodiversity and human health [4]. Furthermore, 2 international overview reports initiated by the European Commission (Directorate General Environment) on one hand [5] and WHO/Europe on the other hand [6] are included as they illustrate the new trend in the international interest, especially in industrialized and urbanized countries, for the potential human health benefits from nature. The first report gives an overview of the health and social benefits of nature and biodiversity protection [5]. The second report includes a review on the effects of urban green space in relation to human health [6]. Although these reports largely focus on human health benefits from nature, especially the WHO/Europe report incorporates an effort to also address potential human health risks (such as infectious disease, allergy, and injury) related to the greening of urban areas. To further address the human health risks from nature, another report led by the United Nations Environment Programme on a healthy environment [7] is included in this review. In this report, a number of international governmental organizations worked together, including the WHO and CBD and conventions related to environmental pollution, such as the Stockholm Convention on Persistent Organic Pollutants [7]. Finally, a report derived from the Rockefeller Foundation-Lancet Commission on planetary health is included as it is a more science-driven initiative reviewing the relation between nature and human health [8].

The selection of international overview reports is complemented by a search for scientific literature in Web of Science (WOS) and PubMed. The literature search run in WOS from inception to May 2017. We conducted a first search by combining the search strings for “nature” and “PHC” in both engines. The search in PubMed resulted in a higher number of publications (n=9074) than the search in WOS (n=471). As the screening on relevance of the title and abstract of the first 200 results in both databases indicated that the results in PubMed did not result in additional relevant papers to the results in WOS, the search was restricted to WOS. Else the number of papers to be assessed would make the work practically unfeasible with little added value for the outcomes of our analysis. Besides looking at nature in general in relation to PHC, we adapt the nature-health subthemes presented in the WHO-CBD report [4]: human microbiome, infectious diseases, natural disasters, medicinal plants, and nutrition. We developed an additional subtheme “nature-based care” and considered it as an umbrella term for health care interventions related to the environment or nature. The relevance of each subtheme is explained in the following paragraphs.

Table 1. Overview of selected international overview reports.

Report reference	Title of report	Additional information
WHO[a] [3]	Ecosystems and Human Well-Being: Health Synthesis	Report of the Millennium Ecosystem Assessment
WHO-CBD[b] [4]	Connecting global priorities: biodiversity and human health	State of knowledge review
ten Brink et al [5]	The Health and Social Benefits of Nature and Biodiversity Protection	Report for the European Commission-DG Environment
WHO [6]	Urban green spaces and health. A review of evidence	WHO Regional Office for Europe
UNEP[c] [7]	Healthy Environment, Healthy People	Thematic report: Ministerial policy review
Whitmee et al [8]	Safeguarding human health in the Anthropocene epoch	Report of The Rockefeller Foundation-Lancet Commission on planetary health

[a]WHO: World Health Organization.

[b]CBD: Convention on Biological Diversity.

[c]UNEP: United Nations Environment Programme.

Nature-Based Care

Over the years, several concepts have been developed to grasp nature-health linkages, such as green care, green prescription, green exercise, and nature-based interventions. The concepts and how they are used or interpreted are not always referring to the environment or nature in the same manner. Horton promotes green care to stimulate general practitioners to raise awareness among their patients to maintain their health while respecting the environment and ecosystem, on which their health also depends [9]. Horton gives the examples of overconsumption in relation to both the environment and obesity and walking and cycling as forms of physical exercise that have minimal impact on the environment [9]. In a special issue on green care in the *International Journal of Therapeutic Communities*, green care is referred to as outdoor activities and nature in a therapeutic context [10]. Steigen defines the concept as "using animals, plants and nature in an active process to offer health-promoting activities for people" [11]. Sempik and Bragg define the concept as "utilizing plants, animals, and landscapes to create interventions to promote health and well-being" [12]. Haubenhofer interprets the concept similarly but explicitly linking it to "a person's social, physical, mental, and even educational well-being," linking "traditional healthcare and other sectors of human societies, like agriculture, gardening, landscape and nature conservation, animal keeping and animal husbandry" [13]. Barton et al promote the use of the term green exercise as an umbrella term relating healthy activity to the presence of nature [14]. Green prescription traditionally is defined as "a prescription for exercise" [15] but not specifically linking it to a natural environment [16,17]. Van den Berg particularly links it to the natural environment and emphasizes primary health care professionals as key actors in stimulating nature-based activities [18].

Human Microbiome

Quite some recent studies [19-21] show the importance of contact with nature for a healthy immune system. Declining contact with some forms of environmental microbiota may contribute to the rapidly increasing prevalence of allergies and other chronic inflammatory diseases among urban populations worldwide. This makes the relation between wild microbes and the human microbiome a promising field for health care research.

Nutrition

The contribution of nature to healthy nutrition is a well-established field of expertise: biodiversity contributes to food diversity for healthy human diets as well as supports pollination and soil fertility, which are essential to food production [22].

Medicinal Plants

The importance of nature for providing medicinal plants is also well established: biological resources historically contribute to health care, with medicinal plants being important for traditional medicine and international trade [23].

Infectious Diseases

Nature-related infectious diseases pose an important nature-related human health risk in quite some regions in the world: "Two-thirds of known human infectious pathogens have emerged from animals, with the majority of recently emerging pathogens originating in wildlife," partly driven by anthropogenic disturbance and biodiversity loss [24].

Natural Disasters

Quite some regions, moreover, suffer from natural disasters: "more mid- and small-sized disasters are now occurring more often, while increasing urbanization and the threat of climate change place more focus on the future social, economic, environmental and public health impacts of natural disaster events" [25].

Search Strings

With the help of PHC professionals and the application of PubMed search builder, a search string for PHC has been developed (Table 2). We developed search strings for "nature" in general and the 6 nature-health subthemes described above based on the search strategy for the Regional Assessment for Europe and Central Asia by the Intergovernmental Platform on Biodiversity and Ecosystem Services (IPBES) [26]. This search strategy derives from the WHO and the CBD 2015 state of knowledge review [4] and how this was translated in search strings on biodiversity-health linkages and further fine-tuned (with coauthor HK) for the application by the IPBES. A selection of these search strings has been slightly adapted for the development of the search strings of the nature-health subthemes for this protocol. On the basis of the search strings for noncommunicable diseases, mental health and physical fitness in relation to practical nature-related interventions, and keywords present in the paper of Van den Berg, we developed the search string for the subtheme "nature-based care" [18].

First, the search strings for the 6 nature-health subthemes have been separately applied in WOS to get a quantitative view on the research interest for a certain nature-health subtheme. Second, the search strings for the 6 nature-health subthemes have been separately combined with the search string for PHC, using the Boolean operator *AND*. Currently, the results of the combinations of these search strings are being checked on relevance. First insights in the search results showed that many results deviate strongly from the focus of our scoping review and did not link to nature at all. Therefore, we decided to add an additional step in which the search string of each nature-health subtheme is combined with the search string for PHC and the search string developed for "nature" in general, using the Boolean operator *AND*. The initial combination of the search string for PHC and nature allowed to check if some nature-health–related themes were not captured by the 6 nature-health subthemes. The combinations of search strings are summarized below:

1. nature-health subtheme
2. nature-health subtheme AND primary care
3. nature-health subtheme AND primary care AND nature
4. nature AND primary care

Table 2. Overview of search strings applied in Web of Science.

Category	Search strings
Primary health care	"general pract*" OR "GP" OR "primary care" OR "primary health care" OR "primary healthcare" OR "family pract*" OR "family medicine" OR "family physician*" OR "family doctor*"
Nature	"biological diversity" OR biodivers* OR "living natural resource*" OR "living resource*" OR "natur* diversity" OR "diversity in nature" OR "*species diversity" OR "int*-speci* diversity" OR "genetic diversity" OR "diversity of gene*" OR ecosystem* OR "ecological system*" OR "ecosystem service*" OR "landscape service*" OR "environmental service*" OR "ecological service*" OR "natur* capital*" OR "nature based solution*" OR "environmental capital*" OR "green infrastructure" OR greenspace* OR "green space*" OR "blue infrastructure" OR bluespace* OR "blue space*" OR flora* OR fauna* OR wildlife OR "natural habitat*" OR "ecological habitat" OR "wildlife habitat*" OR "invasive * species" OR biogeograph* OR "bio-geograph*" OR "natur* space*" OR "natur* environment*"
Nature-health subthemes	
Nature-based care	"green care" OR "green exercise" OR "green gym" OR "green leisure" OR "green recreation" OR "environmental care" OR "environmental exercise" OR "environmental gym" OR "environmental leisure" OR "environmental recreation" OR "restorative activit*" OR "restorative exercise*" OR "green therap*" OR "environmental therap*" OR "outdoor therap*" OR "green prescription" OR (rehab* AND garden* OR "nature-based rehabilitation" OR "nature based rehabilitation" OR (therap* AND garden*) OR (horticultur* AND therap*) OR "care farm*" OR ("walk" AND "talk" AND "coach*") OR "health walk*"
Microbiome	"gut microbiome" OR "gut microbiota" OR "gut micro-organisms" OR commensal microbiome" OR "commensal microbiota" OR "commensal micro-organisms" OR dermal microbiome" OR "dermal microbiota" OR "dermal micro-organisms" OR intestin* microbiome" OR "intestin* microbiota" OR "intestin* micro-organisms" OR internal microbiome" OR "internal microbiota" OR "internal micro-organisms" OR "hygiene hypothes*s" OR "biodiversity hypothes*s" OR "Old Friends mechanism*"
Infectious diseases	"disease* of plant origin*" OR "disease* of wildlife origin*" OR "disease ecology" OR "disease driver*" OR "disease dynamics" OR "disease emergence" OR "disturbance-disease-*" OR "driver* of emergence" OR "emerg* infectious disease*" OR "emerg* disease*" OR "emerg* infect*" OR nidality OR nidus OR "pathogen ecology" OR enzootic* OR phytonos* OR phytonotic* OR synanthrop* OR "pathogen pollution" OR "amplification effect" OR "spill-over" OR "species barrier*" OR "vector-borne" OR "vector borne" OR "animal host*" OR " ecologic* host*" OR "plant host*" OR "wildlife host*" OR "animal reservoir*" OR "ecologic* reservoir*" OR "plant reservoir*" OR " wildlife reservoir*" OR zooanthropono* OR zoogen* OR zoonos* OR zoonotic* OR "carrier species" OR " competent species" OR "host abundance" OR "host density" OR "host distribution" OR "host diversity" OR "parasite abundance" OR "parasite density" OR "parasite distribution" OR "parasite diversity" OR "pathogen abundance" OR "pathogen density" OR "pathogen distribution" OR "pathogen diversity" OR "reservoir abundance" OR "reservoir density" OR " reservoir distribution" OR "reservoir diversity" OR "vector abundance" OR "vector density" OR "vector distribution" OR "vector diversity" OR "bacterial transmission" OR "disease transmission" OR "parasite transmission" OR "pathogen transmission" OR "viral transmission"
Natural disasters	"biodiversity-disturbance-disease" OR "disease* of animal origin*" OR "disease* of plant origin*" OR "disease* of wildlife origin*" OR "disease ecology" OR "disease driver*" OR "disease dynamics" OR "disease emergence" OR "disturbance-disease-*" OR "driver* of emergence" OR "emerg* infectious disease*" OR "emerg* disease*" OR "emerg* infect*" OR nidality OR nidus OR "pathogen ecology" OR enzootic* OR phytonos* OR phytonotic* OR synanthrop* OR "pathogen pollution" OR "amplification effect" OR "spill-over" OR "species barrier*" OR "vector-borne" OR "vector borne" OR "animal host*" OR " ecologic* host*" OR "plant host*" OR "wildlife host*" OR "animal reservoir*" OR "ecologic* reservoir*" OR "plant reservoir*" OR " wildlife reservoir*" OR zooanthropono* OR zoogen* OR zoonos* OR zoonotic* OR "carrier species" OR " competent species" OR "host abundance" OR "host density" OR "host distribution" OR "host diversity" OR "parasite abundance" OR "parasite density" OR "parasite distribution" OR "parasite diversity" OR "pathogen abundance" OR "pathogen density" OR "pathogen distribution" OR "pathogen diversity" OR "reservoir abundance" OR "reservoir density" OR " reservoir distribution" OR "reservoir diversity" OR "vector abundance" OR "vector density" OR "vector distribution" OR "vector diversity" OR "bacterial transmission" OR "disease transmission" OR "parasite transmission" OR "pathogen transmission" OR "viral transmission"
Medicinal resources	"biodiversity for medicine" OR "biological diversity for medicine" OR "biodiversity-based medicin*" OR "biodiversity-derived medicin*" OR bioprospecting OR "biodiversity-based prospecting" OR "biodiversity based prospecting" OR "prospecting from natur*" OR "medicine* from natur*" OR "medicine* derived from natur*" OR "medicinal plant*" OR "medicinal animal*" OR "medicinal fung*"
Nutrition	"biodiversity for food" OR "biological diversity for food" OR agrobiodivers* OR "agro-biodivers*" OR "*managed agrobiodiversity" OR "crop diversity" OR "crop wild relative*" OR "dietary *diversity" OR "food *diversity" OR "diverse diet*" OR "foods of wildlife origin*" OR bushfood* OR "bush food*" OR "home garden*" OR "species used for food" OR "food resource*" OR "nutritional resource*" OR "local food species" OR "traditional food species" OR "traditional food*" OR "traditional crop*" OR "traditional variet*" OR "wild food harvest*"

Selection of Relevant Scientific Literature

The titles and abstracts of the results of the search string combinations 2, 3, and 4 are checked on relevance by 2 independent reviewers (first reviewer: HK; second reviewer: HB or RR). Relevance is attributed if the publications approach the nature-health subthemes in accordance with their relevance

to health, as described above, and if they pay attention to PHC in a nonsuperficial manner. Publications are included when explicitly relating the research findings on NHI to PHC, with references to PHC according to the keywords of the search string. Publications are excluded from further analysis when only mentioning PHC but not linking the NHI knowledge to PHC. For pragmatic reasons, publications are only checked on relevance when the number of results is not too large (below 100). On the basis of the titles and abstracts, the reviewers make for each publication 1 of following decisions: relevant, in doubt, or irrelevant. Each decision is supported by a short argumentation. In case the first reviewer defines a publication "relevant" or "irrelevant" and the second reviewer agrees with this decision, the publication will be either included in or excluded from the scoping review. In case the first reviewer is in doubt or the second reviewer is not convinced by the decision of the first reviewer, the first reviewer reads the full text of the publication to make a final decision in consultation with the second reviewer. Foreign language material, except for papers with an English abstract, will be excluded because of the cost and time involved in translating material. Although these limits have to be adopted for practical reasons, it is worth pointing out that potentially relevant papers can be missed. As this is only a scoping review, for pragmatic reasons, the quality of the papers will not be assessed. The scoping review is only meant to give an indication of the potential.

Content Analysis

The international overview reports on NHI have been screened for the presence of the keywords included in the search string for PHC. A quantitative overview of the scientific literature has been done, but the selection of relevant publications needs to be finalized.

The content from the international overview reports and relevant scientific publications will be presented in a way to identify the main areas of interest and gaps. Information will be extracted to answer the following questions:

- Which arguments are given to engage with PHC to integrate nature-health linkages?
- Which practice supporting tools and methods for this integration are provided?
- Which management approaches are recommendable for this integration?
- Which challenges and constraints characterize this integration?

Ethics

Ethical approval for this protocol and planned systematic review was not required.

Results

International Overview Reports

A first screen of the selected international overview reports on NHI through the search for the PHC keywords has shown that the role of PHC remains mainly underreported. Therefore, we have decided to screen for the additional keyword "health prof*" as we noticed that some reports only mention this more general category of health care professionals, while also potentially intending to include PHC professionals.

Scientific Literature

Table 3 summarizes the quantitative results of the combinations of the search strings in WOS as described in the Methods section. The combination of the search string for PHC and nature resulted in a low number of publications (n=471), especially when compared with the number of publications only linked to nature (n=525,365) or only linked to PHC (n=206,256). Similarly, the combination of the search string for each nature-health subtheme with the search string for PHC separately or combined with the search string for nature resulted in a strongly reduced number of publications compared with the total number of publications found for each nature-health subtheme.

Table 3. Quantitative overview of the combinations of search strings applied in Web of Science.

Nature-health subthemes	Total	Reviews		Papers	
		PHC[a]	PHC+nature	PHC	PHC+nature
Nature-based care	1140	3	0	35	2
Human microbiome	5017	4	1	14	1
Nutrition	14,026	1	0	16	1
Medicinal plants	29,803	22	2	198	35
Infectious diseases	60,142	14	1	202	5
Natural disasters	49,256	72	0	901	1

[a]PHC: primary health care.

Discussion

To our knowledge, this scoping review is the first of its kind to explore NHI in relation to PHC. The findings of this scoping review will provide a first state of the art of NHI in relation to PHC in international overview and scientific publications. By including subthemes such as "natural disasters" and "infectious diseases" besides the other subthemes, the review attempts to include both the risks and benefits related to nature's impact on health. The quantitative overview of the scientific literature is a first indication of a missed potential in research and practice to link evidence on NHI to PHC. A content analysis of the selected literature will allow to draw lessons on the integration

of NHI in PHC. The findings are expected to identify gaps in the integration of NHI in current medical practices and to orient recommendations toward needs for action and capacity building. The presentation of the protocol of the scoping review allows researchers to build upon and improve our work in future research on the practical implementation of NHI. Results synthesized and limitations to our search strategy will be disseminated by means of a published work in a peer-reviewed journal.

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Authors' Contributions

HK, RR, and HB conceptualized the scoping review protocol. HK developed the search strategy with guidance from Conor Kretsch (COHAB) and Bram Oosterbroek (ICIS-University of Maastricht). LL wrote the manuscript of the scoping review protocol with critical inputs and appraisal from HK, RR, and HB. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

References

1. Hartig T, Mitchell R, de Vries S, Frumkin H. Nature and health. Annu Rev Public Health 2014;35:207-228. [doi: 10.1146/annurev-publhealth-032013-182443] [Medline: 24387090]
2. Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health. Stockholm: Institute for future studies; 1991. URL: https://tinyurl.com/kb6chqj [accessed 2019-01-11] [WebCite Cache ID 75LXzjanH]
3. World Health Organization. Washington DC: Island Press; 2005. Ecosystems and Human Well-Being: Health Synthesis URL: https://tinyurl.com/y7q9myxw [accessed 2019-01-11] [WebCite Cache ID 75LYy6BGY]
4. World Health Organization, Convention on Biological Diversity. Connecting Global Priorities: Biodiversity and Human Health. A State of Knowledge Review. Geneva: WHO Press; 2015. URL: http://apps.who.int/iris/bitstream/handle/10665/174012/9789241508537_eng.pdf?sequence=1 [WebCite Cache ID 75LaRp1k0]
5. Ten Brink BP, Mutafoglu K, Schweitzer JP, Kettunen M, Twigger-Ross C, Baker J, et al. Institute for European Environmental Policy. 2016. The Health and Social Benefits of Nature and Biodiversity Protection URL: https://tinyurl.com/ycgpjvvr [WebCite Cache ID 75Lb5Gxnr]
6. Thompson CW, de Oliveira ES, Wheeler BW, Depledge MH, van den Bosch MA. World Health Organization. Copenhagen: WHO Regional Office for Europe; 2016. Urban green spaces and health. A review of evidence URL: http://www.euro.who.int/__data/assets/pdf_file/0005/321971/Urban-green-spaces-and-health-review-evidence.pdf?ua=1 [WebCite Cache ID 75LbexM9e]
7. Healthy Environment, Healthy People. Nairobi: United Nations Environment Programme; 2016. URL: https://wedocs.unep.org/bitstream/handle/20.500.11822/17602/K1602727%20INF%205%20Eng.pdf?sequence=1&isAllowed=y [WebCite Cache ID 75Lc7KAPD]
8. Whitmee S, Haines A, Beyrer C, Boltz F, Capon AG, de Souza Dias BF, et al. Safeguarding human health in the Anthropocene epoch: report of The Rockefeller Foundation-Lancet Commission on planetary health. Lancet 2015 Nov 14;386(10007):1973-2028. [doi: 10.1016/S0140-6736(15)60901-1] [Medline: 26188744]
9. Horton G, Magin P. Healthy patients, healthy planet-green recommendations for GP health promotion. Aust Fam Physician 2007 Dec;36(12):1006-1008 [FREE Full text] [Medline: 18075623]
10. Freestone M, McArdle S, Yates R, Bracey A, Broekaert E, De Leon G, et al. International Journal of Therapeutic Communities, The Association of Therapeutic Communities. 2008. Therapeutic Communities: Green Care edition URL: http://www.dldocs.stir.ac.uk/documents/ijtc291.pdf [WebCite Cache ID 75UUoQUdJ]
11. Steigen AM, Kogstad R, Hummelvoll JK. Green Care services in the Nordic countries: an integrative literature review. Eur J Soc Work 2015;19(5):692-715. [doi: 10.1080/13691457.2015.1082983]
12. Sempik J, Bragg R. Green Care: Origins and Approaches. In: Gallis C, editor. Green Care: For Human Therapy, Social Innovation, Rural Economy, and Education. New York: Nova Science Publishers; 2013.
13. Haubenhofer DK, Elings M, Hassink J, Hine RE. The development of green care in western European countries. Explore (NY) 2010;6(2):106-111. [doi: 10.1016/j.explore.2009.12.002] [Medline: 20362268]

14. Barton J, Bragg R, Wood C, Pretty J, editors. Green Exercise: Linking Nature, Health and Well-Being. London: Routledge; 2016.
15. Swinburn BA, Walter LG, Arroll B, Tilyard MW, Russell DG. The green prescription study: a randomized controlled trial of written exercise advice provided by general practitioners. Am J Public Health 1998 Feb;88(2):288-291. [doi: 10.2105/AJPH.88.2.288] [Medline: 9491025]
16. Lobelo F, Stoutenberg M, Hutber A. The Exercise is Medicine Global Health Initiative: a 2014 update. Br J Sports Med 2014 Dec;48(22):1627-1633. [doi: 10.1136/bjsports-2013-093080] [Medline: 24759911]
17. Patel A, Schofield GM, Kolt GS, Keogh JW. General practitioners' views and experiences of counselling for physical activity through the New Zealand Green Prescription program. BMC Fam Pract 2011 Nov 02;12:119 [FREE Full text] [doi: 10.1186/1471-2296-12-119] [Medline: 22044577]
18. Van den Berg AE. From green space to green prescriptions: challenges and opportunities for research and practice. Front Psychol 2017 Feb 27;8:268 [FREE Full text] [doi: 10.3389/fpsyg.2017.00268] [Medline: 28289398]
19. Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, Torppa K, Laatikainen T, et al. Environmental biodiversity, human microbiota, and allergy are interrelated. Proc Natl Acad Sci U S A 2012 May 22;109(21):8334-8339 [FREE Full text] [doi: 10.1073/pnas.1205624109] [Medline: 22566627]
20. Rook G, Bäckhed F, Levin BR, McFall-Ngai MJ, McLean AR. Evolution, human-microbe interactions, and life history plasticity. Lancet 2017 Dec 29;390(10093):521-530. [doi: 10.1016/S0140-6736(17)30566-4] [Medline: 28792414]
21. Ruokolainen L, Paalanen L, Karkman A, Laatikainen T, von Hertzen L, Vlasoff T, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. Clin Exp Allergy 2017 May;47(5):665-674. [doi: 10.1111/cea.12895] [Medline: 28165640]
22. World Health Organization, Convention on Biological Diversity. Biodiversity and nutrition. In: Romanelli C, Cooper D, Campbell-Lendrum D, Maiero M, Karesh WB, Hunter D, et al, editors. Connecting Global Priorities: Biodiversity and Human Health: a State of Knowledge Review. Geneva: WHO Press; 2015:79-127.
23. World Health Organization, Convention on Biological Diversity. Traditional medicine. In: Connecting Global Priorities: Biodiversity and Human Health: a State of Knowledge Review. Geneva: WHO Press; 2015:180-196.
24. World Health Organization, Convention on Biological Diversity. Infectious diseases. In: Connecting Global Priorities: Biodiversity and Human Health: a State of Knowledge Review. Geneva: WHO Press; 2015:130-144.
25. World Health Organization, Convention on Biological Diversity. Increasing resilience and disaster risk reduction: the value of biodiversity and ecosystem approaches to resistance, resilience and relief. In: Connecting Global Priorities: Biodiversity and Human Health: a State of Knowledge Review. Geneva: WHO Press; 2015:238-246.
26. Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. Bonn, Germany: IPBES secretariat; 2018. The regional assessment report on biodiversity and ecosystem services for Europe and Central Asia: Summary for Policymakers URL: https://www.ipbes.net/system/tdf/spm_2b_eca_digital_0.pdf?file=1&type=node&id=28318 [WebCite Cache ID 75LgT6KWe]

Abbreviations

CBD: Convention on Biological Diversity
IPBES: Intergovernmental Platform on Biodiversity and Ecosystem Services
NHI: interlinkages between nature and human health
PHC: primary health care
UNEP: United Nations Environment Programme
WHO: World Health Organization
WOS: Web of Science

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Protocol

Data Quality and Cost-Effectiveness Analyses of Electronic and Paper-Based Interviewer-Administered Public Health Surveys: Protocol for a Systematic Review

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Abstract

Background: Population-level survey is an essential standard method used in public health research to quantify sociodemographic events and support public health policy development and intervention designs with evidence. Although all steps in the survey can contribute to the data quality parameters, data collection mechanisms seem the most determinant, as they can avoid mistakes before they happen. The use of electronic devices such as smartphones and tablet computers improve the quality and cost-effectiveness of public health surveys. However, there is lack of systematically analyzed evidence to show the potential impact on data quality and cost reduction of electronic-based data collection tools in interviewer-administered surveys.

Objective: This systematic review aims to evaluate the impact of interviewer-administered electronic device data collection methods concerning data quality and cost reduction in population-level surveys compared with the traditional paper-based methods.

Methods: We will conduct a systematic search on Medical Literature Analysis and Retrieval System Online, PubMed, CINAHL, PsycINFO, Global Health, Trip, ISI Web of Science, and Cochrane Library for studies from 2007 to 2018 to identify relevant studies. The review will include randomized and nonrandomized studies that examine data quality and cost reduction outcomes. Moreover, usability, user experience, and usage parameters from the same study will be summarized. Two independent authors will screen the title and abstract. A third author will mediate in cases of disagreement. If the studies are considered to be combinable with minimal heterogeneity, we will perform a meta-analysis.

Results: The preliminary search in PubMed and Web of Science showed 1491 and 979 resulting hits of articles, respectively. The review protocol is registered in the International Prospective Register of Systematic Reviews (CRD42018092259). We anticipate January 30, 2019, to be the finishing date.

Conclusions: This systematic review will inform policymakers, investors, researchers, and technologists about the impact of an electronic-based data collection system on data quality, work efficiency, and cost reduction.

Trial Registration: PROSPERO CRD42018092259; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018092259

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KEYWORDS

data collection; demographic and health surveys; tablet computers; smartphone; mobile phone; data quality; cost comparison

Introduction

Population-level survey or public health survey is an important method of public health research. It helps monitor sociodemographic events and support policy development and intervention designs with evidence [1,2]. Most developing countries conduct a census or periodic demographic and health surveys to determine national and regional estimates. The population-level epidemiologic indicators help identify the determinants of mortality and morbidity. Although all steps of the data collection and management processes impact data quality, the mechanism of data capture seems to be the main determinant of data quality to avoid mistakes before they happen [1,3,4].

Conducting surveys includes a lot of manual tasks to manage the data collection and reporting processes [5]. Additionally, broader field-based surveys require human and material resources. Inherently, paper data collection processes are labor intensive, time consuming, and susceptible to errors. They incur high printing and running costs and are cumbersome and uncomfortable for the field data collectors [6,7]. The data quality, survey period, and the overall cost of the process can be affected with the above intrinsic nature of paper-based data capturing tools [8,9].

The growth of information and communication technologies such as electronic data collection systems have mitigated some of the challenges encountered in paper-based data collection. Implementation of tablet- or smartphone-based data collection tools is becoming increasingly popular in public health surveys [10,11]. The potential of electronic data collection tools varies according to their intended area of intervention (disease or health care event), country setting, mode of administration (self- or interviewer-administered), and type of research study (clinical trial or survey). A comparison between computer-assisted self-interviews and face-to-face or telephone interviews was conducted in public health studies regarding drug abuse [12] and sexual health and HIV [13-15]. The findings showed that computer-assisted self-interviews were preferable as they resulted in more significant reportings of potentially stigmatized drug, sex, and HIV risks.

Other studies compared paper-based clinical case report forms (CRFs) with electronic CRFs (eCRFs) [16-18]. Electronic data captures (EDCs) were found to be advantageous in broad, low-risk studies and could contribute to improving the data quality and reducing cost. A recent review also showed that the use of EDC in clinical research is cost effective and improves the quality of data [19].

The potential of mobile devices can be seen in demographic health surveys [4,20], general surveys [21], and longitudinal surveys [22]. Studies have proved that electronic data collection tools can improve data quality and work efficiency and reduce overall costs of the survey. However, those studies embedded the impact of the mobile device for data collection in electronic health or mobile health (mHealth) research outcomes. This embedding may compromise the self-standing effect of mobile devices in improving the data collection and management processes of surveys [10,23,24]. Therefore, the impact of electronic data collection tools in surveys needs to be separately analyzed and reported.

A recent review by the Cochrane Collaboration compared the impact of apps and alternative instruments such as paper, laptop computers, and tablet computers for self-administered health surveys [11]. Data collection process involves an interaction between the questionnaire, the respondent, and, in the case of interviewer-administered surveys, the interviewer. In contrast with self-administered surveys, during the interviewer-administered survey, the interviewer or data collector is an additional mediating factor in the interactions of interview tools and the respondents. The difference in the mode of questionnaire administration can have serious effects on data quality [9]. A systematic review considering interviewer-administered data collection may complement that evidence. As to the knowledge of the investigators, there is no systematic review that has analyzed data quality and cost-effectiveness of electronic and paper-based interviewer-administered public health surveys. This systematic review will fill this gap by answering the following question for interviewer-administered public health surveys: What evidence is available for the differences in data quality and cost-effectiveness between electronic and paper-based capture of data?

Methods

Study Registration

The protocol is registered in the International Prospective Register of Systematic Reviews (CRD42018092259). This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 guideline [25].

Eligibility Criteria

We have categorized the inclusion criteria for this systematic review according to study design, study participants, types of intervention, types of technology, and study setting.

Study Design

We will include parallel randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials, crossover RCTs, paired repeated measures, cohort and case-control studies, and comparative cross-sectional studies that compare the electronic interviewer-administered survey with paper-based methods.

Study Participants

This review focuses on data quality outcomes from the data collected by data collectors who used paper or electronic data collection modalities during public health surveys. We will also include data collectors, supervisors, or data managers for opinion-, preference-, and usability-related analysis.

Types of Intervention

Any mobile device data collection tool that was designed to support interviewer-administered data collection processes in public health surveys will be included.

Types of Technology

Electronic data collection in our review refers to portable, wireless digital devices usually supported by mobile network or satellite communication infrastructures, such as cell phones, smartphones, personal digital assistants, and tablet computers. The given support includes data capture and instant, stored, and forward transfers to the research center. We will include all apps with technologies that directly support the data collection process by enabling data collectors or interviewers to collect and send data as well as enabling supervisors or data managers to monitor the data collection process.

Study Setting

Our review will include national demographic surveys, demographic and health surveillance systems, and household surveys. We will include all countries and research facilities regardless of the socioeconomic status of the country.

Exclusion Criteria

We will exclude the following study types from the review: all studies that compare electronic and paper-based tools in self-administered surveys; studies that are performed in settings other than a house-to-house field survey (eg, electronic medical records and eCRFs); studies not performed on human subjects; studies reported before January 1, 2007; studies that are experience reports, letters, reviews, commentaries, and editorials; and non-English language publications.

Outcomes

The primary outcomes in this review will be data quality indicators and cost-effectiveness evidence. According to Bowling [9], data quality is a vague concept, and it is hard to find any gold standard or framework. Data quality could be defined in terms of survey response rates, questionnaire item response rates, the accuracy of responses, the absence of bias, and completeness of the information obtained from respondents [9]. For this review, we will focus on two data quality indicators: data completeness and data accuracy. Accuracy is hereby defined as the absence of typographical errors, decimal point faults, and illogical values, whereas the completeness of items is inversely proportional to the number of missing responses in the questionnaire. In general, we will compare the proportion of errors or missing items between electronic and paper-based data collection methods [9,11,26,27]. Cost-effectiveness outcomes will be measured using resource costing methods, which include provider perspective direct cost comparing the cost of conducting a survey using electronic and paper-based data collection methods. The secondary outcomes include work efficiency, usability, user experience, and acceptability.

Information Source

We will conduct a systematic keyword search on electronic databases such as Medical Literature Analysis and Retrieval System Online, PubMed, CINAHL, PsycINFO, Global Health, Trip, ISI Web of Science, and Cochrane Library. In addition, we will screen the reference list citations of included articles. Unpublished and in-progress studies will be identified from the following trial registries: ClinicalTrials.gov, ISRCTN registry, Australian New Zealand Clinical trial Registry, International Clinical Trials Registry Platform.

We will restrict our search to articles published in English from 2007 to mid-2018 (as mobile devices that became available during this time are compatible with the mobile operating system framework that focuses on apps, and most of the EDC apps were tested during this period [11]).

Search Strategy

The search strategy will consider 3 categories: the technology or intervention used (eg, mobile device, mobile phone, mHealth, or EDC), area of application (eg, data collection, demographic and health surveys, or large-scale surveys), and the outcome of interest (eg, data quality, missing data, and cost-effectiveness). We will connect all the similar terms in the same group with the Boolean operators “OR” and “AND” (Table 1).

Data Management

Endnote software (Clarivate Analytics) will be used to import the retrieved literature from all databases to manage duplication and further screening. The Covidence (Veritas Health Innovation) Web-based screening tool will be used to import the set of deduplicated citations and to manage the title and abstract screening process. We will screen the titles and abstracts for the inclusion criteria. Potentially relevant full-text papers will be reviewed, including reference lists of these papers.

Selection Process

Two authors (AAZ and TN) will screen titles and abstracts independently and identify potentially eligible studies based on the eligibility criteria. Review author pairs will then screen the full-text reports and decide whether these meet the inclusion criteria. Any disagreements in each phase will be resolved first by discussion among the review authors using the prespecified inclusion criteria. If the disagreement or uncertainty continues, a consulting third author (FF) will mediate the final decision. We will note the reasons for inclusion and exclusion using a flowchart diagram.

Data Extraction

An excel sheet for data extraction will be used based on the inclusion criteria and the objectives of the review. To ensure uniformity across reviewers, we will conduct a pretest standardization exercise before starting the data extraction process. Textbox 1 presents the data items that we will extract.

Table 1. Search terms and preliminary search results from PubMed and Web of Science searched in March 2018.

#	Category	Terms	PubMed	Web of Science
1	Technology or intervention	(mobile phone OR cellular phone OR Cell Phone OR cellphone OR smart phone OR smartphone OR tablet device OR Tablet Computers OR Computers, Handheld OR Computer, PDA OR personal digital assistant OR electronics data capture OR EDC OR electronic survey OR eCRF OR electronic forms OR eHealth[a] OR mHealth[b] OR Mobile Technology OR Mobile Application OR Mobile Apps OR App, Mobile OR Apps)	111,669	125,598
2	Area of application	(Data collection OR electronic data collection OR electronic data capture OR Paper-Based data collection OR data entry OR data capture OR data gathering OR questionnaires OR survey OR health survey OR interview OR demographic OR household survey OR large-scale surveys OR population surveillance OR Demographic Health Survey OR DHS[c])	3,248,226	2,601,782
3	Outcome of interest	((Cost Analysis OR Cost Comparison OR cost saving OR Costs OR Cost Measures OR Cost-Benefit Analyses OR Cost Effectiveness OR Cost-Utility Analysis OR Economic Evaluation) AND (Data quality OR Data accuracy* OR error OR error rate OR missing OR incompleteness OR inaccuracy))	24,247	67,272
Combined		1 AND 2 AND 3	1491	979

[a]eHealth: electronic health.

[b]mHealth: mobile health.

[c]DHS: demographic health survey.

Textbox 1. List of the data items that will be extracted based on the inclusion criteria and the objectives of the review.

- Author and year
- National affiliation of the author
- Country in which the study was conducted
- Study design
- Health care or research site setting
- Target users
- Size of enumerated population dataset or data elements
- Type of mobile device, delivery mode, app type
- Stated purpose of intervention
- Range of data quality outcome measures described based on our operational definition for data quality parameters
- Range of economic evaluation outcomes used to evaluate the cost-effectiveness
- Types of economic evaluation models or outcomes assessed
- Usability, user experience, and work efficiency outcomes or descriptions
- Key findings from each included study will be summarized and tabulated

Outcomes and Prioritization

The primary outcomes of this review are the following data quality indicator parameters: error rates quantified from missing items (number of incomplete records per interview questionnaire) and inaccuracy (mean number of problematic records per interview questionnaire). The secondary outcomes are cost-effectiveness parameters and cost-related outcomes. Moreover, we will consider usability scale and qualitative user satisfaction indices for the secondary outcomes analysis. Multiple definitions of usability, acceptability, user satisfaction, and related terminologies exist [11]. We will extract, summarize, and categorize the definitions in the final filtered full-text papers to include efficiency, acceptability, usability, and user experience outcomes.

Risk of Bias in Individual Studies

The quality of the included studies will be assessed using parameters such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. We will grade each parameter as a low, high, or unclear risk of bias [28]. All assessments of study quality will be performed by at least two reviewers (AAZ and

TN), with any disagreement resolved by consensus or mediation with a third reviewer (FF or RR) where necessary.

Data Synthesis

We will present the analyzed data in a tabular and narrative form. Where possible, meta-analyses will be performed on methodologically comparable studies (comparable particularly with regards to the study design and endpoint measures in the outcomes) reporting primary and secondary outcomes. The choice of statistical tests will depend on the nature of the outcome variable. Where relevant data are missing, we will contact the authors. If we cannot obtain missing data by contacting the authors, we will use an imputation method. If the number of included studies per outcome is sufficient, publication bias will be assessed visually through funnel plots and tested by Egger's regression test. The Mantel-Haenszel method will be used for the fixed effect model if tests of heterogeneity are not significant. If our data displays statistical heterogeneity, the random effects model will be selected. In cases of significant heterogeneity, we will perform a qualitative narrative summary instead of a meta-analysis.

Ethics and Dissemination

As only previously published studies are included and reported in the review, no additional formal ethical assessment and no informed consent is required. The findings will be disseminated through publication of a single manuscript in a peer-reviewed journal.

Results

We anticipate January 30, 2019, to be the finishing date.

Discussion

This systematic review will identify and synthesize the available evidence on data quality and cost-effectiveness outcomes of electronic data collection tools for interviewer-administered surveys. The evidence from the systematic review is supposed to complement the available evidence on the impact of mHealth on demographic and health care data collections [29].

Conflicts of Interest

None declared.

References

1. Bocquier P, Sankoh O, Byass P. Are health and demographic surveillance system estimates sufficiently generalisable? Glob Health Action 2017;10(1):1356621 [FREE Full text] [doi: 10.1080/16549716.2017.1356621] [Medline: 28820344]
2. Timaeus I, Harpham T, Price M, Gilson L. Health surveys in developing countries: the objectives and design of an international programme. Soc Sci Med 1988;27(4):359-368. [Medline: 3175718]
3. Gerritsen A, Bocquier P, White M, Mbacké C, Alam N, Beguy D, et al. Health and demographic surveillance systems: contributing to an understanding of the dynamics in migration and health. Glob Health Action 2013 Jul 11;6:21496 [FREE Full text] [doi: 10.3402/gha.v6i0.21496] [Medline: 23849188]
4. Rutstein SO, Rojas G. The DHS Program. Calverton, Maryland: United States Agency for International Development; 2006. Guide to DHS Statistics: Demographic and Health Surveys Methodology URL: https://dhsprogram.com/pubs/pdf/DHSG1/Guide_to_DHS_Statistics_29Oct2012_DHSG1.pdf [accessed 2018-10-02] [WebCite Cache ID 72rd1SmIW]
5. Central Statistical Agency [Ethiopia] and ICF International. The DHS Program. Addis Ababa, Ethiopia and Calverton, Maryland: Central Statistical Agency and ICF International Ethiopia Demographic and Health Survey 2011 URL: https://dhsprogram.com/pubs/pdf/fr255/fr255.pdf [WebCite Cache ID 72rdJXw7J]
6. Okwaraji YB, Cousens S, Berhane Y, Mulholland K, Edmond K. Effect of geographical access to health facilities on child mortality in rural Ethiopia: a community based cross sectional study. PLoS One 2012;7(3):e33564 [FREE Full text] [doi: 10.1371/journal.pone.0033564] [Medline: 22428070]
7. King JD, Buolamwini J, Cromwell EA, Panfel A, Teferi T, Zerihun M, et al. A novel electronic data collection system for large-scale surveys of neglected tropical diseases. PLoS One 2013;8(9):e74570 [FREE Full text] [doi: 10.1371/journal.pone.0074570] [Medline: 24066147]
8. Toninelli D, Pinter R, de Pedraza P. Mobile Research Methods: Opportunities and challenges of mobile research methodologies. London: Ubiquity Press; 2015.
9. Bowling A. Mode of questionnaire administration can have serious effects on data quality. J Public Health (Oxf) 2005 Sep;27(3):281-291. [doi: 10.1093/pubmed/fdi031] [Medline: 15870099]
10. Braun R, Catalani C, Wimbush J, Israelski D. Community health workers and mobile technology: a systematic review of the literature. PLoS One 2013;8(6):e65772 [FREE Full text] [doi: 10.1371/journal.pone.0065772] [Medline: 23776544]
11. Marcano Belisario JS, Jamsek J, Huckvale K, O'Donoghue J, Morrison CP, Car J. Comparison of self-administered survey questionnaire responses collected using mobile apps versus other methods. Cochrane Database Syst Rev 2015 Jul 27(7):MR000042. [doi: 10.1002/14651858.MR000042.pub2] [Medline: 26212714]
12. Perlis TE, Des Jarlais DC, Friedman SR, Arasteh K, Turner CF. Audio-computerized self-interviewing versus face-to-face interviewing for research data collection at drug abuse treatment programs. Addiction 2004 Jul;99(7):885-896. [doi: 10.1111/j.1360-0443.2004.00740.x] [Medline: 15200584]

13. Adebajo S, Obianwu O, Eluwa G, Vu L, Oginni A, Tun W, et al. Comparison of audio computer assisted self-interview and face-to-face interview methods in eliciting HIV-related risks among men who have sex with men and men who inject drugs in Nigeria. PLoS One 2014;9(1):e81981 [FREE Full text] [doi: 10.1371/journal.pone.0081981] [Medline: 24416134]
14. Beauclair R, Meng F, Deprez N, Temmerman M, Welte A, Hens N, et al. Evaluating audio computer assisted self-interviews in urban South African communities: evidence for good suitability and reduced social desirability bias of a cross-sectional survey on sexual behaviour. BMC Med Res Methodol 2013 Jan 31;13:11 [FREE Full text] [doi: 10.1186/1471-2288-13-11] [Medline: 23368888]
15. Richens J, Copas A, Sadiq ST, Kingori P, McCarthy O, Jones V, et al. A randomised controlled trial of computer-assisted interviewing in sexual health clinics. Sex Transm Infect 2010 Aug;86(4):310-314. [doi: 10.1136/sti.2010.043422] [Medline: 20551234]
16. Walther B, Hossin S, Townend J, Abernethy N, Parker D, Jeffries D. Comparison of electronic data capture (EDC) with the standard data capture method for clinical trial data. PLoS One 2011;6(9):e25348 [FREE Full text] [doi: 10.1371/journal.pone.0025348] [Medline: 21966505]
17. Le Jeannic A, Quelen C, Alberti C, Durand-Zaleski I, CompaRec Investigators. Comparison of two data collection processes in clinical studies: electronic and paper case report forms. BMC Med Res Methodol 2014 Jan 17;14:7 [FREE Full text] [doi: 10.1186/1471-2288-14-7] [Medline: 24438227]
18. Pavlović I, Kern T, Miklavcic D. Comparison of paper-based and electronic data collection process in clinical trials: costs simulation study. Contemp Clin Trials 2009 Jul;30(4):300-316. [doi: 10.1016/j.cct.2009.03.008] [Medline: 19345286]
19. Rorie DA, Flynn RWV, Grieve K, Doney A, Mackenzie I, MacDonald TM, et al. Electronic case report forms and electronic data capture within clinical trials and pharmacoepidemiology. Br J Clin Pharmacol 2017 Sep;83(9):1880-1895 [FREE Full text] [doi: 10.1111/bcp.13285] [Medline: 28276585]
20. Paudel D, Ahmed M, Pradhan A, Lal Dangol R. Successful use of tablet personal computers and wireless technologies for the 2011 Nepal Demographic and Health Survey. Glob Health Sci Pract 2013 Aug;1(2):277-284 [FREE Full text] [doi: 10.9745/GHSP-D-12-00056] [Medline: 25276539]
21. Singh T, Roy P, Jamir L, Gupta S, Kaur N, Jain DK, et al. Assessment of Universal Healthcare Coverage in a District of North India: A Rapid Cross-Sectional Survey Using Tablet Computers. PLoS One 2016;11(6):e0157831 [FREE Full text] [doi: 10.1371/journal.pone.0157831] [Medline: 27351743]
22. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol 2014 Feb;43(1):61-68 [FREE Full text] [doi: 10.1093/ije/dys203] [Medline: 23243115]
23. Iribarren SJ, Cato K, Falzon L, Stone PW. What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. PLoS One 2017;12(2):e0170581 [FREE Full text] [doi: 10.1371/journal.pone.0170581] [Medline: 28152012]
24. Agarwal S, Perry HB, Long L, Labrique AB. Evidence on feasibility and effective use of mHealth strategies by frontline health workers in developing countries: systematic review. Trop Med Int Health 2015 Aug;20(8):1003-1014 [FREE Full text] [doi: 10.1111/tmi.12525] [Medline: 25881735]
25. 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 Dec 02;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
26. King JD, Buolamwini J, Cromwell EA, Panfel A, Teferi T, Zerihun M, et al. A novel electronic data collection system for large-scale surveys of neglected tropical diseases. PLoS One 2013;8(9):e74570 [FREE Full text] [doi: 10.1371/journal.pone.0074570] [Medline: 24066147]
27. Zhang SY, Wu Q, van Velthoven MH, Chen L, Car J, Rudan I, et al. Smartphone versus pen-and-paper data collection of infant feeding practices in rural China. J Med Internet Res 2012 Sep 18;14(5):e119 [FREE Full text] [doi: 10.2196/jmir.2183] [Medline: 22989894]
28. 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:d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]
29. Labrique AB, Vasudevan L, Kochi E, Fabricant R, Mehl G. mHealth innovations as health system strengthening tools: 12 common applications and a visual framework. Glob Health Sci Pract 2013 Aug;1(2):160-171 [FREE Full text] [doi: 10.9745/GHSP-D-13-00031] [Medline: 25276529]

Abbreviations

CRF: case report form
eCRF: electronic case report form
eHealth: electronic health
EDC: electronic data capture
mHealth: mobile health

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Viewpoint

Integrating Taxonomies Into Theory-Based Digital Health Interventions for Behavior Change: A Holistic Framework

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Abstract

Digital health interventions (DHIs) have been emerging in the last decade. Due to their interdisciplinary nature, DHIs are guided and influenced by theories (eg, behavioral theories, behavior change technologies, and persuasive technology) from different research communities. However, DHIs are always coded using various taxonomies and reported in insufficient perspectives. This inconsistency and incomprehensiveness will cause difficulty in conducting systematic reviews and sharing contributions among communities. Therefore, based on existing related work, we propose a holistic framework that embeds behavioral theories, behavior change technique taxonomy, and persuasive system design principles. Including four development steps, two toolboxes, and one workflow, our framework aims to guide DHI developers to design, evaluate, and report their work in a formative and comprehensive way.

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KEYWORDS

behavior change technique; behavior change technique taxonomy; digital health interventions; persuasive technology; persuasive system design

Introduction

According to the County Health Rankings [1], variation in health can be accounted for by health behaviors (30%), clinical care (20%), social and economic factors (40%), and physical environment (10%). Increasing evidence shows that lifestyle-related behaviors such as diet, exercise, sleeping, emotion, and smoking play an essential role in people's health. Chronic diseases caused by unhealthy behaviors and habits are among the leading causes of mortality [2]. Some of the chronic diseases, for example, type 2 diabetes, could be lifelong and bring a heavy burden to the patients and their family. The only way to prevent many chronic diseases is to change unhealthy lifestyles, for example, diet and physical activity.

With the potential for low cost and high scalability for chronic disease prevention, in the past decade, digital health interventions (DHIs) have been widely discussed by government stakeholders, clinicians, and researchers [3]. Designing and deploying DHIs are challenging due to the complexity of human behavior, which could be affected by individuals' motivation, emotion, ability, social environment, and physical environment. Therefore, DHI design could accordingly require theories and practice from several disciplines, including phycology, public health, behavioral science, human-computer interaction, and so on. The interdisciplinary nature of DHIs calls for a comprehensive framework to guide the development, evaluation, and report.

As DHIs are expected to change human behavior, behavioral theories can serve as the development foundation. It has been

shown that theory-based behavior change interventions are more effective than others [4,5]. Nevertheless, behavioral theories could also be ignored [6] or misused [7]. Although behavioral theories allow the explanation and prediction of behavior, they lack the guidance for translating into operational techniques.

The behavior change technique (BCT) taxonomy [8] and persuasive system design (PSD) principles [9] are two widely used taxonomies in DHI research [10-13]. These taxonomies not only inform DHI design but also enable precise reporting, which is favored by systematic reviewers. Although derived from different philosophies, BCTs and PSDs have some common elements. However, they are used separately in many DHI studies. To benefit from both, we combined the BCT taxonomy and PSD principles into a more comprehensive taxonomy in the light of the behavioral intervention technology (BIT) model [14].

In this paper, we aim to put the puzzles together and build a holistic framework to aid DHI researchers to design, evaluate, and report their studies. In short, our contributions include the following:

1. We provide a holistic framework that allows DHI developers to design, evaluate, and report their work in a formative and comprehensive way.
2. We propose the DHI taxonomy including the strategy part and the characteristic part. Our DHI taxonomy enables more comprehensive description of DHIs.
3. We classify PSD principles into two parts: strategies and characteristics. We then combine the BCT taxonomy and PSD principles (strategies related) into our DHI taxonomy (the strategy part).
4. We integrate the intervention characteristics from the BIT model with the ones we extract from PSD principles (characteristic related) as the characteristic part of the DHI taxonomy.

Related Work

Summary

As this paper is for DHI developers from different communities, it is necessary to clarify the terms and our scope before we present the related work. Digital health or electronic health (eHealth) is the umbrella concept referring to the use of information and communication technologies for health [15]. According to the World Health Organization, DHIs cover systematic functionalities to support clients, health care providers, health system or resource managers, and data services [3]. In this paper, however, we limit our scope to the DHIs aiming to change users' lifestyle behavior (eg, food intake, physical activity, and smoking) using digital technology to prevent or manage health problems.

CeHRes Roadmap

In 2011, a holistic framework (ie, the CeHRes Roadmap) was proposed to improve the uptake and impact of eHealth technology. The CeHRes Roadmap was built upon 16 existing frameworks via a systematic review and emphasized the importance of holism [16]. Human characteristics, socioeconomic and cultural environments, and technology are closely connected to affect human behavior. Therefore, developers should always keep these holistic factors in mind when building eHealth technologies. Within this framework, the CeHRes Roadmap was illustrated as a practical guideline to help plan, coordinate, and execute the participatory development process of eHealth technologies. The CeHRes Roadmap consists of five steps, namely, contextual inquiry, value specification, design, operationalization, and summative evaluation, which integrate persuasive technology design, human-centered design, and business modeling. Although the CeHRes Roadmap integrates behavioral theories as its foundation, it does not explicitly show how to apply them in the intervention design. Besides, the CeHRes Roadmap does not adopt any persuasive technology taxonomy.

Behavioral Intervention Technology Model

In 2014, Mohr and colleagues proposed the BIT model, aiming to support the translation of treatment and intervention aims into an implementable treatment model [14]. The BIT model includes a theoretical phase followed by an instantiation phase. The theoretical phase consists of the intervention aims and behavior change strategies, whereas the instantiation level consists of intervention elements, characteristics, and workflow. Thus, the BIT model can serve as a supplement to the CeHRes Roadmap. However, the BIT model only provides some examples in each component. For example, behavior change strategies include education, goal setting, monitoring, feedback, and motivation enhancement. As the author mentioned, the BIT model is a simplification and should be modified and elaborated to fit users' needs [14]. In this paper, we will adjust and elaborate the BIT model to fit into our holistic framework.

Integrate, Design, Assess, and Share Framework

In 2016, Mummah et al proposed IDEAS (Integrate, Design, Assess, and Share) as a framework and toolkit of strategies for the development of DHIs [17]. IDEAS was built on three essential components: behavioral theory, design thinking, and evaluation and dissemination. The IDEAS framework emphasizes the importance of behavioral theories and introduces the taxonomy of BCTs. However, the BCT taxonomy is regarded as an alternative to using behavioral theories to identify target constructs in interventions. In our holistic framework, we suggest using both of them as two necessary steps because they correspond to the intervention aims and strategies, respectively.

Behavioral Theories

All the three reviewed works above mention behavioral theories, but only IDEAS explicitly integrates behavioral theories into the steps of the development process. Behavioral theories refer to the social-psychological theories of behavior change, which explain and predict human behavior. As depicted by Sutton [18], each of the behavioral theories specifies a small number of cognitive and affective factors as the proximal determinants of behavior (see Figure 1). These factors are called constructs in behavioral science [7]. We will use this term to refer to the fundamental components of behavioral theories in the rest of the paper.

Figure 1. Our hypothesized continuum model of behavior change.

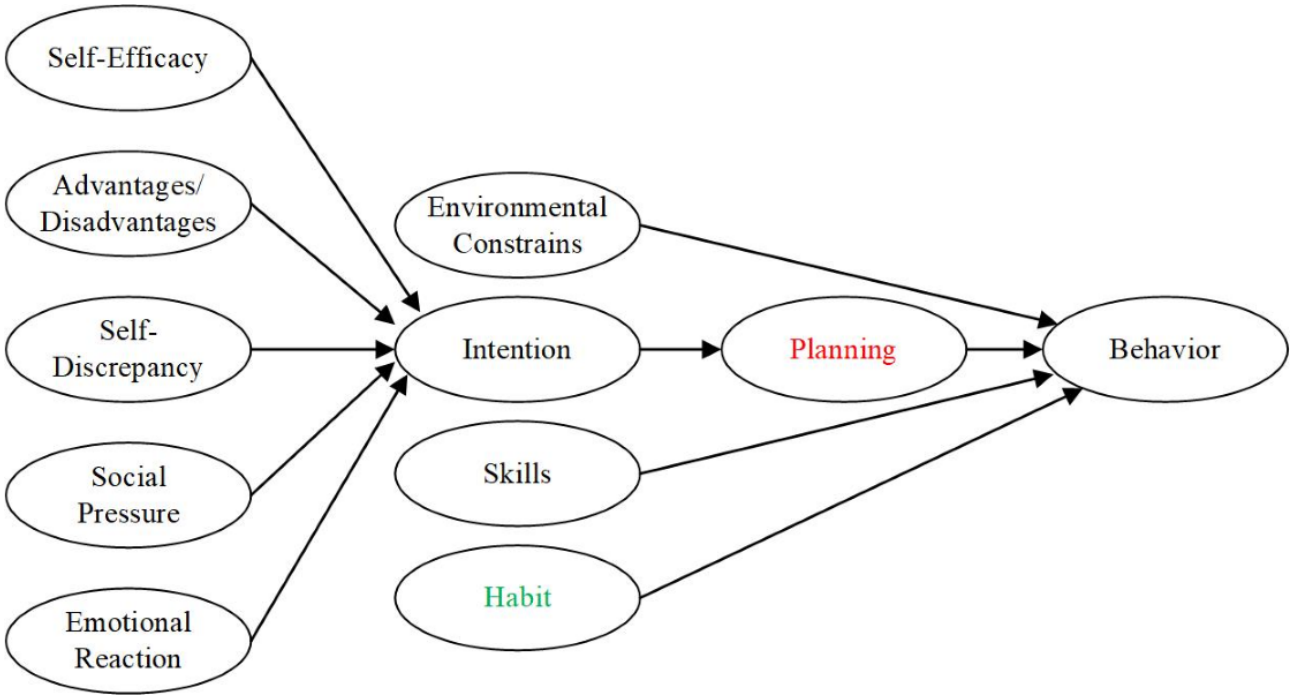
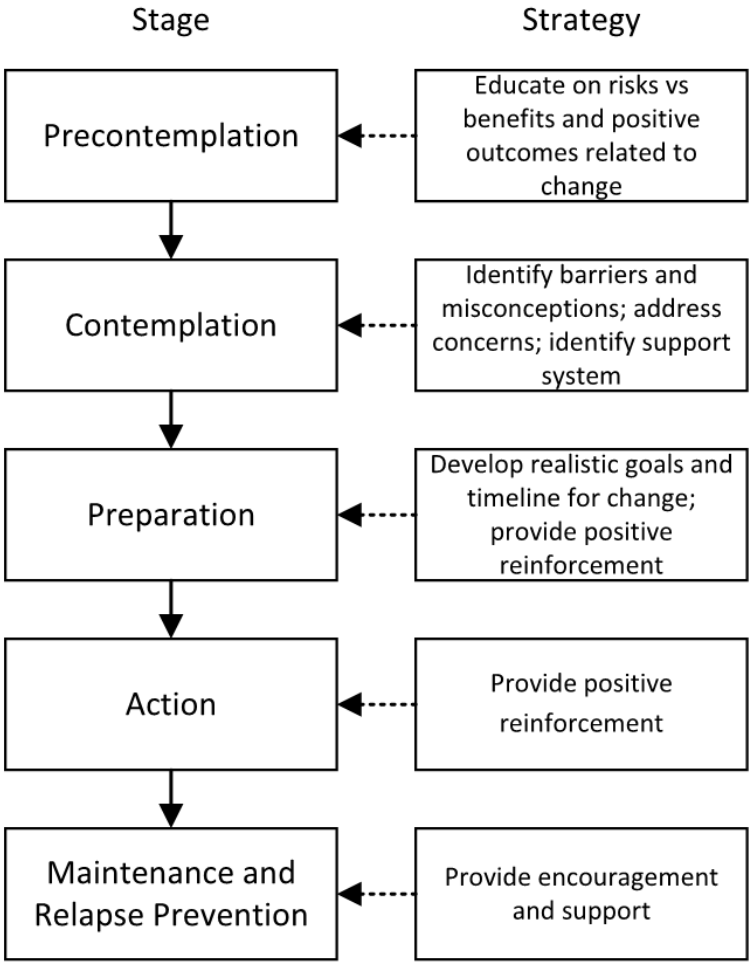


Figure 2. The transtheoretical model of behavior change.



Glanz et al [19] illustrated the most frequently used behavioral theories published before 2010: the social cognitive theory (SCT) [20], the transtheoretical model of behavior change (TTM) [21], the health belief model (HBM) [22], and the theory of planned behavior (TPB) [23]. Davis et al [24] also identified 82 behavioral theories, among which the most frequently used

theories are TTM, TPB, SCT, the information-motivation-behavioral skills model, HBM, the self-determination theory [25], the health action process approach (HAPA) [26], and the social learning theory [27]. Based on different assumptions of human behavior, these behavioral theories can be grouped into continuum theories and stage theories [28].

Continuum theories assume people's behavior is caused by a set of variables, for example, intention and skills. Except for TTM, all other mentioned theories fall into this group. Based on the behavioral model integrating several existing ones [28], we present a hypothesized continuum model as shown in Figure 1. The constructs in black are borrowed from the integrated behavioral model in [28]. Planning (shown in red in Figure 1) is specified as a mediator of the intention-behavior relationship in HAPA [26,29,30]. The habit (shown in green in Figure 1) has been found to moderate the effects of planning on behavior change [31].

Stage theories assume people change their behavior in a process including several stages. The factors pushing people from one stage to the next are believed to be different. Therefore, the strategies at each state should be adapted accordingly. For example, Figure 2 shows the stages and strategies of TTM, which is adapted from [32]. This model divides the behavior change process into five stages, namely *precontemplation*, *contemplation*, *preparation*, *action*, *and maintenance and relapse prevention*. Depending on the stage of change, different strategies could be applied accordingly to make the intervention effective.

Behavioral theories provide a toolbox to understand human behavior and explain the rationale behind interventions. However, their shortcomings should be noted before they are used. Hekler and colleagues [7] have pointed out three shortcomings of behavioral theories: (1) most behavioral theories explain only a small portion of variance in the outcomes they are trying to account for, (2) many behavioral theories, in their current form, are not falsifiable, and (3) there is a fragmentation and an overabundance of different theories. Therefore, DHI developers should not be limited to behavioral theories. With the emergence of DHIs, the existing behavioral theories can be further evaluated and improved [33]. Here we list some guidelines when using specific behavioral theories: [34] and [35] for the SCT, [36] for the HBM, [37] for the TPB, and [38] for the HAPA.

Digital Health Intervention Taxonomy

While behavioral theories can predict and explain human behavior, there is a gap between theories and operational interventions. Will self-monitoring increase self-efficacy for promoting physical activity? Will information about health consequences affect perceived advantages or disadvantages? Due to the high complexity of human behavior and health, one DHI may involve several techniques. The lack of a consistent taxonomy of DHIs will lead to poor replicability and low comparability of the results from related studies. Although there exists taxonomies to bridge the theory-intervention gap, the use of different taxonomies still hinders the understanding and contribution among communities. Therefore, we present the DHI taxonomy, a unified taxonomy taking advantage of two widely used taxonomies (the BCT taxonomy and PSD principles) in light of the BIT model.

BCTs are defined as observable, replicable, and irreducible components of an intervention designed to change behavior [8,39], for example, self-monitoring or goal setting. Abraham and Michie developed a taxonomy of BCTs that identified 22 BCTs and 4 BCT packages [8] and was later extended to a taxonomy containing 93 BCTs in 16 groups, called BCT taxonomy (v1) [39]. The BCT taxonomy has been used for informing intervention development and report [40,41] and identifying the effectiveness of BCTs [13,42-44]. It also provides a means to evaluate health and fitness apps [12,45-47] and wearables [48]. From the official website of the BCT taxonomy [49], we found a collection of 405 intervention studies with BCT coding. We show the word cloud of BCTs based on this collection in Multimedia Appendix 1. The top five used or tested BCTs are goal setting (behavior), instruction on how to perform a behavior, problem solving, information about health consequences, and action planning.

In related work, we have introduced the BIT model [14]. In terms of the intervention strategies in the BIT model, only some examples (ie, education, goal setting, monitoring, feedback, and motivation enhancement) were provided. We think the BCT taxonomy can serve as a strategy pool for the BIT model.

Aiming to create a conceptual framework that can be directly applied to persuasive system development, the PSD model describes 28 principles in four categories (supporting primary task, computer-human dialogue, system credibility, and social) as an extension of Fogg's work on persuasive technology [50]. Table 1 describes the details of PSD principles. We found 16 principles that have the same or similar definitions with counterparts from the BCT taxonomy. For example, self-monitoring appears both in PSD principles and the BCT taxonomy. Tunneling (1.2) in PSD principles has the same meaning as the BCT "4.1 structure on how to perform the behavior" (refer to Multimedia Appendix 2 for more details). There are three PSD principles (ie, cooperation, competition, and recognition) whose counterparts could not be found from the BCT taxonomy; these can serve as a supplement to the BCT taxonomy.

Next, we present the diagram of our DHI taxonomy (see Figure 3). The blue part is the strategy part, whereas the green part is the characteristic part. We have just shown its strategy part, which includes 93 (the BCTs from the BCT taxonomy) plus 3 (*cooperation*, *competition*, and *recognition* from PSD principles) strategies. The other part of our DHI taxonomy corresponds to the characteristics. The BIT model described four characteristics (*medium*, *complexity, aesthetics, and personalization*). Inspired by the characteristics-related PSD principles (Table 1), we included *social role* and *trustiness*, in addition to the mentioned four from the BIT model, into the characteristic part of the DHI taxonomy.

We divided the PSD principles into two groups. The ones fitting the definition of the BCT were placed in the strategies group, while the others fell into the characteristics group. *Personalization* is one of the characteristics in the BIT model.

We found that *tailoring* has a very close meaning to personalization according to their definitions in the PSD principles [51], whereas *similarity* and *liking* are also in line with the definition of *personalization*. Therefore, we regard *tailoring*, *similarity* and *liking* the same as *personalization*. Likewise, *trustworthiness*,*surface credibility, real-world feel,* and *verifiability* were merged to one characteristic as *trustiness*. By dividing the PSD principles and merging the overlapping principles, we hope our new taxonomy can reduce the confusion and difficulty of coding DHIs [6,10] (see Multimedia Appendix 3 for the complete list of elements in our DHI taxonomy).

Table 1. Persuasive system design principles.

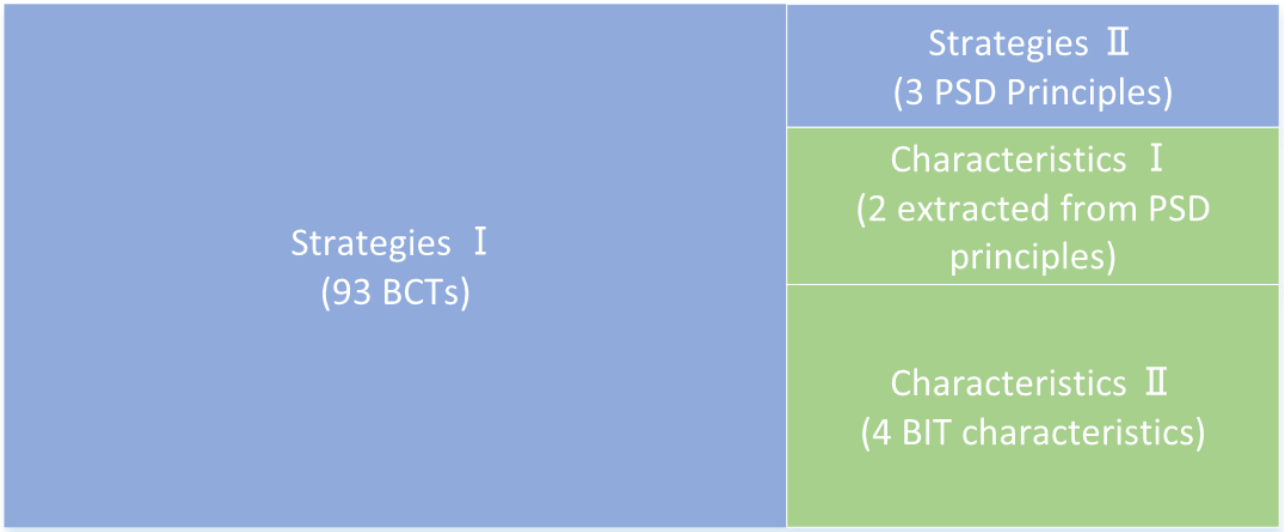
Persuasive system design principle[a]	Definition
Primary task support	
Reduction (1.1)	System should reduce steps users take when performing target behavior.
Tunneling (1.2)	System should guide users in attitude or behavior change process by providing means for action.
Tailoring (1.3)[b]	System should provide tailored info for user groups.
Personalization (1.4)[b]	System should offer personalized content and services for individual users.
Self-monitoring (1.5)	System should provide means for users to track their performance or status.
Simulation (1.6)	System should provide means for observing link between cause & effect with regard to users' behavior.
Rehearsal (1.7)	System should provide means for rehearsing target behavior.
Dialogue support	
Praise (2.1)	System should use praise to provide user feedback based on behaviors.
Rewards (2.2)	System should provide virtual rewards for users to give credit for performing target behavior.
Reminders (2.3)	System should remind users of their target behavior while using the system.
Suggestion (2.4)	System should suggest users carry out behaviors while using the system.
Similarity (2.5)[b]	System should imitate its users in some specific way.
Liking (2.6)[b]	System should have a look & feel that appeals to users.
Social role (2.7)[b]	System should adopt a social role.
System credibility support	
Trustworthiness (3.1)[b]	System should provide info that is truthful, fair & unbiased.
Expertise (3.2)	System should provide info showing knowledge, experience & competence.
Surface credibility (3.3)[b]	System should have competent and truthful look & feel.
Real-world feel (3.4)	System should provide info of the organization or actual people behind it content & services.
Authority (3.5)	System should refer to people in the role of authority.
Third-party endorsements (3.6)	System should provide endorsements from external sources.
Verifiability (3.7)	System should provide means to verify accuracy of site content via outside sources.
Social support	
Social learning (4.1)	System should provide means to observe others performing their target behaviors.
Social comparison (4.2)	System should provide means for comparing performance with the performance of others.
Normative influence (4.3)	System should provide means for gathering people who have same goal & make them feel norms.
Social facilitation (4.4)	System should provide means for discerning others who are performing the behavior.
Cooperation (4.5)[c]	System should provide means for cooperation.
Competition (4.6)[c]	System should provide means for competing with others.
Recognition (4.7)[c]	System should provide public recognition for users who perform their target behavior.

[a]The rest principles have counterparts with the same or similar definitions in the behavior change technique taxonomy.

[b]The principles are interventions characteristics.

[c]The principles have no counterparts in the behavior change technique taxonomy but can also be regarded as intervention strategies.

Figure 3. Diagram of our digital health intervention taxonomy. BCT: behavior change technique; BIT: behavioral intervention technology; PSD: persuasive system design.



The Holistic Framework

The Framework Structure

The proposed holistic framework (see Figure 4) is called TUDER (Targeting, Understanding, Designing, Evaluating and Refining), which consists of four steps, two toolboxes (behavioral theories and the DHIs taxonomy), and a workflow. In each step, going back and updating corresponding information is allowed.

Targeting the User Group, the Health Problem, and the Behavior

The target group, health problem, and behavior define the intervention aim(s). For example, an intervention to promote the use of standing desks (the behavior) to reduce the prolonged sedentary behavior (the behavior) of office workers (the user group) to prevent chronic diseases, such as type 2 diabetes (the health problem) [52]. The intervention designers should explain the relationship between the health problem and the behavior. Scientific evidence provides the rationale. For example, the evidence that sedentary behavior and moderate-to-vigorous physical activity are independently associated with clustered cardiometabolic health supports the development of interventions to reduce office workers' sedentary behavior [53]. Another example concerns myopia among children. A study showed that the time of outdoor activities was the most significant factor of myopia in 6-year and 7-year-old Chinese children [54]. Therefore, a reasonable intervention to reduce myopia (the health problem) among children (the user group) would be increasing their outdoor activity time (the behavior). Besides the scientific support, another rule concerns the measurability to enable quantitative analysis. The target health problem is not necessarily measurable in an intervention study, while the target behavior must be [55].

Behavioral theories (eg, see Figures 1 and 2) provide DHI developers with a toolbox to understand human behavior. Given the target user group, health problem, and behavior, developers ought to take one behavioral theory or a set of constructs from behavioral theories as the base of intervention design in the following step. We suggest that theory-based interventions should relate their strategies to specific constructs from behavioral theories. For example, an intervention design based on HAPA intended to support action planning (the construct) to reduce users' sedentary behavior [56]. Therefore, in addition to measuring the sedentary behavior, the constructs in HAPA should also be assessed. When analyzing the intervention effect on action planning, the assessment of action planning is sufficient. However, in the case of analyzing the intervention effect on sedentary behavior, other constructs besides action planning also have to be considered. The participants should be grouped based on the level of their intention in the data analysis. Alternatively, the user group in the previous step can be adjusted to only focus on one user group with a specific level of intention.

Designing the Intervention Strategies, Characteristics, and Workflow

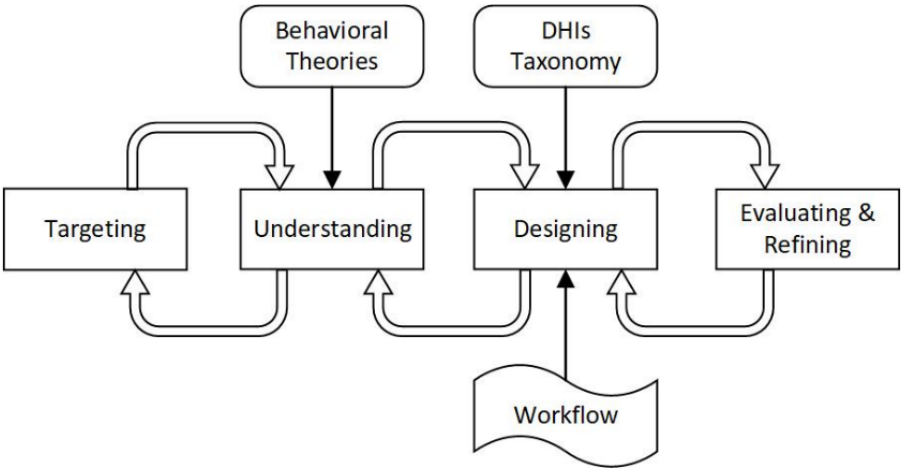
We have included 98 intervention strategies and six characteristics in our DHI taxonomy. DHI developers can select a set of strategies based on their idea and describe the characteristics of their strategies according to the DHI taxonomy. As the context of an intervention may vary over time, the workflow that allows an intervention to be delivered according to time, task, or event would be demanding [14]. The workflow design has been comprehensively illustrated in the BIT model [14] and the just-in-time adaptive intervention framework [57]. From the perspective of implementation difficulty, time-based workflow (eg, an hourly reminder in sedentary behavior interventions [6]) is the easiest. Task-based (eg, a set of interventions delivered to a user sequentially) or event-based (eg, adaptive food recommendation according to a user's previous meal) workflow requires user data input. Because of the difficulty of acquiring users' context data, the research on opportune moments for DHIs is still in the early stage [58,59].

Evaluating and Refining the Intervention Design

Intervention evaluation could include usability evolution (regarding human-computer interaction), an effectiveness

evaluation (regarding behavior change) corresponding to the uptake and impact of the intervention, respectively [16].

Figure 4. TUDER (Targeting, Understanding, Designing, Evaluating and Refining) diagram. DHI: digital health intervention.



During this step, DHI developers may backtrack to the previous step to adjust the target user group and measurements.

Think-aloud [60] and cognitive walkthrough can be used in the early stage of ideation creation and prototype to identify the usability issues. Then, a pilot study with a small number of participants would be deployed to test the feasibility of the whole study procedure. Because many interventions need field study, the pilot can also help find some unknown issues in real-world use. Finally, heuristic evaluations based on randomized controlled trials [17] or sequential multiple assignment randomized trials [61] have to be conducted to generate powerful results. In our framework, an iterative evaluation and refinement process is adopted. Because evaluation and refinement are always intertwined with each other, we place them in one step in our framework.

Discussion

Principal Findings

We have described TUDER, a holistic framework to guide DHI development. We also provide a checklist for DHI developers, as shown in Figure 5. By completing the checklist and reporting all the details of a DHI study, the data coding work in systematic reviews could be much reduced.

We have built TUDER based on several existing related works [8,9,14,16,17]. The key contribution of this work is to embed behavioral theories, BCT taxonomy, and PSD principles into a holistic framework. We believe this framework will be beneficial to each of them. This holistic framework and the DHI taxonomy will also enable more research questions. We provide some examples as follows:

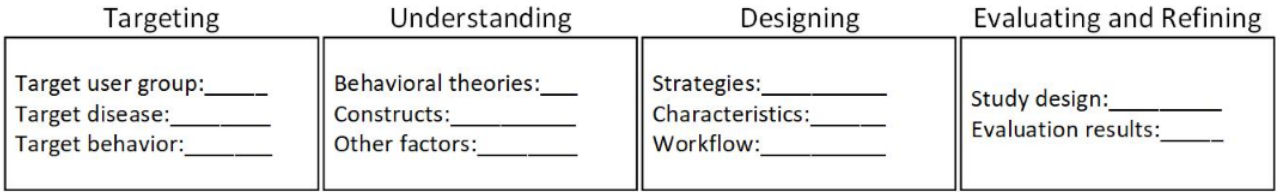
1. What combinations of DHI strategies, characteristics, and workflow work better than others? In [62], a meta-analysis shows several combinations of PSD principles were more effective, for example, tunneling and tailoring, reminders and similarity, and social learning and comparison. With consideration of the characteristics and workflow when coding the interventions, the results of intervention effectiveness analysis may change.
2. Is the DHI taxonomy able to explain more variance in DHI adherence? Kelders et al [11] systematically reviewed the impact of the PSD principles on adherence to Web-based interventions. Their model explained 55% of the variance in users' adherence. The DHI taxonomy brings more perspectives to analyze the effects of the components in interventions.

As the TUDER framework is expected to be comprehensive, some parts are simplistic. For example, only a few behavioral theories are discussed. The DHI taxonomy is built upon two existing taxonomies. The DHI developers who are unfamiliar with the BCT taxonomy and PSD principles will find it challenging to use the DHI taxonomy.

Conclusion

This work presented the TUDER framework, containing four steps (targeting, understanding, designing, and evaluating and refining), two toolboxes (behavioral theories and DHI taxonomy), and a workflow. The framework aims to integrate the advantages of behavioral theories, BCT taxonomy, and persuasive technology design principles. Thus, it can help DHI researchers to design, evaluate, and report their studies in a formative and comprehensive way. By using this framework, future systematic reviews could have broader insights into DHI studies. To better bridge the research from different communities, we will continue to test and improve this framework.

Figure 5. Checklist for using TUDER (Targeting, Understanding, Designing, Evaluating and Refining).



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Conflicts of Interest

None declared.

Multimedia Appendix 1

Behavior change techniques word cloud.

[PNG File, 251KB - resprot_v8i1e8055_app1.png]

Multimedia Appendix 2

Overlap between persuasive system design principles and the behavior change technique taxonomy.

[XLSX File (Microsoft Excel File), 12KB - resprot_v8i1e8055_app2.xlsx]

Multimedia Appendix 3

The complete list of elements in our DHI taxonomy.

[XLSX File (Microsoft Excel File), 20KB - resprot_v8i1e8055_app3.xlsx]

References

1. County Health Rankings & Roadmaps. What is Health? URL: http://www.countyhealthrankings.org/what-is-health [accessed 2019-01-08] [WebCite Cache ID 75HCG0y3u]
2. US National Center for Health. Leading Causes of Death URL: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm [accessed 2018-11-20] [WebCite Cache ID 744wjk9lH]
3. World Health Organization. Classification of Digital Health Interventions v1.0 URL: https://www.who.int/reproductivehealth/topics/mhealth/en/ [accessed 2019-01-08] [WebCite Cache ID 75HCL9UhN]
4. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev 2015;9(3):323-344 [FREE Full text] [doi: 10.1080/17437199.2014.941722] [Medline: 25104107]
5. Glanz K, Bishop DB. The role of behavioral science theory in development and implementation of public health interventions. Annu Rev Public Health 2010;31:399-418 [FREE Full text] [doi: 10.1146/annurev.publhealth.012809.103604] [Medline: 20070207]
6. Wang Y, Wu L, Lange JP, Fadhil A, Reiterer H. Persuasive technology in reducing prolonged sedentary behavior at work: A systematic review. Smart Health 2018 Jun;7-8:19-30 [FREE Full text] [doi: 10.1016/j.smhl.2018.05.002]
7. Hekler E, Klasnja P, Froehlich JE, Buman MP. Mind the Theoretical Gap: Interpreting, Using, and Developing Behavioral Theory in HCI Research. 2013 Presented at: CHI 2013; 2013; Paris, France URL: https://doi.org/10.1145/2470654.2466452
8. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol 2008 May;27(3):379-387 [FREE Full text] [doi: 10.1037/0278-6133.27.3.379] [Medline: 18624603]
9. Oinas-Kukkonen H. Persuasive Systems Design: Key Issues, Process Model, and System Features. CAIS 2009;24. [doi: 10.17705/1CAIS.02428]
10. Geuens J, Swinnen TW, Westhovens R, de Vlam K, Geurts L, Vanden Abeele V. A Review of Persuasive Principles in Mobile Apps for Chronic Arthritis Patients: Opportunities for Improvement. JMIR Mhealth Uhealth 2016 Oct 13;4(4):e118 [FREE Full text] [doi: 10.2196/mhealth.6286] [Medline: 27742604]

11. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JEWC. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res 2012 Nov 14;14(6):e152 [FREE Full text] [doi: 10.2196/jmir.2104] [Medline: 23151820]
12. Middelweerd A, Mollee JS, van der Wal CN, Brug J, Te Velde SJ. Apps to promote physical activity among adults: a review and content analysis. Int J Behav Nutr Phys Act 2014 Jul 25;11:97 [FREE Full text] [doi: 10.1186/s12966-014-0097-9] [Medline: 25059981]
13. Olander EK, Fletcher H, Williams S, Atkinson L, Turner A, French DP. What are the most effective techniques in changing obese individuals' physical activity self-efficacy and behaviour: a systematic review and meta-analysis. Int J Behav Nutr Phys Act 2013 Mar 03;10:29 [FREE Full text] [doi: 10.1186/1479-5868-10-29] [Medline: 23452345]
14. Mohr DC, Schueller SM, Montague E, Burns MN, Rashidi P. The behavioral intervention technology model: an integrated conceptual and technological framework for eHealth and mHealth interventions. J Med Internet Res 2014 Jun 05;16(6):e146 [FREE Full text] [doi: 10.2196/jmir.3077] [Medline: 24905070]
15. World Health Organization. eHealth URL: https://www.who.int/ehealth/about/en/ [accessed 2019-01-08] [WebCite Cache ID 75HCQ08L9]
16. van Gemert-Pijnen JEWC, Nijland N, van Limburg M, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011 Dec 05;13(4):e111 [FREE Full text] [doi: 10.2196/jmir.1672] [Medline: 22155738]
17. Mummah SA, Robinson TN, King AC, Gardner CD, Sutton S. IDEAS (Integrate, Design, Assess, and Share): A Framework and Toolkit of Strategies for the Development of More Effective Digital Interventions to Change Health Behavior. J Med Internet Res 2016 Dec 16;18(12):e317 [FREE Full text] [doi: 10.2196/jmir.5927] [Medline: 27986647]
18. Sutton SR. Health Behavior: Psychosocial Theories. In: International Encyclopedia of the Social & Behavioral Sciences. London: Elsevier; 2002:10.
19. Glanz K, Rimer BK, Viswanath K. Health Behavior and Health Education: Theory, Research, and Practice. San Francisco: Jossey-Bass; 2008.
20. Bandura A. Self-efficacy: Toward a unifying theory of behavioral change. Psychological Review 1977;84(2):191-215 [FREE Full text] [doi: 10.1037/0033-295X.84.2.191]
21. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997;12(1):38-48 [FREE Full text] [doi: 10.4278/0890-1171-12.1.38] [Medline: 10170434]
22. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the Health Belief Model. Health Educ Q 1988;15(2):175-183. [Medline: 3378902]
23. Ajzen I. The theory of planned behavior. Organizational Behavior and Human Decision Processes 1991 Dec;50(2):179-211 [FREE Full text] [doi: 10.1016/0749-5978(91)90020-T]
24. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev 2015;9(3):323-344 [FREE Full text] [doi: 10.1080/17437199.2014.941722] [Medline: 25104107]
25. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000 Jan;55(1):68-78. [Medline: 11392867]
26. Schwarzer R. Modeling Health Behavior Change: How to Predict and Modify the Adoption and Maintenance of Health Behaviors. Applied Psychology 2008 Jan;57(1):1-29 [FREE Full text] [doi: 10.1111/j.1464-0597.2007.00325.x]
27. Miller NE, Dollard J. Social learning and imitation. In: Journal of Communication. New Haven, CT: Yale University Press; 1941.
28. Conner M, Norman P. Predicting Health Behaviour. London: Open University Press; 2005.
29. Sutton S. How does the Health Action Process Approach (HAPA) Bridge the Intention–Behavior Gap? An Examination of the Model's Causal Structure. Applied Psychology 2008 Jan;57(1):66-74 [FREE Full text] [doi: 10.1111/j.1464-0597.2007.00326.x]
30. Schwarzer R. Health Action Process Approach (HAPA) as a Theoretical Framework to Understand Behavior Change. AP 2016 Dec 05;30(121):119 [FREE Full text] [doi: 10.15517/ap.v30i121.23458]
31. Maher JP, Conroy DE. Habit strength moderates the effects of daily action planning prompts on physical activity but not sedentary behavior. J Sport Exerc Psychol 2015 Feb;37(1):97-107. [doi: 10.1123/jsep.2014-0258] [Medline: 25730895]
32. Adult Meducation. Facilitating Behavior Change URL: http://adultmeducation.com/FacilitatingBehaviorChange.html [accessed 2019-01-08] [WebCite Cache ID 75HBU9rN2]
33. Klasnja P, Hekler EB, Korinek EV, Harlow J, Mishra SR. Toward Usable Evidence: Optimizing Knowledge Accumulation in HCI Research on Health Behavior Change. In: Proc SIGCHI Conf Hum Factor Comput Syst. 2017 May Presented at: CHI 2017; May 6-11, 2017; Colorado p. 3071-3082 URL: http://europepmc.org/abstract/MED/30272059 [doi: 10.1145/3025453.3026013]
34. Mark C, Paul N. Predicting health behaviour: Research and practice with social cognition models. Safety Science 2005;24 [FREE Full text] [doi: 10.1016/S0925-7535(97)81483-X]

35. Maberry SL. Physical Activity Promotion from the Social Cognitive Theory Perspective: An Examination of Mobile Fitness Apps. 2016. URL: https://digitalcommons.lsu.edu/gradschool_dissertations/3803/ [accessed 2019-01-08] [WebCite Cache ID 75HCAdhG8]
36. Champion VL. Instrument development for health belief model constructs. ANS Adv Nurs Sci 1984 Apr;6(3):73-85. [Medline: 6426380]
37. Ajzen I. Constructing a TpB Questionnaire: Conceptual and Methodological Considerations. 2006. URL: http://citeseerx.ist.psu.edu/viewdoc/summary;jsessionid=011E42C7D4396A688EA04E1D0DFBF6F0?doi=10.1.1.601.956
38. Schwarzer R. The Health Action Process Approach. URL: http://www.hapa-model.de
39. 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 [FREE Full text] [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
40. Mummah SA, King AC, Gardner CD, Sutton S. Iterative development of Vegethon: a theory-based mobile app intervention to increase vegetable consumption. Int J Behav Nutr Phys Act 2016 Aug 08;13:90 [FREE Full text] [doi: 10.1186/s12966-016-0400-z] [Medline: 27501724]
41. Mummah SA, Mathur M, King AC, Gardner CD, Sutton S. Mobile Technology for Vegetable Consumption: A Randomized Controlled Pilot Study in Overweight Adults. JMIR Mhealth Uhealth 2016 May 18;4(2):e51 [FREE Full text] [doi: 10.2196/mhealth.5146] [Medline: 27193036]
42. Dombrowski S, Sniehotta F, Avenell A, Johnston M, MacLennan G, Araújo-Soares V. Identifying active ingredients in complex behavioural interventions for obese adults with obesity-related co-morbidities or additional risk factors for co-morbidities: a systematic review. Health Psychology Review 2012 Mar;6(1):7-32 [FREE Full text] [doi: 10.1080/17437199.2010.513298]
43. Gardner B, Smith L, Lorencatto F, Hamer M, Biddle SJH. How to reduce sitting time? A review of behaviour change strategies used in sedentary behaviour reduction interventions among adults. Health Psychol Rev 2016;10(1):89-112 [FREE Full text] [doi: 10.1080/17437199.2015.1082146] [Medline: 26315814]
44. 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 [FREE Full text] [doi: 10.1037/a0016136] [Medline: 19916637]
45. Conroy DE, Yang CH, Maher JP. Behavior change techniques in top-ranked mobile apps for physical activity. Am J Prev Med 2014 Jun;46(6):649-652 [FREE Full text] [doi: 10.1016/j.amepre.2014.01.010] [Medline: 24842742]
46. Crane D, Garnett C, Brown J, West R, Michie S. Behavior change techniques in popular alcohol reduction apps: content analysis. J Med Internet Res 2015 May 14;17(5):e118 [FREE Full text] [doi: 10.2196/jmir.4060] [Medline: 25977135]
47. Direito A, Dale LP, Shields E, Dobson R, Whittaker R, Maddison R. Do physical activity and dietary smartphone applications incorporate evidence-based behaviour change techniques? BMC Public Health 2014 Jun 25;14:646 [FREE Full text] [doi: 10.1186/1471-2458-14-646] [Medline: 24965805]
48. 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]
49. BCT Taxonomy v1. Intervention Collection URL: http://www.bct-taxonomy.com/interventions [accessed 2019-01-08] [WebCite Cache ID 75HC21GLW]
50. Fogg BJ. Persuasive Technology: Using Computers to Change What We Think and Do. Burlington: Morgan Kaufmann; 2002.
51. Oinas-Kukkonen H. A foundation for the study of behavior change support systems. Pers Ubiquit Comput 2012 Jul 19;17(6):1223-1235 [FREE Full text] [doi: 10.1007/s00779-012-0591-5]
52. De Cocker K, Veldeman C, De Bacquer D, Braeckman L, Owen N, Cardon G, et al. Acceptability and feasibility of potential intervention strategies for influencing sedentary time at work: focus group interviews in executives and employees. Int J Behav Nutr Phys Act 2015 Feb 18;12:22 [FREE Full text] [doi: 10.1186/s12966-015-0177-5] [Medline: 25881297]
53. Knaeps S, Bourgois JG, Charlier R, Mertens E, Lefevre J, Wijndaele K. Ten-year change in sedentary behaviour, moderate-to-vigorous physical activity, cardiorespiratory fitness and cardiometabolic risk: independent associations and mediation analysis. Br J Sports Med 2018 Aug;52(16):1063-1068 [FREE Full text] [doi: 10.1136/bjsports-2016-096083] [Medline: 27491779]
54. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. Arch Ophthalmol 2008 Apr;126(4):527-530 [FREE Full text] [doi: 10.1001/archopht.126.4.527] [Medline: 18413523]
55. Stephen. W. Designing For Behavior Change: Applying Psychology And Behavioral Economics. Sebastopol, California: O'Reilly Media; 2018.
56. Yunlong W, Ahmed F, Harald R. Supporting Action Planning for Sedentary Behavior Change by Visualizing Personal Mobility Patterns on Smartphone. 2018 Presented at: PervasiveHealth '18; May 21- May 24, 2018; New York, USA.

57. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-Time Adaptive Interventions (JITAIs) in Mobile Health: Key Components and Design Principles for Ongoing Health Behavior Support. Ann Behav Med 2018 May 18;52(6):446-462. [doi: 10.1007/s12160-016-9830-8] [Medline: 27663578]
58. Akane S, Paul J, Mary C. 2017. In: Designing Opportune Stress Intervention Delivery Timing using Multi-modal Data. 2017 Presented at: 2017 Seventh International Conference on Affective Computing and Intelligent Interaction (ACII); 23-26 Oct. 2017; San Antonio, TX, USA.
59. Wang Y, Duan L, Mueller J, Butscher S, Reiterer H. "Fingerprints": Detecting meaningful moments for mobile health intervention. 2016 Presented at: The 18th International Conference on Human-Computer Interaction with Mobile Devices and Services Adjunct, MobileHCI 2016; 6TH - 9TH, 2016; Florence, Italy URL: https://doi.org/10.1145/2957265.2965006 [doi: https://doi.org/10.1145/2957265.2965006]
60. Joe J, Chaudhuri S, Le T, Thompson H, Demiris G. The use of think-aloud and instant data analysis in evaluation research: Exemplar and lessons learned. J Biomed Inform 2015 Aug;56:284-291 [FREE Full text] [doi: 10.1016/j.jbi.2015.06.001] [Medline: 26071683]
61. Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions. Am J Prev Med 2007 May;32(5 Suppl):S112-S118 [FREE Full text] [doi: 10.1016/j.amepre.2007.01.022] [Medline: 17466815]
62. Wildeboer G, Kelders SM, van Gemert-Pijnen JEWC. The relationship between persuasive technology principles, adherence and effect of web-Based interventions for mental health: A meta-analysis. Int J Med Inform 2016 Dec;96:71-85 [FREE Full text] [doi: 10.1016/j.ijmedinf.2016.04.005] [Medline: 27117057]

Abbreviations

BCT: behavior change technique
BIT: behavioral intervention technology
DHI: digital health intervention
eHealth: electronic health
HAPA: Health Action Process Approach
HBM: Health Belief Model
IDEAS: Integrate, Design, Assess, and Share
PSD: persuasive system design
SCT: Social Cognitive Theory
TPB: Theory of Planned Behavior
TTM: Transtheoretical Model of Behavior Change
TUDER: Targeting, Understanding, Designing, Evaluating and Refining

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Protocol

Testing MD-Link, a Low-Cost Mobile Electrocardiography Monitoring Device, in Patients With Irregular Heartbeat: Protocol for a Cross-Sectional Study

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Abstract

Background: Having mobile devices that provide patients with the ability to record and monitor the electrical activity of their heart enhances patient self-care and the early detection of irregular heartbeat (cardiac arrhythmia), yet few such devices exist in Vietnam. Challenges exist for introducing mobile electrocardiography (ECG) monitoring devices in Vietnam, including patient accessibility and affordability. A low-cost mobile ECG monitoring device designed and developed in Vietnam, which allows patients to easily measure their heart's electrical activity and navigate recordings, may be a solution.

Objective: The aim of this project is to assess the usability of the MD-Link system, a newly developed mobile handheld 1-lead ECG device, in detecting patients with irregular heartbeat. We will compare its outputs to the standard printed outputs of a 12-lead electrocardiogram generated by the Nihon Kohden Cardiofax S Electrocardiograph Model ECG-1250K.

Methods: We will conduct a cross-sectional study in two stages, including the measurement of ECG signals of patients using the MD-Link and the Nihon Kohden Cardiofax S and analysis of the selected standard outputs collected from the ECG recordings of the MD-Link and the Nihon Kohden Cardiofax S. The MD-Link consists of (1) a mobile device (eg, a smartphone); (2) a lead wire with 2 disposable electrodes; and (3) an easy-to-use mobile app interface enabling the upload and accurate display of ECG recordings to patients and their clinicians. Our research team, consisting of members from Dartmouth College; the Institute of Health, Population and Development; Hanoi University of Science and Technology; and physicians and nurses from Thanh Chan Clinic, will assist in carrying out this project.

Results: We will proceed with a publication plan that includes a project report and, ultimately, articles for peer-reviewed journals. We also hope to disseminate our work at relevant conferences to provide more coverage and exposure to the MD-Link mobile device. Recruitment and data collection were completed in January 2018. Data analysis started in February 2018 and is ongoing. Results are expected mid-2019.

Conclusions: At the end of this project, we will have developed and tested the MD-Link, a low-cost mobile ECG monitoring device, with some supportive comparisons to standard ECG devices commonly used in heart clinics or hospitals in Vietnam. Our long-term goal is for the MD-Link to be easily accessible, affordable, and to fit into a patient's daily routine, thus improving the care and treatment of patients with cardiovascular diseases (CVDs).

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KEYWORDS

cardiac arrhythmia; cardiovascular diseases; ECG; electrocardiography; irregular heartbeat; mHealth; mobile devices; mobile phone

Introduction

Background

Noncommunicable diseases, particularly cardiovascular diseases (CVDs), are currently the leading cause of death globally, with an estimated 17.7 million people dying annually [1,2]. Combined effects of population growth, aging of populations, and epidemiological changes in CVDs have resulted in increasing global deaths from CVDs [3]. Among these diseases, myocardial infarction (heart attack) and stroke account for 80% of all the CVD deaths [2].

In Vietnam, there has been an epidemiological change in which the overall morbidity and mortality patterns have shifted from communicable to noncommunicable diseases [4,5]. A recent global burden of disease study shows that cerebrovascular disease (including stroke) and ischemic heart disease are the leading causes of deaths in Vietnam [6]. Indeed, the number of people suffering from CVDs has been increasing yearly, with CVDs accounting for about 33% of the total deaths among the Vietnamese population [7,8]. However, while CVDs are highly preventable and treatable, particularly when detected early, accessibility to electrocardiography (ECG) services—the common and widely used method to assess cardiovascular problems—is not available at primary care level in Vietnam and its related cost is high. [4,6]. As a result, it is becoming increasingly important to have easily accessible and affordable procedures at primary care level for early detection of cardiovascular issues to ensure timely intervention and treatment.

There is ongoing biomedical research into the development of portable ECG devices for real-time ECG signal analysis [7-9]. Additionally, feasibility studies have been conducted on a variety of mobile ECG devices [10-14]. Handheld or finger ECG mobile devices currently dominate the portable ECG device market and are widely available for both patient and physician use [10]. Table 1 lists some of the current commercially available handheld mobile ECG devices. Although there are several mobile ECG devices commercially available, they are still inaccessible and unaffordable to most of the general Vietnamese population. Consequently, a mobile ECG device that allows patients to easily navigate their ECG recordings while still being affordable and convenient for use in a Vietnamese context is needed. The MD-Link will be a much more affordable ECG device because it is estimated to be within the price range of US $20-$25 or approximately one-fourth of the current lowest price of handheld ECG devices in the United States. In addition, mobile phone use is ubiquitous in Vietnam, and mobile health (mHealth) implementation is emerging in the country [15], which will thus increase the affordability and practicality of the use of the MD-Link device as it requires a mobile device [16].

Objective

The main aim of this study is to examine the accuracy of the MD-Link device for detecting irregular heartbeat in a hospital population by comparing some of the standard printed outputs from a 12-lead electrocardiogram generated by the Nihon Kohden Cardiofax S Electrocardiograph Model ECG-1250K, to the calculated standard outputs from the MD-Link 1-lead mobile ECG device [17].

Table 1. Commercially available handheld or finger mobile electrocardiography devices.

Device	Price (US $)[a]
AfibAlert, Lohman Technologies, United States	249
ECG Check, CardiacDesigns, United States	139
HeartCheck ECG Pen, CardioComm Solutions, Inc, United States	259
InstantCheck, DailyCare BioMedical Inc, Taiwan	299
Kardia Mobile, AliveCor, Inc, United States	99
ME 90, Beurer GmbH, Germany	120
REKA E100, REKA Health Pte Ltd, Singapore	Not available
WIWE, Sanatmetal, Hungary	438
Zenicor-ECG, Zenicor Medical Systems AB, Sweden	1460

[a]Prices are as indicated on the companies' websites or as indicated by official distributors.

Methods

The MD-Link system consists of the following 3 key elements: (1) a mobile device (eg, a smartphone or a tablet); (2) a mobile ECG device that can capture ECG signals through either the 2 built-in dry electrodes or a detachable wire system with 2 disposable Ag-AgCl electrodes; and (3) an easy-to-use mobile app interface to display and upload ECG recordings (see Figure 1). As described in [18], the mobile ECG device was designed

to measure 1-lead ECG signals; however, it can be easily expanded to measure up to 3 leads—DI, DII, and DIII.

We will conduct this study in two stages. In the first stage, we will measure the ECG signals of the participants using both the MD-Link and the Nihon Kohden Cardiofax S. The MD-Link system will be used first to record 3 leads as follows: (1) DI, which is a signal between the right arm and left arm; (2) DII, which is a signal between the right arm and left leg; and (3) DIII, which is a signal between the left arm and left leg. The Nihon Kohden Cardiofax S will then be used to record a 12-lead ECG. In the second stage, the ECG Viewer software will be used to extract data of the 3 leads (DI, DII, and DIII) from the 12-lead recordings measured by the Nihon Kohden Cardiofax S for comparison against the 3-lead signals captured by the MD-Link system. The wavelet transform method [19-21] will be utilized to calculate clinical standard outputs from the MD-Link system, such as PR interval, QRS duration, QT or corrected QT (QTc) interval, etc, in comparison against the ones provided by the Nihon Kohden Cardiofax S. The final step of analysis will involve the interpretation by two cardiologists to compare the signals and standard outputs of the two systems (see Figure 2).

Figure 1. Complete system of the MD-Link mobile electrocardiography device.

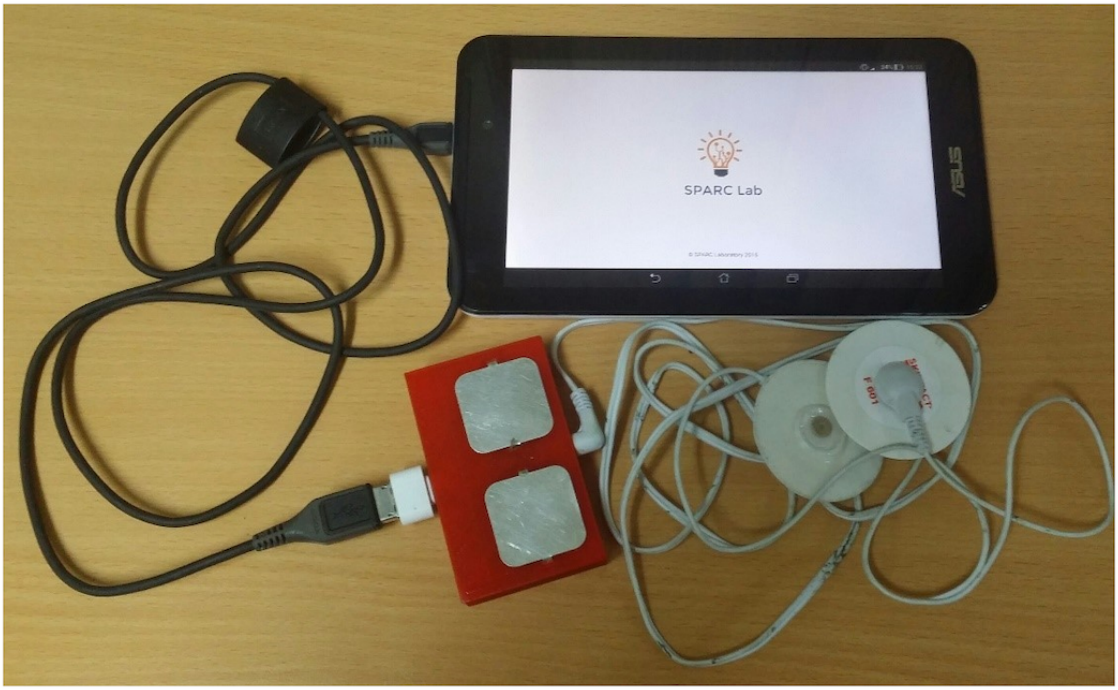
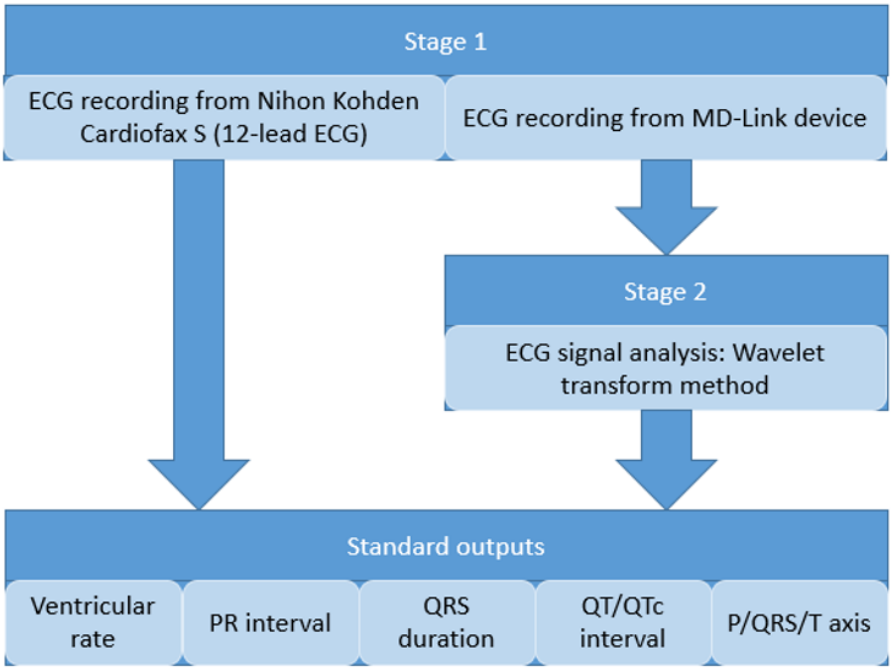


Figure 2. Stages of testing the MD-Link mobile electrocardiography (ECG) device. QTc: corrected QT.



Stage 1: Electrocardiographic Measurements

Overview

The first step to compare ECG recordings of the MD-Link to the Nihon Kohden Cardiofax S is to take ECG measurements from both devices. We will conduct several on-site visits and will begin our study from July 2018 to October 2018 at Thanh Chan Clinic, a primary care clinic in Hanoi, Vietnam, where ECG measurements will take place.

Participants

Subjects will be recruited from among patients with cardiac arrhythmia who receive treatment at Thanh Chan Clinic. To be enrolled in the study, patients must be aged 18 years or older and agree to follow study procedures and provide informed consent. Exclusion criteria include any patient who has a mental health condition sufficiently serious to prevent them from understanding informed assent, including the voluntary nature of participation.

Sample Size Determination

As this is a preliminary comparison method study, no formal sample size analysis has been conducted. We anticipate recruiting 30 patients from Thanh Chan Clinic. This number was estimated based on the average number of patients receiving treatment for cardiovascular complications at the clinic.

Data Collection

The data acquisition process will proceed in the following 3 steps: (1) an interview before ECG measurement to collect patient demographics and CVD risk factors will be conducted; (2) ECG measurement using the Nihon Kohden Cardiofax S, specifically a full 12-lead ECG recording, will be performed by a trained technician and saved on an SD-card; and (3) successive lead I, lead II, and lead III ECG measurements using the MD-Link mobile device will be performed immediately after step 2. The MD-Link will record the ECG signals for 1 minute per lead and then store data in the app and transfer it to a Web-based software platform by 3G or Wi-Fi. We anticipate the total time for conducting an interview and taking ECG measurements for each patient to be 30 minutes.

Ethics

This study has received Institutional Review Board approval from the Committee for the Protection of Human Subjects at Dartmouth College (STUDY00030415) and the Institute of Population, Health and Development in Hanoi, Vietnam (2017/PHAD/ECG-01).

Stage 2: Data Analysis

Overview

The second stage will involve an assessment by two cardiologists and the calculation of the selected clinical standard outputs from the MD-Link in comparison against the ones from the Nihon Kohden Cardiofax S.

We will use the ECG Viewer software to extract DI, DII, and DIII signals from the collected 12-lead ECG signals by the Nihon Kohden Cardiofax S. The wavelet transform method [19-21] will be utilized to calculate standard clinical outputs from the MD-Link system such as PR interval, QRS duration, QT, or QTc interval, etc. The aim of this work is to have ECG signals recorded by two devices with the same indicators. The next step is to export the ECG waves with clinical standard outputs and send to the cardiologists, who are blinded to the devices and results, for clinical interpretation.

Following this, we will compare the final standard outputs from both devices beginning with univariate statistics (mean, median, SD, and 95% CIs) and distribution. We will also analyze the general information and risk factor data collected from the interviews.

Analysis

Based on the ECG recordings and outputs of each device, the cardiologists will interpret the results as having an irregular heartbeat or not. Therefore, the sensitivity and specificity of MD-Link and Nihon Kohden Cardiofax S will be calculated and compared. The kappa coefficient will be determined to assess the agreement results between the Nihon Kohden Cardiofax S, the MD-Link, and the cardiologists' interpretation. A kappa value of more than 0.8 will be considered an "excellent agreement" [22].

Data entry for general information and risk factor data as well as the clinical standard outputs (heart rate, PR interval, etc) will be conducted using the EpiData software (EpiData Association). Stata 12.0 (StataCorp) will be used to perform data analyses. Descriptive statistics will be calculated for patient sociodemographic variables and study outcomes. We plan to use 2-sample *t* tests to compare the clinical standard outputs and kappa values of both devices. Generalized logistic mixed regression including age, risk factors, and medical history will also be used in the analysis. The statistical method results will be considered statistically significant when $P<.05$.

Results

At the completion of this research, we will have evaluated the accuracy of the MD-Link device in recording ECG signals through the two cardiologists' interpretations and the comparison of its calculated standard outputs to the printed-out standard outputs of a 12-lead electrocardiogram generated by the Nihon Kohden Cardiofax S. Following this, we will proceed with a publication plan that includes a project report and, ultimately, some articles for peer-reviewed journals. We also hope to disseminate our work at relevant national and international conferences. Recruitment and data collection were completed in January 2018. Data analysis started in February 2018 and is ongoing. Results are expected mid-2019.

Discussion

Summary

We propose to conduct a study to investigate the specificity and sensitivity of the MD-Link mobile ECG system in recording ECG measurements, in which the standard outputs are compared against the ones on the clinical-grade Nihon Kohden Cardiofax S system. We expect that the MD-Link will measure and provide 3 ECG lead measurements (DI, DII, and DIII) that are similar

to the Nihon Kohden Cardiofax S. The study will also offer participating patients access to their own heartbeat and ECG recordings through a mobile device such as a smartphone or a tablet. The study aims to provide patients with irregular heartbeats a portable solution to monitor changes in their heartbeat over time. Furthermore, patients' ECG recordings will be synchronized to the cardiologists' mobile app, which will allow for more timely comprehensive information and interpretation needed for follow-up screenings and diagnoses of the patients.

Strengths

We have a diverse and multidisciplinary research team whose members are well positioned to successfully complete the proposed study. We have extensive experience in successfully developing and piloting several mHealth projects in recent years as well as implementing these projects in the general Vietnamese population. We have a track record of engaging both local and foreign partners to the success of our mHealth interventions. Importantly, our patient partners and local stakeholders have been engaged from the beginning of the project, and they represent a wide range of perspectives, including our target populations; clinician partners; those with knowledge of mobile technology, hardware engineering, and software development; and those experienced with carrying out public health interventions.

Limitations

There are several limitations to the study. First, due to the relatively small number of participants (about 30 patients) we will recruit for the study, possible statistical tests to learn about the significant differences between the two systems are quite limited. Second, there are several challenges related to the ECG data processing techniques of the two systems. ECG measurement results from the Nihon Kohden Cardiofax S, including standard clinical outputs such as PR interval, QRS duration, and P-QRS-T axis, etc, are processed internally and can be read by the ECG Viewer software. However, at this stage, the MD-Link system does not contain such features; therefore, all necessary calculations will need to be conducted externally using some software tools such as MATLAB (MathWorks) or R. As a result, artificial variations might be introduced to the ECG measurement results of the two devices, which would create more problems for the comparison work. Finally, the ability to study only 3 leads (DI, DII, and DIII) instead of all available 12 leads also limits the complete interpretation of the MD-Link system.

Conclusions

Upon completion of this project, we will have developed and tested the MD-Link, a low-cost mobile ECG monitoring device, which will be ready for large-scale testing. Our long-term goal is to make the MD-Link system easily accessible and affordable to the Vietnamese community. Moreover, we hope the device will be used widely at the primary care level and seamlessly fit into an arrhythmia patient's daily routine to leverage the treatment for patients with cardiovascular health issues and to increase the transparency of care between doctors and patients.

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Conflicts of Interest

None declared.

References

1. World Health Organization. 2018 Jun 1. Noncommunicable diseases URL: http://www.who.int/mediacentre/factsheets/fs355/en/ [WebCite Cache ID 6sBfRCer3]
2. World Health Organization. Cardiovascular disease URL: http://www.who.int/cardiovascular_diseases/en/ [accessed 2017-07-24] [WebCite Cache ID 6sBfugIDU]
3. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med 2015 Apr 02;372(14):1333-1341 [FREE Full text] [doi: 10.1056/NEJMoa1406656] [Medline: 25830423]
4. Ha DA, Chisholm D. Cost-effectiveness analysis of interventions to prevent cardiovascular disease in Vietnam. Health Policy Plan 2011 May;26(3):210-222. [doi: 10.1093/heapol/czq045] [Medline: 20843878]
5. Minh HV, Byass P, Wall S. Mortality from cardiovascular diseases in Bavi District, Vietnam. Scand J Public Health Suppl 2003;62:26-31. [Medline: 14649634]
6. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 08;388(10053):1545-1602 [FREE Full text] [doi: 10.1016/S0140-6736(16)31678-6] [Medline: 27733282]
7. Jeon T, Kim B, Jeon M, Lee B. Implementation of a portable device for real-time ECG signal analysis. Biomed Eng Online 2014 Dec 10;13:160 [FREE Full text] [doi: 10.1186/1475-925X-13-160] [Medline: 25491135]

8. Kristensen AN, Jeyam B, Riahi S, Jensen MB. The use of a portable three-lead ECG monitor to detect atrial fibrillation in general practice. Scand J Prim Health Care 2016 Jul 13:1-5 [FREE Full text] [doi: 10.1080/02813432.2016.1207151] [Medline: 27409151]
9. Szczepański A, Saeed K. A mobile device system for early warning of ECG anomalies. Sensors (Basel) 2014 Jun 20;14(6):11031-11044 [FREE Full text] [doi: 10.3390/s140611031] [Medline: 24955946]
10. Mehta DD, Nazir NT, Trohman RG, Volgman AS. Single-lead portable ECG devices: Perceptions and clinical accuracy compared to conventional cardiac monitoring. J Electrocardiol 2015;48(4):710-716. [doi: 10.1016/j.jelectrocard.2015.04.017] [Medline: 25968916]
11. Haberman ZC, Jahn RT, Bose R, Tun H, Shinbane JS, Doshi RN, et al. Wireless Smartphone ECG Enables Large-Scale Screening in Diverse Populations. J Cardiovasc Electrophysiol 2015 May;26(5):520-526. [doi: 10.1111/jce.12634] [Medline: 25651872]
12. Ehmen H, Haesner M, Steinke I, Dorn M, Gövercin M, Steinhagen-Thiessen E. Comparison of four different mobile devices for measuring heart rate and ECG with respect to aspects of usability and acceptance by older people. Appl Ergon 2012 May;43(3):582-587. [doi: 10.1016/j.apergo.2011.09.003] [Medline: 21962327]
13. Park YM, Lee DI, Park HC, Shim J, Choi J, Lim HE, et al. Feasibility and accuracy of a new mobile electrocardiography device, ER-2000(®), in the diagnosis of arrhythmia. J Arrhythm 2015 Aug;31(4):201-209 [FREE Full text] [doi: 10.1016/j.joa.2014.12.003] [Medline: 26336560]
14. Usadel L, Haverkämper G, Herrmann S, Löber R, Weiss K, Opgen-Rhein B, et al. Arrhythmia Detection in Pediatric Patients: ECG Quality and Diagnostic Yield of a Patient-Triggered Einthoven Lead-I Event Recorder (Zenicor EKG-2™). Pediatr Cardiol 2016 Mar;37(3):491-496. [doi: 10.1007/s00246-015-1304-4] [Medline: 26573815]
15. Lam JA, Dang LT, Phan NT, Trinh HT, Vu NC, Nguyen CK. Mobile Health Initiatives in Vietnam: Scoping Study. JMIR Mhealth Uhealth 2018 Apr 24;6(4):e106 [FREE Full text] [doi: 10.2196/mhealth.8639] [Medline: 29691214]
16. Poushter J. Pew Research Center. 2016 Feb 22. Smartphone ownership and internet usage continues to climb in emerging economies URL: http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/ [accessed 2017-07-24] [WebCite Cache ID 74HvYveml]
17. Nihon Kohden Corporation. Nihon Kohden Cardiofax S Electrocardiograph ECG-1250K brochure URL: http://www.nihonkohden.de/uploads/media/ECG-1250_04.pdf [accessed 2017-08-14] [WebCite Cache ID 6shVP3ew1]
18. Le T, Han D, Hoang H, Nguyen V, Nguyen C. A low cost mobile ECG monitoring device using two active dry electrodes. 2016 Presented at: IEEE Sixth International Conference on Communications and Electronics; 2016 July 27-29; Ha Long, Vietnam p. 271-276.
19. Rabbani H, Mahjoob MP, Farahabadi E, Farahabadi A. R peak detection in electrocardiogram signal based on an optimal combination of wavelet transform, hilbert transform, and adaptive thresholding. J Med Signals Sens 2011 May;1(2):91-98 [FREE Full text] [Medline: 22606663]
20. Fedotov AA, Akulova AS, Akulov SA. Applicability of multiresolution wavelet analysis for QRS-waves detection. Conf Proc IEEE Eng Med Biol Soc 2016 Aug;2016:3793-3796. [doi: 10.1109/EMBC.2016.7591554] [Medline: 28269112]
21. Singh O, Sunkaria R. ECG signal denoising via empirical wavelet transform. Australas Phys Eng Sci Med 2017 Mar;40(1):219-229. [doi: 10.1007/s13246-016-0510-6] [Medline: 28035635]
22. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005 May;37(5):360-363 [FREE Full text] [Medline: 15883903]

Abbreviations

CVD: cardiovascular disease
ECG: electrocardiography
mHealth: mobile health
QTc: corrected QT

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Protocol

YouthCHAT as a Primary Care E-Screening Tool for Mental Health Issues Among Te Tai Tokerau Youth: Protocol for a Co-Design Study

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Abstract

Background: In New Zealand (NZ), 1 in 4 adolescents is affected by mental health issues (eg, depression and anxiety) and engages in risk behaviors (eg, harmful drinking and substance abuse), with rates among Māori youth being significantly higher. The majority of NZ secondary school students visit their local primary health care providers (PHPs) at least annually, yet most do not seek help for mental health and risk behavior (MHB) concerns. While youth think it acceptable to discuss sensitive issues during a consultation with their PHPs, unless problems are severe, such conversations are not initiated by PHPs. Early intervention for MHB concerns can prevent long-term health and well-being issues. However, this relies on the early identification of developing problems and youth being offered and accepting help. YouthCHAT is an electronic, multi-item screening tool developed in 2016 to assess MHB concerns among youth. YouthCHAT is completed before a consultation with the PHP, who can access a summary report straight away. A help question allows young people to identify issues that need addressing. A resource pack uses stepped care pathways to guide providers to use appropriate brief interventions.

Objective: This study aimed to explore the utility, feasibility, and acceptability of YouthCHAT when tailored for use with youth in primary care settings with large Māori populations. Objectives of the study are to evaluate the implementation of YouthCHAT in nurse-led youth clinics, school-based clinics, and general practice in Te Tai Tokerau (Northland, NZ); to develop a framework for the scaling up of YouthCHAT across further settings; to assess health provider and youth acceptability of the tool; to improve screening rates for mental health and help-seeking behavior; to enable early identification of emerging problems; and to improve brief intervention delivery.

Methods: Using a bicultural mixed-methods co-design approach, 3 phases over a 3-year period will provide an iterative evaluation of the utility, feasibility, and acceptability of YouthCHAT, aiming to create a framework for wider-scale rollout and implementation.

Results: Recruitment for the first phase began in September 2018. YouthCHAT was implemented at the first site in October 2018 and is expected to be at a further two sites in late January to early February 2019. The study is due for completion at the end of 2021.

Conclusions: YouthCHAT has potential as a user-friendly, time efficient, and culturally safe screening tool for early detection of MHB issues in NZ youth. The resource pack assists the clinician to provide appropriate interventions for emerging and developed youth mental health and lifestyle issues. Involving input from community providers, users, and stakeholders will ensure that modifiable elements of YouthCHAT are tailored to meet the health needs specific to each context and will have a positive influence on future mental, physical, and social outcomes for NZ youth.

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KEYWORDS

adolescents; brief intervention; co-design; mental health; primary health care; protocol; risk behavior; YouthCHAT

Introduction

Background

Mental health issues have overtaken cardiovascular disease and cancer as the leading cause of health loss in New Zealand (NZ) [1,2]. The majority of people affected by mental health concerns (eg, depression and anxiety) also exhibit more than 1 risk behavior (eg, smoking, problem drinking, substance abuse, and physical inactivity) [2]. These mental health and risk behaviors (MHBs) are the major contributing factors to NZ's health loss [2]. The Ministry of Health recognizes that to improve the health of NZ, reduction of these MHBs is needed [2].

Most mental health disorders begin in adolescence [3-5], and risk behaviors established at this time can continue into adulthood [6-9], significantly impacting on long-term mental, physical, and social well-being [10-12]. Mental health issues affect 1 in 4 of NZ youth [4,13], and the number of NZ secondary school students reporting mood disorders, self-harm, and peer problems has increased [14]. NZ has the highest rate of youth suicide in the Organisation for Economic Cooperation and Development countries [15]. Māori (the indigenous people of NZ) youth living in deprived, rural areas have significantly higher rates of MHBs and suicide than their non-Māori peers. Further, educational, employment, and health outcomes are worse for adolescent Māori, and their life expectancy is much lower [16-21].

Rather than disclose their MHB concerns at primary care, adolescents often present primarily with vague, physical symptoms [8,9,16,22-25]. Opportunistic discussions about MHB do not occur in primary health care unless the problems are severe [9,26-34]. Yet, if the conversation is initiated by the clinician, young people are willing to discuss MHB [28,34-41]. Screening for youth MHB concerns occurs in less than 50% of primary health care provider (PHP) consultations, with the result that over half of adolescent MHB concerns are not detected [34,35,42]. Clinicians in primary care describe being underresourced in terms of time, appropriate screening tools, and experience in youth health [28,34,36]. Screening can reveal issues that may otherwise be overlooked and facilitate discussions between PHPs and young people [31]. This process can be therapeutic for youth, increasing their satisfaction with care and the likelihood that they will ask for help in the future [28,31,34].

There are a number of MHB screening tools available [41], but it can be time-consuming to administer these and interpret the results [43], and not all screening tools are suitable for use in all clinical contexts [43,44]. Where MHB screening for youth does occur, rates of follow-up and service use remain low [42,44,45]. The referral of every positive screen to secondary services creates an overwhelming need for appointments, delaying timely access to care [17,28,41,42,46]. In a stepped care approach, the primary health care team forms the hub of care for mild-to-moderate mental health issues. Increasing levels of care are added stepwise relative to the severity of more complex or worsening issues, providing effective management in primary care and more efficient use of specialist services [47].

The NZ-developed electronic Case-finding and Help Assessment Tool is a multi-item, electronic screening tool for use in primary health care to screen adults for substance misuse (smoking, alcohol, and drugs), problem gambling, depression, anxiety, exposure to abuse, difficulty controlling anger, and physical inactivity [48]. A youth version, YouthCHAT, has been developed using a co-design approach with input from clinicians and young people[49], and it contains 4 additional youth-specific modules: sexual health, youth stress, conduct disorder, and eating issues [10,48,50-55]. For positive screens in the smoking, substance abuse, depression, and anxiety modules, branching logic links users to validated assessment tools (eg, the Substances and Choices Scale [56], the Patient Health Questionnaire-Depression Adolescent version [57], and general anxiety disorder assessment, GAD-7 [58]). Some modules provide a nonclinical score that indicates the number of positive responses to questions (eg, the behavior or conduct module), and others simply indicate the presence of risky behavior (eg, gambling). The help question allows young people to prioritize concerns and indicate the areas where they are ready to accept help [51,59,60]. A stepped care-based resource pack guides clinicians to effective evidence-based interventions. Youth health providers in Northland have also undertaken mental health credentialing through the Primary health organisation (PHO) in order to provide brief interventions to clients for low to moderate mental health issues at the time of the screening.

Youth can complete YouthCHAT on an electronic device (eg, a tablet) before their consultation; completion takes approximately 5-15 minutes. A video briefly introduces the screen and explains confidentiality before giving the option to "start" or "exit" the screen. Upon completion of the screen, a clinical summary report is available to the clinician seeing them, indicating which domains screened positive, the severity of the condition (from validated assessments), and where help is

sought. This report facilitates a conversation between the clinician and the young person, supporting shared decision making and youth input into their plan of care.

YouthCHAT has been successfully used in 1 rural NZ youth clinic and found to be acceptable to clinic staff (CS) and young people [54]. A randomized trial in an urban high school indicates that YouthCHAT compares favorably to the HEEADSSS (Home, Education, Eating, Activities, Drugs and Alcohol, Sexuality, Suicide and Depression, Safety) interview-based assessment, currently used to screen all Year 9 students in NZ low-decile secondary schools for psychosocial issues [49].

Aim

This study will evaluate the implementation of the YouthCHAT program into primary health clinics in Te Tai Tokerau (Northland, NZ). Using a co-design approach, YouthCHAT, the processes around its use, and the stepped care resources offered will be tailored to meet the needs of local communities, with the aim of improving screening rates and brief intervention delivery for MHB concerns as well as developing a framework for scaling up the implementation of YouthCHAT more widely across Northland.

Objectives

Specific objectives are to assess YouthCHAT with respect to the following:

1. Utility (does YouthCHAT lead to increased screening and detection rates of mental health issues?)
2. Feasibility (is it feasible to conduct e-screening and deliver stepped care support to young people attending youth clinics, school-based clinics, and general practice?)
3. Acceptability (is YouthCHAT acceptable to clinicians to use as a screening and stepped care intervention tool for youth?)
4. Provide a modifiable framework for scaling up implementation to meet specific health needs in specific contexts in consultation with community stakeholders, utilizing local agencies and cultural and community groups to deliver stepped care support.

Methods

Co-design and New Zealand Research

Considered the founding document of NZ, the Treaty of Waitangi was signed by Māori Chiefs and representatives of the British Crown in 1840. The agreement ratified the unification of Pākehā (Western settlers) and Māori as a nation while affording Māori values, traditions, and practices [61]. Inherent in the Treaty of Waitangi is the Māori principles of kāwanatanga (giving governance to the Crown) and tino rangatiratanga (respecting Māori self-determination). The Treaty of Waitangi Act in 1975 [62] outlined the principles of partnership, participation, and protection as representing the true intent of the Treaty [63-65]. The principles continue to be the foundation of the relationship between Māori and the New Zealand Government today [66]. Research involving Māori in NZ must be carried out in accordance with the principles of the Treaty of Waitangi and ensure that Māori culture, values, and beliefs are respected and protected [67-71].

A randomized controlled trial, considered the epitome of clinical trials, would provide evidence about how an intervention is used in a controlled context with a specific population. However, these findings may not apply to the use of the intervention with real populations in actual clinical settings [71-73], particularly in areas of wide cultural diversity, such as NZ [71].

Kaupapa Māori (research for the benefit of Māori by Māori) is influenced by Māori culture, history, indigenous knowledge (Mātauranga), language (te reo), values, and worldview [67,68,70,71,74-76]. The proverb “kaua e takahia te mana o te tangata” (do not trample on “mana” or dignity and status) highlights the guiding principle of Kaupapa Māori, to respect the mana not only of individuals but also of the Māori culture, values, and beliefs [67,68,77]. The self-determination of Māori to identify challenges, solve problems, and form new knowledge (tino rangatiratanga) affords control over research processes and the protection of Mātauranga [67-71]. This study was not conceived as a Kaupapa Māori project; however, as the majority of participants are envisaged to be Māori, their culture, values, and beliefs must be validated, respected, and protected. Provided Māori retain control of the research, non-Māori researchers can undertake research involving Māori. To do so, they must first reflect on their own culture, worldview, values, and beliefs and, having done so, acknowledge, give credence to, and respect those of Māori [67-71,77]. Non-Māori researchers can then work in partnership with Māori, as long the methodology affiliates with the principles and values of Kaupapa Māori and is undertaken in collaboration with those who will benefit from the research [78].

In a co-design approach, research is undertaken with, rather than on, people [67,79]. The research processes evolve in conjunction with and from the perspectives of the participants [79-82], allowing researchers to gain an understanding of context-specific requirements and challenges [79-84]. Participants become actively involved in the research process as partners, designers, and developers alongside the research team. The knowledge, experiences, ideas, and skills of the participants are used to help find acceptable and workable ways of identifying and overcoming problems [80,85,86]. Co-design research, therefore, aligns with Kaupapa Māori, and in this study, researchers from both cultures will work alongside each other sharing research principles, processes, and skills in bicultural research [87].

Māori have been involved in the development of YouthCHAT. The tool has been translated into te reo Māori (Māori language) and tested to ensure acceptability among Māori youth and clinicians in Te Tai Tokerau [54]. The same clinical educator (CE) who was part of the proof of concept trial noted above is a qualified nurse educator and registered nurse. As a coinvestigator and the Kaitautoko (support person or advocate) for this project, she will implement YouthCHAT in her clinical practice first and then train and work with other clinical staff as YouthCHAT is iteratively implemented in other clinics. Further, this research will be developed through engagement with young people, local iwi (confederation of Māori tribes),

the local PHO and District Health Board, CS, and community providers for their input and participation. The cultural relevance of YouthCHAT and its implementation has been valued in its development. Equitable approaches will be taken with all participants in all locations, and the findings of this study may contribute to a long-term reduction in disparities between Māori and non-Māori young people. Engaging and partnering with stakeholders and users throughout the research process will respect Māori tikanga (customs and etiquette), and validation of Māori culture, values, and beliefs will be integral to the success of the study [75,82]. With the assistance of local project investigators, the bicultural, co-design approach will ensure that the YouthCHAT model initially employed, further scaled up, and then rolled out is culturally appropriate and meets the needs of the local community.

Procedures

This study has received approval from the New Zealand Health and Disability Ethics Committee (reference 18/CEN/31) on May 05, 2018. A pragmatic rollout of YouthCHAT will take place over 3 years using an iterative process of implementation, modification, and evaluation to assess the processes for using YouthCHAT across different clinical settings in Te Tai Tokerau.

Whiringa Tuatahi Tahi (Phase 1)

After consultation with local health providers and other community resources, YouthCHAT will be implemented in 5 nurse-led youth clinics. Utility, feasibility, and acceptability data will be gathered and used to modify and improve YouthCHAT operational processes. The implementation of the YouthCHAT tool will be evaluated at each site. In response to the feedback received from participants at each clinic, modifications will be made to YouthCHAT processes.

Whiringa Tuatahi Rua (Phase 2)

After the changes from phase 1 have been incorporated and after further consultation with local providers and resources, using the updated implementation processes, YouthCHAT will be rolled out to 4 school-based clinics in Northland. Utility, feasibility, and acceptability data will be gathered and modifications made as before.

Whiringa Tuatahi Toru (Phase 3)

After the changes from phase 2 have been incorporated and after further consultation with local providers and resources, the updated implementation processes will then be used to roll out YouthCHAT to 3 general practice clinics in Northland. Utility, acceptability, and feasibility data will be gathered as before. The data from all 3 phases will be used to develop an implementation framework for a wider rollout of the YouthCHAT program across different primary health care settings in NZ.

Setting, Participants, and Recruitment

The YouthCHAT program is being implemented into the youth screening policies and procedures across all the clinics taking part in this study. Youth between 12-24 years of age visiting the clinic will be asked to complete YouthCHAT as per the clinic's screening procedures. Feedback about YouthCHAT will be sought in the form of surveys, interviews, and focus groups from 3 participant groups: (1) the CE, (2) CS, and (3) young people aged 16-24 years who have used YouthCHAT.

All CS, including the CE, will be informed about the study and invited to participate by members of the research team before the implementation of YouthCHAT into their practice. All youth meeting the participation criteria will be informed about and invited to take part in the study after their consultation with the clinician. This will be done by either the clinician or by administration staff, depending on each clinic's systems. Young people who are interested in taking part will leave their contact details and will be contacted by the research team to arrange a suitable time for the focus groups. All participation is voluntary. Written, informed consent will be obtained prior to their participation. Youth taking part in the focus groups will receive a NZ $20 voucher, and kai (food) will be provided.

Inclusion Criteria

The study participants will include youth (over 16 years old) who have used YouthCHAT, CS from participating clinics who use the YouthCHAT tool, and the YouthCHAT CE, who provides training and support in the use of YouthCHAT.

Exclusion Criteria

Youth under 16 years old will be excluded as parental consent would have to be sought, and since young people often visit clinics without parental or guardian knowledge, seeking such consent would violate their confidentiality. Youth over 16 who are not able to provide their own consent (eg, due to cognitive difficulties) will be excluded.

Data Collection

Utility Data and Measures

Data pertaining to each participating clinic's screening rates for mental health issues and risky health behaviors and early identification of emerging problems and delivery of brief interventions before and after YouthCHAT implementation will be gathered by way of a summary report from the clinic administrator. The collated deidentified data will enable the calculation of screening rates and help-seeking behavior before and after the implementation of YouthCHAT. For all YouthCHAT modules, a simple "yes" or "no" metric will be used to determine rates of detection. Rates of health-seeking behavior will be assessed via the "help" question, which offers "yes," "no," and "yes but not today" responses that will be collected.

Acceptability and Feasibility Data

Acceptability and feasibility data will be gathered via surveys and interviews with the CE, CS, and focus groups with a subset of youth who have used YouthCHAT. Survey and interview questions will be framed around the mechanisms of normalization process theory (NPT): (1) coherence, for example, does it make sense for participants to implement YouthCHAT into their practice? (2) cognitive participation, for example, are participants able to easily engage with the tool? (3) collective action, for example, how hard is it to implement and use YouthCHAT? and (4) reflexive monitoring, for example, are there clear benefits of using YouthCHAT? Are the advantages

or disadvantages of using the tool easily identifiable and how could disadvantages be minimized? [88-90].

Surveys and semistructured interviews with CS will gather feedback on their experience of using YouthCHAT, for example, perceptions of its usefulness, whether they would recommend it to others, and concerns about privacy and identify aspects that limit or encourage the use of YouthCHAT in their daily practice. A CE semistructured interview will be conducted at the end of data collection to discuss program feasibility, utility, acceptability, and suggested improvements in the setup processes of YouthCHAT and in training for its use.

Focus groups will be held with youth participants to gather in-depth feedback on their experience including the acceptability of the electronic method, perceptions of the look of the electronic interface, and the length of screening; whether they would recommend it to others; and concerns about privacy. Interviews and focus groups will be audiotaped and transcribed with consent.

Data Handling

All information will be kept confidential, and analyzed data will be presented in a deidentified manner. HealthLink will provide secure storage of all YouthCHAT screening data and transmit encrypted, secure data to the clinics' practice management system software by the same private network used for their electronic referrals. Participant data will be deidentified before being stored by the research team. Clinical data obtained through YouthCHAT will be available to relevant health providers. All surveys are Web-based and anonymous and will be completed using Qualtrics. Recordings of semistructured interviews and focus groups will be transcribed (without anything that could identify participants), and the recordings will be deleted. The transcriber will be asked to sign a confidentiality agreement. Data will be retained for 10 years as per the University of Auckland protocol.

Data Analyses

Quantitative Data

Quantitative data will be analyzed using Microsoft Excel and a statistical software package. Analyses will include basic descriptive statistics (eg, number of youth screened and YouthCHAT summary data). Cross-tabulation analyses will explore differences in detection rates between different population subgroups (eg, ethnicity, age, and gender) across sites and compare pre-and post-YouthCHAT implementation. Subgroup analyses of differences in help-seeking behavior, uptake of the initiative, and delivery of interventions will also be analyzed if there are sufficient numbers to permit such analysis. This information will provide insights into important heterogeneities in our population of interest that may aid an effective intervention strategy.

Qualitative Data

Focus groups and semistructured interviews will be audiotaped and confidentially transcribed, and suggestions will be categorized and tabulated. Any modification to the implementation processes will follow majority opinion. Data will be analyzed using a general inductive approach [91], with collated text categorized and thematically analyzed according to the mechanisms of NPT. Data will be independently coded by 2 researchers, with a consensus reached by adjudication [88-90].

Presentation of the results will depend on the nature of the data collected. If substantial qualitative data allows, a thematic analysis will be conducted and presented separately. Irrespective of this, the results will be synthesized in the discussion.

Results

Recruitment for the first phase began in September 2018. YouthCHAT was implemented at the first site in October 2018 and is expected to be at a further two sites in late January to early February 2019. The study is due for completion at the end of 2021.

Discussion

Expected Findings

Early detection intervention for mental health disorders and risky behaviors in youth can prevent long-term health and psychosocial issues [9,30,41,92]. For this to happen, it is imperative that a means of detecting existing and developing MHBs in adolescence is found and timely management initiated [22]. Interventions need to respect the ability of youth to change risk behaviors and provide them with the resources, skills, and support to do so [6,17,18,22,31,36,60,93,94]. YouthCHAT promotes wellness planning and supports youth to self-manage. The systematic approach of screening and provision of guides for stepped care intervention aims to lead to the early and more comprehensive intervention of youth mental health, substance misuse, and other lifestyle issues, which will have substantial impacts on future physical, mental, and social health as well as well-being. It is anticipated that a successful rollout of YouthCHAT will be associated with improved health and social outcomes through early identification of and intervention for mental health concerns, leading to an improvement in youth help-seeking behavior.

Complex interventions, such as YouthCHAT, with the potential to improve health outcomes, can only do so if they can be successfully implemented and then integrated or normalized into routine clinical practice [88-91]. However, this will not happen unless those who will be using the tool find it acceptable and unless its delivery is feasible. The implementation of YouthCHAT requires the necessary internet capability and availability of mobile devices, such as tablets, for the completion of the screen. The feasibility of implementing YouthCHAT relies on more than technological infrastructure, it is dependent on the impact YouthCHAT has on the people who will be using it [88-90]. For example, if clinical staff see the benefit of using YouthCHAT in their daily practice, enhancing engagement with young people and improving health outcomes while reducing their workload, then it is feasible that the tool can become normalized in their daily practice [88,89]. Feasibility is also reliant on factors that encourage or inhibit the uptake of the screen by young people, for example, the length of the screen, ease of completion, and the electronic interface. A co-design

approach will assist the research team to identify and overcome barriers to the use of YouthCHAT.

With the assistance of local project investigators, the co-design, bicultural approach will ensure that the YouthCHAT model initially employed, further scaled up, and then rolled out, is culturally appropriate, meets the needs of the local community, and is easily integrated into practice. This study, underpinned by NPT, seeks to develop YouthCHAT as a sustainable, culturally acceptable, cost-effective, and time-saving screening tool for clinicians in primary care to identify mental health concerns and ultimately improve equity for Māori youth. This is particularly important in rural NZ where provider recruitment and retention remain difficult.

Conclusions

If YouthCHAT can be implemented across a variety of primary health care settings in NZ, it has potential to be a user-friendly, time efficient, and culturally safe screening tool for early detection of psychosocial issues in NZ youth. The resource pack assists clinicians to provide appropriate intervention for emerging and developed youth mental health and lifestyle issues. The bicultural approach involving input from community providers, users, and stakeholders will ensure that modifiable elements of YouthCHAT can be tailored to meet the specific health needs of each context and could have a positive influence on future mental, physical, and social outcomes for NZ youth.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Health Research Council of New Zealand peer review report.

[PDF File (Adobe PDF File), 460KB - resprot_v8i1e12108_app1.pdf]

References

1. Ministry of Health. 2016. Health Loss in New Zealand 1990–2013. A report from the New Zealand Burden of Diseases, Injuries and Risk Factors Study URL: https://www.health.govt.nz/system/files/documents/publications/health-loss-in-new-zealand-1990-2013-aug16.pdf [accessed 2018-11-12] [WebCite Cache ID 73t0KOVJM]
2. Ministry Of Health. 2015. Health and Independence Report 2015 URL: https://www.health.govt.nz/system/files/documents/publications/health-and-independence-report-2015-oct15.pdf [accessed 2018-11-13] [WebCite Cache ID 73t0TPSIW]
3. Jones PB. Adult mental health disorders and their age at onset. Br J Psychiatry Suppl 2013 Jan;54:s5-10. [doi: 10.1192/bjp.bp.112.119164] [Medline: 23288502]
4. World Health Organisation. Child and adolescent mental health URL: http://www.who.int/mental_health/maternal-child/child_adolescent/en/ [accessed 2018-11-13] [WebCite Cache ID 73t0jOYkY]
5. McGorry PD, Purcell R, Goldstone S, Amminger GP. Age of onset and timing of treatment for mental and substance use disorders: implications for preventive intervention strategies and models of care. Curr Opin Psychiatry 2011 Jul;24(4):301-306. [doi: 10.1097/YCO.0b013e3283477a09] [Medline: 21532481]
6. Prime Minister's Science Advisory Committee. Minister's Science Advisory Committee. 2011. Improving the Transition Reducing Social and Psychological Morbidity During Adolescence URL: http://www.pmcsa.org.nz/wp-content/uploads/2011/06/Improving-the-Transition-report.pdf [accessed 2018-11-12] [WebCite Cache ID 73t46ZWcD]
7. Youth health: Enhancing the skills of primary health care practitioners in caring for all young New Zealanders, A resource manual. Christchurch, New Zealand: The Collaborative for Research and Training in Youth Health and Development Trust; 2011.
8. Taliaferro LA, Borowsky IW. Beyond prevention: promoting healthy youth development in primary care. Am J Prev Med 2012 Jun;42(6 Suppl 2):S117-S121. [doi: 10.1016/j.amepre.2012.03.017] [Medline: 22704429]

9. Sanci L, Chondros P, Sawyer S, Pirkis J, Ozer E, Hegarty K, et al. Responding to Young People's Health Risks in Primary Care: A Cluster Randomised Trial of Training Clinicians in Screening and Motivational Interviewing. PLoS One 2015;10(9):e0137581 [FREE Full text] [doi: 10.1371/journal.pone.0137581] [Medline: 26422235]
10. Goodyear-Smith F, Warren J, Elley CR. The eCHAT program to facilitate healthy changes in New Zealand primary care. J Am Board Fam Med 2013;26(2):177-182 [FREE Full text] [doi: 10.3122/jabfm.2013.02.120221] [Medline: 23471931]
11. Bartlett R, Holditch-Davis D, Belyea M. Problem behaviors in adolescents. Pediatr Nurs 2007;33(1):13-18. [Medline: 17410996]
12. Băban A, Crăiun C. Changing health-risk behaviors: A review of theory and evidence-based interventions in health psychology. Journal of Cognitive and Behavioral Psychotherapies 2007;7(1):45-56.
13. Clark T, Fleming T, Bullen P, Denny S, Crengle S, Dyson B, et al. Youth2000 Survey Series. 2012. The Health and Wellbeing of New Zealand Secondary School Students in 2012. Youth'12 Overview URL: https://www.fmhs.auckland.ac.nz/assets/fmhs/faculty/ahrg/docs/2012-overview.pdf [accessed 2018-11-12] [WebCite Cache ID 73szrzI6D]
14. Fleming TM, Clark T, Denny S, Bullen P, Crengle S, Peiris-John R, et al. Stability and change in the mental health of New Zealand secondary school students 2007-2012: results from the national adolescent health surveys. Aust N Z J Psychiatry 2014 May;48(5):472-480. [doi: 10.1177/0004867413514489] [Medline: 24317154]
15. Organisation for Economic Co-operation Development, Social Policy Division. OECD Family Database. Paris: Organisation for Economic Co-operation Development; 2012. Teenage suicide (15-19 years old) URL: https://www.oecd.org/els/family/CO_4_4_Teenage-Suicide.pdf [accessed 2018-11-13]
16. Mental Health Commission. Wellington, New Zealand: Mental Health Commission; 2011. Child and youth mental health and addiction URL: https://www.mentalhealth.org.nz/assets/ResourceFinder/Child-and-youth-mental-health-and-addiction-2011-MHC.pdf [accessed 2018-11-12] [WebCite Cache ID 73t6BUaGw]
17. Malatest International. Wellington, New Zealand: Ministry of Health; 2016 Jan. Evaluation Report: The Youth Primary Mental Health Service URL: https://www.health.govt.nz/system/files/documents/publications/evaluation-report-youth-primary-mental-health-service-dec16.pdf [accessed 2018-11-12] [WebCite Cache ID 73t6Zn44F]
18. Ministry of Health. Wellington, New Zealand: Ministry of Health; 2018. Mental Health and Addiction Workforce Action Plan 2017-202 URL: https://www.health.govt.nz/system/files/documents/publications/mental-health-addiction-workforce-action-plan-2017-2021-2nd-edn-apr18.pdf [accessed 2018-11-12] [WebCite Cache ID 73t6pBrCD]
19. Houkamau CA, Sibley CG. Māori Cultural Efficacy and Subjective Wellbeing: A Psychological Model and Research Agenda. Soc Indic Res 2010 Sep 8;103(3):379-398. [doi: 10.1007/s11205-010-9705-5]
20. Kovach M. Emerging from the margins: Indigenous methodologies. In: Brown L, Strega S, editors. Research as Resistance. Toronto: Canadian Scholars' Press; 2015.
21. Ministry of Health. Wellington, New Zealand: Ministry of Health; 2017. Suicide Facts: provisional data URL: https://www.health.govt.nz/publication/suicide-facts-2015-data [accessed 2018-11-12] [WebCite Cache ID 73t84dQD0]
22. Mariu KR, Merry SN, Robinson EM, Watson PD. Seeking professional help for mental health problems, among New Zealand secondary school students. Clin Child Psychol Psychiatry 2012 Apr;17(2):284-297. [doi: 10.1177/1359104511404176] [Medline: 21852315]
23. Bradford S, Rickwood D. Psychosocial assessments for young people: a systematic review examining acceptability, disclosure and engagement, and predictive utility. Adolescent Health, Medicine and Therapeutics 2012;3:111-125 [FREE Full text] [doi: 10.2147/AHMT.S38442] [Medline: 24600292]
24. Schaeuble K, Haglund K, Vukovich M. Adolescents' preferences for primary care provider interactions. J Spec Pediatr Nurs 2010 Jul;15(3):202-210. [doi: 10.1111/j.1744-6155.2010.00232.x] [Medline: 20618634]
25. Viner RM, Barker M. Young people's health: the need for action. BMJ 2005 Apr 16;330(7496):901-903 [FREE Full text] [doi: 10.1136/bmj.330.7496.901] [Medline: 15831880]
26. Roberts J, Sanci L, Haller D. Global adolescent health: is there a role for general practice? Br J Gen Pract 2012 Nov;62(604):608-610 [FREE Full text] [doi: 10.3399/bjgp12X658458] [Medline: 23211175]
27. Alexander SC, Fortenberry JD, Pollak KI, Bravender T, Davis JK, Ostbye T, et al. Sexuality talk during adolescent health maintenance visits. JAMA Pediatr 2014 Feb;168(2):163-169 [FREE Full text] [doi: 10.1001/jamapediatrics.2013.4338] [Medline: 24378686]
28. Ham P, Allen C. Adolescent health screening and counseling. Am Fam Physician 2012 Dec 15;86(12):1109-1116 [FREE Full text] [Medline: 23316983]
29. Kang M, Bernard D, Booth M, Quine S, Alperstein G, Usherwood T, et al. Access to primary health care for Australian young people: service provider perspectives. Br J Gen Pract 2003 Dec;53(497):947-952 [FREE Full text] [Medline: 14960219]
30. Denny S, Balhorn A, Lawrence A, Cosgriff J. Student access to primary health care and preventive health screening at a school-based health centre in South Auckland, New Zealand. N Z Med J 2005 Jul 15;118(1218):U1561. [Medline: 16027750]
31. Hacker K, Arsenault L, Franco I, Shaligram D, Sidor M, Olfson M, et al. Referral and follow-up after mental health screening in commercially insured adolescents. J Adolesc Health 2014 Jul;55(1):17-23. [doi: 10.1016/j.jadohealth.2013.12.012] [Medline: 24525226]

32. Gadomski AM, Fothergill KE, Larson S, Wissow LS, Winegrad H, Nagykaldi ZJ, et al. Integrating mental health into adolescent annual visits: impact of previsit comprehensive screening on within-visit processes. J Adolesc Health 2015 Mar;56(3):267-273 [FREE Full text] [doi: 10.1016/j.jadohealth.2014.11.011] [Medline: 25586231]
33. Chisolm DJ, Klima J, Gardner W, Kelleher KJ. Adolescent behavioral risk screening and use of health services. Adm Policy Ment Health 2009 Nov;36(6):374-380. [doi: 10.1007/s10488-009-0245-8] [Medline: 19777336]
34. Brown JD, Wissow LS. Discussion of sensitive health topics with youth during primary care visits: relationship to youth perceptions of care. J Adolesc Health 2009 Jan;44(1):48-54 [FREE Full text] [doi: 10.1016/j.jadohealth.2008.06.018] [Medline: 19101458]
35. Ungar M, Theron L, Liebenberg L, Tian G, Restrepo A, Sanders J, et al. Patterns of individual coping, engagement with social supports and use of formal services among a five-country sample of resilient youth. Glob Ment Health (Camb) 2015;2:e21 [FREE Full text] [doi: 10.1017/gmh.2015.19] [Medline: 28596868]
36. Kadivar H, Thompson L, Wegman M, Chisholm T, Khan M, Eddleton K, et al. Adolescent views on comprehensive health risk assessment and counseling: assessing gender differences. J Adolesc Health 2014 Jul;55(1):24-32 [FREE Full text] [doi: 10.1016/j.jadohealth.2013.12.002] [Medline: 24613096]
37. The Lancet. Maturing dangers. The Lancet 1995 Apr 22;345(8956):997-998. [Medline: 7619126]
38. Walker Z, Townsend J, Oakley L, Donovan C, Smith H, Hurst Z, et al. Health promotion for adolescents in primary care: randomised controlled trial. BMJ 2002 Sep 07;325(7363):524 [FREE Full text] [Medline: 12217993]
39. Klein JD, McNulty M, Flatau CN. Adolescents' access to care: teenagers' self-reported use of services and perceived access to confidential care. Arch Pediatr Adolesc Med 1998 Jul;152(7):676-682. [Medline: 9667540]
40. Jacobson LD, Wilkinson C, Owen PA. Is the potential of teenage consultations being missed?: a study of consultation times in primary care. Fam Pract 1994 Sep;11(3):296-299. [Medline: 7843521]
41. Webb MJ, Kauer SD, Ozer EM, Haller DM, Sanci LA. Does screening for and intervening with multiple health compromising behaviours and mental health disorders amongst young people attending primary care improve health outcomes? A systematic review. BMC Fam Pract 2016 Dec 04;17:104 [FREE Full text] [doi: 10.1186/s12875-016-0504-1] [Medline: 27488823]
42. Wissow LS, Brown J, Fothergill KE, Gadomski A, Hacker K, Salmon P, et al. Universal mental health screening in pediatric primary care: a systematic review. J Am Acad Child Adolesc Psychiatry 2013 Nov;52(11):1134-1147.e23 [FREE Full text] [doi: 10.1016/j.jaac.2013.08.013] [Medline: 24157388]
43. Connors EH, Arora P, Blizzard AM, Bower K, Coble K, Harrison J, et al. When Behavioral Health Concerns Present in Pediatric Primary Care: Factors Influencing Provider Decision-Making. J Behav Health Serv Res 2018 Jul;45(3):340-355. [doi: 10.1007/s11414-017-9580-9] [Medline: 29209899]
44. Brown JD, Wissow LS. Screening to identify mental health problems in pediatric primary care: considerations for practice. Int J Psychiatry Med 2010;40(1):1-19. [doi: 10.2190/PM.40.1.a] [Medline: 20565041]
45. Gardner W, Kelleher KJ, Pajer K, Campo JV. Follow-up care of children identified with ADHD by primary care clinicians: A prospective cohort study. J Pediatr 2004 Dec;145(6):767-771. [doi: 10.1016/j.jpeds.2004.08.028] [Medline: 15580198]
46. Sanci L, Grabsch B, Chondros P, Shiell A, Pirkis J, Sawyer S, et al. The prevention access and risk taking in young people (PARTY) project protocol: a cluster randomised controlled trial of health risk screening and motivational interviewing for young people presenting to general practice. BMC Public Health 2012 Jun 06;12:400 [FREE Full text] [doi: 10.1186/1471-2458-12-400] [Medline: 22672481]
47. Hickie IB, Groom GL, McGorry PD, Davenport TA, Luscombe GM. Australian mental health reform: time for real outcomes. Med J Aust 2005 Apr 18;182(8):401-406. [Medline: 15850437]
48. Goodyear-Smith F, Warren J, Bojic M, Chong A. eCHAT for lifestyle and mental health screening in primary care. Ann Fam Med 2013;11(5):460-466 [FREE Full text] [doi: 10.1370/afm.1512] [Medline: 24019278]
49. Thabrew H, Corter A, Goodyear-Smith F, Goldfinch M. Randomized Trial Comparing the Electronic Composite Psychosocial Screener YouthCHAT With a Clinician-Interview Assessment for Young People: A Study Protocol. JMIR Res Protoc 2017 Jul 31;6(7):e135 [FREE Full text] [doi: 10.2196/resprot.7995] [Medline: 28760727]
50. Goodyear-Smith F. University of Auckland. 2011. Evolution of the eCHAT: Case-finding to improve health and happiness [MD] URL: https://researchspace.auckland.ac.nz/bitstream/handle/2292/10622/whole.pdf?sequence=2 [WebCite Cache ID 75FwJ3FyW]
51. Goodyear-Smith F, Arroll B, Coupe N. Asking for help is helpful: validation of a brief lifestyle and mood assessment tool in primary health care. Ann Fam Med 2009;7(3):239-244 [FREE Full text] [doi: 10.1370/afm.962] [Medline: 19433841]
52. Goodyear-Smith F, Arroll B, Coupe N, Buetow S. Ethnic differences in mental health and lifestyle issues: results from multi-item general practice screening. N Z Med J 2005 Apr 01;118(1212):U1374. [Medline: 15806177]
53. Goodyear-Smith F, Arroll B, Kerse N, Sullivan S, Coupe N, Tse S, et al. Primary care patients reporting concerns about their gambling frequently have other co-occurring lifestyle and mental health issues. BMC Fam Pract 2006 Apr 10;7:25 [FREE Full text] [doi: 10.1186/1471-2296-7-25] [Medline: 16606465]
54. Goodyear-Smith F, Corter A, Suh H. Electronic screening for lifestyle issues and mental health in youth: a community-based participatory research approach. BMC Med Inform Decis Mak 2016 Dec 08;16(1):140 [FREE Full text] [doi: 10.1186/s12911-016-0379-z] [Medline: 27821128]

55. Goodyear-Smith F, Coupe NM, Arroll B, Elley CR, Sullivan S, McGill A. Case finding of lifestyle and mental health disorders in primary care: validation of the 'CHAT' tool. Br J Gen Pract 2008 Jan;58(546):26-31 [FREE Full text] [doi: 10.3399/bjgp08X263785] [Medline: 18186993]
56. Christie G, Marsh R, Sheridan J, Wheeler A, Suaalii-Sauni T, Black S, et al. The substances and choices scale (SACS)--the development and testing of a new alcohol and other drug screening and outcome measurement instrument for young people. Addiction 2007 Sep;102(9):1390-1398. [doi: 10.1111/j.1360-0443.2007.01916.x] [Medline: 17645425]
57. 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] [Medline: 11556941]
58. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
59. Harris SK, Knight JR. Putting the Screen in Screening: Technology-Based Alcohol Screening and Brief Interventions in Medical Settings. Alcohol Res 2014;36(1):63-79 [FREE Full text] [Medline: 26259001]
60. Goodyear-Smith F, Martel R, Darragh M, Warren J, Thabrew H, Clark TC. Screening for risky behaviour and mental health in young people: the YouthCHAT programme. Public Health Rev 2017;38:20 [FREE Full text] [doi: 10.1186/s40985-017-0068-1] [Medline: 29450092]
61. New Zealand History. Wellington, NZ: Ministry for Culture and Heritage; 2017. The Treaty in brief. Page 2 – Treaty FAQs URL: https://nzhistory.govt.nz/politics/treaty/treaty-faqs [accessed 2018-09-25] [WebCite Cache ID 72giBlZ2S]
62. New Zealand Legislation. 1975 Oct. Treaty of Waitangi Act 1975 URL: http://www.legislation.govt.nz/act/public/1975/0114/107.0/DLM435368.html [accessed 2018-11-12] [WebCite Cache ID 73t9WChwU]
63. The English version of the Treaty of Waitangi. 2013 Dec 23. Waitangi Tribunal Internet URL: https://www.waitangitribunal.govt.nz/ [accessed 2018-09-25] [WebCite Cache ID 72giTHxo9]
64. Nursing Council of New Zealand. Wellington, New Zealand: Nursing Council of New Zealand; 2011. Guidelines for Cultural Safety, the Treaty of Waitangi and Māori Health in Nursing Education and Practice URL: https://bit.ly/2Ql8Iad [accessed 2018-11-13] [WebCite Cache ID 73tHXMpLO]
65. New Zealand History. 2018. The Treaty in brief: Page 1 – Introduction URL: https://nzhistory.govt.nz/politics/treaty/the-treaty-in-brief [WebCite Cache ID 72gizqJig]
66. Ministry of Health. Wellington: Ministry of Health; 2014. Treaty of Waitangi principles URL: https://www.health.govt.nz/our-work/populations/maori-health/he-korowai-oranga/strengthening-he-korowai-oranga/treaty-waitangi-principles [WebCite Cache ID 72gjRTFop]
67. Cram F, Phillips H. Claiming Interstitial Space for Multicultural, Transdisciplinary Research Through Community-up Values. IJCIS 2012 Jun 01;5(2):36-49 [FREE Full text] [doi: 10.5204/ijcis.v5i2.89]
68. Cunningham C. A framework for addressing Māori knowledge in research, science and technology. Pac Health Dialog 2000 Mar;7(1):62-69. [Medline: 11709883]
69. Porsanger J. An Essay about Indigenous Methodology. Nordlit 2004 Jul 01;8(1):105-120. [doi: 10.7557/13.1910]
70. Wilson C. Decolonizing Methodologies: research and indigeneous peoples. Social Policy Journal of New Zealand 2001:214-218 (forthcoming) [FREE Full text]
71. Oetzel J, Scott N, Hudson M, Masters-Awatere B, Rarere M, Foote J, et al. Implementation framework for chronic disease intervention effectiveness in Māori and other indigenous communities. Global Health 2017 Sep 05;13(1):69 [FREE Full text] [doi: 10.1186/s12992-017-0295-8] [Medline: 28870225]
72. Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci 2011;13(2):217-224 [FREE Full text] [Medline: 21842619]
73. Peters D, Adam T, Alonge O, Agyepong I, Tran N. Implementation research: what it is and how to do it. BMJ 2013 Nov 20;347:f6753. [doi: 10.1136/bmj.f6753] [Medline: 24259324]
74. Wehipeihana N, McKegg K. Values and Culture in Evaluative Thinking: Insights from Aotearoa New Zealand. Evaluation 2018 Apr 16;2018(158):93-107. [doi: 10.1002/ev.20320]
75. Andrzejewski J, Symcox L, Baltodano M. Mai i te maramatanga, ki te putanga mai o te tahuritanga: From conscientization to transformation. In: Social Justice, Peace, and Environmental Education: Transformative Standards. New York: Taylor & Francis, Inc; 2009.
76. Tipene-Matua B, Phillips H, Cram F, Parsons M, Taupo K. Old ways of having new conversations. Katoa Ltd 2009 (forthcoming) [FREE Full text]
77. Smith L. Decolonizing Methodologies. London: Zed Books Ltd; 2013.
78. National Ethics Advisory Committee. Ministry of Health. Wellington, New Zealand: Ministry of Health; 2012. Āhuatanga ū ki te tika me te pono mō te Rangahau Māori: Māori Research Ethics - An overview URL: https://neac.health.govt.nz/system/files/documents/publications/neac-maori-research-ethics-an-overview-2012.doc [accessed 2018-11-13] [WebCite Cache ID 73tH2SzEu]
79. Goodyear-Smith F, Jackson C, Greenhalgh T. Co-design and implementation research: challenges and solutions for ethics committees. BMC Med Ethics 2015 Nov 16;16:78 [FREE Full text] [doi: 10.1186/s12910-015-0072-2] [Medline: 26573410]
80. Morales E, Rousseau J, Passini R. Using a Co-Design Methodology for Research on Environmental Gerontology. J Gerontol Geriatric Res 2015;01(03). [doi: 10.4172/2167-7182.1000106]

81. Janols R, Lindgren H. A Method for Co-Designing Theory-Based Behaviour Change Systems for Health Promotion. Stud Health Technol Inform 2017;235:368-372. [Medline: 28423816]
82. Te Morenga L, Pekepo C, Corrigan C, Matoe L, Mules R, Goodwin D, et al. Co-designing an mHealth tool in the New Zealand Māori community with a "Kaupapa Māori" approach. AlterNative: An International Journal of Indigenous Peoples 2018 Jan 23;14(1):90-99. [doi: 10.1177/1177180117753169]
83. Peters D, Tran N, Adam T. Implementation Research in Health: A Practical Guide. In: Implementation Research In Health. Geneva: World Health Organization; 2014.
84. Ramaswamy V, Gouillart F. Build the co-creative enterprise. Harv Bus Rev 2010 Oct;88(10):100-9, 150. [Medline: 20929195]
85. Sanders E, William C. Harnessing people's creativity: Ideation and expression through visual communication. In: Langford J, McDonagh-Philp D, editors. Focus groups: Supporting effective product development. UK: Taylor & Francis, Inc; 2002.
86. Sanders E, Stappers P. Probes, toolkits and prototypes: three approaches to making in codesigning. CoDesign 2014 Mar 06;10(1):5-14. [doi: 10.1080/15710882.2014.888183]
87. Hudson M, Russell K. The Treaty of Waitangi and Research Ethics in Aotearoa. Bioethical Inquiry 2008 Nov 27;6(1):61-68. [doi: 10.1007/s11673-008-9127-0]
88. May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, et al. Development of a theory of implementation and integration: Normalization Process Theory. Implement Sci 2009 May 21;4:29 [FREE Full text] [doi: 10.1186/1748-5908-4-29] [Medline: 19460163]
89. May C. A rational model for assessing and evaluating complex interventions in health care. BMC Health Serv Res 2006 Jul 07;6:86 [FREE Full text] [doi: 10.1186/1472-6963-6-86] [Medline: 16827928]
90. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 2010 Oct 20;8:63 [FREE Full text] [doi: 10.1186/1741-7015-8-63] [Medline: 20961442]
91. Petty NJ, Thomson OP, Stew G. Ready for a paradigm shift? Part 1: introducing the philosophy of qualitative research. Man Ther 2012 Aug;17(4):267-274. [doi: 10.1016/j.math.2012.03.006] [Medline: 22480950]
92. Hacker KA, Penfold RB, Arsenault LN, Zhang F, Murphy M, Wissow LS. Behavioral health services following implementation of screening in Massachusetts Medicaid children. Pediatrics 2014 Oct;134(4):737-746 [FREE Full text] [doi: 10.1542/peds.2014-0453] [Medline: 25225135]
93. Bradford S, Rickwood D. Young People's Views on Electronic Mental Health Assessment: Prefer to Type than Talk? J Child Fam Stud 2015;24(5):1213-1221 [FREE Full text] [doi: 10.1007/s10826-014-9929-0] [Medline: 25960628]
94. Logan J, Crosby A, Hamburger M. Suicidal ideation, friendships with delinquents, social and parental connectedness, and differential associations by sex: findings among high-risk pre/early adolescent population. Crisis 2011;32(6):299-309. [doi: 10.1027/0227-5910/a000091] [Medline: 21940255]

Abbreviations

CE: clinical educator
CS: clinical staff
MHB: mental health and risk behavior
NPT: normalization process theory
NZ: New Zealand
PHO: primary health organization
PHP: primary health care provider

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Protocol

Using an Electronic Tablet to Assess Patients' Home Environment by Videoconferencing Prior to Hospital Discharge: Protocol for a Mixed-Methods Feasibility and Comparative Study

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Abstract

Background: Occupational therapists working in hospitals are usually involved in discharge planning to assess patients' safety and autonomy upon returning home. However, their assessment is usually done at the hospital due to organizational and financial constraints. The lack of visual data about the patients' home may thus reduce the appropriateness and applicability of the support recommended upon discharge. Although various technological tools such as mobile devices (mobile health) are promising methods for home-based distance assessment, their application in hospital settings may raise several feasibility issues. To our knowledge, their usefulness and added value compared to standard procedure have not been addressed yet in previous studies. Moreover, several feasibility issues need to be explored.

Objective: This paper aims to (1) document the clinical feasibility of using an electronic tablet to assess the patient's home environment by mobile videoconferencing and (2) explore the added value of using mobile videoconferencing, compared to the standard procedure.

Methods: A feasibility and comparative study using a mixed-methods (convergent) design is currently undergoing. Six occupational therapists will assess the home environment of their patients in the hospital setting: they will first perform a semistructured interview (a) and then use mobile videoconferencing (b) to compare "a versus a+b." Interviews with occupational therapists and patients and their caregivers will further explore the advantages and disadvantages of mobile videoconferencing. Two valid tools are used (the Canadian Measure of Occupational Performance and the telehealth responsivity questionnaire). Direct and indirect time is also collected.

Results: The project was funded in the spring of 2016 and authorized by the ethics committee in February 2017. Enrollment started in April 2017. Five triads (n=4 occupational therapists, n=5 clients, n=5 caregivers) have been recruited until now. The experiment is expected to be completed by April 2019 and analysis of the results by June 2019.

Conclusions: Mobile videoconferencing may be a familiar and easy solution for visualizing environmental barriers in the home by caregivers and clinicians, thus providing a promising and inexpensive option to promote a safe return home upon hospital discharge, but clinical feasibility and obstacles to the use of mobile videoconferencing must be understood.

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KEYWORDS

caregivers; feasibility; mixed-methods; mobile videoconferencing; mobile phone; occupational therapists

Introduction

Occupational therapists working in hospitals are usually involved in discharge planning by making recommendations—such as environmental adaptations, assistive technologies, home care services—in order to promote a safe return home. To ensure the applicability and appropriateness of these recommendations, they must consider not only the functional capabilities of their patients, but also the environmental conditions in which they will evolve once they return home. For example, it is often essential for occupational therapists to know the number of stairs to access the home, the kitchen layout and hygiene, the availability of support surfaces in their bathroom, the distance to be covered to get to the toilet, and the thresholds around the house. These visual data are thus crucial to select the type of assistive technologies needed in the home, to provide relevant home care services upon discharge, and even to recommend moving into a new living environment [1,2].

Studies have shown that predischarge home visits help to improve patients' performance in activities of daily living and quality of life [3] and reduce the risk of falls [4], especially in those with orthopedic problems. However, home visits are not always done prior to discharge. Assessments are therefore generally performed in the hospital, mainly because of organizational and financial constraints. More precisely, the costs and time associated with occupational therapists' travel to patients' living environment, as well as the short length of hospitalization, make home assessments difficult to perform before discharge [3].

The use of technologies—such as mobile or portable videoconferencing—is thus an innovative solution, as well as an alternative to predischarge home visit. Specifically, mobile videoconferencing would imply that a patient's relative moves around the home with an electronic tablet or smartphone using Skype software, in order to allow occupational therapist to assess the home environment (furniture, moving areas, etc) from the hospital setting. Although the use of videoconferencing is recognized to provide distance services such as telemedecine between the hospital and the home [5-9], our recent rapid review (submitted manuscript) only identified 6 studies involving the use of videoconferencing to assess the home environment [10-16]. The work of Sandford et al [14-16] highlighted the use of videoconferencing (including several sophisticated cameras) to adequately identify most (86.4%) of the problems observed during a "standard" home visit (eg, going up or down stairs, using kitchen or bathroom facilities). Moreover, the degree of agreement between the recommendations made by the clinicians to overcome the problems identified was high (P<.001) for both types of methods (videoconference vs home visit). Although these studies suggest that the use of videoconferencing is an interesting alternative to conducting a home visit, they have been performed in a nonhospital setting, using technicians to operate complex technological equipment. Their results therefore offer very little information about the feasibility of using a mobile videoconferencing (such as Skype) in a real hospital care context to support discharge planning.

Some disadvantages related to the use of telehealth in "real" contexts of care have been reported: low receptivity of the clinician to accept a change of practice [17], difficulty of some users to understand its functioning [9], cost related to the purchase of equipment [17]. However, these disadvantages are not necessarily applicable to the use of "mobile" videoconferencing. Indeed, it is anticipated that the use of mobile videoconferencing is familiar and simple to use for several relatives at the time of discharge, which suggest a promising and inexpensive solution (Skype is free) to support patients with physical disabilities upon returning home.

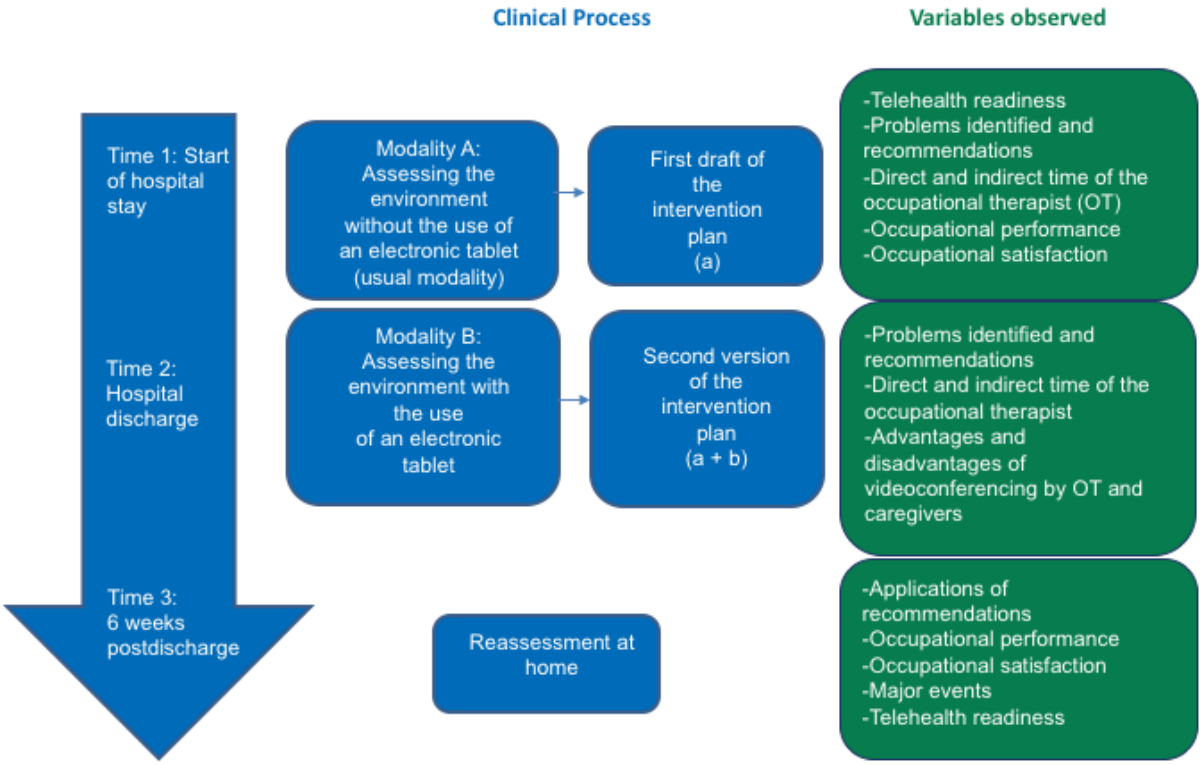
Given the need to improve knowledge about the patient's home environment prior to the hospital discharge and the limited evidence currently available for the use of mobile videoconferencing, it is essential to document the feasibility to use mobile videoconferencing in this context of care and to explore its effects using a patient-centered approach. This study has 2 objectives: (1) to document the clinical feasibility of using an electronic tablet to assess the patient's home environment by videoconference and (2) to explore the added value of using mobile videoconferencing, compared to the standard procedure.

Methods

Design

A feasibility and comparative study using a mixed-methods (convergent) design is currently undergoing. Qualitative and quantitative data are collected at the same time. Then, these data are merge in the analysis and interpretation of the results [18].The occupational therapist assesses the patient's home environment from an acute care setting prior to being discharged (*a*) first by conducting an interview (*standard procedure*) and (*b*) then by using mobile videoconferencing, with the aim to compare *a* versus *a+b*. Figure 1 shows, from left to right, the 3 measurement times (with a downward pointing arrow), the clinical process (in the middle), and the study variables (in green). These should be assessed with occupational therapists, their patients, and their relatives.

Figure 1. Mapping of the research design. The 3 measurement times are shown in the downward pointing arrow, theclinical process is shown in the middle, and the study variables are shown in green.



Technology

Following a positive experience with another clinical project conducted in the same institution, an electronic tablet and Skype software for businesses was selected for this study.

Sampling

The target sample is 44 participants, including 8 occupational therapists, and 18 patient-relative dyads. As a feasibility study involving an exploratory approach, this number of participants was deemed appropriate [19]. Recruitment takes place in 2 hospitals located in Quebec, Canada among adult patients presenting a loss of functional autonomy mainly due to physical disabilities (orthopedic, neurology). Eligibility criteria are verified for potential participants (patients or relatives) who have agreed to be contacted by a member of the research team.

The inclusion criteria are as follows: (1) for the patient to be hospitalized at the time of recruitment, to have a relative available, and to plan a return home (or residence for seniors); (2) for the family relative to be able to express oneself (in French or English) and move without technical assistance; (3) for the occupational therapist to have at least 1 year of clinical experience. Exclusion criteria are (1) for the patient to have regular follow-up at home by a community-based occupational therapist before the hospitalization and be unable to express themselves and (2) for the relative to be presenting sensory impairments (hearing) likely to interfere with the comprehension of verbal instructions (clinical judgment). Efforts are made to obtain different profiles of participants (age, gender, diagnosis). All participants must be able to consent to the research.

Ethics Approval

The ethical aspects of this study were approved by the Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux of Estrie—CHUS (#MP-31-2017-1485) and the Research Ethics Committee of the Quebec University Hospital—Université Laval (#2017-3047).

Participant Information and Informed Consent

With the authorization of the coordinators of services, the research project is presented to the occupational therapists of the different units targeted by the project by one of the researchers. Occupational therapists interested in participating must sign a consent form previously approved by the 2 ethics committees. Afterwards, when they meet a patient who meets the inclusion criteria and the assessment of the home is relevant, they briefly present the project to the patient and their caregiver and request authorization for a research assistant to contact them. For patients and caregivers who have accepted, the research assistant makes contact with them by phone or in person and presents the research project in detail, insisting that a refusal does not prevent them from having a quality occupational therapy service. For each patient and caregiver who has agreed to participate in the project, a consent form is signed.

Quantitative Outcomes

Four tools were used to document the quantitative variables:

1. The Evaluation of the Receptivity to Telehealth [20] allows for the evaluation of occupational therapists' receptivity to the utilization of mobile videoconferencing. This is a French

version of a questionnaire validated by clinicians, aiming to assess their receptivity to the introduction of telehealth services. The variables evaluated are the receptivity of the clinician (15/85), the clinician's commitment or involvement or engagement (35/85), and the receptivity of infrastructures from the clinician's perspective (35/85). Interpretation of the instrument is as follows: >80 indicates that the practitioners are well positioned to use telehealth; 60-80 indicates that certain factors or items may negatively affect the use of telehealth; and <60 indicates that there are obstacles to the successful use of telehealth by practitioners.

2. A Grid documenting the process of home environment assessment, completed by the occupational therapist, serves to note the time devoted to the evaluation of the environment at the time of hospital discharge (the number of minutes for discussions, arranging an appointment with the relative, and explanations prior to the evaluation) a) with and b) without the use of mobile videoconferencing (see Multimedia Appendix 1) [18].
3. The *Canadian Measure of Occupational Performance* (COPM) [21,22] allows for the measurement of performance and client satisfaction at Times 2 and 3. The COPM is a recognized standardized questionnaire comprising of a semistructured interview format and offering an excellent reliability test-retest [22] with the targeted clientele. A research version is used [23]. This version can be administered over a short period of time (10 minutes), with precise questions for the evaluator and some elements in red that must be filled in by the participant. This will allow for a determination of whether performance and satisfaction have improved between the 2 evaluation periods. A 2-point change is considered a clinically relevant improvement or deterioration [24].
4. Finally, the *Social Readjustment Rating Questionnaire* [25] is used to identify major events (confounding variables) occurring between the 2 points in time or measurement periods. The instrument lists 43 possible events, such as another hospitalization or the reception of home support services different from those recommended during the hospital stay.

Qualitative Outcomes

Three instruments are used to document the qualitative variables:

1. Grid documenting the characteristics of the intervention plan, completed by the occupational therapist, allows for documentation of the situation, with the help of items to be checked off and short answer questions, problems identified in the client's home (eg, architectural obstacles), and the resulting recommendations (technical aids or adaptation, the teaching of energy-saving techniques or prevention of falls, reference to home or community support services, etc) a) with and b) without the use of mobile videoconferencing (see Multimedia Appendix 2).
2. A Grid to follow up on recommendations serves to document their applicability immediately after discharge from the hospital (completed by the occupational therapist), as well as 6 weeks later (completed by a research assistant; see Multimedia Appendix 3). For example, following the occupational therapist's recommendation to use a 19-inch wheeled commode chair over the toilet, it is specified that the patient procured this equipment and continues to use it. The grid was pretested with an occupational therapist not involved in the project before the study begins.
3. A *semistructured individual interview* was conducted to document the perceptions of the occupational therapist and the relative concerning the advantages and disadvantages related to the utilization of mobile videoconferencing. The semistructured interview follows the rules of qualitative research [26], and the interview guide was pretested [27]. The thematic variables documented are previous and current experience with the use of mobile videoconferencing, the obstacles and problems encountered with the use of mobile videoconferencing during the study, and the perceived advantages of using this method. The interview will be audio recorded.

The clinical and sociodemographic profile of patients (gender, age, diagnosis, comorbidities, admission date, and discharge date), caregivers (gender, age, relationship to the patient, and familiarity with the technology: weak, moderate, or substantial) and occupational therapists (gender, years of experience in the profession, and number of years in the program or department) is also collected.

The Sequence of Research Stages

- Time 1 (Ti, interview): The researcher meets the previously recruited patient-relative dyad to confirm their participation and sign the consent form. Each occupational therapist involved in the project completes the *Telehealth Readiness Assessment* prior to the beginning of the study and then convene with the relative of a moment to perform videoconferencing prior to discharge. The occupational therapist then collects data on the clinical and sociodemographic profile of the participants and conducts the semistructured interview (as per the standard procedure) to assess the client's home environment. The occupational therapist gathers information about the problems identified, the recommendations made, and the time required (direct-indirect) to carry out the interview (*Intervention plan*). The research assistant administers the COPM to the patient prior to discharge.
- Time 2 (T2, mobile videoconferencing): The occupational therapist uses mobile videoconferencing to remotely assess the patients' home environment with the help of the relative. The latter is asked to move around with the device (electronic tablet or smartphone) in the various rooms of the home according to occupational therapist's indications. The relative was previously trained by the occupational therapist to become more familiar with the use of mobile videoconferencing. Using the notes recorded at the time of the previous assessment (interview), the occupational therapist must complete the home assessment with mobile videoconferencing within 48 hours in order to review the problems identified and modify the recommendations made upon discharge. Recommendations based on this last revised intervention plan are those transmitted to the patient. The problems identified, the recommendations made, and the time (direct-indirect) required by the occupational therapist to carry out the mobile videoconferencing are documented.

Finally, the researcher assistant conducts an interview with the occupational therapist and a second with the family relative to document their perception of the mobile videoconferencing (Individual Interview Guide).

- Time 3 (T3, 6 weeks postdischarge): The research assistant goes to the home to document (1) the perception of the applicability of the recommendations and whether they are applied or currently used (15-minute follow-up chart and 15-minute interview with the patient) and (2) performance and satisfaction (COPM) and major events since hospital discharge (Social Readjustment Rating Questionnaire). Upon completion of the study, the occupational therapist completes again the Telehealth Readiness Assessment.

Data Analysis

Descriptive analyses are performed to report the clinical and sociodemographic profile, the direct or indirect time, the nature or number of unforeseen events, the receptivity, and the occupational performance and satisfaction scores (means, frequencies, SDs). Wilcoxon tests are used to compare the receptivity scores collected from occupational therapists at the beginning (T1, before the first client) and at the end of the study (T3, after the last client). This will allow us to explore the hypothesis that an improvement in receptivity supports the feasibility of the project. The same test is used to compare COPM scores (T1 vs T3) to explore the hypothesis of postdischarge changes in patient performance and satisfaction.

A qualitative analysis using analytical questioning [28] is currently being carried out based on the verbatim of interviews. The purpose is to identify the variations in themes related to the subquestions emerging from 3 sources: the interview guide, the intervention plan (recommendations made at discharge), and the follow-up grid (recommendations applied postdischarge). N'Vivo software is used to support this analysis. The analysis highlights how respondents' perceptions differ from one to another and how the problems identified and the recommendations made based on the interview (*a*) are different from those made with the combination with mobile videoconferencing (*a+b*). This helps to document the link between the recommendations made, the application of the recommendations, and the improvement of the occupational performance or satisfaction, taking into account unforeseen events. Crossing qualitative and quantitative data from a matrix created by the N'Vivo software will be performed to improve the understanding and interpretation of the data [29].

Participant Confidentiality and Security

All data concerning the participants (occupational therapist, patient, and caregiver) is considered confidential. The documents are coded by patient by the research assistants who meet the triad. The recordings of the interviews are transcribed by a research assistant and denominated. Apart from the research assistants conducting the data collection, individuals will not be recognized through the results. The raw data (grids, questionnaires, records) are stored on a secure server at the Integrated University Health and Social Services Center of the Capitale-Nationale and in a locked file in a secure research center. The data are kept for 5 years. Mobile videoconference is not recorded. Apart from the occupational therapist who performed the home assessment, no one can see the patient's home. The Skype software for businesses was chosen because it complies with the safety level regulations of the Quebec Health and Social Services Network. In addition, the devices used (electronic tablet) are only used for this project. Some occupational therapists use their office computer at the hospital where they work to conduct the home visit. These computers are also secure.

Results

The project was funded in the spring of 2016 and authorized by the ethics committee in February 2017. Enrollment started in April 2017. Five triads (4 occupational therapists, 5 clients, and 5 caregivers) have been recruited until now. The experiment is expected to be completed by April 2019 and analysis of the results by June 2019.

Discussion

The current protocol describes a mixed-methods feasibility and comparative study to document the clinical feasibility of using an electronic tablet to assess the patient's home environment by mobile videoconferencing and to explore the added value of using mobile videoconferencing compared to the standard procedure (interview). This study uses 4 ways to document the quantitative variables and 3 ways to document the qualitative variables. Crossing qualitative and quantitative data from a matrix will be performed to improve the understanding and interpretation of the data.

Mobile videoconferencing may be a familiar and easy solution for visualizing environmental barriers in the home by caregivers and clinicians, thus providing a promising and inexpensive option to promote a safe return home upon hospital discharge, but clinical feasibility and obstacles to the use of mobile videoconferencing must be understood.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Grid documenting the process of home environment assessment.

[PDF File (Adobe PDF File), 53KB - resprot_v8i1e11674_app1.pdf]

Multimedia Appendix 2

Grid documenting the Characteristics of the Intervention Plan.

[PDF File (Adobe PDF File), 53KB - resprot_v8i1e11674_app2.pdf]

Multimedia Appendix 3

Grid to follow up on recommendations.

[PDF File (Adobe PDF File), 58KB - resprot_v8i1e11674_app3.pdf]

References

1. Harris S, James E, Snow P. Predischarge occupational therapy home assessment visits: towards an evidence base. Aust Occup Ther J 2008 Jun;55(2):85-95. [doi: 10.1111/j.1440-1630.2007.00684.x] [Medline: 20887443]
2. Mountain G, Pighills A. Pre-discharge home visits with older people: time to review practice. Health Soc Care Community 2003 Mar;11(2):146-154. [Medline: 14629217]
3. Lannin NA, Clemson L, McCluskey A, Lin CC, Cameron ID, Barras S. Feasibility and results of a randomised pilot-study of pre-discharge occupational therapy home visits. BMC Health Serv Res 2007 Mar 14;7:42 [FREE Full text] [doi: 10.1186/1472-6963-7-42] [Medline: 17355644]
4. Johnston K, Barras S, Grimmer-Somers K. Relationship between pre-discharge occupational therapy home assessment and prevalence of post-discharge falls. J Eval Clin Pract 2010 Dec;16(6):1333-1339. [doi: 10.1111/j.1365-2753.2009.01339.x] [Medline: 20738473]
5. Agrell H, Dahlberg S, Jerant AF. Patients' perceptions regarding home telecare. Telemed J E Health 2000;6(4):409-415. [doi: 10.1089/15305620050503889] [Medline: 11242549]
6. Duffy JR, Werven GW, Aronson AE. Telemedicine and the diagnosis of speech and language disorders. Mayo Clin Proc 1997 Dec;72(12):1116-1122. [doi: 10.1016/S0025-6196(11)63673-2] [Medline: 9413290]
7. Hill AJ, Theodoros D, Russell T, Ward E. Using telerehabilitation to assess apraxia of speech in adults. Int J Lang Commun Disord 2009;44(5):731-747. [doi: 10.1080/13682820802350537] [Medline: 18821157]
8. Theodoros D, Russell TG, Hill A, Cahill L, Clark K. Assessment of motor speech disorders online: a pilot study. J Telemed Telecare 2003;9 Suppl 2:S66-S68. [doi: 10.1258/135763303322596318] [Medline: 14728766]
9. Tousignant M, Boissy P, Moffet H, Corriveau H, Cabana F, Marquis F, et al. Patients' satisfaction of healthcare services and perception with in-home telerehabilitation and physiotherapists' satisfaction toward technology for post-knee arthroplasty: an embedded study in a randomized trial. Telemed J E Health 2011 Jun;17(5):376-382. [doi: 10.1089/tmj.2010.0198] [Medline: 21492030]
10. Greenup EP, McCusker M, Potts BA, Bryett A. The Efficacy of Telemedicine-Supported Discharge Within an In Home Model of Care. Telemed J E Health 2017 Dec;23(9):763-765. [doi: 10.1089/tmj.2016.0216] [Medline: 28328390]
11. Hoenig H, Sanford JA, Butterfield T, Griffiths PC, Richardson P, Hargraves K. Development of a teletechnology protocol for in-home rehabilitation. J Rehabil Res Dev 2006;43(2):287-298 [FREE Full text] [Medline: 16847794]
12. Hoffmann T, Russell T. Pre-admission orthopaedic occupational therapy home visits conducted using the Internet. J Telemed Telecare 2008;14(2):83-87. [doi: 10.1258/jtt.2007.070808] [Medline: 18348754]
13. Nix J, Comans T. Home Quick - Occupational Therapy Home Visits Using mHealth, to Facilitate Discharge from Acute Admission Back to the Community. Int J Telerehabil 2017;9(1):47-54 [FREE Full text] [doi: 10.5195/ijt.2017.6218] [Medline: 28814994]
14. Sanford JA, Jones M, Daviou P, Grogg K, Butterfield T. Using telerehabilitation to identify home modification needs. Assist Technol 2004;16(1):43-53. [doi: 10.1080/10400435.2004.10132073] [Medline: 15357147]
15. Sanford JA, Butterfield T. Using remote assessment to provide home modification services to underserved elders. Gerontologist 2005 Jun;45(3):389-398. [Medline: 15933279]
16. Sanford J, Hoenig H, Griffiths P, Butterfield T, Richardson P, Hargraves K. A Comparison of Televideo and Traditional In-Home Rehabilitation in Mobility Impaired Older Adults. Physical & Occupational Therapy In Geriatrics 2009 Jul 28;25(3):1-18. [doi: 10.1080/J148v25n03_01]
17. Jennett P, Yeo M, Pauls M, Graham J. Organizational readiness for telemedicine: implications for success and failure. J Telemed Telecare 2003;9 Suppl 2:S27-S30. [doi: 10.1258/135763303322596183] [Medline: 14728753]
18. Fortin MF, Gagnon J. Fondements et étapes du processus de recherche : méthodes quantitatives et qualitatives. 3e édition ed. Montréal: Chenelière éducation; 2015:1-518.

19. Nicholson J, Wright SM, Carlisle AM. Pre-post, mixed-methods feasibility study of the WorkingWell mobile support tool for individuals with serious mental illness in the USA: a pilot study protocol. BMJ Open 2018 Dec 06;8(2):e019936 [FREE Full text] [doi: 10.1136/bmjopen-2017-019936] [Medline: 29437756]
20. Légaré E, Vincent C, Lehoux P, Anderson D, Kairy D, Gagnon M, et al. Developing and validating the French-Canadian version of the practitioner and organizational telehealth readiness assessment tools. J Telemed Telecare 2010;16(3):140-146. [doi: 10.1258/jtt.2009.090514] [Medline: 20386034]
21. Chan C, Lee T. Validity of the Canadian occupational performance measure. Occup Ther Int 2006 Aug;4(3):231-249. [doi: 10.1002/oti.58]
22. Cup EHC, Scholte op Reimer WJM, Thijssen MCE, van Kuyk-Minis MAH. Reliability and validity of the Canadian Occupational Performance Measure in stroke patients. Clin Rehabil 2003 Jul;17(4):402-409. [doi: 10.1191/0269215503cr635oa] [Medline: 12785249]
23. Vincent C, Gagnon DH, Routhier F, Dumont F, Poissant L, Corriveau H, et al. Service Dogs for People with Spinal Cord Injury: Outcomes Regarding Functional Mobility and Important Occupations. Stud Health Technol Inform 2015;217:847-851. [Medline: 26294573]
24. Carswell A, McColl MA, Baptiste S, Law M, Polatajko H, Pollock N. The Canadian Occupational Performance Measure: a research and clinical literature review. Can J Occup Ther 2004 Dec;71(4):210-222. [doi: 10.1177/000841740407100406] [Medline: 15586853]
25. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. J Psychosom Res 1967 Aug;11(2):213-218. [Medline: 6059863]
26. Fontana A, Frey JH. The interview: From structured questions to negotiated text. In: Denzin KN, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks, CA: Sage Publications; 2000:645-672.
27. Morgan D. Why Things (Sometimes) Go Wrong in Focus Groups. Qual Health Res 1995 Nov 01;5(4):516-523. [doi: 10.1177/104973239500500411]
28. Paillé P, Mucchielli A. L'analyse qualitative en sciences humaines et sociales. 3e éd ed. Paris: A. Colin; 2012:1-424.
29. Creswell J. A concise introduction to mixed methods research. Los Angeles: SAGE; 2015:1-132.

Abbreviations

COPM: Canadian Measure of Occupational Performance

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Protocol

Web-Based Stress Management Program for University Students in Indonesia: Systematic Cultural Adaptation and Protocol for a Feasibility Study

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Abstract

Background: The number of university students experiencing stress is increasing, which often leads to adverse effects such as poor grades, academic probation, and emotional problems. Unfortunately, most of these problems remain untreated because of limited professional resources and fear of stigma. Several Web-based stress management interventions are now available for student populations, but these treatments are not yet available in Indonesia. To make treatment for stress more acceptable in Indonesia, a cultural adaptation process is needed, and part of the process is assessing the feasibility of the adapted intervention.

Objective: This paper describes the first two stages of a cultural adaptation process and the protocol of a feasibility study that will assess the acceptability of a culturally adapted stress management intervention for university students in Indonesia.

Methods: Focus group discussions with Indonesian university students were held, and input from Indonesian psychologists was gathered for developing the adapted intervention. A single-group feasibility study with a pre-post design will be conducted. We will recruit at minimum 50 university students who have an elevated level of stress (Depression, Anxiety, and Stress Scales–42 stress subscale score ≥15), identify themselves as being of Indonesian culture (eg, able to speak Bahasa Indonesia fluently), and are studying at a university in Indonesia. The primary endpoints of this study will be rates of participant satisfaction, system usability, dropout rates, and level of adherence. We will also use qualitative data to assess the adapted intervention more thoroughly. Secondary study endpoints will be quality of life, stress, anxiety, and depression levels. Feasibility parameters (eg, participant satisfaction, system usability, and level of adherence) will be summarized with descriptive statistics. Two-tailed paired within-group t tests will be used to analyze stress, anxiety, depression, and quality of life.

Results: The enrollment of pilot study is currently ongoing. First results are expected to be ready for analysis in the second half of 2019. The project was funded as part of a PhD trajectory in 2015 by the Indonesian Endowment Fund for Education.

Conclusions: This is one of the first studies to assess the feasibility of a culturally adapted Web-based stress management intervention for university students in Indonesia. Strengths and limitations of the study are discussed.

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KEYWORDS

internet intervention; stress management; cultural adaptation; feasibility study; low and middle income countries (LMICs); university student; Indonesia

Introduction

Stress is a common phenomenon experienced by many people, including university students. To a certain extent, stress is desirable for human thriving to prevent understimulation [1]. However, ongoing high levels of stress may lead to psychological distress, anxiety, depression, physical illness, substance abuse, and impaired performance at school or work [1,2]. Globally, studies indicate an increasing number of university students experience stress [3-10]. These students are challenged to cope with academic and social demands encountered during their studies and career preparation after university graduation [3,5,11]. Stress experienced by university students can lead to poor grades and academic probation, which in turn may lead to depression, poorer emotional and behavioral skills, social isolation, lower academic performance, and study dropout [12]. Students' ability to successfully deal with stress during their academic trajectory is an important factor for their academic success and well-being.

A meta-analysis showed that stress management based on cognitive, behavioral, and mindfulness interventions can significantly reduce symptoms of stress and anxiety [13]. Despite existing stress management interventions and the increasing number of university students experiencing general mental health problems [12] including high levels of stress [14], most students do not get help for various reasons [12,14], including limited availability of skilled professionals within universities who can provide counseling for stress management [12,15-17] and fear of the stigma of mental illness if they seek help [12]. Thus, there is a gap between the need for help and the availability of help for university students who are experiencing stress during their studies.

Web-based interventions might encourage university students to seek help for stress-related issues. Compared with traditionally delivered stress-related support, Web-based interventions have the advantages of being more accessible and cost effective and less stigmatizing than traditional face-to-face interventions. Moreover, studies report that most university students are using the internet to seek information and help for emotional and mental health problems [18,19]. Many studies have assessed the clinical effectiveness of Web-based interventions among student populations for a wide range of conditions including stress [20,21], depression and anxiety [21], alcohol misuse [22-24], smoking cessation [25], and obesity [26] with positive results. Furthermore, a meta-analysis showed the potential effectiveness of a Web-based intervention for reducing stress [27]. These studies have mainly been conducted in high-income European countries, the United States, and Australia. By contrast, little is known about the effectiveness of Web-based interventions for stress reduction in low- and middle-income countries such as Indonesia.

A national survey conducted by the Ministry of Health of the Republic of Indonesia estimated the national prevalence rate of psychological distress in Indonesia to be 6% in 2013 [28]. Distress was indicated using the Self-Reporting Questionnaire (SRQ), which consists of 20 questions reflecting symptoms of psychological distress including several items that measure stress (eg, Are you easily tired? Is your daily work suffering? Do you have trouble thinking clearly? [28]). This study included university students but did not report the exact prevalence rates for this population. Although data on national prevalence rates of stress among university students in Indonesia are scarce and related to psychological distress, some local studies among nursing and medical students revealed that most of the students experience stress that has negative consequences for their academic performance and health [29-31]. It is reported that the majority of nursing students were experiencing levels of stress that were moderate (43.4%), mild (30.8%), severe (11.5%), or very severe (1.9%) [30]. Among medical students, a high prevalence was found as well (71%) with students experiencing moderate (54.1%), mild (34.7%), and severe (11.2%) levels of stress [31]. Student willingness to seek counseling inside or outside the university was generally low [32]. Reluctance to disclose problems to a counselor, confidentiality issues, feeling embarrassed if seen going to a counselor, difficulty in finding a counselor or reaching counseling service locations were some of the factors that discouraged Indonesian university students from seeking help [32].

Web-based interventions might increase the help-seeking behavior among Indonesian students due to their easy access and high anonymity level and their 24/7 availability, thereby helping students overcome the perceived stigma of being mentally ill. In Indonesia, this stigma applies to everyone who is seeing a mental health care provider for help even though stress is not a mental illness. Providing Web-based intervention for stress among university students in Indonesia is increasingly feasible because all university students have access to the internet. Internet penetration has improved rapidly in Indonesia and was 54.7% in 2017, with young people the predominant internet users [33]. The field of Web-based interventions is relatively new in Indonesia, and to the best of our knowledge, Web-based stress management for a university student population in Indonesia is not yet available nor are there studies on its effectiveness in terms of stress reduction.

We therefore decided to develop such an intervention for Indonesian university students and evaluate its acceptability and feasibility as a starting point for a future randomized controlled trial (RCT). In order to avoid "reinventing the wheel," we have chosen an existing evidence-based work-stress–related intervention as a starting point. GET.ON Stress is an evidence-based online stress management intervention for adults appears applicable to a wide range of settings [34,35]. The GET.ON Stress intervention was developed for German employees and is based on the Lazarus transactional model [36]. In this model, coping with stress consists of problem-focused and emotion-focused strategies, which can be considered to be a general framework applicable to many areas of life [37] including the student context [38].

As we wanted to apply this intervention in a context that is different from the target group and culture where the intervention was developed, we decided to culturally adapt it in order to increase the potential acceptability, user satisfaction, and user engagement among our intended target group (ie, Indonesian university students) [39-43]. A Web-based stress

management intervention is a novelty in Indonesia and cultural adaptation was therefore recommended [43]. The cultural adaptation process may also increase the probability that the adapted intervention would be more clinically effective than the nonadapted version [44,45]. The evidence addressing this issue is still mixed, however, because in most comparative studies, a culturally adapted intervention is compared with a control condition and not with unchanged versions of the original intervention [43,46].

Details on cultural adaptation methodologies in most studies are not well reported, and this includes the area of Web-based interventions [45]. A meta-analysis on cultural adaptation of Web-based interventions for common mental disorders, including stress, found a wide range in the scope of cultural adaptation across the studies, with language translation and use of metaphors the most frequently recurring applied elements of adaptation [45].

We considered various cultural adaptation methods including the intervention mapping method [39], formative method for adapting psychotherapy [47], and ecological validity model or Bernal Framework [48]. These models and frameworks proposed different methods for carrying out cultural adaptation, although some steps are similar. However, Barrera et al [42] proposed an integrated cultural adaptation method as a consensus derived from the cultural adaptation methods offered in the field. Based on this reasoning, we use as a guideline Barrera's integrative cultural adaptation model, which consists of five stages: information gathering, preliminary adaptation design, feasibility study, adaptation refinement, and an RCT [42].

In this paper we describe the first two stages, information gathering and preliminary adaptation, and present the protocol of the feasibility study. The remaining stages, including an RCT, will be published in due course.

Methods

Stages of the Cultural Adaptation Process

Stage 1. Team Setup, Translation, and Information Gathering

A local research team in Indonesia was set up to provide technical support for the research project in Indonesia. The original German version of the GET.ON Stress intervention was translated into English by the intervention's authors and subsequently translated into Bahasa Indonesia by an independent professional translator who is fluent in both English and Bahasa Indonesia. A process of back translation will be incorporated in a later phase of the project (adaptation refinement, stage 4).

The main aim of stage 1 was to determine which components of the original intervention needed to be modified [42] and explore culturally sensitive aspects related to stress [48].

We conducted 5 focus group discussions (FGDs) aimed at exploring end-user opinions concerning the general impression, look and feel, content, wording, and interface of the GET.ON Stress intervention. We also explored signs of stress the students experienced, idioms related to stress, and how they perceived stress in general. The FGDs comprised 25 Indonesian master's and PhD students who were studying in the Netherlands, divided into 5 small groups. We recruited these students through announcements made in the Indonesian Students' Association social media link. The FGDs were held in October 2016 at the VU University in Amsterdam. Each group session lasted for 90 minutes and was led by the principal investigator with help of an assistant. The FGDs yielded the following results: the intervention should be shorter, not contain too much text, use more everyday language that is not too formal, and be more interactive. The signs of stress students mentioned could be categorized into psychological and biological symptoms such as easily irritated, feeling low, headache, and loss of appetite.

A literature search was conducted to find a term that represents stress in Indonesian culture. " *Banyak pikiran/kepikiran* " in Bahasa Indonesia ("thinking too much") was found as an idiom for expressing stress with a negative effect [49]. This was confirmed by the focus group participants. Most participants said that the terms *stres* and *banyak pikiran* are common terms used to define stress among Indonesians. Participants also saw stress as being a less stigmatizing term than depression.

Four bilingual Indonesian psychologists who speak Bahasa Indonesia and English reviewed the first version of the adaptation to identify any potentially problematic features and translation mistakes [42]. Both the English version and the Bahasa Indonesia version of the intervention were reviewed. These psychologists provided information on what they thought was needed to change the intervention in terms of content, structure, and instructions in order for it to be more suitable for Indonesian students. They were also asked whether the therapeutic elements of the original version (ie, problem solving and emotion regulation) would be feasible for the target group [50]. This resulted in several suggestions for change including adaptations of pictures, case examples, metaphors, and examples of activities given in exercises; there was no need expressed for changing the core therapeutic elements. A detailed summary of this stage can be found in Multimedia Appendix 1.

Stage 2. Preliminary Adaptation Design

Based on input gathered in stage 1, we modified the original GET.ON Stress intervention, balancing fidelity to the original intervention with the necessary modification of the intervention to the Indonesian cultural context [51-54]. In doing so, we kept the core elements—theory, internal logic processes, and main content—of the GET.ON Stress program [39,51]. However, due to technological, budgetary, and time constraints, the following suggestions for change from the focus group participants and review psychologists could not be effectuated: share function to social media, tangible rewards for participants, more animation, live session with eCoach, offline accessibility of the intervention, speech-to-text feature, use of a mobile app, and option for participants to choose which session they want to start with.

Many adaptations were made. We shortened the intervention by compressing problem-solving modules 2 and 3 in GET.ON Stress into one module in the adapted intervention. We deleted the imaginary traveling element and the souvenir element, designed to motivate participants, after FGD results indicated this might not be suitable for our target population. We made

some changes related to pictures, case examples, metaphors, and examples of activities given in exercises to be more suitable to the Indonesian context. We also tried to use more everyday language in each module. Due to the limitations of internet connections in Indonesia, we omitted videos and included slide shows instead. Detailed examples of these changes can be found in Multimedia Appendix 2.

We named the adapted intervention Rileks, which has a meaning similar to *relax* in English and is an abbreviation of " *intervensi melalui web untuk stres* " (Web-based intervention for stress). Rileks consists of 6 weekly sessions: psychoeducation, problem solving, emotional regulation (muscle and breathing relaxation, acceptance and tolerance of emotions, and effective self-support), and future planning. The final module is an optional booster session that can be accessed 4 weeks after completing the intervention. Screenshots from Rileks can be found in Figure 1.

eCoach support, asynchronous email communication, is retained in Rileks. During the intervention, each participant will receive feedback on the exercises within 2 days of completing a session. Feedback will be given by eCoaches, Indonesian psychologists who have been trained by the principal investigator. For this training, the standardized GET.ON Stress feedback guide will be used (written communication, E Heber, PhD, 2013). Communication between participant and eCoach will take place on a secure Web-based platform to which both participant and eCoach will have access based on their email addresses and passwords. In addition, participants will receive an email reminder if they have not completed a session within 7 days.

Stage 3. Protocol of the Feasibility Study

We will conduct a feasibility study aiming to evaluate the acceptability and feasibility of Rileks among university students in Indonesia using a pretest and posttest design. A secondary aim is to evaluate the success of the study flow (eg, recruitment methods and data collection procedure) in order to set up the RCT in stage 5. If results indicate that Rileks is not yet acceptable and feasible for Indonesian university students, we will complete another information gathering process and adaptation refinement before we proceed with an RCT.

Study Design

This feasibility study uses a single-group with a pretest (t0) and posttest (t1) design with t1 taking place 10 weeks after t0.

Sample Size

Due to the aim of our feasibility study, a formal calculation of sample size may not be suitable [55]. Thus, we use convenience sampling in determining sample size. In this study, we intend to include at least 50 participants with a saturation of 75 participants. We believe this number will enable us to obtain sufficiently reliable estimates of our main study parameters.

Inclusion Criteria

The participants should (1) be aged 19 years or older, (2) be experiencing mild to severe stress, defined as a score of 15 or higher on the 42-item Depression, Anxiety, and Stress Scales (DASS-42), (3) identify themselves as belonging to the Indonesian culture, defined as having the ability to speak Bahasa Indonesia fluently and having grown up with Indonesian customs and lifestyle, and (4) study at a university in Indonesia.

Procedure

YARSI University, a private university in Jakarta, has agreed to collaborate with this study by allowing us to recruit students for study participation. We will recruit participants by placing standing banners, presenting the project to students, and distributing flyers through student associations in each faculty. In addition to these activities at YARSI, we will also disseminate information via social media such as Facebook and Instagram. Interested students can read detailed information about the study on a dedicated website, where they can also sign up by entering a valid email address. Subsequently, applicants will receive a link to the screening questionnaire. Those who meet the inclusion criteria will be sent a detailed information letter by email about the study and an electronic informed consent form. After the applicants return the electronic informed consent, participants will receive a link to the online baseline questionnaires (t0). All included participants will receive access to the intervention. At the end of each module, we will ask for the participants' general feedback on the module. Posttreatment assessments (t1) will be scheduled 10 weeks after baseline (t0). In addition, we will invite 10 participants with differing levels of satisfaction for an in-depth interview to evaluate the intervention. It will be clearly indicated to the participants that participation is voluntary and they may discontinue participation at any time and without having to provide any reason for doing so.

Primary Outcomes

Participant Satisfaction

We will use the Client Satisfaction Questionnaire–8 (CSQ-8) [56,57] to assess user perspective on the value of Rileks. The CSQ-8 was translated into Bahasa Indonesia for a previous study in Indonesia [58]. The CSQ-8 is a standardized measure consisting of 8 questions with 4-point response scales (scored 1-4) for a total score range of 8 (great dissatisfaction) to 32 (great satisfaction). Our endpoint of an average score of 20 or higher corresponds to acceptable satisfaction. The CSQ-8 shows high internal consistency with a Cronbach alpha of .93. The CSQ-8 will be administered at posttreatment (t1). In order to obtain more in-depth data related to participant satisfaction, we will invite 10 participants to semistructured interviews after t1.

System Usability

We will use the Indonesian version of the System Usability Scale (SUS) [59-61] to assess the usability of the adapted intervention. The SUS comprises 10 questions, and participants will rate the overall usability of all components of the adapted intervention with 5 response options, ranging from strongly disagree to strongly agree. Total scores range from 0 to 100, with higher scores representing higher usability. A score of 70 or higher will be considered adequate as a feasibility criterion [60]. The Indonesian version is considered reliable, with a Cronbach alpha of .84 [61]. The SUS will be administered at posttreatment (t1).

Figure 1. Screenshots from Rileks.

Log Data and Adherence to Treatment

Use of the intervention will be measured by tracking the website use automatically: number of sessions completed, time spent per session, and number of log-ins.

Acceptable adherence is defined as 60% [62] or more of participants completing the core online sessions (sessions 1 through 5), where participants will learn the basic principles of problem solving and emotion regulation.

eCoach Evaluation

To gain feedback related to eCoach support, we will ask participants questions related to their experience with their eCoaches (eg, how understandable and helpful the feedback from the eCoach was).

Rates of Dropout From Study

Study dropout rates are defined as the number of participants who fail to complete the posttreatment assessment.

Secondary Outcomes

Stress, Anxiety, and Depression

To assess the severity of stress, anxiety, and depression, we will use the Indonesian version of the Depression, Anxiety, and Stress Scales (DASS-42) [63]. The DASS-42 is a self-report measure of stress, depression, and anxiety developed by Lovibond and Lovibond [64] consisting of 42 items divided into 3 subscales each containing 14 items. Each item can be answered on a 4-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). The DASS-42 has a total score range from 0 to 42 for each subscale with a higher score indicating a higher degree of severity [65]. The Indonesian version of DASS-42 shows excellent overall reliability with a Cronbach alpha of .95 and high internal consistency in the separate depression, anxiety, and stress subscales (alphas .91, .85, and .88, respectively) [63]. We will administer the Indonesian DASS-42 at t0 and t1.

Quality of Life

Quality of life will be measured by the Indonesian version of the World Health Organization abbreviated quality of life assessment (WHOQOL-BREF) [66], which consists of 26 items that measure how the respondent felt in the last 2 weeks, across the 4 domains (ie, physical health, psychological health, social relations, and environment) [66,67]. The WHOQOL-BREF is a valid assessment for use in the Indonesian population as reflected by its internal consistency of .41 to .77 in the 4 domains [68] and its reliability, with intraclass correlation coefficients of .70 to .79 in the 4 domains [66]. The WHOQOL-BREF will be administered at t0 and t1.

Demographic Variables

We will request demographic information of each participant, including as age, gender, socioeconomic status, education, marital status, ethnicity, whether they live with parents or live alone, and whether they identify themselves as belonging to the Indonesian culture.

Analysis

Feasibility Parameters

Participant satisfaction (CSQ-8), system usability (SUS), and level of adherence as feasibility parameters will be summarized with descriptive statistics. Point estimates and 95% confidence intervals will be calculated and tested against the feasibility criteria, which were previously defined. Qualitative data, especially related to cultural suitability, will be synthesized and described using thematic analysis, a method for identifying, analyzing, and reporting patterns or themes within data [69].

Other Study Parameters

The continuous measures stress, anxiety, depression, and quality of life will be analyzed using 2-tailed paired within-group *t* tests with a level of significance of alpha=.05.

Ethical Consideration

The study will be conducted in line with the appropriate privacy regulations, and all researchers will follow the Good Clinical Practice guidelines according to Indonesian regulations. The Indonesian ethics committee at YARSI University has given ethical clearance for this research to be conducted (project number: 193/KEP-UY/BIA/VIII/2017).

Results

The project was funded in 2015 by the Indonesian Endowment Fund for Education as part of the first author's PhD trajectory. Enrollment for the pilot study is currently ongoing. First results are expected to be submitted by the end of 2019.

Discussion

To our knowledge, this is the first study to develop and investigate the feasibility of a Web-based stress management intervention for university students in Indonesia. In this paper we described stages 1 and 2 of the cultural adaptation process, as well as the protocol of a feasibility study (ie, stage 3). Data on feasibility will inform further adjustments to the intervention (stage 4) and the potential to conduct an RCT (stage 5), which will provide information on the efficacy of this kind of intervention among Indonesian university students. This study will provide insight into the feasibility of offering a Web-based intervention for stress to university students in Indonesia, which can inform future implementation and dissemination of Web-based interventions in this context.

Implementation and dissemination of evidence-based Web-based mental health care might constitute one of a number of possible strategies to tackle the mental health care gap in low- and middle-income countries where there is disparity between the availability of mental health care providers and the number of individuals in need of mental health care [70-72]. Using internet interventions to deliver self-help and guided psychological interventions is likely to be one possibility for increasing access to mental health care with minimum input from professionals [72]. Rapid increase of internet penetration and the use of technological devices in low- and middle-income countries will accelerate the implementation of a Web-based intervention [73,74]. Furthermore, Web-based mental health care might help to overcome stigma, since patients, including university students, can access mental health care from any location with internet connection [75].

A strength of this study is that we apply a systematic approach to the cultural adaptation process. We involve Indonesian university students as end-user representatives and Indonesian psychologists as lead-user representatives throughout the adaptation stages as we try to integrate "top-down" and "bottom-up" approaches in the adaptation and evaluation process. In doing so, we make sure that Rileks still retains fidelity to the original intervention, while we also take input related to Indonesian cultural context into account [39,42].

The new field and context in which we are working poses challenges for this project. One of those challenges is to include all relevant stakeholders in the developmental process. Ideally, we would have included representatives from the Indonesian professional association in the area of university student mental health as well as policy makers. These stakeholders are considered important for long-term implementation and

dissemination in Indonesian mental health care. However, at this stage of the project, involving these stakeholders is not feasible due to time constraints. Another challenge is funding. The platform we use is relatively affordable by Western European standards; however, it is still too expensive if we want to implement Rileks in Indonesia. Thus, with the limited funding that we had, we were restricted in incorporating all the input gathered from stage 1 into stage 2 (preliminary adaptation design).

Despite these limitations, we hope that this study can contribute to the development of student mental health treatment in Indonesia in general. More specifically for university students in Indonesia, we hope this kind of intervention will help to overcome discouraging factors in help-seeking behavior among those who are experiencing stress during their studies and ultimately reduce the stress levels experienced.

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Authors' Contributions

DJ is the primary investigator and drafted the manuscript; WvB, EK, AvS, and HR provided guidance and supervision; JP and SSS provided input and field resources in Indonesia; and EH and DL provided resources related to the GET.ON Stress intervention. All authors were involved in finalizing the manuscript and have reviewed the manuscript and given final approval for it to be published.

Conflicts of Interest

DL and EH hold shares in the GET.ON Institute for Online Health Training, Hamburg, which aims to transfer scientific knowledge related to this research into routine mental health care in Germany. This institute is licensed to provide the German version of the intervention from the Leuphana University, Lüneburg, as part of routine preventive services covered by health insurance companies in Germany. There are no other conflicts of interest.

Multimedia Appendix 1

Stage 1. Information gathering.

[PDF File (Adobe PDF File), 100KB - resprot_v8i1e11493_app1.pdf]

Multimedia Appendix 2

Stage 2. Preliminary adaptation design.

[PNG File, 94KB - resprot_v8i1e11493_app2.png]

References

1. Alzahem AM, van der Molen HT, Alaujan AH, Schmidt HG, Zamakhshary MH. Stress amongst dental students: a systematic review. Eur J Dent Educ 2011 Feb;15(1):8-18. [doi: 10.1111/j.1600-0579.2010.00640.x] [Medline: 21226800]
2. Misra R, Castillo LG. Academic stress among college students: comparison of American and international students. Int J Stress Manag 2004;11(2):132-148. [doi: 10.1037/1072-5245.11.2.132]
3. Bayram N, Bilgel N. The prevalence and socio-demographic correlations of depression, anxiety and stress among a group of university students. Soc Psychiatry Psychiatr Epidemiol 2008 Aug;43(8):667-672. [doi: 10.1007/s00127-008-0345-x] [Medline: 18398558]
4. Wong PTP, Wong LCJ, Scott C. Beyond stress and coping: the positive psychology of transformation. In: Wong PTP, Wong LCJ, editors. Handbook of Multicultural Perspectives on Stress and Coping. International and Cultural Psychology. Boston: Springer; 2006:1-26.
5. Robotham D. Stress among higher education students: towards a research agenda. High Educ 2008 Apr 4;56(6):735-746. [doi: 10.1007/s10734-008-9137-1]
6. Stallman HM. Psychological distress in university students: A comparison with general population data. Aust Psychol 2010;45(4):249-257. [doi: 10.1080/00050067.2010.482109]
7. Beiter R, Nash R, McCrady M, Rhoades D, Linscomb M, Clarahan M, et al. The prevalence and correlates of depression, anxiety, and stress in a sample of college students. J Affect Disord 2015 Mar 01;173:90-96. [doi: 10.1016/j.jad.2014.10.054] [Medline: 25462401]
8. Iqbal S, Gupta S, Venkatarao E. Stress, anxiety and depression among medical undergraduate students and their socio-demographic correlates. Indian J Med Res 2015 Dec;141(3):354-357 [FREE Full text] [Medline: 25963497]

9. Larcombe W, Finch S, Sore R, Murray C, Kentish S, Mulder R, et al. Prevalence and socio-demographic correlates of psychological distress among students at an Australian university. Studies in Higher Education 2014 Oct 02;41(6):1074-1091. [doi: 10.1080/03075079.2014.966072]
10. Dachew B, Azale Bisetegn T, Berhe Gebremariam R. Prevalence of mental distress and associated factors among undergraduate students of University of Gondar, Northwest Ethiopia: a cross-sectional institutional based study. PLoS One 2015;10(3):e0119464 [FREE Full text] [doi: 10.1371/journal.pone.0119464] [Medline: 25794278]
11. Robotham D, Julian C. Stress and the higher education student: a critical review of the literature. J Further Higher Educ 2006 May;30(2):107-117. [doi: 10.1080/03098770600617513]
12. Storrie K, Ahern K, Tuckett A. A systematic review: students with mental health problems—a growing problem. Int J Nurs Pract 2010 Feb;16(1):1-6. [doi: 10.1111/j.1440-172X.2009.01813.x] [Medline: 20158541]
13. Regehr C, Glancy D, Pitts A. Interventions to reduce stress in university students: a review and meta-analysis. J Affect Disord 2013 May 15;148(1):1-11. [doi: 10.1016/j.jad.2012.11.026] [Medline: 23246209]
14. Hunt J, Eisenberg D. Mental health problems and help-seeking behavior among college students. J Adolesc Health 2010 Jan;46(1):3-10. [doi: 10.1016/j.jadohealth.2009.08.008] [Medline: 20123251]
15. Stanley N, Manthorpe J. Responding to students' mental health needs: impermeable systems and diverse users. J Mental Hlth 2001 Feb 1;10(1):41-52. [doi: 10.1080/09638230020023606]
16. Mowbray CT, Megivern D, Mandiberg JM, Strauss S, Stein CH, Collins K, et al. Campus mental health services: recommendations for change. Am J Orthopsychiatry 2006 Apr;76(2):226-237. [doi: 10.1037/0002-9432.76.2.226] [Medline: 16719642]
17. Drum DJ, Denmark AB. Campus suicide prevention: bridging paradigms and forging partnerships. Harv Rev Psychiatry 2012;20(4):209-221. [doi: 10.3109/10673229.2012.712841] [Medline: 22894730]
18. Burns K. At issue: community college student success variables: a review of the literature. Community College Enterprise 2010;16(2).
19. Escoffery C, Miner KR, Adame DD, Butler S, McCormick L, Mendell E. Internet use for health information among college students. J Am Coll Health 2005;53(4):183-188. [doi: 10.3200/JACH.53.4.183-188] [Medline: 15663067]
20. Chiauzzi E, Brevard J, Thurn C, Decembrele S, Lord S. MyStudentBody-Stress: an online stress management intervention for college students. J Health Commun 2008 Aug 28;13(6):555-572. [doi: 10.1080/10810730802281668] [Medline: 18726812]
21. Day V, McGrath PJ, Wojtowicz M. Internet-based guided self-help for university students with anxiety, depression and stress: a randomized controlled clinical trial. Behav Res Ther 2013 Jul;51(7):344-351. [doi: 10.1016/J.BRAT.2013.03.003] [Medline: 23639300]
22. Paschall MJ, Antin T, Ringwalt CL, Saltz RF. Evaluation of an internet-based alcohol misuse prevention course for college freshmen. Am J Prev Med 2011 Sep;41(3):300-308. [doi: 10.1016/J.AMEPRE.2011.03.021] [Medline: 21855745]
23. Kypri K, McCambridge J, Vater T, Bowe SJ, Saunders JB, Cunningham JA, et al. Web-based alcohol intervention for Māori university students: double-blind, multi-site randomized controlled trial. Addiction 2013 Feb;108(2):331-338 [FREE Full text] [doi: 10.1111/j.1360-0443.2012.04067.x] [Medline: 22925046]
24. Kypri K, Vater T, Bowe SJ, Saunders JB, Cunningham JA, Horton NJ, et al. Web-based alcohol screening and brief intervention for university students: a randomized trial. JAMA 2014 Mar 26;311(12):1218-1224 [FREE Full text] [doi: 10.1001/jama.2014.2138] [Medline: 24668103]
25. An L, Hennrikus D, Perry C, Lein E, Klatt C, Farley D, et al. Feasibility of internet health screening to recruit college students to an online smoking cessation intervention. Nicotine Tob Res 2007;9(1):11-18. [doi: 10.1080/14622200601083418] [Medline: 17365722]
26. LaChausse RG. My Student Body: effects of an internet-based prevention program to decrease obesity among college students. J Am Coll Health 2012 May;60(4):324-330. [doi: 10.1080/07448481.2011.623333] [Medline: 22559092]
27. Heber E, Ebert DD, Lehr D, Cuijpers P, Berking M, Nobis S, et al. The Benefit of Web- and Computer-Based Interventions for Stress: A Systematic Review and Meta-Analysis. J Med Internet Res 2017 Dec 17;19(2):e32 [FREE Full text] [doi: 10.2196/jmir.5774] [Medline: 28213341]
28. Badan Penelitian dan Pengembangan Kesehatan. Riset Kesehatan Dasar (RISKESDAS) 2013. Lap Nas 2013:1-384.
29. Rakhmawati I, Farida P. [Academic stress sources and its impact to nursing student stress level]. J Keperawatan 2014;2(3):72-84.
30. Purwati S. Tingkat Stres Akademik pada Mahasiswa Reguler Angkatan 2010.: Fakultas Ilmu Keperawatan Universitas Indonesia; 2012. URL: http://lib.ui.ac.id/file?file=digital/20299163-S1958-Tingkat%20stres.pdf [accessed 2019-01-13] [WebCite Cache ID 75OdAs67P]
31. Augesti G, Lisiswanti R, Saputra O, Nisa K. Differences in Stress Level Between First Year and Last Year Medical Students in Medical Faculty of Lampung. Medical Journal of Lampung University 2015 Feb;4(4):50-56 ISSN: 2337-3776.
32. Setiawan JL. Willingness to seek counselling, and factors that facilitate and inhibit the seeking of counselling in Indonesian undergraduate students. Br J Guid Couns 2006 Aug;34(3):403-419. [doi: 10.1080/03069880600769654] [Medline: 26281194]

33. Penetrasi & Perilaku Pengguna Internet Indonesia 2017.: Asosiasi Penyelenggara Jasa Internet Indonesia URL: https://web.kominfo.go.id/sites/default/files/Laporan%20Survei%20APJII_2017_v1.3.pdf [accessed 2019-01-13] [WebCite Cache ID 75OeU0MP0]
34. Heber E, Lehr D, Ebert DD, Berking M, Riper H. Web-based and mobile stress management intervention for employees: a randomized controlled trial. J Med Internet Res 2016;18(1):e21 [FREE Full text] [doi: 10.2196/jmir.5112] [Medline: 26818683]
35. Ebert DD, Heber E, Berking M, Riper H, Cuijpers P, Funk B, et al. Self-guided internet-based and mobile-based stress management for employees: results of a randomised controlled trial. Occup Environ Med 2016 Feb 16;73(5):315-323. [doi: 10.1136/oemed-2015-103269]
36. Lazarus R, Folkman S. Stress, Appraisal, and Coping. New York: Springer; 1984.
37. Heber E, Ebert DD, Lehr D, Nobis S, Berking M, Riper H. Efficacy and cost-effectiveness of a web-based and mobile stress-management intervention for employees: design of a randomized controlled trial. BMC Public Health 2013 Jul 15;13:655 [FREE Full text] [doi: 10.1186/1471-2458-13-655] [Medline: 23855376]
38. Jensen C, Forlini C, Partridge B, Hall W. Australian university students' coping strategies and use of pharmaceutical stimulants as cognitive enhancers. Front Psychol 2016;7:277 [FREE Full text] [doi: 10.3389/fpsyg.2016.00277] [Medline: 26973573]
39. Leerlooijer JN, Ruiter RAC, Reinders J, Darwisyah W, Kok G, Bartholomew LK. The World Starts With Me: using intervention mapping for the systematic adaptation and transfer of school-based sexuality education from Uganda to Indonesia. Transl Behav Med 2011 Jun;1(2):331-340 [FREE Full text] [doi: 10.1007/s13142-011-0041-3] [Medline: 21765883]
40. Bernal G, Scharrón-del-Río MR. Are empirically supported treatments valid for ethnic minorities? Toward an alternative approach for treatment research. Cultur Divers Ethnic Minor Psychol 2001 Nov;7(4):328-342. [Medline: 11759270]
41. Sue S, Chu JY. The mental health of ethnic minority groups: challenges posed by the Supplement to the Surgeon General's Report on Mental Health. Cult Med Psychiatry 2003 Dec;27(4):447-465. [Medline: 14727680]
42. Barrera M, Castro FG, Strycker LA, Toobert DJ. Cultural adaptations of behavioral health interventions: a progress report. J Consult Clin Psychol 2013 Apr;81(2):196-205 [FREE Full text] [doi: 10.1037/a0027085] [Medline: 22289132]
43. Castro F, Barrera M, Holleran Steiker L. Issues and challenges in the design of culturally adapted evidence-based interventions. Annu Rev Clin Psychol 2010;6:213-239 [FREE Full text] [doi: 10.1146/annurev-clinpsy-033109-132032] [Medline: 20192800]
44. Bernal G, Sáez-Santiago E. Culturally centered psychosocial interventions. J Community Psychol 2006 Mar;34(2):121-132. [doi: 10.1002/jcop.20096]
45. Harper SM, Heim E, Chowdhary N, Maercker A, Albanese E. Cultural adaptation of minimally guided interventions for common mental disorders: a systematic review and meta-analysis. JMIR Ment Health 2016 Sep 26;3(3):e44 [FREE Full text] [doi: 10.2196/mental.5776] [Medline: 27670598]
46. Griner D, Smith T. Culturally adapted mental health intervention: a meta-analytic review. Psychotherapy (Chic) 2006;43(4):531-548. [doi: 10.1037/0033-3204.43.4.531] [Medline: 22122142]
47. Hwang W. The Formative Method for Adapting Psychotherapy (FMAP): a community-based developmental approach to culturally adapting therapy. Prof Psychol Res Pr 2009 Aug;40(4):369-377 [FREE Full text] [doi: 10.1037/a0016240] [Medline: 20625458]
48. Bernal G, Bonilla J, Bellido C. Ecological validity and cultural sensitivity for outcome research: issues for the cultural adaptation and development of psychosocial treatments with Hispanics. J Abnorm Child Psychol 1995 Feb;23(1):67-82. [Medline: 7759675]
49. Kaiser BN, Haroz EE, Kohrt BA, Bolton PA, Bass JK, Hinton DE. Thinking too much: a systematic review of a common idiom of distress. Soc Sci Med 2015 Dec;147:170-183. [doi: 10.1016/J.SOCSCIMED.2015.10.044]
50. Borsa J, Figueiredo B, Denise D, Bandeira R. Cross-cultural adaptation and validation of psychological instrumentsome considerations. Paidéia 2012;22(53):423-432. [doi: 10.1590/1982-43272253201314]
51. Castro FG, Barrera M, Martinez CR. The cultural adaptation of prevention interventions: resolving tensions between fidelity and fit. Prev Sci 2004 Mar;5(1):41-45. [Medline: 15058911]
52. Bell CC, Bhana A, McKay MM, Petersen I. A commentary on the triadic theory of influence as a guide for adapting HIV prevention programs for new contexts and populations. Soc Work Mental Health 2008 Sep 22;5(3-4):243-267. [doi: 10.1300/J200v05n03_01]
53. Card JJ, Solomon J, Cunningham SD. How to adapt effective programs for use in new contexts. Health Promot Pract 2011 Jan;12(1):25-35. [doi: 10.1177/1524839909348592] [Medline: 19858321]
54. Kumpfer KL, Pinyuchon M, Teixeira DMA, Whiteside HO. Cultural adaptation process for international dissemination of the strengthening families program. Eval Health Prof 2008 Jun;31(2):226-239. [doi: 10.1177/0163278708315926] [Medline: 18448857]
55. Billingham SAM, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Methodol 2013;13:104 [FREE Full text] [doi: 10.1186/1471-2288-13-104] [Medline: 23961782]

56. Attkisson CC, Zwick R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. Eval Program Plann 1982;5(3):233-237. [Medline: 10259963]
57. Nguyen TD, Attkisson C, Stegner BL. Assessment of patient satisfaction: development and refinement of a Service Evaluation Questionnaire. Eval Program Plann 1983 Jan;6(3-4):299-313. [doi: 10.1016/0149-7189(83)90010-1]
58. Utoyo DB, Lubis DU, Jaya ES, Arjadi R, Hanum L, Astri K, et al. Preliminary study on the effectiveness of short group cognitive behavioral therapy (GCBT) on Indonesian older adults. PLoS One 2013;8(2):e57198 [FREE Full text] [doi: 10.1371/journal.pone.0057198] [Medline: 23437339]
59. Brooke J. SUS - A quick and dirty usability scale. In: Usability evaluation in industry. London: Taylor and Francis; 1996:189-194.
60. Bangor A, Kortum P, Miller J. An empirical evaluation of the system usability scale. Int J Hum Comput Interact 2008;24(6):574-594. [Medline: 33402155]
61. Sharfina Z, Santoso H. An Indonesian adaptation of the System Usability Scale (SUS). 2016 Presented at: Int Conf Adv Comput Sci Inf Syst ICACSIS; 2016; Malang. [doi: 10.1109/ICACSIS.2016.7872776]
62. van Ballegooijen W, Cuijpers P, van Straten A, Karyotaki E, Andersson G, Smit JH, et al. Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. PLoS One 2014 Jul;9(7):e100674 [FREE Full text] [doi: 10.1371/journal.pone.0100674] [Medline: 25029507]
63. Damanik ED. The Measurement of Reliability, Validity, Items Analysis and Normative Data of Depression Anxiety Stress Scale (DASS). URL: http://www2.psy.unsw.edu.au/Groups/Dass/Indonesian/DASS42%20Bahasa%20Indonesia%20Damanik.doc [accessed 2019-01-13] [WebCite Cache ID 75Oaq88vt]
64. 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. [Medline: 7726811]
65. Depression Anxiety Stress Scale (DASS). URL: http://www2.psy.unsw.edu.au/dass/Download%20files/Dass42.pdf [accessed 2019-01-13] [WebCite Cache ID 75Ob9l2DY]
66. Purba FD, Hunfeld JAM, Iskandarsyah A, Fitriana TS, Sadarjoen SS, Passchier J, et al. Quality of life of the Indonesian general population: test-retest reliability and population norms of the EQ-5D-5L and WHOQOL-BREF. PLoS One 2018 May;13(5):e0197098 [FREE Full text] [doi: 10.1371/journal.pone.0197098] [Medline: 29750806]
67. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 2004 Mar;13(2):299-310. [Medline: 15085902]
68. Ch Salim O, Sudharma N, Kusumaratna R, Hidayat A. Validity and reliability of World Health Organization Quality of Life–BREF to assess the quality of life in the elderly. Universa Medicina 2007;26(1):27-38. [doi: 10.18051/UnivMed.2007.v26.27-38]
69. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
70. mhGAP Intervention Guide.: World Health Organization URL: http://apps.who.int/iris/bitstream/handle/10665/44406/9789241548069_eng.pdf [accessed 2019-01-13] [WebCite Cache ID 70dlFQT9l]
71. Patel V, Boyce N, Collins PY, Saxena S, Horton R. A renewed agenda for global mental health. Lancet 2011 Oct 22;378(9801):1441-1442 [FREE Full text] [doi: 10.1016/S0140-6736(11)61385-8] [Medline: 22008422]
72. Bockting CLH, Williams AD, Carswell K, Grech AE. The potential of low-intensity and online interventions for depression in low- and middle-income countries. Glob Ment Health (Camb) 2016;3:e25 [FREE Full text] [doi: 10.1017/gmh.2016.21] [Medline: 28596893]
73. Watts SE, Andrews G. Internet access is NOT restricted globally to high income countries: so why are evidenced based prevention and treatment programs for mental disorders so rare? Asian J Psychiatr 2014 Aug;10:71-74. [doi: 10.1016/J.AJP.2014.06.007]
74. Arjadi R, Nauta MH, Scholte WF, Hollon SD, Chowdhary N, Suryani AO, et al. Guided Act and Feel Indonesia (GAF-ID)—internet-based behavioral activation intervention for depression in Indonesia: study protocol for a randomized controlled trial. Trials 2016 Dec 17;17(1):1-10 [FREE Full text] [doi: 10.1186/s13063-016-1577-9] [Medline: 27639557]
75. Rochlen AB, Zack JS, Speyer C. Online therapy: review of relevant definitions, debates, and current empirical support. J Clin Psychol 2004 Mar;60(3):269-283. [doi: 10.1002/jclp.10263] [Medline: 14981791]

Abbreviations

CSQ-8: Client Satisfaction Questionniare–8
DASS-42: Depression, Anxiety, and Stress Scales–42
FGD: focus group discussion
RCT: randomized controlled trial
SUS: System Usability Scale
WHOQOL-BREF: World Health Organization abbreviated quality of life assessment

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Protocol

Determining the Cause of Death Among Children Hospitalized With Respiratory Illness in Kenya: Protocol for Pediatric Respiratory Etiology Surveillance Study (PRESS)

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Abstract

Background: In sub-Saharan Africa, where the burden of respiratory disease–related deaths is the highest, information on the cause of death remains inadequate because of poor access to health care and limited availability of diagnostic tools. Postmortem examination can aid in the ascertainment of causes of death. This manuscript describes the study protocol for the Pediatric Respiratory Etiology Surveillance Study (PRESS).

Objective: This study protocol aims to identify causes and etiologies associated with respiratory disease–related deaths among children (age 1-59 months) with respiratory illness admitted to the Kenyatta National Hospital (KNH), the largest public hospital in Kenya, through postmortem examination coupled with innovative approaches to laboratory investigation.

Methods: We prospectively followed children hospitalized with respiratory illness until the end of clinical care or death. In case of death, parents or guardians were offered grief counseling, and postmortem examination was offered. Lung tissue specimens were collected using minimally invasive tissue sampling and conventional autopsy where other tissues were collected. Tissues were tested using histopathology, immunohistochemistry, and multipathogen molecular-based assays to identify pathogens. For each case, clinical and laboratory data were reviewed by a team of pathologists, clinicians, laboratorians, and epidemiologists to assign a cause of and etiology associated with death.

Results: We have enrolled pediatric cases of respiratory illness hospitalized at the KNH at the time of this submission; of those, 14.8% (140/945) died while in the hospital. Both analysis and interpretation of laboratory results and writing up of findings are expected in 2019-2020.

Conclusions: Postmortem studies can help identify major pathogens contributing to respiratory-associated deaths in children. This information is needed to develop evidence-based prevention and treatment policies that target important causes of pediatric respiratory mortality and assist with the prioritization of local resources. Furthermore, PRESS can provide insights into the interpretation of results using multipathogen testing platforms in resource-limited settings.

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KEYWORDS

cause of death; pneumonia; etiology; infectious disease; postmortem; mortality; respiratory illness

Introduction

Background

Pneumonia is a leading cause of death among children aged <5 years [1], and approximately 50% of this burden is borne by children in sub-Saharan Africa [2]. Nonetheless, in most resource-limited countries, the relative contribution of different pathogens leading to respiratory illness-related deaths remains largely unknown. Understanding the etiologies of respiratory illness-related deaths is key to targeting resources and informing policies for the treatment and prevention of respiratory illnesses. In resource-limited settings, information on the cause of death is determined through clinical diagnosis prior to death or, more frequently, verbal autopsy [3] because many deaths occur outside hospitals. The introduction and expansion of vaccination against major causes of childhood respiratory disease–related mortality, such as measles, *Streptococcus pneumoniae* and *Haemophilus influenzae B*, over the past decade and the availability of highly active antiretroviral treatment (HAART) [4] may have changed the relative roles of different etiologies of respiratory disease–related mortality in sub-Saharan Africa. Moreover, with improved multipathogen diagnostic techniques, studies have suggested a more substantial role of respiratory viruses in severe acute respiratory illnesses in young children [5-8].

Postmortem examination and laboratory testing of tissue specimens can aid in improving the ascertainment of causes of death [9]. However, few clinical postmortem examinations are currently performed [10], especially in sub-Saharan Africa where the respiratory disease burden is the highest [11]; this is partly attributed to a lack of resources and inadequate technical capacity to perform detailed postmortem examinations. Moreover, the poor understanding of the utility and practice of conventional autopsy allows for misinformation and stigma among patients and clinicians alike, hampering informed consent, which is required for the procedure. Families can be reluctant to consent to autopsy fearing that the bodies of their loved ones will be disfigured [12].

This study describes the methodology for the Pediatric Respiratory Etiology Surveillance Study (PRESS), which was conducted prospectively to investigate the cause of death and associated microbial etiologies among children (age 1-59 months) hospitalized for respiratory illness in Kenya. For children who died, we undertook a postmortem evaluation of gross pathology and histopathological findings and implemented multipathogen diagnostic and immunohistochemical procedures to identify pathogens potentially associated with death. Furthermore, we compared minimally invasive tissue sampling techniques (MITS) with conventional autopsy procedures to obtain lung tissue specimens.

Research Objectives

The primary research goals of PRESS are to (1) describe the leading etiologies of pediatric respiratory disease–related deaths in a tertiary care hospital in Kenya, a low-middle-income country and (2) evaluate methodologies that could establish the etiology of respiratory disease–related mortality most efficiently in this setting.

Hypothesis

Our primary hypothesis is that a high proportion of pediatric deaths are associated with viral etiology. The secondary hypothesis is that MITS can be successfully implemented in low-middle-resource countries to aid the cause-of-death diagnosis in hospital settings.

Methods

Study Setting and Overall Design

The Kenyatta National Hospital (KNH) is Kenya's national referral and teaching hospital, located in Nairobi. The hospital has 4 general pediatric medical wards with 180-bed capacity, a 6-bed pediatric intensive care unit (ICU), a 20-bed general ICU, and a 20-bed high dependency unit that serve critically ill patients of all ages. The majority of its patients are referred from health facilities within Nairobi and the surrounding counties; however, tertiary referrals come from all over the country. In addition, the hospital has a 24-hour mortuary where bodies of deceased patients are refrigerated, as well as a facility for postmortem examination (autopsy).

The study enrollment is based on the prospective identification of children who were hospitalized for respiratory illness (based on case definition) and monitored throughout their hospital stay. Those who died were enrolled in the postmortem investigation portion of the study.

A case of respiratory illness was defined as a hospitalized child aged 1-59 months, who presented with a cough or difficulty in

breathing or if an attending physician diagnosed respiratory illness. At enrollment, we collected sociodemographic and clinical data and obtained nasopharyngeal and oropharyngeal swabs from consented patients. We then followed participants until discharge (or death) and abstracted additional data from the hospital files on the results of laboratory investigations, discharge diagnoses, and outcome of hospitalization. In addition, we included children who died of respiratory illness (per parental or guardian interview or physician's assessment) at admission or soon after admission, regardless of enrollment while patients were still alive and collected as much data as available from hospital records. Trained grief counselors approached parents or guardians of deceased children and offered them counseling before seeking consent to perform postmortem examination. We performed MITS to obtain lung tissue specimens followed by the conventional autopsy to collect multiple tissue specimens. Tissues were examined through histopathology and tested using multiple laboratory techniques to identify etiologies potentially associated with respiratory disease–related death. Figure 1 summarizes these procedures and specimen collection and testing.

Procedures

Premortem Enrollment of Hospitalized Respiratory Cases

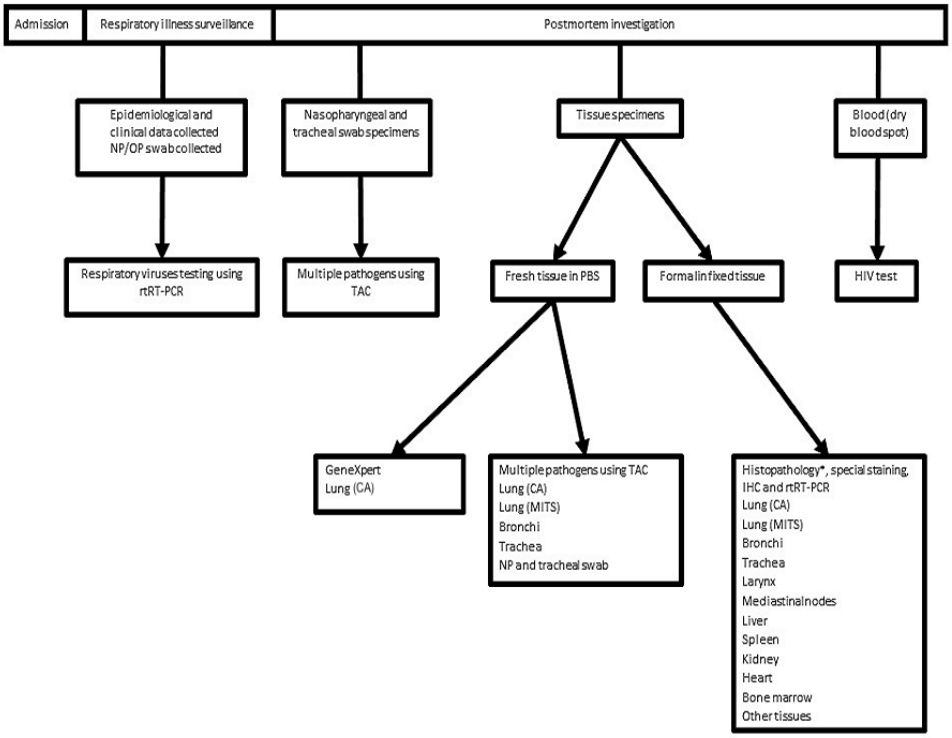
We trained surveillance officers (clinical officers and nurses) on the study protocol and standard operating procedures (SOPs). We then assigned surveillance officers to each of the 4 pediatric wards of the KNH to provide 24/7 coverage for the identification of eligible children. Furthermore, surveillance officers visited the ICU or high dependency unit to enroll critically ill children who met the study case definition (described above) but who bypassed admission to the general ward.

For each eligible child, parents or guardians were approached to provide consent for their child's enrollment in the study. Once consent was obtained, a structured enrollment questionnaire was administered to parents or guardians to collect demographics, duration of illness, care-seeking history for the current illness, symptoms and signs on admission, underlying chronic illnesses, indoor smoke exposure, and childhood vaccination status.

In addition, we abstracted from medical charts the recorded body temperature, oxygen saturation (assessed through pulse oximetry), anthropometric measurements on admission, and mother and child's HIV status, and child's antiretroviral therapy use, where available.

We followed enrolled children until discharge or death and collected additional data on the results of routine laboratory investigations conducted during hospitalization, radiological investigation reports, medications, and other treatment and discharge diagnoses (when available).

Figure 1. In-hospital surveillance and postmortem specimens and laboratory testing summary. CA: conventional autopsy; IHC: immunohistochemistry; MITS: minimally invasive tissue sampling; NP/OP: nasopharyngeal/oropharyngeal swabs; PBS: phosphate buffered saline; rtRT-PCR: real-time reverse transcription polymerase chain reaction; TAC: TaqMan array card. *The Kenyatta National Hospital/University of Nairobi did routine histopathology only. The Infectious Disease Pathology Branch laboratory did routine histopathology, special staining, IHC, and molecular tests.



Premortem Nasopharyngeal and Oropharyngeal Specimen Collection

At enrollment, we collected nasopharyngeal or oropharyngeal swabs. We used a polyester-tipped, flexible, aluminum-shafted applicator (25-801D; Puritan) to collect nasopharyngeal specimens. The swab was inserted into one of the patient's nostrils, gently pushed in parallel to the palate onto the nasopharyngeal wall from the edge of the nostril to the approximate level of the lower margin of the ear lobe. The swab was rotated 2-3 times and held in place for 3-5 seconds to absorb as much sample material as possible. The swab was removed and placed into a prelabeled cryovial containing 3 mL of viral transport media prepared at the Kenya Medical Research Institute (KEMRI) and the Centers for Disease Control and Prevention (CDC)-Kenya laboratory following the standard World Health Organization's protocol [13]. The oropharyngeal swab was collected using a nylon-flocked, plastic-shafted applicator (Copan Diagnostics). Using a tongue depressor, the oropharyngeal swab was inserted to contact the posterior OP wall and rotated against the mucosal membrane for 3-5 seconds. The oropharyngeal swabs were then placed into the same prelabeled cryovial containing nasopharyngeal swab. The cryovial was stored and shipped to the KEMRI and CDC-Kenya laboratory in Nairobi at 2°C-8°C daily where it was stored at −80°C until testing.

Death, Body Handling and Preservation, and Consenting for Postmortem Examination

In the event of a death of a child with a respiratory illness, nurses wrapped the body in a clean sheet and labeled it. Technicians collected the body within 6 hours postmortem and transferred it to the mortuary where it was stored in a study-designated refrigerator at 4°C-8°C without embalming. A trained study counselor made a telephone call to the parents or guardians, scheduled an appointment for grief counseling, and explained the importance of conducting postmortem examination in establishing the actual cause and etiology of death. Written consent for a postmortem examination of the decedent's body was obtained from parents or guardians following counseling.

For children who died before being enrolled into surveillance (eg, died at or soon after admission), we also contacted their parents or guardians and offered them grief counseling. We then interviewed them to determine if their child was eligible for enrollment. For parents or guardians whose children met our case definition, we asked for their consent for an interview about the child and to collect data on the child through medical chart abstraction and postmortem examination. If a parent or guardian declined to provide consent for postmortem examination, the body was removed from the designated refrigerator, embalmed, and stored in a nonstudy-designated refrigerator.

Postmortem Examination Data and Nasopharyngeal Specimen Collection

Study pathologists received a 1-week training on postmortem examination SOPs by 2 practicing autopsy pathologists with expertise in pediatric pathology from the University of Washington and Massachusetts General Hospital, and a lead pathologist from the Infectious Disease Pathology Branch (IDPB) of the CDC-Atlanta (Georgia, USA). The training, conducted at the KNH mortuary, ensured a consistent autopsy procedure and standardized specimen collection. Once consent for postmortem examination was obtained, the study pathologists were notified and arranged to perform the postmortem examination. The autopsies were performed as soon as possible but no more than 5 days after death.

We used standard data collection study tools to obtain data on the general examination findings, including the appearance of the body and anthropometric measurements. In addition, photographs of the face (for study identification purpose only) and of any abnormal physical features were taken. Furthermore, a nasopharyngeal swab specimen was obtained, as previously described, and placed it into a cryovial containing 3 mL of viral transport media.

Postmortem Collection of Specimen Using Minimally Invasive Tissue Sampling Techniques

The initial procedure was to sample the bilateral lungs through a needle biopsy. The skin was cleaned on the bilateral supraclavicular and anterior chest regions using alcohol swabs, until the swabs appeared clean, and the skin was allowed to air dry. Three sets of lung tissue specimens were separately collected by 11-gauge biopsy needle (ACECUT, Automatic Biopsy System, Ace-1152 the 11g 115mm 22mm, 2016 TSK Laboratory Europe B.V.). Each set of tissue contained specimens from 4 sites—bilateral 4th intercostal spaces just lateral to the sternal border, and the supraclavicular region, in the midclavicular line, with the needle aimed inferiorly (Figures 2 and 3). The first set of lung tissue specimens collected was placed into a tissue jar containing phosphate buffered saline (PBS) and sent to the KEMRI and CDC laboratory in Nairobi for testing for multiple pathogens using TaqMan Array Cards (TAC), as described below. The second set of lung tissues was placed into labeled tissue cassettes, which were placed into a tissue jar containing formalin and sent to the University of Nairobi histopathology laboratory where 3 sets of tissue slides were prepared and later shipped to the 3 US-based pathologists for analysis. The third set was prepared similar to the second set of tissues and sent to the CDC IDPB laboratory in Atlanta for histology, special staining immunohistochemistry, and molecular tests. All laboratory tests performed are detailed below.

Figure 2. Minimally invasive tissue sampling of the lung at supraclavicular notch.

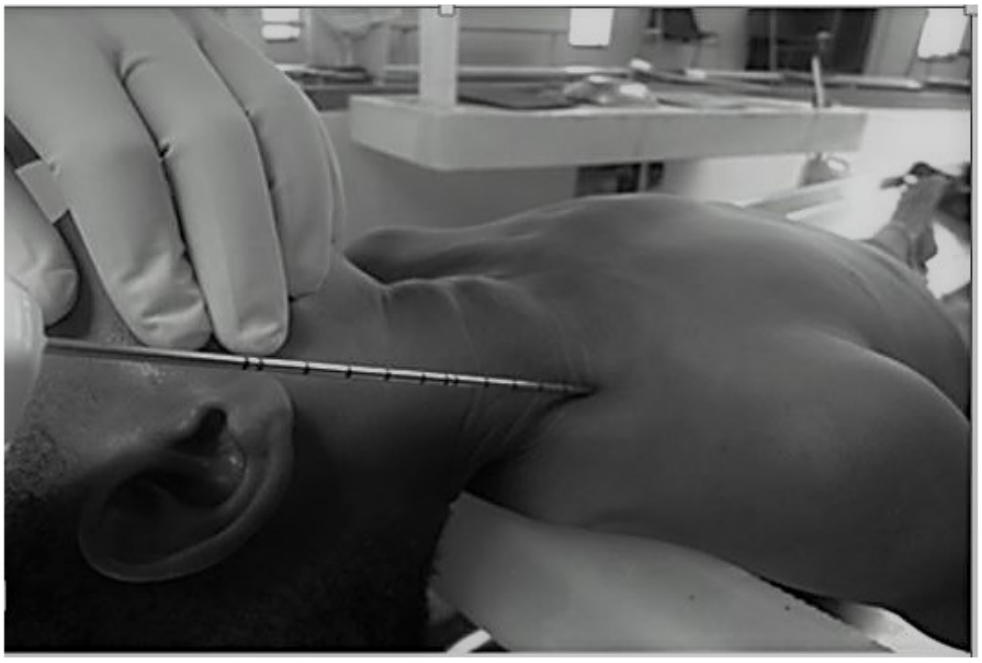
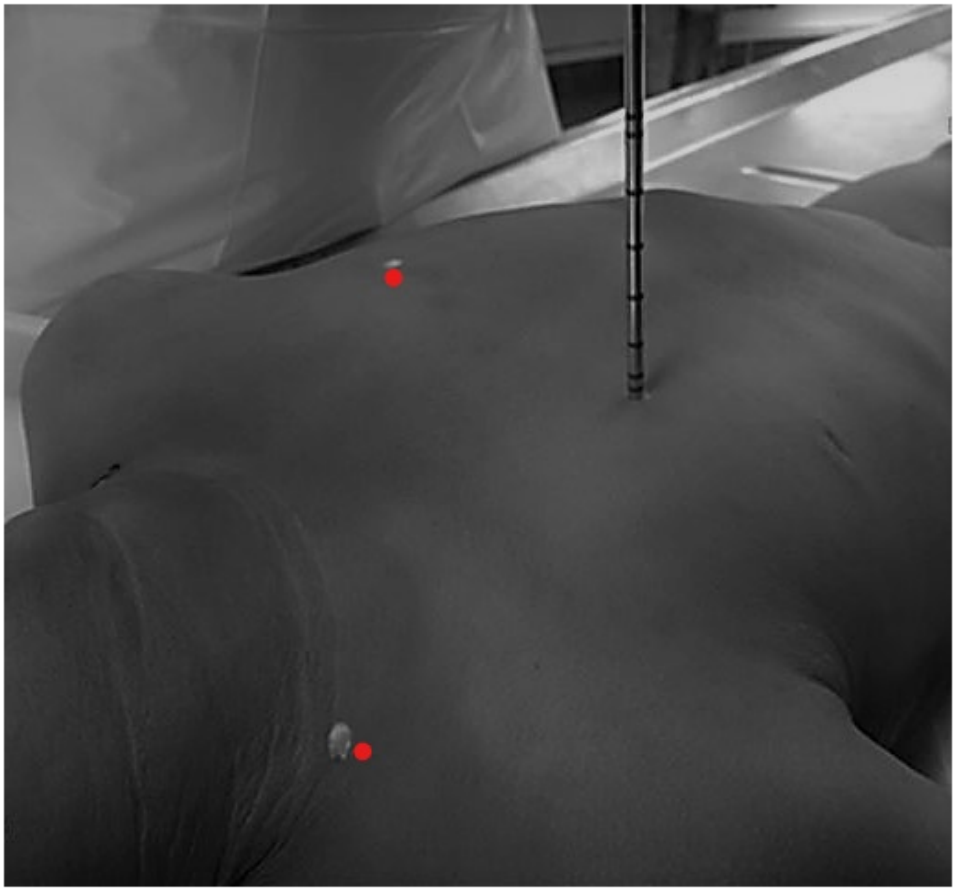


Figure 3. The fourth intercostal space midclavicular line, the red dot indicating the size and aspect of the biopsy needle point of entry.



Postmortem Collection of Specimen Using Conventional Autopsy Methods

Using a sterile blade, a midline incision was made below the chin to the pubic symphysis. The skin was reflected to expose the internal organs. Using a sterile blade, a transverse incision was made in the anterior trachea below the thyroid process and a tracheal swab specimen collected from the internal trachea, using a Dacron-tipped swab, inserted, rotated, and held against the internal posterior tracheal wall collecting any secretions and placed into the same cryovial containing the previously collected nasopharyngeal swab. Using sterile instruments, the following

tissue specimens were collected following standard procedures for autopsy: 4 pieces of trachea, 5 pieces of lung (one from each lobe of both lungs), 2 pieces of myocardium, 4 paired bronchial specimens (pair represents—one piece from each main bronchus), 4 mediastinal lymph node specimens, and 3 pieces from each of the liver, spleen, and bilateral kidneys; these tissues from each site were separately placed into a 10% formalin solution and fixed for 4-24 hours and, then, stored in 70% ethanol. Additional tissue specimens were collected from organs with visible or suspected pathology and placed separately into tissue jars containing formalin. Using aseptic techniques, blood was collected from the heart ventricles prior to dissection, and dried blood spots (DBS) were prepared by spotting whole blood on 5 circles of filter paper. The DBS cards were placed on a drying rack and left to dry overnight in a biosafety cabinet at room temperature (20°C). After drying, each card was placed in a glycine envelope. The glycine envelopes were subsequently packaged in a zip-lock plastic bag containing 4 desiccants and a humidity indicator card and stored at −20°C until testing. Any other fluids (pleural and pericardial space, abdominal cavity) and cerebrospinal fluid (CSF) were collected and placed into separate sterile specimen jars. The brain was examined using standard procedures. Microscopy of all organs and tissues was performed. At the end of the autopsy, a standard list of anatomic diagnoses based on the pathological findings was completed, as was a pathological cause of death based on the integration of the clinical and pathological findings.

Laboratory Testing

Respiratory Virus Testing on Premortem Nasopharyngeal and Oropharyngeal Specimens

Combined nasopharyngeal or oropharyngeal specimens stored in –80°C freezers at the KEMRI and CDC laboratory in Nairobi were retrieved and nucleic acid purification performed for individual real-time reverse transcription polymerase chain reaction (RT-PCR) assays. Total nucleic acids were extracted from 100 µL aliquots of each sample using the MagNA Pure 96 DNA & Viral Nucleic Acid Kit in a MagNA Pure 96 instrument (Roche Inc), and the final material eluted in 100-µL buffer according to the manufacturer's instructions.

Processing of Lung Tissue for TaqMan Array Cards Testing

Briefly, 30-mg frozen tissue was placed in a 2-mL microcentrifuge tube containing a 5-mm prechilled stainless steel bead (Sigma-Aldrich Chemie Gmbh, Munich, Germany) and incubated on dry ice for 15 minutes. The microcentrifuge tubes were placed in a TissueLyser LT Adapter (Qiagen Inc) and incubated at room temperature for 2 minutes, followed by the addition of 400 µL of MagNa Pure lysis buffer (Roche Diagnostics Corporation). The disruption and homogenization of the tissue were performed for 5 minutes at 50 Hz in TissueLyser LT (Qiagen Inc.). The subsequent total nucleic acid purification was performed using MagNA Pure 96 DNA & Viral Nucleic Acid Kit in a MagNA Pure 96 System (Roche Inc.) following the manufacturer's instructions. Total nucleic acids were finally eluted in 100 µL and 46 µL tested in TAC as described below.

Multipathogen Testing Using TaqMan Array Cards

Total nucleic acids from nasopharyngeal or tracheal swabs, tracheal, bronchial, and lung specimens collected using MITS and conventional autopsy techniques were tested at the KEMRI/CDC laboratories in Nairobi using a TAC that tests for 21 pathogens as follows: 13 bacteria (*Bordetella pertussis*, *Chlamydia pneumoniae*, *Haemophilus influenzae all types*, *Haemophilus influenzae type B*, *Klebsiella pneumoniae*, *Legionella* spp, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*, and *Mycobacterium tuberculosis)*; 1 parasite (*Pneumocystis jirovecii)*; and 15 viral pathogens (adenoviruses, coronaviruses 1,2,3,4, Enteroviruses, human metapneumovirus [hMPV], Influenza A, B viruses, parainfluenza 1,2,3,4, respiratory syncytial virus, and rhinoviruses). Assays were run on the ViiA-7 Real-Time PCR System with AgPaTH-ID One-Step Real-Time PCR Kits (Applied Biosystems). PCR Master Mix for each card included 1× RT-PCR buffer RT-PCR enzyme in the final volume of 100 µL reaction volume. We added 46 µL of nucleic acid extract to the master mix. Each run consisted of a negative control and a positive control for the first card of the day to be tested. A minimum of 3 cards were tested per day, with thermal cycling conditions as follows: 45°C for 10 minutes, 94°C for 10 minutes, and 45 cycles of 94°C for 30 seconds and 60°C for 1 minute. For each target, a TAC test result was considered positive if an exponential fluorescence curve was produced that crossed the assigned cycle threshold at ≤35.0. Previous studies have shown that specimens with TAC cycle threshold >35.0 may be less likely to be verified by sequencing of the amplicon [14,15].

Individual Real-Time Reverse Transcription Polymerase Chain Reaction

Individual real-time RT-PCR (IRTP) was carried out using AgPath-ID One-Step RT-PCR Reagents (Applied Biosystems). The TAC assays were compared with the cognate IRTP assays on 96-well plates under the same thermocycling conditions using the same PCR Master Mix and 5 µL of total nucleic acids as a template. Specimens were tested in duplicates for the presence of adenoviruses, hMPV, influenza A and B viruses, parainfluenza virus types 1-3, and respiratory syncytial virus. In addition, each clinical specimen was tested for the human ribonuclease protein gene to measure the nucleic acid integrity and confirm the sample adequacy. A qRT-PCR test result was considered positive if an exponential fluorescence curve was produced that crossed the assigned cycle threshold at <40.0.

Histopathology at Kenyatta National Hospital on Postmortem Specimens

Tissue specimens from the lungs, hilar lymph nodes, heart, kidneys, spleen, liver, brain, and other organs were fixed in a 10% formalin solution prepared in 0.9% buffered saline, for 24 hours prior to the slide preparation. Study-engaged pathologists reviewed the histology slides stained with hematoxylin and eosin (H&E) stain and documented observed pathological changes using structured data abstraction forms.

Tuberculosis Testing Using GenXpert

Lung tissues were sent to the KEMRI-CGHR TB laboratory for screening of *Mycobacterium tuberculosis* using GeneXpert (Figure 1); this is an off-label evaluation of tissue with the GeneXpert as the Food and Drug Administration Market Authorization only extends to testing of sputum in nonpediatric patients. Lung tissues were processed to remove all fats and 5 g of tissue diced into 0.5-cm pieces using a sterile scalpel blade. The diced tissues were placed in a homogenizing container and 10 mL sterile distilled water added. The specimen was homogenized for 3 minutes at 5000 rpm followed by decontamination using 10 mL of 0.5-M NaOH - NALC. Thereafter, pellets were washed with 50 mL of 0.067-M PBS (pH 6.8) pelleted again and reconstituted in 2 mL PBS. Next, 1 mL of the suspended specimen was transferred to a 5-mL falcon tube and 3-mL Xpert MTB/RIF sample reagent added followed by vigorous shake 20 times. This was incubated at room temperature (24°C) for 15 minute with agitation every 5 minute. The liquefied sample was transferred to Xpert MTB/RIF cartridge (Cepheid) and tested following the manufacturer's instructions.

HIV Testing

HIV antigen testing was done at the Kenya AIDS Vaccine Initiative laboratory on DBS collected during the autopsy. The Roche Amplicor HIV DNA PCR Kit was used for the PCR procedures, with some modifications. Briefly, a clean handheld punch (1/4 inch) was used to punch a disk (6 mm^2) from the DBS into a 2 mL screw cap tube, and 1 mL of Roche Specimen Wash Buffer added. Then, DNA extraction, PCR amplification, and analysis by enzyme-linked immunosorbent assay were performed per the manufacturer's recommendations [16]. Specimens were considered unequivocally positive if they had an optical density (OD) of 0.8 and negative if they had an OD <0.2 using an A450 filter. Specimens that had ODs >0.2 but <0.8 were considered indeterminate and retested.

Histopathology, Special Staining, Immunohistochemistry, and Molecular Tests

Minimally invasive lung autopsy tissues and full diagnostic pulmonary and extrapulmonary autopsy tissues fixed in a 10% buffered formalin solution were sent to the CDC IDPB where the tissues were paraffin-embedded, sectioned at 4 µm, and stained by routine H&E. For each case, the H&E from the minimally invasive lung autopsy tissues were evaluated and interpretations recorded prior to the pulmonary and extrapulmonary full diagnostic autopsy tissues. Based on the clinical information, TAC results and the evaluations from both sets of tissues histochemical stains, immunohistochemistry, and molecular testing were pursued, as summarized in Tables 1 and 2. Additional histochemical stains including Grocott's methenamine silver (GMS), Lillie-Twort Gram (LT), Warthin–Starry silver (WS), Fontana-Masson, Prussian blue iron, and Ziehl–Neelsen acid-fast (ZN) were available for further testing as needed. Immunohistochemical assays were performed using a polymer-based colorimetric indirect immunoalkaline phosphatase detection system with colorimetric detection of antibody or polymer complex with Fast Red Chromogen (Thermo Fisher Scientific or Biocare Medical) with appropriate positive and negative control tissues tested in parallel for each assay. A multitude of antibodies targeting bacteria, fungi, and viruses were also utilized in some cases; these are summarized in Supplementary Tables 1 and 2. Molecular assays were performed in-house at IDPB or in conjunction with internal collaborators at the CDC. Optimized extraction protocols were used as previously published [17], and assay specifics are available upon request to IDPB.

Table 1. Outline of standard screening tests done at the Infectious Diseases Pathology Laboratory (IDPL), CDC-Atlanta.

Type of test	Screening tests[a]
Histological evaluation	Hematoxylin & Eosin
Histochemical stains	Lillie-Twort Gram
	Grocott's methenamine silver
Molecular viral panel	Influenza A and B viruses
	Parainfluenza viruses
	Respiratory syncytial virus

[a]Screening tests performed on the upper and lower airway tissue from complete diagnostic autopsy specimens and needle core tissues from minimally invasive tissue sampling.

Table 2. Outline of standard follow-up and confirmatory tests at the Infectious Diseases Pathology Laboratory (IDPL), CDC-Atlanta.

Category	Primary testing	Findings that trigger follow-up assay	Follow-up assay
Fungal	H&E[a]	Frothy intra-alveolar eosinophilic material	*Pneumocystis* spp IHC[b]
	GMS[c]	Crescentic fungal forms	*Pneumocystis* spp IHC
	H&E and H&E	Fungal hyphae and yeast	Fungal IHC assays[d]; Broad-range fungal PCR[e,f]
Viral	H&E and PCR	Phase I viral panel negative and interstitial pneumonitis	Additional PCR[g]; *Mycoplasma* spp; Rhinovirus; Human metapneumovirus
	GMS and IHC	Pneumocystis organisms	CMV[h] IHC
	H&E	Compatible viral inclusions	CMV IHC
	H&E, GMS, IHC and clinical history	Concomitant diseases associated with immunosuppression	CMV IHC
Bacterial	H&E, LT[i], and GMS	Gram-negative bacteria	*Klebsiella* /*Enterobacteriaceae* IHC[j] (and confirmatory PCR)
	H&E and LT/GMS	Acute inflammation without bacteria on special stains	*Mycobacterium* spp IHC; *Streptococcus* spp IHC; *Staphylococcus* spp IHC; *Group B Streptococcus* spp IHC; *Group A Streptococcus* spp IHC; Warthin starry special stain
	H&E, LT/GMS, and IHC	Acute inflammation without bacteria on special stains or IHC	Pan eubacterial PCR
	LT	Gram-positive cocci	*Streptococcus* spp IHC; *Group A Streptococcus* spp IHC
	LT	Small Gram-negative coccobacilli	*Haemophilus influenzae* IHC

[a]H&E: Hematoxylin & Eosin.

[b]IHC: immunohistochemistry.

[c]GMS: Grocott's methenamine silver.

[d]Fungal IHC panel consists of one or more of the following based on H&E and GMS morphology and Gram stain characteristics when applicable: Polyfungal IHC, mucormycete fungus IHC, *Aspergillus* spp IHC, and *Candida* spp IHC.

[e]Broad-range fungal PCR performed by colleagues at the Mycotics Diseases Branch.

[f]PCR: polymerase chain reaction.

[g]Additional pneumonia-associated PCR assays based on H&E, clinical history, and TAC results.

[h]CMV: cytomegalovirus.

[i]LT: Lillie-Twort Gram.

[j]Polyclonal IHC known to cross-react with other *Enterobacteriaceae* bacteria.

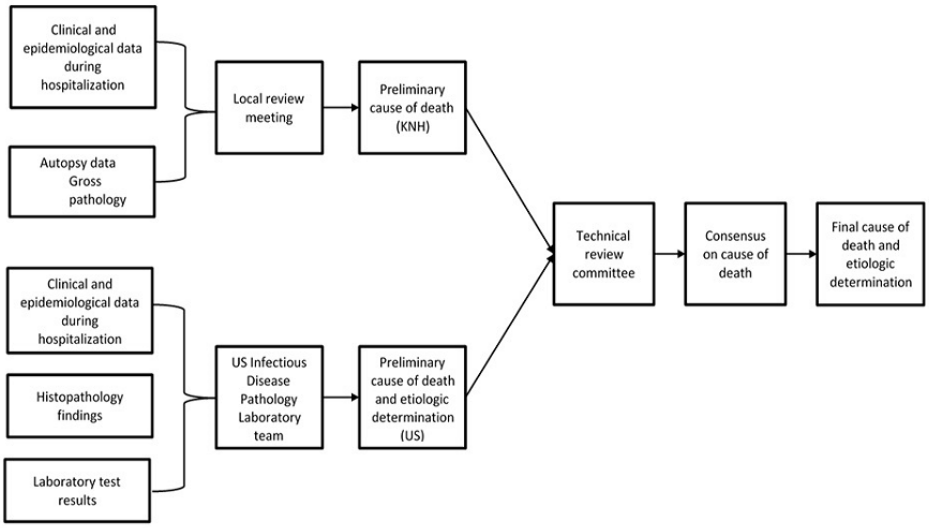
Data Review Process to Determine Cause of Death and Etiologic Determination

To determine the cause of death, clinical data, pathology findings (gross and histopathology reports), and results of laboratory investigations for each case were reviewed separately by a Kenya- and a US-based team of experts. The Kenya-based team (composed of 2 pediatricians, 3 pathologists and a medical epidemiologist) held monthly meetings to review data for each case. Based on the data reviewed, the team agreed on a preliminary cause of death. As local review of cases occurred close to real time, it did not include laboratory results from the other collaborating laboratories (in KEMRI-CDC and IDPB Atlanta) owing to delays in processing results.

A separate review was done by CDC IDPB, which reviewed histopathology findings and laboratory results, including special stains, immunohistochemistry, and other pathogen identification studies. Based on these data, they identified probable pathological (histopathological) diagnosis and suggested a pathogen etiology when possible.

A final technical review committee was established comprising Kenya-based pediatricians and pathologists, laboratorians, epidemiologists, and US-based pathologists. This committee would review each case, assessing all clinical and postmortem findings, including laboratory investigation results, and agreed on a final cause of death and where applicable, identified etiologic pathogens associated with the cause of death (Figure 4). For cause of death determination, the consensus was sought, and the final classification followed the World Health Organization's guidelines for medical certification of cause of death [18]. For etiology determination, the pathogen was considered on the basis of the presence in multiple tissues and from different tests (to exclude possible contamination or overgrowth), biological plausibility, and fit within the clinical presentation.

Figure 4. The algorithm to establish the final etiologic cause of death.



Procedures for Comparing Findings From Minimally Invasive Tissue Sampling Techniques and Conventional Autopsy Techniques for Lung Specimens

Lung tissue specimens obtained through MITS and conventional autopsy techniques were sent decoded and unmatched to 2 US-based pathologists (from different institutions) for H&E diagnoses. The cases were reviewed separately, as slides were randomly labeled and not associated by case, independent of any clinical or pathological information. Then, the code was revealed, and specimens were matched and diagnoses compared between the Kenya-based team and the US-based team. Any discrepancy for each case and type of sample was resolved by consensus. In addition, for each case, we were able to compare pathogens detected by TAC in lung tissue collected using MITS to those collected using conventional autopsy.

Dissemination of Study Findings

After each postmortem examination, Kenya-based pathologists provided feedback to parents or guardians on their gross examination findings. As histopathology and laboratory test results became available, parents or guardians were called and an appointment scheduled to relay this information. We participated in continuous medical education sessions targeting pathology and pediatric residents, their consultants, and pediatric ward nurses, where study cases were presented. Special emphasis was placed on children for whom the diagnosis was missed during the clinical evaluation and whose death could have been averted if diagnosis and right treatment was offered. Providing feedback to clinicians was an important strategy to engage hospital staff in our study, create awareness of clinical case definitions, and improve enrollment. In addition, results from our postmortem investigation were communicated back to parents and caregivers who accepted postmortem examination. All parents of children who died during the study period (whether they agreed to participate in the postmortem investigation or not) were later interviewed to assess whether they would have a change in perception toward the need for an autopsy and whether the use of only a MITS technique could have influenced their original reply to participation.

Ethics Approval and Consent to Participate

The study protocol and procedures were reviewed and approved by the Institutional Review Board (IRB) at KEMRI (SSC no. 2692). We obtained ethical approval reliance from the IRB at CDC (6599) and KNH or University of Nairobi. The study was registered by the KNH's Research & Programs Department (registration No. PEADS/0014/2014). Written informed consent was completed in either English or Swahili, depending on the parents or guardian's language proficiency. Data collected from each case was identified using unique study identification numbers. We created a link log that was kept under lock and key and used for the sole purposes of linking patient data that were collected separately over time. No study participant was identified by name in any report or publication derived from information collected for the study. Furthermore, we paid for the cost of postmortem examination and associated histopathology and laboratory tests. We also paid for mortuary fees incurred for body storage at the mortuary for up to 10 days.

Results

We have enrolled 945 pediatric cases of respiratory illness hospitalized in the KNH at the time of this submission; of those, 14.8% (140/945) died while in the hospital. We were able to successfully enroll 45.7% (64/140) deceased children for postmortem examination. The analysis and interpretation of laboratory results and writing of findings are expected in 2019-2020. We expect to have a manuscript on the comparison of MITS and conventional autopsy to detect pulmonary pathology among respiratory illness-related deaths; summary of the cause of deaths and associated etiologies among children who died from respiratory illness during hospitalization; factors influencing acceptance of postmortem examination of children; and will explore risk factors associated with in-hospital death in a resource-limited setting.

Discussion

We describe a comprehensive approach to assess the causes of child respiratory mortality in a large urban Kenyan hospital.

We brought together a diverse set of experts and applied a range of tests from basic histopathology to state-of-the-art immunohistochemistry and multipathogen molecular testing to detect a comprehensive range of pathogens in a wide range of tissues. We anticipate that study findings will add to the literature, as we will be able to compare the assessment of the cause of respiratory disease–related death based on the lung tissues collected using both MITS and conventional autopsy techniques. In addition, we will explore the use of multipathogen molecular-based diagnostic tools that can be used to support the cause of death determinations. Furthermore, we will be able to explore different pathogens simultaneously, including bacterial, fungi, mycobacterial, and viral agents and advise future studies in similar settings.

This study was not only designed to detect pathogens of clinical relevance in childhood respiratory disease–related deaths but also improve clinical care at the KNH and inform future studies of similar nature. Many studies have relied on the clinical assessment to determine the cause of death despite well-documented discrepancies between the clinical diagnosis and findings from autopsy [19-21]. Even with the improvement in diagnostic tools currently available to physicians in high-resource countries, an autopsy can aid in detecting up to 30% of causes of deaths missed during clinical evaluation [22,23]; this figure may be higher in resource-limited settings. However, autopsy rates throughout the world have declined [10]. The idea of using MITS to aid in postmortem investigations in remote areas where the capacity to perform a full autopsy is limited, and modern imaging techniques are not available, is not new [24]. MITS may improve acceptance rates among communities where autopsy procedures can be culturally less acceptable or feasible [25].

Investigation of postmortem-collected specimens may identify etiologic agents, which are not suspected antemortem, which is particularly relevant for respiratory illnesses, as many respiratory pathogens can cause similar syndromic presentations. For example, a retrospective study of adenoviruses in autopsies of pediatric patients who died of pneumonia in South China identified adenovirus by PCR in 9.1% (16/175) of lung tissues [26]. Another example is undiagnosed deaths due to influenza virus infection. This could be blamed on late care-seeking (where influenza viruses may no longer be detected in upper respiratory specimens) or lack of accurate diagnostic tests in the health care system. A study conducted among 1611 coronial autopsy cases in Western Australia found influenza in 8% of deceased children (age <10 years), none of whom were suspected of having influenza during clinical evaluation [27]. Moreover, it is difficult to ascertain the contribution of complications due to coinfections, such as secondary bacterial infection following influenza or other infections that could contribute to death, without the evaluation of lung or other tissues in the postmortem setting. Respiratory illness associated with viruses or fungi can be particularly difficult to detect as part of the routine clinical evaluation because of the limitations associated with antemortem sampling and the low sensitivity of available tests (eg, rapid antigen tests and blood culture) [28,29]. Another added benefit of postmortem investigation can be the possibility to assess a child's neglect, abuse, and genetic conditions, which can go undetected until autopsy.

In this study, we enrolled patients to be followed from admission to final disposition (hospital discharge or death); this would allow us to integrate clinical history and management during hospitalization with the findings from postmortem investigation that can assist with defining the cause of death. Moreover, we will be able to compare pathogens detected during life with those detected postmortem to better understand the significance of findings when assessing causality.

As this study is hospital-based, our population may not be representative of deaths that occur in the community and may underestimate causes of death that rapidly progress in severity, leading to death prior to health care seeking. This is a limitation of a hospital-based study, especially in our case, where most patients are referred from other health care facilities. Additional problems could include contamination of postmortem tissue during collection (a special concern when using MITS techniques) [30], but the hospital setting may minimize this risk compared with studies conducted at the community. Moreover, percutaneous sampling methods could miss areas of pathology [31]. However, in this study, we will be able to link results from tissues collected using MITS with those collected during the full autopsy and assess MITS methods. Finally, postmortem investigative studies are associated with the immediate widespread cellular degradation after death facilitating bacterial translocation [32]. Bacteria, fungi, and endotoxins can cross the mucosal barrier of the gastrointestinal tract, and interpretation of multipathogen molecular diagnostic results can be complicated as these pathogens can multiply after death, masking the real etiologic agent. We hope to overcome the challenge of interpreting the relevance of pathogens detected using TAC testing by adding clinical history and information on the course of illness while a patient is alive and contrasting findings with that from different testing methodologies and tissue specimens to assist with the interpretation of etiology.

In conclusion, we describe important methodological procedures to assess the leading causes of pediatric respiratory disease–related deaths that can be adopted in similar hospital-based studies. In addition, this study would provide insights into the interpretation of results using multipathogen testing platforms and comparing different techniques (MITS and specimens through conventional autopsy) that can be used in studies or surveillance undertaken in other resource-limited settings.

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The authors specially thank the team of histopathology technicians at the KNH for preparing tissue slides for review by pathologists. In addition, they thank the entire team at IDPB for collective involvement in the receiving, processing, testing, and interpretation of specimens, and colleagues at the Mycotic Diseases Branch, Division of Global HIV and TB, Measles Mumps, Rubella and Herpesvirus Laboratory Branch, and Division of Bacterial Diseases-Streptococcus Laboratory for diagnostic testing. They would also like to thank the data team for creating study databases and maintaining data integrity. Finally, special thanks to parents and guardians who consented to have their decedent children's bodies undergo postmortem examination. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' Contributions

HNN, SRZ, DJR, CLF, ER, BF, MAW, and JAM designed the study protocol. SSC supervised the implementation of the study, data collection, and provided leadership for the manuscript writing. HNN, SRZ, DJR, CLF, ER, BF, MAW, JAM, SSC, MKK, J Mathaiya, EW, AKG, EMO, GI, NO, RL, J Maina, GOE, COO, SG, CO, PK, and MB contributed intellectually to the manuscript writing.

Conflicts of Interest

None declared.

References

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn J, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. The Lancet 2015 Jan;385(9966):430-440. [doi: 10.1016/S0140-6736(14)61698-6] [Medline: 25280870]
2. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ 2008 May;86(5):408-416 [FREE Full text] [Medline: 18545744]
3. Black R, Cousens S, Johnson H, Lawn J, Rudan I, Bassani D, Child Health Epidemiology Reference Group of WHOUNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010 Jun 05;375(9730):1969-1987. [doi: 10.1016/S0140-6736(10)60549-1] [Medline: 20466419]
4. Chintu C, Mudenda V, Lucas S, Nunn A, Lishimpi K, Maswahu D, UNZA-UCLMS Project Paediatric Post-mortem Study Group. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. Lancet 2002 Sep 28;360(9338):985-990. [doi: 10.1016/S0140-6736(02)11082-8] [Medline: 12383668]
5. Kodani M, Yang G, Conklin LM, Travis TC, Whitney CG, Anderson LJ, et al. Application of TaqMan low-density arrays for simultaneous detection of multiple respiratory pathogens. J Clin Microbiol 2011 Jun;49(6):2175-2182 [FREE Full text] [doi: 10.1128/JCM.02270-10] [Medline: 21471348]
6. Jain S, Williams D, Arnold S, Ampofo K, Bramley A, Reed C, CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015 Feb 26;372(9):835-845 [FREE Full text] [doi: 10.1056/NEJMoa1405870] [Medline: 25714161]
7. Hasan R, Rhodes J, Thamthitiwat S, Olsen S, Prapasiri P, Naorat S, et al. Incidence and etiology of acute lower respiratory tract infections in hospitalized children younger than 5 years in rural Thailand. Pediatr Infect Dis J 2014 Feb;33(2):e45-e52 [FREE Full text] [doi: 10.1097/INF.0000000000000062] [Medline: 24030346]
8. Nasreen S, Luby S, Brooks W, Homaira N, Al Mamun A, Bhuiyan M, et al. Population-based incidence of severe acute respiratory virus infections among children aged <5 years in rural Bangladesh, June-October 2010. PLoS One 2014;9(2):e89978 [FREE Full text] [doi: 10.1371/journal.pone.0089978] [Medline: 24587163]
9. Cox JA, Lukande RL, Nelson AM, Mayanja-Kizza H, Colebunders R, Van Marck E, et al. An autopsy study describing causes of death and comparing clinico-pathological findings among hospitalized patients in Kampala, Uganda. PLoS One 2012;7(3):e33685 [FREE Full text] [doi: 10.1371/journal.pone.0033685] [Medline: 22432042]
10. Turnbull A, Osborn M, Nicholas N. Hospital autopsy: Endangered or extinct? J Clin Pathol 2015 Aug;68(8):601-604 [FREE Full text] [doi: 10.1136/jclinpath-2014-202700] [Medline: 26076965]
11. Nair H, Simões EA, Rudan I, Gessner B, Azziz-Baumgartner E, Zhang J, Severe Acute Lower Respiratory Infections Working Group. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet 2013 Apr 20;381(9875):1380-1390 [FREE Full text] [doi: 10.1016/S0140-6736(12)61901-1] [Medline: 23369797]
12. Blokker B, Wagensveld I, Weustink A, Oosterhuis J, Hunink M. Non-invasive or minimally invasive autopsy compared to conventional autopsy of suspected natural deaths in adults: a systematic review. Eur Radiol 2016 Apr;26(4):1159-1179 [FREE Full text] [doi: 10.1007/s00330-015-3908-8] [Medline: 26210206]
13. World Health Organization. 2006. Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection: Guide for field operations URL: http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/ [accessed 2018-12-03] [WebCite Cache ID 74OCSU15p]

14. Olsen S, Thamthitiwat S, Chantra S, Chittaganpitch M, Fry A, Simmerman J, et al. Incidence of respiratory pathogens in persons hospitalized with pneumonia in two provinces in Thailand. Epidemiol Infect 2010 Dec;138(12):1811-1822. [doi: 10.1017/S0950268810000646] [Medline: 20353622]
15. Liu J, Ochieng C, Wiersma S, Ströher U, Towner JS, Whitmer S, et al. Development of a TaqMan Array Card for Acute-Febrile-Illness Outbreak Investigation and Surveillance of Emerging Pathogens, Including Ebola Virus. J Clin Microbiol 2016 Jan;54(1):49-58 [FREE Full text] [doi: 10.1128/JCM.02257-15] [Medline: 26491176]
16. Zijenah LS, Humphrey J, Nathoo K, Malaba L, Zvandasara P, Mahomva A, et al. Evaluation of the prototype Roche DNA amplification kit incorporating the new SSK145 and SKCC1B primers in detection of human immunodeficiency virus type 1 DNA in Zimbabwe. J Clin Microbiol 1999 Nov;37(11):3569-3571 [FREE Full text] [Medline: 10523553]
17. Bhatnagar J, Blau DM, Shieh W, Paddock CD, Drew C, Liu L, et al. Molecular detection and typing of dengue viruses from archived tissues of fatal cases by rt-PCR and sequencing: diagnostic and epidemiologic implications. Am J Trop Med Hyg 2012 Feb;86(2):335-340 [FREE Full text] [doi: 10.4269/ajtmh.2012.11-0346] [Medline: 22302871]
18. World Health Organization. Medical certification of cause of death URL: http://www.who.int/sorry/ [accessed 2018-12-03] [WebCite Cache ID 74OCnVJK2]
19. Kabra N, Udani R. Correlation between clinical diagnoses at the time of death and autopsy findings in critically sick neonates at a regional neonatal intensive care unit in India. J Trop Pediatr 2001 Dec;47(5):295-300. [doi: 10.1093/tropej/47.5.295] [Medline: 11695730]
20. Tai D, El-Bilbeisi H, Tewari S, Mascha E, Wiedemann H, Arroliga A. A study of consecutive autopsies in a medical ICU: a comparison of clinical cause of death and autopsy diagnosis. Chest 2001 Feb;119(2):530-536. [Medline: 11171734]
21. Twigg SJ, McCrirrick A, Sanderson PM. A comparison of post mortem findings with post hoc estimated clinical diagnoses of patients who die in a United Kingdom intensive care unit. Intensive Care Med 2001 Apr;27(4):706-710. [Medline: 11398697]
22. Kuijpers C, Fronczek J, van de Goot FRW, Niessen H, van Diest PJ, Jiwa M. The value of autopsies in the era of high-tech medicine: discrepant findings persist. J Clin Pathol 2014 Jun;67(6):512-519. [doi: 10.1136/jclinpath-2013-202122] [Medline: 24596140]
23. Shojania K, Burton E, McDonald K, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. JAMA 2003 Jun 04;289(21):2849-2856. [doi: 10.1001/jama.289.21.2849] [Medline: 12783916]
24. Martínez MJ, Massora S, Mandomando I, Ussene E, Jordao D, Lovane L, et al. Infectious cause of death determination using minimally invasive autopsies in developing countries. Diagn Microbiol Infect Dis 2016 Jan;84(1):80-86. [doi: 10.1016/j.diagmicrobio.2015.10.002] [Medline: 26508103]
25. Gurley E, Parveen S, Islam M, Hossain M, Nahar N, Homaira N, et al. Family and community concerns about post-mortem needle biopsies in a Muslim society. BMC Med Ethics 2011 Jun 13;12:10 [FREE Full text] [doi: 10.1186/1472-6939-12-10] [Medline: 21668979]
26. Ou Z, Zeng Q, Wang F, Xia H, Lu J, Xia J, et al. Retrospective study of adenovirus in autopsied pulmonary tissue of pediatric fatal pneumonia in South China. BMC Infect Dis 2008 Sep 21;8:122 [FREE Full text] [doi: 10.1186/1471-2334-8-122] [Medline: 18803877]
27. Speers D, Moss D, Minney-Smith C, Levy A, Smith DW. Influenza and respiratory syncytial virus are the major respiratory viruses detected from prospective testing of pediatric and adult coronial autopsies. Influenza Other Respir Viruses 2013 Nov;7(6):1113-1121 [FREE Full text] [doi: 10.1111/irv.12139] [Medline: 23855988]
28. Garbino J, Fluckiger U, Elzi L, Imhof A, Bille J, Zimmerli S. Survey of aspergillosis in non-neutropenic patients in Swiss teaching hospitals. Clin Microbiol Infect 2011 Sep;17(9):1366-1371 [FREE Full text] [doi: 10.1111/j.1469-0691.2010.03402.x] [Medline: 20950331]
29. Millman A, Reed C, Kirley P, Aragon D, Meek J, Farley M, et al. Improving Accuracy of Influenza-Associated Hospitalization Rate Estimates. Emerg Infect Dis 2015 Sep;21(9):1595-1601 [FREE Full text] [doi: 10.3201/eid2109.141665] [Medline: 26292017]
30. Morris J, Harrison L, Partridge S. Postmortem bacteriology: a re-evaluation. J Clin Pathol 2006 Jan;59(1):1-9 [FREE Full text] [doi: 10.1136/jcp.2005.028183] [Medline: 16394274]
31. Castillo P, Ussene E, Ismail M, Jordao D, Lovane L, Carrilho C, et al. Pathological Methods Applied to the Investigation of Causes of Death in Developing Countries: Minimally Invasive Autopsy Approach. PLoS One 2015;10(6):e0132057 [FREE Full text] [doi: 10.1371/journal.pone.0132057] [Medline: 26126191]
32. Balzan S, de Almeida Quadros C, de Cleva R, Zilberstein B, Cecconello I. Bacterial translocation: overview of mechanisms and clinical impact. J Gastroenterol Hepatol 2007 Apr;22(4):464-471. [doi: 10.1111/j.1440-1746.2007.04933.x] [Medline: 17376034]

Abbreviations

CDC: Centers for Disease Control and Prevention
DBS: dried blood spots
H&E: hematoxylin and eosin

IDPB: Infectious Disease Pathology Branch
KEMRI: Kenya Medical Research Institute
KNH: Kenyatta National Hospital
LT: Lillie-Twort Gram
MITS: minimally invasive tissue sampling techniques
OD: optical density
PBS: phosphate buffered saline
PCR: polymerase chain reaction
PRESS: Pediatric Respiratory Etiology Surveillance Study
TAC: TaqMan Array Cards

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Protocol

Investigating Health Risk Environments in Housing Programs for Young Adults: Protocol for a Geographically Explicit Ecological Momentary Assessment Study

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Abstract

Background: Young adults who experience homelessness are exposed to environments that contribute to risk behavior. However, few studies have examined how access to housing may affect the health risk behaviors of young adults experiencing homelessness.

Objective: This paper describes the Log My Life study that uses an innovative, mixed-methods approach based on geographically explicit ecological momentary assessment (EMA) through cell phone technology to understand the risk environment of young adults who have either enrolled in housing programs or are currently homeless.

Methods: For the quantitative arm, study participants age 18-27 respond to momentary surveys via a smartphone app that collects geospatial information repeatedly during a 1-week period. Both EMAs (up to 8 per day) and daily diaries are prompted to explore within-day and daily variations in emotional affect, context, and health risk behavior, while also capturing infrequent risk behaviors such as sex in exchange for goods or services. For the qualitative arm, a purposive subsample of participants who indicated engaging in risky behaviors are asked to complete an in-depth qualitative interview using an interactive, personalized geospatial map rendering of EMA responses.

Results: Recruitment began in June of 2017. To date, 170 participants enrolled in the study. Compliance with EMA and daily diary surveys was generally high. In-depth qualitative follow-ups have been conducted with 15 participants. We expect to recruit 50 additional participants and complete analyses by September of 2019.

Conclusions: Mixing the quantitative and qualitative arms in this study will provide a more complete understanding of differences in risk environments between homeless and housed young adults. Furthermore, this approach can improve recall bias and enhance ecological validity.

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KEYWORDS

homelessness; ecological momentary assessment; experience sampling; social environment; qualitative research; geography

Introduction

Background

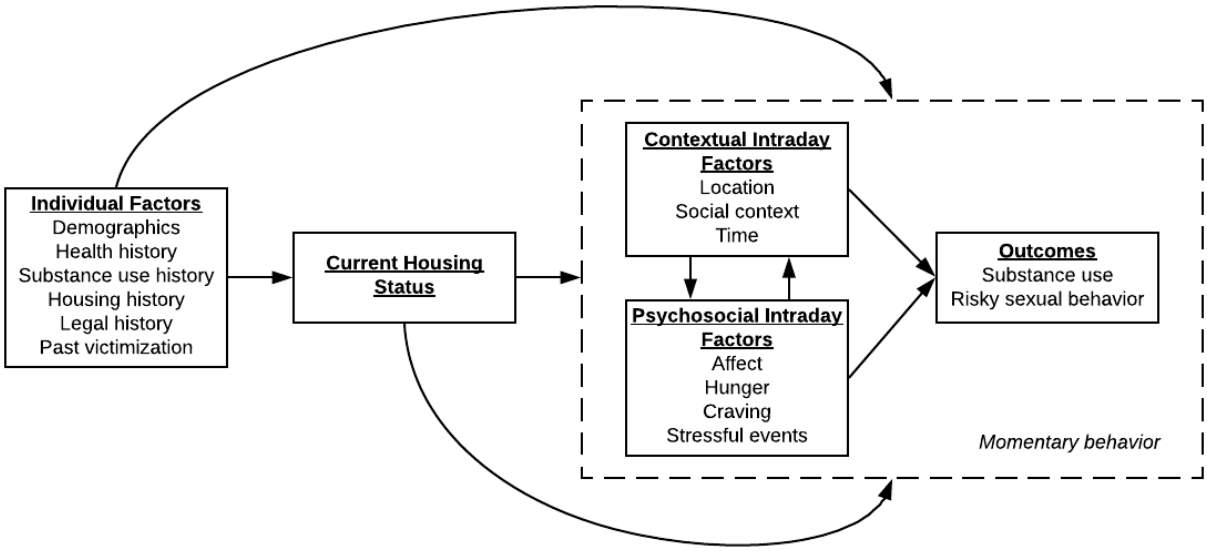
Risk environment has been defined as the space—whether social or physical—in which factors external to a person interact to increase the chances of certain health risk behaviors [1-3]. Young adults between the ages of 18 and 25 years old, sometimes referred to as transition-aged youth, who experience homelessness live in an unstable and sometimes chaotic risk environment that has resulted in high rates of substance use and sexually transmitted infections, including HIV [4-7]. For example, Noell et al found the incidence of sexually transmitted infections in a homeless adolescent population to be as high as 17% and the prevalence and incidence of certain infections to be 10 to 12 times higher than those found in the same age group among the general population [7]. Homelessness services programs that provide housing to young adults have the capacity to change their risk environment, and housing might serve as a protective factor by providing safe, independent living arrangements that can alleviate stress related to being homeless [8,9]. Housing programs may also expose young adults to positive social influences, because street-based peers have been associated with risk behaviors in this population [10,11]. However, these programs may also change the contextual factors that influence health risk behaviors in unforeseen or unexpected ways; for example, being placed in a housing program may increase social pressures from network members who are still experiencing homelessness and need a place to stay or the privacy afforded by housing could permit misuse and sale of drugs or easier engagement in risky sex [12,13]. To date, there has been limited investigation of young adults with a history of homelessness who have enrolled in housing programs [14] or differences in the risk environment between those experiencing homelessness and those who have moved into housing programs. Furthermore, past studies typically relied on self-report methods that are burdened by recall bias [1,3,5].

Objectives

The Log My Life (LML) study seeks to fill this gap in the literature by developing an innovative, mixed-methods approach using geographically explicit ecological momentary assessments (GEMA) to understand the risk environment of young adults who have either enrolled in housing programs or are currently experiencing homelessness. GEMA is considered the gold standard for capturing valid intensive longitudinal self-report information that is embedded in important contextual factors and can be used to understand and predict health risk behaviors [15-19]. The conceptual model for this study (see Figure 1) is based on prior research, showing that within-day variation in various psychosocial characteristics (eg, mood and substance use craving) affects both drug use and sexually risky behavior [20-25]. We hypothesize that access to housing for individuals experiencing homelessness will affect where, when, and with whom they spend time daily [26-28]. Furthermore, we hypothesize that these contextual factors can influence HIV risk and within-day psychosocial characteristics [6,21,29-34], which in turn could impact one's ability to access or maintain stable housing.

This paper describes the protocols of the LML study and highlights innovative aspects of its design, including the use of geospatial data, ecological momentary assessments (EMA), dynamic social contexts, and in-depth interviews to assess the built and social context and psychosocial factors influencing risky health behavior. We also present preliminary recruitment progress to date and describe additional avenues of potential inquiry.

Figure 1. Log My Life conceptual framework.



Methods

Design Overview

Leveraging the widespread use of smartphone technology, including among homeless populations [35,36], this study uses a mixed-methods, prospective longitudinal design to recruit young adults who are in either of the following sampling frames: (1) enrolled in a housing program (eg, transitional housing and permanent supportive housing) or (2) currently homeless. For the quantitative arm, participants in both sampling frames complete a baseline questionnaire and are observed for 1 week by responding to repeated momentary surveys prompted and administered through a smartphone app developed for this study. A 7-day period was chosen to have adequate power (ie, 8 prompts per day for a total of 56 within-subject observations) to detect within-subject changes over time and to capture variation in behavior based on the day of the week. Both EMAs and daily diaries are prompted, and responses are used to explore within-day and daily variations in emotional affect, context, and risk behavior, while also capturing infrequent risk behaviors such as sex in exchange for goods or services. The geospatial location of the participant is also continuously recorded for the monitoring period, to the degree permitted by the phone. For the qualitative arm, a purposive subsample of participants who indicated engaging in risky behaviors are asked to complete an in-depth qualitative interview using an interactive, personalized geospatial map rendering of EMA responses as an elicitation device. Similar methods have been used to better understand contextual factors that influence tobacco use [15]. Mixing the quantitative and qualitative arms in this study provides a more complete understanding of differences in risk environments between homeless and formerly homeless young adults. Study protocols were approved by the institutional review board at the University of Southern California.

Participants

Participants include young adults residing in Los Angeles County who either have or are experiencing homelessness. Approximately 200 participants are currently being recruited from 11 agencies that run permanent supportive or transitional living housing programs as well as from shelter sites and drop-in facilities serving youth experiencing homelessness. To investigate the various contextual mechanisms that could explain risk behaviors among young adults, a power analysis was conducted to determine that we need approximately 100 young adults in housing programs and 100 young adults who remain homeless. In both sampling frames, individuals are eligible to participate if they can be interviewed in English, can read and understand smartphone items in English without assistance, and are willing to provide written informed consent. To be included in the housed sample, young adults must be aged between 18 and 25 years and residing in a housing program that serves homeless young adults. Individuals as old as 27 years are allowed to participate if they entered the housing program before the age of 25 years. Young adults are considered to be part of the unhoused sample if they are aged between 18 and 25 years and meet the McKinney-Vento Homeless Assistance Act [37] definition of homelessness that specifies lack of a fixed, regular, and adequate nighttime residence.

Recruitment

Young adults are being recruited through flyers and informational sessions held at housing programs or drop-in facilities. Study staff members have or will recruit youth at 6 permanent housing programs, 9 transitional living programs, and 6 drop-in facilities across Los Angeles County. Young adults recruited at permanent or transitional living programs are considered to be eligible if they are enrolled in the housing program and fit inclusion criteria. During informational sessions at drop-in sites, youth complete a self-administered screener on an electronic tablet that indicates whether they meet the eligibility criteria for homelessness or are enrolled in a housing program.

Procedures

Upon enrollment, participants receive an iPad (Apple, USA) to complete a self-administered questionnaire via a secure Web-based platform. Due to the potentially sensitive nature of the questions, the questionnaire is administered using computer-assisted self-interviewing techniques. These baseline meetings last approximately 45 to 75 min and include a questionnaire with 2 components: one that assesses demographics and historical experiences and another that explores participants' social network (subsequently described). Participants then have the option to use a study-provided phone, usually a third-generation MotoG (Motorola, USA) smartphone that has an unlimited data plan, or their personal smartphone if they own an Android-based phone that is compatible with the study smartphone app. Youth who agree to use their personal phone receive an additional US $10 to offset the cost of cellular data. Throughout the study period, momentary and daily surveys are prompted using a custom software app for smartphones running the Android operating system (Google, USA). Participants can earn up to US $130 for completing the main study components, but some incentives are task-based (ie, each participant's total incentive amount is driven by compliance with prompted EMAs and daily diaries). Research staff members assist the participant in setting up the smartphone app during baseline meetings, and each participant completes 1 practice EMA and daily diary demonstration. During setup, participants specify normal sleep and wake times, so they do not receive prompts outside their typical waking hours.

For the next 7 days, participants complete EMAs on the smartphone app. EMAs allow repeated collection of real-time data, eliminate the need for retrospective recall, and are particularly well suited for examining episodic behavior that may be affected by context such as substance use [19,38-40]. Participants receive 7 to 8 prompts per day, depending on the number of waking hours. Participants are prompted randomly during 30-min windows separated by 2-hour intervals. For example, if a participant is normally awake from 9 am to 11 pm, 1 EMA survey will be triggered randomly between 9:30 am and 10 am, 11:30 am and 12 pm, 1:30 pm and 2 pm, and so on. The app delivers a push notification with a chime or vibration, if the phone is not set to silent. Participants are instructed to stop their current activity and complete a short EMA survey on their phone. This process requires about 1 to 3 min. If no entry is made, the app emits up to 3 push

notifications at 3-min intervals (3, 6, and 9 min after the first prompt). Each EMA survey becomes inaccessible 10 min after the initial prompt, unless the participant is answering the survey. Participants are instructed to ignore signals that occur during an incompatible activity (eg, driving, sleeping, or bathing). EMA surveys contain skip logic to minimize burden on the participant while optimizing the quality of data received in each brief survey. A minimum of 15 items appear at each EMA prompt. A maximum of 31 items appear in the event that a participant reports all permutations of risk behavior and social context. Soliciting multiple EMA entries per day has been shown to be acceptable in previous studies with youth and adults [41-44] and had been pilot tested for this study.

Starting on the second day of the observation period and continuing for 7 consecutive days, participants are asked to complete a daily diary in which they reflect on their behavior during the previous day. Participants can self-initiate and complete the daily diary at any point during the day, but they are also automatically prompted to do so if the daily diary has not already been completed. Participants select 3 times throughout the day (eg, 9 am, 12 pm, and 2 pm) to receive reminder prompts to complete the daily diary. Reminders do not deploy within 15 min of EMA prompting windows to avoid conflict between surveys. Although momentary data capture can be considered an improvement over self-report methods, there is still a need to include daily assessments as a complement to EMA as we continue to build these methods [45]. Capturing assessments in both momentary and daily methods will provide an opportunity to evaluate how well daily diaries replicate momentary data. Use of daily methods permits more flexibility in how questions are asked. In addition, daily diaries are useful for querying infrequent risk behaviors that would be unnecessary to ask multiple times per day (eg, frequency of sex), as is often done with studies deploying EMA methods. To date, studies comparing collection methods have found close approximate aggregated ratings of behavior or affect between daily and momentary collection [46], but daily collection provides a much better representation of real-time experiences than longer recall methods [47,48]. Responses on both EMA and daily diaries are encrypted, wirelessly uploaded after each entry, and stored on a server accessible to the research team for compliance monitoring.

During the monitoring week, study personnel contact participants by phone twice to check on progress, encourage compliance, and address any technical issues. Participants can also email, call, or text a study helpline number any time they have issues or questions. Google Voice is used to maintain a record of calls, texts, and emails as well as allow multiple staff members to address concerns and mask their own personal phone numbers. After the monitoring period is completed, participants meet with the study staff to complete a 30-min exit appointment, during which they respond to additional questionnaires, receive compensation (calculated based on their compliance), and return the study phone and charger if borrowed.

Study personnel invite a purposive subsample of study participants (n=30) who (1) indicate high-risk behavior (eg, hard drug use and frequent alcohol or marijuana use) during their observation week or during their lifetime and (2) display adequate compliance (ie, 70% or greater) on EMA and daily diaries to participate in an additional in-depth, 45- to 60-min qualitative interview. This interview is used to explore dynamic socioenvironmental factors that affect health risk behaviors and how youth navigate risky environments. The structured open-ended interview also uses an interactive, personalized geospatial map rendering of EMA responses that are generated through the smartphone's built-in location-finding system as an elicitation device, similar to a method proposed by McQuoid et al [15]. These interviews are conducted in private rooms at drop-in sites or housing programs. Audio of the session are recorded and transcribed using a professional service, and participants receive US $30.

Measures

Baseline and Exit Questionnaires

Baseline Questionnaire

The baseline questionnaire addresses factors and characteristics shown to be related to housing stability among youth [9,49-51], including demographics (eg, age, sex, gender, race and ethnicity, education, income, and current and past employment), physical and mental health conditions, lifetime and recent drug and alcohol use, trauma history, homelessness history, life skill development, and emotional regulation. Participant mental health is assessed with the Patient Health Questionnaire [52,53], General Anxiety Disorder Scale [54], Primary Care PTSD Screener [55], Difficulties in Emotion Regulation Scale Short Form [56], Perceived Stress Scale [57], and the COPE scale [58], all of which have been validated with young adult populations. Mental health diagnoses, suicidality, and care engagement are also assessed. Participants rate their current physical health, list their chronic illnesses, assess sleep impairment, and complete a checklist about difficulties in health care access. Items to address youth sexual history and sex-related HIV risk behaviors are based on the Centers for Disease Control and Prevention Youth Risk Behavior Survey's sexual behaviors subsection [59-61], a validated tool that details past 90-day sexual behaviors of adolescents. Items in this portion of the baseline questionnaire also assess HIV and sexually transmitted infection testing, status, and treatment and are based on previous studies by this research team [26,62]. Youth provide a detailed account of lifetime and past 30-day substance use, including type of drug, typical quantity and frequency of consumption, and route of administration (eg, injected, swallowed, or smoked). Probable alcohol or other substance use disorder is determined with the CAGE substance abuse screening tool [63,64], a short, validated assessment that examines substance use issues among individuals aged 16 years or above. In addition to risky behaviors, positive youth development, such as ability to communicate, look forward, manage money, or practice self-care, is measured with the Ansell-Casey Life Skills assessment [65,66].

The baseline questionnaire additionally focuses on participants' historical life experiences such as duration of homelessness, foster care involvement, and justice system involvement, also based on measures used in other studies with homeless youth [26,62]. Childhood trauma is assessed with the University of

California, Los Angeles Post-Traumatic Stress Disorder Reaction Index for the Diagnostic and Statistical Manual of Mental Disorders-IV [67], and participants also reflect on past experiences with trauma in their community, including incidents of robbery, violent assault, intimate partner violence, or other experiences perceived as discrimination. Participants are asked to recall their past experiences with police and gangs and discuss their access to guns. In addition to past experiences, youth complete the Stress on the Streets Checklist [68] to describe their current level of stress with their living environment and the Food Insecurity Scale [69] to assess their typical access to food. Finally, youth comment on their knowledge of housing options, engagement with meaningful activities, and access to supportive services (eg, drop-in center, shelter, and mental health counseling).

Social Networks

To assess social networks, participants also complete a short egocentric social network inventory (based on REALYST [70]; also refer to the study by Burt [71]). Participants initially identify 5 people (commonly referred to as *alters* in social network analysis [72]) that they interact with most frequently (eg, friend from the street, family member, romantic partner, or caseworker). Then, participants respond to questions about each named individual's characteristics, including the alter's gender, age, sexual orientation, race and ethnicity, nature of relationship, frequency of contact, substance use belief and behaviors, sexual beliefs and behaviors, and whether the alter is a source of advice or support.

Exit Questionnaire

During the exit meeting, participants complete an additional computer-assisted questionnaire that includes items about life skill development [65] and if housed, their current housing experience based on items from the Housing Experience Survey [73]. During the exit meeting, youth have an opportunity to describe any events that may have made the observation week atypical and reflect on their experience in the study, such as whether EMA prompts or time spent responding to surveys interfered with their daily life, caused any stress or anxiety, or altered their typical behavior. Participants also indicate the extent to which they felt comfortable answering items honestly and accurately and whether they generally had a negative or positive experience using the smartphone app.

Ecological Momentary Assessment and Daily Diaries

Ecological Momentary Assessments

Surveys prompted by the phone during each EMA query momentary positive and negative affect, hunger, significant events (eg, involved in a physical fight), and further details and contextual factors concerning alcohol use, other drug use, and temptation to drink or use drugs. These items have been successfully applied in other EMA studies of affect and substance use [21,22,25,74-78]. EMA also prompts request information about the participant's social context (subsequently described), and each response is time stamped. A complete list of EMA items and their response options along with sample screenshots can be found in Multimedia Appendices 1 and 2.

Daily Diaries

Daily diaries capture risk behaviors of the previous day and infrequent behavior that may be missed by EMAs. In daily diaries, participants respond to items that aim to provide more in-depth details about any drug use events (eg, quantity and mode of use) or sexual encounters that occurred during the previous day (eg, partner's gender, nature of relationship with partner, and use of a condom). Participants also reflect on their sleep behavior during the past evening, including the duration, location, and quality. Items in the daily diary, available in Multimedia Appendix 3, were adapted from the Youth Risk Behavior Surveillance System survey [61] and tools developed by our team in previous studies [62].

Dynamic Social Context

The names of the 5 individuals with whom the participant interacts most (ie, alters) elicited from the baseline questionnaire are entered into the smartphone app during setup. The app stores each entry, subsequently adding the variables as responses into the social context items of each EMA and daily diary. At the start of each EMA (see Multimedia Appendix 1), participants select which alters (if any) they interacted with during the past 2 hours; if any alters were present, participants indicate whether alcohol, tobacco, or other drugs were consumed. A participant may also specify the presence of other individuals, as desired. If a participant reports interacting with someone other than 1 of the 5 alters, an additional follow-up question gathers data on the relationship between that person and the participant. Although EMA items assess the presence of alters and other individuals at a given moment, daily diaries assess with which specific alters the participant may have consumed alcohol or drugs, if at all (see Multimedia Appendix 3). Relevant alter-level characteristics from the baseline questionnaire (eg, alter uses illicit substances) can be used to generate risk profiles corresponding to the social context of each assessed interaction. For example, prompt-level data may contain a sum of the total number of alters who use illicit substances with whom the respondent reported interacting during that prompt (range: 0-5), and day-level data may contain the overall sum of illicit substance–using alters across all prompts that day or the proportion of prompts to which the respondent reported interacting with any substance-using alter.

Location and Geographic Information Systems Data

Location data are collected once every minute using a background system process on the participant's device. Android's location system uses a multiple-mode sensing method to estimate location relying on a combination of WiFi, cellular triangulation, and global positioning system (GPS) satellites. The software reports accuracy as a 68% CI (1 SD) in meters; epochs with a CI greater than 100 meters were excluded. Activity spaces for participants are defined at the day level using minimum convex hulls and standard deviational ellipses (at 1, 2, and 3 SD). A minimum convex hull is a rudimentary algorithm that creates the smallest possible simple convex polygon encompassing all the points in a dataset, whereas standard deviational ellipses are mean-centered ellipses that cover 68%, 95%, and 99% of GPS data, depending on the specified SD [79]. Location activity spaces are calculated using

Zone 5 of the California State Plane Coordinate System (Datum: WSG84) based on the expected geospatial distribution of data. Coordinates for activity spaces can be used to map additional data layers using geographic information systems, such as crime rate and proximity to services.

In-Depth Follow-Up Qualitative Interviews

As part of the in-depth qualitative follow-up interviews, interactive geospatial maps personalized with GEMA data are shown to participants as a visual elicitation tool to explore participant risk behavior and living environment. Maps are generated in Google Maps (see example in Figure 2), and responses can be displayed on satellite imagery, a road map, or Google Street View. The maps are generated using location sensor data and momentary self-report survey data. They display where the participant traveled during the monitoring week and the locations of any drug use, stressful events, and particular areas participants may have felt positive or negative emotions (ie, happier or sadder than usual).

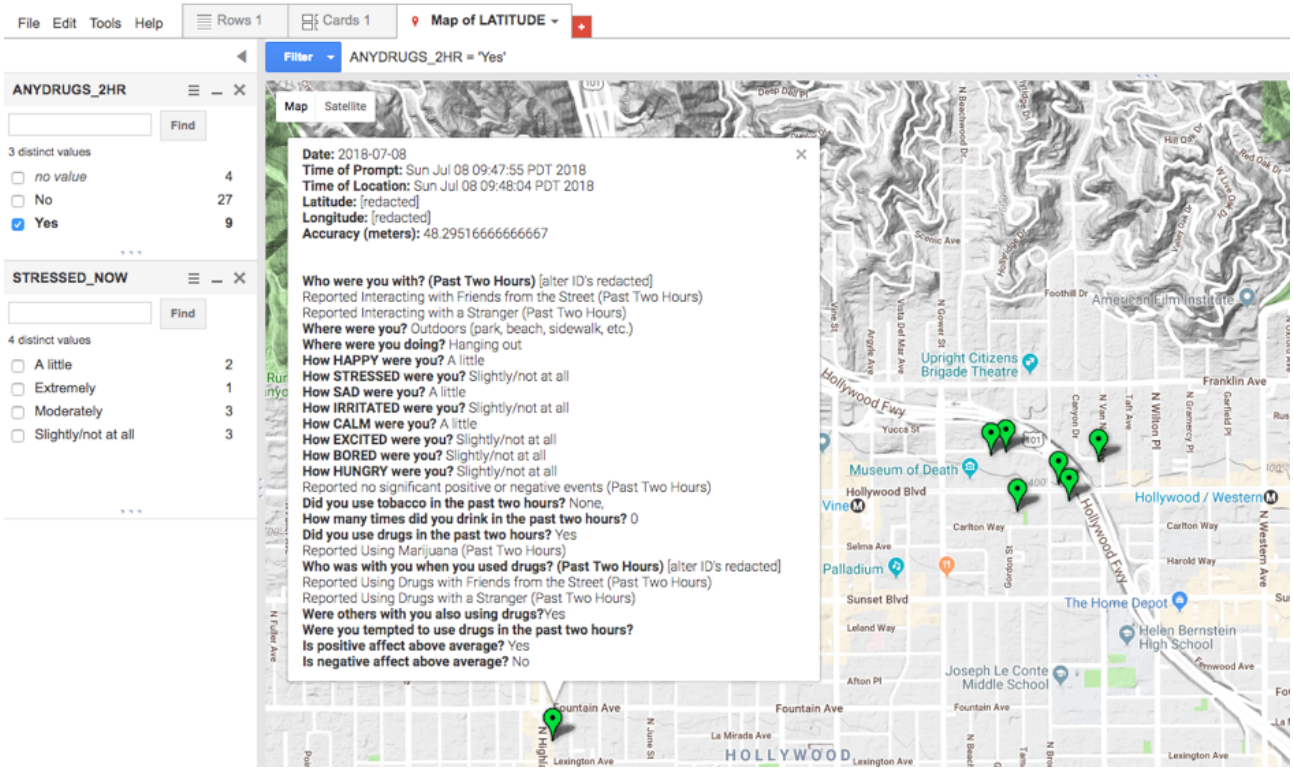
Interviewers first highlight responses associated with higher levels of risk behaviors (ie, drug use or risky sexual behavior) and ask participants to discuss these instances and any patterns they perceive. For example, interview questions that aim to solicit a conversation on substance use and the social contexts that affect use include: “What are your thoughts as to whether these locations influenced your using?” and “You also indicated you were/weren’t with [list any alter identified]? What role do you think this person(s) played in your using?” During the interview, participants can interact with the map, and different responses can be displayed based on any set of EMA items. Interviewers are also trained to request geospatial identifiers for daily activities, interaction with network members, and HIV risk and prevention behaviors that are not already part of the EMA response.

Data Analysis

Quantitative Data Integration

EMA and daily diary data from smartphones are encrypted and then subsequently wirelessly uploaded to a secure server for further data processing. The differences in temporality between location (minute level), EMA (multiple times per day), daily diary (day level), and questionnaire (week level) data are reconciled after questionnaire data are deidentified and location and EMA data are unencrypted. Days are offset by 3 hours, ending at 2:59 am and beginning at 3:00 am to account for delayed sleep schedules in the study population. Coordinates for mean latitude and longitude during the 30-min period surrounding an EMA prompt are generated based on minute-level location data. An aggregate measure is used to limit missing data in the event that a location estimate is unavailable at the exact moment a participant answered a survey. Similarly, daily diary location data is generated using the previous day’s coordinates for mean latitude and longitude, in addition to the area of the minimum convex hull and standard deviational ellipses for that day. Daily diary data are then merged with EMA data, repeating daily diary entries across all prompts for each person-day, and questionnaire data are merged, repeating questionnaire responses across all prompts for each participant.

Figure 2. Example Google map generated from geographically explicit ecological momentary assessments responses of a participant. The exact geospatial coordinates and alter identifiers have been redacted to maintain confidentiality.



Statistical Models

All data are screened for violations of statistical assumptions, such as non-normality or outliers, and transformed to satisfy assumptions for subsequent data analyses. Pairwise correlations are used to screen for multicollinearity and exclude variables that represent similar constructs. Generalized linear models are used to examine relationships between baseline items (ie, demographics and history) with exit questionnaire outcomes. Furthermore, these models are used to predict the likelihood that an individual is assigned to supportive housing for each individual factor, as depicted in Figure 1.

Generalized linear mixed models (GLMMs) are used to address the primary aims of the study for day-level and intraday analyses and missing data analyses. Given the expected differences in contextual and psychosocial factors contingent on housing status (see Figure 1), GLMMs are conducted separately for participants in supportive housing and participants who are not housed. Model fit parameters, such as random effects and specification of variance-covariance matrices, are specified for each GLMM. All level 1 (ie, within-subject) predictors (eg, affect and hunger) are disaggregated into 2 variables through grand-mean centering and person-mean centering to examine both interindividual and intraindividual effects on the outcomes, respectively. Level 2 (ie, between-subject) factors act as covariates in all GLMMs. Depending on the outcome, contextual or psychosocial factors may act as intraday predictors, mediators, or moderators.

Qualitative Data Analysis and Integration

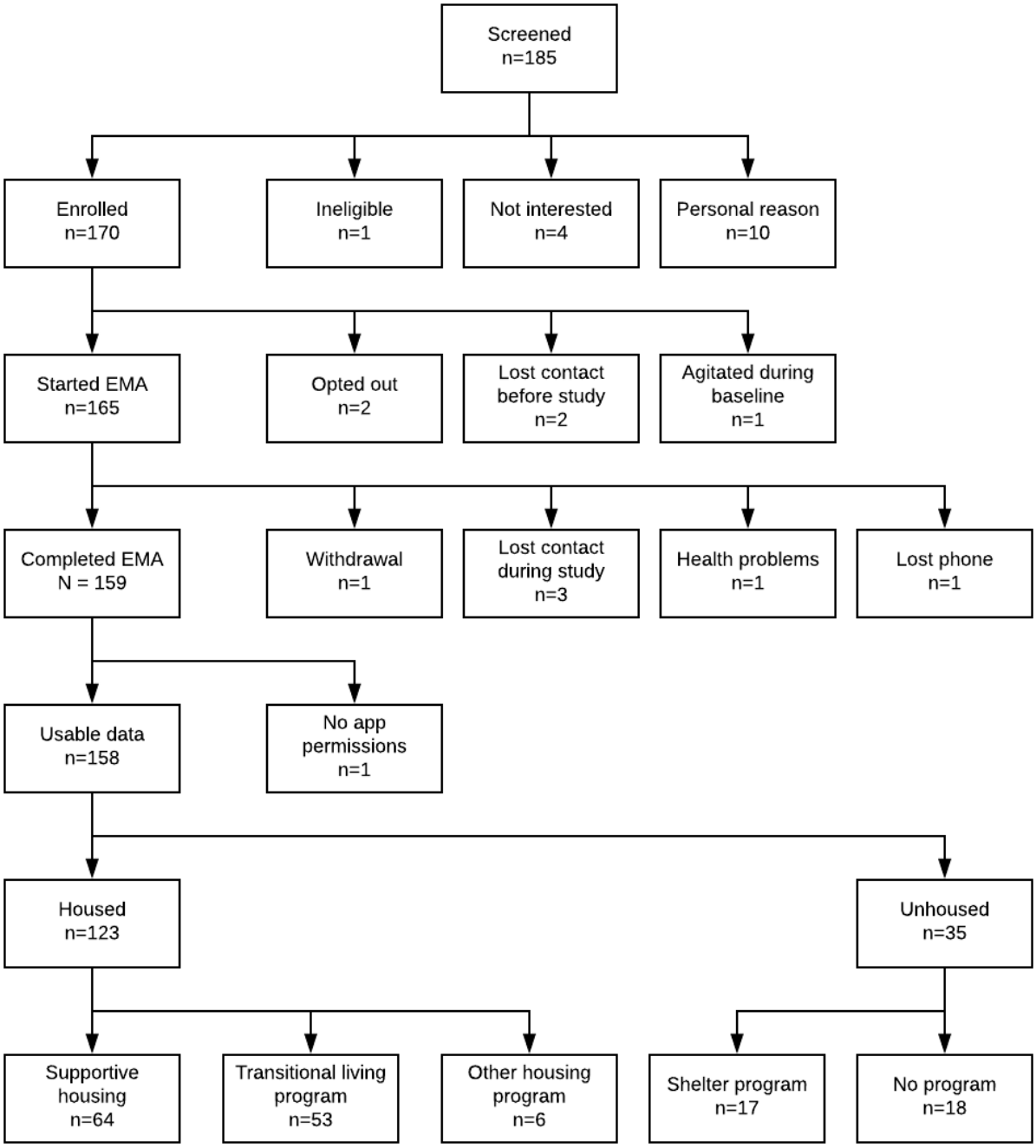
In-depth qualitative interviews are analyzed using a comparative case study analysis [80]. Case studies emphasize uniqueness in context and are used to consider complex phenomenon with interrelated influences that can exist on multiple levels (eg, individual, interpersonal, and structural). Following standard procedures for case study analysis [80,81], a case record or summary is developed for each participant using information extracted from transcripts. Transcripts are thematically analyzed using codes that help identify whether risk or protective factors are influenced by participants' social networks, housing environment, activities participants tend to engage in, or some combination. The use of a case summary matrix that displays salient information from individual case summaries in a table format facilitates cross-case comparisons that can be used to identify broader themes [82].

Integrating qualitative and quantitative findings is done by adding significant quantitative findings to the case summary matrix to facilitate discussion of comparisons between the results. This triangulating process is used to determine the extent to which qualitative findings converge with, are complementary to, or expand upon the quantitative findings [83,84]. Discrepant findings are also noted and further considered. This information is then added to the mixed-methods matrix [85].

Results

Recruitment began in June of 2017. To date, 185 people have attended information sessions and were screened to participate in the study. Furthermore, 170 individuals enrolled in the study and 165 started EMA (Figure 3). Out of the 159 participants with usable data, 6 did not initially complete the protocol but then restarted the EMA and daily log component to satisfy study parameters, either by borrowing a new study phone (n=4), restarting on their personal phone after losing a study phone (n=1), or restarting on a new study phone after attempting to finish on their personal phone (n=1). Overall, 6 study phones were not returned at the end of the study, although 1 participant restarted the EMA protocol on a personal phone and the other participants opted to complete the exit questionnaire. In-depth qualitative follow-ups have been conducted with 9.5% (15/158) participants with usable data. Initial analyses of quantitative and qualitative data have begun with mixed-methods analysis planned for the near future. We expect to recruit 50 additional participants and complete analyses by September of 2019.

Figure 3. Consolidated Standards of Reporting Trials diagram for the Log My Life study. EMA: ecological momentary assessment.



Discussion

Overview

This paper presents the protocols of a mixed-methods prospective longitudinal study designed to explore risk behavior of recently or currently homeless youth. This study is one of the few studies that have used EMA with homeless populations [20,38] and is the first, to our knowledge, that incorporates social networks with specific, identified alters in EMA, which can help improve our understanding of the role of social context. This study is also one of the first to leverage smartphone location-sensing capabilities and phone-based EMA to permit participants to report on a variety of contextual (location and physical or social surroundings) and psychosocial factors that vary throughout the day (current affect, substance use cravings, and hunger) [15]. The use of GEMA has clear methodological advantages over other approaches used in studies on homeless youth behavior, in that it can improve recall bias and ecological validity and is particularly well suited to studying substance use given its episodic nature and relation to context and current affect [15]. The use of geographic information systems also provides the ability to overlay neighborhood- or community-level data such as crime rates or density of alcohol outlets or marijuana dispensaries.

Strengths and Limitations

We note the importance of using a mixed-methods GEMA that can provide insights into the strengths and weaknesses of traditional EMA studies [15]. EMA surveys are generally short and do not necessarily capture the richness of experiences, which is something that this study addresses through in-depth qualitative interviews that incorporate geographical considerations. Further consideration will be needed when integrating quantitative and qualitative data, especially if those data sources appear to be in conflict. Although this is the first study to use this type of mixed-methods approach to examine substance use and sexual risk behavior among homeless youth, mixed-methods studies that have included geographical data have focused on how environment affects access to public transit [86], arrhythmia in old age [87], or tobacco use [15].

Although the goal of this paper is to describe study protocols and highlight innovative aspects of the study design, we also note that the study has been successful in recruiting homeless youth who have been considered hard to engage and formerly homeless youth living in housing programs who have been understudied [88]. To date, we have had high EMA compliance and few lost phones. Further efforts are needed to understand if an incentive structure based on compliance, which has resulted in high compliance, may adversely affect data quality. Other potential challenges may include discrepancies between qualitative and quantitative reporting, missing or inaccurate geospatial data, and youth failing to admit to drug use or other risky behavior due to stigma.

Conclusions

Despite limitations, this mixed-methods design provides rich data difficult to collect with traditional survey methodology. We know context influences health behavior [20], but we know little about the daily environments of recently homeless young adults, particularly how their movements in space and time can result in dangerous substance use or sexual activity. At a minimum, information gained from this project can inform providers of the typical risks experienced by their clients and potentially inform structural interventions in housing programs. Geospatial data could point to *hotspots* (see Veldhuizen et al [89]) or specific risky environments in which young adults often interact. Furthermore, ecologically valid methods allow researchers to approximate what might be occurring in real time and bring us one step closer to identifying leverage points where intervention might be particularly fruitful. The combination of EMA and geospatial data can greatly enhance the development of ecological momentary interventions or just-in-time adaptive interventions [90,91]. Theoretically, these interventions harness the power of mobile phone technology, particularly geospatial sensors and app-based momentary prompts, to intervene at just the right time to shift an individual's behavior. Mobile interventions are potentially affordable solutions to intervening among populations that are typically hard to reach. We now have the technology to deliver preventive interventions in situ, but we do not yet fully understand the dynamic nature of health risk behaviors [92]. We hope that studies such as this can begin to untangle this complexity.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Ecological momentary assessment (EMA) items.

[PDF File (Adobe PDF File), 40KB - resprot_v8i1e12112_app1.pdf]

Multimedia Appendix 2

Sample smartphone app screen images.

[PDF File (Adobe PDF File), 147KB - resprot_v8i1e12112_app2.pdf]

Multimedia Appendix 3

Daily log items.

[PDF File (Adobe PDF File), 47KB - resprot_v8i1e12112_app3.pdf]

References

1. Latkin C, German D, Vlahov D, Galea S. Neighborhoods and HIV: a social ecological approach to prevention and care. Am Psychol 2013;68(4):210-224 [FREE Full text] [doi: 10.1037/a0032704] [Medline: 23688089]

2. Rhodes T, Simic M. Transition and the HIV risk environment. Br Med J 2005 Jul 23;331(7510):220-223 [FREE Full text] [doi: 10.1136/bmj.331.7510.220] [Medline: 16037463]
3. Strathdee S, Hallett T, Bobrova N, Rhodes T, Booth R, Abdool R, et al. HIV and risk environment for injecting drug users: the past, present, and future. Lancet 2010 Jul;376(9737):268-284 [FREE Full text] [doi: 10.1016/S0140-6736(10)60743-X]
4. Beech B, Myers L, Beech D. Hepatitis B and C infections among homeless adolescents. Fam Community Health 2002;25(2):28-36 [FREE Full text] [doi: 10.1097/00003727-200207000-00005]
5. Rice E, Milburn N, Monro W. Social networking technology, social network composition, and reductions in substance use among homeless adolescents. Prev Sci 2011 Mar;12(1):80-88 [FREE Full text] [doi: 10.1007/s11121-010-0191-4] [Medline: 21194011]
6. Rice E. The positive role of social networks and social networking technology in the condom-using behaviors of homeless young people. Public Health Rep 2010;125(4):588-595 [FREE Full text] [doi: 10.1177/003335491012500414] [Medline: 20597459]
7. Noell J, Rohde P, Ochs L, Yovanoff P, Alter MJ, Schmid S, et al. Incidence and prevalence of chlamydia, herpes, and viral hepatitis in a homeless adolescent population. Sex Transm Dis 2001;28(1):4-10 [FREE Full text] [doi: 10.1097/00007435-200101000-00003]
8. Coates J, McKenzie-Mohr S. Out of the frying pan, into the fire: trauma in the lives of homeless youth prior to and during homelessness. J Sociol Soc Welfare 2010 Dec;37(4):65-96 [FREE Full text]
9. Edidin J, Ganim Z, Hunter S, Karnik N. The mental and physical health of homeless youth: a literature review. Child Psychiatry Hum Dev 2012 Jun;43(3):354-375 [FREE Full text] [doi: 10.1007/s10578-011-0270-1] [Medline: 22120422]
10. Rice E, Monro W, Barman-Adhikari A, Young S. Internet use, social networking, and HIV/AIDS risk for homeless adolescents. J Adolesc Health 2010 Dec;47(6):610-613 [FREE Full text] [doi: 10.1016/j.jadohealth.2010.04.016] [Medline: 21094441]
11. Rice E, Barman-Adhikari A, Milburn N, Monro W. Position-specific HIV risk in a large network of homeless youths. Am J Public Health 2012 Jan;102(1):141-147 [FREE Full text] [doi: 10.2105/AJPH.2011.300295] [Medline: 22095350]
12. Henwood B, Rhoades H, Hsu H, Couture J, Rice E, Wenzel S. Changes in social networks and HIV risk behaviors among homeless adults transitioning into permanent supportive housing: a mixed-methods pilot study. J Mix Methods Res 2016 Jul 08;11(1):124-137 [FREE Full text] [doi: 10.1177/1558689815607686]
13. Wenzel S, Rice E, Henwood B, Rhoades H. Grantome. Bethesda, MD: National Institute of Drug Abuse; 2014. HIV Risk, Drug Use, Social Networks: Homeless Persons Transitioned to Housing URL: http://grantome.com/grant/NIH/R01-DA036345-04 [accessed 2018-11-22] [WebCite Cache ID 748R1NbIs]
14. Pierce S, Grady B, Holtzen H. Daybreak in Dayton: assessing characteristics and outcomes of previously homeless youth living in transitional housing. Child Youth Serv Rev 2018 May;88:249-256 [FREE Full text] [doi: 10.1016/j.childyouth.2018.03.021]
15. McQuoid J, Thrul J, Ling P. A geographically explicit ecological momentary assessment (GEMA) mixed method for understanding substance use. Soc Sci Med 2018 Dec;202:89-98 [FREE Full text] [doi: 10.1016/j.socscimed.2018.02.014] [Medline: 29518701]
16. Kirchner T, Shiffman S. Spatio-temporal determinants of mental health and well-being: advances in geographically-explicit ecological momentary assessment (GEMA). Soc Psychiatry Psychiatr Epidemiol 2016 Dec;51(9):1211-1223 [FREE Full text] [doi: 10.1007/s00127-016-1277-5] [Medline: 27558710]
17. Stone A, Shiffman S. Ecological validity for patient reported outcomes. In: Steptoe A, editor. Handbook of Behavioral Medicine: Methods and Applications. New York, NY: Springer; 2010:99-112.
18. Hufford M, Shiffman S, Paty J, Stone A. Ecological momentary assessment: Real-world, real-time measurement of patient experience. In: Fahrenberg J, Myrtek M, editors. Progress in Ambulatory Assessment: Computer-Assisted Psychological and Psychophysiological Methods in Monitoring and Field Studies. Ashland, NC: Hogrefe & Huber; 2001:69-92.
19. Shiffman S, Stone A, Hufford M. Ecological momentary assessment. Annu Rev Clin Psychol 2008 Apr;4(1):1-32 [FREE Full text] [doi: 10.1146/annurev.clinpsy.3.022806.091415]
20. Santa Maria D, Padhye N, Yang Y, Gallardo K, Santos G, Jung J, et al. Drug use patterns and predictors among homeless youth: results of an ecological momentary assessment. Am J Drug Alcohol Abuse 2018;44(5):551-560 [FREE Full text] [doi: 10.1080/00952990.2017.1407328] [Medline: 29286835]
21. Linas B, Latkin C, Westergaard R, Chang L, Bollinger R, Genz A, et al. Capturing illicit drug use where and when it happens: an ecological momentary assessment of the social, physical and activity environment of using versus craving illicit drugs. Addiction 2015 Feb;110(2):315-325 [FREE Full text] [doi: 10.1111/add.12768] [Medline: 25311241]
22. Epstein D, Marrone G, Heishman S, Schmittner J, Preston K. Tobacco, cocaine, and heroin: craving and use during daily life. Addict Behav 2010 Apr;35(4):318-324 [FREE Full text] [doi: 10.1016/j.addbeh.2009.11.003] [Medline: 19939575]
23. Epstein D, Willner-Reid J, Vahabzadeh M, Mezghanni M, Lin J, Preston K. Real-time electronic diary reports of cue exposure and mood in the hours before cocaine and heroin craving and use. Arch Gen Psychiatry 2009 Jan;66(1):88-94 [FREE Full text] [doi: 10.1001/archgenpsychiatry.2008.509] [Medline: 19124692]

24. Kennedy A, Epstein D, Phillips K, Preston K. Sex differences in cocaine/heroin users: drug-use triggers and craving in daily life. Drug Alcohol Depend 2013 Sep 01;132(1-2):29-37 [FREE Full text] [doi: 10.1016/j.drugalcdep.2012.12.025] [Medline: 23357742]
25. Lin JL, Vahabzadeh M, Mezghanni M, Epstein DH, Preston KL. A high-level specification for adaptive ecological momentary assessment: real-time assessment of drug craving, use and abstinence. AMIA Annu Symp Proc 2005:455-459 [FREE Full text] [Medline: 16779081]
26. Milburn N, Rice E, Rotheram-Borus M, Mallett S, Rosenthal D, Batterham P, et al. Adolescents exiting homelessness over two years: the risk amplification and abatement model. J Res Adolesc 2009 Dec 01;19(4):762-785 [FREE Full text] [doi: 10.1111/j.1532-7795.2009.00610.x] [Medline: 25067896]
27. Padgett D. There's no place like (a) home: ontological security among persons with serious mental illness in the United States. Soc Sci Med 2007 May;64(9):1925-1936 [FREE Full text] [doi: 10.1016/j.socscimed.2007.02.011] [Medline: 17355900]
28. Padgett D, Henwood B, Abrams C, Drake R. Social relationships among persons who have experienced serious mental illness, substance abuse, and homelessness: implications for recovery. Am J Orthopsychiatry 2008 Jul;78(3):333-339 [FREE Full text] [doi: 10.1037/a0014155] [Medline: 19123752]
29. Jennings J, Woods S, Curriero F. The spatial and temporal association of neighborhood drug markets and rates of sexually transmitted infections in an urban setting. Health Place 2013 Sep;23:128-137 [FREE Full text] [doi: 10.1016/j.healthplace.2013.06.002] [Medline: 23872251]
30. Skelly A, Arcury T, Gesler W, Cravey A, Dougherty M, Washburn S, et al. Sociospatial knowledge networks: appraising community as place. Res Nurs Health 2002 Mar 14;25(2):159-170 [FREE Full text] [doi: 10.1002/nur.10024]
31. Petering R, Rice E, Rhoades H, Winetrobe H. The social networks of homeless youth experiencing intimate partner violence. J Interpers Violence 2014 Aug;29(12):2172-2191 [FREE Full text] [doi: 10.1177/0886260513516864] [Medline: 24421071]
32. El-Bassel N, Gilbert L, Wu E, Chang M. A social network profile and HIV risk among men on methadone: do social networks matter? J Urban Health 2006 Jul;83(4):602-613 [FREE Full text] [doi: 10.1007/s11524-006-9075-0] [Medline: 16755389]
33. Friedman S, Mateu-Gelabert P, Curtis R, Maslow C, Bolyard M, Sandoval M, et al. Social capital or networks, negotiations, and norms? A neighborhood case study. Am J Prev Med 2007 Jun;32(6 Suppl):S160-S170 [FREE Full text] [doi: 10.1016/j.amepre.2007.02.005] [Medline: 17543707]
34. Latkin C, Forman V, Knowlton A, Sherman S. Norms, social networks, and HIV-related risk behaviors among urban disadvantaged drug users. Soc Sci Med 2003 Feb;56(3):465-476 [FREE Full text] [doi: 10.1016/S0277-9536(02)00047-3]
35. Rice E, Lee A, Taitt S. Cell phone use among homeless youth: potential for new health interventions and research. J Urban Health 2011 Dec;88(6):1175-1182 [FREE Full text] [doi: 10.1007/s11524-011-9624-z] [Medline: 22076445]
36. Rhoades H, Wenzel S, Rice E, Winetrobe H, Henwood B. No digital divide? Technology use among homeless adults. J Soc Distr Homeless 2017 Mar 22;26(1):73-77 [FREE Full text] [doi: 10.1080/10530789.2017.1305140]
37. United States Congress. 2009. The McKinney-Vento Homeless Assistance Act As amended by S. 896 The Homeless Emergency Assistance and Rapid Transition to Housing (HEARTH) Act of 2009 URL: https://www.hudexchange.info/resources/documents/HomelessAssistanceActAmendedbyHEARTH.pdf [accessed 2018-11-23] [WebCite Cache ID 748UFhHBQ]
38. Tyler K, Olson K. Examining the feasibility of ecological momentary assessment using short message service surveying with homeless youth: lessons learned. Field Methods 2018 Apr 16;30(2):91-104 [FREE Full text] [doi: 10.1177/1525822X18762111]
39. Field M. Ecological momentary assessment - new insights and opportunities. Addiction 2015 Jun;110(6):1043-1044. [doi: 10.1111/add.12925] [Medline: 25963876]
40. Smyth J, Smyth JM. Ecological momentary assessment research in behavioral medicine. J Happiness Stud 2003;4(1):35-52 [FREE Full text] [doi: 10.1023/A:1023657221954]
41. Dunton G, Atienza A, Castro C, King A. Using ecological momentary assessment to examine antecedents and correlates of physical activity bouts in adults age 50+ years: a pilot study. Ann Behav Med 2009 Dec;38(3):249-255 [FREE Full text] [doi: 10.1007/s12160-009-9141-4] [Medline: 20052568]
42. Dunton G, Kawabata K, Intille S, Wolch J, Pentz M. Assessing the social and physical contexts of children's leisure-time physical activity: an ecological momentary assessment study. Am J Health Promot 2012;26(3):135-142 [FREE Full text] [doi: 10.4278/ajhp.100211-QUAN-43] [Medline: 22208410]
43. Dunton G, Liao Y, Intille S, Wolch J, Pentz M. Physical and social contextual influences on children?s leisure-time physical activity: an ecological momentary assessment study. J Phys Act Health 2011 Jan;8(s1):S103-S108 [FREE Full text] [doi: 10.1123/jpah.8.s1.s103]
44. Dunton G, Whalen C, Jamner L, Floro J. Mapping the social and physical contexts of physical activity across adolescence using ecological momentary assessment. Ann Behav Med 2007 Jun;34(2):144-153 [FREE Full text] [doi: 10.1007/BF02872669]

45. Trull T, Ebner-Priemer U. 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]
46. Broderick JE, Schwartz JE, Schneider S, Stone AA. Can End-of-day reports replace momentary assessment of pain and fatigue? J Pain 2009 Mar;10(3):274-281 [FREE Full text] [doi: 10.1016/j.jpain.2008.09.003] [Medline: 19070550]
47. Stockwell T, Donath S, Cooper-Stanbury M, Chikritzhs T, Catalano P, Mateo C. Under-reporting of alcohol consumption in household surveys: a comparison of quantity-frequency, graduated-frequency and recent recall. Addiction 2004 Aug;99(8):1024-1033 [FREE Full text] [doi: 10.1111/j.1360-0443.2004.00815.x] [Medline: 15265099]
48. Broderick J, Schwartz J, Vikingstad G, Pribbernow M, Grossman S, Stone A. The accuracy of pain and fatigue items across different reporting periods. Pain 2008 Sep 30;139(1):146-157 [FREE Full text] [doi: 10.1016/j.pain.2008.03.024] [Medline: 18455312]
49. Perron J, Cleverley K, Kidd S. Resilience, loneliness, and psychological distress among homeless youth. Arch Psychiatr Nurs 2014 Aug;28(4):226-229 [FREE Full text] [doi: 10.1016/j.apnu.2014.05.004] [Medline: 25017554]
50. Tyler K, Melander L. Child abuse, street victimization, and substance use among homeless young adults. Youth Soc 2013 Jan 06;47(4):502-519 [FREE Full text] [doi: 10.1177/0044118X12471354]
51. Heerde J, Scholes-Balog K, Hemphill S. Associations between youth homelessness, sexual offenses, sexual victimization, and sexual risk behaviors: a systematic literature review. Arch Sex Behav 2015 Jan;44(1):181-212 [FREE Full text] [doi: 10.1007/s10508-014-0375-2] [Medline: 25411128]
52. Kroenke K, Spitzer R, Williams J. 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]
53. Spitzer R, Williams J, Kroenke K, Linzer M, deGruy FV, Hahn S, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. J Am Med Assoc 1994 Dec 14;272(22):1749-1756. [Medline: 7966923]
54. Spitzer R, Kroenke K, Williams J, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
55. Prins A, Ouimette P, Kimerling R, Camerond RP, Hugelshofer D, Shaw-Hegwer J, et al. The primary care PTSD screen (PC–PTSD): development and operating characteristics. Prim Care Psych 2004 Jan 01;9(1):9-14 [FREE Full text] [doi: 10.1185/135525703125002360]
56. Kaufman E, Xia M, Fosco G, Yaptangco M, Skidmore C, Crowell S. The Difficulties in Emotion Regulation Scale Short Form (DERS-SF): validation and replication in adolescent and adult samples. J Psychopathol Behav Assess 2015 Nov 23;38(3):443-455 [FREE Full text] [doi: 10.1007/s10862-015-9529-3]
57. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385 [FREE Full text] [doi: 10.2307/2136404]
58. Carver C, Scheier M, Weintraub J. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol 1989;56(2):267-283 [FREE Full text] [doi: 10.1037/0022-3514.56.2.267]
59. Brener N, Collins J, Kann L, Warren C, Williams B. Reliability of the Youth Risk Behavior Survey Questionnaire. Am J Epidemiol 1995 Mar 15;141(6):575-580. [Medline: 7900725]
60. Brener N, Kann L, Mcmanus T, Kinchen S, Sundberg E, Ross J. Reliability of the 1999 Youth Risk Behavior Survey Questionnaire. J Adolesc Health 2002 Oct;31(4):336-342 [FREE Full text] [doi: 10.1016/S1054-139X(02)00339-7]
61. Centers for Disease Control and Prevention. 2015 Youth Risk Behavior Survey Questionnaire URL: https://www.cdc.gov/healthyyouth/data/yrbs/index.htm [accessed 2018-11-21] [WebCite Cache ID 746ekwonw]
62. Rice E. Grantome. Bethesda, MD: National Institute of Mental Health; 2011. HIV Risk in Large Networks of Homeless Youth URL: http://grantome.com/grant/NIH/R01-MH093336-01 [accessed 2018-11-23] [WebCite Cache ID 748UgXIxd]
63. Ewing J. Detecting alcoholism: the CAGE questionnaire. J Am Med Assoc 1984 Oct 12;252(14):1905 [FREE Full text] [doi: 10.1001/jama.1984.03350140051025]
64. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J 1995;94(3):135-140. [Medline: 7778330]
65. Casey K, Reid R, Trout A, Hurley K, Chmelka M, Thompson R. The transition status of youth departing residential care. Child Youth Care Forum 2010 Apr 29;39(5):323-340 [FREE Full text] [doi: 10.1007/s10566-010-9106-6]
66. Ansell D, Morse J, Nollan K, Hoskins R. Life Skills Guidebook. Seattle, WA: Casey Family Programs; 2004.
67. Steinberg A, Brymer M, Decker K, Pynoos R. The University of California at Los Angeles post-traumatic stress disorder reaction index. Curr Psychiatry Rep 2004 Mar;6(2):96-100 [FREE Full text] [doi: 10.1007/s11920-004-0048-2]
68. Rew L, Powell T, Thompson S. Stress on the streets: validation of a measurement. J Soc Dist Homeless 2016 Jan 08;25(1):11-18 [FREE Full text] [doi: 10.1080/10530789.2015.1116837]
69. Coates J, Swindale A, Bilinsky P. Food and Nutrition Technical Assistance. Household Food Insecurity Access Scale (HFIAS) for Measurement of Household Food Access: Indicator Guide (v. 3) URL: http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf [accessed 2018-11-23] [WebCite Cache ID 748UvYD9T]
70. Research, Education and Advocacy Co-Lab for Youth Stability and Thriving. 2018. Homeless youth risk and resilience survey URL: https://www.realyst.org/hyrrs [accessed 2018-11-21] [WebCite Cache ID 746h5Rq0o]

71. Burt R. Network items and the general social survey. Soc Networks 1984 Dec;6(4):293-339 [FREE Full text] [doi: 10.1016/0378-8733(84)90007-8]
72. Wasserman S, Faust K. Social Network Analysis: Methods and Applications. New York: Cambridge University Press; 1994.
73. Kloos B, Shah S. A social ecological approach to investigating relationships between housing and adaptive functioning for persons with serious mental illness. Am J Community Psychol 2009 Dec;44(3-4):316-326 [FREE Full text] [doi: 10.1007/s10464-009-9277-1] [Medline: 19862615]
74. Ben-Zeev D, McHugo G, Xie H, Dobbins K, Young M. Comparing retrospective reports to real-time/real-place mobile assessments in individuals with schizophrenia and a nonclinical comparison group. Schizophr Bull 2012 May;38(3):396-404 [FREE Full text] [doi: 10.1093/schbul/sbr171] [Medline: 22302902]
75. Epstein D, Preston K. Daily life hour by hour, with and without cocaine: an ecological momentary assessment study. Psychopharmacology (Berl) 2010 Aug;211(2):223-232 [FREE Full text] [doi: 10.1007/s00213-010-1884-x] [Medline: 20532873]
76. Kowalczyk W, Phillips K, Jobes M, Kennedy A, Ghitza U, Agage D, et al. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. Am J Psychiatry 2015 Aug 01;172(8):760-767 [FREE Full text] [doi: 10.1176/appi.ajp.2014.14081014] [Medline: 25783757]
77. Phillips K, Epstein D, Vahabzadeh M, Mezghanni M, Lin J, Preston K. Substance use and hepatitis C: an ecological momentary assessment study. Health Psychol 2014 Jul;33(7):710-719 [FREE Full text] [doi: 10.1037/hea0000087] [Medline: 24977312]
78. Vahabzadeh M, Lin J, Mezghanni M, Epstein D, Preston K. Automation in an addiction treatment research clinic: computerised contingency management, ecological momentary assessment and a protocol workflow system. Drug Alcohol Rev 2009 Jan;28(1):3-11 [FREE Full text] [doi: 10.1111/j.1465-3362.2008.00007.x] [Medline: 19320669]
79. Jones M, Pebley A. Redefining neighborhoods using common destinations: social characteristics of activity spaces and home census tracts compared. Demography 2014 Jun;51(3):727-752 [FREE Full text] [doi: 10.1007/s13524-014-0283-z] [Medline: 24719273]
80. Stake R. Multiple Case Study Analysis. New York: Guilford Press; 2005.
81. Yin R. Case Study Research: Design and Method. Thousand Oaks, CA: Sage Publications; 2003.
82. Miles MB, Huberman AM, Saldana J. Qualitative Data Analysis. Thousand Oaks, CA: Sage Publications; 2013.
83. Plano Clark VL, Creswell JW. Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: Sage Publications; 2010.
84. Palinkas L, Horwitz S, Chamberlain P, Hurlburt M, Landsverk J. Mixed-methods designs in mental health services research: a review. Psychiatr Serv 2011 Mar;62(3):255-263. [doi: 10.1176/ps.62.3.pss6203_0255] [Medline: 21363896]
85. 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]
86. Hernandez D, Rossel C. Inequality and access to social services in Latin Americapace-time constraints of child health checkups and prenatal care in Montevideo. J Transp Geogr 2015;44:24-32. [doi: 10.1016/j.jtrangeo.2015.02.007]
87. Lager D, Van Hoven B, Huigen P. Rhythms, ageing and neighborhoods. Environ Plan 2018;48(8):1565-1580. [doi: 10.1177/0308518X16643962]
88. Henwood BF, Redline B, Semborski S, Rhoades H, Rice E, Wenzel S. A grounded theory of the relationship between ontological security, mental health, social relationships, and identity formation for young adults in supportive housing. Cityscape 2019 (forthcoming).
89. Veldhuizen EM, Osté J, Kunst A. Environmental characteristics of hotspots of alcohol-related health incidents outside of the entertainment districts of Amsterdam. GeoJournal 2017 Oct 6;83(5):1053-1066 [FREE Full text] [doi: 10.1007/s10708-017-9818-3]
90. Nahum-Shani I, Smith S, Spring B, Collins L, Witkiewitz K, Tewari A, et al. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med 2018 May 18;52(6):446-462 [FREE Full text] [doi: 10.1007/s12160-016-9830-8] [Medline: 27663578]
91. Intille SS. Technological innovations enabling automatic, context-sensitive ecological momentary assessment. In: Stone A, Shiffman S, Atienza A, Nebeling L, editors. The Science of Real-Time Data Capture: Self-Report in Health Research. Oxford: Oxford University Press; 2007:308-337.
92. Riley W, Rivera D, Atienza A, Nilsen W, Allison S, Mermelstein R. Health behavior models in the age of mobile interventions: are our theories up to the task? Transl Behav Med 2011 Mar;1(1):53-71 [FREE Full text] [doi: 10.1007/s13142-011-0021-7] [Medline: 21796270]

Abbreviations

EMA: ecological momentary assessment
GEMA: geographically explicit ecological momentary assessments
GLMM: generalized linear mixed model

GPS: global positioning system
LML: Log My Life

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Protocol

Use of Mental Health Apps by Breast Cancer Patients and Their Caregivers in the United States: Protocol for a Pilot Pre-Post Study

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Abstract

Background: Over one-third of cancer patients experience clinically significant mental distress, and distress in caregivers can exceed that of the cancer patients for whom they care. There is an urgent need to identify scalable and cost-efficient ways of delivering mental health interventions to cancer patients and their loved ones.

Objective: The aim of this study is to describe the protocol to pilot a mobile app–based mental health intervention in breast cancer patients and caregivers.

Methods: The IntelliCare mental health apps are grounded in evidence-based research in psychology. They have not been examined in cancer populations. This pilot study will adopt a within-subject, pre-post study design to inform a potential phase III randomized controlled trial. A target sample of 50 individuals (with roughly equal numbers of patients and caregivers) at least 18 years of age and fluent in English will be recruited at a US National Cancer Institute designated clinical cancer center. Consent will be obtained in writing and a mobile phone will be provided if needed. Self-report surveys assessing mental health outcomes will be administered at a baseline session and after a 7-week intervention. Before using the apps, participants will receive a 30-min coaching call to explain their purpose and function. A 10-min coaching call 3 weeks later will check on user progress and address questions or barriers to use. Self-report and semistructured interviews with participants at the end of the study period will focus on user experience and suggestions for improving the apps and coaching in future studies.

Results: This study is ongoing, and recruitment will be completed by the end of 2018.

Conclusions: Results from this study will inform how scalable mobile phone-delivered programs can be used to support breast cancer patients and their loved ones.

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KEYWORDS

cancer; caregivers; mental health; mHealth

Introduction

Background

In the United States, an estimated 266,120 new cases of invasive breast cancer are expected to be diagnosed in 2018 [1]. Breast cancer is the most common form of cancer in women and the second leading cause of cancer-related deaths in women. In the United States, over 40% of newly diagnosed breast cancer patients report clinically significant distress [2]. Cancer affects not only patients but also their caregivers, which can include a partner, relative, or friend. Responsibilities directly (eg, coordinating care) and indirectly (eg, providing emotional support) linked to their loved one's care leave caregivers at high risk for burnout [3]. However, despite levels of psychological distress that can exceed those of the cancer patients for whom they care [4], caregivers of cancer patients remain an underserved, yet vulnerable, population. Thus, there is an urgent need to identify ways to provide supportive care to both cancer patients and their loved ones.

Mobile Interventions for Cancer Populations

Although distress screening has become a standard practice for many cancer programs [5], distress intervention through mobile technology remains an important need in the cancer community [6]. Community and health care organizations are important providers of support services for both cancer patients and their caregivers. Many of them are beginning to provide services through virtual means such as the phone and internet. However, existing models of psychosocial intervention that are heavily reliant on human support are costly and not readily scalable to large populations. For example, on-demand phone helplines need to be constantly staffed by nurses or mental health professionals and are limited in their ability to address the needs of a large and growing cancer population in the United States. Given that over 77% of American adults own a mobile phone [7], it is an ideal platform from which to deliver brief, empirically supported interventions to anyone that needs them. Mental health apps are easily scalable and can provide tailored interventions when and where they are most needed.

Limitations of Prior Work

Despite the promise of mobile phone mental health apps, significant issues need to be addressed before making them widely available to cancer populations. Although researchers are increasingly examining the efficacy and effectiveness of mental health apps, reviews have found that few publicly available apps have any empirical evidence supporting them [8,9]. These reviews generally paint a bleak outlook for the presence of empirically supported mental health apps, which is negatively impacted by the proliferation of mental health apps in recent years. Although more than 10,000 mental health–related apps are available for download, the lack of thorough investigation of these apps by clinical scientists, combined with a lack of government regulatory oversight, makes many of these apps unhelpful at best and dangerous at worst [10-13]. It is, therefore, imperative to empirically validate mental health apps for the population they are intended for, such as mental health apps for cancer populations. Research has found that the majority of apps for cancer either focus on cancer-symptom monitoring or are intended to raise awareness of cancer through fundraising or promoting a charitable organization [6]. A conclusion to be made from these papers is that a dearth of mental health apps have been tested and designed for cancer populations, which served as the impetus for undertaking this study.

Most health-related apps suffer from poor usability for a variety of reasons such as requiring lengthy engagement times that do not match user preferences [14]. In reality, people use apps in short, frequent time bursts and prefer apps that support a single or limited set of tasks [15]. Providing brief and targeted interventions is particularly important for cancer patients and caregivers as the demands of cancer treatment often leave them with small pockets of time throughout the day. Importantly, pairing an app with light coaching can further increase motivation and adherence [16,17]. In contrast to the majority of support apps that do not provide human assistance, light phone coaching can increase adherence by focusing on how apps can address people's needs and by identifying obstacles to their effective use [16,17].

Objective of This Study

The purpose of this study is to conduct a pilot study that uses a set of brief, targeted app-delivered interventions that promote mental health. IntelliCare is a collection of apps that use an elemental, skill-based approach to improving mental health [18]. App content is based on evidence-based approaches in cognitive behavioral therapy (CBT) as well as concepts from mindfulness and positive psychology. For example, one of the apps, Thought Challenger (see Figure 1), guides individuals through an exercise to identify and challenge negative thinking styles, a common CBT approach for anxiety and depression. Another app, Purple Chill, provides users with mindfulness audios that can be accessed at any time. Users can download up to 12 publicly available intervention apps, each of which targets a specific aspect of mental health and well-being (eg, identifying maladaptive thoughts, promoting sleep, and increasing relaxation skills). The apps are designed to be interactive and intuitive. Users can complete many exercises (eg, identifying and challenging an unhelpful thought) in less than a minute. Exercises require few instructions to complete and are usually found on the first screen that is presented. Each IntelliCare app has a *help* feature that contains educational and technical content regarding the specific app in question. See Table 1 for a description of IntelliCare apps and their objectives.

IntelliCare apps are available on both Android and iPhone stores. Those from the general public who download the apps are free to use the apps as desired [19]. Similar to prior IntelliCare work [18], participants in this study are instructed to systematically try 1 to 2 apps per week and retain the ones that are most helpful to them. The purpose of this strategy is to gradually expose participants to all of the apps in a systematic manner, until all available apps have been tried. This mirrors face-to-face CBT in which clients are encouraged to acquire various skills through practice. Users will determine which apps to use (see Methods section). In an 8-week study with light phone coaching, over 90% of users with elevated depression and anxiety symptoms used the apps an average of 195 times, for an average length of

1 min [18]. In this initial study, IntelliCare usage was notably higher than what has been observed in other electronic health and mobile health (mHealth) intervention programs. It was also found that using the apps led to large and significant decreases in depression (Cohen *d*=1.4) and anxiety symptoms (Cohen *d*=1.2), as measured by the Patient Health Questionnaire (9-item version [20]) and the Generalized Anxiety Disorder questionnaire (7-item version [21]), respectively [18]. However, the acceptability, usability, and potential impact of IntelliCare apps in *cancer* patients and caregivers are unknown. Cancer patients and caregivers are faced with the multiple physical and emotional sequalae of cancer treatment, making them potentially unique from other populations. To design mental health apps that can benefit cancer populations, it is important to understand their preferences for using them.

The purpose of this trial was to conduct a pilot study to inform a potential phase III randomized controlled trial (RCT). Consistent with prior definitions and reasons for conducting a pilot study [22,23], the goals of this study are to (1) assess the feasibility of various components (eg, recruitment rates, retention rates, and refusal rates) that need to take place in a larger study; (2) understand and identify potential human and data optimization issues (eg, issues of managing the study in a busy clinic and identifying challenges to recruitment from doctors and nurses, whether data show too much or too little variability); and (3) examine whether participants respond to the intervention. Importantly, a pilot study is not only concerned with whether something can be done and how to proceed but includes implementing something in a way intended in part of a future study [22].

Figure 1. Screenshots of the Thought Challenger app as seen on a mobile phone screen.

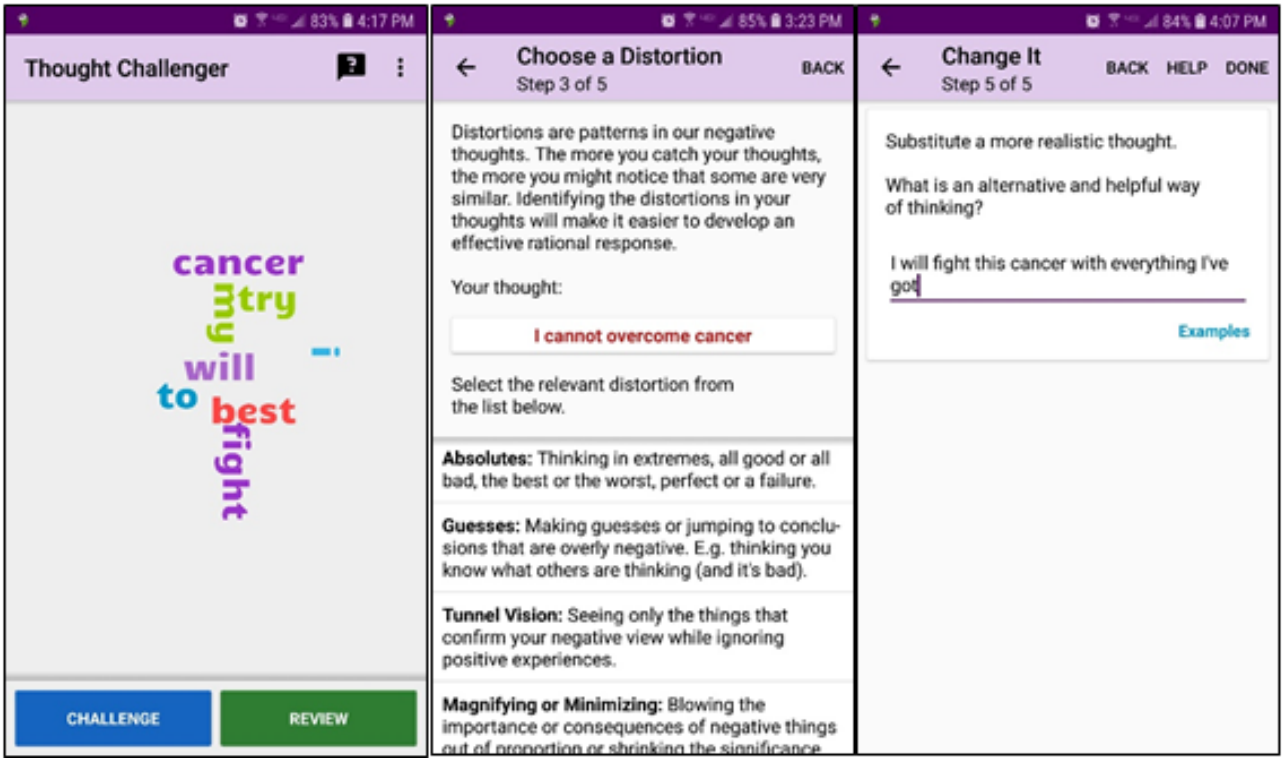

Table 1. Description of IntelliCare apps and their objectives.

App name	Objective
Aspire	Promote awareness of and striving toward personal goals and values. Helps users identify their values and keep track of their progress.
Day to Day	Promote knowledge about ways to bolster mood. Users receive a daily stream of knowledge tidbits and are prompted to build on a theme every day (eg, cultivate gratitude and problem solve).
Daily Feats	Promotes goal setting and attainment. An in-app built calendar allows users to track their successes and identify new tasks to complete.
Worry Knot	Promotes knowledge about worry and provides an interactive exercise to decrease worry. The app also tracks the user's progress and provides tailored feedback on ways to distract oneself from worrying thoughts.
Social Force	Encourages users to identify supportive individuals in their life. The app prompts users to reach out to these people for encouragement.
My Mantra	Increases self-efficacy and a positive perspective of oneself. The app prompts users to come up with personal mantras and to construct personalized photo albums that serve as reminders of these mantras.
Thought Challenger	Increases the ability to identify and challenge negative thinking patterns. Guides users through a cognitive restructuring exercise and tracks the output of past exercises.
iCope	Promotes coping and positive reinforcement by having users write and send themselves encouraging messages when they are most needed.
Purple Chill	Increases relaxation skills by providing a library of mindfulness and guided meditation audio files.
MoveMe	Promotes mood through physical activity. The app prompts users to schedule exercises throughout the day or week and provides instructional videos and lessons to increase motivation to exercise.
Slumber Time	Promotes healthy sleeping by prompting users to keep an active sleep diary. The app also provides a checklist of things to do before bedtime to promote healthy sleep habits.
Boost Me	Promotes positive mood by having users schedule positive activities throughout the day. A mood tracker allows users to see their progress and the impact of different activities on their mood.

Methods

Study Design

This single-group, 7-week, pre- and posttest pilot study will provide IntelliCare apps to a sample of breast cancer patients and their caregivers in the United States. A mixed-methods approach using self-report measures and qualitative interviews will be used to evaluate user satisfaction and potential for adoption in a larger and more diverse cancer population. In addition, because the apps used in this study are not tailored for breast cancer populations, qualitative interviews will yield crucial feedback to determine what changes to the IntelliCare apps can be made in a larger trial. Passively collected app usage data (ie, app launches and app session duration) will inform our understanding of engagement with the apps among cancer patients and caregivers. The decision to use a 7-week duration was based on the duration of brief face-to-face psychotherapy (typically 6-8 weeks) as well as prior reviews of mHealth studies, finding that the duration of app interventions range between 6 days and 8 weeks [8].

Participants

To limit barriers to entry, inclusion criteria are limited to the following: (1) breast cancer patient or informal caregiver (ie, not receiving compensation for providing care); (2) at least 18 years of age; (3) proficient in English at a sixth grade level; and (4) has a mobile phone or is willing to carry one around if provided. Participants are not required to have a minimum level of familiarity with mobile devices or technology. Participants will be eligible to receive a US $50 gift card for providing user feedback at the end of the study. Study procedures, including the coaching protocol and access to IntelliCare apps, will be identical for both breast cancer patients and caregivers.

A target sample size of 50 (25 patients and 25 caregivers) was chosen, given the exploratory nature of this study. Recruitment of participants will occur in a small breast surgical oncology clinic. Clinics are held on 4 out of 5 weekdays, and the 3 surgical oncologists do not have overlapping clinic times. The recruitment goals were influenced by several factors. First, the patients seen in this clinic are generally early in the breast cancer diagnostic pathway and although it is a time of need for the type of mental health support these apps can provide, it is also a time when it may not be appropriate to recruit them to a study that requires an immediate face-to-face consent and app download process. Second, the logistics of clinic flow, space, and time constraints also influence the pace of recruitment. Overall, 1 to 2 participants per week became the targeted number, which over the course of 29 weeks of active recruitment would yield a sample size between 29 and 58 consented participants.

The primary objective of this study is to inform the feasibility of a larger randomized trial in a clinical setting [22]. Data on usability and user experience from this sample will enable researchers to make iterative changes for future studies. A secondary objective of this study is to provide effect size estimates for a future trial and to pilot the data analyses. This will allow us to explore potential data analytic issues that might arise in a large trial such as missingness and skewness. Within-group analyses will be performed for both breast cancer patients and caregivers (see Data Analysis section). For

reference, an effect size of d= 1.4 for change in depression and anxiety symptoms was found in a prior noncancer sample [18] at 80% power. However, it may not be appropriate to generalize an effect size from a symptomatic depressed sample to an unselected cancer population. For general reference, the smallest effect size that can be detected with a sample size of 25, using paired t tests with 80% power and alpha of .05, is d=0.58, whereas the smallest effect sizes that can be detected with a sample size of 35, using paired t tests with 80% power and alpha of .05, is d=0.49 [24].

Materials

Participants will use their own personal mobile phone (Android or iPhone). Some individuals may not own a mobile phone or have an appropriate mobile phone plan that enables downloading and using a native mobile phone app. To address these issues, those who do not own a mobile phone or have an incompatible device will be provided with a Samsung S7 Android phone with an unlimited data plan. Those who are provided a phone will be able to use it for nonstudy purposes. A concerted effort was made to include both Android and iPhone users in the study, given the differences between users of these platforms in some prior work [25]. All IntelliCare apps are currently available for Android users, and a subset of iPhone apps are available (as of March 2018), although more are planned for release.

Recruitment Procedure

Breast cancer patients and their caregivers will be recruited from a breast care clinic. Surgical oncologists will help to identify potential participants, who will be introduced to the study during a normal scheduled visit. Surgical oncologists will offer a study flyer to breast cancer patients and their caregivers during a normal scheduled visit. Patients and caregivers who express an interest in learning about the study will then speak to a research staff member, who will provide more details about the study and answer any questions. If an eligible patient or caregiver expresses interest in participating in the study, he or she will be led through the consenting process by a research staff member. Research staff will describe the aims of the study, introduce the IntelliCare apps, and review the study timeline. Infographics will serve as visual aids to improve understanding of the study components and timeline. Individuals who provide written consent will schedule a 30-min coaching call to take place sometime within the next 10 days. They will also be guided to download the apps but will be told not to open them until the coaching call. Downloading the apps at the end of the consenting process will allow coaching calls to be kept to within the allotted 30-min time frame. Participants will also have the option to download a separate app (ie, not part of the IntelliCare app suite) that passively collects location and movement data from their phone's sensors. This app, Sensus, was developed by University of Virginia researchers [26] and has been used to collect location and movement data in college student samples [27]. Data collected from this app will be used in exploratory analyses to determine whether it is possible to identify behavioral markers of mood and well-being. For example, in a prior study of college students, it was found that the amount of time spent at home was associated with a higher level of anxiety and that more negative affect was linked to a longer homestay duration [27]. Participants will be asked to spend 10 to 15 min to complete measures that assess depression and anxiety symptoms, physical and social functioning, and subjective well-being. Measures will be completed via the Web using Qualtrics Survey Platform through a desktop or laptop computer. Recruitment will cease if the target enrollment is met or funding expires at the end of 2018. The same research staff members are each responsible for consenting participants, conducting coaching calls, and collecting feedback from participants.

Phone Coaching

A coaching protocol was developed based on the Efficiency Model of behavioral intervention technology support [16] and supportive accountability [17]. A similar coaching protocol has been implemented in a prior study of the IntelliCare apps [18]. The primary aims of coaching are to address usability issues, increase engagement with the apps, promote fit by assessing participants' needs, promote knowledge acquisition of the skills found in the apps, and encourage implementation of the skills in participants' lives. In keeping with the prior study of IntelliCare [18], coaches are instructed to focus on app-related issues and to refrain from doing more traditional counseling with participants. An initial 30-min coaching call will focus on orienting participants to downloading and using the apps, setting expectations of the coach's role, assessing how the apps may meet participants' needs, and building rapport. Participants will also be told that they can contact coaches at any time with any app-related questions. Participants who contact coaches for crisis management will be connected with a nearby mental health service provider. Any participant inquiries will receive a response within 1 working day. Following the initial coaching call, participants will receive a short message service (SMS) text message (via Qualtrics Survey Platform SMS tool) every week to remind them to download and try 1 to 2 new IntelliCare apps. Coaches have a bachelor's degree (not in counseling) and are trained and monitored by the lead author (PC), who has a PhD in clinical and community psychology and over 8 years of experience in conducting psychological assessments and psychotherapy. Coaches received a detailed coaching manual and will attend weekly supervision meetings throughout the duration of the study.

To encourage engagement with the apps, coaches will refrain from making explicit recommendations regarding which apps to use and how often to use them. Instead, following prior work [18], coaches will instruct participants to review the apps, remind them of their needs and goals, and ultimately allow participants to make their own decisions regarding which apps to use. If participants are resistant to making their own decision regarding which apps to use, coaches will be permitted to give recommendations. Precautions were made to help ensure that coaching calls focus on the IntelliCare apps. Specifically, coaches are provided a detailed and scripted coaching manual that they are told to follow closely. Coaches received weekly training and engaged in role playing exercises with the lead author (PC) on how to conduct coaching calls. Finally, a 10-min phone call 3 weeks after the initial coaching call will serve as a check-in to make sure that participants have a clear understanding of the app program and to answer any lingering questions. All described components of this study have been

approved by the University of Virginia institutional review board for Health Sciences Research.

Measures and Outcomes

Primary Objective and Measures

Because a significant barrier to conducting this study is the enrollment of participants in a busy clinical setting, we will consider the study feasible if (1) we are able to recruit 1 to 2 participants per week from a single clinic over 29 weeks; (2) complete follow-up in at least 50% of all recruited subjects; and (3) observe a median app launch rate of around 3.0, as found in prior work [18]. Participants will be asked to provide feedback on the apps and coaching at the end of the study period. The Usability, Satisfaction, and Ease of use (USE [28]) short form scale will be used to examine usability of the IntelliCare apps. It is composed of items that assess user experience (eg, "I would recommend it to a friend," "It is easy to learn to use it," and "It is simply to use"). Items are scored on a 7-point Likert scale (1=strong disagree and 7=strongly agree). The USE measure is a validated scale that is commonly used to evaluate user experience of digital interventions. Participants will be asked to describe the most positive and negative aspects of the apps and which apps were most and least helpful and why. If participants stopped using the apps, they will be asked to comment on why and barriers to using the apps.

Participants will also be asked to provide open-ended feedback. Research staff will conduct telephone interviews with participants, which will cover the following topics related to using the apps: general impressions, design quality, technical needs, and design suggestions to promote app implementation and usage. In addition, participants will be asked to provide feedback on the following aspects of phone coaching: general experience with coaches, usefulness of coaching, additional or unmet coaching needs, and suggestions to improve the coaching experience. Thematic analysis will be used to analyze qualitative data gathered from interviews. Data yielded from this mixed-methods approach will be used to make improvements to the apps and phone coaching in future work.

Secondary Objectives and Measures

Several measures will be administered at baseline and after 7 weeks. Demographic and background variables (eg, age, gender, and race or ethnicity) will be collected at the baseline session. Disease variables (eg, cancer site, stage, and treatments) will also be collected from the patient's electronic medical records. Measures will be administered and completed via a secure data collection website (Qualtrics Survey Platform). Data are stored in a secure database that is only accessible to study personnel to ensure confidentiality.

Depression symptoms will be assessed with the 4-item scale from the Patient-Report Outcomes Measurement Information System [29] 29-item profile version 2.0 (PROMIS-29 Profile v2.0). PROMIS, a US National Institutes of Health Roadmap program, provides sensitive and reliable measures of patient-reported outcomes. A goal of PROMIS is to allow organized and effective assessment of patient-reported outcomes across a range of chronic diseases. Participants are asked to report (1=never and 5=always) the degree to which they experienced various depressed states (eg, "I felt worthless" and "I felt hopeless") over the past 7 days. Continuous anxiety symptoms will be assessed with the 4-item scale from the PROMIS-29 Profile v2.0. Participants are asked to report (1=never and 5=always) how much they have experienced different anxious states (eg, "My worries overwhelmed me" and "I felt fearful") over the past 7 days.

The Patient Health Questionnaire-4 (PHQ-4; [30]) is widely used in cancer settings as a brief screener of general distress and symptom burden [30] and is well validated in both general and clinical samples [30,31]. The PHQ-4 will be administered to examine whether using mental health apps leads to a clinically significant decrease in general distress and overall symptom burden and will be used to classify individuals based on the severity of their mood symptoms at baseline and postassessment. Individuals are asked to rate (0=not at all and 3=nearly every day) the degree to which they have experienced different states (eg, "Little interest or please in doing things") over the past 2 weeks. Scores range from 0 to 12. A score of 6 to 8 indicates moderate mood symptoms, whereas a score of 9 and higher indicates severe mood symptoms. Symptoms assessed by the PHQ-4 and PROMIS anxiety and depression subscales (of PROMIS-29) will be used to obtain estimates of the treatment effects and the variances of treatment effects for a larger trial.

Several measures will be administered to both patients and caregivers. Life meaning will be assessed with the 4-item PROMIS [29] Life Meaning/Purpose scale. Participants are asked to report (1=not at all and 5=very much) the degree to which they agree with 4 statements (eg, "My life has meaning" and "I have a clear sense of direction in life"). Sleep quality will be assessed with the 4-item PROMIS [29] Sleep Disturbance scale from the PROMIS-29 Profile v2.0. Participants are asked to report (1=very poor and 5=very good) on their sleep quality over the last 7 days. They are also asked to report (1=not at all and 5=very much) the degree to which they experienced sleep difficulties (eg, "I had difficulty falling asleep") over the last 7 days. Patients and caregivers will also complete a measure of health care utilization. Patients will be asked whether they visited the emergency department over the past 2 months, whether any of these visits were related to side effects from cancer treatment, whether they missed a scheduled appointment for cancer treatment, and whether they have used cancer support services in the past 2 months. Caregivers will be asked whether they visited the emergency department over the past 2 months, how many times they visited a primary care doctor for anything other than routine care, and whether they have used cancer support services in the past 2 months.

Several additional scales will be administered to patients. Physical functioning will be assessed with the 4-item PROMIS [29] Physical Health scale from the PROMIS-29 Profile v2.0. Participants are asked to report (1=unable to do and 5=without any difficulty) the degree to which they are able to perform 4 activities (eg, "Are you able to go for a walk of at least 15 minutes?" and "Are you able to run errands and shop?"). Engagement in social activities will be assessed with the 4-item PROMIS [29] Ability to Participate in Social Roles and Activities scale from the PROMIS-29 Profile v2.0. Participants are asked to report (1=never and 5=always) the degree to which

they agree with 4 statements (eg, "I have trouble doing all of my regular leisure activities with others" and "I have trouble doing all of the family activities that I want to"). Fatigue will be assessed with the 4-item PROMIS [29] Fatigue scale from the PROMIS-29 Profile v2.0. Participants are asked to report (1=not at all and 5=very much) the degree to which they agree with 4 statements and questions (eg, "I feel fatigued" and "How run-down did you feel on average?") as it pertains to the prior 7 days. Finally, pain interference will be assessed with the 4-item PROMIS [29] Pain Interference scale from the PROMIS-29 Profile v2.0. Participants are asked to respond (1=not at all and 5=very much) to questions assessing pain interference in daily life (eg, "How much did pain interfere with your day to day activities?" and "How much did pain interfere with your household chores?") as it pertains to the prior 7 days. Finally, participants will respond to a single item assessing pain level over the past 7 days, on a 0 (no pain) to 10 (worst pain imaginable) scale.

Caregivers will be administered the 21-item Caregiver Self-Efficacy scale (CaSES [32]), which was developed to measure self-efficacy in informal cancer caregivers. The CaSES was found to have good validity and reliability in a large sample of caregivers [32]. Items assess caregivers' perceptions of their duties and capabilities (eg, "I can be positive when I need to be," "I can continue to provide care when I feel scared," and "I have the ability to talk openly with the person I care for") and are scored on a 4-point scale (0=not at all confident and 4=very confident).

Finally, IntelliCare app use data will be collected passively. Specifically, engagement will be ascertained from the number of app launches, defined as a user-initiated event after at least 5 min of no activity [18]. The duration of individual app use sessions will also be used to reflect engagement and is defined as the length between an app launch at the last event in that session.

To understand the preliminary impact of IntelliCare on daily mood, social functioning, and health behavior during the study, patients and caregivers will respond to a short survey every week throughout the study period via the Web. Surveys will be delivered using the Qualtrics Survey Platform SMS tool. Participants will receive an SMS text message on their phone at 8 pm. An embedded link within the SMS text message will automatically connect participants to a secure Qualtrics Survey Platform Web page containing survey items. Weekly surveys are each expected to take 1 to 2 min to complete.

All participants will be asked to report (1=very negative and 5=very positive) how they have felt over the past week and how they expect to feel the following week. They will also be asked about the following behaviors or activities over the past week: how well they have managed negative feelings, how much they have used alcohol or tobacco to cope with negative feelings, amount of physical pain experienced, how connected they felt to family and friends, how much support they received from loved ones, how much support they were able to provide to loved ones, how much anxiety they experienced, how much interest or pleasure they had in doing things, and amount of physical activity. At the end of the survey, participants are reminded to focus on trying out new IntelliCare apps for the upcoming week. They will be asked to note which specific apps they intend to use during the upcoming week.

Data Analysis

All data will be stored in a secured server for highly sensitive data. Data will be cleaned and analyzed in statistical software packages (ie, SPSS, SAS, and R). Protocol nonadherence will be defined as individuals who fail to complete the baseline and postintervention surveys. Because this pilot study is only being conducted at a single site, a data monitoring committee was not utilized.

Quantitative data on user experience will be analyzed descriptively, to be compared with user data in existing literature. Qualitative user experience data will be reviewed for content and emerging themes through content analysis. Participants' interview responses will be recorded by research staff. Qualitative responses will be coded and evaluated according to the general domains of (1) ways to improve the design and user interface of the apps; (2) the specific apps that were most helpful (and why); (3) the specific apps that were least helpful (and why); (4) obstacles and barriers to using the apps; and (5) ways to improve the usefulness of coaching calls. Initial coding of the data will be based on a priori domains and will be refined during the analysis process conducted by investigators. Additional themes that are identified will be defined and coded.

Due to the within-subject pre-post design, changes in outcome measures in both cancer patients and caregivers will primarily be analyzed using paired *t* tests. Descriptive statistics will primarily be used to examine whether IntelliCare app use is associated with changes in process variables (ie, mood, social functioning, and health behavior) during the study period. These analyses will be performed separately for patients and caregivers. Because the IntelliCare apps are intended as an intervention package, we will be evaluating the app suite as a whole in breast cancer patients and caregivers rather than selecting specific apps for patients and caregivers. A separate set of analyses will examine associations between changes in cancer patient and caregiver outcomes. Specifically, zero-order correlations will be computed to examine whether improvement in caregiver depression or anxiety symptoms is positively associated with improvement in patient depression or anxiety symptoms. Correlations will also be computed to examine whether improvement in caregiver self-efficacy is positively associated with improvement in patient mood symptoms. The purpose of these analyses is to obtain estimates of effect size that can be used to inform future trials. Additional discussions with cancer clinicians will be used to obtain additional information on possibility effect size and variance estimates [33]. We do not intend to perform any between-group contrast analyses (ie, between patient and caregiver or between different IntelliCare apps).

Results

This study will run for 8 months, and recruitment will be completed by the end of 2018. The study was approved by the

local university's institutional review board. Research staff has been hired and trained, and set up has been completed to store all data on secure university servers. Recruitment commenced in March 2018. As of the end of June 2018, 17 breast cancer patients and 7 cancer caregivers have been consented. We will monitor participants' progress and continue to recruit participants over the next 4 months or until we successfully hit our target enrollment.

Discussion

Principal Findings

A cancer diagnosis impacts both patients and their loved ones. Over a third of US cancer patients experience clinically significant mental distress [34]. Studies also show a high level of distress in cancer caregivers in the United States, with over 25% screening positive for depression and 35% screening positive for anxiety [35]. Unfortunately, face-to-face models of mental health care are not sufficient to meet the growing demand for mental health resources in cancer populations. Mental health and support apps may, therefore, address a critical health care gap, although few studies have evaluated the impact of mental health apps in cancer populations. To understand whether existing mental health apps can benefit cancer populations, it is important to understand their preferences for using them as well as gather information about how these apps can be tailored for cancer populations. Findings from this study will help to address this weakness in clinical care, by providing preliminary data to estimate the effect of a suite of mobile phone apps on mental health outcomes in breast cancer patients and caregivers, as well as tailor an existing intervention to better suit the needs of cancer patients and caregivers. In addition, although some studies have found unique benefits of interventions target patient-caregiver dyads [36], this study will be among the first to examine the preliminary effects of providing mental health apps to patient-caregiver dyads.

Although many apps are available on app stores, digital health technologies (which include apps, wearable sensors, and internet-delivered interventions) that are connected to a care manager in a health care setting are increasingly being used as a method of providing technology-enabled services [37,38]. Such systems can be managed by care managers, physician assistants, nurses, or other trained individuals. Although pairing an app with light coaching is a potential limitation to scalability and real-world implementation in some settings, studies such as these are critical to continue to explore the practicality and feasibility of these blended interventions (ie, interventions that combine an automated intervention with some provision of human support) as well as identify which users may or may not need human coaching or additional human support in larger trials.

Findings from systematic reviews indicate that despite a plethora of mental health apps available in app stores, only a few are empirically supported [8,9,39] and the few that target cancer populations have little to no empirical support [6]. IntelliCare apps are publicly available through both the Google Play store (for Android phones) and the App Store (for iPhones) and have been tested in individuals with clinical mood symptoms [18]. These factors create an ideal situation to conduct a pilot study in cancer patients and caregivers. Findings from this study will extend existing work on how mobile technology can be used to address mental health needs in cancer populations.

Limitations

This study should be interpreted in light of several limitations. Because the focus of this study is to conduct a pilot study of a potential phase III trial, the sample size will be relatively small and there will be no comparison condition. Thus, it is impossible to rule out the possibility that improvement in psychosocial outcomes is because of IntelliCare apps or outside factors. We also recognize that effect sizes obtained from relatively small sample sizes can be somewhat unreliable and, thus, will be interpreted with caution [40,41]. Recruiting a larger sample size, combined with an RCT design, is an appropriate next step to understand whether using the IntelliCare apps leads to improvement compared with standard treatment. Furthermore, because this study will be recruiting individuals directly from the clinic to achieve the targeted sample size, there are few exclusion criteria that may lead to potential confounders (eg, psychiatric diagnosis). In addition, this study is conducted in a US National Cancer Institute designated clinical cancer center, and therefore, findings may have limited generalizability to settings that do not possess as many resources. Thus, we hope that data from this pilot study will inform future work that attempts to administer IntelliCare apps from those recruited from a range of clinical settings.

It should be noted that some individuals may not possess a personal mobile phone or have a data plan that allows them to participate in this study. Our strategy to help mitigate this problem will be to provide interested participants who do not have a mobile phone with an Android device and an unlimited data plan to ensure equal access to the mHealth intervention. Given that mobile phone ownership, comfort using phones, and the role of mobile phones in daily life are all interconnected, it is important to acknowledge that problems with generalizability will emerge and grow as time elapses from the end of the trial. Providing people with a mobile phone, therefore, only addresses part of this complex problem that impacts the broader field of mHealth. Similarly, future research may wish to examine barriers to scalability of mHealth interventions for cancer populations. For example, to supplement individuals with limited or prepaid phone plans, researchers may want to examine the feasibility of a partial payment plan that would enable users to upgrade their plans. What this pilot study will also provide is an estimate of the approximate percentage of individuals who require a mobile phone in future trials. Finally, to address low literacy of using technology and mobile devices, phone coaching will provide participants with any needed instructions on how to download, use, and manage the IntelliCare apps. Coaches will also be available to provide technical support as needed.

Conclusions

Very little work has examined the potential effectiveness of mental health apps in cancer patients and their informal caregivers. This pilot study will provide preliminary data regarding the usability and acceptability of a suite of mental health apps in a sample of cancer patients and caregivers in the

United States. The mixed-methods approach to gathering user feedback will provide a rich dataset that will guide improvements to the apps and coaching procedure in future studies.

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Conflicts of Interest

DCM has equity ownership in and EGL has received consulting fees from Actualize Therapy, a company developing and making available mobile technology products related to the research reported in this manuscript. DCM and EGL will not have direct access to the final raw dataset.

References

1. Breastcancer.org. U.S. Breast Cancer Statistics URL: https://www.breastcancer.org/symptoms/understand_bc/statistics [accessed 2018-10-05] [WebCite Cache ID 72wmvVjY6]
2. Hegel MT, Moore CP, Collins ED, Kearing S, Gillock KL, Riggs RL, et al. Distress, psychiatric syndromes, and impairment of function in women with newly diagnosed breast cancer. Cancer 2006 Dec 15;107(12):2924-2931 [FREE Full text] [doi: 10.1002/cncr.22335] [Medline: 17103381]
3. Sklenarova H, Krümpelmann A, Haun MW, Friederich H, Huber J, Thomas M, et al. When do we need to care about the caregiver? Supportive care needs, anxiety, and depression among informal caregivers of patients with cancer and cancer survivors. Cancer 2015 May 01;121(9):1513-1519 [FREE Full text] [doi: 10.1002/cncr.29223] [Medline: 25677095]
4. Grunfeld E, Coyle D, Whelan T, Clinch J, Reyno L, Earle CC, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. Can Med Assoc J 2004 Jun 8;170(12):1795-1801 [FREE Full text] [Medline: 15184333]
5. Pirl WF, Fann JR, Greer JA, Braun I, Deshields T, Fulcher C, et al. Recommendations for the implementation of distress screening programs in cancer centers: report from the American Psychosocial Oncology Society (APOS), Association of Oncology Social Work (AOSW), and Oncology Nursing Society (ONS) joint task force. Cancer 2014 Oct 01;120(19):2946-2954 [FREE Full text] [doi: 10.1002/cncr.28750] [Medline: 24798107]
6. Bender JL, Yue RY, To MJ, Deacken L, Jadad AR. A lot of action, but not in the right direction: systematic review and content analysis of smartphone applications for the prevention, detection, and management of cancer. J Med Internet Res 2013;15(12):e287 [FREE Full text] [doi: 10.2196/jmir.2661] [Medline: 24366061]
7. Pew Research Center. Mobile Fact Sheet URL: http://www.pewinternet.org/fact-sheet/mobile/ [WebCite Cache ID 72wmbOFRu]
8. Donker T, Petrie K, Proudfoot J, Clarke J, Birch M, Christensen H. Smartphones for smarter delivery of mental health programs: a systematic review. J Med Internet Res 2013;15(11):e247 [FREE Full text] [doi: 10.2196/jmir.2791] [Medline: 24240579]
9. Bakker D, Kazantzis N, Rickwood D, Rickard N. Mental health smartphone apps: review and evidence-based recommendations for future developments. JMIR Ment Health 2016;3(1):e7 [FREE Full text] [doi: 10.2196/mental.4984] [Medline: 26932350]
10. Torous J, Roberts LW. Needed innovation in digital health and smartphone applications for mental health: transparency and trust. JAMA Psychiatry 2017 May 01;74(5):437-438. [doi: 10.1001/jamapsychiatry.2017.0262] [Medline: 28384700]
11. Torous J, Luo J, Chan S. Mental health apps: what to tell patients: an evaluation model created specifically for such apps can help guide your discussions. Curr Psychiatry 2018;17(3):21-25 [FREE Full text]
12. Mani M, Kavanagh DJ, Hides L, Stoyanov SR. Review and evaluation of mindfulness-based iPhone apps. JMIR Mhealth Uhealth 2015;3(3):e82 [FREE Full text] [doi: 10.2196/mhealth.4328] [Medline: 26290327]
13. Wilson H, Stoyanov SR, Gandabhai S, Baldwin A. The quality and accuracy of mobile apps to prevent driving after drinking alcohol. JMIR Mhealth Uhealth 2016 Aug 08;4(3):e98 [FREE Full text] [doi: 10.2196/mhealth.5961] [Medline: 27502956]
14. Torous J, Nicholas J, Larsen ME, Firth J, Christensen H. Clinical review of user engagement with mental health smartphone apps: evidence, theory and improvements. Evid Based Ment Health 2018 Aug;21(3):116-119. [doi: 10.1136/eb-2018-102891] [Medline: 29871870]
15. Oulasvirta A, Tamminen S, Roto V, Kuorelahti J. Interaction in 4-second bursts: the fragmented nature of attentional resources in mobile HCI. 2005 Apr 02 Presented at: Proceedings of the ACM SIGCHI conference on Human factors in computing systems; 2005; Oregon, USA p. 919-928. [doi: 10.1145/1054972.1055101]
16. Schueller SM, Tomasino KN, Mohr DC. Integrating human support into behavioral intervention technologies: the efficiency model of support. Clin Psychol Sci Pract 2016;24(1):27-45. [doi: 10.1111/cpsp.12173]

17. 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;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]
18. Mohr DC, Tomasino KN, Lattie EG, Palac HL, Kwasny MJ, Weingardt K, et al. IntelliCare: an eclectic, skills-based app suite for the treatment of depression and anxiety. J Med Internet Res 2017 Jan 05;19(1):e10 [FREE Full text] [doi: 10.2196/jmir.6645] [Medline: 28057609]
19. Lattie EG, Schueller SM, Sargent E, Stiles-Shields C, Tomasino KN, Corden ME, et al. Uptake and usage of IntelliCare: a publicly available suite of mental health and well-being apps. Internet Interv 2016 May;4(2):152-158 [FREE Full text] [doi: 10.1016/j.invent.2016.06.003] [Medline: 27398319]
20. Kroenke K, Spitzer R, Williams J. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [Medline: 11556941]
21. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
22. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. PLoS One 2016;11(3):e0150205 [FREE Full text] [doi: 10.1371/journal.pone.0150205] [Medline: 26978655]
23. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010;10:1 [FREE Full text] [doi: 10.1186/1471-2288-10-1] [Medline: 20053272]
24. Benner A. Sample Size Tables For Clinical Studies. (2nd edn). Oxford, London, Berlin: Blackwell Science Ltd; Feb 28, 1999:494-495.
25. Lane W, Manner C. The impact of personality traits on smartphone ownership and use. IJBSS 2011;2(17):22-28.
26. Xiong H, Huang Y, Barnes L, Gerber M. Sensus: a cross-platform, general-purpose system for mobile crowdsensing in human-subject studies. 2016 Sep 12 Presented at: Proceedings of the ACM International Joint Conference on Pervasive and Ubiquitous Computing; 2016; Heidelberg, Germany. [doi: 10.1145/2971648.2971711]
27. Chow PI, Fua K, Huang Y, Bonelli W, Xiong H, Barnes LE, et al. Using mobile sensing to test clinical models of depression, social anxiety, state affect, and social isolation among college students. J Med Internet Res 2017 Mar 03;19(3):e62 [FREE Full text] [doi: 10.2196/jmir.6820] [Medline: 28258049]
28. Lund A. Measuring usability with the use questionnaire. Usability Interface 2001;8(2):3-6.
29. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010 Nov;63(11):1179-1194 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.04.011] [Medline: 20685078]
30. Kroenke K, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]
31. 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]
32. Ugalde A, Krishnasamy M, Schofield P. Development of an instrument to measure self-efficacy in caregivers of people with advanced cancer. Psychooncology 2013 Jun;22(6):1428-1434. [doi: 10.1002/pon.3160] [Medline: 22941754]
33. Lenth RV. Some practical guidelines for effective sample size determination. Am Stat 2001 Aug;55(3):187-193. [doi: 10.1198/000313001317098149]
34. Carlson LE, Bultz BD. Cancer distress screening: needs, models, and methods. J Psychosom Res 2003 Nov;55(5):403-409. [doi: 10.1016/S0022-3999(03)00514-2]
35. Vanderwerker LC, Laff RE, Kadan-Lottick NS, McColl S, Prigerson HG. Psychiatric disorders and mental health service use among caregivers of advanced cancer patients. J Clin Oncol 2005 Oct 01;23(28):6899-6907 [FREE Full text] [doi: 10.1200/JCO.2005.01.370] [Medline: 16129849]
36. Kurtz ME, Kurtz JC, Given CW, Given B. A randomized, controlled trial of a patient/caregiver symptom control intervention: effects on depressive symptomatology of caregivers of cancer patients. J Pain Symptom Manage 2005 Aug;30(2):112-122 [FREE Full text] [doi: 10.1016/j.jpainsymman.2005.02.008] [Medline: 16125026]
37. Gilbody S, Brabyn S, Lovell K, Kessler D, Devlin T, Smith L, REEACT collaborative. Telephone-supported computerised cognitive-behavioural therapy: REEACT-2 large-scale pragmatic randomised controlled trial. Br J Psychiatry 2017 May;210(5):362-367. [doi: 10.1192/bjp.bp.116.192435] [Medline: 28254959]
38. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World Psychiatry 2014 Oct;13(3):288-295 [FREE Full text] [doi: 10.1002/wps.20151] [Medline: 25273302]
39. Neary M, Schueller SM. State of the field of mental health apps. Cogn Behav Pract 2018 Mar;25(4):531-537. [doi: 10.1016/j.cbpra.2018.01.002]
40. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry 2006 May;63(5):484-489. [doi: 10.1001/archpsyc.63.5.484] [Medline: 16651505]

41. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res 2011 May;45(5):626-629 [FREE Full text] [doi: 10.1016/j.jpsychires.2010.10.008] [Medline: 21035130]

Abbreviations

CaSES: Caregiver Self-Efficacy Scale
CBT: cognitive behavioral therapy
mHealth: mobile health
PHQ-4: Patient Health Questionnaire-4
PROMIS: Patient-Report Outcomes Measurement Information System
RCT: randomized controlled trial
SMS: short message service

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Protocol

American Heart Association's Cholesterol CarePlan as a Smartphone-Delivered Web App for Patients Prescribed Cholesterol-Lowering Medication: Protocol for an Observational Feasibility Study

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Abstract

Background: Adoption of healthy lifestyle and compliance with cholesterol-lowering medication reduces the risk of cardiovascular disease (CVD). The use of digital tools and mobile technology may be important for sustaining positive behavioral change.

Objective: The primary objective of this study is to evaluate the feasibility and acceptability of administering the Cholesterol CarePlan Web app developed by the American Heart Association aimed at improving lifestyle and medication adherence among patients prescribed cholesterol-lowering medication. The secondary objective is to assess the Web app's efficacy.

Methods: A prospective, observational feasibility study will be conducted to demonstrate whether the Web app may be successfully taken up by patients and will be associated with improved clinical and behavioral outcomes. The study will aim to recruit 180 study participants being prescribed cholesterol-lowering medication for at least 30 days across 14 general practices in London, England. Potentially eligible patients will be invited to use the Web app on a smartphone and visit general practice for three 20-minute clinical assessments of blood pressure, height, weight, smoking, and nonfasting cholesterol over 24 weeks. The feasibility of administering the Web app will be judged by recruitment and dropout statistics and the sociodemographic and comorbidity profile of consenting study participants, consenting nonparticipants, and all potentially eligible patients. Acceptability will be assessed using patients' readiness to embrace new technologies, the usability of the Web app, and patient satisfaction. The efficacy of the Web app will be assessed by changes in medication adherence and clinical risk factors by levels of the Web app compliance.

Results: This study is currently funded by the American Heart Association. Initial study recruitment will take place between February and July 2018 followed by patient follow-up. Patient level data will be obtained in January 2019. Data analysis will be completed by February 2019. Results will be submitted for publication in March 2019.

Conclusions: The potential of an app to improve patients' lifestyle and management of cholesterol may inform the design of a randomized controlled trial and the delivery of more effective CVD prevention programs.

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KEYWORDS

behavioral change; cholesterol; lifestyle; mHealth; medication adherence

Introduction

Background

Cardiovascular disease (CVD) is a major cause of disability and premature mortality worldwide accounting for a third of deaths annually in England [1,2]. CVD contributes considerably to the rising cost of health care and is estimated to cost the National Health Service (NHS) and the United Kingdom economy £30 billion annually [1]. Much of the CVD burden is largely preventable [3-5]. Behavioral modification in relation to physical activity, nutrition, smoking, and alcohol consumption, as well as adherence to cholesterol-lowering and blood pressure- lowering medication, is associated with a reduction in the risk of CVD [5]. Prescribing statins is important for the primary prevention of CVD [6-11]. With a lower threshold for statin prescription in the United Kingdom and the United States, many more people will be prescribed lipid-lowering drugs [12-14]. Despite statin therapy, many individuals remain at risk of CVD events owing to behavioral factors such as poor medication adherence and adoption of healthy lifestyles [15]. A combined approach to control cholesterol should include better medication adherence and changes to lifestyle.

Primary CVD prevention programs are increasingly delivered using digital tools and mobile technology [16]. Used in health promotion, digital interventions may enable patient-centered care with improved communication, greater responsiveness to patient needs, and shared decision making [17,18]. Research showed digital interventions to be effective in improving cholesterol levels, medication adherence, weight loss, physical activity, smoking cessation, hypertension, and self-management of diabetes mellitus [16,19,20]. Such research was limited to short message services (SMS) text messages. In contrast, smartphones may enable accessing sophisticated content, such as self-monitoring programs and educational videos, to help patients monitor their risk factors and educate themselves to improve lifestyle and medication adherence. Growing smartphone ownership in the United Kingdom in the adult population makes smartphones an attractive platform for health interventions [21]. Nonetheless, a lack of scientifically designed and tested interventions impedes the successful primary prevention of CVD [22]. Of more than 43,000 apps listed in the health and fitness category of Apple's iTunes Store in 2014, almost half were misclassified or were loosely affiliated with health and fitness [22]. Of 710 cardiology-related apps available in 2013, very few were designed for CVD prevention [22]. In addition, few health-related apps were developed per evidence-based guidelines and had quantifiable benefit for improving clinical outcomes [22]. Health-related apps are not being rigorously evaluated for the acceptability, sustainability of engagement, and the impact on clinical risk factors [16]. Good compliance with smartphone apps was described as content completion ranging from 69% to 72% [23-25]. Reportedly, declining engagement and attrition are the main barriers to the efficacy of digital health interventions [16,26].

The American Heart Association (AHA), a US charity devoted to CVD prevention, developed the Cholesterol CarePlan Web app for patients prescribed a cholesterol-lowering medication. This Web app delivered to patients on their smartphones through the internet aims to increase patients' awareness of the benefits associated with compliance with medication, regular physical activity, and a healthy diet while monitoring these behavioral risk factors over time. The Cholesterol CarePlan is a 12-week care plan for self-management of cholesterol focusing on lifestyle and medication compliance, with weekly reminders and educational videos designed using evidence-based guidelines such as AHA's CVD risk, cholesterol, and lifestyle guidelines [13,27,28]. Using 7 health factors and lifestyle behaviors that support heart health, it is based on the AHA's "ideal cardiovascular health." These factors and behaviors, called "Life's Simple 7," are smoking status, healthy diet, physical activity, healthy weight, blood pressure, cholesterol, and blood glucose. Improvements in these 7 areas can increase the quality of life and lifespan [29]. The Web app is simple to use, comes from credibly sourced information, contains educational information including benefits of behavioral change, real-time tracking of biometric data, and may be self-administered by patients in consultation with their health care providers. The feasibility, acceptability, and efficacy of the AHA Cholesterol CarePlan have not been assessed among patients.

Aims and Objectives

The main aim of this work is to establish whether the AHA Cholesterol CarePlan may be administered to patients as a Web app to improve cholesterol management and lifestyle among patients prescribed a cholesterol-lowering medication. The primary study objectives are to evaluate the feasibility and acceptability of the AHA Cholesterol CarePlan delivered as a Web app. The secondary objectives are to evaluate the Web app's efficacy.

Methods

Study Design

This is a prospective, observational feasibility study involving the use of a Web app on a smartphone for 24 weeks along with the collection of clinical measurements in general practice at baseline and 12 and 24 weeks after the Web app administration.

Sample Size

This study will aim to recruit 180 patients to participate in the study and come for clinical assessments. A formal power calculation for the sample size was not conducted as this project was funded as a feasibility study. Therefore, sample size estimates are not required.

Inclusion Criteria

Adults aged >18 years being prescribed cholesterol-lowering medication for established vascular disease, diabetes, familial hypercholesterolemia, or high-risk primary prevention for at least 30 days prior to being invited to take part in the study will be included. Cholesterol-lowering medication includes statins (atorvastatin, pravastatin, rosuvastatin, and simvastatin), ezetimibe, aspirin, clopidogrel, and colesevelam. In addition, patients must own any Apple or Android smartphone with access

to the internet, give informed consent, and provide 3 nonfasting blood samples.

Exclusion Criteria

Patients not currently being prescribed cholesterol-lowering medication or being prescribed for <30 days prior to being invited to take part in the study will be excluded. In addition, patients not owning a smartphone, unable to consent to research, and having insufficient command over English will be excluded. The capacity of participants will be monitored by a health care professional during 3 clinic visits. Individuals who lose capacity during the course of the study will also be excluded.

Setting and Site Selection

The National Institute for Health Research (NIHR) Clinical Research Network North West London will contact research active practices with the goal of setting up to 14 general practices for research across North West London. Research active practices are defined as practices with a previous record of carrying out research activities.

Participant Enrollment

To participate in the study, potentially eligible patients will be identified from the general practice databases by administrative staff at each participating general practice using automated eligibility search pertaining to prescribed medication. To maximize recruitment, patients will be invited by post, SMS text messaging, and opportunistically. General practices using post and text invitations will invite patients to come to prescheduled appointments. Practices inviting patients opportunistically will invite patients as part of routine clinical care. Patients will be invited in the order of acceptance until 180 patients come into their first visit.

Patients invited by post will be mailed study materials (invitation and patient information sheet) by general practice administrative staff. Opportunistically recruited patients will be invited by their health care professionals and receive study materials in paper copy. Finally, patients invited by SMS text messaging on their mobile phones by general practice administrative staff will receive study materials electronically. Patients who decide not to participate will be given an option to complete an anonymous sociodemographic survey either in paper copy with a prepaid envelope (if invited by post or opportunistically) or using a weblink to a Web-based Qualtrics survey (if invited by SMS text messaging). There will be no financial incentives for study participation.

Data Collection

The sociodemographic survey containing information on comorbidities (stroke, heart disease, hypertension, familial hypercholesterolemia, kidney disease, type 2 diabetes, and dementia), age, gender, ethnicity, education, partial postcode, and smartphone ownership will be collected among study participants through the Web app. In addition, sociodemographic data (not including smartphone ownership or education) for study participants will be obtained from their medical records by general practices. Among consenting nonparticipants, the sociodemographic survey will be administered anonymously (with no possibility of further data linkage) either using a paper or a Web-based survey. All potentially eligible patients will not be asked to respond to the sociodemographic survey. Instead, anonymous sociodemographic data will be obtained from these patients' medical records by general practices. The number of invited individuals will be recorded by the general practice staff. Medication adherence at weeks 1, 12, and 24 will be collected from secondary data.

During the baseline visit, health care professionals will set up participants to use the Web app from their work computer with the internet using a prespecified Web address on a clinician interface of the Web app. During 20-minute consultations at weeks 1, 12, and 24, a health care professional will take and input clinical measurements (blood pressure, height, weight, smoking, and nonfasting cholesterol) into the clinician interface of the Web app (see Multimedia Appendix 1).

The Web app will send out an invitation to patients' smartphone. Patients will be asked to log in and respond to the sociodemographic survey during baseline visit and medication adherence questions during 3 clinic visits. All other questions will be completed outside clinic. The AHA Cholesterol CarePlan consists of 12 weekly components. This includes Life Simple 7 questions; 12 weekly questionnaires pertaining to diet, physical activity, and taking of medication; 12 self-reported weight and blood pressure readings; 9 educational videos; and a Patient Satisfaction Survey. This is a total of 76 multiple choice questions (46 unique questions) and 9 videos (6 unique videos). In addition, the following questionnaires will be administered through the Web app: sociodemographics, Technology Readiness Index (TRI) [30], System Usability Scale (SUS) [31], Medication Adherence Rating Scale (MARS) [32], and Short-Form Health Survey (SF-12) [33]. This is a total of 99 multiple choice questions (55 unique questions). It should take a patient 5-15 minutes to complete questions on a weekly basis. Patients will have a week to answer each week's questions and may resume at a later time. Patients will be sent electronic reminders to complete weekly questions and book follow-up consultations (see Multimedia Appendix 2).

No equipment will be provided for self-monitoring of blood pressure and weight, and these questions will be optional. Multimedia Appendix 3 shows a timeline of quantified assessments recorded through the Web app.

Among patients who may choose not to complete the CarePlan, the questionnaires including sociodemographics, TRI, SUS, MARS, SF-12, and Patient Satisfaction will be administered through a Web-based Qualtrics survey after 12 weeks. These patients will be asked to complete sociodemographic and MARS in clinic and all other questions outside clinic. In addition, the MARS and SF-12 will be administered after 24 weeks through a Web-based Qualtrics survey. Patients will be asked to complete the MARS in clinic and the SF-12 outside clinic. Patients will have a week to complete these questions.

Data Handling and Security

Data collected through the Web app, including responses to weekly questionnaires, clinical measurements (cholesterol, blood pressure, weight, and self-reported smoking), and personal data (including the name, date of birth, and mobile number),

will be hosted securely by the Digital Healthcare Management (DHM) in partnership with UKCloud. Upon study completion, the host will deidentify data and transfer anonymous data to Imperial College London (ICL). In addition to the data collected through the Web app, ICL will collect secondary data pertaining to prescribed medication among study participants directly from general practices. Furthermore, ICL will analyze all data and send data in aggregate form to the AHA (see Multimedia Appendix 4).

To eliminate the potential breaches of confidentiality, all necessary measures were taken to ensure the data are safe and that all data captured electronically are only transferred in an anonymized form. The DHM will act as the data host that will initialize and run the Web app. The DHM is a provider of a complete end-to-end patient health monitoring system using mobile consumer electronics and is a preferred partner of UKCloud. The DHM will use UKCloud's infrastructure to store the data collected through the Web app. UKCloud (formerly Skyscape Cloud Services) Enterprise Compute Cloud provides a trusted, connected, and flexible cloud platform for critical enterprise apps. It is Pan-Government Accredited by the National Cyber Security Centre from UK government accreditors. In addition, it is an N3 (the trusted broadband network for NHS healthcare) aggregator that has been approved by NHS Digital to allow NHS and non-NHS organizations to host apps and data on its cloud that connect to the N3 and transmit or store Patient Identifiable Data. UKCloud manages the external firewalls that connect to the internet and other government networks. In addition, it uses trend micro for antivirus, malware, and vulnerability scanning purposes. UKCloud notifies customers of breaches to the firewall. Data stored on UKCloud are backed up daily. The data will be stored in accordance with Vivify's BYOD (Bring Your Own Device) and Caregiver Portal requirements. VivifyHealth is a digital health platform designed to streamline remote care. Confidentiality of the data will be maintained by the DHM and ICL through password protection of the data and stored in secure servers at ICL following a transfer from the DHM. Moreover, survey data collected via Qualtrics, a survey provider available by subscription to Imperial College London, will be accessible with a password by the study team and will not contain any personal data.

Statistical Analysis

The feasibility of administering the AHA Cholesterol CarePlan will be judged by recruitment and dropout statistics as well as by the sociodemographic and comorbidity profile of study participants in comparison with those of invited patients and all eligible patients. The participation rate will be judged as the percentage of people who consent to take part in the study out of all invited patients. General descriptive statistics will describe the sociodemographics and comorbidities of (1) consenting study participants; (2) consenting nonparticipants; and (3) all potentially eligible study patients. Invited patients will be described in terms of self-reported smartphone ownership. This will inform the likely generalizability of subsequent findings.

Compliance with the Web app will be measured using the frequency and duration of use. Patients' weekly participation in the Web app will be automatically tracked, as well as whether they download educational videos. Compliance with the Web app will be measured using the number of weekly questionnaires attempted, the number of questions completed, and the number of educational videos downloaded. Furthermore, compliance will be described as a percentage of content accessed out of all content presented through the Web app throughout the 12-week care plan, as well as on a weekly basis.

It is anticipated that patients may be grouped into full compliers if they complete 12 weeks, good compliers if they complete 8 weeks, poor compliers if they complete 1-7 weeks, and noncompliers if they do not complete any of the weekly AHA Cholesterol CarePlan questions. Among compliers with the Web app, medication persistence and changes in diet and physical exercise will be examined throughout the 12-week Cholesterol CarePlan, and changes in the quality of life, self-reported medication adherence will be assessed at weeks 1, 12, and 24. In addition, the self-reported quality of life will be assessed using the Short-Form Health Survey [33]. The self-reported behavioral change in relation to diet and physical exercise, as well as medication persistence, will be assessed through weekly questions in the AHA Cholesterol CarePlan. Furthermore, self-reported adherence to cholesterol- lowering medication will be examined using the MARS [32].

The acceptability of the Cholesterol CarePlan will be assessed using patients' readiness to embrace new technologies, the usability of the Web app, and patient satisfaction. Patients' behavior in relation to readiness to adopt new technology will be examined using the 12-item TRI [30]. The Web app usability will be assessed using the 10-item SUS [31]. Furthermore, patient satisfaction with the Cholesterol CarePlan will be assessed using a questionnaire developed by the AHA.

The efficacy of the Cholesterol CarePlan will be judged by examining the Web app compliance with changes in medication adherence and clinical risk factors. Medication adherence will be collected from secondary data using the Medication Possession Ratio and Proportion of Days Covered. These measures are based on the number of days medication supplied and the quantity of medication dispensed for each filled prescription [34,35]. A difference-in-difference (DID) analysis using multiple linear regression, controlling for education, socioeconomic deprivation, ethnicity, gender, and age will be performed. Using DID, a time-series average change in medication adherence, cholesterol, smoking, blood pressure, and body mass index over 3 time-points will be compared among full compliers and partial compliers, respectively, with Web app noncompliers. Interactions in regression models will be explored using explanatory variables. In addition, subgroups analyses (by education, socioeconomic deprivation, ethnicity, gender, and age) will explore differences in medication adherence and clinical outcomes among full compliers, partial compliers, and noncompliers with the Web app. Finally, using multiple regression modeling while controlling for education, socioeconomic deprivation, ethnicity, gender and age, average changes in diet, physical exercise, and quality of life will be examined among Web app compliers.

As this is a feasibility study, the anticipated effects are neither known in terms of the prespecified compliance level with the Web app nor in terms of the expected reduction in behavioural risk factors or clinical outcomes. The feasibility study will assess possible effects in the first place. The number of invited participants from the potentially eligible population group will be monitored each week with the invitations sent out dependent upon the response rate and the achievement of this sample size. The feasibility will be evaluated through the invitations sent out and the number agreeing to participate each week. This feasibility study will inform us of the possibility of obtaining a sample of study participants among the potentially eligible population for a larger trial. For the same reason, we will not adjust *P* value thresholds for multiple testing; statistical significance will be judged using the $P<.05$ threshold.

Ethical Considerations

Prior to being awarded the funding grant, the study underwent AHA's internal medical review examining its medical importance, design, quality, and safety reporting. In addition, the study underwent external peer review, received favorable ethics opinion from the North of Scotland Research Ethics Committee, Health Research Authority approval, and was adopted onto the NIHR Clinical Research Network portfolio.

Results

This study is currently funded by the American Heart Association. Initial study recruitment will take place between February and July 2018 followed by patient follow-up. Patient level data will be obtained in January 2019. Data analysis will be completed by February 2019. Results will be submitted for publication in March 2019.

Discussion

To the best of our knowledge, this is the first study examining the feasibility and acceptability of administering AHA's Cholesterol CarePlan as a Web app to patients. The benefits to patients of using the AHA Cholesterol CarePlan may be improved medication adherence, changes to diet, physical exercise, clinical risk factors, and quality of life. The benefits to the scientific community include an understanding of whether the Web app may be successfully taken up by patients and whether it may help improve lifestyle and management of cholesterol. The benefits to health services may be the delivery of more effective CVD prevention programs.

Although patients treated for hyperlipidemia with cholesterol-lowering drugs will be aware of their CVD risk and the need for cholesterol-lowering medication, as well as lifestyle changes, they may not adhere to medication, engage in a regular physical activity, or consume a healthy diet, all of which are needed for successful cholesterol management. The action and maintenance of behavioral change may require ongoing motivational support. The maintenance of behavioral change in relation to medication adherence and lifestyle is important for controlling cholesterol and preventing the premature onset of CVD [12,14,36]. To change patients' behavior to prevent the premature onset of CVD, according to the Health Belief Model, patients must perceive themselves to be at increased risk of CVD, perceive the severity of illness, and weigh the barriers to behavioral change against the benefits thereof [37]. An important factor for controlling cholesterol, according to the Transtheoretical Model, is the maintenance of behavioral change in relation to medication adherence and lifestyle [38].

Persuasive technology using convincing and effective communication is theorized to help change behavior in relation to CVD. This technology is modeled on ideas that behaviors change only when people are motivated, able and have appropriate triggers [22]. Interventions delivered through smartphones may improve medication adherence [36]. Given the high level of penetration of smartphones among people of lower socioeconomic status, there is an opportunity for health-related mobile apps to overcome traditional barriers to CVD prevention. Nonetheless, a possible limitation of using smartphones for the prevention of CVD is the existence of the digital divide with lower socioeconomic groups retaining older technologies. An important barrier to app use is privacy concerns in relation to data sharing and personal safety. Despite observed associations between app use and positive behavioral change, there is limited evidence on the sustainability of behavioral change using apps [22].

A possible methodological threat to study design may be in selection bias with more wealthy patients owning a smartphone being able to participate in the study; we will be able to assess to what extent those who take part in our study represent the wider eligible population. Another possible limitation may be the use of self-reported questionnaires. However, the use of biometric assessments and medication prescribing may cross-validate the self-reported medication compliance. As this is a feasibility study, no sample size calculations were required. Once study effects are established, the aim is to apply for further funding to design a randomized controlled trial with fully specified sample size criteria.

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Authors' Contributions

MW, AB, and KKR designed the study and secured funding. GG advised on prescribed medication analyses. MW drafted the first study protocol. KID revised the protocol for submission to Ethics. MW drafted the manuscript for publication. All authors discussed the protocol for publication.

Conflicts of Interest

KKR received a research grant from the American Heart Association.

Multimedia Appendix 1

Data collected by the Web app.

[PPTX File, 45KB - resprot_v8i1e9017_app1.pptx]

Multimedia Appendix 2

Patient pathway.

[PPTX File, 47KB - resprot_v8i1e9017_app2.pptx]

Multimedia Appendix 3

The timeline of quantified assessments recorded through the Web app.

[XLSX File (Microsoft Excel File), 13KB - resprot_v8i1e9017_app3.xlsx]

Multimedia Appendix 4

Data flow diagram.

[PPTX File, 48KB - resprot_v8i1e9017_app4.pptx]

References

1. World Health Organization. 2007. Prevention of Cardiovascular Disease - Guidelines for assessment and management of cardiovascular risk URL: http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf [accessed 2018-02-09] [WebCite Cache ID 6x6I6yDKw]
2. Murray CJL, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet 2013 Mar 23;381(9871):997-1020. [doi: 10.1016/S0140-6736(13)60355-4] [Medline: 23668584]
3. Barton GR, Goodall M, Bower P, Woolf S, Capewell S, Gabbay MB. Increasing heart-health lifestyles in deprived communities: economic evaluation of lay health trainers. J Eval Clin Pract 2012 Aug;18(4):835-840. [doi: 10.1111/j.1365-2753.2011.01686.x] [Medline: 21518152]
4. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364(9438):937-952. [doi: 10.1016/S0140-6736(04)17018-9] [Medline: 15364185]
5. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, American Heart Association Stroke Council, Council on CardiovascularStroke Nursing, Council on Clinical Cardiology, Council on Functional GenomicsTranslational Biology, Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014 Dec;45(12):3754-3832 [FREE Full text] [doi: 10.1161/STR.0000000000000046] [Medline: 25355838]
6. Brown WV. Debate: “How low should LDL cholesterol be lowered for optimum prevention of vascular disease?” Viewpoint: “Below 100 mg/dl”. Curr Control Trials Cardiovasc Med 2001;2(1):12-15 [FREE Full text] [Medline: 11806767]
7. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. JAMA 2015;314(12):1255-1263. [doi: 10.1001/jama.2015.10945] [Medline: 26393848]
8. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012 Aug 11;380(9841):581-590 [FREE Full text] [doi: 10.1016/S0140-6736(12)60367-5] [Medline: 22607822]
9. Ziaeian B, Dinkler J, Watson K. Implementation of the 2013 American College of Cardiology/American Heart Association Blood Cholesterol Guideline Including Data From the Improved Reduction of Outcomes: Vytorin Efficacy International Trial. Rev Cardiovasc Med 2015;16(2):125-130 [FREE Full text] [Medline: 26198559]

10. Sahebkar A, Watts GF. New LDL-cholesterol lowering therapies: pharmacology, clinical trials, and relevance to acute coronary syndromes. Clin Ther 2013 Aug;35(8):1082-1098. [doi: 10.1016/j.clinthera.2013.06.019] [Medline: 23932550]
11. Pedersen TR. Pleiotropic effects of statins: evidence against benefits beyond LDL-cholesterol lowering. Am J Cardiovasc Drugs 2010;10 Suppl 1:10-17. [doi: 10.2165/1158822-S0-000000000-00000] [Medline: 21391729]
12. National Institute for Health and Care Excellence. 2014 Jul 18. Cardiovascular disease: risk assessment and reduction, including lipid modification URL: https://www.nice.org.uk/guidance/cg181 [accessed 2018-02-09] [WebCite Cache ID 6x6JBLf22]
13. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014 Jul 01;63(25 Pt B):2935-2959 [FREE Full text] [doi: 10.1016/j.jacc.2013.11.005] [Medline: 24239921]
14. Nayor M, Vasan RS. Recent Update to the US Cholesterol Treatment Guidelines: A Comparison With International Guidelines. Circulation 2016 May 03;133(18):1795-1806 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.116.021407] [Medline: 27143546]
15. Lester WT, Grant R, Barnett GO, Chueh H. Facilitated lipid management using interactive e-mail: preliminary results of a randomized controlled trial. Stud Health Technol Inform 2004;107(Pt 1):232-236. [Medline: 15360809]
16. Burke LE, Ma J, Azar KMJ, Bennett GG, Peterson ED, Zheng Y, et al. Current Science on Consumer Use of Mobile Health for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. Circulation 2015 Sep 22;132(12):1157-1213. [doi: 10.1161/CIR.0000000000000232] [Medline: 26271892]
17. Pelzang R. Time to learn: understanding patient-centred care. Br J Nurs 2010;19(14):912-917. [doi: 10.12968/bjon.2010.19.14.49050] [Medline: 20647984]
18. Little P, Everitt H, Williamson I, Warner G, Moore M, Gould C, et al. Preferences of patients for patient centred approach to consultation in primary care: observational study. BMJ 2001 Feb 24;322(7284):468-472 [FREE Full text] [Medline: 11222423]
19. van Driel ML, Morledge MD, Ulep R, Shaffer JP, Davies P, Deichmann R. Interventions to improve adherence to lipid-lowering medication. Cochrane Database Syst Rev 2016 Dec 21;12:CD004371. [doi: 10.1002/14651858.CD004371.pub4] [Medline: 28000212]
20. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol 2014 Oct;78(4):684-698 [FREE Full text] [Medline: 25364801]
21. Ofcom. 2015 Aug 6. The UK is now a smartphone society URL: https://www.ofcom.org.uk/about-ofcom/latest/media/media-releases/2015/cmr-uk-2015 [accessed 2018-02-09] [WebCite Cache ID 6x6K9Wv1C]
22. Neubeck L, Lowres N, Benjamin EJ, Freedman SB, Coorey G, Redfern J. The mobile revolution--using smartphone apps to prevent cardiovascular disease. Nat Rev Cardiol 2015 Jun;12(6):350-360. [doi: 10.1038/nrcardio.2015.34] [Medline: 25801714]
23. Ainsworth J, Palmier-Claus JE, Machin M, Barrowclough C, Dunn G, Rogers A, et al. A comparison of two delivery modalities of a mobile phone-based assessment for serious mental illness: native smartphone application vs text-messaging only implementations. J Med Internet Res 2013;15(4):e60 [FREE Full text] [doi: 10.2196/jmir.2328] [Medline: 23563184]
24. Swendsen J, Ben-Zeev D, Granholm E. Real-time electronic ambulatory monitoring of substance use and symptom expression in schizophrenia. Am J Psychiatry 2011 Feb;168(2):202-209. [doi: 10.1176/appi.ajp.2010.10030463] [Medline: 21078705]
25. Granholm E, Loh C, Swendsen J. Feasibility and validity of computerized ecological momentary assessment in schizophrenia. Schizophr Bull 2008 May;34(3):507-514 [FREE Full text] [doi: 10.1093/schbul/sbm113] [Medline: 17932087]
26. Eysenbach G. The law of attrition. J Med Internet Res 2005 Mar 31;7(1):e11-e63 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
27. Stone NJ, Robinson JG, Lichtenstein AH, Bairey MCN, Blum CB, Eckel RH, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014 Jun 24;129(25 Suppl 2):S1-45 [FREE Full text] [doi: 10.1161/01.cir.0000437738.63853.7a] [Medline: 24222016]
28. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014 Jun 24;129(25 Suppl 2):S76-S99. [doi: 10.1161/01.cir.0000437740.48606.d1] [Medline: 24222015]
29. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010 Feb 2;121(4):586-613 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.109.192703] [Medline: 20089546]
30. Parasuraman A, Colby CL. An Updated and Streamlined Technology Readiness Index. Journal of Service Research 2014 Jun 22;18(1):59-74. [doi: 10.1177/1094670514539730]

31. Lewis J, Sauro J. The Factor Structure of the System Usability Scale. In: HCD 09 Proceedings. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009 Presented at: 1st International Conference on Human Centered Design: Held as Part of HCI International 2009; July 19-24, 2009; San Diego, CA, USA p. 978-973. [doi: 10.1007/978-3-642-02806-9_12]
32. Fialko L, Garety PA, Kuipers E, Dunn G, Bebbington PE, Fowler D, et al. A large-scale validation study of the Medication Adherence Rating Scale (MARS). Schizophr Res 2008 Mar;100(1-3):53-59. [doi: 10.1016/j.schres.2007.10.029] [Medline: 18083007]
33. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [Medline: 8628042]
34. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med 2005 May 23;165(10):1147-1152. [doi: 10.1001/archinte.165.10.1147] [Medline: 15911728]
35. Nau, David P. Pharmacy Quality Alliance. 2012. Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence URL: http://www.pqaalliance.org/images/uploads/files/PQA%20PDC%20vs%20%20MPR.pdf [accessed 2018-04-25] [WebCite Cache ID 6ywYdQJAn]
36. Treskes RW, Van der Velde ET, Schoones JW, Schalij MJ. Implementation of smart technology to improve medication adherence in patients with cardiovascular disease: is it effective? Expert Rev Med Devices 2018 Feb;15(2):119-126. [doi: 10.1080/17434440.2018.1421456] [Medline: 29271661]
37. Hsu HY, Gallinagh R. The relationships between health beliefs and utilization of free health examinations in older people living in a community setting in Taiwan. J Adv Nurs 2001 Sep;35(6):864-873. [Medline: 11555034]
38. Prochaska J, Redding C. The Transtheoretical Model and Stages of Change. In: Glanz K, Mareus Lewis F, Rimer BK, editors. Health Behavior and Health Education: Theory, Research and Practice. San Francisco: Jossey-Bass; 1997.

Abbreviations

AHA: American Heart Association
CVD: cardiovascular disease
DHM: Digital Healthcare Management
DID: difference-in-difference
ICL: Imperial College London
MARS: Medication Adherence Rating Scale
NHS: National Health Service
NIHR: National Institute for Health Research
N3: the trusted broadband network for NHS healthcare
SF-12: Short-Form Health Survey
SMS: short message services
SUS: System Usability Scale
TRI: Technology Readiness Index

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Protocol

User-Driven Living Lab for Assistive Technology to Support People With Dementia Living at Home: Protocol for Developing Co-Creation–Based Innovations

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Abstract

Background: Owing to no cure for dementia currently, there is an urgent need to look for alternative ways to support these people and their informal caregivers. Carefully designed interventions can answer the unmet needs of both people with dementia and their informal caregivers in the community. However, existing products, systems, and services are often too complex or unsuitable.

Objective: This study aims to identify, longitudinally, the changing needs (as dementia progresses) of people with dementia living at home and their informal caregivers. By developing co-creation-based innovations, these changing needs will hopefully be met.

Methods: A user-driven Living Lab design is used to structurally explore the needs over time of people with dementia (and their informal caregivers) living in the community in the North Brabant region of the Netherlands. In addition, co-creation-based innovations will be developed, tested, and evaluated by these people and their caregivers at home. All participants will complete complaints-oriented questionnaires at 3 time-points—at the baseline, 1 year, and 2 years after they start participating. Home interviews are scheduled to explore if and how these complaints translate into participants' specific needs or wishes. Focus groups meet on a monthly basis to further identify the needs of people with dementia and their informal caregivers and provide feedback to the stakeholders. In the context field, participants have an opportunity to actually test the products at home and provide feedback. Quantitative outcome measurements include neuropsychiatric symptoms, cognitive decline, independence in activities of daily living, safety, and caregiver burden. Qualitative outcome measurements include feedback to the stakeholders regarding the needs of people with dementia and their informal caregivers and how these needs change over time, as well as user experiences about the specific innovations.

Results: Participant recruitment will start in September 2018 and is ongoing. The first results of data analyses are expected in the spring of 2019.

Conclusions: The overall aim of Innovate Dementia 2.0 is to facilitate person-centered innovations developed for people with dementia and their informal caregivers at all stages as dementia progresses. This should lead to newly designed concepts and innovations, which are better able to answer the needs of people with dementia and their caregivers in the community.

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KEYWORDS

dementia; family caregivers; longitudinal studies; technology

Introduction

According to the World Alzheimer Report, there were approximately 47 million people with dementia worldwide in 2016, and this number is expected to increase to 131 million by 2050 [1]. Dementia affects all aspects of a person's life, and the progression is highly variable in individuals. As dementia progresses, people with dementia experience more problems in activities of daily living (ADL) such as dressing, toileting, and bathing [2]. Consequently, more responsibility is required from informal caregivers (eg, spouses, children, or friends), which can lead to increased stress and burden for them. Research indicates that informal caregivers of people with dementia experience higher rates of burden compared with other (nondementia) informal caregivers [3]. Owing to no cure for dementia currently, there is an urgent need to look for alternative ways to help and support people with dementia and their informal caregivers in the community [4].

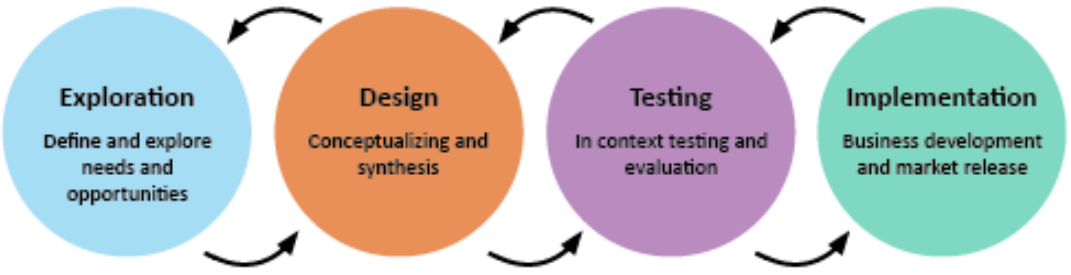
Carefully designed interventions can answer the unmet needs of both people with dementia and informal caregivers at various stages as dementia progression. However, existing products, systems, and services are often too complex to be used by people with dementia [5]. The usability and adaptability of newly designed innovations, therefore, deserves more attention. To address this challenge, the Innovate Dementia project was set up in 2012 and was funded by Interreg IVB NEW [6]. The ambition of this project was to create a network of experts in the Northwest region of Europe who would enable the development of user friendly or user-based innovative solutions for people with dementia and informal caregivers living at home. Based on the Interreg program outline, 3 main challenges were defined as follows: to analyze the needs of people with dementia and their informal caregivers (in care and support); to develop innovative solutions; and to establish a sustainable collaboration between different stakeholders involved in dementia care innovations. By the end of this successful project in December 2015, several innovations had been developed and tested at home [7-9], and some have already been implemented into the daily care of people with dementia. After 2015, the European collaboration ended, and the Dutch partners continued the project under the name Innovate Dementia 2.0 (ID 2.0) as a sustainable regional collaboration. The current collaboration is between Geestelijke Gezondheidszorg Eindhoven en de Kempen (GGzE; Mental Health Care Institute Eindhoven), other health care organizations (Zuidzorg, Archipel), higher educational institutes (Tilburg University, Eindhoven University of Technology, and Fontys), business network Brainport, and governmental bodies. By using a Living Lab (LL) design [10] (see Methods for details), we primarily aim to explore, on a longitudinal basis, the changing needs of people with dementia and their informal caregivers in the community as dementia progresses. The secondary aim is to develop co-created (by innovators, people with dementia, and informal caregivers) innovations, which are tested and evaluated in real-life situations. To enhance the usability and adaptability of newly designed concepts, the involvement of people with dementia and their informal caregivers is crucial [10]. A user-driven LL design is an innovative method that allows for active user involvement in a realistic context [11]. A user-driven LL focuses on solving users' specific problems in everyday life in a way that is consistent with the values and requirements of users and are sustainable because they are built around users [12]. Bharucha et al [13] underline the need to evaluate concepts in a real-life context when developing assistive technology for people with dementia. The ecological validity of the study also improves [14], as well as the likelihood that these innovative proposals will be adopted and implemented by business stakeholders [15], which is essential if these products are to be brought to the market. By using this design, people with dementia and informal caregivers are directly involved in each phase (from idea to concept to product to testing the innovations) to enhance the adaptability and usability of new products, services, and tools. This study describes the design and protocol of ID 2.0.

Methods

Study Design

In the ID 2.0 LL, people with dementia and their informal caregivers have a central position in the development of innovations [16,17]. They are involved in the different stages of the development process; these stages include exploration, design, testing and evaluation, and finally implementation (Figure 1).

Figure 1. Stages in the development in a Living Lab design.



During the exploration stage, validated questionnaires, interviews during home visits, and focus group meetings are used structurally to explore the needs of people with dementia and their informal caregivers. At the design stage, these needs (gathered during the exploration stage) are used to find a suitable design concept during the focus group meetings. In the evaluation stage, a design proposal is evaluated in context-field studies on the potential of the innovation in the real-life setting and on its usability for people with dementia and their informal caregiver. In these field studies, participants use the innovations for a certain period of time (often 2-3 weeks) in the real-life setting to experience the product's usability, feasibility, safeness, and provide feedback. In the implementation phase, further activities, including long-term testing, fundraising, and building production lines, are needed to bring a design to the market.

Study Population

The study population comprises people with dementia and their informal caregivers, all living in the North-Brabant region of the Netherlands, who are recruited from the following institutions: Geestelijke Gezondheidzorg Eindhoven en de Kempen, Archipel and Zuidzorg (elderly federations); Alzheimer Nederland; centers for daytime activities for people with dementia; and through social media.

Inclusion and Exclusion Criteria

The inclusion criteria are met if a person has the diagnosis of dementia (every subtype) and is living at home; there is a committed informal caregiver (spouse, family member, or friend) for people with dementia and both have sufficient understanding and mastery of the Dutch language. Of note, no exclusion criteria have been formulated.

Measurements

Data Collection

In this ongoing initiative, quantitative data will be obtained using questionnaires to assess the cognitive, emotional, and behavioral complaints of both people with dementia and their informal caregivers.

The quantitative data will be used as a starting point to obtain further qualitative data to extract, in detail, the specific individual needs in the daily functioning of people with dementia and their informal caregivers. Furthermore, qualitative data will be obtained using home interviews, focus group meetings, and context-field evaluation (see below for details of all measurements procedures).

Background Information and Questionnaires

The following details will be obtained from a list of written questions regarding people with dementia: age, gender, marital status, the highest educational level achieved [18], previous employment, living situation, diagnosis, global staging of the severity, time since diagnosis, and comorbidity (Tables 1 and 2). In addition, informal caregivers' age and their relationship (spouse, child, brother or sister, other family, friend, other specified) with persons with dementia will be obtained. An expert panel of 4 professional caregivers selected validated questionnaires to assess the social, emotional, cognitive, and physical status of people with dementia and the burden experienced by informal caregivers. Informal caregivers together with people with dementia fill in these questionnaires at 3 time-points—at the start of participation (T0), 1-year (T1), and 2-year (T2) follow-up.

Table 1. Demographics of people with dementia.

Sociodemographic variable and questionnaire	At the baseline	1-year follow-up	2-year follow-up
Age, gender, marital status, education level, and former employment of people with dementia			
What is the date of birth of the person with dementia?	✓	✓	✓
What is the marital status of the person with dementia?	✓	N/A[a]	N/A
Highest level of education [18]	✓	N/A	N/A
Former occupation of the person with dementia?	✓	N/A	N/A
Living situation			
Current living situation?	✓	N/A	N/A
Diagnosis			
Alzheimer's disease/vascular dementia/Parkinson's disease/frontotemporal dementia/other	✓	N/A	N/A
Global staging of severity			
Clinical Dementia Rating Scale [19]	✓	✓	✓
Time since diagnosis			
Date of diagnosis?	✓	N/A	N/A

[a]N/A: not applicable.

Table 2. Demographics of caregivers.

Sociodemographic variable	Variable or questionnaire	At the baseline	1-year follow-up	2-year follow-up
Relationship of caregiver with person with dementia	What is your relationship with the person with dementia?	✓	N/A[a]	N/A
Age of caregiver	What is the caregiver's date of birth?	✓	✓	✓

[a]N/A: not applicable.

Social Emotion Status

To evaluate the neuropsychiatric symptoms of people with dementia, the Dutch version of the Neuropsychiatric Inventory Questionnaire (NPI-Q) is used [20]. The NPI-Q is a retrospective caregiver-informant questionnaire covering the following 12 domains: delusions, hallucinations, agitation or aggression, dysphoria or depression, anxiety, euphoria or elation, apathy or indifference, disinhibition, irritability or lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite or eating disturbances. The informal caregiver is asked to circle a "yes" or "no" in response to each question and to either proceed to the next question if the answer is "no" or to rate the symptoms severity in the last 4 weeks if the answer is "yes." Severity is rated for each question as 1 (mild), 2 (moderate), or 3 (severe). The total NPI-Q severity score represents the sum of individual symptom scores and ranges from 0 to 36. Caregiver distress associated with the symptom is rated on a 0- to 5-point scale. The total NPI-Q distress score represents the sum of individual symptom scores and ranges from 0 to 60.

Background Information

Cognitive Status

To evaluate the cognitive decline of a person with dementia—from the viewpoint of a caregiver—the Dutch version of the Informant Questionnaire on Cognitive Decline in the Elderly is used at the baseline [21]. The Informant Questionnaire on Cognitive Decline in the Elderly is a questionnaire that asks informal caregivers about changes in an elderly person's everyday cognitive function over the past 10 years. The questionnaire aims to assess the cognitive decline over these past 10 years. The cutoff scores are based on the total score divided by the number of questions (range 1-5). A score <3.00 indicates progression in cognitive functioning; a score of 3.00 indicates no change; 3.01-3.50 indicates low decline; 3.51-4.00 indicates moderate decline; and 4.01-5.00 indicates a severe decline.

Physical Status

To measure the independence of ADL, the Katz Index of Independence in Activities of Daily Living is used [22]. The Katz Index of Independence in Activities of Daily Living is a questionnaire that aims to evaluate the following ADL: walking, feeding, dressing and grooming, toileting, bathing, and transferring. For each ADL, people with dementia are scored yes (1 point) or no (0 points) for independence in each of the 6 domains. A total score of 6 indicates full function, 4 indicates moderate impairment, and ≤2 implies severe functional impairment.

To assess instrumental ADL, the Lawton-Body instrumental ADL scale is used [23], which assesses the ability to manage finances, transportation, shopping and meal preparation, housecleaning and home maintenance, communication, and medications. People with dementia are scored ranging from 0 (low function, dependent) to 8 (high function, independent).

Experienced Burden by Informal Caregiver

To measure caregivers' burden, the Dutch questionnaire "Ervaren Druk door Informele Zorg/Experienced Burden due to Informal Care" is used [24]. The Ervaren Druk door Informele Zorg/Experienced Burden due to Informal Care consists of 9 statements, whereby an informal caregiver rates these statements on a 5-point Likert scale ranging from No! to Yes! The answers "Yes!" "Yes," and "Less or more" are scored with a 1, the answers "No!" and "No" are scored with a 0. The total score is calculated by adding the scores of the 9 statements and ranges from 0 to 9; this total score is interpreted as follows: 0-3, low burden; 4-6, moderate burden; and 7-9, high levels of burden.

Safety Issues

The informal caregiver is asked the following 3 (self-made) questions concerning the safety of people with dementia at home:

- Are there any people or agencies around the person with dementia who want to hurt him or her, profit from him or her, or make him or her anxious?
- Does the person with dementia sometimes think of harming him or herself or actually harming him or herself?
- Does the person with dementia ever cause unintended things that endanger him or her or his or her surroundings?

Interviews During Home Visits

After assessing complaints by questionnaires, which are mostly problem-oriented, an interview at home will be scheduled to qualitatively assess personal problems, needs, and wishes of people with dementia and informal caregivers. Textbox 1 provides an overview of the questions asked.

Textbox 1. Questions asked during the home-visit interview.

- What is the impact of dementia on your life? What is the most urgent problem? What could help you to cope with the consequences of dementia?
- What things or tools did you think of yourself?
- For which problems, needs or wishes would you like to see a solution?
- Which activities do you like? What else can you enjoy?

Focus Groups Meetings

In the focus groups meetings, which are organized every second Tuesday morning of the month, a supervised group of, a minimal of 6 and maximum of 10 [25], people with dementia and their informal caregivers come together. In these meetings, participants explore the possibilities of developing innovations regarding their needs and wishes in coping in daily life and provide feedback to developers of the innovations. The qualitative information is merged into an anonymous summary and is communicated with participants and relevant stakeholders and stored in a database by GGzE.

Context-Field Studies

In the context-field studies, people with dementia and their informal caregivers have an opportunity to test a prototype of an innovation in the home setting for 2-3 weeks. AAfter testing, their experiences with regard to the prototype's usability, feasibility and safety are evaluated. They receive a topic list with general and product-specific questions either digitally or by regular post (Textbox 2) and a home interview to evaluate that topic list is also scheduled. After multiple context-field studies of a prototype, the qualitative data are transcribed, and the written report is presented to participants and presented anonymously to the stakeholders of the prototype or design.

Procedure

Every eligible person with the diagnosis of any form of dementia seen by case managers, specialized nurses, psychologists, or geriatricians receives oral and written information about ID 2.0 from an LL Leader (case manager or specialized nurse) at the GGzE. In addition, written information is shared by social media and at "Alzheimer Café" meetings. When interested, participants are contacted by phone by an LL Leader and additional information is provided about ID 2.0 and the LL design. Both people with dementia and informal caregivers are informed. Written informed consent is obtained from both by a case manager during a home visit when participants decide to collaborate as a dyad. The questionnaires (Table 3) are sent digitally or by post at the start of participation (T0), after 12 months (T1), and 24 months (T2).

In addition to completing the questionnaires, participants have an opportunity to take part in monthly "Focus group meetings," which are co-creation sessions, in which people with dementia, informal caregivers, researchers, and stakeholders come together. The contents of the focus group meetings are driven by the needs of participants or by the input from stakeholders. These groups are open, which allows a continuous in- and outflow of participants.

Textbox 2. Questions asked during the evaluation interview of the context-field studies.

- General questions
  - What was your expectation of the product?
  - In what kind of situations did you use the product?
  - Did using this product fulfill the need for example in agitation, safety and well-being?
- Product-specific questions
  - How often did you use this product on average per week?
  - How much time did you spend (in minutes) per week using this product?
  - Was your experience with this product pleasant?
  - Would you recommend this product?
  - Do you have suggestions for improvements?

Table 3. Questionnaires.

Outcomes	Questionnaire or instrument	At the baseline	1-year follow-up	2-year follow-up
Neuropsychiatric symptoms	Neuropsychiatric Inventory Questionnaire	✓	✓	✓
Subjective cognitive decline	Informant Questionnaire on Cognitive Decline in the Elderly	✓	N/A[a]	N/A
Level of independence in activities of daily living	Katz Index of Independence in Activities of Daily Living	✓	✓	✓
Level of independence in instrumental activities of daily living	Lawton-Body instrumental activities of daily living scale	✓	✓	✓
Caregiver burden	Ervaren Druk door Informele Zorg	✓	✓	✓
Safety	Three self-made items	✓	✓	✓

[a]N/A: not applicable.

Furthermore, participants also have an opportunity to evaluate designs of innovations in daily living in context-field studies. Participants reflect and evaluate the proposed design after testing it for 2-3 weeks in the home setting.

Data Storage

The questionnaire data and the qualitative information obtained from home interviews, focus group meetings, and context-field studies are anonymously coded and uploaded by the team members of ID 2.0 and stored in a secured database stored at GGzE.

Planned Statistical Analyses

For ID 2.0, new longitudinal quantitative and qualitative data will be collected and used to answer both scientific and clinically relevant questions. The longitudinal quantitative data will be analyzed using multilevel analysis, which enables the inclusion of all available data (ie, also those from participants with missing data). The predictive value of the determinants for the primary outcome measures at T1 and T2 will be determined using multivariate regression analysis (2 time-points). SPSS Statistics 24 will be used for these statistical analyses.

To analyze the qualitative data responses from the interviews, focus groups and context-field studies will be transcribed. After transcribing, the raw data will be uploaded to Atlas.ti, which enables a systematic content analysis by following the procedures of qualitative analysis according to Polit and Beck [26].

Ethical Considerations

This protocol was approved by the Institutional Review Board of the GGzE. In addition, this protocol was approved by the Ethical Review Board of Tilburg University, Tilburg, the Netherlands. Written informed consent is obtained from all participants, in accordance with the Declaration of Helsinki (Seoul Revision, 2008) and the General Data Protection Regulation (AVG) [27].

Participants are given an opportunity to consult an independent professional about participating in the study and can withdraw at any time. The data are stored anonymously, and only team members of ID 2.0 have access. This initiative is conducted in accordance with the “Medical Research Involving Human Subjects Act” (Wet Medisch-Wetenschappelijk Onderzoek met mensen or WMO).

Dissemination

The results obtained will be disseminated to the scientific and general public by publication in national and international (peer-reviewed) scientific and professional journals, as well as through presentations at conferences or meetings and the ggzei website [28]. The data will not be made public, assuring the study participants’ privacy. Request for data sharing will be considered on an individual basis.

Results

The ID 2.0 initiative will be launched in September 2018 and is an ongoing research line. Our target population is people with dementia living in the community and their informal caregivers. The first results of the data analysis are expected in the spring of 2019.

Discussion

By actively involving people with dementia and their informal caregivers during the process of developing interventions designed to meet their needs, newly designed concepts are more able to answer any unmet needs as dementia progresses [29-31]. ID 2.0 has high practical relevance for people with dementia and their informal caregivers; designers and innovators; formal caregivers; and researchers. For designers and innovators, the feedback of people with dementia and their informal caregivers is highly valuable in enhancing the usability of their innovations in daily living. By involving them in each phase of the developmental process, innovators are then able to make the required adjustments during this process based on the comments and suggestions of people with dementia and their informal caregivers. Eventually, these efforts will result in products and services that are more adaptable and usable for these people in their daily lives. An LL design can have commercial value for stakeholders by helping alleviate the risk involved when launching a new product or service [32]. Second, by gaining insight into people with dementia and their caregivers’ needs, designers and innovators become (more) aware in which areas of daily living future innovations are needed. Furthermore, the longitudinal design of ID and the multiple assessments not only provide a broad range of data about neuropsychiatric symptoms, (subjective) cognitive decline, and problems in the daily functioning of people with dementia but also about the burden informal caregivers experience. These data can be useful in both clinical practice and research. Professional caregivers gain more insights into the daily problems of people with dementia as dementia progresses and can, subsequently, adapt their care based on these insights. Future research could potentially use these valuable data to enhance health care for this vulnerable group in the community.

People with dementia and their caregivers might find this initiative time-consuming and could increase the burden they experience and lead to a potentially high percentage of dropouts during this longitudinal initiative, which could lead to challenges when attempting to compare data over time. However, attempts have been made to reduce the number of questions asked, and all measurements (except for the focus group meetings) take place in the home setting. In addition, participation in this initiative can be experienced as positive and fulfilling, as several studies have reported that people with dementia say that they want to be useful in society, to have a chance to voice their meaning (and be heard), and that they find it very rewarding if their experiences can benefit others [33-35]. People with dementia and their informal caregivers may not personally benefit from their own efforts during the development of the assistive technologies because products are not always immediately available for purchase. However, ID 2.0 actively informs people with dementia and their informal caregivers about new developments and products in the field in a very hands-on way. Another limitation of this longitudinal initiative is the degree of subjectivity of the obtained information, which might be viewed as negatively influencing the validity of the

quantitative analyses. However, the ultimate goal of ID 2.0 is to provide valuable insights about the highly variable progression in personal needs and problems during the process of dementia; therefore, personal information is essential. By creating a sustainable collaboration with active user involvement, the 2 worlds of design and daily practice can finally come together and hopefully benefit the people who need help the most.

Conflicts of Interest

None declared.

References

1. Alzheimer's Disease International. 2016. World Alzheimer Report 2016 URL: https://www.alz.co.uk/research/world-report-2016 [accessed 2018-11-15] [WebCite Cache ID 73wkkN6Ac]
2. Giebel CM, Sutcliffe C, Challis D. Activities of daily living and quality of life across different stages of dementia: a UK study. Aging Ment Health 2015 Jan;19(1):63-71. [doi: 10.1080/13607863.2014.915920] [Medline: 24831511]
3. Bertrand RM, Fredman L, Saczynski J. Are all caregivers created equal? Stress in caregivers to adults with and without dementia. J Aging Health 2006 Aug;18(4):534-551. [doi: 10.1177/0898264306289620] [Medline: 16835388]
4. Black BS, Johnston D, Rabins PV, Morrison A, Lyketsos C, Samus QM. Unmet needs of community-residing persons with dementia and their informal caregivers: findings from the maximizing independence at home study. J Am Geriatr Soc 2013 Dec;61(12):2087-2095 [FREE Full text] [Medline: 24479141]
5. Astell A, Ellis M, Bernardi L, Alm N, Dye R, Gowans G, et al. Using a touch screen computer to support relationships between people with dementia and caregivers. Interacting with Computers 2010 Jul;22(4):267-275. [doi: 10.1016/j.intcom.2010.03.003]
6. Interreg IVB NEW. URL: http://4b.nweurope.eu/
7. Brankaert R, Suijkerbuijk S, den Ouden OP, Snaphaan LJAE. VitalLight: The evaluation of a sleep-wake cycle regulating light system for elderly with dementia in the home-context. Gerontechnology 2014;13(2):172. [doi: 10.4017/gt.2014.13.02.268.00]
8. Suijkerbuijk S, Brankaert R, de Kort Y, Snaphaan L, den Ouden E. Seeing the First-Person Perspective in Dementia: A Qualitative Personal Evaluation Game to Evaluate Assistive Technology for People Affected by Dementia in the Home Context. Interact. Comput 2014 Oct 26;27(1):47-59. [doi: 10.1093/iwc/iwu038]
9. van Lieshout-van Dal EE, Snaphaan L, Bongers I. Does dynamic lighting improve the sleeping pattern and general functioning in people with dementia? Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2017;13(7):1253-1254. [doi: 10.1016/j.jalz.2017.06.1866]
10. Brankaert, R. Business Process Design. 2016. Design for dementia: a design-driven living lab approach to involve people with dementia and their context Eindhoven: Technische Universiteit Eindhoven URL: https://research.tue.nl/en/publications/design-for-dementia-a-design-driven-living-lab-approach-to-involv [accessed 2018-11-15] [WebCite Cache ID 73wlDPYae]
11. Kareborn B, Stahlbrost A. Living Lab: an open and citizen-centric approach for innovation. IJIRD 2009;1(4):356. [doi: 10.1504/IJIRD.2009.022727]
12. Leminen S, Westerlund M, Nyström A. Living labs as open-innovation networks. Technology Innovation Management Review 2012;2(9):6-11 [FREE Full text]
13. Bharucha AJ, Anand V, Forlizzi J, Dew MA, Reynolds CF, Stevens S, et al. Intelligent assistive technology applications to dementia care: current capabilities, limitations, and future challenges. Am J Geriatr Psychiatry 2009 Feb;17(2):88-104 [FREE Full text] [doi: 10.1097/JGP.0b013e318187dde5] [Medline: 18849532]
14. Koskinen I, Zimmerman J. Design Research Through Practice. In: Computer Graphics. United States of America: Elsevier Science Ltd; 2018.
15. Brankaert RGA, Ouden PH. Designing New Ecosystems: The Value Flow Model. In: Innovation Technology Entrepreneurship & Marketing Business Process Design. Den Haag: Design United; 2013.
16. Sanders E, Stappers P. Co-creation and the new landscapes of design. CoDesign 2008 Mar;4(1):5-18. [doi: 10.1080/15710880701875068]
17. Wallace J, Wright P, McCarthy J, Green D, Thomas J, Olivier P. A design-led inquiry into personhood in dementia. 2013 Presented at: the SIGCHI Conference on Human Factors in Computing Systems; April 27 - May 02, 2013; Paris, France. [doi: 10.1145/2470654.2481363]
18. Verhage F. Intelligentie en leeftijd: Onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. Assen: Van Gorcum; 1964.
19. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;9 Suppl 1:173-176. [Medline: 9447441]
20. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000;12(2):233-239. [doi: 10.1176/jnp.12.2.233] [Medline: 11001602]

21. de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. [Abbreviated form of the Informant Questionnaire on cognitive decline in the elderly]. Tijdschr Gerontol Geriatr 1997 Oct;28(5):224-229. [Medline: 9526793]
22. Hartigan I. A comparative review of the Katz ADL and the Barthel Index in assessing the activities of daily living of older people. Int J Older People Nurs 2007 Sep;2(3):204-212. [doi: 10.1111/j.1748-3743.2007.00074.x] [Medline: 20925877]
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9(3):179-186. [Medline: 5349366]
24. Pot AM, van Dyck R, Deeg DJH. Ervaren druk door informele zorg: constructie van een schaal. Tijdschrift voor Gerontologie en Geriatrie 1995;26:214-219.
25. Morgan D. Focus Groups As Qualitative Research. Thousand Oaks, CA: Sage Publications; 1996.
26. Polit D, Beck C. Nursing Research: Principles and Methods. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
27. The EU General Data Protection Regulation. URL: https://www.eugdpr.org/
28. GGzEi. Hier broeit iets URL: https://www.ggzei.nl/ [accessed 2018-11-15] [WebCite Cache ID 73wml0FwR]
29. Span M, Hettinga M, Vernooij-Dassen M, Eefsting J, Smits C. Involving people with dementia in the development of supportive IT applications: a systematic review. Ageing Res Rev 2013 Mar;12(2):535-551. [doi: 10.1016/j.arr.2013.01.002] [Medline: 23318684]
30. Robinson L, Brittain K, Lindsay S, Jackson D, Olivier P. Keeping In Touch Everyday (KITE) project: developing assistive technologies with people with dementia and their carers to promote independence. Int Psychogeriatr 2009 Jun;21(3):494-502. [doi: 10.1017/S1041610209008448] [Medline: 19193255]
31. Rivett E. Research involving people with dementia: a literature review. Working with Older People 2017 Jun 12;21(2):107-114. [doi: 10.1108/WWOP-11-2016-0033]
32. Liedtke C, Jolanta Welfens M, Rohn H, Nordmann J. Living Lab: user - driven innovation for sustainability. Int J of Sus in Higher Ed 2012 Apr 06;13(2):106-118. [doi: 10.1108/14676371211211809]
33. Barnett E, Marshall M. Including the Person with Dementia in Designing and Delivering Care: I Need to Be Me!. London, UK: Jessica Kingsley Publishers; 2000.
34. Clarke C, Keady J. Getting down to brass tacks: a discussion of data collection. In: Wilkinson H, editor. The Perspectives of People with Dementia: Research Methods and Motivations. London, UK: Jessica Kingsley Publishers; 2002:25-46.
35. Dewing J. From Ritual to Relationship. Dementia 2016 Jul 25;1(2):157-171. [doi: 10.1177/147130120200100204]

Abbreviations

ADL: activities of daily living
ID 2.0: Innovate Dementia 2.0
GGzE: Geestelijke Gezondheidszorg Eindhoven en de Kempen (Mental Health Care Institute Eindhoven)
LL: Living Lab
NPI-Q: Neuropsychiatric Inventory Questionnaire
WMO: Medical Research Involving Human Subjects Act (Wet Medisch-Wetenschappelijk Onderzoek met mensen)

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Protocol

Promising Approaches for Engaging Youth and Young Adults Living with HIV in HIV Primary Care Using Social Media and Mobile Technology Interventions: Protocol for the SPNS Social Media Initiative

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Abstract

Background: In the United States, disparities in the rates of HIV care among youth and young adults result from the intersections of factors that include stigma, substance use, homelessness or marginal housing, institutional neglect, and mental health issues. Novel interventions are needed that are geared to youth and young adults.

Objective: In this paper, we aim to describe the interventions used by participating sites for Using Social Media initiative, the process for classifying the intervention components, and the methods for conducting a comprehensive evaluation of the interventions.

Methods: In 2015, the Health Resources and Services Administration (HRSA) HIV/AIDS Bureau, Special Projects of National Significance (SPNS) funded the Evaluation and Technical Assistance Center (ETAC) at the University of California, Los Angeles and 10 demonstration projects at sites across the United States that incorporated innovative approaches using a variety of social media and mobile technology strategies designed specifically for youth and young adults living with HIV. The ETAC developed a typology, or a classification system, that systematically summarizes the principal components of the interventions into broader groups and developed a multisite, mixed-methods approach to evaluate them based on the Department of Health and Human Services HIV health outcomes along the HIV care continuum. The mixed-methods approach is key to remove potential biases in assessing the effectiveness of demonstration projects.

Results: This SPNS project was funded in September 2015, and enrollment was completed on May 31, 2018. A total of 984 participants have been enrolled in the multisite evaluation. Data collection will continue until August 2019. However, data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Conclusions: This HRSA-funded initiative seeks to increase engagement in HIV medical care, improve health outcomes for people living with HIV, and reduce HIV-related health disparities and health inequities that affect HIV-positive youth and young adults.

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KEYWORDS

HIV; health outcomes; mobile technology; social media; youth; young adult; mobile phone

Introduction

Background

In the United States, HIV-positive youth and young adults have disproportionately lower rates of HIV care engagement, retention, medication adherence, and viral suppression compared with older HIV-positive populations. Zanoni and Mayer [1] estimate that only 25% of HIV-positive youth and young adults in the United States are linked to care, 11% retained in care, and 6% virally suppressed. Data on HIV clinical outcomes among youth are limited, but their retention-in-care rates suggest that they are less likely to be meaningfully engaged in care and to achieve viral suppression [2-4]. Although current antiretroviral therapy regimes are less toxic and simpler, factors that are more likely to be present in younger populations are also associated with suboptimal adherence [2,5,6]. HIV-positive youth and young adults face HIV-related health disparities resulting from the intersections of multiple and concurrent stigmas (eg, homophobia, race or ethnicity, and HIV), substance use, homelessness or marginal housing, institutional neglect, mental health issues, and other challenges [2,5,6].

The largest percentage of HIV-positive youth and young adults are men who have sex with men (MSM). Among Ryan White HIV/AIDS Program (RWHAP) clients aged 13-30, male-to-male sexual contact was the transmission category for 60% of HIV infections, with African Americans (54%) and Latinos (22%) being the largest racial or ethnic groups affected [7]. The RWHAP is a federally funded program, authorized by title XXVI of the Public Health Service Act, which provides a comprehensive system of care–primary medical care and support services–for people living with HIV who are uninsured or underinsured. Challenges to engagement in HIV care and viral suppression for young MSM include substance use disorders, mental health issues, stigma, discrimination, and marginalization [8]. Stigma resulting from an HIV-diagnosis and fear of familial, peer, and community rejection profoundly impact youth and young adults [9] and is associated with higher rates of depression, anxiety, and social isolation [10-12]. Aspects of the health care environment exacerbate care engagement challenges because medical providers often reproduce and communicate larger social homophobia and HIV-related stigma [13,14]. Furthermore, there are structural barriers that limit access to HIV care, such as limited health care insurance and lack of transportation, especially among those with a low income and racial or ethnic minorities [14-16].

Most interventions that address barriers to HIV care have been developed for adults [1] and have not been tailored to youth struggling with a variety of unique issues including identity formation, economic hardship, and unstable housing among other daily survival issues [1,7]. A recent randomized control trial attests the importance of tailoring medication adherence interventions to an increasingly young HIV-infected population [17]. However, one promising new strategy with the potential to help young people overcome these challenges is the use of mobile technology. The type of technology use among youth is constantly increasing, and new forms of communication technology and Web-based social networking offer opportunities to reach and engage young people for health promotion [18-20].

Mobile Technology and Social Media

Significant gains can be made to improve the health outcomes of HIV-infected youth and young adults using mobile technology and social media for engagement and retention in HIV medical care. Media and technology that facilitate social interaction (ie, social media) are preferred among young adults, who spend more time with social media and mobile technology than any other activity [21,22]. The science and practice of leveraging social media and mobile apps to support youth in accessing care hold great promise for better patient outcomes. A growing body of evidence suggests that mobile app interventions and social media can help in achieving HIV care program priorities, including linkage to care, engagement and retention in care, and adherence to HIV medications [23-26]. Significant advantages to using mobile technologies and social media apps for engagement and retention in HIV primary care include convenience to the user, reaching larger numbers of people, consistency in delivery, real-time exchange, and potential privacy protections [17,27]. Smartphones have revolutionized the mobile communications markets, and mobile phone health interventions are increasingly being used for the care and prevention of HIV and other sexually transmitted diseases [28-31]. Over 95% of all Americans own a cell phone [32], and over 3-quarters (77%) own a smartphone; the majority (92%) of smartphone owners are between the ages of 18 and 29 years [32].

Overview of the Special Projects of National Significance Social Media Initiative

To harness and test the potential of social media in the interest of better HIV care engagement for youth, the Health Resources and Services Administration (HRSA) HIV/AIDS Bureau, Special Projects of National Significance (SPNS) program launched the Using Social Media to Improve Engagement, Retention, and Health Outcomes along the HIV Care Continuum initiative (SMI) in 2015. The 4-year initiative includes ten demonstration projects in HIV care sites (n=5), health

departments (n=2), and community-based organizations (n=3) located throughout the United States. An Evaluation and Technical Assistance Center (ETAC) was awarded to the Department of Family Medicine at the University of California, Los Angeles (UCLA) to provide technical assistance to the demonstration projects and to develop and implement a rigorous multisite evaluation. Demonstration projects developed mobile technology and social media interventions for linking, retaining, and supporting HIV-positive, underserved, underinsured, hard-to-reach youth (ages 13-24 years) and young adults (ages 25-34 years) in HIV primary care and supportive services. The overarching goal of this initiative is to create a system change—improvements in policies and procedures using social media and mobile technologies—that results in improved HIV health outcomes for HIV-positive youth and young adults.

In this paper, we describe the interventions used by participating sites for this initiative, the process for classifying the intervention components, and the methods for conducting a comprehensive evaluation of the interventions.

Methods

Demonstration Sites

Through a competitive proposal process, HRSA selected demonstration sites using innovative mobile technology and social media strategies deployed via the internet or mobile apps designed to improve engagement and retention in care, medication adherence, and to help achieve viral load suppression among youth and young adults living with HIV (see Multimedia Appendix 1 for a more detailed description of the interventions). The ten demonstration sites are located in Los Angeles, California; San Francisco, California; Chicago, Illinois; St Louis, Missouri; Winston-Salem, North Carolina; New York, New York; Cleveland, Ohio; Hershey, Pennsylvania; Philadelphia, Pennsylvania; and Corpus Christi, Texas. Each demonstration site used its own outreach, linkage, and retention strategies tailored to their local target populations. They all used youth advisory boards either to modify and tailor existing intervention approaches or to develop new intervention approaches for the populations they are serving.

Target Population

The initiative focuses on youth and young adults. HRSA defined youth as persons between the ages of 13 and 24 years and young adults as persons between the ages of 25 and 34 years. The sites focused on the age ranges of their target population based on the groups most affected by HIV in their local communities. The SMI includes all genders, races or ethnicities, and sexual orientations. Nonetheless, some interventions focus on specific populations, such as transgender women, MSM, or MSM within specific racial or ethnic groups such as African American or Latino. Demonstration sites classified and described the respective target population for their intervention by setting, age, gender, race or ethnicity, and sexual orientation.

Youth Involvement

An important component of this initiative is the involvement of youth advisory groups providing input in the design of intervention and outreach strategies, typically via focus group discussions. Engaging the target population to guide intervention design is important in developing an intervention that resonates with them and ensures cultural and linguistic appropriateness crucial to the development of messaging in social media-based components [33]. Across the demonstration sites, youth and young adults have been engaged in multiple ways such as guiding the process and design of messages that market the interventions to potential users and providing feedback on the content of intervention messaging and informing app feature priorities and functions. Demonstration site staff typically recruited youth to attend regular meetings to ensure young people had consistent opportunities to provide input in developing components of the intervention and to gather feedback about the effectiveness of implemented strategies. Youth advisory groups give voice to young adults' own lived experiences from different regions in the United States, serving as an important step forward in understanding the connection between social media and technology use and young adult health behaviors [33]. Thus, the involvement of youth in the project design is critical for sustainability and meaningful, long-term impact.

Social Media Initiative Interventions Typology

The UCLA ETAC reviewed each of the funded proposals and their intervention descriptions to establish a classification system that systematically summarizes the main components of the interventions into a typology. We chose this approach because the use of typologies has proved more useful than hierarchies of evidence (systematic reviews, meta-analyses, randomized controlled trials, cohort studies, etc) in conceptualizing the strengths and weaknesses of different methodological approaches [34]. In other words, hierarchies of evidence misrepresent the interplay between the question being asked and the type of approach most suited to answering it. Typologies systematically indicate the relative contributions that different kinds of methods can make to different kinds of research or, in this case, evaluation questions [35]. The typology developed includes a description of the target population, inclusion criteria, intervention components and functions, and how these correspond to the HIV health outcomes along the HIV care continuum. The typology provided a framework to develop the multisite evaluation of these interventions, discussed below.

Table 1 includes information on the respective target populations by setting, age, gender, race or ethnicity, and sexual orientation for each demonstration site. Most sites target similar populations, with few exceptions. There is one demonstration site that is a community research site, two are Departments of Health, one is a hospital system, and the rest are clinics in either a community or a university setting. There are 6 sites that target participants under the age of 18, while the others focused on ages 18-34 years. There is one site where the intervention is designed specifically for transgender women and another specifically for men, while half are designed for all genders and sexual orientations.

Inclusion Criteria for Enrollment in the Multisite Evaluation

HIV medical eligibility criteria for enrollment in the multisite evaluation is based on the US Department of Health and Human

Services (HHS) common core indicators for monitoring HHS-funded HIV care services [36] and include (1) being newly diagnosed, which is defined as testing HIV positive for the first time within the last 12 months prior to enrollment; (2) not being linked to HIV medical care, including participants who are aware of their HIV infection status but have never engaged in care (never having an HIV medical visit after being diagnosed with HIV); (3) being out of care or not fully retained in care, which includes participants diagnosed with HIV more than 12 months prior to enrollment who had a gap in their HIV care that was >6 months, within the last 24 months; or (4) not being virally suppressed, defined as having a viral load of ≥200 copies/mL at their last lab test.

Table 1. Target populations for the Using Social Media to Improve Engagement, Retention, and Health Outcomes along the HIV Care Continuum initiative (SMI).

Demonstration site	Setting	Age (years)	Gender	Race or ethnicity	Sexual orientation
Coastal Bend Wellness, Corpus Christi, Texas	Community clinic	13-34	Male and female	All (focus on African American and Latino)	All
Friends Research Institute, Los Angeles, California	Community research site	18-34	Transwomen	All	All
Howard Brown Health Center, Chicago, Illinois	Community clinic	13-34	Male and transwomen	All	MSM[a] and heterosexual
MetroHealth System, Cleveland, Ohio	Hospital system	13-34	All	All	All
New York State Department of AIDS, New York, New York	Health department	18-34	All	All	All
Pennsylvania State University Medical Center, Hershey, Pennsylvania	Community and university clinic	13-34	All	All	All (primarily MSM[a])
Philadelphia FIGHT and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	Community clinic	14-29	All	All	All
San Francisco Department of Public Health, San Francisco, California	Health department	18-34	All	All	All (primarily MSM[a])
Wake Forest University, Winston-Salem, North Carolina	University clinic	13-34	Male	All	MSM[a]
Washington University St Louis, St Louis, Missouri	University clinic	18-29	Male and female	All (primarily African American)	MSM[a] and heterosexual

[a]MSM: men who have sex with men.

Additional eligibility criteria included (1) being between the ages of 13 and 34 years; (2) meeting at least one of the above medical criteria determined from tests or medical records; (3) providing informed consent (if 18 years or older) or providing informed assent (if 13-17 years) and, if required by state laws and regulations, obtaining consent from a parent or legal guardian; and (4) meeting any demonstration site-specific criteria (eg, smartphone ownership or being a patient at the site's clinic) as necessary.

Technology Platforms

While each demonstration site's intervention is unique, there are general commonalities listed in the typology framework (Table 2). For example, all ten demonstration sites include a text messaging service component, three of which use text messaging services exclusively. Text messaging is done through short message service (SMS) or private messaging apps such as WhatsApp [37] or Kik [38], while private messaging also functions in mobile Web apps or social media apps and sites. There are six sites that developed new mobile apps specifically for their intervention, while one site has adapted an existing mobile app. The different technology platforms used in each intervention are described in Table 2.

For outreach and recruitment, almost all (n=9) of the sites use social networking sites or apps and other social media platforms (Table 2). Of these, seven have corresponding websites, with three using apps optimized for mobile devices to support the promotion of their interventions. There is one site that uses YouTube, Twitter, and Instagram as platforms for their graphic serial.

Functions of the Interventions

The interventions offer a range of functions, as represented in Table 3. Most interventions have seven to nine functions (an average of seven functions). There is one intervention that has only one function, namely, automated information delivered through SMS, and one other intervention contains all ten functions. The most common components of the interventions are communication, information, social support or networking, and reminders for HIV medical care appointments, HIV medication, and non-HIV care-related issues. The least common components are the skills building and gaming components. In general, youth advisory groups across the ten demonstration

sites communicated in focus groups during formative research that medical appointment reminders and support for medication adherence were most important, followed by receiving lab results for HIV viral load. As a result, most interventions focus on helping participants to develop good habits relating to retention in medical care, medication adherence, and monitoring viral load. Developing skills and gaming are functions of interventions that target younger youth (13-24 years of age). The idea of gaming includes interactive games, quizzes, and puzzles and a points system for the use of the mobile app in achieving appointment, adherence, and viral suppression milestones. There is one site where the mobile app offers immediate feedback and incentives while using avatars to be more attractive to their target population.

Table 2. Technology platforms for the Using Social Media to Improve Engagement, Retention, and Health Outcomes along the HIV Care Continuum initiative (SMI).

Demonstration site	Text messaging	Mobile apps	Social networking sites or apps	Social Media[a]	Website
Coastal Bend Wellness, Corpus Christi, Texas	All types	—[b]	✓	✓	✓[c]
Friends Research Institute, Los Angeles, California	Automated, unidirectional	—	✓	✓	—
Howard Brown Health Center, Chicago, Illinois	Automated	✓ (adapted)[d]	—	—	✓
MetroHealth System, Cleveland, Ohio	Automated	✓ (new)	—	✓	✓
New York State Department of AIDS, New York, New York	All types	✓ (new)	✓	✓	✓[c]
Pennsylvania State University Medical Center, Hershey, Pennsylvania	All types	✓ (new)	✓	✓	✓[c]
Philadelphia FIGHT and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	All types	✓ (new)	✓	✓	✓
San Francisco Department of Public Health, San Francisco, California	Live, bidirectional	✓ (new)	✓	✓	✓
Wake Forest University, Winston-Salem, North Carolina	Live, bidirectional	—	✓	✓	—
Washington University St Louis, St Louis, Missouri	All types	✓ (new)	—	✓	—

[a]Facebook, Instagram, Twitter, Snapchat, and YouTube.

[d]Not applicable.

[c]Mobile optimized.

[d]Adapted apps signify that institutions have existing mobile apps that they have adapted for this intervention and target population.

Table 3. Intervention functions of the Using Social Media to Improve Engagement, Retention, and Health Outcomes along the HIV Care Continuum initiative (SMI).

Function	Definition	Interventions (N=10)
Communication	Interactive communication between participants and service providers.	9
Education	Interactive teaching of information or content.	6
Gaming	Rewards, incentives, or a points system embedded in the social media/mobile digital tool that may or may not include competition between peers.	2
Information	One-way or "push" of content to inform participants (eg, tips, referral resources)	9
Skills building	Social media tools specifically designed to build skills through demonstration and practice.	3
Social support or social networking	Provides participants with opportunities to receive social support from peers, family, service providers, or others.	9
General reminder	Reminders other than for HIV care appointments or HIV adherence.	9
Medical appointment reminder	Appointment reminders for HIV medical care, delivered via the social media intervention tool (can be automated).	9
Medication adherence reminder	Antiretroviral medication reminder that can by automated, live, or both.	8
Monitoring or tracking reminder	Participants record or report information via the social media tools (ie self-monitoring, logging, self-tracking)	7

Table 4. Data collection tools for the Using Social Media to Improve Engagement, Retention, and Health Outcomes along the HIV Care Continuum initiative (SMI).

Methods	Time frame
Audio Computer-Assisted Self-interview Surveys	Baseline and 6, 12, and 18 months
Cost assessments	Annually
Intervention exposure	Monthly or every encounter
Back-end data	Weekly
Medical chart data	Every 6 months

Comprehensive Evaluation Strategy

In order to determine the relative effectiveness of the interventions taking part in this initiative, the ETAC is conducting a rigorous, multisite evaluation of the demonstration sites' interventions. The evaluation plan assesses the outcomes, processes, and cost of using social media- and technology-based interventions to ensure that they have maximum impact on engagement, retention, adherence, and health outcomes of HIV-infected youth and young adults. The design of the quantitative multisite evaluation is informed by the components of each site's interventions and the type of data the components capture (eg, intervention exposure such as back-end data or person-to-person contact by intervention staff) as well as engagement and outcomes of care measures approved by HHS for funded HIV care services [39]. The demonstration sites recruited a convenience sample of 984 participants across a 20 month period from October 2016 through May 2018 (see Inclusion Criteria above). Intervention participant data is being collected using audio computer-assisted self-interview (ACASI) survey software to increase privacy and confidentiality in the data collection process. Table 4 provides a list of the data collection tools being used in the multisite evaluation. All data are submitted to the ETAC through a Web-based secure portal at UCLA for data management and analysis.

Audio Computer-Assisted Self-Interview Surveys

ACASI surveys are conducted at baseline enrollment and repeated at 6-, 12-, and 18-month intervals. The five primary domains of the ACASI surveys are: (1) sociodemographic characteristics (eg, age, education, housing stability, and incarceration); (2) biomedical health, linkage, engagement, and retention in care; (3) intervention exposure; (4) barriers to care; and (5) media technology usage and attitudes. In addition, the surveys collect information on the popularity, adoption, and usability of social media-based interventions among participants. Surveys also gather information on the broader barriers and facilitators of engagement and retention in medical care.

Cost Assessments

Cost assessments are being conducted annually to determine the cost of implementing each intervention. Sites use standard microcosting techniques (incremental time required for each intervention) combined with direct costs to obtain an estimate of total incremental recurring costs. Development and ongoing maintenance costs of the studies are collected through a cost assessment tool that captures personnel information, recurring goods and services, capital equipment, and facility costs. The costs of developing new mobile apps are captured in the recurring costs reported by the five sites developing them. Cost assessments also indicate successful strategies for labor and programmatic costs for each intervention in this SPNS initiative to inform future replication.

Intervention Exposure: Back-End Data and Person-to-Person

Intervention exposure collected weekly helps identify which components of the interventions contribute to desired outcomes. There are two forms of exposure data being captured in the SMI: person-to-person and back-end data. Person-to-person exposure is defined as any type of contact between participants and intervention staff in person, by phone, by text, or by other mobile messaging services. Back-end data include participants' activities on mobile apps, private Facebook pages, or other social media platforms used in this intervention. Back-end data will be used to measure intervention exposure in the multisite evaluation. Some sites have used real-time measures of back-end data to adjust their intervention. For example, one demonstration intervention removed the gamification component of their mobile app due to lack of use.

Medical Data

Data about participants' HIV health outcomes (medical data) are collected every 6 months to assess changes in health outcomes over time. Sites use either the administrative data associated with the receipt of RWHAP funds or abstracted data collected from medical records by hand. Participants' identification is coded to protect their identities before sites submit data to the ETAC. Information from medical data includes: core service visits for HIV care, substance abuse, mental health, CD4 cell count testing, viral load testing, the first date of antiretroviral prescription, and any breaks in the use of highly active antiretroviral therapy.

Qualitative Methodology

Qualitative analysis will document the effective implementation of these interventions. Data is being collected by ETAC investigators during years three and four of the initiative through key informant interviews with participants and providers and tracking reports and forms kept by demonstration sites. Qualitative research methodologies are valuable for understanding factors that facilitate or inhibit the implementation and the effectiveness of the intervention, thus providing context and informing quantitative HIV health outcome data . In addition, qualitative methods afford a better understanding of participants' experiences with social media and mobile

technology to link, engage, and keep them in HIV medical care. It also provides a means to capture any unanticipated themes that may emerge from the data regarding intervention implementation and acceptability.

Multisite Evaluation

The multisite evaluation is assessing engagement in care, health outcomes associated with participation in the social media and mobile technology-based interventions, and individual-level factors that influence the effectiveness of these interventions.

The quantitative evaluation primarily looks at associations between intervention type and exposure and changes in HIV care continuum outcomes and related health outcomes over time. Statistically significant changes in outcomes over time will be indicative of a possible intervention effect; we are cautious against using more causal language in the absence of a control group. We will conduct subgroup analyses for data from each of the ten demonstration sites as well as in aggregate to evaluate differential intervention effects across sites. Random effects will be included for each study participant to account for correlations between outcome observations on the same study participant and properly adjust SEs that will be estimated by the regression models. Most of the analyses will be conducted on nonnormally distributed outcomes and will use random effects generalized linear models with appropriate outcome link functions.

The qualitative evaluation will document the barriers and facilitators to the effective implementation of interventions. Qualitative data sources include individual, semistructured interviews with participants or clients and key informants (site staff implementing the social media interventions), review of secondary sources of information (eg, demonstration site grant proposals, notes from ETAC site liaisons, and ETAC site visit reports) and site presentations at grantee meetings, and observations of project operations at intervention sites. Interview transcripts will be iteratively coded, sorted, and analyzed using a thematic analysis process [40]. Themes will be selected based on their prevalence across the dataset and importance in assessing barriers and facilitators to implementation and acceptability among participants.

This mixed-methods approach will be important in removing potential bias in establishing the effectiveness of demonstration projects. The findings from the evaluation will provide insight for the future use of social media and mobile technology to improve health outcomes for HIV-positive youth and young adults. The results will include best practices from the demonstration sites, lessons learned, and implications for system change or system integration of social media and mobile technology.

Privacy, Confidentiality, and Security

Privacy, confidentiality, and security are paramount in designing an intervention that uses social media or mobile technology for engaging and retaining HIV-infected persons in medical care. In addition to firewalls and information technology security procedures required by the Health Insurance Portability and Accountability Act (HIPAA) regulations, unintentional disclosures can result in stigma, discrimination, and prejudice, particularly for HIV-positive patients. Participants in the SMI are trained in device security, such as using passwords to access phones, added layers of password protection to access specific apps, how to clear text message logs, etc, by SPNS staff at the demonstration sites. Awareness of current privacy concerns associated with each technology has helped alleviate participant concerns. HIPAA requirements must be adhered to when using mobile technologies and social media connected to patients' personal health information.

Results

This SPNS project was funded in September 2015, and enrollment was completed on May 31, 2018. A total of 984 participants have been enrolled in the multisite evaluation. Data collection will continue until August 2019. However, data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Discussion

The Social Media Initiative is an HRSA SPNS initiative that emphasizes the primary goals for HIV prevention and care outlined in the US National HIV/AIDS Strategy: to reduce new infections, increase access to care, improve health outcomes for people living with HIV, and reduce HIV-related health disparities and health inequities that HIV-positive youth and young adults face. The innovative interventions included in this initiative have the potential to improve the health outcomes of youth and young adults who are living with HIV.

The ETAC at UCLA aims to complete the analysis and dissemination of findings, best practices, and lessons learned from using social media and mobile technology to support the engagement of HIV-positive youth and young adults in medical care by the end of 2019. The ETAC hopes that the findings will serve to inform future policy and practices for programs seeking to use ever-changing and improving social media platforms and mobile technology in the delivery of high quality, culturally appropriate HIV primary health care interventions. Successful scale-up of these types of interventions will require understanding how and why youth and young adults use social media and emerging mobile technologies for personal health.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Demonstration site interventions.

[PDF File (Adobe PDF File), 34KB - resprot_v8i1e10681_app1.pdf]

References

1. Zanoni B, Mayer K. Mary Ann Liebert, Inc. 2014 Mar 06. The Adolescent and Young Adult HIV Cascade of Care in the United States: Exaggerated Health Disparities URL: https://www.liebertpub.com/action/captchaChallenge?redirectUrl=https%3A%2F%2Fwww.liebertpub.com%2Fdoi%2F10.1089%2Fapc.2013.0345 [accessed 2018-11-30] [WebCite Cache ID 74K7FiB3r]
2. Hightow-Weidman LB, Jones K, Phillips G, Wohl A, Giordano, YMSM of Color SPNS Initiative Study Group. Baseline clinical characteristics, antiretroviral therapy use, and viral load suppression among HIV-positive young men of color who have sex with men. AIDS Patient Care STDS 2011 Aug;25 Suppl 1:S9-14 [FREE Full text] [doi: 10.1089/apc.2011.9881] [Medline: 21711145]
3. Naar-King S, Bradford J, Coleman S, Green-Jones M, Cabral H, Tobias C. Retention in care of persons newly diagnosed with HIV: outcomes of the Outreach Initiative. AIDS Patient Care STDS 2007;21 Suppl 1:S40-S48. [doi: 10.1089/apc.2007.9988] [Medline: 17563289]
4. Conviser R, Pounds M. Background for the studies on ancillary services and primary care use. AIDS Care 2002 Aug;14 Suppl 1:S7-14. [doi: 10.1080/09540120220149993] [Medline: 12204138]
5. Mocroft A, Ruiz L, Reiss P, Ledergerber B, Katlama C, Lazzarin A, EuroSIDA study group. Virological rebound after suppression on highly active antiretroviral therapy. AIDS 2003 Aug 15;17(12):1741-1751. [doi: 10.1097/01.aids.0000076310.76477.27] [Medline: 12891060]
6. Munakata J, Benner J, Becker S, Dezii C, Hazard E, Tierce J. Clinical and economic outcomes of nonadherence to highly active antiretroviral therapy in patients with human immunodeficiency virus. Med Care 2006 Oct;44(10):893-899. [doi: 10.1097/01.mlr.0000233679.20898.e9] [Medline: 17001259]
7. Health Resources and Services Administration (HRSA), HIV/AIDS Bureau (HAB). HIV/AIDS Bureau. 2015 Sep. Youth and Young Adults and the Ryan White HIV/AIDS Program URL: https://hab.hrsa.gov/sites/default/files/hab/data/datareports/youthdatareport2015.pdf [accessed 2018-11-30] [WebCite Cache ID 74K7rXehy]
8. Minniear T, Gaur A, Thridandapani A, Sinnock C, Tolley E, Flynn P. Delayed entry into and failure to remain in HIV care among HIV-infected adolescents. AIDS Res Hum Retroviruses 2013 Jan;29(1):99-104. [doi: 10.1089/AID.2012.0267] [Medline: 23033848]
9. Moore RD. Epidemiology of HIV infection in the United States: implications for linkage to care. Clin Infect Dis 2011 Jan 15;52 Suppl 2:S208-S213 [FREE Full text] [doi: 10.1093/cid/ciq044] [Medline: 21342909]
10. Futterman D. HIV and AIDS in adolescents. Adolescent Medicine Clinics 2004 Jun;15(2):369-391. [doi: 10.1016/j.admecli.2004.02.009]
11. Pao M, Lyon M, D'Angelo LJ, Schuman WB, Tipnis T, Mrazek DA. Psychiatric diagnoses in adolescents seropositive for the human immunodeficiency virus. Arch Pediatr Adolesc Med 2000 Mar;154(3):240-244. [Medline: 10710020]
12. Safren S, Hendriksen E, Mayer K, Mimiaga M, Pickard R, Otto M. Cognitive-behavioral therapy for HIV medication adherence and depression. Cognitive and Behavioral Practice 2004 Sep;11(4):415-424 [FREE Full text] [doi: 10.1016/S1077-7229(04)80058-0]

13. Lichtenstein B, Bachmann LH. Staff affirmations and client criticisms: staff and client perceptions of quality of care at sexually transmitted disease clinics. Sex Transm Dis 2005 May;32(5):281-285. [Medline: 15849528]
14. Kempf M, McLeod J, Boehme A, Walcott M, Wright L, Seal P, et al. A qualitative study of the barriers and facilitators to retention-in-care among HIV-positive women in the rural southeastern United States: implications for targeted interventions. AIDS Patient Care STDS 2010 Aug;24(8):515-520 [FREE Full text] [doi: 10.1089/apc.2010.0065] [Medline: 20672971]
15. Zaller ND, Holmes L, Dyl AC, Mitty JA, Beckwith CG, Flanigan TP, et al. Linkage to treatment and supportive services among HIV-positive ex-offenders in Project Bridge. J Health Care Poor Underserved 2008 May;19(2):522-531. [doi: 10.1353/hpu.0.0030] [Medline: 18469423]
16. Fortenberry JD, Martinez J, Rudy BJ, Monte D, Adolescent Trials Network for HIV/AIDS Interventions. Linkage to care for HIV-positive adolescents: a multisite study of the adolescent medicine trials units of the adolescent trials network. J Adolesc Health 2012 Dec;51(6):551-556 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.03.012] [Medline: 23174464]
17. Mimiaga M, Kuhns L, Biello K, Olson J, Hoehnle S, Santostefano C, et al. Positive STEPS - a randomized controlled efficacy trial of an adaptive intervention for strengthening adherence to antiretroviral HIV treatment among youth: study protocol. BMC Public Health 2018 Jul 13;18(1):867 [FREE Full text] [doi: 10.1186/s12889-018-5815-9] [Medline: 30001703]
18. Chan A, Kow R, Cheng J. Adolescents' Perceptions on Smartphone Applications (Apps) for Health Management. JournalMTM 2017 Aug;6(2):47-55 [FREE Full text] [doi: 10.7309/jmtm.6.2.6]
19. Nguyen V. Counselling against HIV in Africa: a genealogy of confessional technologies. Culture, Health & Sexuality 2013 Aug 13;15(sup4):S440-S452. [doi: 10.1080/13691058.2013.809146] [Medline: 23862739]
20. Ulett K, Willig J, Lin H, Routman J, Abroms S, Allison J, et al. The therapeutic implications of timely linkage and early retention in HIV care. AIDS Patient Care STDS 2009 Jan;23(1):41-49 [FREE Full text] [doi: 10.1089/apc.2008.0132] [Medline: 19055408]
21. Coyne S, Padilla-Walker L, Howard E. Emerging in a Digital World. Emerging Adulthood 2013 Mar 26;1(2):125-137. [doi: 10.1177/2167696813479782]
22. Xenos M, Foot K. UW Faculty Web Server. Boston: MIT Press; 2008. Not your father's internet: the generation gap in online politics URL: http://faculty.washington.edu/kfoot/Publications/Xenos-Foot-2008-Not-Your-Fathers-Internet-Civic%20Life%20Online.pdf [accessed 2018-11-30] [WebCite Cache ID 74K8iWHCN]
23. Catalani C, Philbrick W, Fraser H, Mechael P, Israelski DM. mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature. Open AIDS J 2013;7:17-41 [FREE Full text] [doi: 10.2174/1874613620130812003] [Medline: 24133558]
24. Lester R, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 2010 Nov;376(9755):1838-1845. [doi: 10.1016/S0140-6736(10)61997-6]
25. Pop-Eleches C, Thirumurthy H, Habyarimana J, Zivin J, Goldstein M, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS 2011 Mar 27;25(6):825-834 [FREE Full text] [doi: 10.1097/QAD.0b013e32834380c1] [Medline: 21252632]
26. Dowshen N, Kuhns L, Gray C, Lee S, Garofalo R. Feasibility of interactive text message response (ITR) as a novel, real-time measure of adherence to antiretroviral therapy for HIV+ youth. AIDS Behav 2013 Jul;17(6):2237-2243. [doi: 10.1007/s10461-013-0464-6] [Medline: 23546844]
27. Thurston IB, Bogart LM, Wachman M, Closson EF, Skeer MR, Mimiaga MJ. Adaptation of an HIV Medication Adherence Intervention for Adolescents and Young Adults. Cognitive and Behavioral Practice 2014 May;21(2):191-205. [doi: 10.1016/j.cbpra.2013.11.001]
28. Muessig K, Pike E, Fowler B, LeGrand S, Parsons J, Bull S, et al. Putting prevention in their pockets: developing mobile phone-based HIV interventions for black men who have sex with men. AIDS Patient Care STDS 2013 Apr;27(4):211-222 [FREE Full text] [doi: 10.1089/apc.2012.0404] [Medline: 23565925]
29. Lim MSC, Hocking JS, Hellard ME, Aitken CK. SMS STI: a review of the uses of mobile phone text messaging in sexual health. Int J STD AIDS 2008 May;19(5):287-290. [doi: 10.1258/ijsa.2007.007264] [Medline: 18482956]
30. Mukund Bahadur KC, Murray P. Cell phone short messaging service (SMS) for HIV/AIDS in South Africa: a literature review. Stud Health Technol Inform 2010;160(Pt 1):530-534. [Medline: 20841743]
31. Ybarra M, Bull S. Current trends in Internet- and cell phone-based HIV prevention and intervention programs. Curr HIV/AIDS Rep 2007;4(4):7.
32. Anderson S, Jiang J. Pew Research Center's Internet & American Life Project. 2018 Nov 28. Teens' Social Media Habits and Experiences URL: http://www.pewinternet.org/2018/11/28/teens-social-media-habits-and-experiences/ [accessed 2018-11-30] [WebCite Cache ID 74K9XYqPk]
33. Vaterlaus JM, Patten EV, Roche C, Young JA. #Gettinghealthy: The perceived influence of social media on young adult health behaviors. Computers in Human Behavior 2015 Apr;45:151-157. [doi: 10.1016/j.chb.2014.12.013]
34. Petticrew M. Evidence, hierarchies, and typologies: horses for courses. Journal of Epidemiology & Community Health 2003 Jul 01;57(7):527-529. [doi: 10.1136/jech.57.7.527]

35. Muir Gray JA. Evidence based policy making. BMJ 2004 Oct 30;329(7473):988-989 [FREE Full text] [doi: 10.1136/bmj.329.7473.988] [Medline: 15514318]
36. Secretary Sebelius Approves Indicators for Monitoring HHS-Funded HIV Services. 2012 Aug. URL: https://www.hiv.gov/blog/secretary-sebelius-approves-indicators-for-monitoring-hhs-funded-hiv-services [accessed 2018-12-05] [WebCite Cache ID 74SkGFzjY]
37. WhatsApp. URL: https://www.whatsapp.com/ [accessed 2018-12-06] [WebCite Cache ID 74SkYZJyC]
38. Kik. URL: https://www.kik.com/ [accessed 2018-12-06] [WebCite Cache ID 74SkdXH0f]
39. Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: from cascade to continuum to control. Clin Infect Dis 2013 Oct;57(8):1164-1171. [doi: 10.1093/cid/cit420] [Medline: 23797289]
40. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]

Abbreviations

ACASI: audio computer-assisted self-interview
ETAC: Evaluation and Technical Assistance Center
HHS: Health and Human Services
HIPAA: Health Insurance Portability and Accountability Act
HRSA: Health Resources and Services Administration
MSM: men who have sex with men
RWHAP: Ryan White HIV/AIDS Program
SMI: Using Social Media to Improve Engagement, Retention, and Health Outcomes along the HIV Care Continuum initiative
SMS: short message services
SPNS: Special Projects of National Significance
UCLA: University of California, Los Angeles

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Protocol

Investigating Intervention Components and Exploring States of Receptivity for a Smartphone App to Promote Physical Activity: Protocol of a Microrandomized Trial

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Abstract

Background: Smartphones enable the implementation of just-in-time adaptive interventions (JITAIs) that tailor the delivery of health interventions over time to user- and time-varying context characteristics. Ideally, JITAIs include effective intervention components, and delivery tailoring is based on effective moderators of intervention effects. Using machine learning techniques to infer each user's context from smartphone sensor data is a promising approach to further enhance tailoring.

Objective: The primary objective of this study is to quantify main effects, interactions, and moderators of 3 intervention components of a smartphone-based intervention for physical activity. The secondary objective is the exploration of participants' states of receptivity, that is, situations in which participants are more likely to react to intervention notifications through collection of smartphone sensor data.

Methods: In 2017, we developed the *A*ssistant to *L*ift your *L*evel of activit*Y* (Ally), a chatbot-based mobile health intervention for increasing physical activity that utilizes incentives, planning, and self-monitoring prompts to help participants meet personalized step goals. We used a microrandomized trial design to meet the study objectives. Insurees of a large Swiss insurance company were invited to use the Ally app over a 12-day baseline and a 6-week intervention period. Upon enrollment, participants were randomly allocated to either a financial incentive, a charity incentive, or a no incentive condition. Over the course of the intervention period, participants were repeatedly randomized on a daily basis to either receive prompts that support self-monitoring or not and on a weekly basis to receive 1 of 2 planning interventions or no planning. Participants completed a Web-based questionnaire at baseline and postintervention follow-up.

Results: Data collection was completed in January 2018. In total, 274 insurees (mean age 41.73 years; 57.7% [158/274] female) enrolled in the study and installed the Ally app on their smartphones. Main reasons for declining participation were having an incompatible smartphone (37/191, 19.4%) and collection of sensor data (35/191, 18.3%). Step data are available for 227 (82.8%, 227/274) participants, and smartphone sensor data are available for 247 (90.1%, 247/274) participants.

Conclusions: This study describes the evidence-based development of a JITAI for increasing physical activity. If components prove to be efficacious, they will be included in a revised version of the app that offers scalable promotion of physical activity at low cost.

Trial Registration: ClinicalTrials.gov NCT03384550; https://clinicaltrials.gov/ct2/show/NCT03384550 (Archived by WebCite at http://www.webcitation.org/74IgCiK3d)

International Registered Report Identifier (IRRID): DERR1-10.2196/11540

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KEYWORDS

physical activity; mHealth; walking; smartphone; incentives; self-regulation

Introduction

Background

Mobile health (mHealth) and sensing technologies recently sparked excitement because of their capability to deliver large-scale personalized behavior change interventions at low cost [1], which can potentially reduce the disease burden associated with health behaviors, such as diet behavior, smoking, or physical inactivity [2]. Beyond passive monitoring of health behavior, smartphones and wearables collect a wealth of contextual information (such as time, location, communication logs, or physical activities) that can be used to tailor the delivery of interventions to participant states that increase the intervention's likelihood of success. For example, an intervention could only be delivered at points in time when the participant is likely to change her or his behavior (state of opportunity) or is likely to engage with the intervention content (state of receptivity) [3]. mHealth apps that utilize this kind of dynamic tailoring are referred to as just-in-time adaptive interventions (JITAIs) [3].

During the development process of a JITAI, it is crucial to decide what key intervention components are needed to affect the desired intervention outcome and what information should be used to tailor the delivery of each component to participants over time [4]. The first question involves an empirical evaluation of single candidate intervention components. The second question involves identifying effective time-varying moderators that indicate in which situations the intervention component is or is not effective. Unfortunately, these decisions can hardly be informed by past research because traditional study designs (eg, randomized controlled trials) rarely evaluate single intervention components or time-varying moderators of intervention effects. To facilitate the development of JITAIs, Klasnja et al, therefore, proposed the microrandomized trial (MRT) [5].

The goals of an MRT are to quantify proximal (short-term) main effects of single intervention components, to investigate how these effects change over time, and to identify which contextual variables moderate the effects of single intervention components. MRTs use repeated randomization of participants to different versions, or presence and absence, of individual intervention components over time, which enables estimation of time-averaged main effects of single intervention components on proximal outcomes as well as time-varying effects and their contextual moderators. Results of an MRT can consequently inform the researcher which components to include in an optimized version of the intervention and how to adapt the delivery of each intervention component to maximize effectiveness.

Although MRTs are designed to accommodate contextual moderation, context is likely to be multidimensional —for example, not just time or location but rather the nexus of time and location (or other higher order interactions) define opportune moments for intervention. This limits the approach of investigating single variables as potential tailoring variables within MRTs. A potential way of overcoming this limitation is to train machine learning models that classify the participants' latent *states* of intervention receptivity or vulnerability given a vector of high-resolution smartphone sensor data. Research on interruptibility, for example, demonstrated that models trained on smartphone sensor data successfully predict the quality and quantity of participants' reactions to notifications on their smartphone [6-8]. Thus, this approach could allow to continuously model each participant's state of receptivity (ie, the likelihood of engaging with an intervention) from a vast number of variables. Predictions of these models can in turn be used to inform intervention delivery of a JITAI.

In this paper, we describe the rationale and design of a 6-week MRT that evaluates main effects and moderators of 3 different intervention components (self-monitoring prompts, planning, and incentives) of the *A*ssistant to *L*ift your *L*evel of activit*Y* (Ally), a smartphone app to promote physical activity. Ally delivers interventions via an interactive text-based chatbot interface and simultaneously collects contextual data using the smartphone's built-in sensors. We also report descriptive statistics from our remote recruiting process and baseline characteristics of participants.

Objectives

To inform the evidence-based development of JITAI for physical activity, the described study has the following objectives:

- To quantify main effects and interactions of main effects of 3 intervention components of Ally, an mHealth intervention for physical activity.
- To explore how the effects of intervention components are moderated by contextual factors and change over time.
- To collect a wide range of high-resolution smartphone sensor data to predict the participants' states of receptivity.

Methods

Study Setting

This study is part of a research collaboration between the Center for Digital Health Interventions, a joint initiative of the Department of Management, Technology, and Economics at ETH Zurich and the Institute of Technology Management at the University of St. Gallen and the CSS insurance, a large health insurer in Switzerland. Data for this study were collected from October to December 2017 in the German-speaking part of Switzerland. The study is registered on ClinicalTrials.gov (NCT03384550) and was approved by the ethical committee of ETH Zurich.

The Assistant to Lift Your Level of Activity App

The Ally app focuses on measuring and increasing walking, a popular and safe activity [9,10] that is known to have positive health effects independent of other types of physical activity [11]. Steps per day as an objective measure of walking can be obtained from the majority of commercially available smartphones with acceptable accuracy [12]. The Ally smartphone app tracks participants' daily step counts and provides interventions to help participants reach daily step goals. It contains a dashboard that displays basic information such as the participants' current step count and the step goal of the current day as well as an activity overview of the past 7 days (Figure 1). Ally runs on the common operating systems Android and iPhone operating system (iOS). On Android smartphones, Ally obtains all physical activity–related information from GoogleFit, a health-tracking platform developed by Google. On iOS smartphones, the same information is obtained from the HealthKit, an application programming interface for health apps provided by Apple. To obtain smartphone sensor data, we used EmotionSense, a framework to support smartphone-based data collection originally developed for experimental social psychology research [13].

Step goals are personalized and calculated daily for each participant based on the participant's activity over the past 9 days employing the moving-window percentile-rank algorithm described by Adams et al [14]. This adaptive goal-setting algorithm sets the daily step goal to the sixtieth percentile of the participant's step count distribution of the past 9 days, meaning that the participant reaches her or his step goal 40% of the times when maintaining her or his recent activity level. Previous studies demonstrated that this adaptive goal setting outperforms static step goals [14,15]. To facilitate maintenance of behavior change, adaptive step goals are capped at 10,000 steps per day, which approximates the World Health Organization recommendations for physical activity [16,17].

To administer the intervention components evaluated in this study, the Ally app includes a chatbot (Ally) that provides interactive coaching dialogues similar to other messaging apps such as Apple's iMessage, Facebook's Messenger, or WhatsApp. The open source behavioral intervention platform MobileCoach [18] was used to build the chatbot and deliver the interactive coaching dialogues. In previous studies, MobileCoach-based interventions have successfully reduced problem drinking in adolescents [19] and engaged the majority of participants of a 3-month smoking cessation program [20]. Participants interact with Ally by selecting predefined answer options (Figure 1) that trigger a response by the chatbot according to the conversational rules specified in the MobileCoach system.

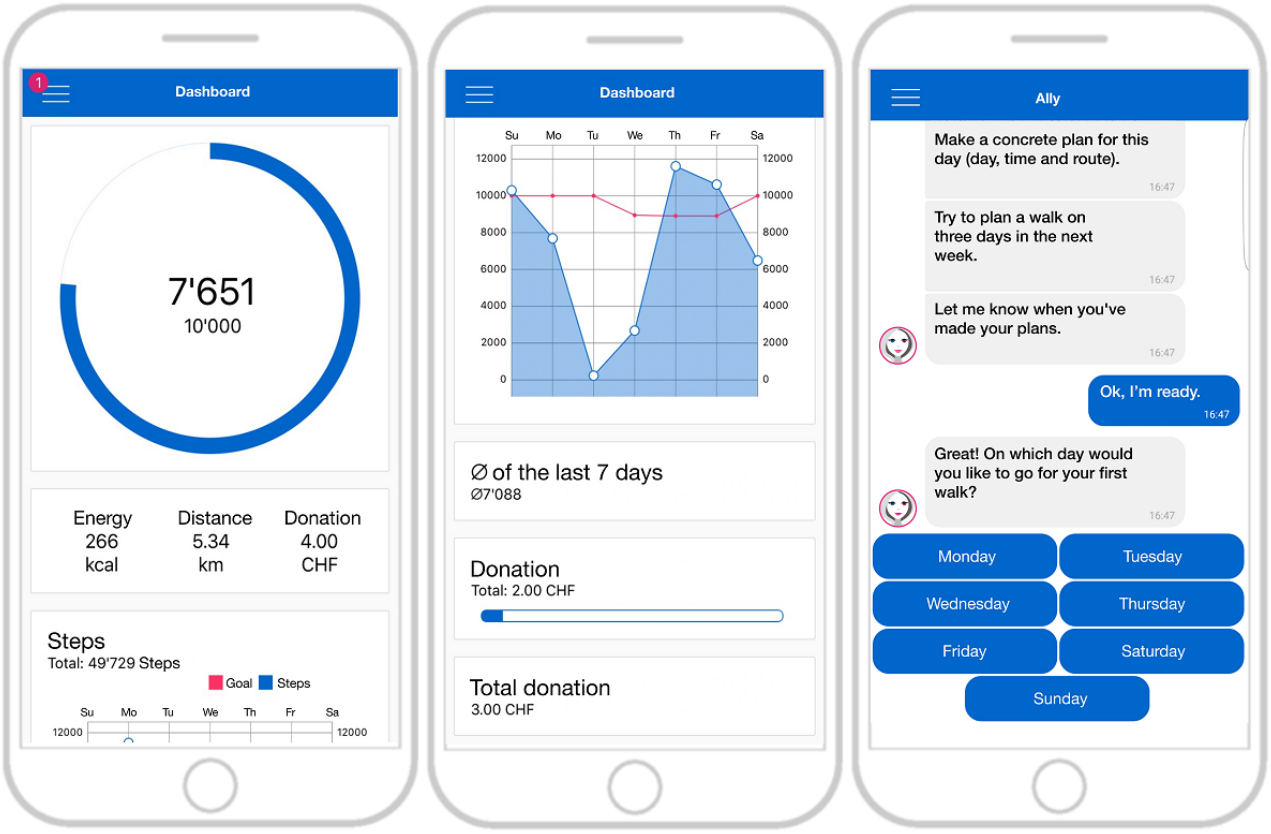
Beyond specific interventions, the chatbot also communicates the daily step goal in the morning and feedback regarding the goal together with informative facts about physical activity at 8 pm in the evening to all participants.

Study Design

From October to December 2017, insurees of a large Swiss health insurance used the Ally app over a 12-day baseline and a 6-week intervention period. During the baseline period, participants only had access to the dashboard of the app, and no interventions were administered. Over the course of the 6-week intervention period, we randomized participants to different versions of 3 intervention components: daily self-monitoring prompts (2 levels; within-subjects), a weekly planning intervention (3 levels; within-subjects), and daily incentives (3 levels; between-subjects). The rationale for these intervention components is described below. To meet study objective three, we aimed to explore if and how participants' reaction to intervention components were dependent on their context. To do so, we ideally need to observe reactions to intervention notifications in a wide variety of contexts. We, therefore, sent out intervention and step goal–related notifications at random points in time but within prespecified time windows that guaranteed delivery at appropriate times. For example, daily step goal notifications were delivered at a random point in time between 8 am and 10 am as users likely expect to be notified about their goal early in the day. Participants completed a Web-based questionnaire at baseline and at postintervention follow-up and received CHF 10 (US $10 as of 2017) for the successful completion of both questionnaires. If participants provided consent, they were invited to participate in exit interviews after the end of the study that investigate perceptions of participants and mechanisms of behavior change.

The following subsections first describe details and rationale for each intervention component as well as for potential moderators. Subsequently, we outline how each component was randomized during the intervention period and how we define the proximal outcome to evaluate each component.

Figure 1. The Ally app: Dashboard with daily (left) and weekly overview (middle) and chat interactions with the Ally chatbot (right).



Intervention Components

Self-Monitoring Prompts

Self-regulatory processes have been identified as a key factor for health behavior change [21,22]. To support participants' self-regulation, we designed short dialogue-based self-monitoring prompts. Self-monitoring prompts remind the participants of their daily step goal, compare the participants' current step count to their daily goal, and provide an estimate of walking minutes necessary to reach the goal together with an actionable tip on how to increase physical activity. These dialogues were designed to support the 3 subprocesses of the self-regulatory construct action control, namely self-monitoring, awareness of goals or standards, and self-regulatory effort [23,24]. If a participant had already reached their daily step goal when starting the dialogue, she/he would receive positive and encouraging feedback from the Ally chatbot instead.

Participants were randomized to receive a self-monitoring prompt or no prompt every day during the intervention period except Sunday, as this day was reserved for the planning intervention (see below). Self-monitoring prompts were delivered at a random point in time between 10 am and 6 pm.

Participants' general tendency to self-monitor their physical activity may affect the effect of self-monitoring prompts because the information provided by the prompt is likely to be redundant to participants who are already aware of their activity level. In addition, timing of the self-monitoring prompt may be critical. Research from cognitive psychology demonstrates that people assign more value to performance increases when their current performance is close to their goal [25]. Consequently, self-monitoring prompts may be more effective if they are sent at times when participants are closer to reaching their step goal.

Planning

Even if motivation to change exists, previous studies show that on average, 47% of people fail to act upon their good intentions [26]. Forming specific plans about when and how to act increases the likelihood of performing the intended behavior [27,28] and helps to bridge the so-called intention behavior gap. Planning can be further divided into action planning (AP; specifying when, where, and how to act) and coping planning (CP; specifying coping responses for barriers and difficult situations) [29]. Plans that are articulated in an if-then format (eg, "if I am tired at work, I will go for a brief walk to get new energy") are typically referred to as implementation intentions [30].

Every Sunday during the intervention period, participants received either an AP, a CP, or no planning intervention (control; CC). In the AP condition, Ally asks the participant to plan at least one and up to 3 walks for the upcoming week. To plan a single walk, the participants need to specify the day of the week, the time, and the route that they intend to walk. To create flexible plans and thus increase the likelihood of adherence, Ally advises the participant to choose event-related times (eg, after work) instead of actual times. In the CP condition, Ally asks the participant to identify barriers for physical activity by reflecting on the 2 least active days from the previous week. The participant is then prompted to develop counterstrategies for each barrier using the if-then format of

implementation intentions [30]. Ally guides this process using examples for common barriers for physical activity that have been identified in previous studies [31-33], for example: "If I want to go for a walk but I lack motivation, I will think of the benefits of walking for health to motivate myself." Finally, the participant has the option to anticipate days of the upcoming week where the barrier may arise again. Both AP and CP include reminders for the participant on days when either a walk or a coping reaction was scheduled. To address the third objective of this study, planning interventions were sent out on Sundays at a random point in time between 10 am and 8 pm.

Participants' activity level and contexts may moderate the effects of AP and CP. Participants with low activity levels may be more likely to benefit from AP, which promotes the initiation of action, whereas participants with high activity levels may benefit more from CP, which prevents routines from distraction [29,34]. Furthermore, completing the planning intervention can take several minutes and requires a considerable amount of the participants' attention and cognitive capacity. Ideally, the planning intervention should, therefore, not be delivered in situations where the participant is involved in an attention-consuming activity, such as social activities or work.

Incentives

Meta-analyses [35,36] and recent randomized trials [37-39] have demonstrated the ability of financial incentives to increase physical activity. However, financial incentives may reduce intrinsic motivation [40,41]; thus, charity incentives have been proposed as an alternative incentive strategy. Charity incentives, that is, donations to a charity organization, could foster experiences of autonomy and relatedness, which are known to facilitate rather than impede the buildup of intrinsic motivation [42]. Moreover, 2 recent studies have so far compared financial and charity incentives with mixed results [37,43].

In this study, participants were randomly allocated to either a financial incentive, a charity incentive, or a control condition using an allocation ratio of 1:1:1. In the financial incentive condition, participants received CHF 1 (US $1 as of 2017) for each day they met their personalized step goal. In the charity incentive condition, instead of keeping the reward to themselves, participants made a donation of CHF 1 to a charity of their choice. Participants allocated to the control condition received no incentives. Earned rewards (maximum of CHF 42) were paid to participants or donated to charity after completion of the study.

We hypothesize that the presence of incentives moderates the effect of the other intervention components. Both planning and self-monitoring prompts target the participants' self-regulatory processes and thus require the participant to be motivated to reach the provided step goals to produce an effect [44]. As we expect the incentives to increase the motivation of participants, we hypothesize that effects of self-monitoring prompts and planning are more pronounced for participants receiving financial or charity incentives.

Randomization, Allocation Concealment, and Blinding

The MobileCoach version used in this study requires the time point of dissemination for all dialogues to be known a priori. Therefore, randomization had to be performed upon enrollment of participants for all intervention components. Each participant was randomized to 1 out of 3 incentive conditions using simple randomization and an allocation ratio of 1:1:1. In addition, participants were randomized to 1 out of 9 planning intervention sequences (S_1-S_9) that determine the order in which the participant received the AP intervention, the CP intervention, or CC intervention throughout the intervention period. We used blocked randomization with a block size of 9 to achieve balance between the sequences. The resulting intervention schedule (Table 1) is uniform and strongly balanced, which controls for time and carry-over effects [45]. To avoid interference of self-monitoring prompts and planning, self-monitoring prompts were not delivered on Sundays. Thus, subtracting 6 from 42 left 36 available days for delivering self-monitoring prompts. To prevent repetition of content, we created 18 different versions of self-monitoring prompts that we randomly allocated to the 36 days for each participant. Consequently, at each of the 36 days, half of participants received a self-monitoring prompt (on average), whereas the other half received no prompt. All randomizations were performed using random number sequences generated with the shuffle-array package in JavaScript.

The fully automated randomization process guarantees allocation concealment for everyone involved in the study. Variables in the dataset indicating intervention allocation are encrypted to blind members of the research team involved in data analysis. A researcher at the Swiss Federal Institute of Technology in Zurich who is not involved in data analyses holds the decryption key and is instructed to safely store the key until the analysis script has been finalized. Due to the setting of the study, it is not possible to blind participants to intervention assignments. To reduce the impact of performance and attrition bias, participants were not informed about the details of the intervention components before the study.

Measurements

Primary and Secondary Outcomes

As the intervention components (see Table 2) are randomized on different timescales, we need to define primary and secondary proximal outcomes that correspond to these timescales to correctly evaluate the intervention components. The proportion of overall participant days that step goals are achieved during the intervention period is the primary outcome to evaluate the different incentive conditions. Weekly and daily proportions of participant days that step goals are achieved during the intervention period are the primary outcomes of the planning and self-monitoring prompts, respectively. On the same timescales, differences in steps per day measured with the smartphone are investigated as a secondary outcome.

Table 1. Intervention schedule of the planning intervention.

Sequence	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
S_1	AP[a]	AP	CP[b]	CC[c]	CC	CP
S_2	CP	CP	CC	AP	AP	CC
S_3	CC	CC	AP	CP	CP	AP
S_4	AP	CP	CP	AP	CC	CC
S_5	CP	CC	CC	CP	AP	AP
S_6	CC	AP	AP	CC	CP	CP
S_7	AP	CC	CP	CP	CC	AP
S_8	CP	AP	CC	CC	AP	CP
S_9	CC	CP	AP	AP	CP	CC

[a]AP: action planning.

[b]CP: coping planning.

[c]CC: control condition (no planning).

Table 2. Overview of intervention components of the *A* ssistant to *L* ift your *L* evel of activit*Y* (Ally) app.

Component and intervention options	Randomization	Mode of delivery	Time of delivery	Behavior change techniques [48][a]	Proximal outcome
Self-monitoring prompts					
Prompt	Upon enrollment; allocation ratio 1:1	Chat	Daily except Sunday; randomly between 10 am and 6 pm	1.6; 2.2; 4.1	Daily proportion of participant days that step goals were achieved
Control (no prompt)	Upon enrollment; allocation ratio 1:1	N/A[b]	N/A	N/A	Daily proportion of participant days that step goals were achieved
Planning					
Action planning	Upon enrollment; allocation ratio 1:1:1	Chat	Sundays; randomly between 10 am and 6 pm	1.4	Weekly proportion of participant days that step goals were achieved
Coping planning	Upon enrollment; allocation ratio 1:1:1	Chat	Sundays; randomly between 10 am and 6 pm	1.2	Weekly proportion of participant days that step goals were achieved
Control (no planning)	Upon enrollment; allocation ratio 1:1:1	N/A	N/A	N/A	Weekly proportion of participant days that step goals were achieved
Incentives					
Cash incentives	Upon enrollment; allocation ratio 1:1:1	Dashboard/chat	Daily	10.2	Overall proportion of participant days that step goals were achieved
Charity incentives	Upon enrollment; allocation ratio 1:1:1	Dashboard/chat	Daily	10.3	Overall proportion of participant days that step goals were achieved
Control (no incentives)	Upon enrollment; allocation ratio 1:1:	N/A	N/A	N/A	Overall proportion of participant days that step goals were achieved

[a]1.2=problem solving, 1.4=action planning, 1.6=discrepancy between current behavior and goal, 2.2=feedback on behavior, 4.1=instruction on how to perform a behavior, 10.2=material reward (behavior), and 10.3=nonspecific reward.

[b]N/A: not applicable

Table 3. Summary of collected sensor data.

Sensor	Variable	Data type	Frequency[a]
GPS[b]	Location	3D Float	Every 10 min
Accelerometer	Physical activity	Categorical	Continuous
Time	Time	Integer	Continuous
Proximity	Proximity of the phone	Binary (near and far)	Continuous
Wi-Fi	Wi-Fi connection	Categorical/string	Every 10 min
Bluetooth	Bluetooth connection	Categorical/string	Every 10 min
Ambient light	Ambient light	Float	Continuous
Battery status	Battery status	Float (charged in percentage)	Continuous
Screen events	Screen on/off	Binary (on/off)	Continuous

[a]Estimated frequencies only. Actual frequencies may vary depending on device and operating system.

[b]GPS: global positioning system.

For financial and charity incentives, postintervention differences in intrinsic and extrinsic motivation, and differences in app engagement and nonusage attrition during the intervention period are evaluated as additional secondary outcomes. Dimensions of intrinsic and extrinsic motivation are measured using the Behavioral Regulation for Exercise Questionnaire-2 (BREQ-2) [46]. As the external regulation subscale in the BREQ-2 exclusively relates to external regulation by other people, it is substituted by the more generally worded external regulation subscale of the Situational Motivation Scale (SIMS) [47]. Subscales of both instruments have shown good reliability (Cronbach alpha=.73-.86, BREQ-2 [46] and Cronbach alpha=.86, SIMS external regulation subscale [47]). Validity has been confirmed by factor analysis (BREQ-2) [46] and correlational analysis (SIMS) [47]. We measure engagement with the Ally app using the number and length of app launch sessions per day. An app launch session is defined as any interaction of the participant with the Ally app, separated by 5 min between events. If a participant left the app open and did not take action for 5 min or more, then the next interaction with the app counts as a new session. We coded a participant as "non-usage attrition observed" when she/he stopped using the Ally app at least 7 days before the end of the study.

Other Outcomes

As a preliminary pre-post evaluation of the Ally app, self-reported health outcomes and targeted mediators of behavior change were assessed at baseline and at postintervention follow-up. In addition, we assessed participant's perceptions of the Ally app, of intervention components, and of the chatbot in addition to predictors of technology acceptance at postintervention follow-up. An overview of all measured variables is available in Multimedia Appendix 1 ([49-57]).

Sensor Data

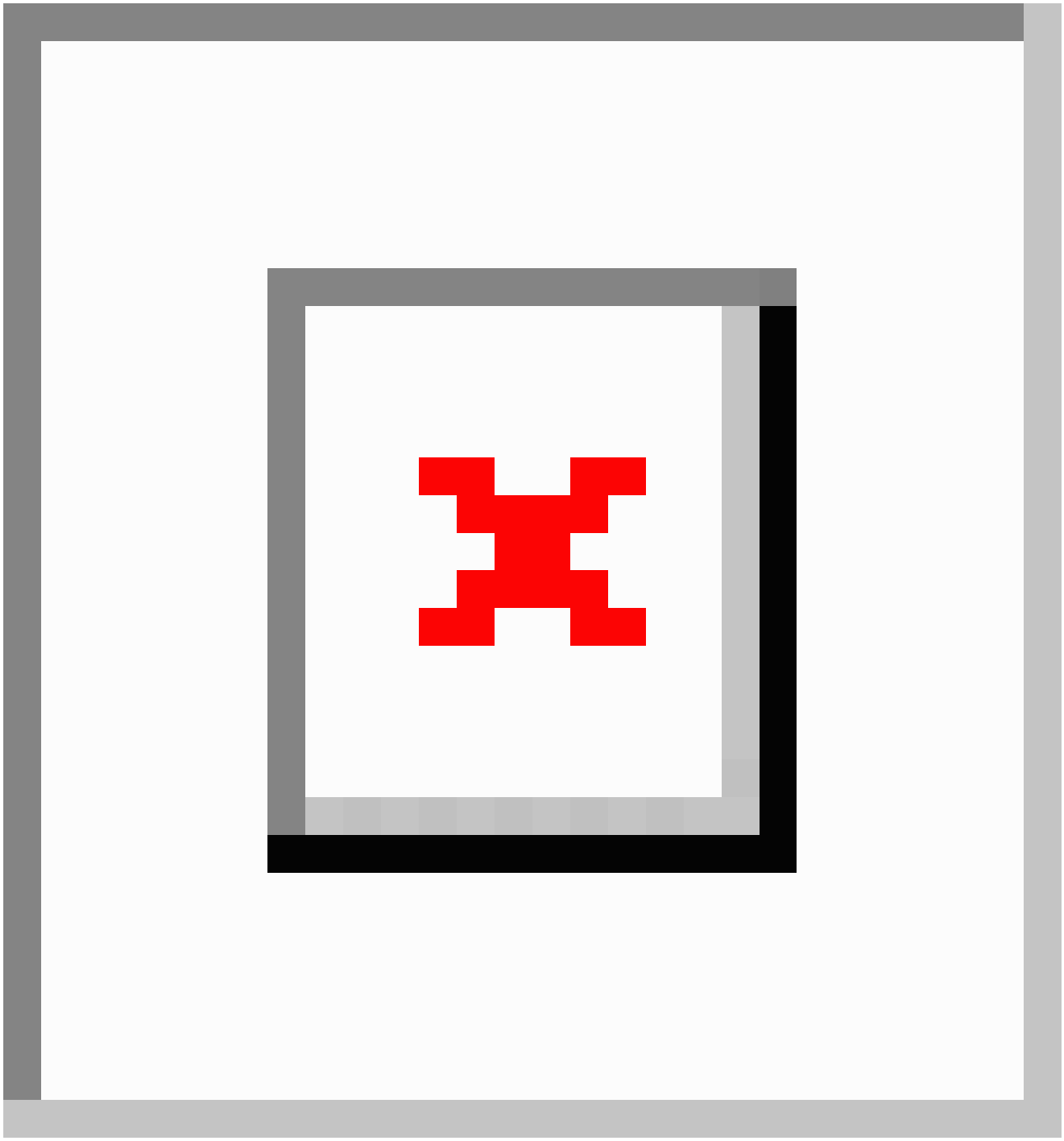
Drawing on previous literature on context-aware mobile notification management systems [58], we identified smartphone sensors that may aid with predicting the participants' state of receptivity. Sensor data were obtained from participants during the intervention period. Table 3 provides a summary of these sensors, their collected data, and their sensing frequency. In line with previous studies, we operationalize state of receptivity by using the response rate (ie, whether a participant responds to a notification or not) and the response time (ie, time between notification and response) to notifications of the Ally app.

Sample Size

We used a simulation-based approach to estimate the power of our study design and determine the necessary sample size. As interaction effects require a greater number of participants to be detected with adequate power [59], we focused the power analysis on the two-way interaction effect of the between-subject factor incentives and the within-subject factor planning. We systematically varied the probability of reaching the step goal p (SG) when no intervention is provided (0.30, 0.40, and 0.50). These values seem reasonable given the fact the probability of step goal achievement according to the goal setting algorithm is 0.40. We further varied the increase in probability because of incentive and planning main effects (0.05, 0.10, and 0.15) and the interaction effect (0.05, 0.10, and 0.15) for sample sizes ranging from n=20 to n= 400. These effect sizes were based on previous studies on the use of incentives to promote physical activity [38,39]. A total of 100 simulations were generated for each scenario. *P* values of interaction effects were obtained by fitting generalized estimating equations (GEEs) models to the simulated data, and power was calculated as the proportion of *P* values below the significance level of alpha=.05. Figure 2 displays simplified results of this simulation with constant main effects of .15 and different values for p (SG) and the interaction effect. The black horizontal line indicates the recommended level of power of 1-beta=.80.

Simulations indicate that a sample size of roughly 220 is sufficient to detect an interaction effect of .05 with a power of 1-beta=.80 and alpha=.05 for p (SG)=.50. Sample sizes to detect an interaction effect .05 considerably increase for smaller values of p (SG) and smaller main effects (not shown). We, therefore, considered a sample size of 220 to be most feasible, and accounting for dropout, we set the target sample size for our study to 300.

Figure 2. Results of the simulation-based power analysis. p (SG): probability of reaching the step goal.



Recruitment and Eligibility

We invited insurees via email to participate in our study. On the basis of a previous study in the same population and with a similar recruiting process [60], we expected a participation rate of approximately 3%. We initially sent the invitation email to 10,000 insurees. However, because initial participation was lower than expected, an additional 20,000 insurees were invited to meet the required sample size.

The invitation email contained brief information about the study, eligibility criteria, and emphasized the benefits of participation. No details about the different intervention conditions were disclosed to the insurees. By following a link in the invitation mail, interested insurees were forwarded to an online survey platform, where they were screened for eligibility. Eligibility criteria were as follows: (1) German-speaking, (2) aged 18 years or older, (3) enrolled in a complementary insurance program, (4) being free of any medical condition that prohibits increased levels of physical activity, (5) not actively using an activity tracker or a comparable smartphone app, and (6) not working night shifts.

As meeting the first 3 eligibility criteria could be determined from the insurance company's database, only insurees meeting these criteria were invited to participate. Due to legal regulations in Switzerland, the Ally app could be offered to insurees with complementary health insurance plans only. Note, however, that in Switzerland, 75% of people are enrolled in complementary insurance plans [61]. We excluded insurees

working night shifts because interventions were sent out on prespecified times during the day only. Eligible insurees could subsequently obtain detailed information about the goals and study procedures, provide consent to participate, and enroll in the study. After enrollment, participants completed the first online questionnaire and subsequently received a 6-digit code, together with instructions on how to download and install the Ally app. Participants had to enter the code once upon first opening the Ally app to connect survey data and app data and to ensure that only study participants were using the app.

Statistical Analyses

All analyses were prespecified before enrolling participants into the study. After completion of the study but before starting data analyses, the statistical methods for analyzing the effects of intervention components were changed from hierarchical linear modeling to a GEE-based approach to avoid biased effect estimates [62].

Primary Analyses

To evaluate main effects and interactions of intervention components, we will use the centered and weighted GEE approach described in the study by Boruvka et al [62]. This approach guarantees unbiased effect estimates when treatment and moderator variables are time-varying. Statistical models will evaluate each main effect and interaction of intervention components of interest on the components appropriate proximal outcome. For all main effects and interactions that include comparisons of multiple conditions, the main comparisons of interest are between the respective intervention and control conditions.

Missing data on covariates and on the dependent variable will be imputed using multiple imputation, provided the missing at random assumption is justified. We will perform sensitivity analyses to assess the robustness of the results of the primary analyses. These analyses include a per-protocol analysis and an adjusted analysis in which effect estimates are adjusted for a linear trend of time, baseline step count, and covariates of physical activity. For all tests, we use 2-sided *P* values with alpha<.05 level of significance.

Secondary Analyses

Secondary analyses focus on the analysis of intervention components on participants' step counts and on the effects of incentives on app engagement, nonusage attrition, and motivation. Steps per day are analyzed using the same modeling approach as described above. Again, if missing data can be assumed to be missing at random, we plan to impute missing step counts using multiple imputations. As evidence suggests that participant days with less than 1000 steps are unlikely to represent accurate activity data [63,64], those days will be set to missing before imputation.

Generalized linear models will be used to analyze the effect of incentives on engagement and nonusage attrition. One-way analysis of variance (ANOVA) is performed for each subscale of the BREQ-2 to analyze the effect of incentives on the different forms of intrinsic and extrinsic motivation. *P* values will be adjusted according to the Holm-Bonferroni method [65]. If the omnibus test of the ANOVA is significant, we will investigate contrasts between the 3 incentive groups. Again, the main comparison of interest is between the intervention groups and the control group. An overview of all planned statistical analysis is available in Multimedia Appendix 2.

Moderators

Due to the lack of existing research in this field, the moderation analyses of main effects are exploratory and may investigate various moderators of intervention components, different forms of operationalizing these moderators, or varying types of relationships (eg, linear or quadratic). Moderations of main effects are investigated by adding a term for the interaction between the main effect and the respective moderator to the statistical model.

State of Receptivity

We will compare several different methodological approaches to predict the participants' state of receptivity. First, we plan to evaluate the performance of supervised learning algorithms in predicting response rate and response time. These algorithms have produced predictions of acceptable accuracy in previous studies on interruptibility [58]. Second, we plan to frame the problem at hand as a classification problem. A classifier will be trained to learn to differentiate between contexts in which the notification is sent (and are assumed to represent nonreceptive contexts) and contexts in which the participant interacts with the app (and in turn are assumed to represent receptive contexts). To this end, we aim to use generalized linear models as a starting point before exploring online learning algorithms that can learn and adapt to each participant's preferences, and any change thereof. This analysis strategy, however, is preliminary at the time of writing, as the final analysis will consider additional factors such as the quality and distribution of collected data.

Results

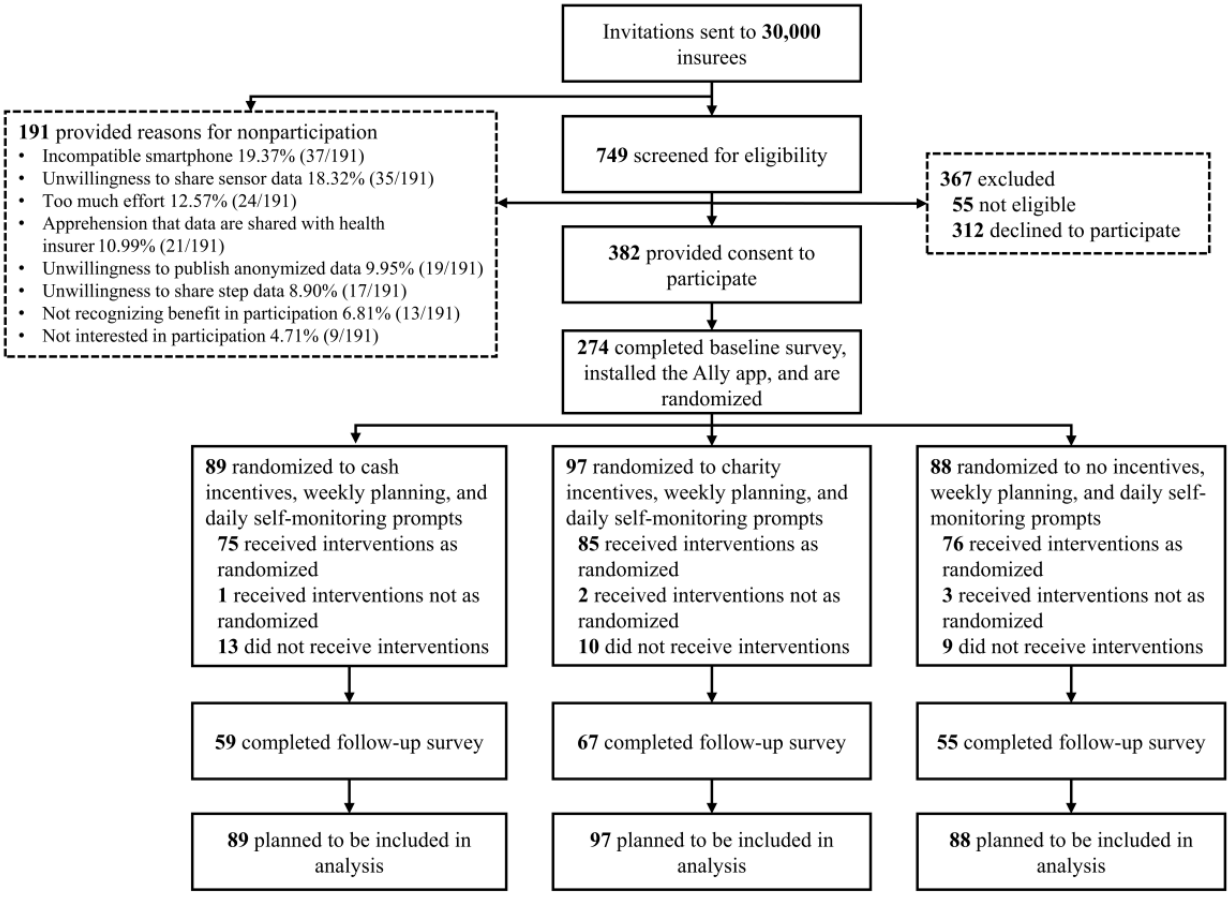
Recruitment

Of all 30,000 invited insurees, 749 (2.50%) clicked the link in the invitation mail and were subsequently screened for eligibility. Of those, 694 (92.7%) were eligible and 382 (51.0%) provided informed consent to participate. Of all insurees who provided informed consent, 274 (71.7%) successfully completed the baseline survey and installed the Ally app on their smartphone (Figure 3). Invited insurees were given the opportunity to select reasons why they declined participation from a list of predefined answer options using a separate survey (n=191). A link to this survey was included in the invitation mail and placed on the informed consent screen. Possession of an incompatible smartphone (37/191, 19.4%) and unwillingness to share smartphone sensor data (35/191, 18.3%) were the most frequently stated reasons to decline participation.

Of 274 participants, 32 (11.7%) did not receive any interventions because they stopped using the app before the start of the intervention period. Due to technical errors, 6 participants did not receive the interventions they were randomized to (eg, a self-monitoring prompt was sent out on a day where the participant was randomized to not receiving a prompt). For the

6 participants, these errors affected between 1 and 25 out of 42 participant days. Steps per day measured with the smartphone are available for 227 (82.8%, 227/274) participants, and smartphone sensor data are available for 247 (90.1%, 247/274) participants. After completing the 6-week intervention period, 181 (66.1%, 181/274) participants filled out the Web-based follow-up survey. Data collection finished in January 2018.

Figure 3. Participant flow.



Baseline Characteristics

Baseline and demographic characteristics of participants are presented in Table 4. Participants (mean age 41.73 years; 57.7% [158/274] female) were mostly Swiss (246/274, 89.8%) and walked on average 6336 (SD 2701) steps per day during the baseline period. The distribution of age and gender is comparable with those of other studies evaluating physical activity apps [66,67]. Self-reported physical activity and comparisons of self-reported health with the German 12-item Short Form norm sample indicate that on average, participants in our study may be healthier and more active than the general population.

Expected Results and Dissemination

We will start data analyses after publication of this study protocol. We anticipate submitting results to a peer-reviewed journal in 2019. Preliminary results of the study may be presented at conferences, workshops, symposia, etc. Results of the analysis of sensor data to predict the participants' state of receptivity will be published separately in a peer-reviewed journal or conference proceedings.

Table 4. Baseline and demographic characteristics of participants (N=274).

Characteristics	Statistics
Age in years, mean (SD)	41.73 (13.54)
Sex, n (%)	
Female	158 (57.7)
Male	111 (40.5)
N/A[a]	5 (1.8)
Education, n (%)	
Compulsory education	3 (1.1)
High school	97 (35.4)
University	164 (59.9)
N/A	10 (3.7)
Nationality, n (%)	
Swiss	246 (89.8)
German	13 (4.7)
Other	12 (4.4)
N/A	3 (1.1)
Employment, n (%)	
Full-time	152 (55.5)
Part-time	76 (27.7)
Retired	22 (8.0)
Unable to work	2 (0.7)
Unemployed	14 (5.1)
N/A	8 (2.9)
Income, n (%)	
<CHF 2500	30 (11.0)
CHF 2501-5000	53 (19.3)
CHF 5001-7500	86 (31.4)
CHF 7501-10,000	37 (13.5)
>CHF 10,000	24 (8.8)
Smartphone, n (%)	
iPhone operating system	186 (67.9)
Android	88 (32.1)
Step count, n (%)	
<5000	74 (27.0)
5000-7499	68 (24.8)
7500-9999	35 (12.8)
>10,000	21 (7.7)
N/A	76 (27.7)
IPAQ[b], n (%)	
Low	31 (11.3)
Moderate	115 (42.0)
High	122 (44.5)

Characteristics	Statistics
N/A	6 (2.2)
BMI[c], mean (SD)	24.44 (4.15)
SF-12[d] physical component summary, mean (SD)	53.32 (4.58)
SF-12 mental component summary, mean (SD)	51.17 (8.11)

[a]N/A: not applicable.

[b]IPAQ: International Physical Activity Questionnaire (short form) [68].

[c]BMI: body mass index.

[d]SF-12: 12-item Short Form.

Discussion

Summary

This study protocol describes the design of an MRT that investigates the effectiveness of 3 intervention components as well as associated moderators to guide the design of a smartphone app to promote physical activity. This study is among the first to generate data for the evidence-based development of a JITAI for physical activity. In addition, a data collection strategy is described that enables the parallel collection of sensor data needed to build predictive models that, when implemented into a JITAI, allow real-time prediction of the state of receptivity. These predictions allow to better inform adaptive intervention delivery by highlighting situations where users are likely to respond to intervention notifications. Insights from this study are of value for anyone involved in the development of mHealth interventions and to support important decisions, such as which components to include in an mHealth intervention or how to tailor intervention delivery to participants over time.

Strengths and Limitations

Our study illustrates potential and challenges associated with mHealth studies. The study's remote recruitment and data collection process allowed recruiting more than 270 participants in less than a week and collecting a unique and powerful high-resolution dataset that contains real-world behavioral and contextual sensor data. In line with other mHealth studies [69], we observed a larger drop in app usage at the beginning of the study, potentially complicating interpretation of our findings. Likewise, step and sensor data were missing for some participants. Explanations for missing data include never reacting to a message of the Ally chatbot, which was required to request step counts from GoogleFit or the HealthKit, or denying app permissions to collect sensor data. Even though the Ally app instructed participants to carry their smartphone whenever possible, other studies observed an underestimation of smartphone-based step counts because smartphones are often not carried consistently in free-living conditions [70]. This may lead to conservative effect estimates, if increases in step counts are not recorded by the Ally app. Sending invitations via email and to insurees of one insurer only, the restricted range of compatible smartphones, and the requirement to share sensitive data (eg, global positioning system sensor data) are likely contributing to a self-selection of participants in our study. This limits the generalizability of our findings and conclusions. Although all participants indicated upon enrollment that they were using no comparable app or device for tracking physical activity, we cannot exclude that such apps or devices were used or that participants primarily used the Apple Health or GoogleFit apps that were required for the Ally app to count steps correctly. Use of such additional apps or devices could potentially affect the use of the Ally app and the effectiveness of intervention components.

If intervention components prove to be effective, we plan to include them in a revised version of the Ally app that provides just-in-time adaptive support depending on identified moderators and predicted states of receptivity. We plan to evaluate this revised version in a randomized controlled trial.

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Authors' Contributions

JNK, TK, and US developed the concept for intervention components and for the Ally app. FK, VM, and TK were responsible for app design and implementation. JNK, FK, TK, and SS developed the study design described in this protocol. JNK and SS developed the methodological approach for the analyses of the different intervention components, and FK, VM, DK, and TK developed the methodological approach for the analyses of smartphone sensor data. BP developed the concept and methodology for the qualitative exit interviews. JNK wrote the manuscript incorporating critical reviews from all authors. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

JNK, FK, and TK are affiliated with the Center for Digital Health Interventions, a joint initiative of the Department of Management, Technology, and Economics at ETH Zurich and the Institute of Technology Management at the University of St. Gallen, which is funded in part by the Swiss health insurer CSS. TK is also cofounder of Pathmate Technologies, a university spin-off company that creates and delivers digital clinical pathways and has used the open source MobileCoach platform for that purpose, too. However, Pathmate Technologies is not involved in the intervention described in this paper. No other conflicts of interests are declared.

Multimedia Appendix 1

Study timeline including intervention components and assessment of outcomes.

[PDF File (Adobe PDF File), 69KB - resprot_v8i1e11540_app1.pdf]

Multimedia Appendix 2

Overview of variables, measures and methods of analysis.

[PDF File (Adobe PDF File), 45KB - resprot_v8i1e11540_app2.pdf]

References

1. Steinhubl SR, Muse ED, Topol EJ. The emerging field of mobile health. Sci Transl Med 2015 Apr 15;7(283):283rv3 [FREE Full text] [doi: 10.1126/scitranslmed.aaa3487] [Medline: 25877894]
2. World Health Organization. World health statistics 2017: monitoring health for the SDGs. 2017. URL: https://www.who.int/gho/publications/world_health_statistics/2017/en/ [accessed 2018-11-30] [WebCite Cache ID 74JjNiLk7]
3. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-Time Adaptive Interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med 2018 May 18;52(6):446-462. [doi: 10.1007/s12160-016-9830-8] [Medline: 27663578]
4. Murray E, Hekler EB, Andersson G, Collins LM, Doherty A, Hollis C, et al. Evaluating digital health interventions: key questions and approaches. Am J Prev Med 2016 Dec;51(5):843-851 [FREE Full text] [doi: 10.1016/j.amepre.2016.06.008] [Medline: 27745684]
5. Klasnja P, Hekler EB, Shiffman S, Boruvka A, Almirall D, Tewari A, et al. Microrandomized trials: an experimental design for developing just-in-time adaptive interventions. Health Psychol 2015 Dec;34S:1220-1228 [FREE Full text] [doi: 10.1037/hea0000305] [Medline: 26651463]
6. Pielot M, Dingler T, Pedro JS, Oliver N. When attention is not scarce-detecting boredom from mobile phone usage. In: Proceedings of the 2015 ACM International Joint Conference on Pervasive and Ubiquitous Computing. New York: ACM; 2015 Presented at: UbiComp '15; September 07-11, 2015; Osaka, Japan. [doi: 10.1145/2750858.2804252]
7. Fischer JE, Greenhalgh C, Benford S. Investigating episodes of mobile phone activity as indicators of opportune moments to deliver notifications. In: Proceedings of the 13th International Conference on Human Computer Interaction with Mobile Devices and Services. New York: ACM; 2011 Presented at: MobileHCI '11; August 30-September 2, 2011; Stockholm, Sweden. [doi: 10.1145/2037373.2037402]
8. Pejovic V, Musolesi M. InterruptMe: designing intelligent prompting mechanisms for pervasive applications. In: Proceedings of the 2014 ACM International Joint Conference on Pervasive and Ubiquitous Computing. 2014 Presented at: UbiComp '14; September 13-17, 2014; Seattle, USA. [doi: 10.1145/2632048.2632062]
9. Lamprecht M, Fischer A, Stamm H. Federal Office of Sport. 2014. Sport Schweiz 2014: Sport activity and sport interest of the Swiss population [in German] URL: https://www.baspo.admin.ch/de/dokumentation/publikationen/sport-schweiz-2014.html [accessed 2018-11-30] [WebCite Cache ID 74Jkch0JZ]
10. Hootman JM, Macera CA, Ainsworth BE, Martin M, Addy CL, Blair SN. Association among physical activity level, cardiorespiratory fitness, and risk of musculoskeletal injury. Am J Epidemiol 2001 Aug 01;154(3):251-258. [doi: 10.1093/aje/154.3.251] [Medline: 11479190]
11. Kelly P, Kahlmeier S, Götschi T, Orsini N, Richards J, Roberts N, et al. Systematic review and meta-analysis of reduction in all-cause mortality from walking and cycling and shape of dose response relationship. Int J Behav Nutr Phys Act 2014 Oct 24;11:132. [doi: 10.1186/s12966-014-0132-x] [Medline: 25344355]
12. Case MA, Burwick HA, Volpp KG, Patel MS. Accuracy of smartphone applications and wearable devices for tracking physical activity data. J Am Med Assoc 2015 Feb 10;313(6):625-626. [doi: 10.1001/jama.2014.17841] [Medline: 25668268]
13. Rachuri K, Musolesi M, Mascolo C, Rentfrow PJ, Longworth C, Aucinas A. EmotionSense: a mobile phones based adaptive platform for experimental social psychology research. In: Proceedings of the 12th ACM international conference on Ubiquitous computing. 2010 Presented at: UbiComp '10; September 26-29, 2010; Copenhagen, Denmark. [doi: 10.1145/1864349.1864393]

14. Adams MA, Hurley JC, Todd M, Bhuiyan N, Jarrett CL, Tucker WJ, et al. Adaptive goal setting and financial incentives: a 2 × 2 factorial randomized controlled trial to increase adults' physical activity. BMC Public Health 2017 Dec 29;17(1):286 [FREE Full text] [doi: 10.1186/s12889-017-4197-8] [Medline: 28356097]
15. Adams MA, Sallis JF, Norman GJ, Hovell MF, Hekler EB, Perata E. An adaptive physical activity intervention for overweight adults: a randomized controlled trial. PLoS One 2013;8(12):e82901 [FREE Full text] [doi: 10.1371/journal.pone.0082901] [Medline: 24349392]
16. Tudor-Locke C, Bassett DR. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med 2004;34(1):1-8. [doi: 10.2165/00007256-200434010-00001] [Medline: 14715035]
17. Tudor-Locke C, Hatano Y, Pangrazi RP, Kang M. Revisiting "how many steps are enough?". Med Sci Sports Exerc 2008 Jul;40(7 Suppl):S537-S543. [doi: 10.1249/MSS.0b013e31817c7133] [Medline: 18562971]
18. Filler A, Kowatsch T, Haug S, Wahle F, Staake T, Fleisch E. MobileCoach: A Novel Open Source Platform for the Design of Evidence-based, Scalable and Low-Cost Behavioral Health Interventions - Overview and Preliminary Evaluation in the Public Health Context. : IEEE; 2015 Presented at: 2015 Wireless Telecommunications Symposium (WTS); April 15-17, 2015; New York, USA. [doi: 10.1109/WTS.2015.7117255]
19. Haug S, Paz Castro R, Kowatsch T, Filler A, Dey M, Schaub MP. Efficacy of a web- and text messaging-based intervention to reduce problem drinking in adolescents: results of a cluster-randomized controlled trial. J Consult Clin Psychol 2017 Dec;85(2):147-159. [doi: 10.1037/ccp0000138] [Medline: 27606700]
20. Paz Castro R, Haug S, Filler A, Kowatsch T, Schaub MP. Engagement within a mobile phone-based smoking cessation intervention for adolescents and its association with participant characteristics and outcomes. J Med Intern Res 2017 Nov 01;19(11):e356 [FREE Full text] [doi: 10.2196/jmir.7928] [Medline: 29092811]
21. 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]
22. Mann T, de Ridder D, Fujita K. Self-regulation of health behavior: social psychological approaches to goal setting and goal striving. Health Psychol 2013 May;32(5):487-498. [doi: 10.1037/a0028533] [Medline: 23646832]
23. Carver CS, Scheier MF. Control theory: a useful conceptual framework for personality-social, clinical, and health psychology. Psychol Bull 1982 Jul;92(1):111-135. [doi: 10.1037/0033-2909.92.1.111] [Medline: 7134324]
24. Sniehotta FF, Nagy G, Scholz U, Schwarzer R. The role of action control in implementing intentions during the first weeks of behaviour change. Br J Soc Psychol 2006 Mar;45(Pt 1):87-106. [doi: 10.1348/014466605X62460] [Medline: 16573874]
25. Heath C, Larrick RP, Wu G. Goals as reference points. Cogn Psychol 1999 Feb;38(1):79-109. [doi: 10.1006/cogp.1998.0708] [Medline: 10090799]
26. Sheeran P. Intention—behavior relations: a conceptual and empirical review. Eur Rev Soc Psychol 2002;12(1):1-36. [doi: 10.1080/14792772143000003]
27. Gollwitzer P, Sheeran P. Implementation intentions and goal achievement: a meta-analysis of effects and processes. Adv Exp Soc Psychol 2006;38(1):69-119. [doi: 10.1016/S0065-2601(06)38002-1]
28. Bélanger-Gravel A, Godin G, Amireault S. A meta-analytic review of the effect of implementation intentions on physical activity. Health Psychol Rev 2013;7(1):23-54. [doi: 10.1080/17437199.2011.560095]
29. Sniehotta FF, Schwarzer R, Scholz U, Schüz B. Action planning and coping planning for long-term lifestyle change: theory and assessment. Eur J Soc Psychol 2005;35(4):565-576. [doi: 10.1002/ejsp.258] [Medline: 25855820]
30. Gollwitzer PM. Implementation intentions: strong effects of simple plans. Am Psychol 1999;54(7):493-503. [doi: 10.1037/0003-066X.54.7.493]
31. Reichert FF, Barros AJ, Domingues MR, Hallal PC. The role of perceived personal barriers to engagement in leisure-time physical activity. Am J Public Health 2007 Mar;97(3):515-519. [doi: 10.2105/AJPH.2005.070144] [Medline: 17267731]
32. Cerin E, Leslie E, Sugiyama T, Owen N. Perceived barriers to leisure-time physical activity in adults: an ecological perspective. J Phys Act Health 2010 Jul;7(4):451-459. [doi: 10.1123/jpah.7.4.451] [Medline: 20683086]
33. Zunft HJ, Friebe D, Seppelt B, Widhalm K, Remaut de Winter AM, Vaz de Almeida MD, et al. Perceived benefits and barriers to physical activity in a nationally representative sample in the European Union. Public Health Nutr 1999 Mar;2(1A):153-160. [Medline: 10933635]
34. Ziegelmann JP, Lippke S, Schwarzer R. Adoption and maintenance of physical activity: planning interventions in young, middle-aged, and older adults. Psychol Health 2006;21(2):145-163. [doi: 10.1080/14768320500188918] [Medline: 21985115]
35. Mitchell MS, Goodman JM, Alter DA, John LK, Oh PI, Pakosh MT, et al. Financial incentives for exercise adherence in adults: systematic review and meta-analysis. Am J Prev Med 2013 Nov;45(5):658-667. [doi: 10.1016/j.amepre.2013.06.017] [Medline: 24139781]
36. Barte JC, Wendel-Vos GW. A systematic review of financial incentives for physical activity: the effects on physical activity and related outcomes. Behav Med 2017;43(2):79-90. [doi: 10.1080/08964289.2015.1074880] [Medline: 26431076]
37. Finkelstein EA, Haaland BA, Bilger M, Sahasranaman A, Sloan RA, Nang EE, et al. Effectiveness of activity trackers with and without incentives to increase physical activity (TRIPPA): a randomised controlled trial. Lancet Diabetes Endocrinol 2016 Dec;4(12):983-995. [doi: 10.1016/S2213-8587(16)30284-4] [Medline: 27717766]

38. Patel MS, Asch DA, Rosin R, Small DS, Bellamy SL, Heuer J, et al. Framing financial incentives to increase physical activity among overweight and obese adults: a randomized, controlled trial. Ann Intern Med 2016 Mar 15;164(6):385-394 [FREE Full text] [doi: 10.7326/M15-1635] [Medline: 26881417]
39. Patel MS, Asch DA, Rosin R, Small DS, Bellamy SL, Eberbach K, et al. Individual versus team-based financial incentives to increase physical activity: a randomized, controlled trial. J Gen Intern Med 2016 Dec;31(7):746-754 [FREE Full text] [doi: 10.1007/s11606-016-3627-0] [Medline: 26976287]
40. Deci EL, Koestner R, Ryan RM. A meta-analytic review of experiments examining the effects of extrinsic rewards on intrinsic motivation. Psychol Bull 1999 Nov;125(6):627-668. [doi: 10.1037/0033-2909.125.6.627] [Medline: 10589297]
41. Cerasoli CP, Nicklin JM, Ford MT. Intrinsic motivation and extrinsic incentives jointly predict performance: a 40-year meta-analysis. Psychol Bull 2014 Jul;140(4):980-1008. [doi: 10.1037/a0035661] [Medline: 24491020]
42. Deci E, Ryan R. Intrinsic Motivation and Self-Determination in Human Behavior. New York, USA: Plenum Press; 1985.
43. Harkins KA, Kullgren JT, Bellamy SL, Karlawish J, Glanz K. A trial of financial and social incentives to increase older adults' walking. Am J Prev Med 2017 May;52(5):e123-e130. [doi: 10.1016/j.amepre.2016.11.011] [Medline: 28062271]
44. Schwarzer R, Luszczynska A. How to overcome health-compromising behaviors: the health action process approach. Eur Psychol 2008 Jan;13(2):141-151. [doi: 10.1027/1016-9040.13.2.141]
45. Hills M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8(1):7-20. [doi: 10.1111/j.1365-2125.1979.tb05903.x]
46. Markland D, Tobin V. A modification to the behavioural regulation in exercise questionnaire to include an assessment of amotivation. J Sport Exerc Psychol 2004 Jun;26(2):191-196. [doi: 10.1123/jsep.26.2.191]
47. Guay F, Vallerand RJ, Blanchard C. On the assessment of situational intrinsic and extrinsic motivation: the Situational Motivation Scale (SIMS). Motiv Emot 2000;24(3):175-213. [doi: 10.1023/A:1005614228250]
48. 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]
49. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [doi: 10.2307/3766749] [Medline: 8628042]
50. Lippke S, Schwarzer R, Ziegelmann JP, Scholz U, Schüz B. Testing stage-specific effects of a stage-matched intervention: a randomized controlled trial targeting physical exercise and its predictors. Health Educ Behav 2010 Aug;37(4):533-546. [doi: 10.1177/1090198109359386] [Medline: 20547760]
51. Scholz U, Keller R, Perren S. Predicting behavioral intentions and physical exercise: a test of the health action process approach at the intrapersonal level. Health Psychol 2009 Nov;28(6):702-708. [doi: 10.1037/a0016088] [Medline: 19916638]
52. Schwarzer R, Lippke S, Luszczynska A. Mechanisms of health behavior change in persons with chronic illness or disability: the Health Action Process Approach (HAPA). Rehabil Psychol 2011 Aug;56(3):161-170. [doi: 10.1037/a0024509] [Medline: 21767036]
53. Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: toward a unified view. MIS Q 2003;27(3):425-478. [doi: 10.2307/30036540]
54. Venkatesh V, Thong J, Xu X. Consumer acceptance and use of information technology: extending the unified theory of acceptance and use of technology. MIS Q 2012;36(1):157-178. [doi: 10.2307/41410412]
55. Bickmore TW, Mitchell SE, Jack BW, Paasche-Orlow MK, Pfeifer LM, Odonnell J. Response to a relational agent by hospital patients with depressive symptoms. Interact Comput 2010 Jul 01;22(4):289-298 [FREE Full text] [doi: 10.1016/j.intcom.2009.12.001] [Medline: 20628581]
56. Spittaels H, Verloigne M, Gidlow C, Gloanec J, Titze S, Foster C, et al. Measuring physical activity-related environmental factors: reliability and predictive validity of the European environmental questionnaire ALPHA. Int J Behav Nutr Phys Act 2010 May 26;7(1):48 [FREE Full text] [doi: 10.1186/1479-5868-7-48] [Medline: 20504339]
57. Rammstedt B, John OP. Measuring personality in one minute or less: a 10-item short version of the Big Five Inventory in English and German. J Res Pers 2007 Feb;41(1):203-212. [doi: 10.1016/j.jrp.2006.02.001]
58. Künzler F, Kramer JN, Kowatsch T. Efficacy of mobile context-aware notification management systems: A systematic literature review and meta-analysis. 2017 Presented at: 13th International Conference on Wireless and Mobile Computing, Networking and Communications (WiMob); October 09-11, 2017; Rome, Italy.
59. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. BMC Med Res Methodol 2003 Nov 24;3:26 [FREE Full text] [doi: 10.1186/1471-2288-3-26] [Medline: 14633287]
60. Kowatsch T, Kramer JN, Kehr F, Wahle F, Elser N, Fleisch E. Effects of charitable versus monetary incentives on the acceptance of and adherence to a pedometer-based health intervention: study protocol and baseline characteristics of a cluster-randomized controlled trial. JMIR Res Protoc 2016 Sep 13;5(3):e181 [FREE Full text] [doi: 10.2196/resprot.6089] [Medline: 27624645]
61. Eisler R, Lüber A. Comparis. 2006. [How important is Swiss supplemental hospital insurance?] URL: https://www.comparis.ch/~/media/files/mediencorner/studies/2006/krankenkassen/spitalzusatzversicherungen_studie.pdf [accessed 2018-11-30] [WebCite Cache ID 74Jn7Pq0k]

62. Boruvka A, Almirall D, Witkiewitz K, Murphy SA. Assessing time-varying causal effect moderation in mobile health. J Am Stat Assoc 2017 Mar 31;113(523):1112-1121. [doi: 10.1080/01621459.2017.1305274]
63. Sequeira MM, Rickenbach M, Wietlisbach V, Tullen B, Schutz Y. Physical activity assessment using a pedometer and its comparison with a questionnaire in a large population survey. Am J Epidemiol 1995 Nov 01;142(9):989-999. [doi: 10.1093/oxfordjournals.aje.a117748] [Medline: 7572981]
64. Bassett DR, Wyatt HR, Thompson H, Peters JC, Hill JO. Pedometer-measured physical activity and health behaviors in US adults. Med Sci Sports Exerc 2010 Oct;42(10):1819-1825 [FREE Full text] [doi: 10.1249/MSS.0b013e3181dc2e54] [Medline: 20305579]
65. Holm S. A simple sequentially rejective multiple test procedure. Scand Stat Theory Appl 1979;6(2):65-70. [doi: 10.2307/4615733]
66. Safran Naimark J, Madar Z, Shahar DR. The impact of a web-based app (eBalance) in promoting healthy lifestyles: randomized controlled trial. J Med Internet Res 2015 Mar 02;17(3):e56 [FREE Full text] [doi: 10.2196/jmir.3682] [Medline: 25732936]
67. Glynn LG, Hayes PS, Casey M, Glynn F, Alvarez-Iglesias A, Newell J, et al. Effectiveness of a smartphone application to promote physical activity in primary care: the SMART MOVE randomised controlled trial. Br J Gen Pract 2014 Jul;64(624):e384-e391 [FREE Full text] [doi: 10.3399/bjgp14X680461] [Medline: 24982490]
68. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
69. Modena BD, Bellahsen O, Nikzad N, Chieh A, Parikh N, Dufek DM, et al. Advanced and accurate mobile health tracking devices record new cardiac vital signs. Hypertension 2018 Aug;72(2):503-510. [doi: 10.1161/HYPERTENSIONAHA.118.11177] [Medline: 29967036]
70. Duncan MJ, Wunderlich K, Zhao Y, Faulkner G. Walk this way: validity evidence of iphone health application step count in laboratory and free-living conditions. J Sports Sci 2018 Aug;36(15):1695-1704. [doi: 10.1080/02640414.2017.1409855] [Medline: 29179653]

Abbreviations

Ally: Assistant to Lift your Level of activitY
ANOVA: analysis of variance
AP: action planning
BREQ-2: Behavioral Regulation for Exercise Questionnaire-2
CP: coping planning
CC: control condition (no planning)
GEE: generalized estimating equation
JITAI: just-in-time adaptive intervention
mHealth: mobile health
MRT: microrandomized trial
p (SG): probability of reaching the step goal
SIMS: Situational Motivation Scale

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Protocol

Human Papillomavirus Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) Cohort Study: Protocol Describing Design, Methods, and Research Goals

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Abstract

Background: Human papillomavirus (HPV) epidemiological research has generally been individual based, typically focusing on women, with couple-based research mostly consisting of cross-sectional assessment of prevalent HPV infection in both partners.

Objective: The HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) study was set up to investigate the transmissibility of HPV among young, recently formed couples in Montreal, Canada. This paper provides an overview of the HITCH cohort study design and procedures as well as a narrative summary of the most important findings.

Methods: HITCH is a longitudinal investigation of HPV transmission in recently formed heterosexual partnerships initiated within 6-month pre-enrollment, a time at which considerable transmission is believed to occur. A total of 549 newly formed dyads were recruited (2005-2011) from postsecondary institutions, including 502 young women and their male partners. An additional 46 males were enrolled at follow-up, as some women enrolled a subsequent partner at follow-up. Women aged 18-24 years were followed for 24 months for acquisition of HPV types not present at enrollment, whereas men returned for a single follow-up visit at month 4, for a sum total of 3361 clinic visits. The last follow-up visit occurred in January 2014. Extensive sociodemographic, sexual behavioral, and medical history data were collected every 2-4 months using computer-assisted, self-administered questionnaires. Furthermore, participants provided genital, blood, oral, and hand specimens for HPV assessment.

Results: Although in its early analysis stage, HITCH has produced important publications. Findings from HITCH have increased the available knowledge about the natural history of HPV transmission and its determinants, provided further evidence regarding oral-oral and oral-genital routes of HPV transmission, and supplied empirically valid epidemiological parameters of HPV transmission to assist mathematical modelers in health economic assessments. In addition, HITCH data were made available to several multistudy collaborations evaluating new HPV detection assays and evidence for-or-against HPV type replacement following the introduction of HPV vaccination.

Conclusions: HITCH will continue to offer a unique resource for research on HPV transmission.

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KEYWORDS

human papillomavirus; HPV transmission; longitudinal study; sex partners; young adults

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection and a necessary cause of all cervical cancer cases in the world [1,2]. Most sexually active persons acquire it over their lifetime [3]. Although HPV is transmitted between sexual partners, the vast majority of HPV epidemiological research has been individual based and typically focused on women. Far less research has been conducted among men or couples. Couple-based HPV research has mostly consisted of cross-sectional assessment of prevalent HPV infection in both partners [4,5]. Study populations included attendees at sexually transmitted infections clinics [6], couples being evaluated for infertility [7], women referred for colposcopy and their partners [8,9], and—within the context of retrospective case-control studies—women with cervical intraepithelial neoplasia or cervical cancer [10-12]. Because most HPV infections are transient [13], infections may have cleared in one or both partners by the time couples have been together for years. To study HPV transmission, one would ideally recruit relatively young couples that are newly forming.

Initiated in 2005, the overarching aim of HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) cohort study was to further our understanding of the transmissibility of HPV among recently formed couples to better inform prevention strategies. When it was developed, no other study had specifically targeted newly forming couples, and some had excluded couples of <6-month duration [10,11]. Research aims were (1) to describe the prevalence and type-specific concordance of HPV infection between young women and men in heterosexual couples; (2) to characterize and quantify risk factors for incident HPV infection among young women and men; (3) to estimate rates of male-to-female and female-to-male HPV transmission; (4) to identify behavioral risk factors and biological determinants of HPV transmission upon exposure; and (5) to characterize HPV infection in the oral tract and fingers, and their agreement with genital infection and partner's infection status.

The HITCH cohort study (referred to hereafter as HITCH) was conducted by a team of researchers at McGill University, led by two of the authors (ELF and ANB), in collaboration with the McGill Student Health Services Clinic, Concordia Health Services Clinic, and Centre Hospitalier de l'Université de Montréal, all located in the province of Québec, Canada. The study was conducted in accordance with the principles and articles stipulated by the Tri-Council Policy Statement Ethical Conduct For Research Involving Humans [14]. It received ethical approval from institutional review boards at McGill University, Concordia University, and Université de Montréal. All participating couples provided written informed consent.

Methods

Study Population and Recruitment

The inclusion criteria for women were as follows: those aged 18-24 years, enrolled at a university or junior college in Montreal, intending to remain in Montreal for the next 2 years, currently heterosexually active with a male partner with whom sexual activity was initiated within the previous 6 months, willing to comply with follow-up, having an intact uterus and no history of cervical lesions or cancer, and neither currently pregnant nor planning to become pregnant in the next 24 months. Men were eligible to participate if they were aged ≥18 years and willing to comply with follow-up.

Recruitment was achieved through printed promotional materials and electronic advertisements on campuses and venues frequented by students. Interested couples were invited to visit the study website and contact study nurses.

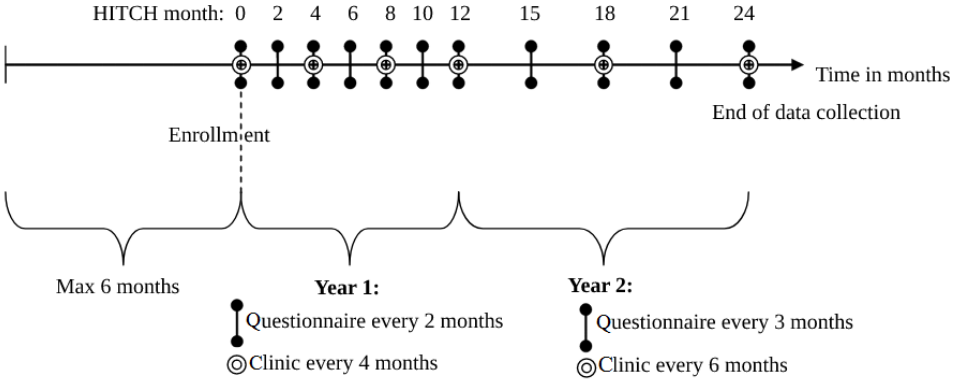
Study Design and Procedures

Couples were recruited for assessment of sexual histories and HPV testing (Figure 1). Women were followed for 24 months for acquisition of HPV types not present at enrollment. Added in October 2006, men returned for a single follow-up visit at month 4. The last follow-up visit occurred in January 2014.

Men and women self-completed separate Web-based questionnaires. Women attended a clinic visit at enrollment and 5 other follow-up visits, whereas men only attended a clinic visit at enrollment and at 4 months.

Extensive efforts were made to prevent attrition, including prescheduled appointments, timely electronic reminders between administered questionnaires, in-person motivation by the research nurse at each visit, and monetary compensation (Can $50 per visit and Can $10 per questionnaire completed by a woman between visits). Reflecting in part the mobile nature of student populations, female attrition rates were 43.0% (216/502) by month 24; 48 women attended 1 visit (baseline) only, 38 attended 2, 38 attended three, 46 attended 4 and 44 women attended 5 visits. Among men who consented to return for a follow-up visit, 22.6% (124/548) were lost to follow-up (113/502 for the first male sexual partner and 11/42 for the second male sexual partner). No statistically significant differences were noted between participants who dropped out and those who remained in terms of age, smoking status, lifetime number of sex partners, age at sexual debut, or HPV status.

Figure 1. Time points and timeline for follow-up of female human papilloma virus infection and transmission among couples through heterosexual activity (HITCH) study participants.



Data Collection and Available Data

Information was collected using Web-based self-completed questionnaires at each visit, and is described herein in accordance with the Checklist for Reporting Results of Internet E-Surveys guidelines [15]. A secure, confidential, study-designated internet site provided participants with protected access to computerized questionnaires by assigned log-in names and passwords. In addition, 4 questionnaire versions were used: a female induction (baseline), a male induction, a female follow-up, and a male follow-up (see Multimedia Appendices 1-4). Women also completed questionnaires between visits from a computer of their choice, such that each completed 11 questionnaires in total. These questionnaires used customized text to refer to specific dates or partners to personalize questions and improve recall. Skip patterns were programmed so that respondents need only answer applicable questions. Respondents had the option of leaving responses blank if they preferred not to answer, but a warning screen appeared to ensure that no question was left blank accidentally. Table 1 shows the main topics addressed in the questionnaires and corresponding variables.

We collected biological specimens at each visit (Multimedia Appendix 5). Participants were asked to abstain from oral, vaginal, or anal sex for 24 hours before the clinic visit. At each visit, men and women provided a blood sample for HPV antibody testing. Women provided a self-collected vaginal sample [16]. For men, the examining nurse collected a specimen of epithelial cells from the penis and scrotum [17]. Beginning in 2008, we assessed oral and hand HPV infection at visits for which both partners attended (enrollment visit, 4-month follow-up visit, and subsequent follow-up visits when women enrolled a new male partner and the accompanying follow-up visit for that new male partner). Participants provided oral rinses (using a soft toothbrush and mouthwash) and a specimen of epithelial cells from the dominant hand (swabs of the index and middle fingers, and nails).

Genital, oral, and hand specimens were tested using a polymerase chain reaction (PCR) protocol based on the amplification of a 450-bp segment in the L1 HPV gene using the Linear Array HPV genotyping assay (Roche Molecular Systems) [18]. Using this technique, 36 mucosal HPV genotypes can be detected: HPVs 6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89. In addition, a molecular variant analysis of HPV16 isolates was done to obtain a more refined taxonomic level of detail. The PCR sequencing method used primers flanking a segment of the long control region of HPV [19-22]. All genital specimens found to be HPV DNA-positive for types 16, 18, 31, 33, 45, and 52 were retested using a quantitative, real-time PCR to measure type-specific viral load using specific primers [23-25].

High-resolution PCR typing of the DQB1 and DRB1 class II loci of the human leukocyte antigen (HLA) system was performed to identify specific alleles that may help explain variations in the HPV susceptibility. HLA testing was done in DNA samples extracted from oral specimens (both male and female) of the enrollment visit or, in case these were unavailable or insufficient for analysis, using specimens from subsequent visits or genital samples. In addition, sequence-based typing with the AlleleSEQR DRB1 and AlleleSEQR DQB1 assays (Abbott Molecular Diagnostics, Inc) was used to identify all possible alleles. Locus-specific exon 2 and 3 amplicons were produced by PCR amplification and then sequenced to determine allele-specific nucleotide sequence variants. To save costs, we tested only specimens from couples with an infection transmission opportunity (ie, at least one partner positive for at least one HPV type during the course of the study).

Table 1. Data collected using Web-based self-completed Human papillomavirus Infection and Transmission among Couples through Heterosexual activity (HITCH) questionnaires, 2005-2011.

Domain	Baseline data	Follow-up data (updates since last interview)
Sociodemographic	Sex, date of birth, place of birth (country, Canadian province), marital status, ethnicity, education status, educational institution, highest education level, employment status, parental highest level of education, financial situation while growing up	Marital status, education status, educational institution, highest education level, employment status
Smoking	Personal history of cigarette smoking (duration, quantity, and frequency)	Initiation and continuation and cessation (quantity)
Reproductive history[a]	Age at menarche, current and previous pregnancies	Current pregnancy, pregnancy since the last interview
Lifetime sexual history	Number of sexual partners (males and females, all routes), number of sexual partners (vaginal), age at first vaginal sexual intercourse, sexual orientation	N/A[b]
Sexual activity with enrolled HITCH partner	Partner date of birth, relationship status with partner, date of first engagement in sexual activity, topics discussed together (pregnancy prevention, sexually transmitted disease prevention, sexual history, ever had a sexually transmitted disease, ever tested for sexually transmitted disease including HIV/AIDS), number of previous partners involving vaginal intercourse, presence of a sexually transmitted infection, partner circumcised, frequency of engagement in sexual activities (per week, per month), frequency of masturbation (for each), frequency of oral sex (for each), vaginal intercourse (date of first and last occurrence, frequency, ie, per week, per month), condom use (frequency, breakage or slip off, put before starting vaginal intercourse, taken off during vaginal intercourse), anal intercourse[c]	Sexual activity with HITCH partner (date of enrollment of HITCH partner[c]; date of birth of HITCH partner[c]; relationship status; date of first engagement in sexual activity; topics discussed together, similar list[c]; lifetime number of partners involving vaginal intercourse[c]; ever had a sexually transmitted infection[c]; partner circumcised[c]; number of times engaged in sexual activities since the last interview, per week, per month; frequency of masturbation, for each; oral sex, for each; vaginal intercourse, date of first and last occurrence; frequency, per week, per month; condom use regarding frequency, breakage or slip off, put before starting vaginal intercourse, taken off during vaginal intercourse; anal intercourse[d]), ongoing sexual relationship, date of end of sexual relationship with HITCH partner, engagement in sexual activity with someone other than HITCH partner
Sexual activity with other partners	Concurrent sexual activity with someone other than current partner (number of sexual partners, number of ongoing sexual partners), lifetime engagement in sexual activity only with HITCH partner	Concurrent sexual activity with someone other than HITCH partner (number of sexual partners, number of ongoing sexual partners)
Contraceptive history[a]	Lifetime use of birth control methods (intrauterine device, hormonal contraceptive, condom, spermicides, diaphragm, cervical cap, sponge, vaginal douche, natural method, withdrawing or pulling out, emergency contraception such as morning-after-pill), age at first use of hormonal contraceptive, duration of use of hormonal contraceptives (months, years), birth control methods used with HITCH partner (similar list)	Use of birth control methods (similar list to baseline data)
Medical history	Number of Pap tests done,[a] date of last Pap test (month and year),[a] ever had a medical condition (trichomonas genital infection, venereal warts or condylomas or papillomavirus infection, chlamydia, genital herpes, syphilis, gonorrhea, ulcers or genital sores, HIV, hepatitis B, ureaplasma hominis, vaginal yeast infection,[a] bacterial vaginosis[a]), medical condition since the start of sexual relationship with HITCH partner, signs and symptoms since the start of sexual relationship with HITCH partner (painful or frequent urination, itching or burning sensation when urinating, blood in urine, abnormal discharge, sores in the genital area, unusually painful or heavy period,[a] vaginal itching or burning,[a] lower back pain not caused by physical exertion)[a]	Pap test done, date of last Pap test (month and year), medical conditions (similar list to baseline data), signs and symptoms (similar list to baseline data)

Domain	Baseline data	Follow-up data (updates since last interview)
Knowledge of human papillomavirus (HPV)	Ever heard of HPV, true or false statements (HPV can cause cervical cancer in women; men can carry HPV; genital warts cause cervical cancer in women; HPV can be cured with antibiotics; a person may be infected with HPV and not know it; HPV can cause penile cancer in men; HPV causes genital herpes; condoms protect against HPV; having multiple sex partners increases one's risk for HPV; regular Pap test can help to prevent complications from HPV; HPV is the most common sexually transmitted infection; a person can get HPV from sharing a plate or fork or glass with someone who has HPV, unprotected sexual intercourse with someone who has HPV, oral sex with someone who has HPV, kissing—with exchange of saliva—someone who has HPV, sharing a washroom or shower with someone who has HPV), chances of becoming infected with HPV, chances of developing cervical or penile cancer	
HPV vaccine	Received the HPV vaccine (received part of participation in a clinical trial, number of injections, date of last injection), likelihood of choosing to be vaccinated if offered	Received the HPV vaccine (received part of participation in a clinical trial, number of injections, date of last injection), likelihood of choosing to be vaccinated if offered

[a]Questions were only asked in female respondents' baseline questionnaires; for men, circumcision was evaluated by the nurse during the clinic visit.

[b]N/A: not applicable.

[c]Questions were only asked in female respondents' follow-up.

[d]Men questionnaire also asked about the number of times of anal intercourse (per week, per month) and frequency of condom use during anal intercourse.

Results

Study Population Characteristics

HITCH enrolled the first couple in May 2005 (McGill University site) and March 2006 (Concordia University site). It reached its enrollment target in January 2011 with a total of 1051 participants (502 women and 549 men) recruited. Of 502 women, 42 enrolled a second male partner and 4 enrolled a third male partner. In total, there were 3361 clinic visits and 4408 and 2495 person-months of follow-up among women and men, respectively. Multimedia Appendix 6 shows the characteristics of the study population.

Findings to Date

HITCH findings, to date, suggest that HPV is highly transmissible. Presented at local, national, and international scientific conferences and meetings, the spectrum of findings regarding HPV transmission have received broad acceptance in the scientific community and considerable press coverage in international media. Results are likely to influence prevention efforts for cervical cancer and other HPV-related diseases, including behavioral strategies to reduce risk.

Prevalence of Human Papillomavirus Infection (Baseline Data for 263 Couples)

At enrollment, similar HPV prevalence (147/263, 55.8%) was detected among women and men, but couples were not necessarily concordant for the same HPV types [26]. In nearly two-thirds of couples, at least one partner was infected with ≥1 HPV type. Current partner's status was the most important risk factor for prevalent infection (women: odds ratio [OR] 55.2, 95% CI 38.0-80.1; men: OR 58.7, 95% CI 39.8-86.3). There was evidence for a protective effect of condoms, but protection was incomplete and stronger among men than among women.

Type-Specific Concordance of Human Papillomavirus Infection (Baseline Data for 263 Couples)

Analysis of patterns of type-specific concordance and discordance at baseline revealed that the extent of concordance was far greater than expected and consistent with rapid transmission of HPV between partners [27]. HPV was detected in 64.3% (169/263) of couples. In 41.4% (109/263) couples, both partners harbored the same HPV type—nearly 4 times more than expected if the HPV status of partners were uncorrelated. Among type-specific HPV infections in couples for whom at least one partner was infected, 42.0% (71/169) were infected with the same type for both partners (95% CI 36%-47%). This proportion provides an estimate of the per-partnership transmission probability; it increased from 25% (18/71) among couples engaging in vaginal sex for <2 months to 68% (48/71) among those at 5-6 months.

Genital Human Papillomavirus Transmission (Longitudinal Data for 179 Couples)

Using data from the first follow-up visit, HPV transmission rates were estimated among participants with documented sexual exposure to an infected partner in couples that were discordant on ≥1 HPV types [28]. We observed little difference between male-to-female (3.5 per 100 person-months, 95% CI 2.7-4.5) and female-to-male transmission rates (4.0 per 100 person-months, 95% CI 3.0-5.5). The transmission was relatively homogeneous across HPV genotypes, alpha species, and oncogenic risk categories. The transmission rates at follow-up were lower than those estimated at baseline. This might be explained by lower infectiousness due to clearance in the index partner, defined as the one infected with a type or types not found in the other partner at baseline (nonindex partner), and lower susceptibility in the nonindex partner due to depletion of susceptibles (ie, that people who are highly susceptible would

have already acquired the infection from their partner by the time of enrollment into the study).

Determinants of Human Papillomavirus Transmission (Baseline Data for 482 Couples)

Correlates of genital HPV infection in partnerships were identified at baseline using the couple or "dyad" as the unit of analysis, rather than the individual [29]. To the best of our knowledge, this was the first analysis of its kind. HPV was detected in 69.1% (333/482) of partnerships, with both partners being HPV-positive in 49.0% (236/482) of dyads, and an equal number of male-positive/female-negative and male-negative/female-positive dyads (43/482, 8.9%). Consistent with the sexual network theory, HPV was more likely to be present in partnerships with (1) a greater total number of lifetime partners, hence more links to the greater sexual network of young adults in Montreal; (2) shorter intervals of time since the most recent extra-dyadic partner (ie, short "gap" lengths or concurrent partnerships); and (3) greater age gaps between the male and female partner, although only the sum total of partners remained independently associated with couple-level HPV in multivariate analysis. A novel finding was that condom use with previous partners predicted lesser likelihood of detecting HPV in the current partnership. This protective effect of condoms remained statistically significant even after adjustment for potential risk factors.

Human Papillomavirus Infection in the Oral Tract (Baseline Data for 222 Couples)

We estimated the prevalence of oral HPV and assessed risk factors among male partners at enrollment [30]. The prevalence of oral HPV among men was 7.2% (16/222). It was higher among men who were ever smokers (12/98, 12.2%), in nonmonogamous relationships (7/39, 17.9%), had a partner with oral (2/7, 28.6%) or genital (15/130, 11.5%) HPV infection. Prevalence increased with frequency of oral sex among men whose partner had a genital infection with the same HPV type. Our results provided further evidence that oral HPV may be transmitted through either oral-oral or oral-genital routes.

Human Papillomavirus Type Replacement

It has been hypothesized that following a reduction in HPV vaccine-targeted genotypes, an increase in the prevalence of other types might occur due to reduced competition during natural infection. Any apparent postvaccination increase must be distinguished from diagnostic artifacts consequent to consensus PCR assays failing to detect HPV types present in low copy numbers in coinfected specimens. The assumption is that with a decline in vaccine-preventable types, there might be increased detection of previously "masked" types. Using data from 6 epidemiological studies, including HITCH, a total of 1200 anogenital specimens (blinded to HPV status) were reanalyzed to evaluate unmasking of HPV52 that might have been caused by elimination of HPV16 [31]. Results indicated that diagnostic artifacts due to masking may occur in some settings in the evaluation of HPV type replacement.

Human Papillomavirus Acquisition and Clearance According to Infection Status With Vaccine-Targeted Types

We used data of 3200 females from 3 cohort studies, including HITCH [32]. Females infected with vaccine-targeted types were at a higher risk of acquiring additional HPV types and at equal risk of clearing existing infections. For example, females infected with HPV16 were at a higher risk of acquiring other alpha-9 HPV types (hazards ratio [HR] 1.9, 95% CI 1.2-3.0) but at a similar risk of clearing existing ones (HR 0.9, 95% CI 0.7-1.3). Our findings suggest that HPV type competition does not exist and type replacement is unlikely to occur.

Natural Human Papillomavirus Type Competition in Unvaccinated Females

Pooling data from 5 prevaccination epidemiological studies, including HITCH, and applying a hierarchical Bayesian regression approach that uses shrinkage and adjustment for confounders (ie, age and lifetime number of sex partners) and other HPV types, we found HPV16 to be the most common type (prevalence range 1.0%-13.8%) [33]. HPV types were more likely to be detected as part of a multiple infection than as single infections. We did not find evidence for natural HPV type competition and type replacement.

Y Chromosome Detection and Concordance of Genital Human Papillomavirus Infection (Baseline Data for 494 Couples)

HPV DNA detection may not always represent true infections but maybe depositions from infected sexual partners. We examined whether sexual risk factors and a biomarker, Y chromosome DNA, were associated with genital HPV partner concordance using baseline genital specimens [34]. HPV DNA Y chromosome DNA predicted type-specific HPV concordance in univariate analyses; however, in multivariable models, the independent predictors of concordance were days since the last vaginal sex and condom use. We estimated that 14% of HPV DNA detections in genital samples could be attributable to vaginal sex in the past week, which has implications not only for couple-based studies but also for individual-based HPV studies.

Y Chromosome Detection as a Biomarker for Recent Sexual Activity (Baseline Data for 494 Couples)

We observed that this biomarker may serve as a measure of recent condomless vaginal sex in HPV studies lacking data on sexual behavior, such as surveillance studies of HPV prevalence [35]. Among female participants, detection of Y chromosome DNA in the vaginal tract decreased from 76.6% (85/111) in women who reported vaginal sex 0-1 day ago to 13% (3/23) in women whose last reported encounter was ≥15 days ago. Self-reported condom use frequency was highly and negatively correlated with Y chromosome DNA detection.

Assortativity and Mixing by Sexual Behaviors and Sociodemographic Characteristics (Baseline Data for 502 Couples)

Sexual mixing refers to whom individuals choose as sexual partners. It is described as assortative on a characteristic if individuals have the tendency to choose partners who are similar to them on that particular characteristic (eg, age), and disassortative if individuals tend to choose partners who are different from them (eg, gender). Among 502 young adults in a new heterosexual dating partnership, we found a moderate to strong assortativity on partners' demographic characteristics, as well as on their number of sexual partners, sexual partner acquisition rates, concurrency, and gap lengths between partnerships [36]. These findings are particularly useful for developing models of sexually transmitted infections.

Generic Human Papillomavirus Probe Assay

The utility of a generic HPV probe assay was compared with the commercial Linear Array (Roche Diagnostics, Laval, Canada) for the detection of HPV DNA in a multistudy collaboration [37]. HITCH vaginal swabs, penile and scrotal scrapings, and fingertip brushings were among the 1013 clinical specimens analyzed. The sensitivity, specificity, and negative predictive value of the assay were 99.5% (95% CI 98.4%-99.9%), 58.6% (95% CI 53.9%-63.1%), and 98.9% (95% CI 96.5%-99.8%), respectively. Thus, the generic assay conveniently identified HPV-positive specimens.

Discussion

Strengths and Limitations

There are two unique features of HITCH that are novel for HPV research. The cohort is the first large-scale study of HPV acquisition involving sexual partners. Previous studies had typically sample sizes of ≤100 couples and some had as few as 25 couples [6,38,39]. More importantly, it is the only study to restrict enrollment to couples in a new sexual relationship, a time at which considerable transmission is believed to occur. Other methodological strengths of HITCH are its prospective approach, interdisciplinary framework, detailed level of assessment and wealth of covariate information, rich collection of biological specimens, and analyses of clinical samples performed according to the latest recommendations and technological advancements. Moreover, the use of frequent self-completed electronic questionnaires contributed to the collection of valid and reliable data on substantive, sensitive topics especially those relating to sexual activity.

HITCH is one of the few studies that could provide empirical estimates of HPV transmission parameters to be used in models for assessing the population health impact and cost-effectiveness of vaccination strategies. There has been an increased awareness about HPV and its role in cervical cancer since the introduction of the first prophylactic HPV vaccine in 2006, 1 year after the initiation of HITCH. Gardasil (Merck, Whitehouse Station, NJ, USA) is a quadrivalent vaccine to prevent genital warts caused by genotypes HPV6 and HPV11, as well as anal, cervical, vulvar, and vaginal cancers caused by HPVs 16/18. Approved in 2009, Cervarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) is a bivalent vaccine against cervical precancerous lesions and cancer caused by HPVs 16/18, which represent 70% of all cervical cancer cases. In 2014, Gardasil 9 (Merck) vaccine was introduced to help prevent against diseases associated with HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 [40].

In the postvaccine era, transmission studies such as HITCH are especially important to inform all possible prevention strategies. First, there are still some cancer caused by other high-risk HPV types, and the duration of immunity is unknown. Second, the benefits of HPV vaccination in young female adolescents will take years before being realized. Third, many teenage girls and women will still be susceptible to infection because vaccination outside of the government-funded program is only available privately at a high cost. Even for girls who may now receive the vaccine free-of-charge, implementation has not occurred without debate [41-43]. If high vaccine coverage cannot be achieved, there will be much continued transmission of the vaccine-preventable HPV types within these adolescent cohorts.

A number of limitations of this study have to be underscored. These include loss to follow-up, volunteer nature of self-selected subjects limiting the generalizability, the unavailability of hand and oral specimens for all participants at all time points, and absence of anal specimens. In addition, the potential for self-report response bias needs to be acknowledged. However, the use of self-completed electronic questionnaires to collect repeated measurements of behavioral data was likely to reduce the potential for social desirability bias. If we were to re-establish HITCH, we would have opted to (1) actively follow men at all visits; (2) collect hand, oral, and anal specimens for both men and women throughout follow-up; (3) collect data on lifetime and recent number of oral sex partners; (4) not perform serology at each visit, as this might have influenced compliance rates; and (5) instruct participants to abstain from sexual activity for a minimum of 48 hours before specimen collection to prevent potential false-positive findings.

Future Plans

Ongoing areas of active analysis and manuscript preparation, as well as planned investigations, from our extensive program of research with HITCH data include (1) influence of HLA types on HPV type-concordance and transmission; (2) hand-genital patterns of HPV type-specific auto-concordance and couple-concordance; (3) assessment of the association between circumcision and condom use and distribution, concordance, and transmission of HPV genotypes in genital specimens; (4) impact of HPV vaccination on the prevalence, concordance, and transmission of type-specific HPV infections; (5) concordance and transmission of specific variants within HPV genotypes; (6) transmissibility of HPV focusing on the viral load and type-specific concordance of HPV infection between young couples; (7) evaluation of HPV acquisition in women for whom HPV positivity was measured both before and after the first sexual activity with a new male sex partner; (8) development and validation of a rapid, easy-to-perform and inexpensive serologic noncompetitive, multiplexed Luminex-based platform to measure total immunoglobulin G antibody; and (9) association between type-specific serological antibodies and HPV prevalence, acquisition, and clearance.

Collaboration

Information about HITCH findings and publications is available at the McGill University Division of Cancer Epidemiology website [44]. A regularly updated list of peer-reviewed scientific publications from HITCH is available [45]. Our team is open to collaboration and data sharing with other research groups. So far, we have contributed HITCH data to multistudy collaborations [31-33,37]. Researchers interested in collaboration or further details are invited to contact the principal investigator, ELF.

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Authors' Contributions

ELF (principal investigator) and ANB were involved in the study concept and design; research nurses and PPT were involved in the data acquisition; MEZ, ANB, and ELF were involved in the drafting of the manuscript; MEZ, FC, PPT, MR, ELF, and ANB were involved in the critical revision of the manuscript. From the HITCH study group, Allita Rodrigues was the study coordinator; Gail Kelsall, Suzanne Dumais, Natalia Morykon, and Amelia Rocamora were responsible for management of subject participation and specimen collection; Nathalie Slavtcheva was responsible for study management; Veronika Moravan and Michel Wissing were responsible for data management; and Hélène Voyer, Véronique Legault, Emilie Comete, and Julie Guénoun were part of the laboratory staff.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Female induction questionnaire.
[PDF File (Adobe PDF File), 189 KB - resprot_v8i1e11284_app1.pdf]

Multimedia Appendix 2
Female follow-up.
[PDF File (Adobe PDF File), 167 KB - resprot_v8i1e11284_app2.pdf]

Multimedia Appendix 3
Male induction questionnaire.
[PDF File (Adobe PDF File), 161 KB - resprot_v8i1e11284_app3.pdf]

Multimedia Appendix 4
Male follow-up.
[PDF File (Adobe PDF File), 108 KB - resprot_v8i1e11284_app4.pdf]

Multimedia Appendix 5
Biological specimens in the HITCH Cohort Study, 2005-2011.
[PDF File (Adobe PDF File), 38 KB - resprot_v8i1e11284_app5.pdf]

Multimedia Appendix 6
Baseline characteristics of the HITCH Cohort Study population (N=502), Montreal, Quebec, 2005-2011.
[PDF File (Adobe PDF File), 64 KB - resprot_v8i1e11284_app6.pdf]

References

1. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999 Sep;189(1):12-19. [doi: 10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F] [Medline: 10451482]
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum 2007;90:1-636. [Medline: 18354839]
3. Aral S, Holmes K. The epidemiology of STIs and their social and behavioral determinants//; industrialized and developing countries. In: Holmes K, Sparling P, Stamm W, Piot P, Wasserheit J, Corey L, et al, editors. Sexually Transmitted Diseases. 4th ed. New York: McGraw Hill Medical; 2008:53-92.
4. Burchell AN, Winer RL, de Sanjosé S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine 2006 Aug 31;24 Suppl 3:S3/52-S3/61. [doi: 10.1016/j.vaccine.2006.05.031] [Medline: 16950018]
5. Bleeker MCG, Snijders PFJ, Voorhorst FJ, Meijer CJLM. Flat penile lesions: the infectious “invisible” link in the transmission of human papillomavirus. Int J Cancer 2006 Dec 01;119(11):2505-2512 [FREE Full text] [doi: 10.1002/ijc.22209] [Medline: 16988942]
6. Baken LA, Koutsky LA, Kuypers J, Kosorok MR, Lee SK, Kiviat NB, et al. Genital human papillomavirus infection among male and female sex partners: prevalence and type-specific concordance. J Infect Dis 1995 Feb;171(2):429-432. [Medline: 7844382]
7. Kyo S, Inoue M, Koyama M, Fujita M, Tanizawa O, Hakura A. Detection of high-risk human papillomavirus in the cervix and semen of sex partners. J Infect Dis 1994 Sep;170(3):682-685. [Medline: 8077728]
8. Hippeläinen MI, Yliskoski M, Syrjänen S, Saastamoinen J, Hippeläinen M, Saarikoski S, et al. Low concordance of genital human papillomavirus (HPV) lesions and viral types in HPV-infected women and their male sexual partners. Sex Transm Dis 1994;21(2):76-82. [Medline: 9071416]
9. Bleeker MCG, Hogewoning CJA, Berkhof J, Voorhorst FJ, Hesselink AT, van Diemen PM, et al. Concordance of specific human papillomavirus types in sex partners is more prevalent than would be expected by chance and is associated with increased viral loads. Clin Infect Dis 2005 Sep 01;41(5):612-620. [doi: 10.1086/431978] [Medline: 16080082]
10. Castellsagué X, Ghaffari A, Daniel RW, Bosch FX, Muñoz N, Shah KV. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. J Infect Dis 1997 Aug;176(2):353-361. [Medline: 9237700]
11. Franceschi S, Castellsagué X, Dal Maso L, Smith J, Plummer M, Ngelangel C, et al. Prevalence and determinants of human papillomavirus genital infection in men. Br J Cancer 2002 Mar 04;86(5):705-711 [FREE Full text] [doi: 10.1038/sj.bjc.6600194] [Medline: 11875730]
12. Thomas D, Ray R, Kuypers J, Kiviat N, Koetsawang A, Ashley RL, et al. Human papillomaviruses and cervical cancer in Bangkok. III. The role of husbands and commercial sex workers. Am J Epidemiol 2001 Apr 15;153(8):740-748. [Medline: 11296145]
13. Lu B, Wu Y, Nielson CM, Flores R, Abrahamsen M, Papenfuss M, et al. Factors associated with acquisition and clearance of human papillomavirus infection in a cohort of US men: a prospective study. J Infect Dis 2009 Feb 01;199(3):362-371. [doi: 10.1086/596050] [Medline: 19133808]
14. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. 2005. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2) URL: http://homelesshub.ca/resource/tri-council-policy-statement-ethical-conduct-research-involving-humans-tcps2 [accessed 2018-11-15] [WebCite Cache ID 73x6I0d9G]
15. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004 Dec 29;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]
16. Petignat P, Faltin D, Bruchim I, Tramèr MR, Franco E, Coutlée F. Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis. Gynecol Oncol 2007 May;105(2):530-535. [doi: 10.1016/j.ygyno.2007.01.023] [Medline: 17335880]
17. Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee S, Meyer C, et al. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis 2004 Feb 15;189(4):677-685. [doi: 10.1086/381395] [Medline: 14767822]
18. Coutlée F, Rouleau D, Petignat P, Ghattas G, Kornegay JR, Schlag P, Canadian Women's HIV study Group, et al. Enhanced detection and typing of human papillomavirus (HPV) DNA in anogenital samples with PGMY primers and the Linear array HPV genotyping test. J Clin Microbiol 2006 Jun;44(6):1998-2006 [FREE Full text] [doi: 10.1128/JCM.00104-06] [Medline: 16757590]
19. Yamada T, Manos MM, Peto J, Greer CE, Munoz N, Bosch FX, et al. Human papillomavirus type 16 sequence variation in cervical cancers: a worldwide perspective. J Virol 1997 Mar;71(3):2463-2472 [FREE Full text] [Medline: 9032384]
20. Wheeler CM, Yamada T, Hildesheim A, Jenison SA. Human papillomavirus type 16 sequence variants: identification by E6 and L1 lineage-specific hybridization. J Clin Microbiol 1997 Jan;35(1):11-19 [FREE Full text] [Medline: 8968874]

21. Chan S, Ho L, Ong C, Chow V, Drescher B, Dürst M, et al. Molecular variants of human papillomavirus type 16 from four continents suggest ancient pandemic spread of the virus and its coevolution with humankind. J Virol 1992 Apr;66(4):2057-2066 [FREE Full text] [Medline: 1312620]
22. Ho L, Tay S, Chan S, Bernard H. Sequence variants of human papillomavirus type 16 from couples suggest sexual transmission with low infectivity and polyclonality in genital neoplasia. J Infect Dis 1993 Oct;168(4):803-809. [Medline: 8397266]
23. Marks M, Gupta SB, Liaw K, Kim E, Tadesse A, Coutlee F, et al. Confirmation and quantitation of human papillomavirus type 52 by Roche Linear Array using HPV52-specific TaqMan E6/E7 quantitative real-time PCR. J Virol Methods 2009 Mar;156(1-2):152-156. [doi: 10.1016/j.jviromet.2008.10.013] [Medline: 19022296]
24. Fontaine J, Hankins C, Money D, Rachlis A, Pourreaux K, Ferenczy A, Canadian Women's HIV Study Group, et al. Human papillomavirus type 16 (HPV-16) viral load and persistence of HPV-16 infection in women infected or at risk for HIV. J Clin Virol 2008 Nov;43(3):307-312. [doi: 10.1016/j.jcv.2008.07.013] [Medline: 18786854]
25. Khouadri S, Villa LL, Gagnon S, Koushik A, Richardson H, Matlashewski G, et al. Viral load of episomal and integrated forms of human papillomavirus type 33 in high-grade squamous intraepithelial lesions of the uterine cervix. Int J Cancer 2007 Dec 15;121(12):2674-2681 [FREE Full text] [doi: 10.1002/ijc.23006] [Medline: 17708553]
26. Burchell AN, Tellier P, Hanley J, Coutlée F, Franco EL. Influence of partner's infection status on prevalent human papillomavirus among persons with a new sex partner. Sex Transm Dis 2010 Jan;37(1):34-40. [doi: 10.1097/OLQ.0b013e3181b35693] [Medline: 19704391]
27. Burchell AN, Tellier P, Hanley J, Coutlée F, Franco EL. Human papillomavirus infections among couples in new sexual relationships. Epidemiology 2010 Jan;21(1):31-37. [doi: 10.1097/EDE.0b013e3181c1e70b] [Medline: 19907332]
28. Burchell AN, Coutlée F, Tellier P, Hanley J, Franco EL. Genital transmission of human papillomavirus in recently formed heterosexual couples. J Infect Dis 2011 Dec 01;204(11):1723-1729 [FREE Full text] [doi: 10.1093/infdis/jir644] [Medline: 21984739]
29. Burchell AN, Rodrigues A, Moravan V, Tellier P, Hanley J, Coutlée F, et al. Determinants of prevalent human papillomavirus in recently formed heterosexual partnerships: a dyadic-level analysis. J Infect Dis 2014 Sep 15;210(6):846-852 [FREE Full text] [doi: 10.1093/infdis/jiu200] [Medline: 24683197]
30. Dahlstrom K, Burchell A, Ramanakumar A, Rodrigues A, Tellier P, Hanley J, et al. Sexual transmission of oral human papillomavirus infection among men. Cancer Epidemiol Biomarkers Prev 2014 Dec;23(12):2959-2964 [FREE Full text] [doi: 10.1158/1055-9965.EPI-14-0386] [Medline: 25392180]
31. Tota JE, Ramanakumar AV, Villa LL, Richardson H, Burchell AN, Koushik A, et al. Evaluation of human papillomavirus type replacement postvaccination must account for diagnostic artifacts: masking of HPV52 by HPV16 in anogenital specimens. Cancer Epidemiol Biomarkers Prev 2015 Jan;24(1):286-290 [FREE Full text] [doi: 10.1158/1055-9965.EPI-14-0566] [Medline: 25277793]
32. Tota JE, Ramanakumar AV, Villa LL, Richardson H, Burchell AN, Coutlée F, et al. Cervical Infection With Vaccine-Associated Human Papillomavirus (HPV) Genotypes as a Predictor of Acquisition and Clearance of Other HPV Infections. J Infect Dis 2016 Dec 01;214(5):676-684 [FREE Full text] [doi: 10.1093/infdis/jiw215] [Medline: 27256157]
33. Tota JE, Jiang M, Ramanakumar AV, Walter SD, Kaufman JS, Coutlée F, et al. Epidemiologic Evaluation of Human Papillomavirus Type Competition and the Potential for Type Replacement Post-Vaccination. PLoS One 2016;11(12):e0166329 [FREE Full text] [doi: 10.1371/journal.pone.0166329] [Medline: 28005904]
34. Malagón T, Burchell AN, El-Zein M, Guénoun J, Tellier PP, Coutlée F, HITCH Study Group. Estimating HPV DNA Deposition Between Sexual Partners Using HPV Concordance, Y Chromosome DNA Detection, and Self-reported Sexual Behaviors. J Infect Dis 2017 Dec 05;216(10):1210-1218. [doi: 10.1093/infdis/jix477] [Medline: 28968731]
35. Malagón T, Burchell A, El-Zein M, Guénoun J, Tellier P, Coutlée F, HITCH study group. Y Chromosome DNA in Women's Vaginal Samples as a Biomarker of Recent Vaginal Sex and Condom Use With Male Partners in the HPV Infection and Transmission Among Couples Through Heterosexual Activity Cohort Study. Sex Transm Dis 2018 Dec;45(1):28-34. [doi: 10.1097/OLQ.0000000000000688] [Medline: 28876295]
36. Malagón T, Burchell A, El-Zein M, Tellier P, Coutlée F, Franco EL, HITCH study group. Assortativity and Mixing by Sexual Behaviors and Sociodemographic Characteristics in Young Adult Heterosexual Dating Partnerships. Sex Transm Dis 2017 Dec;44(6):329-337 [FREE Full text] [doi: 10.1097/OLQ.0000000000000612] [Medline: 28499281]
37. Legault V, Burchell A, Goggin P, Nicolau B, Brassard P, Guenoun J, et al. Generic microtiter plate assay for triaging clinical specimens prior to genotyping of human papillomavirus DNA via consensus PCR. J Clin Microbiol 2011 Nov;49(11):3977-3979 [FREE Full text] [doi: 10.1128/JCM.05646-11] [Medline: 21940471]
38. Widdice LE, Breland DJ, Jonte J, Farhat S, Ma Y, Leonard AC, et al. Human papillomavirus concordance in heterosexual couples. J Adolesc Health 2010 Aug;47(2):151-159 [FREE Full text] [doi: 10.1016/j.jadohealth.2010.01.006] [Medline: 20638007]
39. Hernandez BY, Wilkens LR, Zhu X, Thompson P, McDuffie K, Shvetsov YB, et al. Transmission of human papillomavirus in heterosexual couples. Emerg Infect Dis 2008 Jun;14(6):888-894 [FREE Full text] [doi: 10.3201/eid1406.070616] [Medline: 18507898]

40. Kirby T. FDA approves new upgraded Gardasil 9. Lancet Oncol 2015 Feb;16(2):e56. [doi: 10.1016/S1470-2045(14)71191-X] [Medline: 25532625]
41. Herzog TJ, Huh WK, Downs LS, Smith JS, Monk BJ. Initial lessons learned in HPV vaccination. Gynecol Oncol 2008 May;109(2 Suppl):S4-11. [doi: 10.1016/j.ygyno.2008.01.018] [Medline: 18482557]
42. Lippman A, Melnychuk R, Shimmin C, Boscoe M. Human papillomavirus, vaccines and women's health: questions and cautions. CMAJ 2007 Aug 28;177(5):484-487 [FREE Full text] [doi: 10.1503/cmaj.070944] [Medline: 17671239]
43. Franco E, de Pokomandy A, Spence A, Burchell A, Trottier H, Mayrand M, et al. Vaccination against human papillomavirus. CMAJ 2007 Dec 04;177(12):1524-5; author reply 1527 [FREE Full text] [doi: 10.1503/cmaj.1070120] [Medline: 18056600]
44. McGill University Cancer Epidemiology. Our Studies URL: https://www.mcgill.ca/cancerepi/hpv
45. NCBI. A list of peer-reviewed scientific publications from HITCH URL: https://www.ncbi.nlm.nih.gov/sites/myncbi/eduardo.franco.1/collections/50316309/public/

Abbreviations

HITCH: Human papillomavirus Infection and Transmission among Couples through Heterosexual activity
HLA: human leukocyte antigen
HPV: human papillomavirus
HR: hazards ratio
OR: odds ratio
PCR: polymerase chain reaction

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Protocol

Access to Resources in the Community Through Navigation: Protocol for a Mixed-Methods Feasibility Study

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Abstract

Background: Community-based health and social resources can help individuals with complex health and social needs achieve their health goals. However, there is often inadequate access to these resources due to a lack of physician and patient awareness of available resources and the presence of social barriers that limit an individual's ability to reach these services. Navigation services, where a person is tasked with helping connect patients to community resources, embedded within primary care may facilitate access and strengthen the continuity of care for patients.

Objective: This study aims to describe the protocol to assess whether the implementation of the Access to Resources in the Community (ARC) navigation model (an innovative approach to navigation services) is feasible, including its potential to achieve its intended outcomes, and to assess the viability of the evaluation approach.

Methods: The study consists of a single-arm, prospective, explanatory, mixed-methods, pre-post design feasibility study focusing on primary care practice settings with vulnerable populations. Participants include primary care providers and patients.

Results: Enrollment is closed with 82 patients. Navigation services have ended for 69 patients.

Conclusions: The study of an innovative complex intervention requires an adequate assessment of the feasibility of the intended approach during which the potential challenges of the planned intervention and need for its adaptation may be uncovered. Undertaking a feasibility study of the ARC navigation model from a conceptually clear and methodologically solid protocol will inform on the practicality and acceptability of the approach, demand for the services, ease of implementation, quality of integration of the new services within primary care, and practicality and potential for efficacy prior to initiating a randomized controlled trial.

Trial Registration: ClinicalTrials.gov NCT03105635; https://clinicaltrials.gov/ct2/show/NCT03105635 (Archived by WebCite at hhttp://www.webcitation.org/75FrwXORl)

International Registered Report Identifier (IRRID): RR1-10.2196/11022

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KEYWORDS

access; community resources; feasibility study; navigation; primary health care

Introduction

Equitable access to primary health care (PHC) plays an important role in reducing health inequities [1]. Despite considerable efforts to strengthen that sector in Canada [2], disparities in access to these services continue to affect several populations, including immigrants, indigenous people, individuals of lower socioeconomic status, those living in rural regions, and cultural minorities, including Francophones living in minority situations [3-9]. This problem is compounded by the fact that these social factors are also determinants of health that contribute markedly to the risk of poor health [10] and adequate access to PHC, including health-enabling resources available in the community, which remains a priority strategy to mitigating these inequities [11].

Community resources (CRs) such as smoking cessation, falls prevention, and chronic disease self-management programs can play an important role in supporting individuals achieve their health goals. Primary care providers (PCPs) may offer lifestyle counseling and preventive care support to promote positive health behaviors, but this is often insufficient for individuals to meet their intended goals because the path to healthy behavior is fraught with barriers that thwart their intent and capacity to act [12]. The work done by PCPs in supporting individuals to develop self-efficacy in the management of their health can be complemented by accessing health-enabling CRs, which encompass a broad range of health and social services. Several reviews report positive outcomes with community-based services that aim to reduce the risk of cardiovascular disease [13-15], promote secondary prevention of various chronic diseases [16-18], and improve health-promoting behaviors [19,20]. Such resources are recommended by the US Preventive Services Task Force [21] and the American Heart Association [19]. Similarly, National Guidelines for Diabetes Management highlight the role self-management education and community support programs play in achieving healthy outcomes [22]. Many of these resources have been shown to be useful in meeting the health needs of individuals with complex social profiles [15,23] and some have highlighted their role in reducing health inequities experienced by certain populations [24,25]. Unfortunately, these services remain underused [26], especially by individuals with social disadvantages [27], resulting in the propagation of inequities and unmet health needs.

One response to this multifaceted issue is to facilitate access to health-enabling CRs by embedding navigation services within PHC. Navigators may be nonclinical individuals or health professionals who assist patients in identifying the appropriate CRs and support them in overcoming access barriers and achieving service utilization [28]. However, the navigator role has been almost exclusively studied in disease- or population-specific contexts [29,30]. In the latter role, they are often called community health workers. Two recent meta-analyses focused on medical conditions, the majority of which were cancer-related studies, showed that patients assigned to navigation services exhibited markedly better outcomes across a number of measures, including appropriate health care utilization, disease control, and clinical outcomes, such as mortality [29]. Another review reported similar benefits of navigation services for immigrants and ethnic communities [31].

The current models of navigation services and their implementation have considerable limitations. Models targeting individuals with specific medical conditions do not address the breadth of potential navigation needs individuals may have and may be contributing to a fragmented delivery of care. Population-specific programs only target a subset of the population and, by definition, cannot be applied to the general population. Implementing changes in the way PCPs operate—even when there is agreement within PCPs on the need for the change—is challenging as well. To date, a very few studies have implemented navigation services within primary care, integrating these services within the breadth of care they coordinate [32-37] and supporting the PCPs' efforts to engage patients in self-care. We found a single study that evaluated the role of a patient navigator in providing system navigation support to more complex primary care patients; however, in that study, the navigation services were provided by a social worker [38].

Informed by evidence and in consultation with key stakeholders, we developed a novel approach intended to enhance equitable Access to Resources in the Community (ARC)—the ARC model. The ARC model consists of implementing small changes to primary care practices that would encourage PCPs to direct patients to resources in the community that could help them address their health and well-being needs. In parallel, a nonclinical navigator attached to the practice would support these patients tot identify the most appropriate service and overcome barriers that might prevent them from making use of the recommended resources. This feasibility study will assess whether the ARC model is feasible, including its potential to achieve its intended outcomes, and the viability of the evaluation approach. Ultimately, this feasibility study will strengthen a subsequent randomized controlled trial, which, in turn, will increase the likelihood of collecting reliable and relevant data and produce valid conclusions on the implementation and impact of our navigator program.

Specifically, we will evaluate 8 areas of feasibility: Acceptability, Demand, Implementation, Adaptation, Integration, Practicality, Efficacy of the ARC model, and Appropriateness of the intervention evaluation approach to study participants [39].

Methods

Reporting and Design

We have followed the Standard Protocol Items: Recommendations for Interventional Trials guidelines for reporting on protocols [40]. This is a single-arm, prospective, explanatory, mixed-methods, pre-post design feasibility study.

Setting

The study is set in central Ottawa (Ontario, Canada), a region with broad socioeconomic diversity, including Francophones (19%), immigrants (19%), visible minorities (18%), and seniors (16%) [41].

Participants

The ARC model was implemented in 2 practice contexts to understand the different levers and barriers to implementing the ARC model: (1) the traditional primary care practice, which consists of family physicians, nurses, and administrative staff; and (2) the interprofessional practice model in which patients also have access to various allied health professionals such as nurse practitioners, pharmacists, and social workers, as well as some in-house health programs. Participating PCPs are required to provide comprehensive primary care services to the general population.

Patients of participating PCPs were eligible to participate if one or more needs, which may be addressed by services offered in the community, are identified during an encounter with their PCP, they are able to communicate in English or French or willing to be served by a cultural interpreter or translator, and have no marked cognitive deficiencies or have a family member that can provide proxy consent and participate in the study with the patient.

Ethics Approval

This study was approved by the following ethics boards: Ottawa Health Science Network Research Ethics Board (#20160914-01H), Bruyère Continuing Care Research Ethics Board (#M16-16-055), University of Ottawa Research Ethics Board (#A05-17-04), and L'Hôpital Montfort Research Ethics Board (#SD-DP-27-02-17).

Intervention

We established a Collaborative Partnership of key stakeholders to inform the development, implementation, and evaluation of the ARC navigation model. The partnership includes policy makers, members from community organizations, health care providers, health planners, and people with lived experience of health care as a consumer or caregiver. The ARC intervention intends to promote equitable access to health-enabling resources by engaging PCPs in identifying their patients' needs that could be addressed by a CR and directing them to such services. Patients' access to these resources is subsequently supported through navigation. A logic model (presented in Multimedia Appendix 1) was developed to establish the expected links among the intervention components, planned activities, and anticipated outcomes. The ARC navigation model is presented in Multimedia Appendix 2, and details of the ARC intervention are described in Multimedia Appendix 3 (Template for Intervention Description and Replication Checklist [42]). The study promotional materials for patients are offered in Multimedia Appendices 4 and 5 and the ARC referral form and instructional video for PCPs are presented in Multimedia Appendices 6 and 7. The two main intervention components are (1) changes to the practice environment to enhance PCP recommendations for patients to access CRs that could address their needs; and (2) navigation support for these patients to help them achieve access to resources. Briefly, we relied on Rogers' Diffusion of Innovation theory [43] to underpin the practice changes required to promote referrals to CRs in primary care practices. These changes were informed by a rapid realist review conducted by us to understand the most likely effective approaches and their potential benefit in our context [44]. The navigator's role was founded on the Health Action Process Approach [45] and aims to support patients in achieving their health and wellness goals by promoting access to health-enabling resources in the community.

The role of the navigator is limited to nonclinical activities that support access to community services that address a wide range of health and social needs. Multiple sources were used to inform the role of the navigator including (1) peer-reviewed literature about the scope of navigation activities provided with different populations, medical conditions, and contexts [38,46-49]; (2) best practice guidelines for implementing and evaluating community health worker programs [37]; and (3) literature on navigation training programs.

The ARC navigator is a lay person with no clinical background who is hired by the research team and trained to provide navigation services. PCPs were encouraged to see that new team member as someone lending a helping hand to patients in need of support to gain access to needed services—the type of support a well-informed family member could potentially provide. It was made clear that the navigator is a lay individual and would not be expected to address any clinical issues and that should such issues arise, they would be communicated back to the PCPs for their action. We sought to hire an individual with excellent communication skills, evident empathic qualities, and good management abilities. The navigator training program is based on competencies developed specifically for their role in primary care. The key competencies are to provide basic navigation services and identify appropriate resources within our context, demonstrate effective interpersonal communication including cultural and linguistic sensitivity, collaborate and work effectively with primary care team and CR program staff, advocate for patients and intervene with services to promote access to needed resources, demonstrate commitment to professional responsibilities and ongoing learning, and educate and empower patients about CRs for their health.

The navigator would spend a minimum of one half day at the practice during which they would meet with patients referred to them and interact with the members of the primary care team. The navigator did not chart in the patient medical records. Written communication between the navigator and primary care team was by fax. The expectation was that PCPs, sensitized to the availability of CRs that could complement the care they provide to their patients and confident that more socially

complex patients can receive the assistance they require to support access to these resources (from the navigator), would be more likely to identify patient needs that could be addressed by CRs, discuss these during their encounter, and if appropriate, make the recommendation to access these services. The navigator would then meet with each patient to whom a service was recommended to understand their needs, expectations and priorities, identify anticipated barriers in accessing the resource (eg, knowledge, health literacy, transportation, completing forms, caregiving responsibilities, financial, and motivation), support patients in overcoming these barriers, and facilitate access to the most appropriate resource for patients. In addition, the navigator was trained to use communication strategies, such as motivational interviewing [50], that would encourage engagement of patients in identifying what is important to them, what they perceive as challenges in accessing CRs, and the navigation activities needed. Patient self-efficacy is fostered through providing various forms of social support including providing information, emotional support, and guidance or accompaniment to access CRs. The navigator would report back to the PCP on the plan developed after the first encounter and again at the end of services. Navigation services would be discontinued when a patient has accessed the appropriate service or no longer wants or requires navigation assistance. Navigation services are offered to patients for up to 3 months.

Timelines

The patient recruitment period was 9 months, and individual patient participation will be approximately 3 months.

Sample Size

Sample sizes of 30 [51] or 50 [52] are commonly recommended for feasibility studies. We based our sample size on the ability to adequately assess the demand for the navigation services and to estimate the potential for patients to achieve the intended access to the resource. We estimated that the participation of 4-6 practices, each with at least 3 PCPs (minimum 12 PCPs) caring for a panel size of 1500 patients, would be required. We assumed conservatively that 30% of patients at the practice could potentially benefit from a CR. In the region where the study is being conducted, >60% of the population has insufficient consumption of fruits and vegetables and 28% individuals are obese, 19% drink heavily, 12% smoke, and 22% report feeling stressed “quite a lot” [53]. The 95% CI range for these outcome measures would be <3% for referral rate (5400 potentially eligible individuals), <15% for participation rate (if conservatively 162/5400, 3.00%, are referred), and <22% for the access measure (assuming a participation rate of 81/162, 50.0%). We also aimed to interview a minimum of 1 PCP and 2 patients per practice.

Recruitment

The study was promoted among stakeholders. Providers expressing interest were sent a study information and consent form, and a recruitment session was scheduled with all interested PCPs at the practice.

During encounters with patients, when participating PCPs and their patients identified a need that could be addressed by a CR, the PCP completed a standardized CR referral form, briefly introduced the study, and requested the patient’s agreement to be contacted by a member of the research team. Patients who agreed to be contacted received a study information and consent package and a copy of the completed referral form identifying their need(s). A copy of that form was faxed to the study team who then contacted the patient and provided detailed information about the study. Patients who provided verbal consent to participate in the study were asked to sign and mail in the consent form included in their study information and consent package.

A subsample of PCPs and patients participated in the qualitative component of the study, which consisted of an interview at the beginning and again at the end of their participation in the study. All PCPs were invited to participate in the interviews, with the aim to enroll at least 1 PCP per practice. Patients were purposefully selected to be invited for the interviews based on their responses to the baseline survey. The recruitment aimed to maximize variation in social complexity and ensure variability in age and gender. At least 1 patient from each practice was required.

Data Collection Methods

Table 1 provides a summary of the data collection tools, the dimensions measured, the population targeted, as well as how and when the tools are to be administered.

One practice member, referred to as the practice champion, is the main contact for the practice. The practice champion completes the practice survey, and each participating PCP completes the provider survey. These surveys are completed at baseline before the introduction of the patient navigator in the practice, and again immediately prior to ending the navigation services. These surveys assess the practice’s organization and PCPs’ knowledge, attitudes, and experience with reference to vulnerable populations, as well as factors that can influence the success of the intervention and its implementation from a change management perspective, including the organizational structure [54], climate of their work environment [55], as well as readiness [56] and commitment to change [57]. Furthermore, the postintervention provider survey includes questions relating to their experience with the patient navigator.

Patients complete a preintervention survey immediately after providing consent and prior to meeting with the navigator, and a postintervention survey at 3 months. These surveys assess various dimensions of access, measures of self-efficacy, social vulnerability, and their experience with CRs and the ARC navigation services.

A subset of patients and PCPs are also invited to participate in an interview following the completion of the pre- and postintervention surveys. These interviews explore patients’ access to PHC services and providers’ experience providing care to vulnerable patient populations. In addition, patients and PCPs are asked about their experience with the patient navigator. These interviews will be used to understand and build upon the survey results [58].

Table 1. Data collection tools.

Instrument and dimension	Target population	Administration	
		How	When
Quantitative data			
Referral form: Patient needs; Referral rate	PCPs[a], patients	Completed by PCPs in collaboration with patients	Completed for each referral throughout the study
Practice survey[b]: Organization, services provided	1 per practice	Self-administered by 1 PCP per practice	Baseline and end of the study (1 month prior to end of patient recruitment)
Provider survey[b]			
Equity orientation; Climate; Organizational structure; Change readiness	All PCPs	Self-administered by PCPs	Baseline and end of the study
Experience with the intervention	All PCPs	Self-administered by PCPs	End of the study (1 month prior to end of patient recruitment)
Patient survey			
Experience with health care, various dimensions of access, self-efficacy, social vulnerability, Health Action Process Approach, Patient Activation Measure, experience with community resources	All patients referred	Administered via telephone by the research team	Preintervention and 3 months postintervention
Experience with intervention, utilization of recommended community resource	All patients referred	Administered via telephone by the research team	3 months postintervention
Qualitative data			
Provider interview			
Background (PCP and practice profile) and expectations	2 PCPs per practice	Administered in-person by the research team	Baseline
Experience with intervention	2 PCPs per practice	Administered in-person by the research team	End of the study (after completing "end of the study" survey)
Patient interview			
Experience with health care access	2 patients per practice	Administered in-person or by phone by the research team	Preintervention
Experience with intervention	2 patients per practice	Administered in-person or by phone by the research team	Postintervention
Rapid cycle evaluation: Acceptability of intervention activities; Integration of study activities in the practice	1 per practice	Self-administered by 1 PCP per practice	Set-up of study activities (1-month implementation phase), bimonthly throughout the study
Navigator interview: Training, capacity, challenges, suggestions for improvement	Navigator	Administered in-person by the research team	End of the study
Study documentation			
Coordinator log: Encounters with practices; Weekly (or more) debriefs with Navigator	Study coordinator	Study coordinator	Throughout the study
Navigator log: Encounters with PCPs, patients and community resources; Navigation process and activities; Navigator reflections	Patients who accepted Navigator services	Completed by the navigator	Throughout the study
Ultra-observational tool: Practice environment	1 per practice	Research team	Baseline
TIDieR[c]: Intervention delivery and fidelity	Overall	Research team	Throughout the study
Stange and Glasgow Tool: Practice environment context, validity of the intervention	1 per practice	Research team	End of the study

[a]PCP: primary care provider.

[b]Practice and Provider surveys conducted at "end of study" are delivered 1 month prior to the end of patient recruitment. Provider interviews conducted at "end of the study" are performed after the provider survey has been received.

[c]TIDieR: Template for Intervention Description and Replication.

Conforming to a rapid cycle evaluation (RCE) approach, the designated practice champion completes regular assessments of the study progress to inform the need for adapting the intervention to meet the needs of the practice; this evaluation also informs on levers and barriers to the changes imposed by the introduction of an additional layer of services. The first evaluation was conducted immediately following the initial implementation of the intervention and assessed the practices' experience with the introduction of the components of the ARC intervention. Subsequent evaluations were conducted bimonthly to evaluate their impressions of study progress [59].

Throughout the study, the coordinator maintains a log of activities relating to encounters with practices and weekly debriefs with the navigator. The patient navigator maintains a log of activities relating to patient support, including encounters with patients, their PCPs, and staff from the recommended CR. Furthermore, the patient navigator completes a reflective journal describing their thoughts related to day-to-day activities to promote deeper understanding of the knowledge and skills required to carry out their role.

Outcomes

The feasibility study will assess 8 areas of focus: Acceptability of the ARC model; Demand for the navigation service; Implementation approach viability; Adaptation required; Integration of the navigation service within the practice; Practicality of the ARC model to the practice, providers, and patients; the potential for the intervention Efficacy; and Appropriateness of the intervention evaluation approach to study participants [39]. Table 2 provides the operational definition of the areas and their data source.

Data Management

Procedures developed by the ARC team and captured in various training and "how to" guides contributed to the standardized implementation of study activities related to data collection, coding, entry, and storage. Quantitative data are inscribed directly into Qualtrics, a centralized data collection tool, and transferred to SPSS (IBM) for analyses. For qualitative data, interview notes or transcripts and open-ended answers to survey questions are entered into (NVivo; QSR International), a software that facilitates content analysis.

Analyses

Table 2 provides a summary of the analytical approach to each of the outcome measures related to 8 areas of focus of a feasibility study. Consistent with principles of an explanatory sequential design of a phenomenological tradition, we will begin by analyzing the patient and provider surveys, the results of which will guide the qualitative line of questioning, which will seek to further explore survey findings. The overarching research question guiding this qualitative phase is, "What is the provider and patient experience with navigation to CRs?" Questions for the patient and provider interview guides align with elements of the study's conceptual framework including Rogers' Diffusion of Innovation theory [43], the Health Action Process Approach [45], and elements of the Access Framework [60]. The interview questions will be further developed on the basis of the quantitative results as they emerge, and coding and content analysis will follow a sequential iterative process [61,62]. The RCE data are analyzed qualitatively to inform the ongoing adaptation of the intervention integration within each practice. While the elements of the intervention were theory driven, how these are applied within complex systems, such as primary care practices, must be informed by that context. We anticipated that team composition, use of electronic medical records tools, and clinic layout and flow would be influential factors but expected that additional context factors would emerge through the RCE [43,63,64].

Table 2. Summary of feasibility outcome measures.

Area of focus	Outcome measure	Measurement tool	Analyses
Acceptability	• PCP[a] satisfaction with study activities • PCP commitment to change • PCP and patient experience with the Navigator	• Rapid cycle evaluation (implementation stage) • Post-PCP and patient surveys and interviews	• Level of satisfaction with study activities • Descriptive statistics • Descriptive statistics and content analysis
Demand	• Referral forms completed by PCPs • Patient use of navigation services • Navigator-patient encounters	• Referral form • Navigator log	• Rate of referrals • Proportion of patients using navigation services • Number of navigator-patient encounters
Implementation	• PCP readiness to change to accept the ARC navigation model • Mode of delivery of navigation services	• Pre- and post-PCP surveys • Navigator Log	• Descriptive statistics • Number of telephone versus in-person encounters
Adaptation	• Changes in the planned process to accommodate practices • Changes in the method of navigation services delivery to accommodate patients' expectations	• Rapid cycle evaluation (intervention stage) • Navigator log	• Frequency of adaptation of study activities • Proportion of phone versus in-person encounters • Proportion of in-person encounters at the practice versus elsewhere
Integration	• PCP satisfaction with study activities • PCP satisfaction with intervention activities • Appropriateness of navigator service delivery • Navigator and PCP communication	• Pre- and postpractice surveys • Rapid cycle evaluation (intervention stage) • Navigator log • Rapid cycle evaluation (intervention stage) • Post-PCP survey and interview	• Comparison across practice models • Descriptive statistics and content analysis • Frequency of patient-navigator encounters at the practice site • Descriptive statistics and content analysis
Practicality	• PCPs' ability to perform study activities • Patient ability to use navigator services	• Rapid cycle evaluation (intervention stage) • Postpatient survey and interview	• Descriptive statistics and content analysis
Efficacy	• Ability of patients to access CR that meet their needs • Characteristics of patients and needs according to ability to access CR	• Postpatient survey and interview	• Descriptive statistics and content analysis
Appropriateness of evaluation	• Completeness of surveys (and individual components) by PCPs and patients and participants' comments on these (eg, content, clarity, and length) • Participation of PCP and patients in interviews	• PCP and patient surveys and interviews	• Proportion of surveys included • Number of interviews completed

[a]PCP: primary care provider.

Results

Participant recruitment has ended and data collection is still in progress. Overall, 35 PCPs consented to participate in the study, 29 of which referred at least 1 patient. Across the 9-month intervention period, 131 referrals were received by the research team. Patient enrollment is closed, with 82 patients participating out of a possible 131 patients (62.6% response rate). Of the 131 patients, the research team was unable to make direct contact with 34 (26.0%) patients and 15 (11.5%) patients declined to participate in the study. Of the 82 enrolled patients, 3 (4%) withdrew from the study after completing the baseline survey; 78 (99%) patients accepted navigation services, and 69 (87%) patients completed these services to date. Postintervention data collection is ongoing. Results informing the feasibility of the ARC navigation model according to the 8 areas of focus described above will be made available.

Discussion

There is a need to implement measures that will foster better use of CRs, especially for vulnerable populations. There is also a need to assess the extent to which such measures actually meet their objectives. We identified navigation services attached to primary care as an innovative means by which patients' trajectories from primary care practices to CRs can be facilitated. In addition, we recognize that both the need to implement navigation services in primary care and the need to assess their impact are complex conceptually and operationally. As such, it is sensible and logical to first assess the acceptability, implementation, integration, practicality, and potential adaptation of both the intervention and research process through a feasibility study. This feasibility study will strengthen a subsequent randomized controlled trial, which, in turn, will increase the likelihood of collecting reliable and relevant data and produce valid conclusions on the implementation and impact of our navigator program.

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Authors' Contributions

All authors contributed to the conception and design of the Access to Resources in the Community feasibility study protocol. SD oversaw the study design and implementation plan. SD, FC, and PT provided expertise in the development of quantitative data collection tools and analyses plan. AG, DTS, and ML provided expertise in the development of qualitative data collection tools and analyses plan. CK, DP, and MHC provided expertise about primary care context and vulnerable patient needs. JP provided expertise in research methods and statistical analyses. AP oversaw the plan for implementation and coordination of study activities, including participant recruitment and data collection.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Logic Model.

[PDF File (Adobe PDF File), 28KB - resprot_v8i1e11022_app1.pdf]

Multimedia Appendix 2

The ARC Navigation Model.

[PDF File (Adobe PDF File), 24KB - resprot_v8i1e11022_app2.pdf]

Multimedia Appendix 3

Intervention (Based on TIDieR checklist).

[PDF File (Adobe PDF File), 43KB - resprot_v8i1e11022_app3.pdf]

Multimedia Appendix 4

ARC Promotional Poster.

[PDF File (Adobe PDF File), 548KB - resprot_v8i1e11022_app4.pdf]

Multimedia Appendix 5

ARC Promotional Video.

[MP4 File (MP4 Video), 15MB - resprot_v8i1e11022_app5.mp4]

Multimedia Appendix 6

ARC Referral Form.

[PDF File (Adobe PDF File), 165KB - resprot_v8i1e11022_app6.pdf]

Multimedia Appendix 7

ARC Instructional Video.

[MP4 File (MP4 Video), 29MB - resprot_v8i1e11022_app7.mp4]

References

1. Kringos D, Boerma W, Hutchinson A, van der Zee J, Groenewegen PP. The breadth of primary care: a systematic literature review of its core dimensions. BMC Health Serv Res 2010 Mar 13;10:65 [FREE Full text] [doi: 10.1186/1472-6963-10-65] [Medline: 20226084]
2. Hutchison B, Levesque J, Strumpf E, Coyle N. Primary health care in Canada: systems in motion. Milbank Q 2011 Jun;89(2):256-288 [FREE Full text] [doi: 10.1111/j.1468-0009.2011.00628.x] [Medline: 21676023]
3. Sibley L, Weiner JP. An evaluation of access to health care services along the rural-urban continuum in Canada. BMC Health Serv Res 2011 Jan 31;11:20 [FREE Full text] [doi: 10.1186/1472-6963-11-20] [Medline: 21281470]
4. Lum I, Swartz R, Kwan Matthew YW. Accessibility and use of primary healthcare for immigrants living in the Niagara Region. Soc Sci Med 2016 May;156:73-79. [doi: 10.1016/j.socscimed.2016.03.024] [Medline: 27017093]
5. Ouimet M, Pineault R, Prud'homme A, Provost S, Fournier M, Levesque JF. The impact of primary healthcare reform on equity of utilization of services in the province of Quebec: a 2003-2010 follow-up. Int J Equity Health 2015 Nov 30;14:139 [FREE Full text] [doi: 10.1186/s12939-015-0243-2] [Medline: 26616346]
6. Dahrouge S, Hogg W, Ward N, Tuna M, Devlin RA, Kristjansson E, et al. Delivery of primary health care to persons who are socio-economically disadvantaged: does the organizational delivery model matter? BMC Health Serv Res 2013 Dec 17;13:517 [FREE Full text] [doi: 10.1186/1472-6963-13-517] [Medline: 24341530]
7. Muggah E, Dahrouge S, Hogg W. Access to primary health care for immigrants: results of a patient survey conducted in 137 primary care practices in Ontario, Canada. BMC Fam Pract 2012 Dec 28;13:128 [FREE Full text] [doi: 10.1186/1471-2296-13-128] [Medline: 23272805]
8. Tang SY, Browne AJ. 'Race' matters: racialization and egalitarian discourses involving Aboriginal people in the Canadian health care context. Ethn Health 2008 Apr;13(2):109-127. [doi: 10.1080/13557850701830307] [Medline: 18425710]
9. de Moissac D, Bowen S. Impact of language barriers on access to healthcare for official language minority Francophones in Canada. Healthc Manage Forum 2017 Jul;30(4):207-212. [doi: 10.1177/0840470417706378] [Medline: 28929878]
10. Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P, Consortium for the European Review of Social Determinants of Healththe Health Divide. WHO European review of social determinants of health and the health divide. Lancet 2012 Sep 15;380(9846):1011-1029. [doi: 10.1016/S0140-6736(12)61228-8] [Medline: 22964159]
11. Walley J, Lawn JE, Tinker A, de Francisco A, Chopra M, Rudan I, Lancet Alma-Ata Working Group. Primary health care: making Alma-Ata a reality. Lancet 2008 Sep 13;372(9642):1001-1007. [doi: 10.1016/S0140-6736(08)61409-9] [Medline: 18790322]
12. Sniehotta FF. Towards a theory of intentional behaviour change: plans, planning, and self-regulation. Br J Health Psychol 2009 May;14(Pt 2):261-273. [doi: 10.1348/135910708X389042] [Medline: 19102817]
13. Pennant M, Davenport C, Bayliss S, Greenheld W, Marshall T, Hyde C. Community programs for the prevention of cardiovascular disease: a systematic review. Am J Epidemiol 2010 Sep 01;172(5):501-516. [doi: 10.1093/aje/kwq171] [Medline: 20667932]
14. Kaczorowski J, Del Grande C, Nadeau-Grenier V. Community-based programs to improve prevention and management of hypertension: recent Canadian experiences, challenges, and opportunities. Can J Cardiol 2013 May;29(5):571-578. [doi: 10.1016/j.cjca.2013.02.011] [Medline: 23541658]
15. Smalls BL, Walker RJ, Bonilha HS, Campbell JA, Egede LE. Community Interventions to Improve Glycemic Control in African Americans with Type 2 Diabetes: A Systemic Review. Glob J Health Sci 2015 Feb 24;7(5):171-182 [FREE Full text] [doi: 10.5539/gjhs.v7n5p171] [Medline: 26156923]
16. Quiñones AR, Richardson J, Freeman M, Fu R, O'Neil M, Motu'apuaka M, et al. Educational group visits for the management of chronic health conditions: a systematic review. Patient Educ Couns 2014 Apr;95(1):3-29. [doi: 10.1016/j.pec.2013.12.021] [Medline: 24468199]
17. Croisant S, Scott L. Community-based interventions in asthma. Adv Exp Med Biol 2014;795:105-115. [doi: 10.1007/978-1-4614-8603-9_7] [Medline: 24162905]
18. March S, Torres E, Ramos M, Ripoll J, García A, Bulilete O, et al. Adult community health-promoting interventions in primary health care: A systematic review. Prev Med 2015 Jul;76 Suppl:S94-104. [doi: 10.1016/j.ypmed.2015.01.016] [Medline: 25625691]
19. Mozaffarian D, Afshin A, Benowitz N, Bittner V, Daniels S, Franch H, American Heart Association Council on EpidemiologyPrevention, Council on Nutrition, Physical ActivityMetabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovasc. Population approaches to improve diet,

physical activity, and smoking habits: a scientific statement from the American Heart Association. Circulation 2012 Sep 18;126(12):1514-1563 [FREE Full text] [doi: 10.1161/CIR.0b013e318260a20b] [Medline: 22907934]
20. Dunneram Y, Jeewon R. Healthy Diet and Nutrition Education Program among Women of Reproductive Age: A Necessity of Multilevel Strategies or Community Responsibility. Health Promot Perspect 2015;5(2):116-127 [FREE Full text] [doi: 10.15171/hpp.2015.014] [Medline: 26290827]
21. LeFevre ML, U.S. Preventive Services Task Force. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014 Oct 21;161(8):587-593. [doi: 10.7326/M14-1796] [Medline: 25155419]
22. Powers M, Bardsley J, Cypress M, Duker P, Funnell M, Fischl AH, et al. Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. Clin Diabetes 2016 Apr;34(2):70-80 [FREE Full text] [doi: 10.2337/diaclin.34.2.70] [Medline: 27092016]
23. Fields N, Anderson K, Dabelko-Schoeny H. The effectiveness of adult day services for older adults: a review of the literature from 2000 to 2011. J Appl Gerontol 2014 Mar;33(2):130-163. [doi: 10.1177/0733464812443308] [Medline: 24652952]
24. Hillier-Brown F, Bambra C, Cairns J, Kasim A, Moore H, Summerbell CD. A systematic review of the effectiveness of individual, community and societal level interventions at reducing socioeconomic inequalities in obesity amongst children. BMC Public Health 2014 Aug 11;14:834 [FREE Full text] [doi: 10.1186/1471-2458-14-834] [Medline: 25113624]
25. Vanstone M, Giacomini M, Smith A, Brundisini F, DeJean D, Winsor S. How diet modification challenges are magnified in vulnerable or marginalized people with diabetes and heart disease: a systematic review and qualitative meta-synthesis. Ont Health Technol Assess Ser 2013;13(14):1-40 [FREE Full text] [Medline: 24228077]
26. Office of the Auditor General of Ontario. 2012 Annual Report URL: http://www.auditor.on.ca/en/reports_2012_en.htm [accessed 2018-11-15] [WebCite Cache ID 73wvHd1hP]
27. Fiscella K, Shin P. The inverse care law: implications for healthcare of vulnerable populations. J Ambul Care Manage 2005;28(4):304-312. [Medline: 16172559]
28. Freeman HP. Patient navigation: a community based strategy to reduce cancer disparities. J Urban Health 2006 Mar;83(2):139-141 [FREE Full text] [doi: 10.1007/s11524-006-9030-0] [Medline: 16736361]
29. McBrien K, Ivers N, Barnieh L, Bailey J, Lorenzetti D, Nicholas D, et al. Patient navigators for people with chronic disease: A systematic review. PLoS One 2018;13(2):e0191980 [FREE Full text] [doi: 10.1371/journal.pone.0191980] [Medline: 29462179]
30. Olaniran A, Smith H, Unkels R, Bar-Zeev S, van den Broek N. Who is a community health worker? - a systematic review of definitions. Glob Health Action 2017;10(1):1272223 [FREE Full text] [doi: 10.1080/16549716.2017.1272223] [Medline: 28222653]
31. Shommu N, Ahmed S, Rumana N, Barron G, McBrien K, Turin TC. What is the scope of improving immigrant and ethnic minority healthcare using community navigators: A systematic scoping review. Int J Equity Health 2016 Jan 15;15:6 [FREE Full text] [doi: 10.1186/s12939-016-0298-8] [Medline: 26768130]
32. Esperat M, Flores D, McMurry L, Feng D, Song H, Billings L, et al. Transformacion Para Salud: a patient navigation model for chronic disease self-management. Online J Issues Nurs 2012 May 31;17(2):2 [FREE Full text] [Medline: 22686110]
33. Clark C, Baril N, Kunicki M, Johnson N, Soukup J, Ferguson K, REACH 2010 BreastCervical Cancer Coalition. Addressing social determinants of health to improve access to early breast cancer detection: results of the Boston REACH 2010 Breast and Cervical Cancer Coalition Women's Health Demonstration Project. J Womens Health (Larchmt) 2009 May;18(5):677-690. [doi: 10.1089/jwh.2008.0972] [Medline: 19445616]
34. Carrasquillo O, Lebron C, Alonzo Y, Li H, Chang A, Kenya S. Effect of a Community Health Worker Intervention Among Latinos With Poorly Controlled Type 2 Diabetes: The Miami Healthy Heart Initiative Randomized Clinical Trial. JAMA Intern Med 2017 Jul 01;177(7):948-954 [FREE Full text] [doi: 10.1001/jamainternmed.2017.0926] [Medline: 28459925]
35. Loskutova NY, Tsai AG, Fisher EB, LaCruz DM, Cherrington AL, Harrington TM, et al. Patient Navigators Connecting Patients to Community Resources to Improve Diabetes Outcomes. J Am Board Fam Med 2016;29(1):78-89 [FREE Full text] [doi: 10.3122/jabfm.2016.01.150048] [Medline: 26769880]
36. Palinkas L, Ell K, Hansen M, Cabassa L, Wells A. Sustainability of collaborative care interventions in primary care settings. Journal of Social Work 2010 Dec 05;11(1):99-117. [doi: 10.1177/1468017310381310]
37. Gutierrez KM, Campbell J. Evaluating Community Health Worker Programs in Health Care Settings. Best Practice Guidelines for Implementing and URL: http://www.sinai.org/sites/default/files/SUHI%20Best%20Practice%20Guidelines%20for%20CHW%20Programs.pdf [accessed 2018-11-15] [WebCite Cache ID 73ww9DUQQ]
38. Ferrante JM, Cohen DJ, Crosson JC. Translating the patient navigator approach to meet the needs of primary care. J Am Board Fam Med 2010;23(6):736-744 [FREE Full text] [doi: 10.3122/jabfm.2010.06.100085] [Medline: 21057069]
39. 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]

40. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A, King MT, the SPIRIT-PRO Group, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA 2018 Dec 06;319(5):483-494. [doi: 10.1001/jama.2017.21903] [Medline: 29411037]
41. Champlain LHIN: Ontario Local Health Integration Network. Sub-Region Population Health Profiles Technical Report. 2018. URL: http://www.champlainlhin.on.ca/~/media/sites/champlain/Goals_Achvmnts/IHSP/SubRegions/Data/SRHlthPrflsTechRptEN.pdf?la=en [WebCite Cache ID 73wyJcqHP]
42. Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Michie S: Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ : British Medical Journal 2014;348. [Medline: 24609605]
43. Rogers, Olaguera N. Diffusion of Innovations. In: Diffusion of Innovations, 5th Edition. New York: Simon & Schuster Adult Publishing Group; 2003.
44. Toal-Sullivan D, Rolfe D, Pottie K, Welch V, Thuku M, Gaudet C, et al. P347: Applying the findings of a commissioned rapid realist review to inform the planning for an intervention to increase referrals from primary care to community resources. In: North American Primary Care Research Group. Colorado Springs, Colorado. 2016 Presented at: North American Primary Care Research Group; November 12-16, 2016; Colorado Springs.
45. Schwarzer R. Modeling Health Behavior Change: How to Predict and Modify the Adoption and Maintenance of Health Behaviors. Applied Psychology 2008 Jan;57(1):1-29. [doi: 10.1111/j.1464-0597.2007.00325.x]
46. Goris J, Komaric N, Guandalini A, Francis D, Hawes E. Effectiveness of multicultural health workers in chronic disease prevention and self-management in culturally and linguistically diverse populations: a systematic literature review. Aust J Prim Health 2013;19(1):14-37. [doi: 10.1071/PY11130] [Medline: 22951183]
47. Kangovi S, Grande D, Carter T, Barg FK, Rogers M, Glanz K, et al. The use of participatory action research to design a patient-centered community health worker care transitions intervention. Healthc (Amst) 2014 Jul;2(2):136-144. [doi: 10.1016/j.hjdsi.2014.02.001] [Medline: 26250382]
48. Najafizada S, Bourgeault I, Labonte R, Packer C, Torres S. Community health workers in Canada and other high-income countries: A scoping review and research gaps. Can J Public Health 2015 Mar 12;106(3):e157-e164. [doi: 10.17269/cjph.106.4747] [Medline: 26125243]
49. Willis A, Reed E, Pratt-Chapman M, Kapp H, Hatcher E, Vaitones V, et al. Journal of Oncology Navigation and Survivorship. 2013. Development of a Framework for Patient Navigation: Delineating Roles Across Navigator Types URL: https://tinyurl.com/y73m7uee [WebCite Cache ID 75FrL4w4O]
50. Miller W, Rollnick S, Conforti K. Motivational Interviewing, Second Edition: Preparing People for Change. New York: Guilford Publications, Inc; 2002.
51. Lancaster G, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j.2002.384.doc.x] [Medline: 15189396]
52. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol 2012 Mar;65(3):301-308. [doi: 10.1016/j.jclinepi.2011.07.011] [Medline: 22169081]
53. Canadian socioeconomic database from Statistics Canada (CANSIM). 6-4-2018 URL: https://www150.statcan.gc.ca/n1/en/type/data [accessed 2018-11-15] [WebCite Cache ID 73x2Jw2Qc]
54. Thylefors I, Persson O, Hellström D. Team types, perceived efficiency and team climate in Swedish cross-professional teamwork. J Interprof Care 2005 Mar;19(2):102-114. [doi: 10.1080/13561820400024159] [Medline: 15823885]
55. Anderson NR, West MA. Journal of Organizational Behaviour. 1998. Measuring climate for work group innovation: development and validation of the team climate inventory URL: http://www.psychwiki.com/dms/other/labgroup/Measufsdfsdbger345resWeek1/Danika/Andersen1998.pdf [WebCite Cache ID 75FrSO3pY]
56. Shea C, Jacobs S, Esserman D, Bruce K, Weiner BJ. Organizational readiness for implementing change: a psychometric assessment of a new measure. Implement Sci 2014 Jan 10;9:7 [FREE Full text] [doi: 10.1186/1748-5908-9-7] [Medline: 24410955]
57. Herscovitch L, Meyer JP. Commitment to organizational change: extension of a three-component model. J Appl Psychol 2002 Jun;87(3):474-487. [Medline: 12090605]
58. Creswell J, Clark VL. Designing and conducting mixed methods research. In: Designing and conducting mixed methods research. Thousand Oaks: Sage publications; 2017.
59. Shrank W. The Center For Medicare And Medicaid Innovation's blueprint for rapid-cycle evaluation of new care and payment models. Health Aff (Millwood) 2013 Apr;32(4):807-812. [doi: 10.1377/hlthaff.2013.0216] [Medline: 23535630]
60. Levesque JF, Harris M, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. Int J Equity Health 2013 Mar 11;12:18 [FREE Full text] [doi: 10.1186/1475-9276-12-18] [Medline: 23496984]
61. Sandelowski M. Qualitative analysis: what it is and how to begin. Res Nurs Health 1995 Aug;18(4):371-375. [Medline: 7624531]
62. Thorne S. Interpretive description. Walnut Creek, CA: Left Coast Press, Inc; 2008.
63. Greenhalgh T, Papoutsi C. Studying complexity in health services research: desperately seeking an overdue paradigm shift. BMC Med 2018 Dec 20;16(1):95 [FREE Full text] [doi: 10.1186/s12916-018-1089-4] [Medline: 29921272]

64. Plsek P, Greenhalgh T. Complexity science: The challenge of complexity in health care. BMJ 2001 Sep 15;323(7313):625-628 [FREE Full text] [Medline: 11557716]

Abbreviations

ARC: Access to Resources in the Community
CR: community resource
PHC: primary health care
PCP: primary care provider
RCE: rapid cycle evaluation
TIDieR: Template for Intervention Description and Replication

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Protocol

Exposure to Pesticides and Health Effects on Farm Owners and Workers From Conventional and Organic Agricultural Farms in Costa Rica: Protocol for a Cross-Sectional Study

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Abstract

Background: Pesticide use is increasing in low- and middle-income countries (LMICs) including Costa Rica. This increase poses health risks to farm owners, farm workers, and communities living near agricultural farms.

Objective: We aimed to examine the health effects associated with occupational pesticide exposure in farm owners and workers from conventional and organic smallholder farms in Costa Rica.

Methods: We conducted a cross-sectional study involving 300 owners and workers from organic and conventional horticultural smallholder farms in Zarcero County, Costa Rica. During the baseline study visit, we administered a structured, tablet-based questionnaire to collect data on sociodemographic characteristics, pesticide exposure, and health conditions (eg, respiratory and allergic outcomes and acute pesticide intoxication symptoms) and administered a neurobehavioral test battery (eg, Finger Tapping Test and Purdue Pegboard); we measured blood pressure, anthropometry (height, weight, and waist circumference), and erythrocytic acetylcholinesterase activity and also collected urine samples. In addition, a functional neuroimaging assessment using near-infrared spectroscopy was conducted with a subset of 50 study participants. During the follow-up study visit (~2-4 weeks after the baseline), we administered participants a short questionnaire on recent pesticide exposure and farming practices and collected hair, toenail, and urine samples. Urine samples will be analyzed for various pesticide metabolites, whereas toenails and hair will be analyzed for manganese (Mn), a biomarker of exposure to Mn-containing fungicides. Self-reported pesticide exposure data will be used to develop exposure intensity scores using an exposure algorithm. Furthermore, exposure-outcome associations will be examined using linear and logistic mixed-effects regression models.

Results: Fieldwork for our study was conducted between May 2016 and August 2016. In total, 113 farm owners and 187 workers from 9 organic and 83 conventional horticultural smallholder farms were enrolled. Data analyses are ongoing and expected to be published between 2019 and 2020.

Conclusions: This study is one of the first to examine differences in health effects due to pesticide exposure between farm owners and workers from organic and conventional smallholder farms in an LMIC. We expect that this study will provide critical data on farming practices, exposure pathways, and how occupational exposure to pesticides may affect farm owners and workers' health. Finally, we hope that this study will allow us to identify strategies to reduce pesticide exposure in farm owners and workers and will potentially lay the groundwork for a future longitudinal study of health outcomes in farm owners and workers exposed to pesticides.

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KEYWORDS

acetylcholinesterase; agriculture; Costa Rica; farm workers; near-infrared spectroscopy; neurobehavioral outcomes; pesticides; pesticide exposure assessment; respiratory outcomes

Introduction

Pesticides are extensively used in agriculture and for control of vector-borne diseases across the globe [1,2]. Current data from the Food and Agriculture Organization suggest that pesticide use is increasing globally, with its largest growth in low- and middle-income countries (LMICs) in tropical contexts [3]. Notably, registered pesticides are often not assessed in tropical contexts, where decay rates of active ingredients and metabolites of pesticides differ from other settings [4] and regulatory bodies often fail to phase-out harmful pesticides or monitor their safe use [5]. In LMICs, the smallholder farming sector frequently struggles to use pesticides safely due to a lack of awareness and low risk perception among farm owners and workers [6-8].

Pesticide applicators (either farm owners or workers) in smallholder farms are often exposed to these chemicals at different stages of the process (eg, storage, mixing, preparation, and application) [9,10]. Therefore, uncontrolled and uninformed pesticide use can directly expose workers and surrounding communities through drift and pesticide residues in food and drinking water [11]. Several studies from LMICs have shown that acute pesticide poisoning represents an important cause of morbidity and mortality among farm workers [12]. In addition, long-term exposure to pesticides such as organophosphates and carbamates has been linked to a broad range of chronic health effects, including impaired neurobehavioral function (eg, cognitive and behavioral disorders), respiratory problems, obesity, and diabetes [13-17].

The characterization of pesticide exposures in LMICs is challenging due to the short half-lives of most of these chemicals in the human body, limited availability of biomarkers of exposure, and lack of epidemiological data [18-20]. As highlighted by a recent descriptive review [19], most studies in LMICs have relied on self-reported pesticide exposures. A few studies have generated pesticide exposure matrices, estimating exposure intensity indices using the amount of pesticide used and personal protective equipment worn during the applications [18,21,22]. However, these exposure matrices are prone to information bias and often lack validation against biomarkers of exposure in humans (eg, urine and blood) [18,19].

Several studies have examined the health effects of occupational pesticide exposure in tropical settings [23-29]. In addition, multiple studies outside of LMICs have assessed differences in pesticide use practices from conventional farming systems (ie, using synthetic pesticides) and organic (ie, using biological pest control; certified as organic by third-party agencies) farms [30]. Nevertheless, to the best of our knowledge, only one published study from Portugal has compared pesticide exposure and health outcomes in farm workers from both types of farms [31]. In the present study, we aimed to determine whether occupational pesticide exposure (assessed through self-reported data and biomarkers of exposure) affects the health of farm owners and workers from conventional and organic smallholder farms in Costa Rica.

Methods

Objectives and Study Design

We conducted a cross-sectional study of 300 farm owners and workers with repeated exposure assessment at two time points (to study the variability of pesticide exposure over time) between May 2016 and August 2016 (rainy season, during which the highest pesticide application is expected). The specific objectives of the project are as follows (Figure 1):

1. To assess occupational pesticide exposure in owners and workers of conventional and organic farms, using self-reported pesticide use data and biomarkers of pesticide exposure.
2. To evaluate the association of occupational pesticide exposure (determined using a pesticide exposure matrix and also biomarkers of exposure) with self-reported symptoms of acute intoxication in the last 12 months.
3. To examine the association of occupational pesticide exposure with self-reported respiratory and allergic outcomes in the last 12 months.
4. To evaluate the association between occupational pesticide exposure and cardiometabolic effects, such as adiposity and high blood pressure.
5. To assess the association of occupational exposure to organophosphates and carbamates with erythrocytic acetylcholinesterase (AChE) activity.
6. To assess the association of occupational pesticide exposure with neurobehavioral outcomes, such as working memory, visual perception, and fine motor function.
7. To examine the association of occupational pesticide exposure with changes in brain activity, assessed using functional near-infrared spectroscopy (fNIRS).

This study is part of the Pesticide Use in Tropical Settings (PESTROP) Project, which aims to deepen our understanding of the environmental, health, and regulatory dimensions of pesticide use in conventional and organic agriculture in LMICs. The design of our research was partly informed by a study conducted in the same study area between 2014 and 2016 [32]. This study focused on the diagnosis of pesticide use in farms with conventional practices and highlighted unintended uses of pesticides among farm owners in Zarcero (eg, use of pesticides without appropriate training and personal protective equipment protection and discharge of pesticide containers into the environment). The findings of this study provided orientation on exposure pathways to be expected and influenced the definition of our study groups.

All study materials and procedures were approved by the human subjects committee of the Universidad Nacional in Costa Rica (UNA-CECUNA-ACUE-04-2016) and Ethical Board of the Ethikkommission Nordwest- und Zentralschweiz in Switzerland (EKNZ-UBE 2016-00771). Written informed consent was obtained from all study participants at enrollment. Study results will be communicated back to participants and stakeholders at restitution workshops (Figure 2).

Study Area

The study was conducted in the Tapezco river catchment in the Zarcero County, Costa Rica (Figure 3). This river catchment features approximately 760 small-scale smallholder farms with conventional and organic farming practices (~4 km^2 of horticultural farms) [33] and has been previously used to monitor pesticide levels in the surface water near smallholder farms. Common crops in the area include potatoes, tomatoes, cabbage, carrots, lettuce, cilantro, and onions [32]; chlorothalonil, mancozeb, propineb, and phorate account for >50% of the pesticides used in the County. Notably, potatoes and onions are the crops with the highest pesticide use per hectare [32].

Figure 1. Aims (bold text), research design details and tools used (tick) in the study conducted in Zarcero County, Costa Rica, 2016.

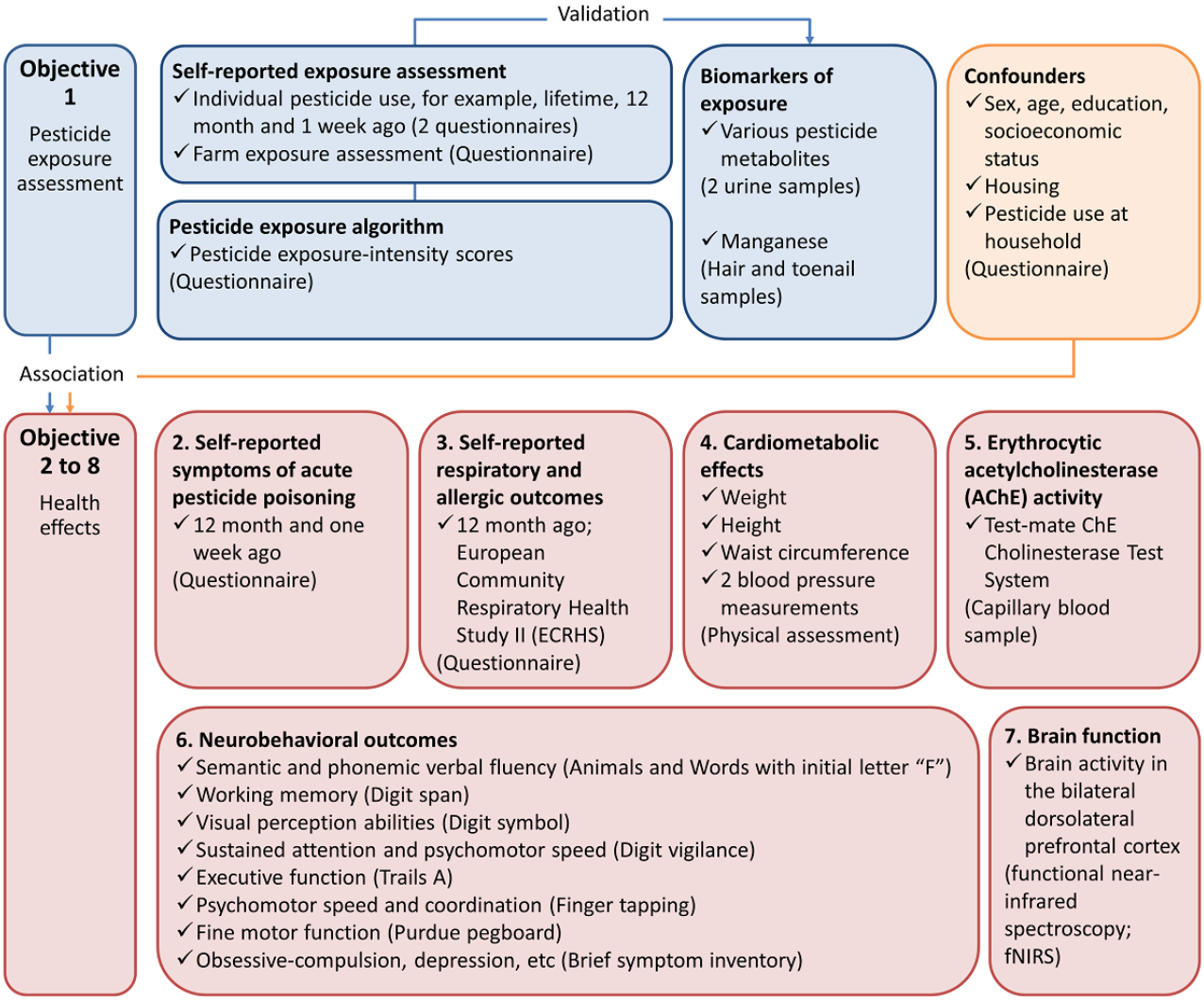


Figure 2. Diagram of the fieldwork setup in the Zarcero study, Costa Rica, 2016.

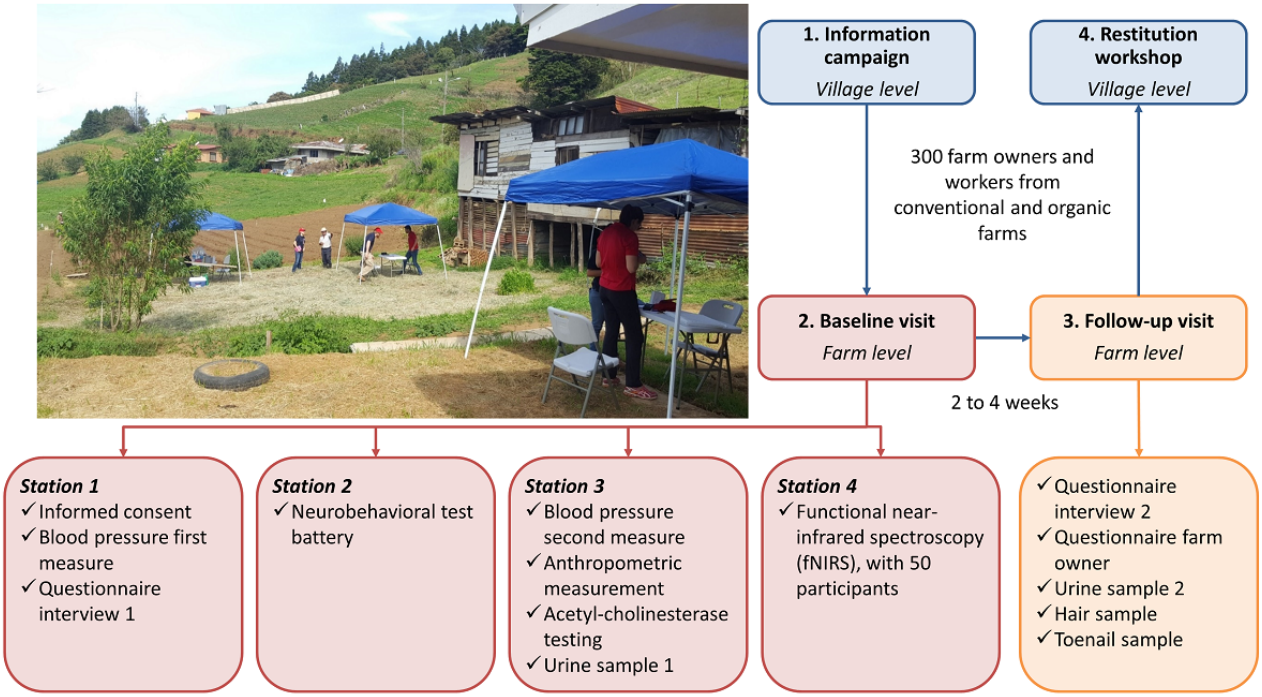
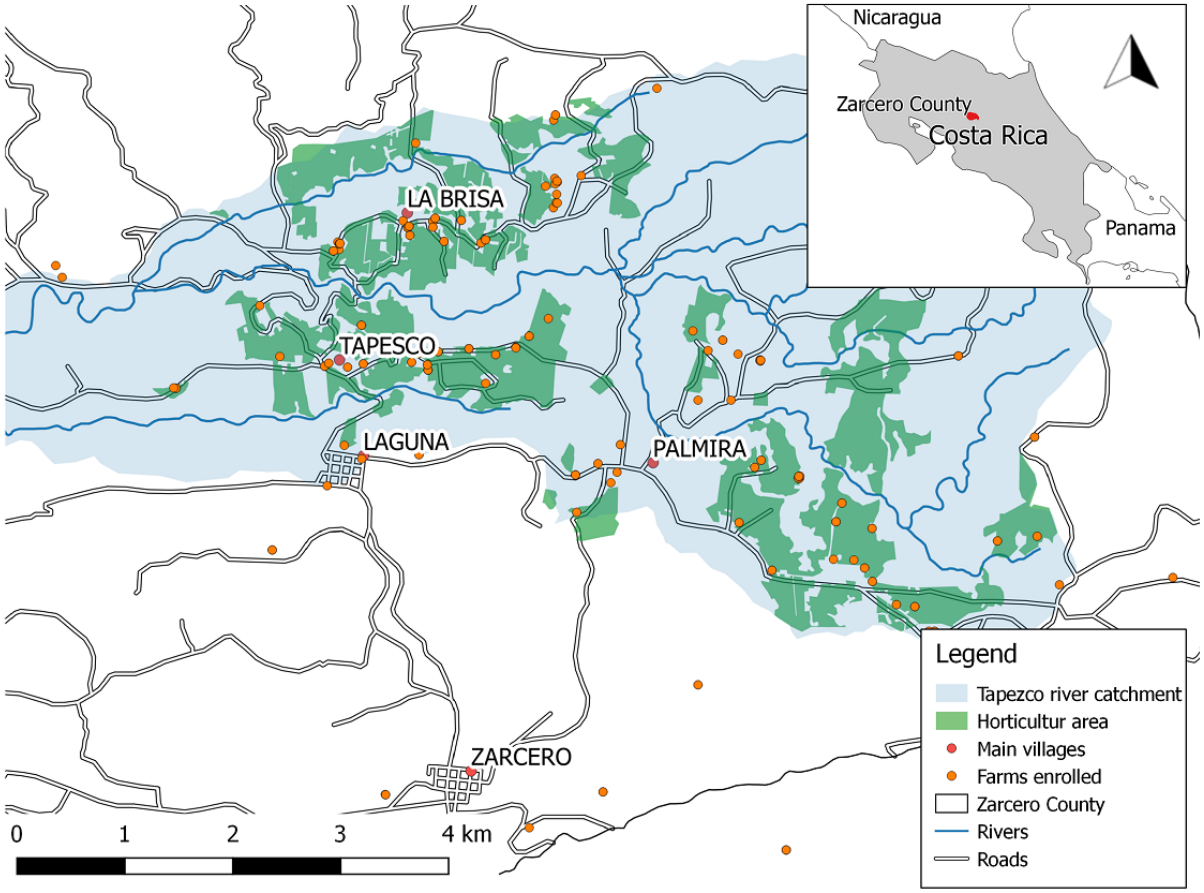


Figure 3. Study area (Tapezco river catchment) with global positioning system locations of 92 farms that were included in our study conducted in Zarcero County, Costa Rica, 2016. Shape files provided by Moraga (2015).



Study Participants' Selection and Study Visits

Conventional farms in the study area were identified using random global positioning system (GPS) points generated on the basis of smallholder land use data from 2015 (Moraga G, unpublished data, 2000) [34]. After a total of 200 GPS points were generated, study staff visited these locations and determined which ones corresponded to smallholder farms by contacting the farm owners or administrators. When the GPS point did not correspond to a horticultural farm, the closest smallholder farm within a radius of 1 km was registered; if no farm was nearby, the GPS point was dropped. Organic farms within the Tapezco river catchment or within 5 km from this area were identified using an existing list provided by the organic farmers' association or through onsite identification.

After organic and conventional farms in the study area were identified, farm owners were briefly informed about the study aims and procedures (initial visits to the farms are, henceforth, called Information campaign; Figure 3). If they showed interest in participating in the study, basic contact information was collected to schedule a later visit to their farms to enroll study participants. Eligible participants were farm owners, permanent workers, or temporary pesticide applicators, all aged ≥18 years, who owned or worked in conventional farms located in the Tapezco river catchment or organic farms within or near the catchment area, and who did not have a diagnosis of psychiatric disease or used psychopharmacological medications.

Participants were visited twice during the study duration, either at the farms where they worked or at their homes (Figure 3). The baseline or initial study visits were conducted by two teams of 3 trained research assistants each and comprised 4 "*Stations* " (duration ~45 minutes each) as follows: "*Station 1* " included the administration of the informed consent and a structured questionnaire to collect data on sociodemographic characteristics, occupational history, pesticide exposure at work and at home, medical history including respiratory and allergic outcomes in the last 12 months, and a blood pressure measurement; "*Station 2* " included the administration of a neurobehavioral test battery (eg, Purdue Pegboard and Finger Tapping Test) and a checklist of acute pesticide intoxication symptoms in the last 12 months; "*Station 3* " included measurements of the erythrocytic AChE activity, anthropometry (ie, height, weight, and waist circumference), and blood pressure (second measurement) and urine sample collection; and "*Station 4* " included the fNIRS assessment (only completed by a subset of study participants).

The follow-up study visits (duration ~15 minutes, 2-4 weeks after the first visit) were conducted by two trained research assistants and included the administration of a short questionnaire on recent pesticide exposure (administered to all participants) and farming practices (administered only to farm owners) and collection of toenail and hair samples and a second urine specimen.

All study instruments were pilot-tested in 10 farmers. Study protocols were administered by trained research assistants in Spanish, and data were entered directly into tablets (Samsung Galaxy Note 10.1 N8010) via an entry mask using Open Data Kit [35]. Questionnaires and other study instruments are available per request.

Power and Sample Size Calculation

We based our sample size calculation on the difference in the erythrocytic AChE activity between organic and conventional farm owners and workers [36]. With a sample size of 300 farm owners and workers, the minimum number of farms to show a significant effect between the 2 groups was calculated to be 50 (ie, 25 conventional and 25 organic farms). In brief, we assumed an average cluster size of 6 farmers per individual farm (this assumption was derived from a pilot visit and expert opinion of local agronomists), an intraclass correlation coefficient (ICC) of 0.1, a ratio of SDs of 1.5 between exposed and unexposed persons regarding the erythrocytic AChE activity, a significance level of 5%, 80% power, and an effect size of 0.4, that is, a difference in the mean of the erythrocytic AChE activity between exposed and unexposed farm owners and workers of $0.4\times\sqrt{[(1 + 2.25)/2}$ SDs].

Interviews and Self-Report Pesticide Exposure

Information on sociodemographic variables and occupational exposure to pesticides was collected using structured questionnaires (Table 1). During the baseline visit, study participants were asked about the crops that they had recently worked on and if they had prepared or applied pesticides. If they reported preparing or applying one of the 15 pesticides most commonly used in the study area (according to a previous study on good farming practices that was conducted in conventional farms from the study area, Table 2; [32]), detailed data on the mode of application, period, dose, frequency of pesticide applications, and personal protective equipment use were collected. In addition, participants were asked about their recent pesticide applications (prior to the collection of each urine sample), previous work in conventional or organic farms, and years of exposure to pesticides during their work life. During the follow-up visit, study participants were asked about changes in their work status and pesticide use since their baseline visit. In addition to the data described above, we collected information on farms' characteristics (eg, size, type of crops grown on the farm, farming practices including pest control management, and water sources located nearby) using a structured questionnaire that was administered only to farm owners.

Table 1. Information collected during the baseline study visit using structured questionnaires.

Questionnaire section	Data collected
Sociodemographic characteristics	Age (years), sex, country of birth, years living in Costa Rica, years living in the Zarcero County, education level (last grade completed), handedness (right or left), smoking (number of cigarettes per day), alcohol consumption (number of glasses), family income (Costa Rican colones per household), computer literacy
Housing characteristics	Years living in the current house, number of bedrooms, number of people living in the house, type of water source, pet ownership (number and type), and farm animals living in or next to the house (number and type)
Work history	Age when started working in agriculture (years), age at first contact with pesticides (years), past jobs, and current jobs in agriculture
Pesticide use	Pesticide use (Table 2) during the last 12 months and last week, mode of application, frequency of pesticide applications (number of times), use of personal protective equipment (type and frequency), and personal hygiene habits (frequency)
Residential pesticide use	Indoor or outdoor pesticide use in the home (type)
Medical history	Respiratory and allergic symptoms, acute pesticide intoxications during the last 12 months (number of times), and other illnesses (type)

Table 2. Most frequently used pesticides (active ingredients; ordered from most frequently use to the least frequently used) in agricultural farms in the Zarcero County, Costa Rica[a].

Active ingredient	Commercial names	Chemical subgroup	Group of action
Chlorothalonil	Bravo, Bravonil, Knight, Talonil, Thalonex, Folio Gold, Odeon	Chloronitriles	Fungicide
Benfuracarb	Oncol	Carbamates	Insecticide
Mancozeb	Dithane, Mancol, Ridomil, Titan	Dithiocarbamates	Fungicide
Boscalid	Bellis, Endura	Pyridinecarboxamids	Fungicide
Carbendazim	Afin, Cozaid, Crotonox, Carbendazina	Benzimidazoles	Fungicide
Acephate	Acefate, Orthene, Yucal	Organophosphates	Insecticide
Phorate	Forato, Thimet, Thimetoato, Timefor	Organophosphates	Insecticide
Fenamiphos	Fenemiphos, Nemacur	Organophosphates	Insecticide
Chlorpyrifos	Agromil, Batazo, Baygon, Lorsban, Solver, Terminator, Swat	Organophosphates	Insecticide
Glyphosate	Atila, Evigras, Ranger, Round Up	Glycine derivatives	Herbicide
Carbofuran	Carbodan, Curator, Furadan	Carbamates	Insecticide
Cypermethrin	Best, Cascabel, Cipermetrina, Combat, Cruz Verde, Tigre, Excalibur	Pyrethroids	Insecticide
Propamocarb	Acrobat CT, Previcur, Proplant, Prevalor	Carbamates	Fungicide
Paraquat	Gramoxone, Preglone, Rafaga	Bipyridiliums	Herbicide
Propineb	Antracol, Inicol, Taifen	Dithiocarbamates	Fungicide

[a]Modified from: Ramírez et al, 2016 [32]. Pesticides are ordered from most frequently used to the least frequently used.

Biological Sample Collection and Analyses

Urine Samples

Spot urine samples were collected during the baseline and follow-up visits in plastic containers of 100 mL **(**Vacuette, sterile**)**. Specimens were stored at 4°C until the end of the fieldwork day. Then, samples were aliquoted in 15-mL plastic test tubes (PerformRTM Centrifuge tubes, Labcon, sterile) and stored at −20°C until their shipment at 4°C to Lund University, Sweden, for analysis.

Urine samples will be analyzed for multiple pesticide metabolites including, but not limited to, ethylenethiourea (ETU, a metabolite of mancozeb); propylenethiourea (PTU, a metabolite of propineb); 3,5,6-trichloropyridinol (TCP, a metabolite of chlorpyrifos); 3-phenoxybenzoic acid (3-PBA, a metabolite of pyrethroids permethrin, cypermethrin, deltamethrin, and cyfluthrin); and hydroxy pyrimethanil (a metabolite of pyrimethanil). These pesticides and their metabolites were selected because they are among the most commonly used in Zarcero [32] and for which biomarkers of exposure are available. Briefly, urine specimens will be analyzed using tandem mass spectrometry and high-performance liquid chromatography [37,38]. The limit of detection (LOD) are as follows: ethylenethiourea, 0.08 ng/mL; propylenethiourea, 0.1 ng/mL; TCP, 0.05 ng/mL; 3-PBA, 0.03 ng/mL; and hydroxy pyrimethanil, 0.1 ng/mL. In all sample batches, chemical blanks and in-house quality control samples will be included to ensure the quality of all measurements; additionally, the analyses of TCP and 3-PBA are part of the round robin interlaboratory

comparison program (University of Erlangen-Nuremberg, Germany) with results within the tolerance limits. Furthermore, urine samples will be analyzed for creatinine and specific gravity so that pesticide metabolite concentrations can be adjusted for differences in urinary dilution [39].

Hair Samples

Hair samples (~20-30 strands) were collected from the occipital region, within 2 mm from the scalp, using stainless-steel scissors during the follow-up study visit. The samples were then stored at room temperature in sterile plastic bags until their shipment to the Federal University of Bahia, Brazil.

Hair specimens will be analyzed for manganese (Mn), which is contained in ethylene bisdithiocarbamate fungicides, such as mancozeb. Briefly, the nearest centimeter scalp (proximal end) of hair will be sonicated for 20 min in 0.5% Triton, rinsed 5 times with ultrapure water, sonicated for 10 min in 1-N nitric acid, rinsed once with 1-N nitric acid, and then rinsed 5 times with ultrapure water [40]. Approximately 10 mg of hair will be digested with 2 mL of concentrated HNO_3 spectroscopic-grade acid in a microwave digestion oven (Mars-Express6, CEM, USA). The digested material will be diluted to 10 mL with ultrapure water. Hair samples, certified reference material (Human hair, International Atomic Energy Agency 086), and reagent blanks will be analyzed using electrothermal atomic absorption spectrometry with Zeeman background correction [41]. The analytical LOD for hair Mn concentrations will be set at 0.05 µg/L.

Toenail Samples

Toenail samples were collected during the follow-up study visit. Participants were asked to cut their toenails with clean stainless-steel nail clippers and put them inside of a sterile plastic bag. Toenail specimens were stored at room temperature until their shipment to Federal University of Bahia, Brazil.

Toenail samples will be analyzed for Mn using the same procedure described above for hair samples. Briefly, nails will be washed in a Triton X-100 solution, put in acetone, repeatedly rinsed with ultrapure water, and then dried in an oven. Later, the dried nails will be digested with spectroscopic-grade acid in a microwave digestion oven (Mars-Express6, CEM), diluted to 10 mL with ultrapure water, and analyzed electrothermal atomic absorption spectrometry with Zeeman background correction [42,43]. All processed samples and reference material from the International Atomic Energy Agency (ie, 085) will be analyzed in duplicates. The analytical LOD for toenail Mn concentrations will be set at 0.05 µg/L.

Assessment of Health Outcomes

Symptoms of Acute Pesticide Poisoning

Participants were administered a checklist of symptoms of acute organophosphate and carbamate poisoning (eg, excessive salivation, lacrimation, vomiting, and diarrhea) during the 12-month period before the baseline study visit. This checklist has been previously used in studies of Latin American farm workers [28,44].

Respiratory and Allergic Outcomes

A short version of the European Community Respiratory Health Study II questionnaire [45] was administered to study participants to identify respiratory symptoms (eg, wheezing, shortness of breath, coughing, and phlegm), respiratory diseases (eg, asthma and chronic bronchitis), allergic outcomes (eg, rhinitis and eczema), and common respiratory hazards such as smoking and pet ownership [46]. This questionnaire has been previously used in studies of Costa Rican populations [47-49].

Neurobehavioral Outcomes

Study participants were administered the following eight neurobehavioral tests: Animals and words with initial letter "F" (to assess semantic and phonemic verbal fluency) [50]; Digit Span (working memory) [51]; Digit Symbol (visual perception abilities) [51]; Digit Vigilance (sustained attention and psychomotor speed) [52]; Trails Making Test Part A (executive function) [53]; Finger Tapping (psychomotor speed and coordination) [53]; Purdue Pegboard (fine motor function) [54]; and Brief Symptom Inventory (behavioral disorders including somatization, obsessive-compulsion, depression, anxiety, hostility, and psychoticism) [55].

These tests were selected on the basis of previous studies of Latin American populations exposed to pesticides [28,29], administration time, and cultural sensitivity [56]. Neurobehavioral assessments were conducted by two trained psychometricians and supervised by a physician with extensive experience on neurobehavioral testing. Quality assurance measures included pilot testing and review of recorded assessments.

Brain Activity

We used fNIRS (NIRSport, NIRx Medical Technologies, Los Angeles, CA, USA) to assess the cortical function associated with pesticide exposure in a random subsample of 50 study participants; a detailed description of our study methods can be found elsewhere [57]. Specifically, in this study, we hypothesized that higher pesticide exposures would be associated with more atypical brain activation patterns related to attention, working memory, and executive function. As these cognitive processes commonly elicit cortical activity within the bilateral dorsolateral prefrontal cortices [58-60], we targeted these regions with fNIRS. To engage our participants in tasks that required these cognitive abilities, each participant completed 3 computer-based tests that were optimized for neuroimaging applications. These tasks included the Wisconsin Card Sort test (an executive function and cognitive flexibility task) [60], Sternberg test (a letter-retrieval working memory task) [59], and Go/No-go test (an attention and impulse control task) [58]. Each task was conducted on a laptop computer that was dedicated to the fNIRS assessment and was completed on site.

Cardiometabolic Outcomes: Blood Pressure and Anthropometric Measurements

Trained research assistants measured systolic and diastolic blood pressure at two different time points (ie, at the beginning of "*Station 1* " and "*Station 3* " and about 1.5 hours apart from each other) during the baseline study visit using an automatic sphygmomanometer (Advantage 6021N). In addition, they

measured participants' height (cm) and weight (kg) using a portable stadiometer and a digital scale (Tanita BC533, Arlington Heights, IL, USA). Waist circumference (cm) was measured using a tape measure Hoechstmass (Hoechstmass Balzer GmbH, Sulzbach, Germany).

Erythrocytic Acetylcholinesterase Activity

Capillary blood samples were collected at the baseline visit according to the manual of the Test-mate ChE Cholinesterase Test System (Model 400; EQM Research Inc, Cincinnati, OH, USA). Briefly, a small lancet (size 30) was used to collect a small sample of 10 µm from the tip of the index finger of each study participant and placed into a capillary tube. Blood samples were analyzed on site for the erythrocytic AChE activity and hemoglobin levels using the same collection instrument [61].

Statistical Analyses

We will explore differences in self-reported pesticide exposures and health outcomes (ie, respiratory and allergic as well as neurobehavioral and cardiometabolic outcomes, brain activity, symptoms of acute pesticide poisoning, and erythrocytic AChE activity) in farm workers from conventional and organic farms. Cumulative lifetime pesticide exposure, exposure during the last 12 months, and during the last week will be estimated using exposure intensity scores derived from a semiquantitative exposure algorithm (based on self-reported data on pesticides, personal protective equipment use, and personal hygiene habits) [18]. Exposure intensity scores will be calculated for each chemical family (eg, organophosphates and carbamates) and active ingredient (eg, phorate and chlorpyrifos) and then validated against urinary pesticide metabolite concentrations and hair and toenail Mn concentrations using Spearman correlation coefficients and multivariate mixed-effects regression models [22]. We aim to use multiple imputation techniques to replace pesticide metabolite or Mn concentrations below the limit of detection [62]. In addition, we will fit mixed-effects models to examine the reproducibility of urinary pesticide concentrations by calculating ICCs (an ICC of <0.50 indicates poor reliability) [63]. If appropriate, we will then average urinary pesticide metabolite concentrations across the repeated samples collected for each study participant.

Associations of pesticide exposure with health outcomes of interest will be examined using both exposure scores and biomarkers of exposure. More specifically, we will fit linear or logistic (depending on the outcome) mixed-effects regression models (with the variable "participant" as random effect and other variables, such as outcome and covariates, as fixed effects) to explore the association of pesticide exposure with the following: (1) self-reported symptoms of acute pesticide poisoning in the last 12 months; (2) self-reported symptoms of respiratory and allergic symptoms and outcomes; (3) neurobehavioral outcomes and brain activity; (4) cardiometabolic effects (ie, obesity and hypertension); and (5) erythrocytic AChE activity. These mixed-effects models will allow us to take into account the correlation between and within farms as well as between and within farm workers. Furthermore, we will fit generalized additive models to examine the nonlinearity of the exposure-outcome associations.

We will identify potential confounders and known predictors of the health outcomes of interest (eg, age and education level for neurobehavioral outcomes) using directed acyclic graphs and will include them *a priori* in our regression models. Furthermore, we will assess other potential confounders by adding them, one at a time, to the final models (models with *a priori* covariates). Additional covariates will be possibly included in the final models if they materially changed the magnitude of one or more exposure coefficients (>10%). Missing values (<10%) for covariates will be imputed by randomly selecting a value from the dataset or using multiple imputation techniques [62]. Statistical analyzes will be performed using STATA (Stata Corporation) and R (R Foundation for Statistical Computing).

Results

The fieldwork for this study was conducted between May 2016 and August 2016. A total of 300 participants, including 113 farm owners and 187 workers from nine organic (48 participants) and 83 conventional (252 participants) horticultural smallholder farms from Zarcero County, Costa Rica, were enrolled. We had a 6.3% (281/300) loss to follow-up of study participants between the baseline and follow-up study visits (conducted ~2-4 weeks apart). During the study implementation, we observed that farms were, on average, smaller than we expected (about three owners or workers per farm) and that there were not as many organic farms in the study area as anticipated (only 10 farms out of the 25 that we expected). Interviews to farm owners and key community actors conducted during this study revealed that many organic farm owners had recently started using synthetic pesticides due to the increasing costs of growing organic produce and getting certified as organic producers. Given the limited number of organic farms in the study area, we decided to include all farm owners and workers from organic farms located in the study area or within 5 km from it. In addition, to reach the targeted sample of 300 participants, we had to enroll more conventional farm owners and workers than what we had anticipated. Data analyses are ongoing and expected to be published between 2019 and 2021.

Discussion

This study has several limitations. First, its cross-sectional design will prevent us from identifying causal associations of pesticide exposure with health effects of interest. Second, we will not be able to exclude the possibility that there is recall or information bias, especially when relying on self-reported exposure to pesticides. In our study population, this bias may have worsened under the following conditions: (1) most study participants had a relatively low educational level; (2) pesticide use varied by crop and season; and (3) some farm owners did not communicate the specific pesticides that were used in their farms by their employees. Therefore, the validation of self-reported pesticide exposure data against biomarkers of exposure is crucial. Third, given that we had to enroll more conventional farm owners and workers than what we expected, and this could potentially threaten the internal validity of our study, we will assess participants' pesticide exposures using

exposure intensity scores and biomarker concentrations in addition to their farming practices. We will also run analyses using only data from the conventional farms to evaluate the effects of the miscalculated sample size on our exposure-outcome associations. Fourth, we observed some significant differences between owners and workers from conventional and organic farms (eg, seasonal workers, differences in country of origin, and education level) that could potentially confound the exposure-outcome associations. Hence, it was important to also collect detailed information on confounding factors and predictors of the outcomes of interest.

The limitations of this study are offset by notable strengths, including (1) the quantification of pesticide metabolites and Mn concentrations in different biological matrices, which will allow us to validate the exposure information collected via questionnaires (or at least data from recent exposures given the relatively short half-lives of some of the biomarkers of exposure); (2) the comparison of workers and owners from conventional and organic farms using comprehensive questionnaires on occupational pesticide exposure; and (3) the assessment of health outcomes using internationally standardized tests that will allow for direct comparison of the results from this study to those from studies of other populations.

This study is one of the first studies to examine the health effects of exposure to a wide range of pesticides on Latin American workers from conventional and organic farms. In addition, this is one the first epidemiological studies to examine the association of pesticide exposure with brain cortical activity in farm workers. We expect that this study will provide critical data on how occupational exposure to common pesticides may affect farm owners' and workers' health. Finally, we hope that this study will allow us to identify strategies to reduce pesticide exposure in farm workers and will lay the groundwork for a future longitudinal study of health outcomes in farm owners and workers exposed to pesticides.

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Authors' Contributions

MSW is the principal investigator of the PESTROP project, responsible for the overall study coordination. AMM is the project leader of the PESTROP project in Costa Rica and, together with SF, is responsible for the study design, fieldwork supervision, and data analyses. JMB and RGV designed and implemented the fNIRS protocol. PS, FTW, CS, RILE, and FRM contributed to the development of the study protocols and questionnaires. PS also contributed to the fieldwork supervision. CHL and JAMF contributed to the development of the study protocols and will be responsible for the analyses of the biological samples. SF, in close collaboration with AMM and MSW, drafted this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review reports.

[PDF File (Adobe PDF File), 199KB - resprot_v8i1e10914_app1.pdf]

References

1. Zhang W, Jiang F, Ou J. Global pesticide consumption and pollution: with China as a focus. 2011 Aug Presented at: International Academy of Ecology and Environmental Sciences; 2011; Hong Kong p. 125-144.
2. van den Berg H, Zaim M, Yadav RS, Soares A, Ameneshewa B, Mnzava A, et al. Global trends in the use of insecticides to control vector-borne diseases. Environ Health Perspect 2012 Apr;120(4):577-582 [FREE Full text] [doi: 10.1289/ehp.1104340] [Medline: 22251458]
3. Food and Agriculture Organization of the United Nations. 2018. Statistics and Database of the Food and agriculture Organization of the United Nations (FAOSTAT) URL: http://www.fao.org/faostat/en/ [accessed 2018-08-31] [WebCite Cache ID 723qXCJRz]
4. Weiss F, Leuzinger M, Zurbrügg C, Eggen R. Chemical Pollution in Low- and Middle-Income Countries Chemical Pollution in Low- and Middle-Income Countries. In: Eawag. Dübendorf: Swiss Federal Institute of Aquatic Science and Technology; 2016.

5. The Lancet. Phasing out harmful use of pesticides. The Lancet 2017 Mar;389(10074):1076. [doi: 10.1016/S0140-6736(17)30766-3]
6. Feola G, Binder CR. Why don't pesticide applicators protect themselves? Exploring the use of personal protective equipment among Colombian smallholders. Int J Occup Environ Health 2010;16(1):11-23. [doi: 10.1179/107735210800546218] [Medline: 20166315]
7. Negatu B, Kromhout H, Mekonnen Y, Vermeulen R. Occupational pesticide exposure and respiratory health: a large-scale cross-sectional study in three commercial farming systems in Ethiopia. Thorax 2017 Dec;72(6):498-499. [doi: 10.1136/thoraxjnl-2016-208924] [Medline: 27879416]
8. Schreinemachers P, Balasubramaniam S, Boopathi NM, Ha CV, Kenyon L, Praneetvatakul S, et al. Farmers' perceptions and management of plant viruses in vegetables and legumes in tropical and subtropical Asia. Crop Protection 2015 Sep;75:115-123. [doi: 10.1016/j.cropro.2015.05.012]
9. Macfarlane E, Carey R, Keegel T, El-Zaemay S, Fritschi L. Dermal exposure associated with occupational end use of pesticides and the role of protective measures. Saf Health Work 2013 Sep;4(3):136-141 [FREE Full text] [doi: 10.1016/j.shaw.2013.07.004] [Medline: 24106643]
10. Suratman S, Edwards JW, Babina K. Organophosphate pesticides exposure among farmworkers: pathways and risk of adverse health effects. Rev Environ Health 2015;30(1):65-79. [doi: 10.1515/reveh-2014-0072] [Medline: 25741936]
11. Deziel NC, Friesen MC, Hoppin JA, Hines CJ, Thomas K, Freeman LEB. A review of nonoccupational pathways for pesticide exposure in women living in agricultural areas. Environ Health Perspect 2015 Jun;123(6):515-524 [FREE Full text] [doi: 10.1289/ehp.1408273] [Medline: 25636067]
12. Thundiyil J, Stober J, Besbelli N, Pronczuk J. Acute pesticide poisoning: a proposed classification tool. Bull World Health Organ 2008 Mar;86(3):205-209 [FREE Full text] [Medline: 18368207]
13. Chakraborty S, Mukherjee S, Roychoudhury S, Siddique S, Lahiri T, Ray MR. Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India. J Occup Health 2009;51(6):488-497 [FREE Full text] [Medline: 19851039]
14. London L, Nell V, Thompson M, Myers J. Effects of long-term organophosphate exposures on neurological symptoms, vibration sense and tremor among South African farm workers. Scand J Work Environ Health 1998 Feb;24(1):18-29 [FREE Full text] [Medline: 9562397]
15. Tago D, Andersson H, Treich N. Pesticides and health: a review of evidence on health effects, valuation of risks, and benefit-cost analysis. Adv Health Econ Health Serv Res 2014;24:203-295. [Medline: 25244910]
16. Azandjeme C, Bouchard M, Fayomi B, Djrolo F, Houinato D, Delisle H. Growing burden of diabetes in sub-saharan Africa: contribution of pesticides ? Curr Diabetes Rev 2013 Nov;9(6):437-449. [Medline: 24160309]
17. Muñoz-Quezada MT, Lucero BA, Iglesias VP, Muñoz MP, Cornejo CA, Achu E, et al. Chronic exposure to organophosphate (OP) pesticides and neuropsychological functioning in farm workers: a review. Int J Occup Environ Health 2016 Dec;22(1):68-79 [FREE Full text] [doi: 10.1080/10773525.2015.1123848] [Medline: 27128815]
18. Negatu B, Vermeulen R, Mekonnen Y, Kromhout H. A Method for Semi-quantitative Assessment of Exposure to Pesticides of Applicators and Re-entry Workers: An Application in Three Farming Systems in Ethiopia. Ann Occup Hyg 2016 Jul;60(6):669-683. [doi: 10.1093/annhyg/mew022] [Medline: 27109466]
19. Carles C, Bouvier G, Lebailly P, Baldi I. Use of job-exposure matrices to estimate occupational exposure to pesticides: A review. J Expo Sci Environ Epidemiol 2017 Dec;27(2):125-140. [doi: 10.1038/jes.2016.25] [Medline: 27189257]
20. Ismail AA, Bonner MR, Hendy O, Abdel Rasoul G, Wang K, Olson JR, et al. Comparison of neurological health outcomes between two adolescent cohorts exposed to pesticides in Egypt. PLoS One 2017;12(2):e0172696 [FREE Full text] [doi: 10.1371/journal.pone.0172696] [Medline: 28231336]
21. Thomas KW, Dosemeci M, Coble JB, Hoppin JA, Sheldon LS, Chapa G, et al. Assessment of a pesticide exposure intensity algorithm in the agricultural health study. J Expo Sci Environ Epidemiol 2010 Sep;20(6):559-569 [FREE Full text] [doi: 10.1038/jes.2009.54] [Medline: 19888312]
22. Coble J, Thomas KW, Hines CJ, Hoppin JA, Dosemeci M, Curwin B, et al. An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. Int J Environ Res Public Health 2011 Dec;8(12):4608-4622 [FREE Full text] [doi: 10.3390/ijerph8124608] [Medline: 22408592]
23. de Araújo AJ, de Lima JS, Moreira J, Jacob Sdo C, Soares Mde O, Monteiro MC, et al. [Multiple exposure to pesticides and impacts on health: a cross-section study of 102 rural workers, Nova Friburgo, Rio de Janeiro State, Brazil]. Cien Saude Colet 2007;12(1):115-130 [FREE Full text] [Medline: 17680063]
24. Ramírez-Santana M, Zúñiga L, Corral S, Sandoval R, Scheepers PTJ, Van der Velden K, et al. Assessing biomarkers and neuropsychological outcomes in rural populations exposed to organophosphate pesticides in Chile--study design and protocol. BMC Public Health 2015 Feb 10;15:116 [FREE Full text] [doi: 10.1186/s12889-015-1463-5] [Medline: 25881174]
25. Mohanty MK, Behera BK, Jena SK, Srikanth S, Mogane C, Samal S, et al. Knowledge attitude and practice of pesticide use among agricultural workers in Puducherry, South India. J Forensic Leg Med 2013 Nov;20(8):1028-1031. [doi: 10.1016/j.jflm.2013.09.030] [Medline: 24237813]
26. Wesseling C, van Wendel de Joode B, Keifer M, London L, Mergler D, Stallones L. Symptoms of psychological distress and suicidal ideation among banana workers with a history of poisoning by organophosphate or n-methyl carbamate

pesticides. Occup Environ Med 2010 Nov;67(11):778-784 [FREE Full text] [doi: 10.1136/oem.2009.047266] [Medline: 20798019]
27. Wesseling C, Keifer M, Ahlbom A, McConnell R, Moon J, Rosenstock L, et al. Long-term neurobehavioral effects of mild poisonings with organophosphate and n-methyl carbamate pesticides among banana workers. Int J Occup Environ Health 2002;8(1):27-34. [doi: 10.1179/oeh.2002.8.1.27] [Medline: 11843437]
28. Wesseling C, Aragón A, Rojas M, Blanco L, López L, Soto A, et al. Efectos del clorpirifos en la salud de trabajadores bananeros de La Lima, Honduras. Heredia: SALTRA, IRET-UNA, CISTA, UNAN-León; 2006:1-56.
29. van Wendel de Joode B, Wesseling C, Kromhout H, Monge P, García M, Mergler D. Chronic nervous-system effects of long-term occupational exposure to DDT. Lancet 2001 Mar 31;357(9261):1014-1016. [doi: 10.1016/S0140-6736(00)04249-5] [Medline: 11293598]
30. Shennan C, Krupnik TJ, Baird G, Cohen H, Forbush K, Lovell RJ, et al. Organic and Conventional Agriculture: A Useful Framing? Annu Rev Environ Resour 2017 Oct 17;42(1):317-346. [doi: 10.1146/annurev-environ-110615-085750]
31. Costa C, García-Lestón J, Costa S, Coelho P, Silva S, Pingarilho M, et al. Is organic farming safer to farmers' health? A comparison between organic and traditional farming. Toxicol Lett 2014 Oct 15;230(2):166-176 [FREE Full text] [doi: 10.1016/j.toxlet.2014.02.011] [Medline: 24576785]
32. Ramírez F, Chaverri F, Fournier M, de la Cruz E, Bravo V, Echeverría S, et al. Las buenas prácticas agrícolas en el uso y manejo de agroquímicos en la zona hortícola de Zarcero, Alajuela. Informe de Avance de Primer Año. Heredia, Costa Rica: Instituto Regional de Estudios en Sustancias Tóxicas; 2016.
33. INEC Costa Rica. 2015. Proyecto VI Censo Nacional Agropecuario 2014 URL: http://www.inec.go.cr/sites/default/files/documentos/agropecuario/metodologias/documentos_metodologicos/meagropeccenagro2014-001.pdf [WebCite Cache ID 723rClMha]
34. Schaub N. Risk of pesticide input into a tropical stream due to spatial proximity and erosion - Case study in the Tapezco catchment (Costa Rica). Institute of Environmental Engineering, ETH Zürich 2016 MSc Thesis.
35. Open Data Kit. 2018. The standard for mobile data collection URL: https://opendatakit.org/ [accessed 2018-08-30] [WebCite Cache ID 723raIBjZ]
36. Neupane D, Jørs E, Brandt L. Pesticide use, erythrocyte acetylcholinesterase level and self-reported acute intoxication symptoms among vegetable farmers in Nepal: a cross-sectional study. Environ Health 2014 Nov 20;13:98 [FREE Full text] [doi: 10.1186/1476-069X-13-98] [Medline: 25409889]
37. Ekman E, Maxe M, Littorin M, Jönsson BAG, Lindh CH. High-throughput method for the analysis of ethylenethiourea with direct injection of hydrolysed urine using online on-column extraction liquid chromatography and triple quadrupole mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2013 Sep 01;934:53-59 [FREE Full text] [doi: 10.1016/j.jchromb.2013.06.035] [Medline: 23896430]
38. Ekman E, Faniband MH, Littorin M, Maxe M, Jönsson BAG, Lindh CH. Determination of 5-hydroxythiabendazole in human urine as a biomarker of exposure to thiabendazole using LC/MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2014 Dec 15;973C:61-67 [FREE Full text] [doi: 10.1016/j.jchromb.2014.10.003] [Medline: 25464096]
39. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ Health Perspect 2005 Feb;113(2):192-200 [FREE Full text] [doi: 10.1289/ehp.7337] [Medline: 15687057]
40. Eastman RR, Jursa TP, Benedetti C, Lucchini RG, Smith DR. Hair as a biomarker of environmental manganese exposure. Environ Sci Technol 2013 Feb 05;47(3):1629-1637 [FREE Full text] [doi: 10.1021/es3035297] [Medline: 23259818]
41. Menezes-Filho JA, Paes CR, Pontes AMDC, Moreira JC, Sarcinelli PN, Mergler D. High levels of hair manganese in children living in the vicinity of a ferro-manganese alloy production plant. Neurotoxicology 2009 Nov;30(6):1207-1213 [FREE Full text] [doi: 10.1016/j.neuro.2009.04.005] [Medline: 19393689]
42. Ayodele JT, Bayero AS. Manganese concentrations in hair and fingernail of some Kano inhabitants. J Appl Sci Environ Manag 2010;14(1). [doi: 10.4314/jasem.v14i1.56472]
43. Mehra R, Juneja M. Fingernails as biological indices of metal exposure. J Biosci 2005 Mar;30(2):253-257. [doi: 10.1007/BF02703706]
44. Rodezno RA, Lundberg I, Escalona E. Development of a questionnaire in spanish on neurotoxic symptoms. Am J Ind Med 1995 Oct;28(4):505-520. [doi: 10.1002/ajim.4700280407]
45. ECRHS. 2018. European Community Respiratory Health Survey URL: http://www.ecrhs.org/Quests.htm [accessed 2018-08-30] [WebCite Cache ID 723pw1cX4]
46. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994 May;7(5):954-960 [FREE Full text] [Medline: 8050554]
47. Fieten KB, Kromhout H, Heederik D, van Wendel de Joode B. Pesticide exposure and respiratory health of indigenous women in Costa Rica. Am J Epidemiol 2009 Jun 15;169(12):1500-1506. [doi: 10.1093/aje/kwp060] [Medline: 19372212]
48. Rodríguez-Zamora MG, Medina-Escobar L, Mora G, Zock J, van Wendel de Joode B, Mora AM. Dust exposure in workers from grain storage facilities in Costa Rica. Int J Hyg Environ Health 2017 Dec;220(6):1039-1045. [doi: 10.1016/j.ijheh.2017.06.002] [Medline: 28663028]

49. Rodríguez-Zamora MG, Zock J, van Wendel de Joode B, Mora AM. Respiratory Health Outcomes, Rhinitis, and Eczema in Workers from Grain Storage Facilities in Costa Rica. Ann Work Expo Health 2018 Nov 12;62(9):1077-1086. [doi: 10.1093/annweh/wxy068] [Medline: 30016387]
50. Ostroski-Solís P, Ardila A, Rosselli M. Neuropsi Evaluación Neuropsicológica. Mexico city: Universitad Nacional Autónoma de México; 1998.
51. Wechsler D. Manual for the Wechsler Adult Intelligence Scale. New York: Psychological Corporation; 1981.
52. Lewis R, Rennick P. Manual for the Repeatable Cognitive-Perceptual-Motor Battery. Grosse Point: Axon; 1979.
53. Reitan R. Neuropsychological Test Battery: Theory and Clinical Interpretation. Tucson: Neuropsychological Press; 1985.
54. Costa LD, Vaughan HGJ, Levita E, Farber N. Purdue Pegboard as a predictor of the presence and laterality of cerebral lesions. Journal of Consulting Psychology 1963;27(2):133-137. [doi: 10.1037/h0040737]
55. Derogatis L, Spencer P. The Brief Symptom Inventory: Administration, ScoringProcedures Manual I. Baltimore: John Hopkins University School of Medicine; 1982.
56. WHO. Neurobehavioral Core Test Battery: Operational Guide. Geneva: World Health Organization; 1986.
57. Baker JM, Rojas-Valverde D, Gutiérrez R, Winkler M, Fuhrimann S, Eskenazi B, et al. Portable Functional Neuroimaging as an Environmental Epidemiology Tool: A How-To Guide for the Use of fNIRS in Field Studies. Environ Health Perspect 2017 Dec 21;125(9):094502 [FREE Full text] [doi: 10.1289/EHP2049] [Medline: 28937962]
58. Cui X, Bray S, Bryant DM, Glover GH, Reiss AL. A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. Neuroimage 2011 Feb 14;54(4):2808-2821 [FREE Full text] [doi: 10.1016/j.neuroimage.2010.10.069] [Medline: 21047559]
59. Ehlis A, Bähne CG, Jacob CP, Herrmann MJ, Fallgatter AJ. Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study. J Psychiatr Res 2008 Oct;42(13):1060-1067. [doi: 10.1016/j.jpsychires.2007.11.011] [Medline: 18226818]
60. Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J Neurosci 2001 Oct 01;21(19):7733-7741 [FREE Full text] [Medline: 11567063]
61. EQM Research, Inc. 2003. Test-mate ChE Cholinesterase Test System (Model 400) URL: http://www.eqmresearch.com/Manual-E.pdf [accessed 2018-11-14] [WebCite Cache ID 73urQFt0E]
62. Lubin JH, Colt JS, Camann D, Davis S, Cerhan JR, Severson RK, et al. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ Health Perspect 2004 Dec 13;112(17):1691-1696 [FREE Full text] [doi: 10.1289/ehp.7199] [Medline: 15579415]
63. 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]

Abbreviations

3-PBA: 3-phenoxybenzoic acid
AChE: acetylcholinesterase
fNIRS: functional near-infrared spectroscopy
GPS: global positioning system
ICC: intraclass correlation coefficient
LOD: limit of detection
LMICs: low- and middle-income countries
Mn: manganese
TCP: 3,5,6-trichloropyridinol

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Original Paper

The Table to Tablet (T2T) Speech and Language Therapy Software Development Roadmap

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Abstract

Background: Few studies have analyzed gains in using computers in speech and language therapy interventions for children with speech and/or language disorders when compared to a control group, but virtual tutors and computer-based visual feedback have been gaining interest in the literature. Previous systematic reviews mainly focused on development technological details of computer-based speech training systems or the potential of integrating mobile technology into education and rehabilitation, but recent systematic reviews have also evaluated the efficacy of computer-based speech and language therapy for children and how digital technology can support different activities, at school or elsewhere.

Objective: This study aimed to analyze a continuous communication and joint team approach to develop solutions focused on the real needs of end users, which digitally emulate reliable and validated physical intervention materials for children with speech sound disorders (SSD).

Methods: The Table to Tablet (T2T) software was developed using a design-based research methodology, which included four phases: activities development; ethnographic pretesting with a sample from the target population; software development; and beta-testing. The technology used to develop the software, the method used to ensure satisfaction and replay ability of the intervention materials, and results from the ethnographic and beta-testing phases are presented.

Results: Nineteen activities were developed during the first phase, which were then tested, with 7 service users, using a physical prototype. The beta-test approach included extensive testing and reformulation, supported by direct, nonparticipant observation and data collection using a questionnaire designed for children. Feedback was used to improve the software and interaction with users.

Conclusions: The use of T2T-based intervention programmes by speech and language therapists (SLTs) will allow these professionals to make a better and more effective communication intervention, based on proven methodologies, that coexists in a structured physical and a digital version. These versions provide a full, 6-week intervention program, with minimal effort in preparing the session by the SLTs while delivering a very consistent intervention, with high replay value. A continuous communication and joint team approach was beneficial to the project and to the development of a solution focused on the real needs of SLTs and children with SSD. All problems were approached as a team with different skills and expertise, which minimized errors (eg, the developer making choices that would save him from spending time doing something that would not be used) and time spent. To add to this, the importance of integrating the end users as testers and collecting their opinions and actions per session allowed the production of better-targeted activities.

Trial Registration: ClinicalTrials.gov NCT02490826; https://clinicaltrials.gov/ct2/show/NCT02490826

(JMIR Res Protoc 2019;8(1):e11596) doi:10.2196/11596

KEYWORDS

software; tablets; children; speech sound disorders; design-based research

Introduction

Background

Children with speech sound disorders (SSD) represent 40% to 90% of pediatric caseloads [1-3]. They present gaps in their speech sound systems that might cause difficulties in producing or understanding speech sounds [4,5]. They can have substitution errors, syllable structure errors, speech sounds distortions, and atypical prosody [4].

A previous paper [2] explored through a Web-based survey the most common intervention strategies used by speech and language therapists (SLTs) to treat children with SSD, concluding that these included auditory bombardment, hearing and discriminating, grapheme-phoneme correspondence, phoneme identity, segmentation, blending, rhyme, and phoneme manipulation. On the basis of these results, a randomized controlled study was conducted [6] to test the efficiency and efficacy of using a combination of these intervention strategies. This approach (a combination of expressive phonological tasks, phonological awareness, and listening and discrimination activities) [6], based on a physical set of activities (tabletop), was shown to be an effective integrated method of treating children with SSD.

Few studies [7-11] analyzed gains in using computers in speech and language therapy intervention for children with speech and language disorders, when compared with a control group, but virtual tutors and computer-based visual feedback have been gaining interest in the literature [12-18]. Previous systematic reviews have mainly focused on the development of technological details of computer-based speech training systems [14,19] or the potential of integrating mobile technology into education and rehabilitation [16,20]; however, recent systematic reviews [21] have also evaluated the efficacy of computer-based speech and language therapy for children with SSD and how digital technology can support different activities, at school or elsewhere [22]. Furlong et al [21] concluded that there were only 14 studies, with small sample sizes and study qualities from moderate to low. They highlighted the importance of collaboration between software developers, designers, and SLTs in developing computer-based interventions and recognized the "rising popularity of mobile applications" [21]. They also concluded that "it is not possible to determine whether results are attributable to intervention or maturation" [21] without a control group.

This paper builds on this previous research [2,6,23,24], by digitally emulating the previously described tabletop approach, which was shown [6] to be a valid framework of intervention materials for children with SSD.

The Table to Tablet Software Intervention Framework

This paper details the development roadmap of the digital version of a novel intervention framework for SLTs named *Table to Tablet* (*T2T*) and how it digitally emulates its physical counterpart, the technology used to develop the software, the methods used to ensure consistency of the intervention materials, and the feedback and results from an ethnographic approach and beta testing. The development framework and the main outcomes of each stage are highlighted in Figure 1.

Our long-term goals are to improve interaction and functionality of software, with more languages offered, different activities to address various areas of speech and language therapy or language acquisition, creation of an easy-to-use database that can be accessed by STLs, and developing digital homework for the children. Regular homework is recommended for maximizing progress [25]. Since the *T2T* software aims to emulate a physical framework of intervention materials for children with SSD, SLTs will be able to seamlessly swap between physical and digital materials, without compromising the efficiency and efficacy of their intervention strategies.

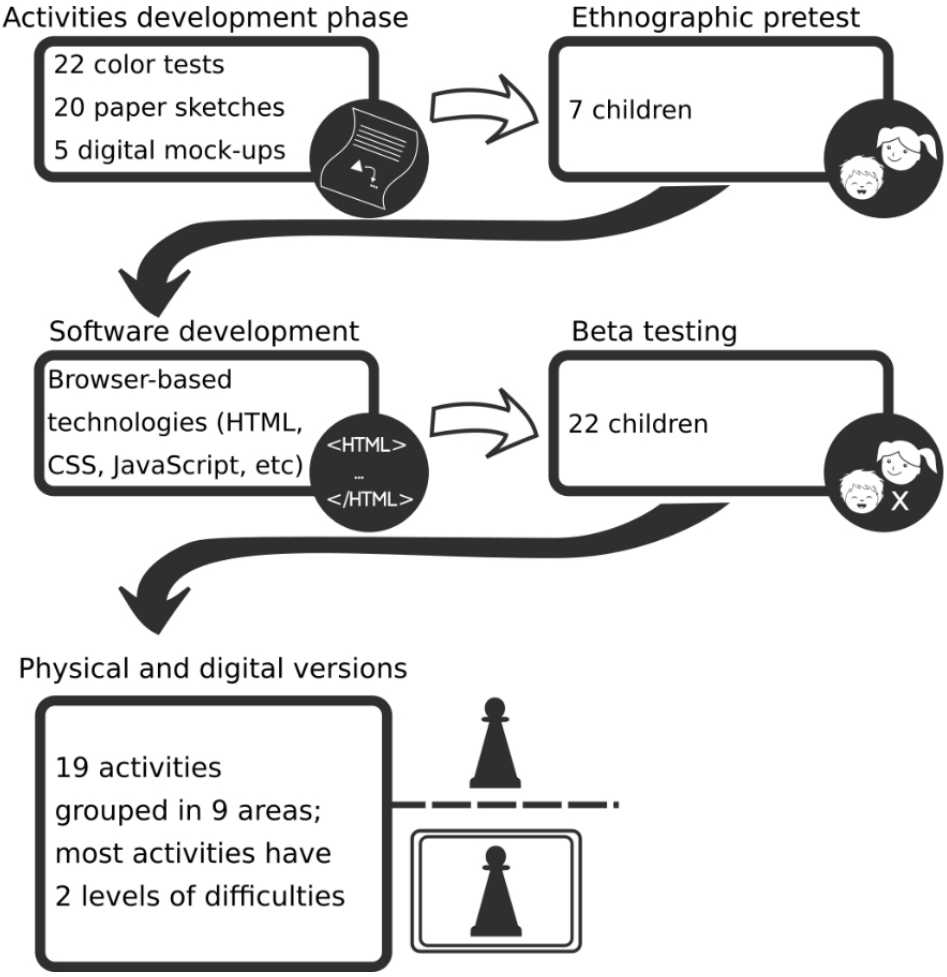
To better understand the market needs, a competitor analysis [26] was conducted. Results showed that there are some off-the-shelf tabletop (eg, board games or physical objects) and digital materials that can be used by SLTs to support the intervention, but they are not widely distributed in some countries, and more importantly, their efficiency has not been tested. Bowen [4] concludes that there is a gap between the technological development and the increase in evidence that technology can enhance intervention outcomes.

However, children nowadays live in an environment surrounded by electronic devices, computers, mobile phones smartphones, and other technologies that change their interactions and learning preferences [27]. To adapt to this new paradigm, SLTs need to innovate and expand the strategies and activities to better suit the interests of today's children. The use of software is one commonly adopted solution [28]. A computer game–based approach in teaching and learning can be an effective tool to promote and enhance learning experiences and children's motivation [29].

SLTs mostly provide individual treatment to children, and the intervention can occur in different contexts: hospitals, clinics, kindergartens, or schools. This usually implies carrying large quantities of intervention materials (such as board games, puppets, and other materials) or alternatively [4], just carry 1 device loaded with specific apps, targeted at SLTs' needs. These apps have, however, varying efficacies [4,21]. The intervention usually takes place once a week, over a period exceeding 6 months [2].

Game activities help the child develop various skills such as visual intelligence, problem solving, and creativity [30]. Another advantage is that intervening with the aid of a computer can be disguised as *gaming time*, thus presenting additional opportunities for learning [31]. The use of these activities provides a selective and individualized therapeutic approach, while being very motivating for children and even for SLTs [32].

Figure 1. The Table to Table to Tablet (T2T) development roadmap. CSS: cascading style sheets.



Computer-Based Speech and Language Therapy Technological Requirements

Tablets are gaining ground over laptops/desktops because of their tactile nature, which is closer to user reality [33,34], and their mobility, dissemination, and growing popularity [35,36]. However, these devices have different operating systems or variations of them, screen sizes, and resolutions. A "write once, run anywhere" (slogan coined by *Sun Microsystems*) mind-set is, therefore, deemed necessary when developing software for tablets. An 8-inch tablet screen size allows the device to be easily held by a child, while having the necessary dimension as to not strain the user's eyes. Moreover, the current worldwide market share of small size (7-9 inch) screen tablets is by far the largest (around 55% according to a study [37]). Tablet-based intervention activities need to be run online or offline, the latter being a necessity due to the variety of locations where a speech and language therapy session might occur (ie, no guaranteed internet or cell phone connectivity at sessions or at the user's household).

The requirements of T2T software were to work nearly identically across all platforms currently available and has the following advantages over more traditional table-based therapy materials: more durable (no wear and tear), reduced preparation time, better organization (all activities and images in one place), easier to carry, and cheaper than a physical version.

Purpose

The purpose of this paper is to document the *T2T* software development roadmap and its implicit joint-team approach. Early studies [6] on the development of intervention approaches for children with SSD were mainly conducted by SLTs. However, the technology evolution and the needs from the users are constantly changing; therefore, multidisciplinary teams are needed [21]. We aim to assess the outcomes of having such teams (as described in the study by Furlong et al [21]) involved in the development and testing processes.

Using a design-based research (DBR) methodology, 4 phases of development and joint collaboration were defined: activities development, ethnographic pretest (with sample from target population), software development, and beta test. Choices and technical aspects behind the *T2T* software, the technology used to develop the software, the method used to ensure satisfaction and replay ability of the intervention materials, and the results of the ethnographic phase and beta test phase are also included.

Methods

The Design-Based Research (DBR) Method

There are several software development methods, from the most traditional approach of the waterfall method to the newest Scrum approach, all with their pros and cons. Similarly, there are several design methods, with different focus, advantages, and

disadvantages. However, their value and significance has to be considered in the context of this particular project's objective, that is, the development of a speech and language therapy intervention tool for children with SSD, with a physical and a digital stand-alone component, based on a multidisciplinary team with very different backgrounds. Both the physical and the digital components had to mimic each other perfectly to avoid any skewing factor. We, therefore, sought a method that is well suited for the creation of prototypes.

DBR, the chosen methodology, is capable of producing 2 nonexclusive outputs [38]: the theoretical and the practical outcomes. The DBR model starts from a complex and real problem (in this case children's SSD and the needs of a digital validated intervention software) and follows an iterative process going back and forth between developing, testing, and rethinking. Therefore, there is a practical outcome (the *T2T* software) and a theoretical contribution (eg, a previous publication [39] focusing on the impact of the service delivery during this project and the current paper produced during this project). The constant iteration and user feedback gathered using the DBR method facilitates an experience akin to the users being cocreators and allows for faster prototype development and more tests.

As previously mentioned, before software development, data to inform the design of intervention materials were collected from end users (SLTs), through an online survey [2]. A combination of the most common intervention strategies reported by the SLTs that participated in our previous study [2], were later [6] shown to be effective when presented in a physical format (tabletop). An emulation of these activities (previously tested in the study by Lousada et al [6]) was the basis for the development of the *T2T* software that went through 4 distinct phases: activities development; ethnographic pretesting with a sample from the target population; software development; and beta testing. Since the DBR method was being used, these 4 distinct phases were iterated more than once, until the final product was deemed stable/finalized. The software development and beta testing phases, in particular, produced several iterations.

Activities Development Phase

During this phase, the research and development team (a speech scientist, 2 SLTs, 2 software developers, and a designer) analyzed traditional/conventional tabletop activities, materials and theories reported in the study by Lousada et al [6], and discussed how they could be implemented in both environments (physical and software). The word "activities" refers to the exercises done by children, with the direct supervision of an SLT that are the basis of interventions for children with SSD. They usually consist of traditional games, for example, a puzzle adapted to achieve a certain therapy goal. In the case of a puzzle, a certain target word can be elicited by showing images related to it and if the child is able to correctly produce the word, he/she can place a piece in the puzzle.

One important issue the team had to tackle was the screen dimensions versus real-world tabletop dimensions. Everything had to be seamless and consistent across media. Low- and high-fidelity prototyping was used to develop 22 color tests, approximately 20 paper sketches, and 5 digital mock-ups. This planning and mock-up building phase allowed the sketching/drafting of several activities for the various intervention areas.

The *T2T* intervention software includes 19 different activities, grouped in 9 areas, namely auditory bombardment, hearing and discriminating, grapheme-phoneme correspondence, phoneme identity, segmentation, blending, rhyme, phoneme manipulation, and generalization task.

The activities combine tasks of phonological expression, phonological awareness, listening, and discrimination that have been shown to be an effective integrated method to remediate SSD [6,23]. Most of the activities have 2 levels of difficulty differentiated by the inclusion or absence of the written word. For each problem addressed, a list of 15 words was selected. Furthermore, as facilitator sounds, 5 contrasting sounds (easily produced by the children) were used, and 10 words where these sounds occur were selected. Furthermore, 18 short stories that used 20 words with the target sound were also created.

Each target word was illustrated by a professional designer, resulting in a total of 335 illustrations. A specific background image was also created (by the same designer) for each short story. The lettering used for all the materials used the Verdana font due to previously published research evidence [40,41] showing that children read and search texts more quickly using this font. Additional graphic materials (for the graphic user interface) were also developed and over 950 sound productions were recorded.

Ethnographic Pretest

Ethnography is a qualitative research method used in human-centered design [42,43] to expose opinions and concepts from groups of people [44]. In this phase, the physical tabletop materials were built and pretested in a sample of the target population. The team opted to use the physical materials first because they would allow them to determine the actual needs, what content to include, and what data to gather. The pretest sample consisted of 7 children, 4 girls and 3 boys, with an age range from 48 to 67 months (mean 57.5 months), all diagnosed with SSD. All ethical procedures were ensured, and informed consent was collected from all carers before any data collection. The testing consisted of 6 sessions based on the materials and predefined activities, with constant monitoring and feedback gathering by an SLT acting as a participant observer (the SLT would record notes during or after session but also engage in the activities with the child) as befits the ethnographic approach. This is particularly difficult in children with SSD because they might struggle to communicate, and sometimes, the speech they produce is difficult to understand [4].

To ensure consistency, validity, minimize errors, and man power costs of the software developed [45], 2 testing periods were conducted: alpha testing, during this pretest ethnographic phase and beta testing on our fourth development phase. An alpha test is the process of testing for the first time, in-house, newly developed hardware or software [46]. In the *T2T* case, the alpha test was conducted using a physical version to ascertain the feasibility of our activities and to ensure that the SLTs' needs were correctly interpreted. The testers were the research and

development team (6 members) and a sample from the target population (7 users), during our second phase. These 7 testers were from a kindergarten in the university campus, minimizing the time spent on trips and allowing for greater control of all variables involved in the sessions.

The feedback and observation allowed the team to modify or even create new activities and validate the intervention materials and techniques. With that information, the team was able to create simplified flowcharts for the software, and the first versions of different tablet-based activities were designed.

Software Development

This development phase started concurrently with the ethnographic pretest phase. To be able to meet the requirements and be platform agnostic, the hybrid app approach was used. Browser-based technologies were used to develop the *T2T* framework so that it would be scalable, faster to develop, and cost/time effective. Hybrid apps are primarily built using HTML, CSS, and JavaScript, which is then wrapped inside a thin native container that provides access to native platform features [47]. The outcome is an .apk file that can be published in an *App Store* and the user can easily install.

The *T2T* software extensively uses HTML5, CSS, JSON, and JavaScript (Phaser framework) [48] as the building blocks of activities. To ensure cross-platform mobile versatility, we used the command line Apache Cordova as a code wrapper for the mobile environment with the Crosswalk plugin to enable cutting-edge HTML5 browser features on the devices. At the moment, user choices regarding sounds and activities are stored and retrieved using HTML5 local storage. In future versions, we plan to use a custom nonrelational database (such as MongoDB) that will store these data and other deemed necessary for the STLs' appraisal of adherence to therapy [49] whenever the device connects to the internet.

Care with expensive processes or requests have been addressed. For example, to avoid several requests to a server (for the online version) we opted to use sprite sheets (collections of static 2D drawings that depict representative poses [50]) that condense figures and textures, as shown in Figure 2. As the development is multi-device ready, the maximum image size was carefully controlled. To be on the safe side, and according to existing metrics [51], we used images with a maximum dimension of 2048×2048 pixels, which a device with as little as 256 MB RAM can still use.

Figure 2. Sprite sheet sub for the Munching Monsters activity.

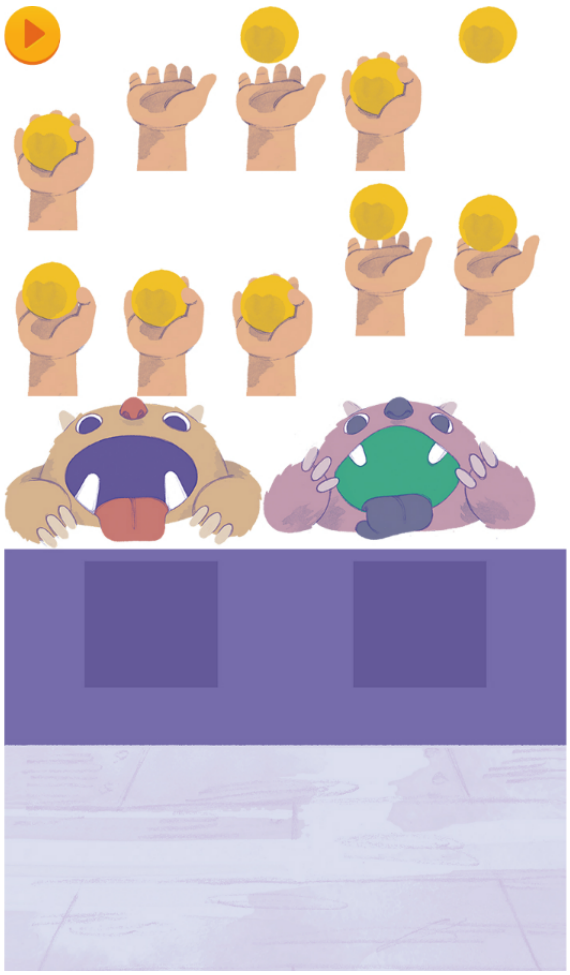


Figure 3. The "smileyometers": Left (question 1 and question 2); right (question 3).

Since different screen dimensions had to be addressed, relative positioning of elements on screen using the dimensions of the Window in *innerWidth* (x) or *innerHeight* (y) as values was used. The *innerWidth* property returns the inner width of a window's content area. The *innerHeight* property returns the inner height of a window's content area. Due to different screen resolutions (eg, Apple Retina, Android Super Amoled, or liquid crystal display), one cannot assume a simple measurement of the window of the device as the size of the active area we can use as these screen technologies increase the number of pixels (or rather subpixels) per inch, improving the resolution. This results in different looks for the same activity, depending on the device characteristics, since a 300×300 pixels object in a device with a device pixel ratio (DPR) of 2 will look like it has 150×150 pixels. Therefore, "in game" scaling was implemented using a constant variable, which is the ratio of the vertical size of 1 pixel on the current display device to the size of 1 device independent pixel [52], divided by the highest DPR we expect the device to support [53].

Beta Testing

Beta testing involves releasing and testing a software version with limited functionality to a group of the target users [54], without the participation of the developers in the test [55]. It can be divided into 5 stages [56]: (1) requirements analysis, (2) testing procedures, (3) reporting systems, (4) defect analysis and retesting, and (5) closure. Beta testing allows to extensively test the software, find bugs, and collect requirements and suggestions of end users [57]. However, these design principles, originally formulated for adults, cannot be scaled down for children due to their own particular needs and goals, which are not necessarily met by tools designed for adults [58]. Therefore, an adapted (in terms of their procedures and reporting systems steps) beta test approach was used to obtain feedback from the users.

We selected qualified participants (who have the characteristics of target population), specified test procedures and schedules, and planned specific roles [56]. Despite having a hypothesis and an expected outcome, we could only ascertain their validity after a set of sessions with the children. The beta testers were 22 children. Their ages were between 42 months and 78 months. The *T2T* materials were tested in 12 weekly individual therapy sessions, 45 min each.

The equipment used in sessions was an Asus Memo Pad 8, with an 8-inch Wide Extended Graphics Array screen, 1 GB memory, Quad-core 1.33 GHz processor, and weighting approximately 320 grams. It was running the *T2T* software as a native offline app.

A similar data gathering approach to the one used during the second phase was used, with the SLT taking extensive notes during each session. Questionnaires based on "smileyometers" [59], as shown in Figure 3, were also used. The following questions were asked to the children: Did you like to play this game? (like factor); Was it fun? (fun factor); and Would you play it again? (play again factor). The possible answers to the first question were as follows: 1–I did not; 2–A little; 3–Liked, 4–Liked a lot; and 5–Loved it. For the second question, they were as follows: 1–No; 2–Not much fun; 3–Some fun; 4–Fun; and 5–A lot of fun. For the third question, children could answer 1–Yes; 2–Maybe; and 3–No.

Direct observation of the children was structured around 3 areas (what were we looking for, who did it, and how did we do it), that is, looking at how children behaved, annotating their interactions with the app, and how one could improve this interaction.

During this phase, several bugs were found and corrected, the interaction design was refined to better suit the users' touch screen capabilities [60], and some illustrations and sound files were improved or recreated. Sound was also exported from the original uncompressed .wav files as .mp3 and .ogg, to cover both Android [61] and Apple [62] operating systems.

Special care was devoted to the audio quality, since adherence to therapy is influenced by audio feedback, and model speech sounds have been shown to be a requirement in speech and language therapy [34]. Sound recordings took place in a cabin, produced by Absorsor, Portugal, with sound reduction of 45dB, located at University of Aveiro's Speech, Language and Hearing Laboratory. Speech samples used for auditory feedback were all based on audio recordings of the same certified SLT (the third author of this paper), involved in *T2T* software development. The participant was sitting comfortably at a distance of about 30 cm, in front of an MKH20-P48 omnidirectional condenser microphone (Sennheiser, Germany) connected to a Scarlett 6i6 audio interface (Focusrite, UK) using a Gold Edition XLR Microphone cable (Mogami, USA). The recordings were made with Adobe Audition 3.0, at a sampling rate of 48,000 Hz, with 16 bits per sample, using the Focusrite Universal Serial Bus 2.0 ASIO Driver Audio Driver 1.8. The data were recorded in mono format .wav (Windows PCM) without compression. Raw audio recordings were manually segmented into around 955 individual .wav files with *Audacity 2.1.2* (Audacity Team).

Results

Activities Development Phase

Flowcharts (see Figure 4) depicting the thought/activity process that resulted from the direct cooperation between the 6 members of the research team were initially produced for all activity areas. These flowcharts were the basis for the first version all computer-based activities, which then entered the beta testing phase.

Figure 4. Simplified flowchart. SLT: speech and language therapist.

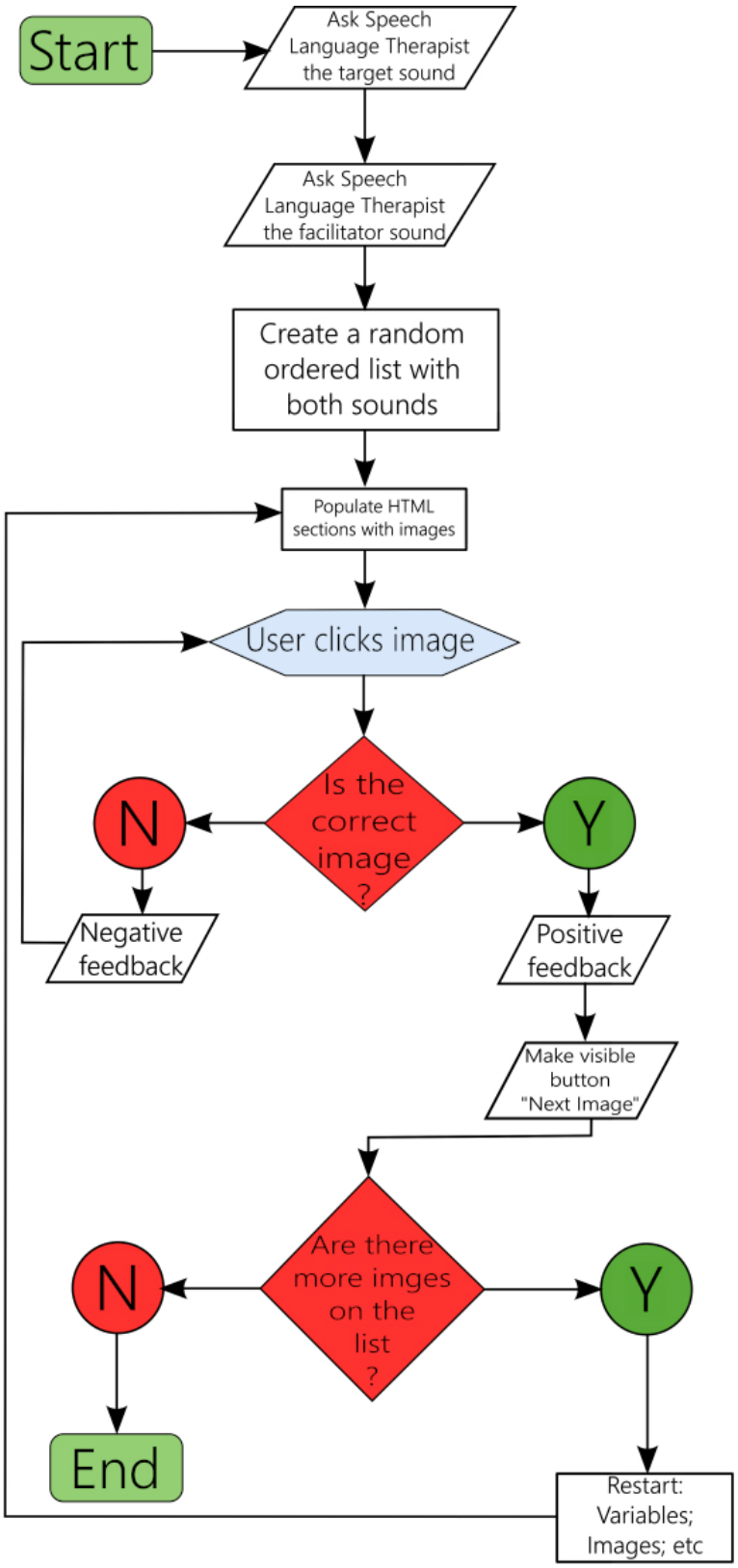


Figure 5 presents an example of the first level of 1 activity of the grapheme-phoneme correspondence area. In this activity, the child must associate the grapheme to its sound in the word: the letter <S> has to be associated with the sound produced at the beginning of the word <sofa> (“couch”), excluding options available in the other 2 pictures. The child will then have a visual and audio feedback. Figure 5 also shows how the app evolved for this activity.

The main menu of the app (shown in Figure 6) shows a list of 9 areas of activities. A help area (mimicking a bent sheet of

paper corner) is always present on the same location, independent of the screen or the area chosen. Inside it, there is a button to return to the home screen and a button to close the help area and resume the activity. The information presented is contextual. When the user chooses an area, 1 to 4 different activities might be found inside the area. Most of these activities have 2 difficulty levels, depending on the existence (level 1) or not (level 2) of a written word along with the recorded sound. The user first chooses 1 activity and then the difficulty level and is taken into a different screen with 9 possible problems (phonological processes) that can be targeted during the activity. After choosing the phonological process in which they aim to intervene, they go to a last panel before the actual activity (an example of an activity is shown in Figure 6). In this panel, they see a visual summary of their choices so far and can select the facilitating phonemes, minimal-pairs words, or rhymes, depending on the activity. Facilitating phonemes are those that the children can produce and should be able to differentiate. This allows an extensive customization of the activities. In this page, as well as in the previous pages, they always have the possibility of going back one step or back to the home screen.

After completing the process referred above, the activity starts (see Figure 6) and the SLT can intervene with the child. After a preset number of times, the activity will stop and the app returns to the home screen. During play, the SLT can read the instructions of the activity, can interact freely with the child, or rely on the app to produce most of the verbal feedback. The sounds can be played as many times as the child or the SLT deem necessary, and moving on to the next set of stimuli depends on the completion of the task.

Ethnographic Pretest and Software Development

The activities' development phase produced 19 activities (see Figure 5 for an example of an activity resulting from this phase); the ethnographic phase involved 7 testers; the software development phase included the activities' development for mobile and desktop (Web) environments; and during the beta-test approach, phase extensive testing and reformulation was supported by direct, nonparticipant observation and a questionnaire adapted to children (with "smileyometer").

Beta Testing

Feedback regarding the activities was registered as part of the beta testing procedures of defect analysis and retesting. Detailed results for the tested activities are presented in Table 1. Due to the iterative nature of the method used, at the time of testing, 4 activities were in the process of being redesigned; therefore, no feedback from the original group of children was collected.

Figure 5. The evolution of the Match activity from the end of second development phase to beta testing. From less buttons and more dependent on the speech and language therapist (left) to less clutter on screen, bigger buttons to accommodate users with less touch screen capacities (middle), and more interactivity in terms of sound production and audiovisual feedback when the user completes an action (right).

Figure 6. The main menu (left) and the Munching Monsters activity (right): area: hearing and discrimination; name: Munching Monsters; description: The child is presented with 2 open-mouth monsters each associated with an illustration of a minimal pair. At the bottom of the screen, there is a hand with a ball moving sideways. When "Play" is pressed, 1 of 2 possible words is heard. The child has to identify the corresponding image and release the ball with the right timing (into the mouth of the monsters). Digital audio feedback is given.

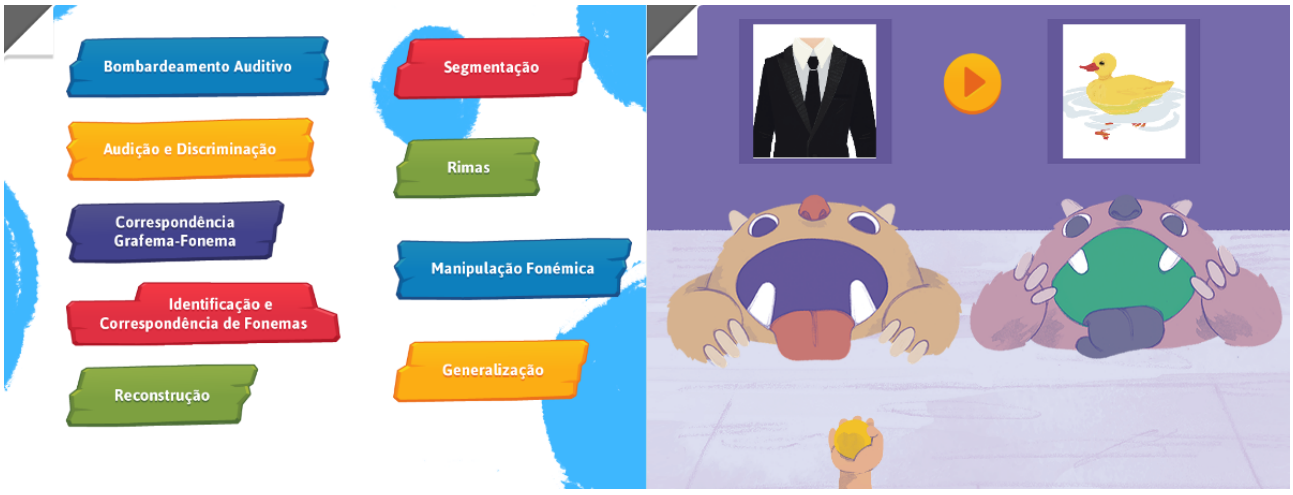


Table 1. Children's feedback. The "smileyometers" have been converted to a 5-point Likert scale (question 1 and question 2)–possible integer values ranging from 1 to 5 and a 3-point Likert scale (question 3)–possible integer values ranging from 1 to 3.

Activity	Like, mean (SD)	Fun, mean (SD)	Play again, mean (SD)
Phoneme Tales	4.29 (1.03)	3.71 (1.28)	1.57 (0.73)
Listen and Build	4.86 (0.35)	4.43 (0.73)	1.00 (0.00)
Let's Throw the Ball	5.00 (0.00)	4.43 (0.73)	1.00 (0.00)
Munching Monsters	5.00 (0.00)	4.86 (035)	1.00 (0.00)
Choose Well	4.43 (0.49)	4.43 (0.73)	1.14 (0.35)
Let's Fish	4.86 (0.35)	4.86 (0.35)	1.00 (0.00)
Colouring Time 1	4.14 (1.12)	4.00 (1.07)	1.43 (0.49)
Colouring Time 2	4.29 (0.88)	4.14 (0.83)	1.57 (0.90)
Match	4.43 (0.73)	4.43 (0.64)	1.14 (0.49)
The Hungry Monster	4.43 (0.73)	4.14 (0.64)	1.43 (0.49)
You Have Mail	5.00 (0.00)	4.71 (0.45)	1.00 (0.00)
Find the Pairs	4.71 (0.45)	4.43 (0.49)	1.14 (0.35)
Blend and Discover	3.71 (0.88)	3.57 (0.90)	1.14 (0.35)
Sweet Tooth Bear	4.71 (0.45)	4.29 (0.88)	1.14 (0.35)

They were, however, tested later on, with a distinct group of children. We believe this would have introduced an additional confounding factor; therefore, we only report results from the same group. Moreover, 1 activity was not tested (the nineteenth activity) because it results in simple "yes-no" answers. Children are shown images (that before intervention they had difficulties in discriminating), and they should be able to produce the correct word elicited by them. If not, it is likely that further therapy is needed.

The activity *Colouring Time 1* was readjusted due to children's lack of motivation to paint large areas. Results show that, overall, children "Liked a lot" all the activities except the *Blend and Discover* with a mean score of 3.71 (the lowest score of all). It should be noted that this activity is one of the least ludic so this factor could influence the children's feedback. Regarding the fun factor, children's overall feedback was "Fun" except for 2 activities: *Phoneme Tales* and *Blend and Discover*. Concerning the replay value (play again factor), there were 10 activities children would play again and 4 that did not present the same unanimity of feedback. *Phoneme Tales* and *Coloring Time 2* presented the least replay value. The similarity between *Coloring Time 1* and *Coloring Time 2*, and the fact that some children did not enjoy painting might have skewed our results.

High levels of satisfaction (question 1 average of 4.6 and SD of 0.5) were observed across the activities, with children liking the activities and finding them fun (question 2 average of 4.3 and SD of 0.7). When asked if they wanted to play them again (question 3 average of 1.2 and SD of 0.3), the result was yes. When combining the results of the Likert scale plus the direct observation in a qualitative fashion, the team was able to perceive some areas of enhancement.

Feedback was used to improve the software and interaction of the users with it [59]. All the code and design (graphic user interface and other elements) went through several iterations, constant optimization, and improvement over the years, and the joint team approach plus the constant data gathering improved several key areas of the app and/or the activities. For example, an activity called *Munching Monsters* had 3 major changes. The first design consisted of 2 pyramids of cans, each with an associated word that the child could try to knock over with a ball. The cans falling on the ground, the commotion, and noise generated proved (as a physical activity) to be too distracting. It was reformulated to 2 open-mouthed monsters, each with an associated word, and the child had to try to throw the ball into the monster's mouth. As a digital app, a hand would be moving from left to right continuously, holding a ball, as shown in Figure 2. After hearing the word to discriminate, the child would tap the corresponding monster to throw the ball. It was observed that the child would try to do a sliding motion toward the monster or tap the hand. The final revision changed the behavior to tapping on the hand.

Discussion

Principal Findings

Different professionals, such as SLTs, kindergarten teachers, or psychologists, need materials that support their interventions. The most common type of materials is still pencil and paper, or card and board games–based, but in an era of technology, it is increasingly common to use tablets and other digital media. However, there are still few apps valid and adapted for languages other than English that allow intervention.

The *T2T* materials have been tested, built, and scientifically validated by a team with great expertise in the areas of speech and hearing sciences, mobile app development, and illustration. The use of *T2T*-based intervention programs by SLTs will allow these professionals to make a better and more effective communication intervention, based on proven methodologies that coexist in a structured physical and a digital version. These

versions provide a full, 6-week intervention program, with minimal effort in preparing the session by the SLTs while delivering a very consistent intervention, with high replay value (as can be seen in Table 1).

A continuous communication and joint team approach was beneficial to the project and to the development of a solution focused on the real needs of SLTs and children with SSD. All problems were approached as a team with different skills and expertise, which minimized errors (eg, the developer making choices that would save him from spending time doing something that would not be used), and time spent. In addition, the importance of integrating the end users as testers and collecting their opinions and actions per session allowed the production of better-targeted activities.

The fact that the "smileyometer" scale used was not balanced in terms of presenting more perceived smiling faces than frowning ones might have biased the results. This feedback-gathering strategy should have been used on a larger sample of children. As the scale was applied by the therapist, it might have influenced the results.

The Web-based approach that allows to write the software once and deploy it across multiple operating systems and devices minimizes time and resources spent while facilitating the use of a natural interaction by the users with a touch capable device. Tablet-based therapy has an added benefit of portability, and the *T2T* app reduces the time spent preparing the sessions, translating in more time for the children.

Future Work

A Web-based survey that has just been completed in Portugal using snowball sampling, showed that 96% of the total sample (N=101 that corresponds to 5% of the Portuguese SLTs) wanted to have more speech and language therapy apps available. In total, 56% (57/101) of respondents were Android users, 30% were iOS users, and 12% windows users, with the remaining 2% using more than 1 operating system. To meet this need, a new start-up company that aims to study, create, develop, and validate digital support materials for professionals working with communication is currently being developed. The aim is to develop specialized, economical, portable, multiplatform material that is able to work online and offline. The core product of this company will be the *T2T* software that is ready for commercialization, having been validated with a group of children proving its effectiveness.

Future studies that gather qualitative feedback regarding user experience and user interaction should rely on someone else besides the therapist to collect the data. The method proposed in this paper could be applied to other activities and materials not yet tested, such as traditional speech and language therapy physical materials or digital educational apps currently available.

Specifically concerning the *T2T* app, future research will improve interaction and functionality of the software, with more languages being offered and the creation of logs with scores and assorted data deemed necessary for the SLTs to better document a child's evolution throughout intervention. Children's feedback in designing new activities should continue to be encouraged. The creation of homework with gamification aspects that can appeal to a child to play and learn, while sending data to the SLTs in a secure way, has been considered as a much-needed companion to the *T2T* software. The first prototypes of 4 games are currently being tested.

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Conflicts of Interest

None declared.

References

1. Mcleod S, Baker E. Speech-language pathologists' practices regarding assessment, analysis, target selection, intervention, and service delivery for children with speech sound disorders. Clin Linguist Phon 2014;28(7-8):508-531. [doi: 10.3109/02699206.2014.926994] [Medline: 25000375]
2. Oliveira C, Lousada M, Jesus LM. The clinical practice of speech and language therapists with children with phonologically based speech sound disorders. Child Lang Teach Ther 2014;31(2):173-194. [doi: 10.1177/0265659014550420]
3. Joffe V, Pring T. Children with phonological problems: a survey of clinical practice. Int J Lang Commun Disord 2008;43(2):154-164. [doi: 10.1080/13682820701660259] [Medline: 18283595]
4. Bowen C. Children's Speech Sound Disorders (2nd edition). Oxford: Wiley-Blackwell; 2015.
5. Dodd B, Holm A, Hua Z, Crosbie S. Phonological development: a normative study of British English ‐ speaking children. Clin Linguist Phon 2009;17(8):617-643. [doi: 10.1080/0269920031000111348]
6. Lousada M, Jesus LM, Capelas S, Margaça C, Simões D, Valente A, et al. Phonological and articulation treatment approaches in Portuguese children with speech and language impairments: a randomized controlled intervention study. Int J Lang Commun Disord 2013;48(2):172-187. [doi: 10.1111/j.1460-6984.2012.00191.x] [Medline: 23472957]

7. Arends N, Povel DJ, van Os E, Michielsen S, Claassen J, Feiter I. An evaluation of the Visual Speech Apparatus. Speech Commun 1991;10(4):405-414. [doi: 10.1016/0167-6393(91)90007-G]
8. Ruscello DM, Cartwright LR, Haines KB, Shuster LI. The use of different service delivery models for children with phonological disorders. J Commun Disord 1993;26(3):193-203. [Medline: 8227504]
9. Rvachew S, Nowak M, Cloutier G. Effect of phonemic perception training on the speech production and phonological awareness skills of children with expressive phonological delay. Am J Speech Lang Pathol 2004;13(3):250-263. [doi: 10.1044/1058-0360(2004/026)]
10. Wren Y, Roulstone S. A comparison between computer and tabletop delivery of phonology therapy. Int J Speech Lang Pathol 2008;10(5):346-363. [doi: 10.1080/17549500701873920] [Medline: 20840034]
11. McLeod S, Baker E, McCormack J, Wren Y, Roulstone S, Crowe K, et al. Cluster-randomized controlled trial evaluating the effectiveness of computer-assisted intervention delivered by educators for children with speech sound disorders. J Speech Lang Hear Res 2017;60(7):1891-1910. [doi: 10.1044/2017_JSLHR-S-16-0385] [Medline: 28672376]
12. Saz O, Yin S, Lleida E, Rose R, Vaquero C, Rodríguez WR. Tools and technologies for computer-aided speech and language therapy. Speech Commun 2009;51(10):948-967. [doi: 10.1016/j.specom.2009.04.006]
13. Popovici D, Buică-Belciu C. Professional challenges in computer-assisted speech therapy. Procedia - Social and Behavioral Sciences 2012;33:518-522. [doi: 10.1016/j.sbspro.2012.01.175]
14. Ramdoss S, Lang R, Mulloy A, Franco J, O'Reilly M, Didden R, et al. Use of computer-based interventions to teach communication skills to children with autism spectrum disorders: a systematic review. J Behav Educ 2010;20(1):55-76. [doi: 10.1007/s10864-010-9112-7]
15. Grossinho A, Guimaraes I, Magalhaes J, Cavaco S. Robust phoneme recognition for a speech therapy environment. 2016 Presented at: IEEE International Conference on Serious Games and Applications for Health (SeGAH); 2016; Orlando, USA p. 1-7.
16. Kagohara DM, van der Meer L, Ramdoss S, O'Reilly MF, Lancioni GE, Davis TN, et al. Using iPods and iPads in teaching programs for individuals with developmental disabilities: a systematic review. Res Dev Disabil 2013 Jan;34(1):147-156. [doi: 10.1016/j.ridd.2012.07.027] [Medline: 22940168]
17. Vuuren S, Cherney L. A Virtual Therapist for Speech and Language Therapy. 2014 Presented at: 14th International Conference on Intelligent Virtual Agents (IVA); 2014; Boston, USA p. 438-448.
18. Madeira RN, Mestre V, Ferreirinha T. Phonological disorders in children? Design and user experience evaluation of a mobile serious game approach. Procedia Comput Sci 2017;113:416-421. [doi: 10.1016/j.procs.2017.08.359]
19. Chen YP, Johnson C, Lalbakhsh P, Caelli T, Deng G, Tay D, et al. Systematic review of virtual speech therapists for speech disorders. Computer Speech & Language 2016 May;37:98-128. [doi: 10.1016/j.csl.2015.08.005]
20. Maich K, Hall C. Implementing iPads in the inclusive classroom setting. Interv Sch Clin 2015;51(3):145-150. [doi: 10.1177/1053451215585793]
21. Furlong L, Erickson S, Morris M. Computer-based speech therapy for childhood speech sound disorders. J Commun Disord 2017 Jul;68:50-69. [doi: 10.1016/j.jcomdis.2017.06.007] [Medline: 28651106]
22. Rubegni E, Landoni M. The TRiTS model: teacher roles in introducing digital technology into a school curriculum. Cogn Tech Work 2015;18(2):237-248. [doi: 10.1007/s10111-015-0360-0]
23. Lousada M, Jesus LM, Hall A, Joffe V. Intelligibility as a clinical outcome measure following intervention with children with phonologically based speech-sound disorders. Int J Lang Commun Disord 2014;49(5):584-601. [doi: 10.1111/1460-6984.12095] [Medline: 24861159]
24. Jesus L, Lousada M, Domingues D, Hall A, Tomé D. Phonological processes in Portuguese children with speech sound disorders. Pozn Stud Contemp Linguist 2015;51(1):75-88. [doi: 10.1515/psicl-2015-0003]
25. Günther T, Hautvast S. Addition of contingency management to increase home practice in young children with a speech sound disorder. Int J Lang Commun Disord 2010;45(3):345-353. [doi: 10.1080/13682820903026762] [Medline: 20144010]
26. de Sousa Monteiro B, Gomes AS, Neto FM. Youubi: open software for ubiquitous learning. Comput Human Behav 2016;55:1145-1164. [doi: 10.1016/j.chb.2014.09.064]
27. Furió D, González-Gancedo S, Juan MC, Seguí I, Rando N. Evaluation of learning outcomes using an educational iPhone game vs traditional game. Comput Educ 2013;64:1-23. [doi: 10.1016/j.compedu.2012.12.001]
28. Pereira LL, Brancalioni AR, Keske-Soares M. Phonological therapy with the use of computers: case report. Rev CEFAC 2013;15(3):681-688 [FREE Full text] [doi: 10.1590/S1516-18462012005000052]
29. Kebritchi M, Hirumi A. Examining the pedagogical foundations of modern educational computer games. Comput Educ 2008;51(4):1729-1743. [doi: 10.1016/j.compedu.2008.05.004]
30. Oliveira A, Peixoto E, Ribeiro F, Mota P, Moreira A. Exploração do jogo "Fazenda Feliz" em contexto educativo. Indag Didact 2014;6(2):121-134 [FREE Full text]
31. Virvou M, Alepis E. Mobile educational features in authoring tools for personalised tutoring. Comput Educ 2005;44(1):53-68. [doi: 10.1016/j.compedu.2003.12.020]
32. Martins JS, Pinheiro MM, Blasi HF. The use of a children software in the treatment of central auditory processing disorder. Rev Soc Bras Fonoaudiol 2008;13(4):398-404 [FREE Full text] [doi: 10.1590/S1516-80342008000400016]

33. Cohé A, Hachet M. Beyond the mouse: understanding user gestures for manipulating 3D objects from touchscreen inputs. Comput Graph 2012 Dec;36(8):1119-1131. [doi: 10.1016/j.cag.2012.09.004]
34. Gačnik M, Starčič AI, Zaletelj J, Zajc M. User-centred app design for speech sound disorders interventions with tablet computers. Univ Access Inf Soc 2017 Jul 1;17(4):821-832. [doi: 10.1007/s10209-017-0545-9]
35. International Data Corporation. 2017. Commercial Notebooks and Detachable Tablets Will Drive a Return to Growth in the Personal Computing Device Market in 2019 (Doc #prUS42595417 / 25-May-2017) Internet URL: https://www.idc.com/getdoc.jsp?containerId=prUS42595417 [accessed 2018-11-27] [WebCite Cache ID 74F01xnXQ]
36. Neumann MM. Parent scaffolding of young children's use of touch screen tablets. Early Child Dev Care 2017;188(12):1654-1664. [doi: 10.1080/03004430.2016.1278215]
37. International Data Corporation. 2016. Worldwide Tablet Market Forecast to Rebound in 2018 as Detachables Gain Traction in Both Mature and Emerging Markets URL: https://www.idc.com/url.do?url=/includes/pdf_download.jsp?containerId=prUS41962916 [accessed 2018-11-27] [WebCite Cache ID 74Ev9SC7U]
38. Barab S, Squire K. Design-based research: putting a stake in the ground. J Learn Sci 2004;13(1):1-14. [doi: 10.1207/s15327809jls1301_1]
39. Jesus LM, Martinez J, Valente AR, Costa MC. Speech and language therapy service delivery: overcoming limited provision for children. Public Health 2017;151:39-50. [doi: 10.1016/j.puhe.2017.06.013] [Medline: 28710926]
40. Wilkins A, Cleave R, Grayson N, Wilson L. Typography for children may be inappropriately designed. J Res Read 2009;32(4):402-412. [doi: 10.1111/j.1467-9817.2009.01402.x]
41. Rello L, Baeza-Yates R. Good fonts for dyslexia. 2013 Presented at: 15th International ACM SIGACCESS Conference on Computers and Accessibility (ASSETS); October 21-23, 2013; Bellevue, Washington p. 1-8. [doi: 10.1145/2513383.2513447]
42. Weightman AP, Preston N, Holt R, Allsop M, Levesley M, Bhakta B. Engaging children in healthcare technology design: developing rehabilitation technology for children with cerebral palsy. J Eng Des 2009;21(5):579-600. [doi: 10.1080/09544820802441092]
43. Hughes JK, Kearney P. Impact of an iDevice application on student learning in an occupational therapy kinesiology course. Mhealth 2017;3:43 [FREE Full text] [doi: 10.21037/mhealth.2017.08.02] [Medline: 29184895]
44. Boy GA. Tangible Interactive Systems. Cham, Switzerland: Springer; 2016.
45. Elghondakly R, Moussa S, Badr N. A Comprehensive Study for Software Testing and Test Cases Generation Paradigms. 2016 Presented at: International Conference on Internet of Things and Cloud Computing; March 22-23, 2016; Cambridge, United Kingdom. [doi: 10.1145/2896387.2896435]
46. Patton R. Software Testing (2nd edition). Indianapolis: SAMS; 2006.
47. Korf M, Oksman E. Salesforce Developers. 2016. Native, HTML5, or Hybrid: Understanding Your Mobile Application Development Options URL: https://developer.salesforce.com/page/Native,_HTML5,_or_Hybrid:_Understanding_Your_Mobile_Application_Development_Options [accessed 2018-11-27] [WebCite Cache ID 74EwZ5Fu0]
48. Faas T. An Introduction to HTML5 Game Development with Phaser.js. Boca Raton: CRC; 2017.
49. McCormack J, Baker E, Masso S, Crowe K, McLeod S, Wren Y, et al. Implementation fidelity of a computer-assisted intervention for children with speech sound disorders. Int J Speech Lang Pathol 2017;19(3):265-276. [doi: 10.1080/17549507.2017.1293160] [Medline: 28351159]
50. Jones B, Popovic J, McCann J, Li W, Bargteil A. Dynamic sprites: artistic authoring of interactive animations. Comput Animat Virtual Worlds 2014;26(2):97-108 [FREE Full text] [doi: 10.1002/cav.1608]
51. Apple Inc. 2016. Creating Compatible Web Content URL: https://developer.apple.com/library/archive/documentation/AppleApplications/Reference/SafariWebContent/CreatingContentforSafarioniPhone/CreatingContentforSafarioniPhone.html [accessed 2018-11-27] [WebCite Cache ID 74F0ZYNF8]
52. MDN web docs. URL: https://developer.mozilla.org/en-US/docs/Web/API/Window/devicePixelRatio [accessed 2018-11-27] [WebCite Cache ID 74EykJKeu]
53. Josh Morony. 2017. How to Scale a Game for All Device Sizes in Phaser URL: https://www.joshmorony.com/how-to-scale-a-game-for-all-device-sizes-in-phaser/ [accessed 2018-12-02] [WebCite Cache ID 74MhEnygf]
54. Schaefer C, Hyunsook D, Slator B. Crushinator: A framework towards game-independent testing. 2013 Presented at: 28th IEEE/ACM International Conference on Automated Software Engineering (ASE); November 11-15, 2013; Silicon Valley, USA p. 726-729. [doi: 10.1109/ASE.2013.6693143]
55. Matsunaga RM, de Oliveira Moraes RL, Borges MA, Matta MA, Ozelo MC. Development of a serious game for children with hemophilia. 2014 Presented at: 3rd International Conference on Serious Games and Applications for Health (SeGAH); May 14-16, 2014; Rio de Janeiro, Brazil p. 1-6. [doi: 10.1109/SeGAH.2014.7067082]
56. Gold SC, Wolfe J. The validity and effectiveness of a business game beta test. Simul Gaming 2011;43(4):481-505. [doi: 10.1177/1046878111431868]
57. Zhu Z. Study on beta testing of web application. 2010 Presented at: 2nd International Conference on Computer and Automation Engineering (ICCAE); February 26-28, 2010; Singapore, Singapore p. 423-426. [doi: 10.1109/ICCAE.2010.5451922]
58. Druin A. A place called childhood. ACM Interact 1996;3(1):17-22. [doi: 10.1145/223500.223506]

59. Read JC. Validating the Fun Toolkit: an instrument for measuring children's opinions of technology. Cogn Technol Work 2008;10(2):119-128. [doi: 10.1007/s10111-007-0069-9]
60. Anthony L, Brown Q, Tate B, Nias J, Brewer R, Irwin G. Designing smarter touch-based interfaces for educational contexts. Pers Ubiquit Comput 2013;18(6):1471-1483. [doi: 10.1007/s00779-013-0749-9]
61. Google Developers. 2017. Supported Media Formats URL: https://developer.android.com/guide/topics/media/media-formats [accessed 2018-11-27] [WebCite Cache ID 74EzoHzLZ]
62. Apple Inc. 2014. Supported Audio File and Data Formats in OS X URL: https://developer.apple.com/library/content/documentation/MusicAudio/Conceptual/CoreAudioOverview/SupportedAudioFormatsMacOSX/SupportedAudioFormatsMacOSX.html [accessed 2018-11-27] [WebCite Cache ID 74F0dDEgr]

Abbreviations

DBR: design-based research
DPR: device pixel ratio
SLT: speech and language therapist
SSD: speech sound disorders
T2T: Table to Tablet

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Protocol

Development of the Gambling Disorder Identification Test (G-DIT): Protocol for a Delphi Method Study

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Abstract

Background: Research on the identification and treatment of problem gambling has been characterized by a wide range of outcome measures and instruments. However, a single instrument measuring gambling behavior, severity, and specific deleterious effects is lacking.

Objective: This protocol describes the development of the Gambling Disorder Identification Test (G-DIT), which is a 9- to 12-item multiple-choice scale with three domains: gambling consumption, symptom severity, and negative consequences. The scale is analogous to the widely used Alcohol Use Disorders Identification Test (AUDIT) and the Drug Use Disorders Identification Test (DUDIT).

Methods: The G-DIT is developed in four steps: (1) identification of items eligible for the G-DIT from a pool of existing gambling measures; (2) presentation of items proposed for evaluation by invited expert researchers through an online Delphi process and subsequent consensus meetings; (3) pilot testing of a draft of the 9- to 12-item version in a small group of participants with problem gambling behavior (n=12); and (4) evaluation of the psychometric properties of the final G-DIT measure in relation to the existing instruments and self-reported criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), among individuals with problem gambling and nonproblematic recreational gambling behaviors (n=600). This protocol article summarizes step 1 and describes steps 2 and 3 in detail.

Results: As of October 2018, steps 1-3 are complete, and step 4 is underway.

Conclusions: Implementation of this online Delphi study early in the psychometric development process will contribute to the face and construct validity of the G-DIT. We believe the G-DIT will be useful as a standard outcome measure in the field of problem gambling research and serve as a problem-identification tool in clinical settings.

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KEYWORDS

consensus methods; Delphi technique; DSM-5; gambling; Gambling Disorder Identification Test; measurement; psychometrics; screening

Protocol

Introduction

Overview

Gambling is the only addiction without any psychopharmacological substance use that has been recognized as a diagnosis by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [1]. Problem gambling is associated with poor mental and physical well-being in individuals with gambling problems [2]; in addition, their partners, parents, and children are negatively affected [3]. Problem gambling leads to severe negative consequences in important life domains such as finance, well-being, health, and relationships [1] and is associated with high rates of suicide ideation and attempts [4]. The clinical diagnostic criteria for pathological gambling were revised in 2013 and termed Gambling Disorder (GD) in the DSM-5 [1]. GD is part of the Substance-Related and Addictive Disorder category in DSM-5, in contrast to the Impulse Disorder category in DSM, 4th edition (DSM-IV) [5,6]. Other updates in the DSM-5 include removal of a previous criterion, illegal acts to finance gambling, and specification of disorder severity. Currently, fulfillment of 4-5 diagnostic criteria leads to a diagnosis of mild GD, 6-7 symptoms are diagnosed as moderate GD, and 8-9 symptoms are diagnosed as severe GD.

As a research field, problem gambling is still in its infancy and is 20-30 years behind research on substance use disorders [7]. Research on the identification and treatment of problem gambling has been characterized by a wide range of outcome measures and instruments [8], leading to difficulties in comparing the effectiveness of different treatments [9]. An additional current challenge for clinical assessment and research outcome measures is that only a few existing instruments have been validated using the relatively new DSM-5 diagnostic criteria for GD. Furthermore, measuring problem gambling from a treatment-oriented perspective is a challenge, as current screening instruments adopt a public health perspective and generally focus on consumption behaviors, symptoms, *or* negative consequences, but do not encompass all three domains.

To address the issue of variation in outcome measures, an expert panel of researchers convened in 2006 and agreed upon a set of characteristics that should define measures of problem gambling in future treatment studies; these characteristics are collectively known as the Banff consensus agreement [8]. Regarding the issue of including DSM-5 criteria in measures for identification of GD, researchers have proposed some specific DSM-5 criteria such as “chasing losses,” “repeated unsuccessful efforts to stop,” “tolerance,” “loss of control,” and “jeopardized/lost relationships/job” as important gambling measures, because they can be used from a psychometric perspective to better differentiate among various gambling groups as compared to the other GD diagnostic criteria [10-12].

In response to the Banff consensus agreement and the discussion regarding inclusion of specific DSM-5 criteria and with a goal of optimizing a treatment-oriented screening measure, our team is developing the Gambling Disorder Identification Test (G-DIT). We aim to establish a problem gambling-screening test analogous to the Alcohol Use Disorders Identification Test (AUDIT) [13] and the Drug Use Disorders Identification Test (DUDIT) [14]. Our test will include items in three domains: gambling consumption, symptom severity, and negative consequences. The development and validation of the G-DIT is part of the ongoing 6-year Responding to and Reducing Gambling Problems research program in Sweden.

The G-DIT is under development in four steps: (1) identification of items eligible for the G-DIT from a pool of existing gambling measures; (2) presentation of proposed items for evaluation by the authors of this article in a pilot Delphi round, followed by presentation of the proposed items for evaluation by a larger group of invited international expert researchers in a formal Delphi process, and finally, an international expert consensus meeting followed by additional smaller consensus meetings to resolve issues tabled at the international meeting; (3) pilot testing of a draft 9- to 12-item version in a small group of participants with problem gambling behavior (n=12); and (4) evaluation of psychometric properties of the final G-DIT measure in relation to existing instruments and self-reported DSM-5 criteria in individuals with problem gambling and nonproblematic recreational gambling behaviors (n=600). This article summarizes step 1 and describes steps 2 and 3 in detail; the results of steps 2 and 3 will be described in an upcoming publication, and an additional publication will detail step 4.

Aims and Research Questions

The research questions are as follows:

- Which of the presented items should have the highest priority?
- What are the potential problems of the proposed G-DIT?
- How is the face validity of the G-DIT perceived?
- What psychometric findings could be of additional importance?

Methods

Study Approval and Consent

This study was approved by the Regional Ethics Board of Stockholm, Sweden (ref. no. 2017/1479-31). Approval was granted for the Delphi procedure and evaluation of the instrument in individuals with problem gambling behavior, individuals from gambling self-help groups, and individuals with recreational gambling behavior from a population sample. Informed consent was obtained from all stakeholders in the Delphi process as well as all participants with problem gambling behavior in the “think aloud” interviews. Participants were approached or volunteered via the methods outlined below. Individual Delphi stakeholders were sent a short email introducing the study, and more information on the study and consent forms were made available online. Individual responses were analyzed and presented anonymously in both the Delphi process and “think aloud” procedure. All participants provided consent for publication.

Analysis of Existing Measures

In step 1, we aimed to identify the maximum number of existing gambling measures. We conducted an extensive literature search of review articles on gambling measures [15-17] and a prior

unpublished collection of gambling measures compiled by local colleagues (A Nilsson and K Magnusson, personal communication, February 2017), which resulted in a list of 47 gambling measures (Table 1) [12,18-63]. Items from the measures were gathered in an item pool. Items with the same meaning were identified as doublets between instruments but classified as unique items within an instrument (eg, items in subscales). The final item pool consisted of 726 items, of which 583 were deemed unique items and 143 were deemed doublets; the latter were excluded from the item pool.

The first author categorized all items based on their content into four main categories and 27 subcategories: Gambling Consumption (Type of Game, Time Gambled, Sums, and Gambling Behavior); DSM-5 Criteria (Preoccupation, Tolerance, Loss of Control, Abstinence Symptoms, Escape, Chasing Losses, Lies, Social Consequences, and Relies on Other); Negative Consequences (General Problem, Health, Financial, Critique from Others, Illegal, and Other Negative Consequences); and Other (Motives for Gambling; Self-Efficacy; Situations or Relapse; Cognitive Distortions or Beliefs; Motivation; Anxiety, Depression, or Negative Effect; Alcohol or Drugs; and Other or Miscellaneous). The Other main item category was excluded, as it was not relevant to the G-DIT domains. Thereafter, three additional authors (blind to the original categorization) individually recategorized each item in the three remaining main categories (Gambling Consumption, DSM-5 Criteria, and Negative Consequences) and the predefined subcategories. Interrater reliability was calculated on the basis of the item-categorization agreement for all items, items per subcategory, and items per main category. Statistical analysis using Fleiss kappa [64] for 4 raters in R [65] showed that the interrater reliability ranged from fair to moderate (k=0.42 for all items and k=0.24, k=0.51, and k=0.51 for the relevant main item categories of Gambling Consumption, DSM-5 Criteria, and Negative Consequences, respectively).

The Delphi Study

We chose the Delphi method to collect feedback from expert researchers. The Delphi method is an iterative technique, comprising sequential questionnaires that are answered anonymously by many relevant stakeholders [66]. To prepare for the formal Delphi process in step 2, we conducted a pilot Delphi procedure in two rounds with the authors of the present study. In the preparation rounds, we evaluated 15 candidate items based on the interrater analysis in step 1. The criteria for selection were 75% agreement on the categorization and importance of these items. These two preparation rounds clarified the variation in expert evaluation of the items and led to a decision to increase the number of candidate items to 30 for the next formal Delphi rounds. The selection of these items was based on interrater agreement of items relevant to the G-DIT domains, previous psychometric findings regarding problem gambling, and the recommendations of the Banff consensus agreement [8]. An overview of the item categories is presented in Figure 1.

Panel Size and Recruitment

There are no accepted guidelines for the panel size in a Delphi analysis. Therefore, we determined our panel size on the basis of the practicality, scope, and time available, similar to previous studies [67,68]. Stakeholders were identified through contacts via our research group and team members of the ongoing research project “Responding to and Reducing Gambling Problems - Studies in Help-Seeking, Measurement, Comorbidity and Policy Impacts” (REGAPS) and through published research in the gambling field. We invited the following stakeholders to participate in the Delphi rounds and requested them to forward the invitation to other researchers in their network (snowball sampling): all authors of the Banff consensus [8] and previous psychometric research targeting specific DSM-5 symptoms [10-12]; presenters at the Alberta Gambling Research Institute’s 17th Annual Conference, 2018, which is the annual independent gambling conference in Banff (these individuals were identified as key influential gambling researchers for the international consensus meeting); all authors of reviews of gambling measures identified in our extended literature search [15-17]; corresponding and first and last authors of published articles or reports of the gambling measures identified in our extended literature search (Table 1); trial investigators including corresponding and first and last authors of reports of randomized trials in the field identified in published systematic reviews [9,69,70]; members of the REGAPS network; and members of the Gambling Research Network, which is a Swedish network for gambling research.

We addressed the potential for attrition between rounds through a personalized invitation, email reminders (every 5 days, but no more than two reminders in total), and provision of an easy interface, which minimized the time required to complete each round [67]. The Delphi-process questionnaire was uploaded on the online SurveyXact platform [71].

Table 1. Gambling measures (n=47) identified in the literature search.

Measure	Reference
The Brief Biosocial Gambling Screen	Gebauer et al, 2010 [41]
The Canadian Problem Gambling Index	Ferris et al, 2001 [23]
The Case-finding and Help Assessment Tool	Goodyear-Smith et al, 2008 [36]
The Consumption Screen for Problematic Gambling	Rockloff et al, 2012 [44]
The Control of Pathological Gambling Questionnaire	Saiz-Ruiz et al, 2005 [33]
The Cumulative Clinical Signs Method	Volberg et al, 1990 [55]
The Early Intervention Gambling Health Test	Sullivan, 2007 [50]
The Gamblers Self-Efficacy Questionnaire	May et al, 2003 [27]
The Gamblers' Belief Questionnaire	Steenbergh et al, 2002 [56]
The Gambling Abstinence Self-Efficacy Scale	Hodgins et al, 2004 [29]
The Gambling Activity Measurement Tool	Jacksson et al, 2013 [57]
The Gambling Anonymous Twenty Questions	Toneatto et al, 2008 [53]
The Gambling Attitudes and Beliefs Survey	Breen et al, 1999 [49]
The Gambling Cognitions Inventory	McInnes et al, 2014 [58]
The Gambling Craving Scale	Young et al, 2009 [40]
The Gambling Follow-Up Scale	de Castro et al, 2005 [34]
The Gambling Motives Questionnaire	Stewart et al, 2008 [52]
The Gambling Motives Questionnaire Financial	Schellenberg et al, 2015 [47]
The Gambling Passion Scale	Rousseau et al, 2002 [25]
The Gambling Pathways Questionnaire	Nower et al, 2016 [48]
The Gambling Problem Index	Neighbors et al, 2002 [24]
The Gambling Quantity and Perceived Norms	Neighbors et al, 2002 [24]
The Gambling Readiness to Change Questionnaire	Raylu et al, 2004 [30]
The Gambling Refusal Self-Efficacy Questionnaire	Casey et al, 2008 [35]
The Gambling Symptom Assessment Scale	Kim et al, 2009 [38]
The Gambling Urge Scale	Raylu et al, 2004 [59]
The Gambling-Related Cognition Scale	Raylu et al, 2004 [30]
The Inventory of Gambling Situations	Turner et al, 2013 [45]
The Lie/Bet	Johnson et al, 1997 [21]
The Maroondah Assessment Profile for Problem Gambling[a]	Shek et al, 2009 [60]
The Massachusetts Gambling Screen	Shaffer et al, 1994 [19]
The NODS[b]-CLIP[c]	Volberg et al, 2011 [12]
The NODS-PERC[d]	Volberg et al, 2011 [12]
The NORC[e] Diagnostic Screen for Gambling Problems	Gerstein et al, 1999 [22]
The NORC Diagnostic Screen for Gambling Problems Self-Administered	Gerstein et al, 1999 [22]
The Pathological Gambling Behavioral Self-Report Scale	Myrseth et al, 2011 [61]
The Problem and Pathological Gambling Measure	Willimas et al, 2013 [46]
The Problem Gamble Research and Treatment Centre Screen	__[f]
The Problem Gambling Severity Index	Ferris et al, 2001 [23]
The Scale of Gambling Choices	Baron et al, 1995 [20]
The South Oaks Gambling Screen	Lesieur et al, 1987 [18]

Measure	Reference
The South Oaks Gambling Screen Short	Room et al, 1999 [62]
The South Oaks Gambling Screen-Revised	Abbott et al, 1990 [63]
The Sydney Laval Gambling Scale	Blaszczynski et al, 2008 [51]
The Temptations for Gambling Questionnaire	Holub et al, 2005 [31]
The Victorian Gambling Screen	Tolchard et al, 2010 [42]
The Yale Brown Obsessive Compulsive Scale adapted for Pathological Gambling	Pallanti et al, 2005 [32]

[a]This measure was excluded from the item pool because it was not possible to obtain the instrument.

[b]NODS: National Opinion Research Center Diagnostic Screen for Gambling Problems.

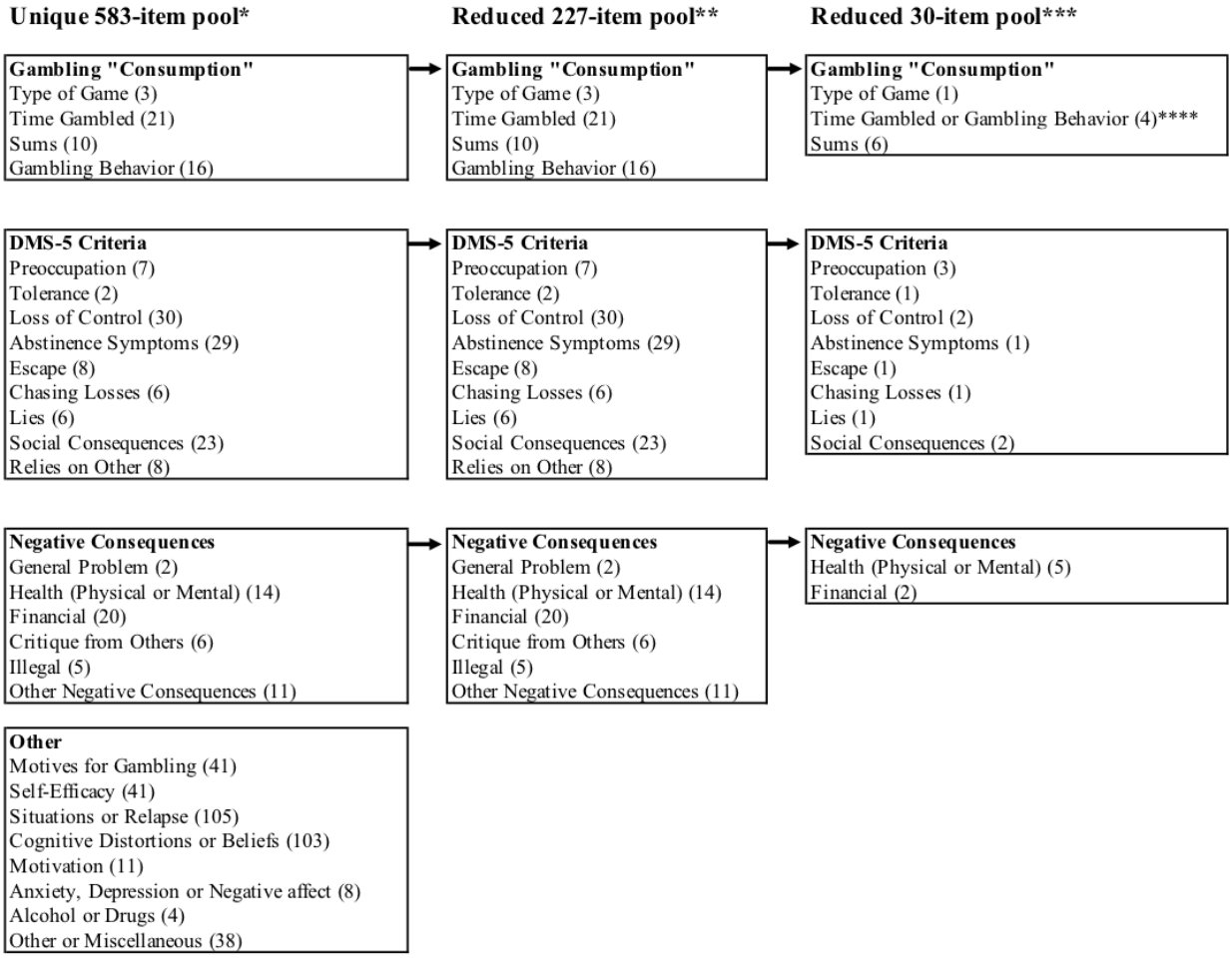
[c]CLIP: Loss of Control, Lying, and Preoccupation.

[d]PERC: The National Opinion Research Center Diagnostic Screen for Gambling Problems - Preoccupation, Escape, Risked Relationships, and Chasing.

[e]NORC: National Opinion Research Center.

[f]Published reference not found.

Figure 1. Item categorization and item selection for the Gambling Disorder Identification Test (G-DIT). The number of items is provided within parentheses. *Five items were lost in the initial categorization. **Interrater recategorization. ***Main Delphi. ****Time gambled and gambling behavior were merged to fit the G-DIT domains. DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition.



The Delphi Questionnaire and Rounds

Stakeholders were instructed to log on to the online questionnaire where they first read information about the study and electronically signed an informed consent form and to provide data on demographic characteristics including gender, country, number of years engaged in gambling-related work, and profession. Thereafter, the stakeholders viewed the proposed items in the measure. The items were listed randomly to avoid assigning any order of importance to the items. For each item, the stakeholders were instructed to provide feedback on the psychometric relevance and accuracy, semantic structure, and multiple-choice alternatives. In addition, the stakeholders were asked to rate each item on a scale of 1-9, where scores of 1-3

were considered "not important for inclusion," 4-6 were considered "important but not critical," and 7-9 were considered "critical for inclusion." Further, an open-text field was provided with each item, through which the stakeholders could provide additional feedback or information; for example, important psychometric findings that were previously not noted by our research group. A rationale for each item shown from a psychometric perspective was presented; for example, "Item 5. How often do you gamble to win back money you lost? Never, Less than monthly, Monthly, Weekly, or Daily or almost daily." The rationale for inclusion of this item is that "Chasing losses" is a key symptom in the diagnostic criteria of GD. A recent latent class analysis of data found that "the main diagnostic item serving to discriminate recreational from problem gamblers was endorsement of 'chasing losses'" [10].

The Delphi survey was repeated in a second round. The importance of completing both rounds was emphasized to the stakeholders in the study information. After completion of Round 1, all stakeholders were invited to Round 2, where they were asked to respond to the questionnaire again. In addition to the previously described content, the stakeholders were presented with an anonymous summary of the other stakeholders' responses. Using this information, each expert was asked to reflect on their own rating in relation to the overall group rating and rate each item again. After Round 2, the results of the Delphi analysis were summarized.

Consensus Meeting

After the end of the Delphi rounds, a consensus meeting was held with a subgroup of international researchers attending the Alberta Gambling Research Institute's 17th Annual Conference. The results from the Delphi were presented and discussed, and a consensus was reached to determine the final G-DIT item structure. To review the results and adjust the G-DIT measure accordingly, subsequent consensus meetings were held on issues tabled at the international consensus meeting. Participants at these meetings were the authors of the present article and two Swedish participants of the international consensus meeting. At the end of the consensus process, the G-DIT was also translated into Swedish using a back-translation procedure [72].

Think Aloud Procedure

Swedish individuals (n=12) with problem gambling behavior were recruited from treatment-seeking and self-help groups. The inclusion criteria were willingness to participate in the study and personal experience of gambling problems. The participants provided feedback according to the "think aloud" procedure [73,74]. They were instructed in advance to think aloud "as if alone in the room." First, the participants practiced the procedure when presented with an instruction text. Subsequently, they were presented with each item in the draft version of the Swedish G-DIT. Their comments were noted by the interviewer, who otherwise did not intervene, except to provide reminders to think aloud. The results of the interviews were analyzed using content analysis. Thereafter, the G-DIT was adjusted further to increase face validity of the measure.

Psychometric Evaluation in Treatment-Seeking and Population Cohorts

In the final step of the study protocol, the psychometric properties of the G-DIT will be evaluated in relation to the DSM-5 diagnostic criteria for GD [1] and other gambling instruments through survey data and clinical interviews. Data will be collected from treatment-seeking and self-help group samples as well as population samples including people with recreational gambling behavior in Sweden (n=600). The inclusion criteria for treatment-seeking and self-help group participants will be a total score of ≥3 on the Problem Gambling Severity Index (PGSI) [23], 18-85 years of age, ability to read and write Swedish, and not fulfilling the criteria for a manic episode. The inclusion criteria for the population sample will be 18-85 years of age and the ability to read and write Swedish. The procedure will first be piloted with a cohort of participants seeking treatment for problem gambling (n=80), after which additional adjustment of the G-DIT, such as further reduction of items, may be performed.

Results

Funding sources for the G-DIT project include the Swedish Research Council for Health, Working Life and Welfare (Grant no. 2016-07091), covering a 6-year program grant entitled REGAPS, and development funds from the Stockholm Health Care Services, Stockholm County Council, for identification and treatment of problem gambling. As of November 2018, steps 1-3 have been completed, and step 4 is underway.

Discussion

This article describes a study protocol to develop a new measure for the assessment of problem gambling. We describe methods for item generation, instrument development, and procedures for testing the face and construct validity by collecting feedback from expert researchers and participants with problem gambling behavior. This study will set the foundation for a subsequent psychometric study that will aim to evaluate the psychometric properties of the G-DIT in relation to existing instruments, clinical interviews, and self-reported DSM-5 criteria among Swedish individuals with problem gambling behavior from treatment-seeking and self-help groups samples as well as population samples including people with recreational gambling behaviors.

This study protocol has several strengths. First, our extensive literature search identified a large number of existing gambling measures. Our overview indicated that no single existing measure seemed to adequately fulfill the recommendations of the Banff consensus. Second, only a few measures have been validated by the DSM-5 diagnostic criteria for GD. Third, many existing measures include item responses with generalized multiple or dichotomous "yes" or "no" response options rather than specific behavior or time frequencies. Fourth, the use of digital platforms in this study facilitates broad national and international collaborations in emerging research fields such as problem gambling. Our scope for recruiting expert researchers was wide. Implementation of a Delphi study early in the

psychometric development process will contribute to the face and construct validity of the final measure. Through the Delphi process, several key problematic issues for measuring gambling-related content were identified and will be discussed in the forthcoming publication. Our systematic procedure will contribute to the establishment of public health guidelines for gambling behavior, similar to the guidelines for alcohol consumption currently available in many countries.

The final G-DIT will consist of three domains: gambling consumption, symptom severity, and negative consequences. In addition, an appendix on expenditure and gambling types will be included. We believe the G-DIT will complement existing screening scales in upcoming intervention trials among community and treatment-seeking groups and prove useful as a standard outcome measure for change in problem gambling behavior. An additional potential area of use is the identification of problem gambling in clinical settings.

Conflicts of Interest

None declared.

Authors' Contributions

AHB, OM, RV, KS, PW, and VM conceived the study. OM compiled and categorized the first item pool. AHB, KS, and VM recategorized the relevant G-DIT items. OM wrote the first manuscript draft, and AHB revised the second draft. RV provided expert guidance on the methodology as an experienced gambling researcher, developer of existing gambling measures, and member of the REGAPS research program. All authors participated in the Delphi pilot rounds. All authors edited and contributed to subsequent manuscript drafts.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5. Washington: American Psychiatric Association; 2013.
2. Dowling NA, Merkouris SS, Lorains FK. Interventions for comorbid problem gambling and psychiatric disorders: Advancing a developing field of research. Addict Behav 2016 Jul;58:21-30. [doi: 10.1016/j.addbeh.2016.02.012] [Medline: 26900888]
3. Rychtarik RG, McGillicuddy NB. Preliminary evaluation of a coping skills training program for those with a pathological-gambling partner. J Gambl Stud 2006 Jun;22(2):165-178. [doi: 10.1007/s10899-006-9008-6] [Medline: 16841184]
4. Newman SC, Thompson AH. A population-based study of the association between pathological gambling and attempted suicide. Suicide Life Threat Behav 2003;33(1):80-87. [Medline: 12710543]
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV. Washington: American Psychiatric Press Inc; 1994.
6. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry 2013 Aug;170(8):834-851 [FREE Full text] [doi: 10.1176/appi.ajp.2013.12060782] [Medline: 23903334]
7. Gooding P, Tarrier N. A systematic review and meta-analysis of cognitive-behavioural interventions to reduce problem gambling: hedging our bets? Behav Res Ther 2009 Jul;47(7):592-607. [doi: 10.1016/j.brat.2009.04.002] [Medline: 19446287]
8. Walker M, Toneatto T, Potenza MN, Petry N, Ladouceur R, Hodgins DC, et al. A framework for reporting outcomes in problem gambling treatment research: the Banff, Alberta Consensus. Addiction 2006 Apr;101(4):504-511. [doi: 10.1111/j.1360-0443.2005.01341.x] [Medline: 16548930]
9. Pallesen S, Mitsem M, Kvale G, Johnsen B, Molde H. Outcome of psychological treatments of pathological gambling: a review and meta-analysis. Addiction 2005 Oct;100(10):1412-1422. [doi: 10.1111/j.1360-0443.2005.01204.x] [Medline: 16185203]
10. Chamberlain SR, Stochl J, Redden SA, Odlaug BL, Grant JE. Latent class analysis of gambling subtypes and impulsive/compulsive associations: Time to rethink diagnostic boundaries for gambling disorder? Addict Behav 2017 Dec;72:79-85 [FREE Full text] [doi: 10.1016/j.addbeh.2017.03.020] [Medline: 28384607]
11. Stinchfield R, McCready J, Turner NE, Jimenez-Murcia S, Petry NM, Grant J, et al. Reliability, Validity, and Classification Accuracy of the DSM-5 Diagnostic Criteria for Gambling Disorder and Comparison to DSM-IV. J Gambl Stud 2016 Sep;32(3):905-922 [FREE Full text] [doi: 10.1007/s10899-015-9573-7] [Medline: 26408026]
12. Volberg R, Williams R. University of Lethbridge. 2011. Developing a Brief Problem Gambling Screen Using Clinically Validated Samples of At-Risk, Problem and Pathological Gamblers URL: https://opus.uleth.ca/handle/10133/2561 [accessed 2018-11-24] [WebCite Cache ID 74A4pLLw9]
13. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993 Jun;88(6):791-804. [Medline: 8329970]

14. Berman AH, Bergman H, Palmstierna T, Schlyter F. Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. Eur Addict Res 2005;11(1):22-31. [doi: 10.1159/000081413] [Medline: 15608468]
15. Caler K, Garcia J, Nower L. Assessing Problem Gambling: a Review of Classic and Specialized Measures. Curr Addict Rep 2016 Oct 5;3(4):437-444. [doi: 10.1007/s40429-016-0118-7]
16. Dowling NA, Merkouris SS, Manning V, Volberg R, Lee SJ, Rodda SN, et al. Screening for problem gambling within mental health services: a comparison of the classification accuracy of brief instruments. Addiction 2018 Jun;113(6):1088-1104. [doi: 10.1111/add.14150] [Medline: 29274182]
17. Pickering D, Keen B, Entwistle G, Blaszczynski A. Measuring treatment outcomes in gambling disorders: a systematic review. Addiction 2018 Mar;113(3):411-426 [FREE Full text] [doi: 10.1111/add.13968] [Medline: 28891116]
18. Lesieur HR, Blume SB. The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. Am J Psychiatry 1987 Sep;144(9):1184-1188. [doi: 10.1176/ajp.144.9.1184] [Medline: 3631315]
19. Shaffer HJ, Labrie R, Scanlan KM, Cummings TN. Pathological gambling among adolescents: Massachusetts Gambling Screen (MAGS). J Gambl Stud 1994 Dec;10(4):339-362. [doi: 10.1007/BF02104901] [Medline: 24234969]
20. Baron E, Dickerson M, Blaszczynski A. The Scale of Gambling Choices: Preliminary Development of an Instrument to Measure Impaired Control of Gambling Behaviour. In: O'Connor J, editor. High stakes in the nineties. National Association of Gambling Studies: Curtin University Press; 1995:153-168.
21. Johnson EE, Hamer R, Nora RM, Tan B, Eisenstein N, Engelhart C. The Lie/Bet Questionnaire for screening pathological gamblers. Psychol Rep 1997 Feb;80(1):83-88. [doi: 10.2466/pr0.1997.80.1.83] [Medline: 9122356]
22. Gerstein D, Volberg R, Toce M, Harwood H, Johnson R, Buie T, et al. National Opinion Research Center, University of Chicago. 1999. Gambling impact and behavior study: Report to the national gambling impact study commission URL: http://www.norc.org/PDFs/publications/GIBSFinalReportApril1999.pdf [accessed 2018-11-23] [WebCite Cache ID 749GHHOUU]
23. Ferris J, Wynne H. The Canadian Problem Gambling Index: Final Report. URL: http://www.ccgr.ca/en/projects/resources/CPGI-Final-Report-English.pdf [accessed 2018-11-27] [WebCite Cache ID 74FHjFMUK]
24. Neighbors C, Lostutter TW, Larimer ME, Takushi RY. Measuring gambling outcomes among college students. J Gambl Stud 2002;18(4):339-360 [FREE Full text] [Medline: 12514914]
25. Rousseau FL, Vallerand RJ, Ratelle CF, Mageau GA, Provencher PJ. Passion and gambling: on the validation of the Gambling Passion Scale (GPS). J Gambl Stud 2002;18(1):45-66. [Medline: 12050847]
26. Hodgins DC, Makarchuk K. Trusting problem gamblers: reliability and validity of self-reported gambling behavior. Psychol Addict Behav 2003 Sep;17(3):244-248. [doi: 10.1037/0893-164X.17.3.244] [Medline: 14498819]
27. May RK, Whelan JP, Steenbergh TA, Meyers AW. The gambling self-efficacy questionnaire: an initial psychometric evaluation. J Gambl Stud 2003;19(4):339-357. [Medline: 14634297]
28. Hodgins DC. Using the NORC DSM Screen for Gambling Problems as an outcome measure for pathological gambling: psychometric evaluation. Addict Behav 2004 Nov;29(8):1685-1690. [doi: 10.1016/j.addbeh.2004.03.017] [Medline: 15451138]
29. Hodgins D, Peden N, Makarchuk K. Self-efficacy in pathological gambling treatment outcome: development of a gambling abstinence self-efficacy scale (GASS). International Gambling Studies 2004 Nov;4(2):99-108. [doi: 10.1080/14459790412331296947]
30. Raylu N, Oei TPS. The Gambling Related Cognitions Scale (GRCS): development, confirmatory factor validation and psychometric properties. Addiction 2004 Jun;99(6):757-769. [doi: 10.1111/j.1360-0443.2004.00753.x] [Medline: 15139874]
31. Holub A, Hodgins D, Peden N. Development of the temptations for gambling questionnaire: A measure of temptation in recently quit gamblers. Addiction Research & Theory 2009 Jul 11;13(2):179-191. [doi: 10.1080/16066350412331314902]
32. Pallanti S, DeCaria CM, Grant JE, Urpe M, Hollander E. Reliability and validity of the pathological gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS). J Gambl Stud 2005;21(4):431-443. [doi: 10.1007/s10899-005-5557-3] [Medline: 16311876]
33. Saiz-Ruiz J, Blanco C, Ibáñez A, Masramon X, Gómez MM, Madrigal M, et al. Sertraline treatment of pathological gambling: a pilot study. J Clin Psychiatry 2005 Jan;66(1):28-33. [Medline: 15669885]
34. de Castro V, Fuentes D, Tavares H. The gambling follow-up scale: development and reliability testing of a scale for pathological gamblers under treatment. Can J Psychiatry 2005 Feb;50(2):81-86. [doi: 10.1177/070674370505000202] [Medline: 15807223]
35. Casey LM, Oei TPS, Melville KM, Bourke E, Newcombe PA. Measuring self-efficacy in gambling: the Gambling Refusal Self-Efficacy Questionnaire. J Gambl Stud 2008 Jun;24(2):229-246. [doi: 10.1007/s10899-007-9076-2] [Medline: 17849178]
36. Goodyear-Smith F, Coupe NM, Arroll B, Elley CR, Sullivan S, McGill A. Case finding of lifestyle and mental health disorders in primary care: validation of the 'CHAT' tool. Br J Gen Pract 2008 Jan;58(546):26-31 [FREE Full text] [doi: 10.3399/bjgp08X263785] [Medline: 18186993]
37. Wickwire EM, Burke RS, Brown SA, Parker JD, May RK. Psychometric evaluation of the National Opinion Research Center DSM-IV Screen for Gambling Problems (NODS). Am J Addict 2008;17(5):392-395. [doi: 10.1080/10550490802268934] [Medline: 18770081]

38. Kim SW, Grant JE, Potenza MN, Blanco C, Hollander E. The Gambling Symptom Assessment Scale (G-SAS): a reliability and validity study. Psychiatry Res 2009 Mar 31;166(1):76-84 [FREE Full text] [doi: 10.1016/j.psychres.2007.11.008] [Medline: 19200607]
39. Toce-Gerstein M, Gerstein DR, Volberg RA. The NODS-CLiP: a rapid screen for adult pathological and problem gambling. J Gambl Stud 2009 Dec;25(4):541-555 [FREE Full text] [doi: 10.1007/s10899-009-9135-y] [Medline: 19603259]
40. Young MM, Wohl MJA. The Gambling Craving Scale: Psychometric validation and behavioral outcomes. Psychol Addict Behav 2009 Sep;23(3):512-522. [doi: 10.1037/a0015043] [Medline: 19769435]
41. Gebauer L, LaBrie R, Shaffer HJ. Optimizing DSM-IV-TR classification accuracy: a brief biosocial screen for detecting current gambling disorders among gamblers in the general household population. Can J Psychiatry 2010 Feb;55(2):82-90. [doi: 10.1177/070674371005500204] [Medline: 20181303]
42. Tolchard B, Battersby MW. The Victorian Gambling Screen: reliability and validation in a clinical population. J Gambl Stud 2010 Dec;26(4):623-638. [doi: 10.1007/s10899-009-9172-6] [Medline: 20035440]
43. Volberg RA, Munck IM, Petry NM. A quick and simple screening method for pathological and problem gamblers in addiction programs and practices. Am J Addict 2011;20(3):220-227 [FREE Full text] [doi: 10.1111/j.1521-0391.2011.00118.x] [Medline: 21477050]
44. Rockloff MJ. Validation of the Consumption Screen for Problem Gambling (CSPG). J Gambl Stud 2012 Jun;28(2):207-216. [doi: 10.1007/s10899-011-9260-2] [Medline: 21830133]
45. Turner NE, Littman-Sharp N, Toneatto T, Liu E, Ferentzy P. Centre for Addiction and Mental Health Inventory of Gambling Situations: Evaluation of the Factor Structure, Reliability, and External Correlations. Int J Ment Health Addict 2013;11:526-545 [FREE Full text] [doi: 10.1007/s11469-013-9446-1] [Medline: 24707240]
46. Williams RJ, Volberg RA. The classification accuracy of four problem gambling assessment instruments in population research. International Gambling Studies 2013 Oct 09;14(1):15-28. [doi: 10.1080/14459795.2013.839731]
47. Schellenberg B, McGrath D, Dechant K. The Gambling Motives Questionnaire financial: factor structure, measurement invariance, and relationships with gambling behaviour. International Gambling Studies 2015 Nov 02;16(1):1-16. [doi: 10.1080/14459795.2015.1088559]
48. Nower L, Blaszczynski A. Development and validation of the Gambling Pathways Questionnaire (GPQ). Psychol Addict Behav 2017 Feb;31(1):95-109. [doi: 10.1037/adb0000234] [Medline: 27936817]
49. Breen R, Zuckerman M. `Chasing' in gambling behavior: personality and cognitive determinants. Personality and Individual Differences 1999 Dec;27(6):1097-1111. [doi: 10.1016/S0191-8869(99)00052-5]
50. Sullivan S. Don't Let an Opportunity Go by: Validation of the EIGHT Gambling Screen. Int J Ment Health Addiction 2007 Apr 17;5(4):381-389. [doi: 10.1007/s11469-007-9064-x]
51. Blaszczynski A, Ladouceur R, Moodie C. The Sydney Laval Universities Gambling Screen: Preliminary data. Addiction Research & Theory 2009 Jul 11;16(4):401-411. [doi: 10.1080/16066350701699031]
52. Stewart SH, Zack M. Development and psychometric evaluation of a three-dimensional Gambling Motives Questionnaire. Addiction 2008 Jul;103(7):1110-1117. [doi: 10.1111/j.1360-0443.2008.02235.x] [Medline: 18554344]
53. Toneatto T. Reliability and Validity of the Gamblers Anonymous Twenty Questions. J Psychopathol Behav Assess 2008 Jan 5;30(1):71-78. [doi: 10.1007/s10862-007-9070-0]
54. Williams RJ, Volberg RA, Stevens RM, Williams LA, Arthur JN. University of Lethbridge Research Repository: OPUS. 2017. The definition, dimensionalization, and assessment of gambling participation: Report prepared for the Canadian Consortium for Gambling Research URL: https://opus.uleth.ca/bitstream/handle/10133/4838/Williams%20the%20defn,%20dimensionalization%20and%20assessment.pdf [accessed 2018-11-23] [WebCite Cache ID 749GXi89Y]
55. Volberg RA, Banks SM. A review of two measures of pathological gambling in the United States. J Gambl Stud 1990 Jun;6(2):153-163. [doi: 10.1007/BF01013495] [Medline: 24242856]
56. Steenbergh TA, Meyers AW, May RK, Whelan JP. Development and validation of the Gamblers' Beliefs Questionnaire. Psychol Addict Behav 2002 Jun;16(2):143-149. [Medline: 12079253]
57. Jackson AC, Francis KL, Byrne G, Christensen DR. Leisure Substitution and Problem Gambling: Report of a Proof of Concept Group Intervention. Int J Ment Health Addiction 2012 Aug 17;11(1):64-74. [doi: 10.1007/s11469-012-9399-9]
58. McInnes A, Hodgins D, Holub A. The Gambling Cognitions Inventory: scale development and psychometric validation with problem and pathological gamblers. International Gambling Studies 2014 Jun 27;14(3):410-431. [doi: 10.1080/14459795.2014.923483]
59. Raylu N, Oei TPS. The gambling urge scale: development, confirmatory factor validation, and psychometric properties. Psychol Addict Behav 2004 Jun;18(2):100-105. [doi: 10.1037/0893-164X.18.2.100] [Medline: 15238051]
60. Shek DTL, Chan EML. Assessment of problem gambling in a Chinese context: the Chinese G-MAP. ScientificWorldJournal 2009 Jul 02;9:548-556 [FREE Full text] [doi: 10.1100/tsw.2009.42] [Medline: 19578712]
61. Myrseth H, Molde H, Støylen I, Johnsen B, Holsten F, Pallesen S. A pilot study of CBT versus escitalopram combined with CBT in the treatment of pathological gamblers. International Gambling Studies 2011 Apr;11(1):121-141. [doi: 10.1080/14459795.2011.559647]

62. Room R, Turner NE, Ialomiteanu A. Community effects of the opening of the Niagara casino. Addiction 1999 Oct;94(10):1449-1466. [Medline: 10790898]
63. Abbott MW, Volberg R. Department of Internal Affairs. 1990. A Report on Phase Two of the 1999 National Prevalence Survey: Problem and Non-Problem Gamblers in New Zealand URL: https://www.dia.govt.nz/diawebsite.nsf/wpg_URL/Resource-material-Our-Research-and-Reports-New-Zealand-Gaming-Survey?OpenDocument [accessed 2018-11-24] [WebCite Cache ID 74A5qNsLz]
64. Fleiss J. Measuring nominal scale agreement among many raters. Psychological Bulletin 1971;76(5):378-382. [doi: 10.1037/h0031619]
65. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013. URL: https://www.r-project.org/ [accessed 2018-11-24] [WebCite Cache ID 74A56AspQ]
66. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. PLoS Med 2011 Jan 25;8(1):e1000393 [FREE Full text] [doi: 10.1371/journal.pmed.1000393] [Medline: 21283604]
67. Blackwood B, Ringrow S, Clarke M, Marshall J, Rose L, Williamson P, et al. Core Outcomes in Ventilation Trials (COVenT): protocol for a core outcome set using a Delphi survey with a nested randomised trial and observational cohort study. Trials 2015 Aug 20;16:368 [FREE Full text] [doi: 10.1186/s13063-015-0905-9] [Medline: 26289560]
68. Shorter GW, Heather N, Bray JW, Giles EL, Holloway A, Barbosa C, et al. The 'Outcome Reporting in Brief Intervention Trials: Alcohol' (ORBITAL) framework: protocol to determine a core outcome set for efficacy and effectiveness trials of alcohol screening and brief intervention. Trials 2017 Dec 22;18(1):611 [FREE Full text] [doi: 10.1186/s13063-017-2335-3] [Medline: 29273070]
69. Cowlishaw S, Merkouris S, Dowling N, Anderson C, Jackson A, Thomas S. Psychological therapies for pathological and problem gambling. Cochrane Database Syst Rev 2012 Nov 14;11:CD008937. [doi: 10.1002/14651858.CD008937.pub2] [Medline: 23152266]
70. Petry NM, Ginley MK, Rash CJ. A systematic review of treatments for problem gambling. Psychol Addict Behav 2017 Dec;31(8):951-961. [doi: 10.1037/adb0000290] [Medline: 28639817]
71. SurveyXact.: Ramböll Management Consulting; 2018. URL: https://www.surveyxact.se/ [accessed 2018-11-27] [WebCite Cache ID 74FIVeBKF]
72. KuliÅ› D, Whittaker C, Greimel E, Bottomley A, Koller M, EORTC Quality of Life Group. Reviewing back translation reports of questionnaires: the EORTC conceptual framework and experience. Expert Rev Pharmacoecon Outcomes Res 2017 Dec;17(6):523-530. [doi: 10.1080/14737167.2017.1384316] [Medline: 28974101]
73. Ericsson K, Simon H. Verbal reports as data. Psychological Review 1980;87(3):215-251. [doi: 10.1037/0033-295X.87.3.215]
74. Boren T, Ramey J. Thinking aloud: reconciling theory and practice. IEEE Trans. Profess. Commun 2000;43(3):261-278. [doi: 10.1109/47.867942]

Abbreviations

CLIP: Loss of Control, Lying, and Preoccupation
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition
G-DIT: Gambling Disorder Identification Test
NODS: National Opinion Research Center Diagnostic Screen for Gambling Problems
NORC: National Opinion Research Center
PERC: The National Opinion Research Center Diagnostic Screen for Gambling Problems - Preoccupation, Escape, Risked Relationships, and Chasing
REGAPS: Responding to and Reducing Gambling Problems - Studies in Help-Seeking, Measurement, Comorbidity, and Policy Impacts

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Protocol

Association Between Residual Inhibition and Neural Activity in Patients with Tinnitus: Protocol for a Controlled Within- and Between-Subject Comparison Study

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Abstract

Background: Electroencephalography (EEG) studies indicate possible associations between tinnitus and changes in the neural activity. However, inconsistent results require further investigation to better understand such heterogeneity and inform the interpretation of previous findings.

Objective: This study aims to investigate the feasibility of EEG measurements as an objective indicator for the identification of tinnitus-associated neural activities.

Methods: To reduce heterogeneity, participants served as their own control using residual inhibition (RI) to modulate the tinnitus perception in a within-subject EEG study design with a tinnitus group. In addition, comparison with a nontinnitus control group allowed for a between-subjects comparison. We will apply RI stimulation to generate tinnitus and nontinnitus conditions in the same subject. Furthermore, high-frequency audiometry (up to 13 kHz) and tinnitometry will be performed.

Results: This work was funded by the Infrastructure Grant of the University of Bern, Bern, Switzerland and Bernafon AG, Bern, Switzerland. Enrollment for the study described in this protocol commenced in February 2018. Data analysis is currently under way and the first results are expected to be submitted for publication in 2019.

Conclusions: This study design helps in comparing the neural activity between conditions in the same individual, thereby addressing a notable limitation of previous EEG tinnitus studies. In addition, the high-frequency assessment will help to analyze and classify tinnitus symptoms beyond the conventional clinical standard.

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KEYWORDS

electroencephalography; heterogeneity; high-frequency audiometry; neural activity; tinnitus; tinnitometry

Introduction

Background

About 10%-15% of the general population is suffering from chronic subjective tinnitus, that is, consciously perceiving sound without the presence of physical sound sources [1]. Tinnitus can lead to health problems, distress, and psychological complaints and can substantially impair the quality of life [2]. In most cases, tinnitus occurs after cochlear damage such as sensorineural hearing loss [3], presbycusis [4], excessive noise exposure, and noise trauma [5]. Chronic tinnitus is also experienced by people with otherwise normal hearing [6]. Furthermore, tinnitus can be generated by head and neck injury, infections and neck illness, drugs, and other medical conditions [5] and may also be influenced by emotional and mental conditions [7]. Extensive causes and symptoms could complicate the diagnosis and treatment of tinnitus; to improve this, studies have proposed classifying tinnitus into different subtypes according to symptoms such as perceptual characteristics, laterality, loudness, or symptom severity, as well as the presence of tinnitus-associated disorders [8-10]. Alternatively, the categorization of tinnitus has been based on the response to applied treatments [11]. Nevertheless, an incomplete understanding of the underlying pathophysiology and the presence of numerous psychosocial and environmental factors that could influence intervention results may cause heterogeneity and preclude tinnitus subgrouping. As an effect, to date, there are no singularly effective clinical evaluation and treatment methods for subjective tinnitus [12]. Moreover, the current tinnitus diagnosis heavily relies on patient-reported assessments such as questionnaires. Currently, more objective assessment methods, which could provide physiology-based measures of comparison, do not exist.

As tinnitus often originates from peripheral and central auditory mechanisms [13,14], the assessment of abnormal neural activity may be a potential approach for objective diagnosis. A number of research groups have suggested that tinnitus is accompanied by changes in the brain [15-20] and can be examined using electroencephalography/magnetoencephalography (EEG/MEG) [17,19,21-27]. In particular, spontaneous brain oscillations, that is, the ongoing brain activity in the absence of external events, have been intensively investigated using EEG/MEG. Traditional EEG/MEG power bands of resting-state activity have been quantified between people with tinnitus and controls [17,22]. One theory explaining group differences in the EEG/MEG power within specific frequency bands focuses on the thalamocortical dysrhythmia model. This model predicts an increase of power in low frequencies (delta and theta bands) and high frequencies (gamma band) in the auditory cortex in subjects with tinnitus [18]. Furthermore, marked alterations of EEG/MEG oscillations across other brain regions and power bands have been reported in the prefrontal cortex [28-31], cingulate cortex [29-38], parahippocampus [15,26,31,34,36,37,39-42], and insula [26,37,43], implying the involvement of other brain areas and power bands. Nevertheless, poor matching of gender, age, and hearing loss status across groups, as well as other confounding factors, hinder the interpretation of study findings and generate inconsistencies [44]. To minimize variance across subjects, a within-subject measurement comparing the brain activity during a baseline period (tinnitus with abnormal brain activity) with a period after the suppression of tinnitus (stabilization of abnormal activity) may overcome this limitation.

Residual inhibition (RI) is a temporary forward tinnitus suppression mechanism, which can reduce or alleviate tinnitus loudness for a short duration after the presentation of an acoustic stimulus [45,46]. Previous work has compared the brain activity between baseline (tinnitus) and poststimulus (reduced tinnitus or nontinnitus) periods on the group level, observing reduced power in the delta frequency band in the temporal region after stimulus exposure, which is in accordance with the thalamocortical dysrhythmia [47]. In a different study, neural activity changes between pre- and poststimulus periods were detected in nonauditory cortices, that is, in the left anterior superior temporal gyrus, the motor cortex, and the posteromedial cortex by a single subject with musical hallucination using music as suppression stimulus [48]. Adjamian et al compared the neural activity during masking and resting state [24]. Sedley et al detected changes in the tinnitus-related neural activity on a single-subject level, indicating the potential for within-subject comparisons to minimize data heterogeneity [49]. Moreover, RI has been investigated with high-precision recordings of the neural activity by using intracranial monitoring of a single subject, in which tinnitus-linked, low-frequency neural oscillations were observed in auditory cortical regions, as well as other brain areas, and interacted with the middle- and high-frequency activity [50]. Reportedly, the distinct response of the neural activity to control stimuli that do not induce RI indicated that these changes correlated with RI [47,49]. Nevertheless, no comparison was performed with nontinnitus subjects perceiving RI stimuli, which could further demonstrate the correlation between RI and the tinnitus-associated neural activity.

This study aims to examine the brain activity in tinnitus and nontinnitus subjects using whole-scalp EEG recordings. RI will be used to modulate the tinnitus perception and enable a within-subject comparison. In addition, the RI stimuli will be matched with the tinnitus frequency of each participant, while the same low-frequency (0.5 kHz) control stimuli will be presented to all participants to exclude any effects of nonspecific sound-induced responses. We extend the applicable frequency range up to 13 kHz to enable a more accurate frequency identification of tinnitus and RI characteristics across a wider portion of the audibility range. Moreover, including nontinnitus subjects enables to compare between matched tinnitus and nontinnitus groups (ie, hearing loss characteristics) to determine whether the observed differences in the neuronal activity after RI are tinnitus-specific.

Objectives

The primary objective of this study is to identify tinnitus-associated neural oscillations in resting-state (spontaneous) scalp EEG data. We hypothesize that differences due to RI in the power spectral density (PSD) of baseline (tinnitus) and poststimulus (reduced tinnitus) measurements within the same subjects can be detected in traditional EEG

power bands. The secondary objectives of this project are as follows; (1) to improve understanding of the RI effect on the tinnitus-associated neural activity; (2) to identify differences in the PSD of the baseline period between the tinnitus and control groups; (3) to identify differences in the PSD of the poststimulus period between the tinnitus and control groups; and (4) to evaluate whether within-subject EEG data collection can reduce heterogeneity.

Methods

Study Design

Background

This research project is an observational study with a mixed design and will be conducted at the Department of Otolaryngology, Head and Neck Surgery at the Bern University Hospital, Inselspital, Bern, Switzerland. The protocol was designed in accordance with the ethical principles in the Declaration of Helsinki and has been approved by the local institutional review board (reference number: 2017-02037).

Participants and Eligibility Criteria

To participate in this study, tinnitus participants have to fulfill the following inclusion criteria: (1) age ≥18 years; (2) subjective tinnitus, that is nonfluctuating; (3) a single-pitched tinnitus perception that is unilateral, bilateral (in both ears), or central (in the head); (4) a difference between the loudness discomfort level (LDL) and minimum masking level (MML) of at least 20 dB; (5) “mild” to “severe” tinnitus, that is, a Tinnitus Handicap Inventory score between 18 and 76 [51]; and (6) sensitivity to RI, that is, a reduction of at least 2 points on a Likert scale of tinnitus loudness change (−5 to +5) directly after the presentation of the acoustic stimulus and for that reduction to be repeated at least 7-10 presentations (see section “Residual Inhibition”).

The exclusion criteria for tinnitus subjects are as follows: (1) LDLs preventing RI stimulation (see section “Tinnitometry”); (2) a history of central nervous system, cardiac, neurologic, psychiatric, or other major diseases or drug abuse, deemed clinically significant at the time of the study by the investigator (Multimedia Appendix 1 for details); (3) moderate or severe depression or generalized anxiety indicated by a Hospital Anxiety and Depression Scale score of at least 11 points on either subscale [52]; and (4) any participant who experiences RI after the 0.5 kHz control stimulus.

Non-tinnitus controls need to meet the following criteria for the study inclusion: (1) age≥18 years; (2) no tinnitus defined by self-reporting; and (3) comparable audiogram to one of the tinnitus subjects, that is, within ±15 dB at each of the frequencies of the extended air conduction hearing thresholds. The values can exceed this threshold at a maximum of 2 frequencies but not at the tinnitus pitch and control frequency.

Sample Size

To estimate the appropriate sample size, we used data from a previous study showing statistically significant differences between the PSDs of EEG recordings from tinnitus and nontinnitus participants [53]. The averaged power in the theta band was approximately 15.6 and 14.3 μV^2 for the tinnitus and nontinnitus subjects, respectively, and the pooled SD was 0.5 μV^2. A power analysis to test a two-sided hypothesis at a significance level of.05 and a power of 80% was estimated to require a sample size of 39 participants in each group. Up to 50 participants in each group meeting the eligibility criteria after pre-enrollment and the screening session will be recruited.

Recruitment

Participants will be recruited through the outpatient clinic and tinnitus consultation at our department. In addition, advertisements will be displayed in public areas and posted on the Web. No staff members from the clinic with a dependency relationship will be recruited. Potential participants who have the willingness and ability to perform all tests required for the study will sign and date an informed consent form before the start of the study procedure.

Study Procedure

Table 1 provides an overview of the study procedure. During pre-enrollment, a checklist will be filled by potential study participants to assess the tinnitus-associated psychological status (tinnitus subjects only), general health conditions, neurological conditions, and medical history. Potential study participants will then be invited to the screening session to assess the study eligibility. The total duration of the screening session will be 70 minutes for tinnitus subjects and 35 minutes for nontinnitus subjects. Eligible subjects will be invited to the assessment session with a total duration of 150 minutes, including preparation and postassessment cleaning time. The assessment consists of 2 subsessions with 30 minutes each, separated by a 10-minute break. All participants will be asked to avoid the consumption of coffee 5 hours before the assessment session [54].

Data Collection

Infrastructure and Measurement Equipment

All study-specific measurements will be performed in an acoustic chamber (6 m × 4 m × 2 m) certified for clinical audiometry with a broadband reverberation time of approximately 200 ms. The chamber is air-conditioned and provides electromagnetic shielding. For extended audiometry, tinnitometry, and RI assessment, we will use a custom-written script (The MathWorks Inc, v.2017b) with the Psychophysics-Toolbox extensions [55]. Acoustic stimuli will be presented through an external ASIO sound card (Scarlett2i2, FocusRite) and high-definition insert earphones (Triple-Driver, 1MORE Inc). Calibration of the acoustic stimuli (ie, pure tone and third-octave noise) will be confirmed using a head and torso simulator, including 2 ear simulators (Type 4128, Brüel & Kjaer) and an audio analyzer (UPV Audio analyzer DC-250 kHz, Rohde & Schwarz).

Table 1. Overview of the study procedure.

Item	Pre-enrollment	Screening session	Assessment session
Medical History	✓	N/A[a]	N/A
Questionnaires (over the Web)	✓	N/A	N/A
Audiometry	N/A	✓	N/A
Tinnitometry	N/A	✓	N/A
Residual Inhibition	N/A	✓	✓
Electroencephalography	N/A	N/A	✓

[a]N/A: not applicable.

Medical History and Questionnaires

The medical history contains information about the patients' health status and the cause of their tinnitus such as the presence of cardiovascular diseases, tinnitus objectivity, signs of otorrhea, and other external or middle ear diseases and drugs that can directly influence the analysis. The following questionnaires will be administered to assess the effects of tinnitus, co-occurring complaints, and health-related quality of life: (1) a general health checklist, aimed at identifying health problems that could affect the brain activity of interest; (2) the Tinnitus Handicap Inventory [56] to assess the severity of tinnitus symptoms; and (3) Hospital Anxiety and Depression Scale [52] to assess depression and anxiety.

Audiometry

Standard pure tone audiometry will be performed to assess bone conduction hearing thresholds (in dB hearing level) at 0.5, 0.75, 1, 2, 3, 4, and 6 kHz and air conduction hearing thresholds (in dB hearing level) at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. In addition, an extended assessment of air conduction hearing thresholds (in dB SPL) will be performed at 9, 10, 11, 12, and 13 kHz using a custom-written script and insert earphones.

Tinnitometry

Subjects will classify the laterality (ie, unilateral left, unilateral right, bilateral "at both ears," or central "in the head") and quality (ie, tonal or noise like) of their tinnitus. The tinnitus pitch will be matched with either pure tone or third-octave noise stimuli ranging from 0.125 to 13 kHz, and the tinnitus loudness at tinnitus pitch (in dB SPL) will be estimated. The MML corresponds to the level of a third-octave noise stimulus (in dB SPL) at which it just renders tinnitus unperceivable. The LDL (in dB SPL) corresponds to the level at which subjects report the stimulus to be uncomfortably loud will be measured.

Residual Inhibition

For both ears, the air conduction thresholds for third-octave noise stimuli will be obtained for a stimulus centered at the tinnitus pitch and a 0.5-kHz control frequency. At the tinnitus pitch, the level of the RI stimulus will be specified by adding 20 dB to the MML [57] of the tinnitus ear (in the unilateral case) and by adding 20 dB to the MML of each ear separately (in bilateral or central cases). In the unilateral case, the contralateral ear will be presented with a stimulus level that is specified by adding the RI stimulation sensation level (the difference between the RI stimulus level and the third-octave noise hearing threshold) of the tinnitus ear to its third-octave noise hearing threshold. The third-octave noise control stimulus centered at 0.5 kHz will be presented at the same sensation level as the RI stimulus.

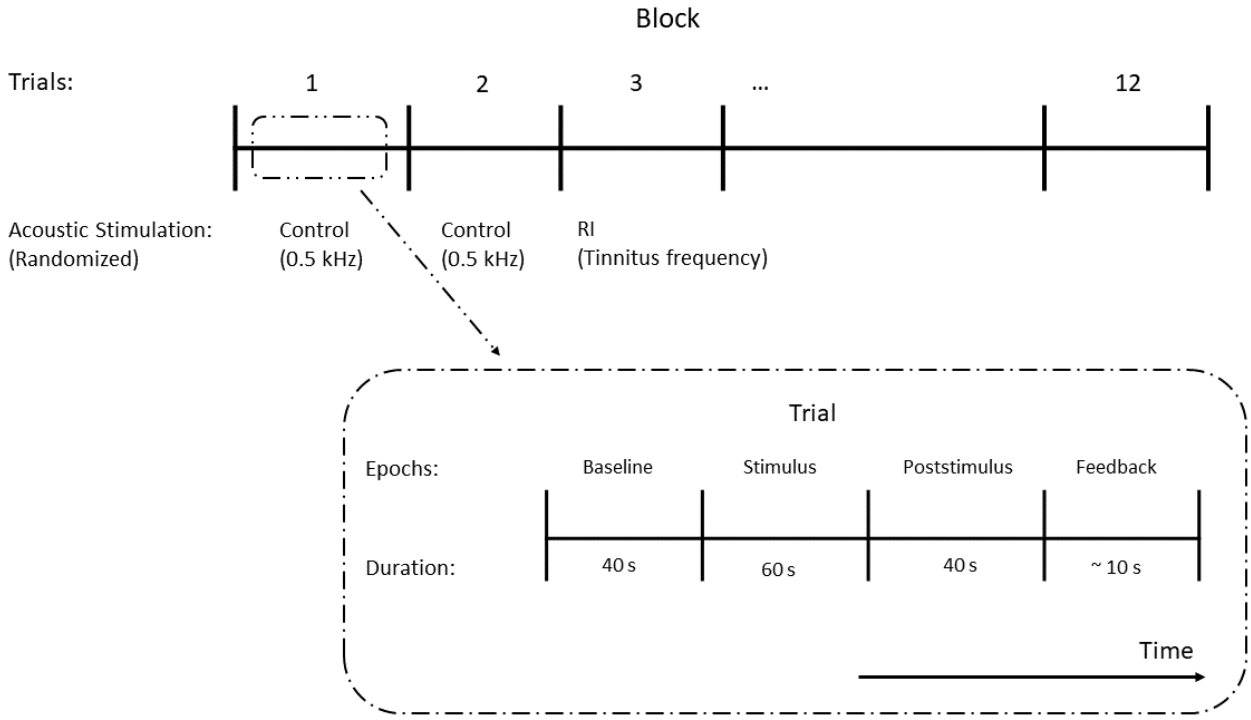
To assess the RI capability, the following procedure will be followed using a 60-second RI stimulus presented through insert earphones. For each of 10 presentations, participants with tinnitus will indicate whether they experience partial or complete suppression of their tinnitus by rating the loudness change on a Likert scale (−5 to +5) immediately after the stimulus presentation. In addition, to obtain time course of their tinnitus change, tinnitus subjects will be asked to continuously rate the loudness change on the Likert scale until their tinnitus has returned to the loudness before the RI stimulus.

Electroencephalography

EEG recording will be performed with an active electrode 64-channel biopotential measurement system (ActiveTwo, Biosemi). After selection of a suitable EEG head cap and adjustment of the cap position, electrode gel (Signa Gel, Parker Laboratories, Inc) will be injected, and the electrodes will be attached. The position of the electrodes was selected according to the 10/20 standard scheme for 64 electrodes and 2 additional channels for the active common mode sense and passive-driven right leg electrodes. In addition, the three-dimensional coordinates of all electrodes will be recorded. For electrooculography (EOG) and electromyography (EMG) recording, 8 adhesive surface electrodes will be placed at the head of subjects (left and right outer canthus, right infraorbital and supraorbital, left and right masseter, and left and right mastoid). The offset of each electrode will be checked, measured, and, if required, electrode gel will be added until the offset falls within ±40 mV. Participants will be instructed to use a response box for an automated recording procedure (MATLAB script). Trigger events, such as measurement start, stimulus onsets or offsets, and participants' responses, will directly recorded by the EEG software (ActiView, Biosemi).

EEGs will be recorded during 2 blocks consisting of 12 trials each (Figure 1). Each trial consists of 4 epochs—"Baseline," "Stimulus," "Poststimulus," and "Feedback." The "Baseline" epoch lasts 40 seconds in which spontaneous resting-state EEG is recorded. During the "Stimulus" epoch, the RI and control stimuli will be presented to subjects through the insert earphones for 60 seconds. The RI and control stimuli are played in a randomized sequence to avoid habituation of neural responses.

Figure 1. Overview of the electroencephalography recording procedure. RI: residual inhibition.



Subjects are blinded with respect to the order of the stimulation sequence. In the "Poststimulus" epoch, spontaneous resting-state EEG will be recorded for 40 seconds. Tinnitus subjects will be asked to indicate the return of their tinnitus to the normal loudness level by a button press and stay with minimal movement until the end of this epoch. Non-tinnitus controls will be asked to press a button immediately after they perceived a narrow-band stimulus with a central frequency and sensation level same as their matched tinnitus subjects. The stimulus has a duration of 3 seconds and will start 37 seconds after turning off the RI or control stimuli. This process will minimize bias by performing a similar task as tinnitus subjects. In the "Feedback" epoch, EEG recording will be stopped, and participants will be asked to rate the degree of tinnitus loudness change immediately after the stimulus presentation, as well as the change of psychological condition on a scale from −5 to 5 (−5 indicating quieter or feeling less burdened, 0 indicating no change, and +5 indicating louder or feeling more burdened) using the response box. The duration of this epoch is approximately 10 seconds.

Several steps will be taken to suppress or reduce artifacts during EEG recording. The acoustic chamber is electromagnetically shielded. The measurement amplifier is connected by a fiber optic data transfer to the measurement computer outside of the chamber. Before EEG recording is started, light and all power lines will be switched off and no electrical devices, except the battery-powered EEG amplifier, will be active inside the chamber In addition, the chamber will be air-conditioned to avoid contact artifacts of electrodes caused by sweating. During the assessment, participants will be asked to sit relaxed with their eyes closed; they will be instructed to move their body or eyes as little as possible to minimize motion artifacts, especially when making a button press response. To account for muscle and eye artifacts, EOG or EMG are additionally recorded.

Data Analysis

Data Preprocessing

Data preprocessing will be performed with the academic software package Python-MNE [58]. Raw EEG data will be filtered with a zero-phase band-pass filter (0.01-100 Hz). Unpublished results from our preliminary EEG assessments suggest that EEG signals collected in an electromagnetically shielded measurement environment may not need notch filtering for the power line noise removal. The EEG data will be referenced with an average reference. The EEG dataset will be decomposed into independent components using the extended infomax independent component analysis algorithm [59]. The obtained independent components will be visually inspected and compared with EOG and EMG data (using correlation-based analysis). After removing independent components related to artifacts, the EEG data will be reconstructed with the inverse independent component analysis procedure and will be segmented into 1-second epochs.

Statistical Analysis

Descriptive statistics will be used to report demographic and baseline characteristics. Quantitative data will be presented as mean, SD, and range (minimum and maximum); qualitative data will be presented as absolute and relative frequencies and, if appropriate, as graphs. We plan to use a linear mixed-effects model to test within-subject and between-group differences in traditional EEG power bands, with the participant group (ie, "tinnitus subject" and "nontinnitus subject"), time-point (ie, "baseline," "stimulus," and "poststimulus"), and stimulus type (ie, "RI stimulus" and "control stimulus") as fixed effects. Subject IDs will be included as a random effect to account for repeated measures. Missing data will not be replaced but treated as "missing" values.

Results

Ethical approval was obtained in December 2017, and enrollment started in February 2018. The first results are expected in 2019.

Discussion

Tinnitus is a complex symptom, the pathophysiology of which has perplexed clinicians over the last decades. Recently, neuroimaging techniques with the ability to investigate neural activities have yielded new insights into the tinnitus research [15-20]. The design of this protocol aims to further study abnormal brain oscillations in the coexistence of tinnitus. With the presented within-subject measurement design, we expect minimized data heterogeneity across subjects, which should improve the outcome quality. In addition, high-frequency audiometry, tinnitometry, and RI may provide a more accurate description of tinnitus symptoms. Furthermore, applying the same low-frequency control stimulus to all subjects will help to exclude induced EEG responses caused by external acoustic stimuli. We plan to publish the results in international peer-reviewed open access journals and present at relevant international tinnitus conferences. After the completion of data analysis, anonymized raw or processed data can be made available to interested parties upon request to the corresponding author.

Recently, a data-driven approach using machine learning-based algorithm has been applied to analyze source-localized, resting-state EEG, which was able to classify tinnitus and healthy control subjects with an average accuracy rate of 87.7%, indicating a potential pattern of the neural activity as a cortical signature for tinnitus [60]. Pure data-driven approaches can be used to validate existing theoretical tinnitus models and might advance tinnitus research. Therefore, this protocol was designed to enable structured labeling of EEG data (different conditions of tinnitus perception before and after RI presentation), which can be used for machine learning-based analysis.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Central nervous system, cardiac, neurologic, psychiatric, or other major diseases that are used as exclusion criteria.

[PDF File (Adobe PDF File), 187KB - resprot_v8i1e12270_app1.pdf]

References

1. Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. Lancet Neurol 2013 Sep;12(9):920-930. [doi: 10.1016/S1474-4422(13)70160-1] [Medline: 23948178]
2. Ahmad N, Seidman M. Tinnitus in the older adult: epidemiology, pathophysiology and treatment options. Drugs Aging 2004;21(5):297-305. [doi: 10.2165/00002512-200421050-00002] [Medline: 15040757]
3. Medical Research Councils Institute of Hearing Research. Epidemiology of Tinnitus. In: David E, Geralyn L, editors. Ciba Foundation Symposium 85 - Tinnitus. Great Britain: The Pitman Press; 1981:16-34.
4. Nicolas-Puel C, Akbaraly T, Lloyd R, Berr C, Uziel A, Rebillard G, et al. Characteristics of tinnitus in a population of 555 patients: specificities of tinnitus induced by noise trauma. Int Tinnitus J 2006;12(1):64-70. [Medline: 17147043]
5. Henry JA, Dennis KC, Schechter MA. General review of tinnitus: prevalence, mechanisms, effects, and management. J Speech Lang Hear Res 2005 Oct;48(5):1204-1235. [doi: 10.1044/1092-4388(2005/084)] [Medline: 16411806]
6. Sanchez TG, Medeiros IRTD, Levy CPD, Ramalho JDRO, Bento RF. Tinnitus in normally hearing patients: clinical aspects and repercussions. Braz J Otorhinolaryngol 2005;71(4):427-431 [FREE Full text] [Medline: 16446955]
7. Hinton DE, Chhean D, Pich V, Hofmann SG, Barlow DH. Tinnitus among Cambodian refugees: relationship to PTSD severity. J Trauma Stress 2006 Aug;19(4):541-546. [doi: 10.1002/jts.20138] [Medline: 16929509]
8. Pan T, Tyler RS, Ji H, Coelho C, Gehringer AK, Gogel SA. The relationship between tinnitus pitch and the audiogram. Int J Audiol 2009 May;48(5):277-294. [Medline: 19842803]
9. Andersson G, McKenna L. Tinnitus masking and depression. Audiology 1998;37(3):174-182. [Medline: 9626862]
10. Levine RA, Nam EC, Melcher J. Somatosensory pulsatile tinnitus syndrome: somatic testing identifies a pulsatile tinnitus subtype that implicates the somatosensory system. Trends Amplif 2008 Sep;12(3):242-253 [FREE Full text] [doi: 10.1177/1084713808321185] [Medline: 18632767]

11. Tyler RS, Gogel SA, Gehringer AK. Tinnitus activities treatment. Prog Brain Res 2007;166:425-434. [doi: 10.1016/S0079-6123(07)66041-5] [Medline: 17956807]
12. Hall DA, Haider H, Szczepek AJ, Lau P, Rabau S, Jones-Diette J, et al. Systematic review of outcome domains and instruments used in clinical trials of tinnitus treatments in adults. Trials 2016 Dec 01;17(1):270 [FREE Full text] [doi: 10.1186/s13063-016-1399-9] [Medline: 27250987]
13. Norena A, Micheyl C, Chéry-Croze S, Collet L. Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. Audiol Neurootol 2002;7(6):358-369. [doi: 10.1159/000066156] [Medline: 12401967]
14. Eggermont JJ, Roberts LE. The neuroscience of tinnitus: understanding abnormal and normal auditory perception. Front Syst Neurosci 2012;6:53 [FREE Full text] [doi: 10.3389/fnsys.2012.00053] [Medline: 22798948]
15. Song JJ, De Ridder D, Van de Heyning P, Vanneste S. Mapping tinnitus-related brain activation: an activation-likelihood estimation metaanalysis of PET studies. J Nucl Med 2012 Oct;53(10):1550-1557 [FREE Full text] [doi: 10.2967/jnumed.112.102939] [Medline: 22917883]
16. Adamchic I, Toth T, Hauptmann C, Tass PA. Reversing pathologically increased EEG power by acoustic coordinated reset neuromodulation. Hum Brain Mapp 2014 May;35(5):2099-2118 [FREE Full text] [doi: 10.1002/hbm.22314] [Medline: 23907785]
17. van der Loo E, Gais S, Congedo M, Vanneste S, Plazier M, Menovsky T, et al. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS One 2009 Oct 09;4(10):e7396 [FREE Full text] [doi: 10.1371/journal.pone.0007396] [Medline: 19816597]
18. Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 1999 Dec 21;96(26):15222-15227 [FREE Full text] [Medline: 10611366]
19. Weisz N, Müller S, Schlee W, Dohrmann K, Hartmann T, Elbert T. The neural code of auditory phantom perception. J Neurosci 2007 Feb 07;27(6):1479-1484 [FREE Full text] [doi: 10.1523/JNEUROSCI.3711-06.2007] [Medline: 17287523]
20. Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology 2007 Aug;49(8):669-679. [doi: 10.1007/s00234-007-0231-3] [Medline: 17404721]
21. Ashton H, Reid K, Marsh R, Johnson I, Alter K, Griffiths T. High frequency localised “hot spots” in temporal lobes of patients with intractable tinnitus: a quantitative electroencephalographic (QEEG) study. Neurosci Lett 2007 Oct 09;426(1):23-28. [doi: 10.1016/j.neulet.2007.08.034] [Medline: 17888572]
22. Weisz N, Moratti S, Meinzer M, Dohrmann K, Elbert T. Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. PLoS Med 2005 Jun;2(6):e153 [FREE Full text] [doi: 10.1371/journal.pmed.0020153] [Medline: 15971936]
23. De Ridder D, Congedo M, Vanneste S. The neural correlates of subjectively perceived and passively matched loudness perception in auditory phantom perception. Brain Behav 2015 May;5(5):e00331 [FREE Full text] [doi: 10.1002/brb3.331] [Medline: 25874164]
24. Adjamian P, Sereda M, Zobay O, Hall DA, Palmer AR. Neuromagnetic indicators of tinnitus and tinnitus masking in patients with and without hearing loss. J Assoc Res Otolaryngol 2012 Oct;13(5):715-731 [FREE Full text] [doi: 10.1007/s10162-012-0340-5] [Medline: 22791191]
25. Balkenhol T, Wallhäusser-Franke E, Delb W. Psychoacoustic tinnitus loudness and tinnitus-related distress show different associations with oscillatory brain activity. PLoS One 2013;8(1):e53180 [FREE Full text] [doi: 10.1371/journal.pone.0053180] [Medline: 23326394]
26. Moazami-Goudarzi M, Michels L, Weisz N, Jeanmonod D. Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. BMC Neurosci 2010 Mar 24;11:40 [FREE Full text] [doi: 10.1186/1471-2202-11-40] [Medline: 20334674]
27. Muthukumaraswamy SD. High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations. Front Hum Neurosci 2013;7:138 [FREE Full text] [doi: 10.3389/fnhum.2013.00138] [Medline: 23596409]
28. Vanneste S, van Dongen M, De Vree B, Hiseni S, van der Velden E, Strydis C, et al. Does enriched acoustic environment in humans abolish chronic tinnitus clinically and electrophysiologically? A double blind placebo controlled study. Hear Res 2013 Feb;296:141-148. [doi: 10.1016/j.heares.2012.10.003] [Medline: 23104014]
29. Silchenko AN, Adamchic I, Hauptmann C, Tass PA. Impact of acoustic coordinated reset neuromodulation on effective connectivity in a neural network of phantom sound. Neuroimage 2013 Aug 15;77:133-147 [FREE Full text] [doi: 10.1016/j.neuroimage.2013.03.013] [Medline: 23528923]
30. Vanneste S, van de Heyning P, De Ridder D. The neural network of phantom sound changes over time: a comparison between recent-onset and chronic tinnitus patients. Eur J Neurosci 2011 Sep;34(5):718-731. [doi: 10.1111/j.1460-9568.2011.07793.x] [Medline: 21848924]
31. Song JJ, Vanneste S, Schlee W, Van de Heyning P, De Ridder D. Onset-related differences in neural substrates of tinnitus-related distress: the anterior cingulate cortex in late-onset tinnitus, and the frontal cortex in early-onset tinnitus. Brain Struct Funct 2015 Jan;220(1):571-584. [doi: 10.1007/s00429-013-0648-x] [Medline: 24135769]

32. Vanneste S, Congedo M, De Ridder D. Pinpointing a highly specific pathological functional connection that turns phantom sound into distress. Cereb Cortex 2014 Sep;24(9):2268-2282. [doi: 10.1093/cercor/bht068] [Medline: 23632885]
33. Vanneste S, De Ridder D. Brain areas controlling heart rate variability in tinnitus and tinnitus-related distress. PLoS One 2013;8(3):e59728 [FREE Full text] [doi: 10.1371/journal.pone.0059728] [Medline: 23533644]
34. Song JJ, Punte AK, De Ridder D, Vanneste S, Van de Heyning P. Neural substrates predicting improvement of tinnitus after cochlear implantation in patients with single-sided deafness. Hear Res 2013 May;299:1-9. [doi: 10.1016/j.heares.2013.02.001] [Medline: 23415916]
35. Adamchic I, Hauptmann C, Tass PA. Changes of oscillatory activity in pitch processing network and related tinnitus relief induced by acoustic CR neuromodulation. Front Syst Neurosci 2012;6:18 [FREE Full text] [doi: 10.3389/fnsys.2012.00018] [Medline: 22493570]
36. Tass PA, Adamchic I, Freund HJ, von Stackelberg T, Hauptmann C. Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor Neurol Neurosci 2012;30(2):137-159. [doi: 10.3233/RNN-2012-110218] [Medline: 22414611]
37. De Ridder D, Vanneste S, Congedo M. The distressed brain: a group blind source separation analysis on tinnitus. PLoS One 2011;6(10):e24273 [FREE Full text] [doi: 10.1371/journal.pone.0024273] [Medline: 21998628]
38. Vanneste S, Plazier M, van der Loo E, Van de Heyning P, De Ridder D. The differences in brain activity between narrow band noise and pure tone tinnitus. PLoS One 2010 Oct 27;5(10):e13618 [FREE Full text] [doi: 10.1371/journal.pone.0013618] [Medline: 21048975]
39. Vanneste S, Joos K, De Ridder D. Prefrontal cortex based sex differences in tinnitus perception: same tinnitus intensity, same tinnitus distress, different mood. PLoS One 2012;7(2):e31182 [FREE Full text] [doi: 10.1371/journal.pone.0031182] [Medline: 22348053]
40. Vanneste S, Heyning PVD, Ridder DD. Contralateral parahippocampal gamma-band activity determines noise-like tinnitus laterality: a region of interest analysis. Neuroscience 2011 Dec 29;199:481-490. [doi: 10.1016/j.neuroscience.2011.07.067] [Medline: 21920411]
41. Vanneste S, Plazier M, van der Loo E, Van de Heyning P, De Ridder D. The difference between uni- and bilateral auditory phantom percept. Clin Neurophysiol 2011 Mar;122(3):578-587. [doi: 10.1016/j.clinph.2010.07.022] [Medline: 20801079]
42. Vanneste S, Plazier M, der Loo EV, de Heyning PV, Congedo M, De Ridder D. The neural correlates of tinnitus-related distress. Neuroimage 2010 Aug 15;52(2):470-480. [doi: 10.1016/j.neuroimage.2010.04.029] [Medline: 20417285]
43. van der Loo E, Congedo M, Vanneste S, Van De Heyning P, De Ridder D. Insular lateralization in tinnitus distress. Auton Neurosci 2011 Dec 07;165(2):191-194. [doi: 10.1016/j.autneu.2011.06.007] [Medline: 21889914]
44. Elgoyhen AB, Langguth B, De Ridder D, Vanneste S. Tinnitus: perspectives from human neuroimaging. Nat Rev Neurosci 2015 Oct;16(10):632-642. [doi: 10.1038/nrn4003] [Medline: 26373470]
45. Roberts LE, Moffat G, Baumann M, Ward LM, Bosnyak DJ. Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. J Assoc Res Otolaryngol 2008 Dec;9(4):417-435 [FREE Full text] [doi: 10.1007/s10162-008-0136-9] [Medline: 18712566]
46. Roberts LE, Moffat G, Bosnyak DJ. Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift. Acta Otolaryngol Suppl 2006 Dec(556):27-33. [doi: 10.1080/03655230600895358] [Medline: 17114139]
47. Kahlbrock N, Weisz N. Transient reduction of tinnitus intensity is marked by concomitant reductions of delta band power. BMC Biol 2008 Jan 16;6:4 [FREE Full text] [doi: 10.1186/1741-7007-6-4] [Medline: 18199318]
48. Kumar S, Sedley W, Barnes GR, Teki S, Friston KJ, Griffiths TD. A brain basis for musical hallucinations. Cortex 2014 Mar;52:86-97 [FREE Full text] [doi: 10.1016/j.cortex.2013.12.002] [Medline: 24445167]
49. Sedley W, Teki S, Kumar S, Barnes GR, Bamiou DE, Griffiths TD. Single-subject oscillatory γ responses in tinnitus. Brain 2012 Oct;135(Pt 10):3089-3100 [FREE Full text] [doi: 10.1093/brain/aws220] [Medline: 22975389]
50. Sedley W, Gander PE, Kumar S, Oya H, Kovach CK, Nourski KV, et al. Intracranial Mapping of a Cortical Tinnitus System using Residual Inhibition. Curr Biol 2015 May 04;25(9):1208-1214 [FREE Full text] [doi: 10.1016/j.cub.2015.02.075] [Medline: 25913402]
51. McCombe A, Baguley D, Coles R, McKenna L, McKinney C, Windle-Taylor P, British Association of Otolaryngologists, HeadNeck Surgeons. Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. Clin Otolaryngol Allied Sci 2001 Oct;26(5):388-393. [Medline: 11678946]
52. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [Medline: 6880820]
53. Weiler EW, Brill K, Tachiki KH, Wiegand R. Electroencephalography correlates in tinnitus. Int Tinnitus J 2000;6(1):21-24. [Medline: 14689613]
54. Landolt HP, Rétey JV, Tönz K, Gottselig JM, Khatami R, Buckelmüller I, et al. Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. Neuropsychopharmacology 2004 Oct;29(10):1933-1939 [FREE Full text] [doi: 10.1038/sj.npp.1300526] [Medline: 15257305]
55. Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C. What's new in Psychtoolbox-3. Perception 2007.
56. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg 1996 Feb;122(2):143-148. [Medline: 8630207]

57. Terry AM, Jones DM, Davis BR, Slater R. Parametric studies of tinnitus masking and residual inhibition. Br J Audiol 1983 Nov;17(4):245-256. [Medline: 6667357]
58. Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, et al. MNE software for processing MEG and EEG data. Neuroimage 2014 Feb 01;86:446-460 [FREE Full text] [doi: 10.1016/j.neuroimage.2013.10.027] [Medline: 24161808]
59. Jung TP, Humphries C, Lee T, Makeig S, McKeown M, Iragui J, et al. Extended ICA removes artifacts from electroencephalographic recordings. Advances in neural information processing systems 1998:894-900.
60. Vanneste S, Song JJ, De Ridder D. Thalamocortical dysrhythmia detected by machine learning. Nat Commun 2018 Dec 16;9(1):1103 [FREE Full text] [doi: 10.1038/s41467-018-02820-0] [Medline: 29549239]

Abbreviations

EEG: electroencephalography
EMG: electromyography
EOG: electrooculography
MEG: magnetoencephalography
MML: minimum masking level
PSD: power spectral density
RI: residual inhibition
LDL: loudness discomfort level

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Protocol

Estimating Vaccine Effectiveness Against Hospitalized Influenza During Pregnancy: Multicountry Protocol for a Retrospective Cohort Study

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Abstract

Background: Although pregnant women are believed to have elevated risks of severe influenza infection and are targeted for influenza vaccination, no study to date has examined influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalizations during pregnancy, primarily because this outcome poses many methodological challenges.

Objective: The Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) was formed in 2016 as an international collaboration with the Centers for Disease Control and Prevention; Abt Associates; and study sites in Australia, Canada, Israel, and the United States. The primary goal of this collaboration is to estimate IVE in preventing acute respiratory or febrile illness (ARFI) hospitalizations associated with laboratory-confirmed influenza virus infection during pregnancy. Secondary aims include (1) describing the incidence, clinical course, and severity of influenza-associated ARFI hospitalization during pregnancy; (2) comparing the characteristics of ARFI-hospitalized pregnant women who were tested for influenza with those who were not tested; (3) describing influenza vaccination coverage in pregnant women; and (4) comparing birth outcomes among women with laboratory-confirmed influenza-associated hospitalization versus other noninfluenza ARFI hospitalizations.

Methods: For an initial assessment of IVE, sites identified a retrospective cohort of pregnant women aged from 18 to 50 years whose pregnancies overlapped with local influenza seasons from 2010 to 2016. Pregnancies were defined as those that ended in a live birth or stillbirth of at least 20 weeks gestation. The analytic sample for the primary IVE analysis was restricted to pregnant women who were hospitalized for ARFI during site-specific influenza seasons and clinically tested for influenza virus infection using real-time reverse transcription polymerase chain reaction.

Results: We identified approximately 2 million women whose pregnancies overlapped with influenza seasons; 550,344 had at least one hospitalization during this time. After restricting to women who were hospitalized for ARFI and tested for influenza, the IVE analytic sample included 1005 women.

Conclusions: In addition to addressing the primary question about the effectiveness of influenza vaccination, PREVENT data will address other important knowledge gaps including understanding the incidence, clinical course, and severity of influenza-related hospitalizations during pregnancy. The data infrastructure and international partnerships created for these analyses may be useful and informative for future influenza studies.

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KEYWORDS

influenza; pregnancy; hospitalization; epidemiology; vaccines

Introduction

Background

Pregnant women are believed to be at greater risk of severe complications from influenza infection than nonpregnant women of childbearing age, based on findings from studies primarily conducted during influenza pandemics [1,2]. Anatomic, immunologic, and physiologic changes during pregnancy that affect respiratory, cardiovascular, and other organ systems might increase the risk and severity of infections, including influenza [3,4]. The risk of hospitalization due to clinically diagnosed influenza or pneumonia appears to increase with each trimester of pregnancy [5-7]. The vulnerability of pregnant women to severe influenza disease was observed during the 2009 A (H1N1) pandemic [8-10] and at least two prior pandemics [11,12]. However, there are substantial gaps in our knowledge regarding the seasonal burden of influenza among pregnant women.

Influenza vaccination is an effective method of influenza prevention, but the vaccine is widely underutilized during pregnancy [13-15]. Although there are ample data on the safety of inactivated influenza vaccination (IIV) during pregnancy [16-18], a major challenge to maternal immunization policy making has been the paucity of data regarding the effectiveness of IIV in preventing severe influenza-related outcomes in pregnant women [2,19]. Serologic studies have found a similar antibody response to the vaccine among pregnant and nonpregnant women [20,21]. Several observational studies have compared the rates of nonspecific respiratory illness among vaccinated and unvaccinated pregnant women with mixed results [20,22-25]. Randomized controlled trials [24,26] and observational studies in pregnant women [27,28] have reported that IIV reduces the risk of mild to moderately severe laboratory-confirmed influenza illness by about half.

Objectives

No study to date has examined influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalization during pregnancy. This is an important gap in knowledge for maternal immunization policy. Perhaps the greatest challenge in addressing this IVE question is identifying study populations with sufficient numbers of influenza-related hospitalizations during pregnancy in nonpandemic seasons. Randomized controlled trials and prospective observational studies are impractical due to the large number of women that would be required to observe a statistically meaningful number of hospitalizations. In addition, randomized controlled trials may be unethical in high-income countries where influenza vaccination is recommended for pregnant women. Large-scale retrospective observational studies may be feasible, but no single public or private health care database with influenza testing results and influenza vaccination records is large enough to adequately address the question. After considering these limitations, the US Centers for Disease Control and Prevention (CDC) reached out to international partners to build a collaboration capable of determining IVE against hospitalization in pregnant women. In addition to addressing the primary IVE question, the collaboration was envisioned as a way to explore other important gaps in our understanding of influenza infection and vaccination during pregnancy.

Methods

Overview

The Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) was formed in 2016 as an international collaboration with the US CDC, Abt Associates, and study sites in 4 countries: Australia, Canada, Israel, and the United States. PREVENT was established to address multiple gaps in knowledge about influenza vaccination and infection during pregnancy (Textbox 1). The primary goal of this collaboration was to estimate IVE in preventing acute respiratory or febrile illness (ARFI) hospitalizations associated with laboratory-confirmed influenza virus infection during pregnancy.

Textbox 1. Study goals and features intended to address specific knowledge gaps.

Primary analysis: assess inactivated influenza vaccine effectiveness (IVE) in preventing severe influenza disease during pregnancy

Knowledge gap:

- No study to date has examined IVE against laboratory-confirmed influenza hospitalization during pregnancy
- Information is limited on how IVE during pregnancy may vary across seasons and by influenza type and subtype
- Information is needed on whether influenza vaccinations received in previous seasons (before pregnancy) affect IVE during pregnancy

Study feature:

- Assess IVE against laboratory-confirmed influenza-associated hospitalization using the test-negative design
- Assess IVE by site and study season and across seasons by influenza type and subtype
- Where prior season vaccination records are available, assess IVE by combinations of current and prior season influenza vaccination status

Secondary analysis: assess the frequency of hospitalization for acute respiratory and febrile illness (ARFI) associated with laboratory-confirmed influenza virus infection during pregnancy

Knowledge gap:

- Studies of influenza during pregnancy using laboratory-confirmed outcomes are scarce
- Studies of influenza-associated hospitalization during pregnancy have been predominantly limited to the United States
- Studies often enroll only during peak periods of virus circulation
- Information is limited on atypical and nonrespiratory disease manifestations of influenza virus infection
- Information on the burden of influenza disease associated with seasonal influenza viruses during pregnancy is limited, especially for severe disease requiring hospitalization

Study feature:

- Identify hospitalizations during influenza season among pregnant women with clinical testing for influenza by real-time reverse transcriptase polymerase chain reaction assay (rRT-PCR)
- Examine influenza-associated hospitalizations in regions of Australia, Canada, Israel, and the United States
- Examine influenza-associated hospitalizations during early, peak, and late periods of influenza circulation
- Assess the frequency of influenza virus infections among women hospitalized without influenza or pneumonia diagnoses, including febrile-only and sepsis-like syndromes
- Assess the incidence of influenza-associated hospitalization during pregnancy over multiple influenza seasons by study site

Secondary analysis: describe the clinical features of influenza-associated hospitalization during pregnancy

Knowledge gap:

- Frequency and application of clinical influenza testing among pregnant women hospitalized with acute respiratory illness during influenza season is unknown
- Information on the clinical epidemiology of severe influenza disease during pregnancy is scarce, especially for seasonal influenza
- Further research is needed to identify risk factors for very severe influenza disease during pregnancy that requires intensive care
- Information on the clinical course of influenza virus infections among pregnant women during hospitalization is limited, especially for those with laboratory-confirmed seasonal influenza
- Variation in illness severity and outcomes among influenza virus type and subtype has not been assessed among pregnant women with seasonal influenza
- Information on the frequency of deliveries among women hospitalized with influenza is limited

Study feature:

- Assess the frequency of clinical influenza testing across health care systems and countries and compare characteristics of tested versus untested pregnant women and their reasons for hospitalization
- Describe the characteristics of pregnant women (eg, age, trimester, underlying health conditions) hospitalized with influenza virus infection and their clinical diagnoses
- Assess the characteristics of pregnant women with influenza virus infection who are admitted to an intensive care unit (ICU) during hospitalization
- Describe the length of stay in the general ward or ICU and the frequencies of pneumonia diagnosis, respiratory failure, and need for intensive care of pregnant women hospitalized with influenza

- Compare indicators of illness severity and selected hospitalization outcomes among women with laboratory-confirmed influenza by type and subtype
- Assess the frequency of deliveries during hospitalizations with ARFI diagnoses associated with maternal influenza virus infection

Secondary analysis: describe the frequency and clinical features of respiratory syncytial virus (RSV)-associated hospitalization during pregnancy

Knowledge gap:

- Despite substantial evidence highlighting the burden of RSV in young children, little is known about RSV infection during pregnancy
- Few studies have documented the impact of antenatal RSV infection on birth outcomes

Study feature:

- Describe the clinical characteristics of RSV infection during pregnancy
- Describe outcomes at birth for women testing positive for RSV during pregnancy compared with women who test negative

Secondary analysis: examine birth outcomes associated with hospitalized influenza infection during pregnancy

Knowledge gap:

- Perinatal risks posed by antenatal influenza virus infection are unclear, especially for seasonal influenza
- Few comparative studies have accounted for gestational timing of influenza infection when comparing birth outcomes in influenza-infected and uninfected women

Study feature:

- Compare birth outcomes of women hospitalized with ARFI with laboratory-confirmed influenza virus infection with birth outcomes of women with ARFI hospitalizations confirmed as influenza-negative and women without ARFI hospitalization during pregnancy
- Compare birth outcomes by gestational age at influenza infection in women hospitalized with laboratory-confirmed influenza

Secondary analysis: assess the frequency of vaccination with inactivated influenza vaccine (IIV) during pregnancy across countries and health care systems

Knowledge gap:

- Information is limited on the uptake of IIV during pregnancy across health care systems and countries
- Information is limited on the timing of IIV vaccination, even though this has implications for the protection of the mother and the transfer of protective antibodies to the fetus
- More information is needed on the differences between IIV vaccinated versus unvaccinated pregnant women who are at greatest risk for influenza hospitalization

Study feature:

- Describe IIV coverage among women pregnant during influenza vaccine campaigns and/or influenza seasons across multiple years and study sites
- Describe the frequency of IIV vaccination among pregnant women by stage of pregnancy and relative to influenza season
- Compare the socio-demographic and underlying health characteristics of pregnant women hospitalized for ARFI during influenza season by seasonal vaccination status

Secondary aims include estimating the incidence of influenza-associated ARFI hospitalization during pregnancy, comparing the characteristics of ARFI-hospitalized pregnant women who were tested for influenza with those who were not tested, describing the clinical course and severity of influenza and noninfluenza ARFI hospitalizations during pregnancy, and describing the clinical course of respiratory syncytial virus (RSV)–associated hospitalizations during pregnancy (Textbox 1). Participating sites will also describe influenza vaccination rates in pregnant women and compare birth outcomes (such as low birth weight, preterm delivery, and small-for-gestational age births) among women with laboratory-confirmed influenza-associated hospitalizations versus other noninfluenza ARFI hospitalizations.

Study Sites and Enrollment

In 2015, study investigators conducted a series of telephone interviews and written surveys to recruit potential international study sites. To be considered a potential PREVENT site, institutions were required to meet several inclusion criteria related to the underlying characteristics of the source population, clinical and laboratory practices, and availability of high-quality regional respiratory virus surveillance and electronic medical record (EMR) data (Textbox 2).

Textbox 2. Eligibility criteria for The Pregnancy Influenza Vaccine Effectiveness Network study site selection.

- Influenza surveillance data to identify weeks of local influenza circulation for multiple years (ideally dating from 2010) were available
- Women who were pregnant during hospitalization for acute respiratory or febrile illness could be identified with electronic medical records, administrative data, or laboratory records
- Diagnostic hospital admission and/or discharge codes (International Classification of Diseases ninth revision or International Classification of Diseases, tenth revision with Australian and Canadian variations) from the records described above were accessible
- Demographic characteristics, underlying medical conditions before pregnancy, pregnancy history, and medical complications during pregnancy were available from medical records or routine registry data
- Pregnant women with acute respiratory or febrile disease during influenza season were routinely tested for influenza with real-time reverse transcriptase polymerase chain reaction (rRT-PCR) at study facilities
- Demographic characteristics, underlying medical conditions, influenza vaccination status, and clinical diagnoses of pregnant women who received clinical virus testing could be compared with those of pregnant women who were not tested during influenza season
- Influenza vaccine coverage among pregnant women in the catchment area was modest to high (10%-70%) but not universal during the study period
- Influenza vaccination records from electronic registries, electronic medical records, or public health records were available

Table 1. Pregnancy Influenza Vaccine Effectiveness Network study countries, sponsors, populations, and data sources.

Country (region)	Sponsoring institution	Local population (million)	Influenza seasons contributed	Pregnant women hospitalized for ARFI[a]
Australia (Western)	Western Australia Department of Health	Approximately 2.6	2012-2015 (southern hemisphere)	1639
Canada (Alberta)	Alberta Health	Approximately 4.1	2011-2015	5042
Canada (Ontario)	ICES	Approximately 14	2010-2016	7738
Israel	Clalit Health Services	Approximately 4.4	2010-2011, 2012-2016	1424[b]
United States (California, Oregon, and Washington)	Kaiser Permanente	Approximately 6.2	2011-2016	2709

[a]ARFI: acute respiratory or febrile illness.

[b]Hospitalization of pregnant women associated with deliveries that occurred in non-Clalit hospitals were not captured.

On the basis of these criteria, 5 study sites were recruited in 4 countries: Australia, Canada, Israel, and the United States (Table 1). Each PREVENT study site developed methods to define local influenza seasons, identify pregnant women, identify relevant ARFI hospitalizations and influenza tests, and extract data about influenza vaccinations and important covariates. Influenza vaccination is recommended and available at no cost to women in all study sites. A brief description of each study site and the methods they used are provided below.

Australia

Western Australia (WA) is the country's largest state in total land area and has about 2.6 million residents, most of whom live in the capital city of Perth. The Western Australia Department of Health has access to data on the annual birth cohort of approximately 34,000 through its state perinatal data collection, the Midwives Notification System. This data collection includes information on >99% of births in the state with gestation ≥20 weeks (live and stillborn) and was used to identify a cohort of pregnant women who gave birth between January 2012 and December 2015. Inpatient records for all public and private hospitals in WA are available in the Hospital Morbidity Data System, which collects information on hospital discharge and was used to identify ARFI hospitalizations. Public immunization providers report influenza vaccines administered to pregnant women to the WA Antenatal Influenza Vaccination Database; the number of pregnant women obtaining vaccines in the private market is thought to be about 4% [29]. An evaluation of this dataset showed it captured 46% of the self-reported influenza vaccinations among a sample of postpartum women surveyed in WA [30]. Influenza surveillance data were obtained from 2 sources: (1) the state's public health reference laboratory (PathWest Laboratory Medicine WA) and (2) state notifications of laboratory-confirmed influenza infection (WA Notifiable Infectious Disease Database). Laboratory real-time reverse transcription polymerase chain reaction (rRT-PCR) testing data from the state's public health reference laboratory were linked to the cohort to identify influenza and RSV testing results.

Canada

Overall, 2 provinces in Canada are participating in PREVENT. The province of Alberta has about 4.1 million residents and 53,500 annual births. The Alberta Ministry of Health (Alberta Health) administers its publicly funded health care system. Each resident registered in the insurance plan has a unique lifetime identifier that can be used to link the data sources described below, including the provincial vaccination repository and the vital statistics registry. All live and stillbirths of at least 20 weeks' gestation are available through the provincial Vital

Statistic Registry, which was used to identify pregnancies. The Canadian Institute for Health Information's Discharge Abstract Database (DAD) captures administrative, clinical, and demographic information on hospital discharges directly from all 106 acute care facilities in the province and was used to identify ARFI hospitalizations. All Albertans are eligible to receive influenza vaccination free of charge, with less than 10% of influenza vaccinations not reported to the registry. Influenza surveillance is conducted continuously in Alberta with year-round laboratory testing and a community-based sentinel physician network, hospital, and emergency room surveillance. Information about clinician-ordered influenza testing with rRT-PCR was obtained through the centralized Provincial Laboratory Information System.

The province of Ontario has about 14 million residents and approximately 147,000 births annually and includes Canada's capital (Ottawa) and Canada's largest city (Toronto). The sponsoring organization, The ICES, is a not-for-profit research institute whose mandate is to enable health system evaluation and research within Ontario. Data from the DAD were extracted to identify pregnant women (using their delivery hospitalization abstract) and ARFI hospitalizations. Physician and pharmacist (starting in 2012) billing claims contained in the Ontario Health Insurance Plan (OHIP) and Ontario Drug Benefits databases, respectively, were used to identify influenza vaccinations. A previous validation study of one of these sources (OHIP) found physician billing claims were 42% sensitive among pregnant women compared with self-reported influenza vaccination status, as individuals can also receive influenza vaccination through public health and workplace clinics [31]. Respiratory specimen results from Public Health Ontario and 8 academic hospital laboratories using rRT-PCR were individually linked to the health administrative data using unique encoded identifiers.

Israel

Clalit Health Services is the largest health care fund in Israel, covering 53% of Israel's population. About 4.4 million people are covered by the fund, including about 93,000 births annually. Nearly all patients (>98%) remain in the fund from year to year, receiving all of their publicly funded health care through the fund. Clalit's comprehensive EMR has been universally adopted among all inpatient and outpatient health care facilities. All live births are captured through hospital EMR data and a demographic registry that feeds into the Clalit data warehouse. An algorithm based on diagnostic and procedure codes was employed to identify pregnancies ≥20 weeks' gestation that did not end in live births. Hospitalizations of pregnant women associated with deliveries that occurred in non-Clalit hospitals (over half to two-thirds of all hospitalizations) were not captured by the EMR. Influenza vaccines are offered free of charge to health care fund members at Clalit clinics, and details regarding influenza vaccination are entered into the EMR. Influenza and RSV testing is conducted using rRT-PCR in Clalit hospitals at the discretion of the physician, and rRT-PCR results are captured in the EMR.

United States

Kaiser Permanente (KP) is an integrated health care delivery system serving over 12 million people in the United States. Moreover, 3 KP sites contributed data to PREVENT—KP Northwest (Portland, OR), KP Northern California (Sacramento, San Francisco Bay Area, Fresno), and KP Washington (Seattle, WA; formerly Group Health Cooperative). The combined population of the KP PREVENT sites is about 6.2 million people, including about 56,000 live births annually. KP Northern California provides inpatient care at 21 KP-owned hospitals, KP Northwest provides inpatient care at 2 KP-owned hospitals and contracts with several other regional hospitals, and KP Washington does not own any hospitals but contracts with regional hospitals for patient care. A common comprehensive EMR system is used at the KP sites. The KP sites identified pregnancies of at least 20 weeks' gestation using a combination of local pregnancy registry data and a validated algorithm that uses diagnosis and procedure codes to identify pregnancy episodes [32]. In addition, 2 sites, KP Washington and KP Northwest, further manually reviewed the medical records of women who were hospitalized with ARFI and excluded those not found to be pregnant. Influenza vaccination records were extracted from the EMR and from state immunization registries in Oregon and Washington states. A previous study found that KP EMR records were 89% sensitive among pregnant women compared with self-reported influenza vaccination status [27]. Influenza surveillance data for Region 10 of the United States were provided by CDC and were used to identify influenza seasons for the KP sites [33]. At KP Northern California and KP Northwest, clinical influenza and RSV rRT-PCR testing dates and results were extracted directly from the EMR. At KP Washington, test dates and results were manually abstracted from medical records.

Influenza Seasons and Peak Period Definitions

With study sites located around the globe and in both hemispheres, a necessary first step in developing the study protocol was to agree upon a shared method for defining influenza seasons and peak periods of circulation. Each site included up to 6 seasons of data starting with the northern hemisphere 2010-2011 season as the earliest. Using a combination of regional surveillance and clinical laboratory records, each site identified the number of respiratory specimens tested and the number of laboratory-confirmed influenza positives identified among tested specimens.

Similar to previous efforts to define influenza seasons consistently across countries [34,35], each study site identified criteria to delineate the start and end of sustained influenza circulation and to identify a period of peak influenza circulation (Table 2). A total of 3 sites (Australia, Ontario [Canada], and the United States) used the mean percentage of specimens that tested positive for influenza A or B virus infection across weeks for each surveillance year to define their threshold of increased or decreased activity. Moreover, 2 sites (Alberta [Canada] and Israel) used a weekly influenza positivity rate of greater than 5% of specimens tested as their threshold.

Table 2. Weeks of local early, peak, and late influenza seasons; earliest and latest week of clinical influenza positives; and predominant local circulating influenza strains by year and study sites.

Region and influenza season	Range of weeks (total weeks)			Weeks, sum	Predominant local strains[a]
	Early season	Peak season	Late season		
Northern Hemisphere 2010-2011					
Canada (Alberta)	50-3 (6)	4-8 (5)	9-15 (7)	18	A (H3N2)
Canada (Ontario)	48-49 (2)	50-6 (9)	7-15 (9)	20	A (H3N2)
Israel	48-50 (3)	51-5 (7)	6-14 (9)	19	A (H1N1)pdm; A (H3N2); B viruses
United States (West)	51-3 (5)	4-11 (8)	12-15 (4)	17	A (H3N2); A (H1N1)pdm; B viruses
Northern Hemisphere 2011-2012					
Canada (Alberta)	2-7 (6)	8-17 (10)	18-26 (9)	25	A (H3N2)
Canada (Ontario)	5-7 (3)	8-15 (8)	16-21 (6)	17	B viruses
United States (West)	6-8 (3)	9-20 (12)	21-25 (5)	20	A (H3N2)
Southern Hemisphere 2012					
Australia (West)	27-30 (4)	31-37 (7)	38-40 (3)	14	A (H3N2)
Northern Hemisphere 2012-2013					
Canada (Alberta)	46-49 (4)	50-10 (13)	11-23 (13)	30	A (H3N2), B (Yamagata)
Canada (Ontario)	46-48 (3)	49-4 (8)	5-12 (8)	19	A (H3N2); A (H1N1)pdm
Israel	2-3 (2)	4-8 (5)	9-14 (6)	13	A (H1N1)pdm; A (H3N2)
United States (West)	48-51 (4)	52-10 (12)	11-20 (10)	26	A (H3N2)
Southern Hemisphere 2013					
Australia (West)	33-35 (3)	36-45 (10)	46-47 (2)	15	A (H3N2); A (H1N1)pdm
Northern Hemisphere 2013-2014					
Canada (Alberta)	48-51 (4)	52-6 (7)	7-10 (4)	21	A (H1N1)pdm
Canada (Ontario)	49-49 (1)	50-11 (14)	12-22 (11)	26	A (H1N1)pdm
Israel	52-4 (5)	5-11 (7)	12-18 (7)	19	A (H1N1)pdm; B (Yamagata)
United States (West)	50-50 (1)	51-9 (11)	10-10 (1)	13	A (H1N1)pdm; A (H3N2)
Southern Hemisphere 2014					
Australia (West)	29-31 (3)	32-40 (9)	41-44 (4)	16	A (H1N1)pdm; A (H3N2)
Northern Hemisphere 2014-2015					
Canada (Alberta)	41-48 (8)	49-7 (12)	8-17 (10)	30	A (H3N2); B (Yamagata)
Canada (Ontario)	49- 49 (1)	50-5 (9)	6-19 (14)	24	A (H3N2)
Israel	45-3 (11)	4-9 (6)	10-10 (1)	18	A (H3N2)
United States (West)	45-48 (4)	49-5 (10)	6-6 (1)	15	A (H3N2)
Southern Hemisphere 2015					
Australia (West)	25-28 (4)	29-40 (12)	41-45 (5)	21	A (H3N2); B (Yamagata)
Northern Hemisphere 2015-2016					
Canada (Ontario)	3-5 (3)	6-13 (8)	14-20 (7)	18	A (H1N1)pdm; B viruses
Israel	49-51 (3)	52-5 (6)	6-14 (9)	18	A (H1N1)pdm; B (Victoria)
United States (West)	52-4 (5)	5-13 (9)	14-21 (8)	22	A (H1N1)pdm; B (Yamagata)

[a]Conclusions regarding prominent strains (believed to represent >20% of circulating viruses) came primarily from real-time reverse transcriptase polymerase chain reaction assay (rRT-PCR) (sub)type results from clinical isolates from this study for Australia and Canada (Alberta and Ontario); for the United States (West) where A subtype results were not available from clinical rRT-PCR results, we referenced US Centers for Disease Control and Prevention West Coast Regional reports [33]; for Israel, where A (H1N1) pandemic (pdm) virus subtyping is consistently done but A (H3N2) virus subtyping is not, we supplemented our data with a review of clinical real-time reverse transcriptase-polymerase chain reaction results with State of Israel Ministry of Health reports [36].

With this information, each site determined for each study season:

- the *start of each season*, defined as the Sunday of the first of 3 consecutive weeks in which the percentage of specimens testing positive for influenza A or B virus infection was higher than the determined threshold;
- the *end of each season*, defined as the Saturday of the first of 3 consecutive weeks in which the percentage of specimens testing positive for influenza was below the threshold;
- the *peak period*, defined as the weeks that included ≥68% of influenza positives between the start and end of each season;
- the *early season*, defined as the weeks from the start of the season through the week before the peak period; and
- the *late season*, defined as the week after the peak period through the end of the season.

Retrospective Cohort Identification

Pregnancies were defined as those that ended in a live birth or stillbirth of at least 20 weeks' gestation. Sites began analysis by identifying all pregnancies during the study years (eg, starting in July of the first year and ending in June of the last year for northern hemisphere sites), with the exception of California and Washington, United States sites that could only examine pregnancies during influenza seasons. Nonetheless, among sites that attempted to identify all pregnancies during study years, 83% (1.72 million/2.07 million) of the pregnancies overlapped with an influenza season.

Study sites subsequently limited their study population to pregnant women who were hospitalized for ARFI during the site-specific influenza seasons. ARFI hospitalizations were identified using a shared list of *International Classification of Diseases, ninth and tenth revision*, diagnosis codes applied in previous studies of medically attended influenza illness [27,37,38] and expanded to include acute illnesses with febrile only, nonrespiratory, or sepsis-like presentations that may be associated with severe influenza disease among adults [39,40]. Canada and Australia used country-specific versions of these codes.

To define the analytic sample for the primary IVE analysis, we further limited the population to women who were clinically tested for influenza virus infection using rRT-PCR with respiratory specimens collected within 3 days before admission through hospital discharge. Women who were ineligible for influenza vaccination (eg, were not covered by health insurance during the vaccination campaign period), those vaccinated within 14 days of admission, and (at some sites) those without documented influenza vaccination status were excluded. ARFI hospitalizations that were readmissions within 14 days of discharge were combined with the index hospitalization and considered single events in the IVE analytic sample.

Data Collection

As an important early step, PREVENT investigators developed and refined a shared data dictionary (Multimedia Appendix 1). Each site developed a site-specific plan to measure the common data requirements for the project. These plans were then compared and harmonized into a common set of requirements and strategies. The shared data dictionary initially focused on variables that were key to the primary aim of estimating IVE. All participating sites were able to provide all the variables in this core dataset. Additional data elements were added to support the secondary aims of the study, and for some of these secondary variables, only a subset of sites was able to provide data.

For women in the retrospective cohort, we extracted the following data from records associated with the index AFRI hospitalization and, where possible, from administrative records or ambulatory care records before hospitalization: (1) basic descriptive demographic information and maternal characteristics (eg, age, race, ethnicity, socioeconomic status, height, weight, and smoking); (2) underlying health conditions before pregnancy (eg, asthma, diabetes, and cancer); (3) pregnancy history and complications with the current pregnancy (eg, gestational hypertension and gestational diabetes; (4) clinical signs and symptoms, course, and treatment during the ARFI hospitalization; (5) respiratory specimen collection and laboratory test results for influenza, RSV, and other pathogens; (6) disposition at hospital discharge (eg, home, hospital transfer, and death); (7) delivery date, gestational age of the infant at delivery, and birth outcomes (eg, birth weight and small-for-gestational age); and (9) influenza vaccination records for the current season. When hospital or birth outcome information was not available in EMR or administrative databases, a limited medical record abstraction was performed by study sites that had direct access to medical records. During the study seasons, most sites only used trivalent inactivated influenza vaccine; quadrivalent inactivated influenza vaccine represented <5% of doses administered to pregnant women starting in 2012 in the United States and 2015 in Israel. Live, attenuated influenza vaccination is contraindicated during pregnancy and was excluded.

Ethical Approval and Considerations

The study protocol and procedures have been reviewed and approved by institutional review boards by Abt Associates (the coordinating institution on which US CDC relies) and at each study site: Human Research Ethics Committee, Department of Health Western Australia; Conjoint Health Research Ethics Board, University of Calgary; University of Alberta Health Research Ethics Board; Sunnybrook Health Sciences Centre, Toronto, Canada; Kaiser Permanente Northwest Institutional Review Board; Clalit Health Services Research Ethics Committee. It was not possible to use a common institutional review board for this project because the institutional and regional human subjects protection policies and regulations varied for each PREVENT site.

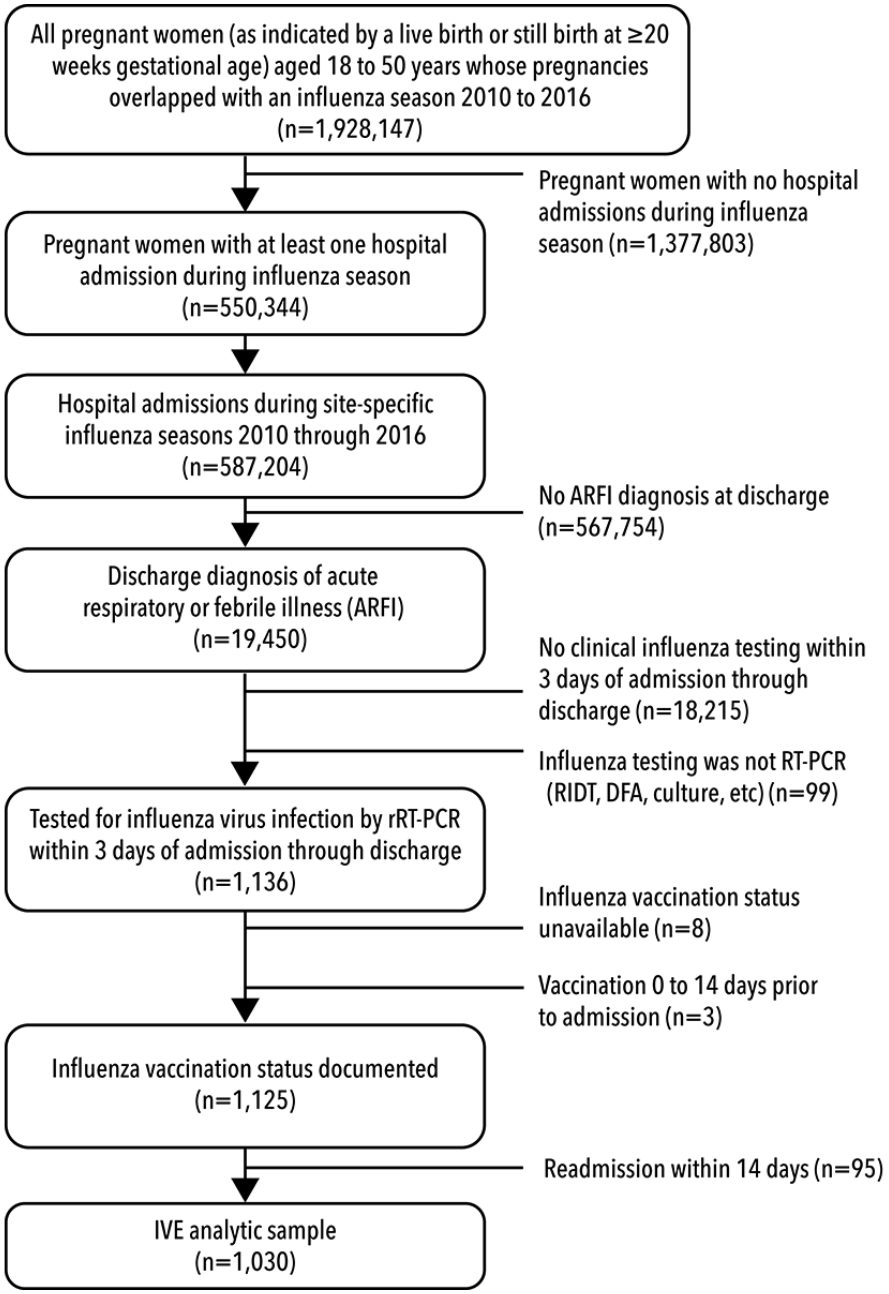
Each site received a waiver of informed consent for all participants. The study presented minimal risk to participants, as there was no interaction or intervention with patients. Although patient information was extracted from existing administrative databases, no personal identifiers were shared between study sites Abt Associates or US CDC. Sites provided aggregate data tables that included summary statistics rather than individual-level datasets, and measures were taken to ensure subject privacy in reports with small cell sizes. There was no

risk to the participants' health from participation in this study because data were collected either as part of patients' routine care or for billing purposes. The study had no impact on patients' current health care or therapeutic management plan. Consequently, patients were not provided information about their participation.

Results

Figure 1 summarizes the steps sites followed to create the retrospective PREVENT cohort, starting with pregnant women aged from 18 to 50 years at the time of inpatient admission whose pregnancies overlapped with the site-specific influenza seasons. This population of 1,928,147 pregnant women will be used in secondary analyses describing vaccination coverage, influenza incidence, and birth outcomes. To refine the sample for the IVE analysis, we limited this population to pregnant women who were hospitalized during influenza season (n=550,344). We identified 19,450 hospitalizations with ARFI diagnoses at discharge and 1136 of these included rRT-PCR influenza testing within the 3 days before admission through discharge. After excluding hospitalizations with incomplete vaccination histories and readmissions, the final IVE analytic dataset included 1030 hospitalizations and 1005 unique women.

Figure 1. Pregnancy Influenza Vaccine Effectiveness Network retrospective inclusion and exclusion criteria. rRT-PCR: real-time reverse transcriptase polymerase chain reaction; RIDT: rapid influenza diagnostic test; DFA: direct fluorescent antibody; IVE: inactivated influenza vaccine.



Discussion

Principal Findings

The PREVENT collaboration will provide important information about the effectiveness of influenza vaccination in preventing severe laboratory-confirmed influenza illness requiring hospitalization in pregnant women and will address additional pertinent knowledge gaps about influenza and pregnancy. As hospitalization for ARFI with laboratory-confirmed influenza is a rare occurrence in pregnant women, an international collaboration was needed to address this question. Out of approximately 2 million women who were pregnant during influenza seasons 2010-2011 through 2015-2016 at 7 study sites in 4 countries, we identified about 1000 who were hospitalized and tested for influenza by rRT-PCR for inclusion in the primary IVE analysis. This analysis to address this important gap in knowledge would not be possible without an international collaboration of this magnitude.

Strengths and Limitations

In addition to the magnitude and geographic diversity of the study cohort, this network has established resources valuable for antenatal influenza research. As part of this collaboration, PREVENT has brought together a pool of international expertise in influenza vaccination and infection during pregnancy. The study investigators worked together to develop methods to harmonize data collection, management, and analyses across different institutions and countries with differing underlying populations, data sources, and human subjects protection regulations. In addition to addressing the primary question about the effectiveness of influenza vaccination, PREVENT data will be used to address other important knowledge gaps including understanding the incidence, clinical course, and severity of hospitalized influenza during pregnancy. The data infrastructure and partnerships created for these analyses may be useful and informative for future studies.

Despite the strengths of this collaboration, there are a few limitations to the analyses within this cohort. Due to the nature of the data sources across sites, we were only able to include pregnancies ending in live birth or stillbirth of at least 20 weeks' gestational age, because several sites were unable to extract reliable data on pregnancies ending in fetal loss before 20 weeks. We are, therefore, not able to examine the impact of influenza infection or influenza vaccination on outcomes early in pregnancy, such as spontaneous abortion. In addition, we included study sites that routinely tested pregnant women for influenza and had maternal influenza immunization programs, which limited our study to the inclusion of 4 high-income countries. Therefore, PREVENT study results may not be generalizable to countries with fewer resources dedicated to testing and vaccination programs or with different underlying population characteristics (eg, high prevalence of HIV or malaria) that may impact IVE or influenza incidence and severity. Finally, there is the potential for misclassification bias in some of our measurements. To ensure consistency across sites, chronic diseases are characterized solely by International Classification of Diseases code, which may underestimate the prevalence of these conditions in the women studied. Misclassification of influenza vaccination is of most concern for the primary IVE analysis; however, the participating sites generally have high rates of influenza vaccination capture, often using a combination of EMR data and regional and national immunization registries.

Conclusions

Due to methodological challenges in researching seasonal influenza infection and vaccination in pregnant women, we have several important unanswered questions, including understanding the effectiveness of influenza vaccination in preventing hospitalization during pregnancy. PREVENT will address this primary IVE question as well as a number of other important gaps in our understanding of influenza and other respiratory infections during pregnancy. This work will be informative for strengthening global influenza prevention strategies and for improving the health of pregnant women.

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Authors' Contributions

ALN and MGT developed the original proposal for Pregnancy Influenza Vaccine Effectiveness Network (PREVENT). All named authors contributed to the development of the common protocol and procedures. SB, BEW, KAS, SAI, MAK, JCK, MGT, and AKR helped coordinate the study. ALN, MGT, and SB wrote the first draft. All named authors contributed to subsequent drafts. All authors read and approved the final manuscript.

Conflicts of Interest

SJD reports that he is a content advisor to Johnson & Johnson (Jannsen Pharmaceuticals) on respiratory virus testing. ALN reports grants from Pfizer, MedImmune/Astra Zeneca, and Merck outside the submitted work. NPK reports grants from GlaxoSmithKline, Sanofi Pasteur, Pfizer, Protein Science (now Sanofi Pasteur), Merck & Co, MedImmune, Novartis (now GSK), and Dynavax, outside the submitted work. SAI reports grants from Medimmune/AstraZeneca, outside the submitted work. MLJ reports research grants from Sanofi Pasteur, outside the submitted work. The remaining authors declare that they have no conflicts of interest.

Multimedia Appendix 1

Data dictionary Pregnancy Influenza Vaccine Effectiveness Network protocol.

[PDF File (Adobe PDF File), 485KB - resprot_v8i1e11333_app1.pdf]

References

1. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2012 Sep;207(3 Suppl):S3-S8. [doi: 10.1016/j.ajog.2012.06.068] [Medline: 22920056]
2. Fell DB, Azziz-Baumgartner E, Baker MG, Batra M, Beauté J, Beutels P, WHO taskforce to evaluate influenza data to inform vaccine impact and economic modelling. Influenza epidemiology and immunization during pregnancy: final report of a World Health Organization working group. Vaccine 2017 Dec 13;35(43):5738-5750 [FREE Full text] [doi: 10.1016/j.vaccine.2017.08.037] [Medline: 28867508]
3. Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med 2005 Oct;33(10 Suppl):S390-S397. [Medline: 16215363]
4. Laibl VR, Sheffield JS. Influenza and pneumonia in pregnancy. Clin Perinatol 2005 Sep;32(3):727-738. [doi: 10.1016/j.clp.2005.04.009] [Medline: 16085029]
5. Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007 Feb 13;176(4):463-468 [FREE Full text] [doi: 10.1503/cmaj.061435] [Medline: 17296958]
6. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998 Dec 01;148(11):1094-1102. [Medline: 9850132]
7. Hartert TV, Neuzil KM, Shintani AK, Mitchel EF, Snowden MS, Wood LB, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol 2003 Dec;189(6):1705-1712. [Medline: 14710102]
8. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. J Am Med Assoc 2010 Apr 21;303(15):1517-1525 [FREE Full text] [doi: 10.1001/jama.2010.479] [Medline: 20407061]
9. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009 Aug 08;374(9688):451-458. [doi: 10.1016/S0140-6736(09)61304-0] [Medline: 19643469]
10. Callaghan WM, Chu SY, Jamieson DJ. Deaths from seasonal influenza among pregnant women in the United States, 1998-2005. Obstet Gynecol 2010 May;115(5):919-923. [doi: 10.1097/AOG.0b013e3181d99d85] [Medline: 20410763]
11. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis 2008 Jan;14(1):95-100 [FREE Full text] [doi: 10.3201/eid1401.070667] [Medline: 18258087]

12. Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? Vaccine 2009 Jul 30;27(35):4754-4770. [doi: 10.1016/j.vaccine.2009.03.079] [Medline: 19515466]
13. Ding H, Black CL, Ball S, Donahue S, Fink RV, Williams WW, et al. Influenza vaccination coverage among pregnant women--United States, 2014-15 influenza season. MMWR Morb Mortal Wkly Rep 2015 Sep 18;64(36):1000-1005 [FREE Full text] [doi: 10.15585/mmwr.mm6436a2] [Medline: 26390253]
14. Wong VW, Lok KY, Tarrant M. Interventions to increase the uptake of seasonal influenza vaccination among pregnant women: a systematic review. Vaccine 2016 Jan 02;34(1):20-32. [doi: 10.1016/j.vaccine.2015.11.020] [Medline: 26602267]
15. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women - a systematic review. Vaccine 2014 Aug 06;32(36):4602-4613. [doi: 10.1016/j.vaccine.2014.06.067] [Medline: 24996123]
16. Keller-Stanislawski B, Englund JA, Kang G, Mangtani P, Neuzil K, Nohynek H, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine 2014 Dec 12;32(52):7057-7064. [doi: 10.1016/j.vaccine.2014.09.052] [Medline: 25285883]
17. Kharbanda EO, Vazquez-Benitez G, Romitti PA, Naleway AL, Cheetham TC, Lipkind HS, Vaccine Safety Datalink. First trimester influenza vaccination and risks for major structural birth defects in offspring. J Pediatr 2017 Aug;187:234-239.e4. [doi: 10.1016/j.jpeds.2017.04.039] [Medline: 28550954]
18. Sukumaran L, McCarthy NL, Kharbanda EO, Weintraub ES, Vazquez-Benitez G, McNeil MM, et al. Safety of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and influenza vaccinations in pregnancy. Obstet Gynecol 2015 Nov;126(5):1069-1074 [FREE Full text] [doi: 10.1097/AOG.0000000000001066] [Medline: 26444109]
19. Savitz DA, Fell DB, Ortiz JR, Bhat N. Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. Vaccine 2015 Nov 25;33(47):6430-6435 [FREE Full text] [doi: 10.1016/j.vaccine.2015.08.041] [Medline: 26319740]
20. Hulka JF. Effectiveness of polyvalent influenza vaccine in pregnancy. Report of a controlled study during an outbreak of Asian influenza. Obstet Gynecol 1964 Jun;23:830-837. [Medline: 14168242]
21. Steinhoff MC, Omer SB, Roy E, Arifeen SE, Raqib R, Altaye M, et al. Influenza immunization in pregnancy--antibody responses in mothers and infants. N Engl J Med 2010 Apr 29;362(17):1644-1646. [doi: 10.1056/NEJMc0912599] [Medline: 20427817]
22. Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D, Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol 2004 Aug;21(6):333-339. [doi: 10.1055/s-2004-831888] [Medline: 15311370]
23. Munoz FM, Greisinger AJ, Wehmanen OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2005 Apr;192(4):1098-1106. [doi: 10.1016/j.ajog.2004.12.019] [Medline: 15846187]
24. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008 Oct 09;359(15):1555-1564. [doi: 10.1056/NEJMoa0708630] [Medline: 18799552]
25. Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med 2013 Jan 24;368(4):333-340 [FREE Full text] [doi: 10.1056/NEJMoa1207210] [Medline: 23323868]
26. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014 Sep 04;371(10):918-931. [doi: 10.1056/NEJMoa1401480] [Medline: 25184864]
27. Thompson MG, Li D, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, PregnancyInfluenza Project Workgroup. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010-2011 and 2011-2012 influenza seasons. Clin Infect Dis 2014 Feb;58(4):449-457. [doi: 10.1093/cid/cit750] [Medline: 24280090]
28. Manske JM. Efficacy and effectiveness of maternal influenza vaccination during pregnancy: a review of the evidence. Matern Child Health J 2014 Sep;18(7):1599-1609. [doi: 10.1007/s10995-013-1399-2] [Medline: 24272875]
29. Mak DB, Regan AK, Joyce S, Gibbs R, Effler PV. Antenatal care provider's advice is the key determinant of influenza vaccination uptake in pregnant women. Aust N Z J Obstet Gynaecol 2015 Apr;55(2):131-137. [doi: 10.1111/ajo.12292] [Medline: 25557858]
30. Regan AK, Mak DB, Moore HC, Tracey L, Saker R, Jones C, et al. Surveillance of antenatal influenza vaccination: validity of current systems and recommendations for improvement. BMC Public Health 2015 Nov 23;15:1155 [FREE Full text] [doi: 10.1186/s12889-015-2234-z] [Medline: 26593061]
31. Schwartz KL, Jembere N, Campitelli MA, Buchan SA, Chung H, Kwong JC. Using physician billing claims from the Ontario Health Insurance Plan to determine individual influenza vaccination status: an updated validation study. CMAJ Open 2016 Aug;4(3):E463-E470 [FREE Full text] [doi: 10.9778/cmajo.20160009] [Medline: 27730110]
32. Naleway AL, Gold R, Kurosky S, Riedlinger K, Henninger ML, Nordin JD, et al. Identifying pregnancy episodes, outcomes, and mother-infant pairs in the Vaccine Safety Datalink. Vaccine 2013 Jun 12;31(27):2898-2903. [doi: 10.1016/j.vaccine.2013.03.069] [Medline: 23639917]
33. Centers for Disease Control and Prevention. Past Weekly Surveillance Reports URL: https://www.cdc.gov/flu/weekly/pastreports.htm [accessed 2018-11-28] [WebCite Cache ID 74HSWlkvA]

34. Durand LO, Cheng P, Palekar R, Clara W, Jara J, Cerpa M, et al. Timing of influenza epidemics and vaccines in the American tropics, 2002-2008, 2011-2014. Influenza Other Respir Viruses 2016 May;10(3):170-175 [FREE Full text] [doi: 10.1111/irv.12371] [Medline: 26701079]
35. Hirve S, Newman LP, Paget J, Azziz-Baumgartner E, Fitzner J, Bhat N, et al. Influenza seasonality in the tropics and subtropics - when to vaccinate? PLoS One 2016;11(4):e0153003 [FREE Full text] [doi: 10.1371/journal.pone.0153003] [Medline: 27119988]
36. State of Israel Ministry of Health. Weekly Influenza Surveillance Reports URL: https://www.health.gov.il/English/MinistryUnits/ICDC/Infectious_diseases/Flu/Pages/FWR.aspx [accessed 2018-11-28] [WebCite Cache ID 74HSnruWQ]
37. McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. J Infect Dis 2015 May 15;211(10):1529-1540 [FREE Full text] [doi: 10.1093/infdis/jiu647] [Medline: 25406334]
38. Sokolow LZ, Naleway AL, Li D, Shifflett P, Reynolds S, Henninger ML, Pregnancy and Influenza Project Workgroup. Severity of influenza and noninfluenza acute respiratory illness among pregnant women, 2010-2012. Am J Obstet Gynecol 2015 Feb;212(2):202.e1-202.11 [FREE Full text] [doi: 10.1016/j.ajog.2014.08.004] [Medline: 25111585]
39. Reed C, Chaves S, Perez A, D'Mello T, Daily Kirley P, Aragon D, et al. Complications among adults hospitalized with influenza: a comparison of seasonal influenza and the 2009 H1N1 pandemic. Clin Infect Dis 2014 Jul 15;59(2):166-174. [doi: 10.1093/cid/ciu285] [Medline: 24785230]
40. Oboho IK, Reed C, Gargiullo P, Leon M, Aragon D, Meek J, et al. Benefit of early initiation of influenza antiviral treatment to pregnant women hospitalized with laboratory-confirmed influenza. J Infect Dis 2016 Dec 15;214(4):507-515. [doi: 10.1093/infdis/jiw033] [Medline: 26908745]

Abbreviations

ARFI: acute respiratory or febrile illness
CDC: Centers for Disease Control and Prevention
DAD: Discharge Abstract Database
EMR: electronic medical record
IIV: inactivated influenza vaccine
IVE: influenza vaccine effectiveness
KP: Kaiser Permanente
NH: northern hemisphere
OHIP: Ontario Health Insurance Plan
PREVENT: Pregnancy Influenza Vaccine Effectiveness Network
rRT-PCR: real-time reverse transcriptase polymerase chain reaction assay
RSV: respiratory syncytial virus
SH: southern hemisphere
WA: Western Australia

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Protocol

A Focus on the HIV Care Continuum Through the Healthy Young Men's Cohort Study: Protocol for a Mixed-Methods Study

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Abstract

Background: No group is at greater risk for acquiring HIV than young men who have sex with men (YMSM), particularly black or African American (AA) and Hispanic or Latino (L) YMSM living in inner cities, who account for the largest number of new HIV infections each year. Although pre-exposure prophylaxis (PrEP), postexposure prophylaxis (PEP), and treatment as prevention hold enormous promise for changing the course of the epidemic, AA/L-YMSM are the least likely population to be receiving primary health care and HIV prevention/care and are the least likely to be using PrEP and PEP.

Objective: The overarching aim of the Healthy Young Men's (HYM) cohort study is to conduct longitudinal research with a cohort of AA/L-YMSM to prevent new HIV infections, reduce transmission, and reduce HIV/AIDS-related disparities by focusing on successful engagement in care. Findings from this research will be used to inform the development of new interventions designed to engage AA/L-YMSM in the HIV prevention and care continua.

Methods: Longitudinal research (baseline and follow-up assessments every 6 months for a total of 8 waves of data collection) is ongoing with a new cohort of 450 high-risk AA/L-YMSM in Los Angeles. Participants were recruited using a venue-based and social media sampling design. In addition to self-report surveys, the study protocol includes the collection of urine to assess recent use of illicit drugs and the collection of blood and rectal/throat swabs to test for current sexually transmitted infection (STI)/HIV infection. An additional sample of blood/plasma (10 mL for 4 aliquots and 1 pellet) is also collected and stored in the HYM cohort study biorepository for future research. By design, we recruited 400 HIV-negative participants and 50 HIV-positive (HIV+) participants. This mixed-methods study design includes collection and triangulated analysis of quantitative, qualitative, and biological measures (ie, drug use, STI/HIV testing, and adherence to antiretroviral therapy among HIV+ participants) at baseline and every 6 months. The HYM cohort study will provide a platform from which new and emerging biomedical prevention strategies (eg, PrEP, rectal microbicides, and PEP) and other HIV prevention and care engagement interventions can be developed and evaluated with AA/L-YMSM.

Results: To date, all participants in the HYM cohort study have been recruited and baseline assessment has been conducted.

Conclusions: The findings from this research will be used to inform the development of new and/or adaptation of existing evidence-based HIV prevention interventions and interventions designed to engage this population in the HIV prevention and care continua.

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acquired immune deficiency syndrome virus; HIV; cohort study; men who have sex with men

Introduction

The HIV Epidemic and Young Men Who Have Sex With Men: Correlates and Risk

In this third decade of the HIV epidemic, we continue to see 50,000 new infections annually in the United States, with the highest rate of diagnosed HIV infection among adolescents and young adults (approximately 25%) [1,2]. No group is at a greater risk for acquiring HIV than young men who have sex with men (YMSM), particularly black or African American (AA) and Hispanic or Latino (L) YMSM living in inner cities, who account for the largest number of new HIV infections each year [3,4]. In 2016, AA men who have sex with men (MSM) accounted for 25% of the new HIV diagnoses and 38% of new diagnoses among all gay and bisexual men in the United States. Among AA MSM testing positive in 2016, 36% were aged between 13 and 24 years and 39% were aged between 25 and 34 years [5]. L-MSM experience similar disparities in HIV rates. Between 2000 and 2014, diagnoses among all L-MSM gay and bisexual men increased by 13%; diagnoses among L-YMSM increased by 16% during this same period [6].

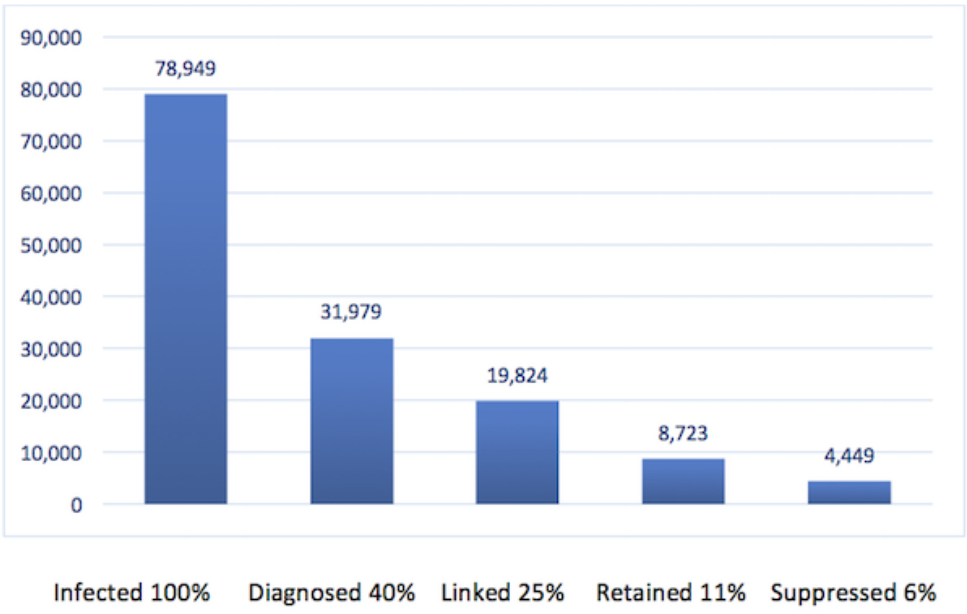
Risk factors associated with HIV and other sexually transmitted infections (STIs) among YMSM include alcohol misuse, illicit drug use, involvement in condomless anal sex, and mental health problems, including depression and anxiety [7-12]. However, there is an emerging literature that suggests that AA-YMSM have a unique risk profile, that is, they are less likely than white and L-YMSM to report binge alcohol use and illicit drug use and yet, they experience high levels of racism, discrimination, and stigma, and these experiences, in turn, put AA-YMSM at increased risk for internalized homophobia, maladaptive coping, and/or mental health problems [13,14]. Poor mental health in turn has been found to put AA-YMSM at increased risk for illicit drug use and sexual risk taking [15]. With respect to L-YMSM, they too appear to have their own, unique risk profile, that is, many have come of age in a culture with a strong emphasis on traditional gender roles, family, and having children [16]. Within this context, sociocultural factors such as community connectedness, social support, adherence to cultural values for sex, sexual discomfort (eg, feeling embarrassed or not being able to speak about sexual matters), and self-efficacy to discuss sexual matters significantly predict illicit drug use and sexual risk taking [17-19]. Our research has found that differences in religious experiences, internalized and community homophobia, and identification/disclosure increase L-YMSM's distress [20].

HIV Prevention and the HIV Care Continuum Among Young African American and Latino Men Who Have Sex With Men

Despite considerable risk and high rates of new infection among AA-YMSM and L-YMSM, today there is greater hope than ever before that we can change the course of the HIV epidemic given a number of biomedical approaches to prevention that leverage the use of antiretroviral therapy (ART), including pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP). PrEP has enormous promise to limit HIV acquisition, with more than 90% efficacy among those with high adherence. Although awareness of and knowledge about PrEP is quite high among YMSM, uptake is extremely low, especially among AA-YMSM and L-YMSM [21]. National data indicate that about 77,000 people are using PrEP, the majority being white and above the age of 30 years [22]. This low uptake points to social and structural determinants, such as poor access to care and financial barriers related to other needs including food and shelter [21,23]. There is growing evidence demonstrating that although YMSM are generally aware of and have knowledge about PrEP, they are significantly less likely than adult MSM to have ever used PrEP [24,25]. Moreover, among YMSM, AA-YMSM, and L-YMSM are the least likely to have ever used PrEP [26].

Early diagnosis of HIV and timely linkage to and retention in care are vital to survival and quality of life. HIV-positive (HIV+) individuals who adhere to ART exhibit slower disease progression, fewer HIV comorbidities, improved overall health outcomes, and less transmission to partners [27]. Unfortunately, there is growing evidence that HIV+ young people are significantly less likely than HIV+ adults to be linked to and retained in care, to initiate ART, and to experience viral suppression [28-30]. Figure 1 reflects the estimated cascade of care in HIV+ youth (ages 13-29 years) in the United States [29]. As reported by Ryscavage et al, AA youth in care were found to have the lowest probability of viral suppression at 6 months and the highest predicted probability of viral rebound, compared with AA adults, non-AA youth, and non-AA adults [30]. In general, it has been shown that HIV is diagnosed at a later stage among Latinos and that these patients have lower CD4 cell counts, higher HIV RNA levels, more AIDS-defining opportunistic infections, and longer hospital stays than whites [31]. Latinos have also been shown to have significant delays in initiation of HIV care. Reasons for delay of care include lack of access to transportation, being too sick to go to the doctor, and having 1 or more competing needs on expenditures, such as rent and food costs [32].

Figure 1. Cascade of care in HIV infected youth in the United States (from Zanoni & Mayer [30]).



Many of the HIV disparities that currently exist relate to different patterns in HIV testing, linkage to care, and engagement/retention in care [33,34]. Christopoulos et al concluded that racial disparities in HIV outcomes persist among MSM in large part because of different patterns of engagement in care [35]. Lack of insurance and patient mistrust of health care/providers may also play a key role in this lack of engagement in care. In addition, Christopoulous et al argued that limited research has been conducted to better understand barriers to engagement and retention in care among MSM in general and YMSM in particular. Moreover, they concluded that there is a dearth of research on culturally relevant strategies designed to engage AA-MSM and L-MSM in HIV care, especially AA-YMSM and L-YMSM [35].

The Healthy Young Men's Cohort Study: Opportunities to Turn the Curve of the HIV Epidemic

Given these multiple factors and opportunities, the Healthy Young Men's (HYM) cohort study was designed to provide rich data to help further understand and characterize AA-YMSM and L-YMSM's engagement in the HIV continuum of care and prevention, including their use of HIV testing services and access to and use of HIV prevention/treatment services. The HYM cohort study was designed to inform the development of developmentally appropriate and culturally relevant interventions addressing the many risk factors that serve as barriers to accessing needed HIV prevention and care services.

Overarching Goal and Specific Aims

The overarching goal of the HYM cohort study is to conduct longitudinal research with a large and diverse cohort of AA-YMSM and L-YMSM to (1) characterize risk in this population and (2) longitudinally examine transitions and associated risk with transitions related to illicit drug use (eg, from nonillicit drug use to illicit drug use), sexual risk (from low to higher risk behaviors), and STI/HIV infection. Moreover, a primary aim of the study is to inform the development of age-appropriate and culturally relevant interventions that help prevent new HIV infections, reduce transmission, and reduce HIV/AIDS-related disparities. A specific focus is on successful engagement, linkage, and retention in care. Building on the HIV continua of care and prevention paradigm (ie, seek, test, treat, and retain in care) and the syndemic theory of risk [8,36-38], this research addresses 4 overarching research questions: (1) Why do some HIV-negative (HIV−) AA/L-YMSM seroconvert (and not others) and how do we more effectively prevent new infections in this population? (2) How can we more effectively engage AA/L-YMSM in all forms of care, including primary care, HIV testing, HIV prevention, and HIV/AIDS treatment services if HIV+? (3) How can we increase demand/uptake of PrEP and PEP as a prevention strategy in this population? and (4) How do we prevent transmission and achieve disease-free survival by achieving viral suppression in this population? The specific aims are as follows:

- Specific aim 1: Better understand and operationally define what linkage, engagement, and retention to care (both primary health and HIV/AIDS treatment) and PrEP/ART adherence mean to HIV− and HIV+ AA-YMSM and L-YMSM. In addition, use these data to inform the development of new assessment tools for future intervention research.
- Specific aim 2: Characterize and monitor over time AA/L-YMSM's (1) use of alcohol and illicit drugs; (2) utilization of HIV testing and prevention services; (3) incidence of HIV and STIs; (4) insurance status and access to health care services, including primary care and HIV/AIDS treatment services; (5) engagement in and utilization of health care and HIV/AIDS treatment services; (6) retention in HIV/AIDS care and adherence to ART; and (7) utilization of biomedical interventions, such as PrEP and PEP. A component of this specific aim will include the procurement of biological specimens and an annual HIV viral load (VL) test for each member of the cohort. The

goal is to be able to query specimens for biological evidence of adherence, potential markers of increased infectious susceptibility (eg, human leukocyte antigen typing and whole virus sequencing), and/or variability in disease progression rates.

- Specific aim 3: Identify barriers/facilitators of engagement along the HIV continua of care and prevention, including HIV testing and biomedical prevention, care engagement and retention, and adherence to ART. The finding from this research will be used to identify risk/protective influences, including structural and social barriers/facilitators, which we hope to use in future studies to design new prevention interventions targeted to this population, and/or inform the adaptations/further refinement of existing evidence-based interventions to ensure they are developmentally appropriate and culturally relevant for AA-YMSM and L-YMSM.

Theoretical Model and Conceptual Framework

Syndemic Theory

The syndemic theory has increasingly been used to explain MSM and YMSM of colors' involvement in HIV risk-taking behaviors [8,36-40]. A syndemic is defined as "two or more afflictions, interacting synergistically, contributing to excess burden of disease in a population." [41]. Syndemic theory posits that a constellation of health problems, including drug use and alcohol misuse, depression, sexual compulsiveness, and intimate partner violence, accumulates across a life span, with each condition potentially amplifying the negative impact of other health problems. For AA/L-YMSM, multiple and overlapping forms of risk—racism, discrimination, and homophobia—correlate with negative health impacts [8,42]. Our previous research has found that AA/L-YMSM experience the highest rates of risk factors as framed by the syndemic theory, including drug use, mental health problems (such as depression), and intimate partner violence. AA-YMSM also experience higher levels of internalized homophobia, which in turn is a strong predictor of sexual risk behaviors. In addition, experiences of racism, homophobia, and violence have been found to be significantly associated with illicit drug use, alcohol misuse, and involvement in HIV sexual risk behaviors [15,43]. The HYM cohort study examines syndemic risk factors as predictors of HIV infection among AA/L-YMSM as well as engagement in care, including HIV prevention, testing and treatment, and adherence to ART.

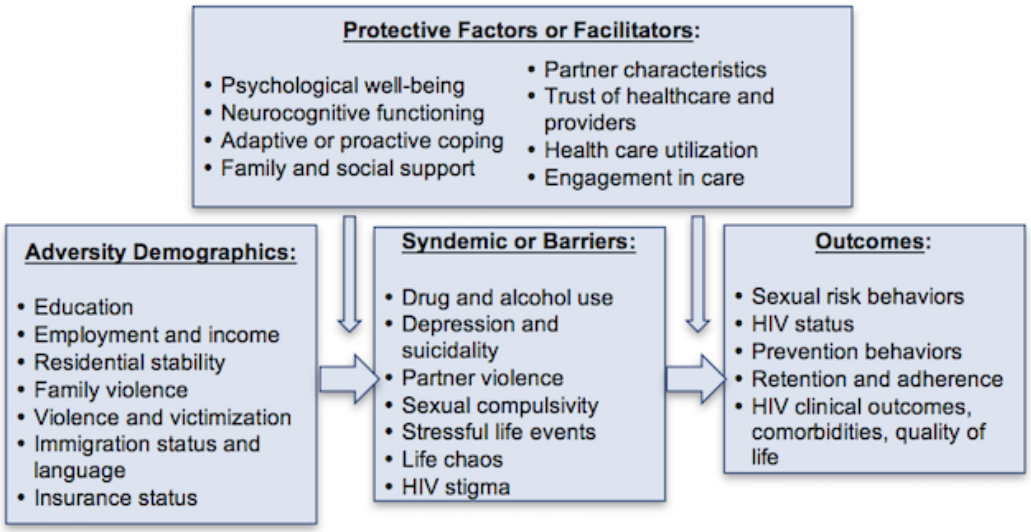
Engagement in the HIV Care Continuum

Successful engagement in care, both primary care for HIV– and HIV care for HIV+ individuals, is now considered essential to achieving critical outcomes required to ensure disease-free survival and to ultimately end the HIV/AIDS epidemic [44]. Under the Affordable Care Act, linkage to HIV testing (as well as affordable insurance) may serve as a critical point of care within the health care system. For those who test HIV+, early diagnosis and linkage to HIV/AIDS care are essential, and yet it is now very clear that *engagement in care* is a complex construct that is perhaps best represented along a continuum of engagement. Moreover, it is also clear that adherence to ART is more likely to occur if individuals are engaged in their own care. Cheever argues that a "person living with HIV may go through several stages and may also return to earlier stages along this continuum throughout his/her life" [45].

Mugavero et al developed a framework with 7 steps along a continuum of HIV service delivery, ranging from not in care/unaware of HIV status, to diagnosis (aware of HIV status), linkage to care (receiving some medical care but not HIV care; entered HIV care but lost to follow-up; in/out of HIV care or infrequent user), retention in care (fully engaged in HIV care), and adherence to ART with the goal of VL suppression [44]. We believe this framework provides a more nuanced understanding of engagement. In addition, we believe that different types of barriers and facilitators are important determinants of engagement along this continuum. On the basis of the literature as well as our own research conducted with YMSM, we firmly believe that YMSM of color experience a unique set of challenges to engagement that are developmentally and culturally defined. Figure 2 provides a conceptual framework and analytical plan for our proposed research. We hypothesize that specific demographic and syndemic risk factors/barriers put AA/L-YMSM at significantly greater risk for HIV infection, poor retention in care and poor adherence to ART, and consequently, poor HIV-related clinical outcomes and continued HIV transmission. We also hypothesize that protective/facilitator factors mediate and/or moderate this risk. The collection of longitudinal data over 4 years with a large cohort of AA/L-YMSM (eg, who are both HIV– and HIV+, in and out of care, adherent, and not adherent) allows us to examine trajectories along this continuum and identify predictors of who is and is not engaged/retained in care at each step along the continuum, and why.

The purpose of this study is to describe the HYM cohort study protocol—that is, study design and research methods for this longitudinal study.

Figure 2. The Healthy Young Men's cohort study conceptual model.



Methods

Consent and Institutional Review Board Approval

This study has been reviewed and approved by Children's Hospital Los Angeles' Institutional Review Board (IRB# 14-00279). All participants were identified, screened for eligibility, and if eligible, invited to participate in the study, as further described below. All participants provided written informed consent during a face-to-face consenting visit. A certificate of confidentiality was obtained from the National Institute on Drug Abuse and a waiver of parental consent/assent was obtained for participants aged 16 to 17 years.

Study Design

Longitudinal research (baseline and follow-up assessment every 6 months) is in progress with our cohort of 450 AA/L-YMSM in Los Angeles. Participants were recruited using a venue-based and social media sampling design, described below. In addition to self-report surveys, data collection includes urine collection to assess recent use of illicit drugs, rectal and throat swabs to test for gonorrhea and chlamydia, blood draw for syphilis testing, and the additional collection/storage of additional blood (10 mL for 4 aliquots and 1 pellet) and a rectal swab to be stored in the HYM biorepository. This mixed-methods study design includes collection and triangulated analysis of quantitative and biological measures (ie, drug use, STI/HIV testing, and adherence to ART among HIV+ participants) at baseline and every 6 months for a total of 8 waves of data collection. In addition, qualitative substudies are integrated into the study using a modified timeline follow-back approach; these are conducted outside the regular study visits on an as-needed basis. The HYM cohort study has been designed to provide a platform from which new and emerging biomedical prevention strategies (eg, PrEP and PEP) can be developed and evaluated with AA/L-YMSM.

Study Participants

YMSM youth were eligible to participate in the cohort if they (1) were aged 16 to 24 years; (2) assigned a male sex at birth; (3) self-identified as gay, bisexual, or uncertain about their sexual orientation; (4) reported a sexual encounter with a male within the previous 12 months; (5) self-identified as black/African American, Latino, or multiethnic; and (6) lived in Los Angeles or a surrounding county, with no expectation of moving outside this area for at least 6 months. The recruitment strategy described below resulted in a geographically dispersed cohort recruited from throughout Los Angeles county, as shown in Figure 3.

Recruitment

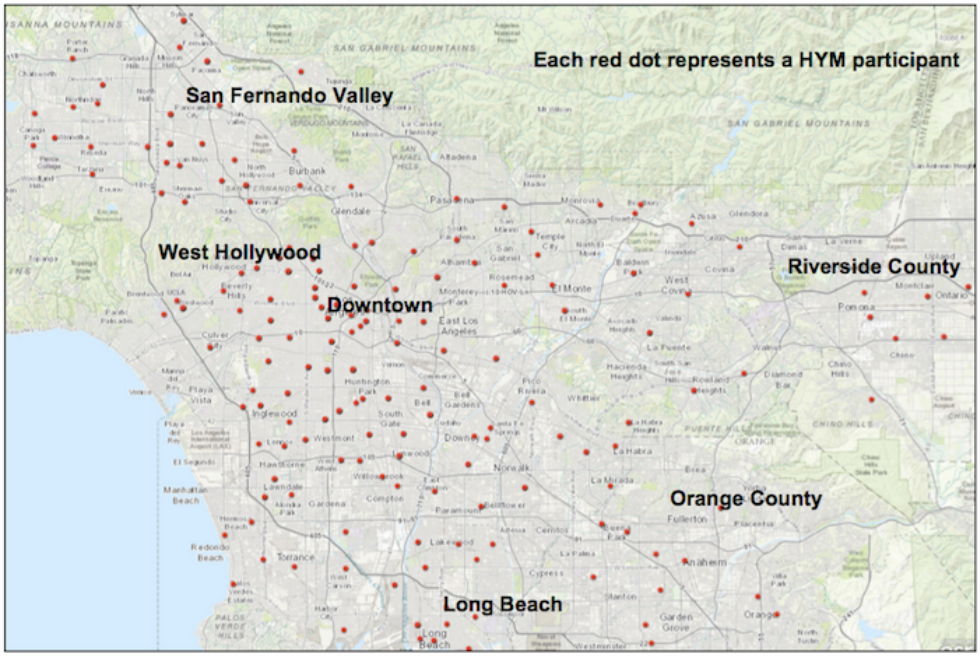
Identifying Public Venues and Social Media Sites

Formative research was first conducted to identify public venues frequented by AA/L-YMSM. Staff contacted and met venue owners/managers (including HIV test sites and clinic directors) of sites identified for recruitment to explain the study and to obtain permission to conduct activities. Facilitated discussions with the study's community advisory board (CAB) and youth advisory board (YAB) identified common social media sites and dating apps that are popular among our target population.

Recruitment in Public Venues

The recruitment methods in this study matched those used in our previous research with the same target population [46]. Young men were recruited from public venues including bars, coffee houses, parks, and high-traffic street locations where YMSM spend time or *hang out*, social events sponsored by an agency or organization that serves YMSM, and special events such as gay pride festivals and balls.

Figure 3. Map indicating where participants of the Healthy Young Men's cohort study reside.



During sampling events, young men who appeared to meet the study criteria were counted and invited to participate in a screening interview conducted in English or Spanish. A total of 1 or 2 researchers counted and identified young men to be screened and tracked individuals to ensure that young men were not approached multiple times. Young men who met the study criteria received a detailed study description, and contact information was obtained from individuals who expressed interest in participating. Follow-up in-person appointments were scheduled within a week of recruitment to complete the informed consent process and to further explain study participation. For each sampling event, the following data were collected: (1) number of YMSM observed; (2) number of YMSM intercepted; (3) age, race, and county of residence of those screened; (4) reasons for refusal; (5) number of eligible YMSM; and (6) number enrolled.

We originally planned to recruit our cohort of AA/L-YMSM using only this recruitment method. However, during our prerecruitment field observations, the research team noted that few AA/L-YMSM were present at these venues. Discussions with our CAB and YAB indicated the low number of YMSM attending gay-identified venues was a common challenge for outreach; YMSM are simply not attending gay-identified venues as they once did.

Recruitment Using Social Media

Given these changes in the community, our team determined that additional recruitment methods were needed to complete recruitment of the cohort within the allotted recruitment time frame. Thus, we partnered with Trialspark, a technology company that supports recruitment for clinical studies/trials using social media sites. The HYM team worked with Trialspark to design social media ads to be placed on sites identified by our YAB including Facebook, Instagram, Grindr, and Jack'd. Through our partnership, Trialspark identified and briefly screened 1371 individuals; of these, 40.11% (550/1371) were identified as eligible. Preliminarily individuals were then independently contacted and rescreened for enrollment by our research team. Young men were also recruited through participant referrals as well as referrals from our partner clinical sites. Table 1 presents the recruitment data for each recruitment method.

Tracking and Retention

Participants were asked to participate in data collection at baseline and follow-up every 6 months. We acknowledge the complexities of tracking and retaining a young and highly mobile population such as YMSM. Our past experience taught us that the key to retaining youth in a research study is developing trusting relationships between the study team and the research participants. To that end, we adapted a tracking protocol used in previous studies [47], which yielded a 94% retention rate across 2 and a half years and 5 waves of data collection. An essential piece of this protocol is assigning staff to a specific participant, with the goal of maintaining that relationship across the course of the study. Staff turnover is inevitable, and when that occurs, we ensure there is contact between the original staff person, the participant, and the newly assigned staff person to ensure continuity in the relationship.

Table 1. Healthy Young Men's cohort study recruitment and eligibility data.

Recruitment method	Social media, n (%)	Venue/events, n (%)	Participant referrals, n (%)	Clinic, n (%)	Total, n (%)
Approached for screening	1371 (67.64)	544 (26.84)	69 (3.40)	43 (2.12)	2027 (100.00)
Screened for eligibility	690 (50.33)	477 (87.68)	69 (100)	42 (97.67)	1278 (63.05)
Determined to be eligible for study	550 (40.12)	206 (37.87)	64 (92.75)	31 (73.81)	851 (41.98)
Completed baseline survey	350 (63.6)	46 (22.3)	37 (57.8)	19 (61.3)	452 (53.1)

In addition, the protocol also includes gathering tracking and location information including (1) address, (2) phone numbers, (3) email, (4) social media, (5) family/friend contact, and (6) school/work information. Every 6 months, this information is reviewed with the participant and updated as needed. Participants are asked to contact their interviewer monthly (eg, text message, phone call, or SnapChat) in return for a US $7 monthly incentive (an additional US $42 added to their data collection incentive). These check-ins are an opportunity to determine whether the participant needs any resources (eg, food bank and physician referrals) and remind them of any upcoming appointments. The HYM team uses this opportunity to catch up on any events in the young men's lives and enter field notes as needed. We learned that the HYM participants tend to enjoy these check-ins and share photos with their assigned staff person (eg, prom and weddings) or ask about different services as needed. If the participant fails to make contact after 2 months, the participant's assigned interviewer uses tracking and location information and/or criminal justice records to make contact. Between baseline and wave 2, only 7% had missed 1 or more check-ins.

Community Advisory Board and Youth Advisory Board

CABs and YABs have played a critical role in our research conducted with YMSM. The HYM CAB and YAB were developed to help to inform all aspects of the study design, implementation, and interpretation of the study findings. CAB members include policy makers, HIV/AIDS service providers, and community advocates. The YAB comprises members of our target population who were recruited from local clinics serving YMSM. The CAB meets on a bimonthly basis and the YAB meets monthly. Agendas typically include brief study updates, information about new proposals in development and upcoming events, a data presentation on a specific topic or construct, and discussions about how to interpret these data and move them to the next stage. Our CAB assisted in developing community forums, coauthored peer-reviewed papers, assisted in outreach, and copresented study results with the HYM team. The YAB has reviewed our data collection tools, provided feedback on proposed interventions, and assisted in outreach efforts at public venues.

Measures

HYM study participants participate in a self-report survey every 6 months. The survey is administered by their assigned staff person, and questions about more private topics (eg, substance use, sexual behavior, violence) are self-administered using a Web-based survey to provide an additional layer of confidentiality and encourage more honest responses [48,49]. The survey takes approximately 1 and a half hours to complete; special topics are integrated into individual waves when only a single assessment point of data is needed (eg, childhood trauma or mindfulness). At baseline, participants completed a *pre-baseline* assessment, a brief (10-min) survey completed during the informed consent process, and received US $10 for the pre-baseline and an additional US $55 for completing the baseline assessment. Participants can earn up to US $100 at follow-up assessments if they complete each monthly check-in (US $55 for the assessment and US $42 for the check-ins, rounded up to total US $100). A description of the study measures is as follows.

Demographic Characteristics

Survey instruments obtain demographic information including age, race/ethnicity, religion residence and residential stability, education/employment, food security/hunger, socioeconomic status, history of foster care and incarceration, and insurance status.

Primary Outcome Measures

Alcohol, Tobacco, Marijuana, and Illicit Drug Use

Scales from the Monitoring the Future study are used to assess lifetime, past 6-month, and past 30-day illicit drug and alcohol use [50]. The drug list includes marijuana, lysergic acid diethylamide or LSD, phencyclidine (more commonly known as PCP or angel dust), mushrooms, cocaine, crack, methamphetamines, ecstasy, stimulants, heroin, fentanyl, and prescription drugs used without a physician's order. We also assessed substance use problems using standardized measures including alcohol and marijuana misuse. Participants are asked the location and circumstances during which they use drugs, particularly around the time when they engage in sexual behaviors. We collect urine samples at baseline and every 6 months to test for metabolites of methamphetamines, cocaine, ecstasy, marijuana, and opiates using the Integrated E-Z Split Key Cup II- 5 Panel (Innovacon Laboratories), which can detect drugs from 1 to 4 days after use, except for chronic marijuana use, which can be detected for up to 30 days [51,53]. Screening for fentanyl is also performed.

Sexual Risk Behaviors, Partners and HIV Risk, and Protective Behaviors

These are assessed using scales adapted from the EXPLORE study and research we previously conducted with YMSM [52,53]. Participants are asked about their *lifetime and recent sexual experiences* (past 1 and 6 months), including insertive/receptive oral sex, insertive/receptive vaginal sex, and insertive/receptive anal sex. Specifically, participants are asked to report the number of times they engaged in each type of

sexual activity and the gender of their partners, each of these types of sexual activity for the *different partner types* (eg, primary, consistent casual, and casual) they might have had in the past 6 months, and the *frequency of condom* use by gender of partner and by sexual activity. This measures *condomless intercourse*. Participants are asked if they have ever and recently (past 6 months) exchanged sex for money, drugs, food, clothes, etc.

Condom Use Self-Efficacy

The 15-item Condom Use Self-Efficacy measures condom use self-efficacy using 5-point Likert scale [54,55]. Condom use intention is assessed using a 9-item condom intention scale [56].

Partner Demographic and HIV Status

Current partner or partners'demographics including race/ethnicity are age, type (primary, casual, and hookup; if primary open vs monogamous), HIV status and HIV concordance/discordance, and partner's use of HIV services and ART adherence if HIV+. Sexual compulsivity is also assessed with the 10-item Sexual Compulsivity Scale, which asks respondents to endorse their agreement with statements related to sexually compulsive behavior [57].

Sexually Transmitted Infection/HIV Testing and Prevention Behaviors

Participants complete HIV testing using fourth-generation point-of-care rapid whole blood finger-stick HIV test (Alere, Inc, Waltham, MA), an FDA-approved diagnostic measure of HIV-1 p24 antigen and HIV-1/2 antibodies. This test is performed every 6 months. We also use scales from our previous study conducted with YMSM to measure self-reported history of HIV/STI testing and HIV status. Participants self-collect rectal and pharyngeal specimens for *Neisseriagonorrhea* and *Chlamydia trachomatis* nucleic acid amplification testing at baseline and every 6 months. Syphilis testing is performed using whole blood collected via venipuncture (or fingerstick) using rapid plasma regain and treponemal antibody testing at baseline and every 6 months. Those with positive results meet the on-site HIV test counselor and then are referred to and treated at 1 of our partner clinical sites.

Health Care, Linkage, Engagement, and HIV Service Utilization

Health care, linkage, engagement, and HIV service utilization dates are collected every 6 months. Participants are asked questions about their current health status using modified questions from the Youth Risk Behavior Survey [58]. These questions ask about the respondent's overall health status, the number of days in the last week they have eaten fruits or vegetables, and the number of days in the last week they have exercised. Participants' access to and use of the health care system was measured using both the Addhealth survey from the National Longitudinal study of Adolescent to Adult Health study and the National Survey of Children's Health [59]. These measures assess the frequency and type of health practitioner seen in the past 12 months, insurance status, reasons for use or nonuse of health care services in the last year, and comfort in speaking with their doctor about sexual health. Trust/mistrust of the health care system is measured with the Health Care System Distrust Scale, a 10-item scale that assesses perceptions of the health care system [60]. Visual analog scale (VAS) for ART adherence asks participants to consider a specific period (eg, last month) and to estimate the percentage of medication doses taken [61,62]. VAS has moderate correlations with unannounced pill counts and self-reported recall and is widely used to assess medication adherence.

Possible Mediating/Moderating Constructs

Depression, Mental Health, Spirituality, Well-Being, Optimism, Resilience, and Mindfulness

To assess depression, anxiety, and somatization, we used the 18-item Brief Symptom Inventory (BSI) [63]. The Patient-Reported Outcomes Measurement Information System (PROMIS) depression short scale assessed depressive symptoms during the previous 7 days [64]. PROMIS was administered during baseline, whereas BSI was administered at baseline and in all follow-up waves. Spirituality was found to be an important aspect of young men's lives in our prior research; thus, we included the spirituality scale, which taps into self-discovery and eco-awareness, 2 of the primary components of spirituality [65]. The 4-item Health as a Value scale measures individuals' perceived importance of health and well-being. We also assess suicidality and self-injurious behaviors, both current and past histories. Optimism is measured using the 10-item Life Orientation Test-Revised [66], and resilience is measured with the Connor-Davidson Resilience Scale [67]. Mindfulness is measured using the Mindful Attention Awareness Scale, a 15-item scale designed to assess a core characteristic of dispositional mindfulness, namely, receptive awareness of and attention to what is taking place in the present [68].

Emotion Regulation and Coping

Emotion regulation and coping data are collected annually. The Difficulties in Emotion Regulation Scale measures participants' ability to be aware of, understand, and accept their emotions as well their ability to act in desired ways regardless of their emotional state [69]. We assessed a variety of coping strategies participants might use in response to a specific stressor using the Brief COPE [70].

Childhood Abuse/Trauma, Internalized Homophobia, Partner Violence, Racism, and Discrimination

Childhood trauma was measured at wave 2 using Bernstein's Childhood Trauma Questionnaire [71]. Internalized homophobia is assessed using a 4-item measure by Ross and Rosser [72]. Partner violence data are collected annually with the revised Conflict Tactics Scale, which measures violence within the context of intimate relationships and identifies lifetime and past 12-months' experiences of physical, sexual, and emotional abuse as a victim and perpetrator [73]. Experiences of racism and discrimination are captured using Diaz and Ayala's 20-item scale that measures lifetime and recent experiences of social discrimination (racism, police brutality, and discrimination due to sexual identity) [74,75]. These data are collected every 6 months.

Stressful Life Events and Life Chaos

Stressful life events and life chaos are measured every 6 months. Stressful life events including health-related stress are assessed using a checklist of life events [76]. The scale provides participants with a list of stressful events and asks them if these events occurred during the previous 6 months and their level of stressfulness on a scale from 1 to 10. We also measure life chaos, a construct found to be associated with poor adherence to ART, using the 6-item Life Chaos scale [77].

Social Support and Connection to Community

These data are collected every 6 months. The Multidimensional Scale of Perceived Social Support, a 12-item scale, measures perceived social support from family, friends, and partner(s) [78]. Participants' connection to community—work, school, spiritual, residential, and ethnic—is measured using a 10-item scale developed by our research team and used in our prior research.

Biological Specimens and Biorepository

A 10-mL EDTA anticoagulated whole blood sample is drawn, and 2 rectal swabs are collected and banked for HIV– participants every 12 months throughout the duration of the study; samples are drawn and banked for HIV+ participants every 6 months. Blood specimens are processed to harvest plasma and a cellular pellet. Plasma is then divided into 4 separate aliquots and stored at −80°C. The red blood cell/buffy coat pellet is harvested and stored for future cellular material and will be made available to investigators for future studies of patient and/or viral genomes. All specimens are entered into a secure, password-protected database noting its position in storage (eg, rack, box, and position) for ease of tracking and retrieval.

Results

To date, the HYM cohort study sample has been recruited and analyses are being conducted with the baseline data. Assessments will continue every 6 months until the end of this project period, in July 2020.

Discussion

To date we want to acknowledge:

- Limitations and implications for generalizability of the findings as they are only representative of YMSM of color in the Los Angeles metropolitan area
- Our retention rate of 97% at 12 months
- Nearly 5% of the HIV-seronegative sample have seroconverted since baseline

Importantly, HYM cohort study participants are recruited from communities experiencing many disparities in health care and other social determinants of health (eg, poverty, low education levels, and crime). Therefore, it is important to consider how both positive and negative changes in these disparities over time may facilitate young men's engagement in HIV care, utilization of prevention strategies, and ultimately predictors of avoiding HIV seroconversion and incident STIs.

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Conflicts of Interest

None declared.

References

1. Eaton LA, Driffin DD, Bauermeister J, Smith H, Conway-Washington C. Minimal Awareness and Stalled Uptake of Pre-Exposure Prophylaxis (PrEP) Among at Risk, HIV-Negative, Black Men Who Have Sex with Men. AIDS Patient Care STDS 2015 Aug;29(8):423-429 [FREE Full text] [doi: 10.1089/apc.2014.0303] [Medline: 26083143]
2. Social determinants of health among adults with diagnosed HIV infection in 20 states, the District of Columbia, and Puerto Rico. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention; 2014. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-22-3.pdf [accessed 2018-11-20] [WebCite Cache ID 7440eiaVS]
3. HIV Among African Americans. Atlanta, GA: Centers for Disease Control and Prevention; 2010. URL: https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/cdc-hiv-aa-508.pdf [accessed 2018-11-20] [WebCite Cache ID 7440LXXfu]

4. Centers for Disease Control and Prevention. HIV and young men who have sex with men URL: https://npin.cdc.gov/publication/hiv-and-young-men-have-sex-men [accessed 2018-11-20] [WebCite Cache ID 7440Wlq1F]
5. Centers for Disease Control and Prevention. 2017. HIV Surveillance Report, 2016 URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2016-vol-28.pdf [accessed 2018-11-20] [WebCite Cache ID 7440kd35E]
6. Centers for Disease Control and Prevention. 2017. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data, United States and 6 dependent areas URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-22-2.pdf [accessed 2018-11-19] [WebCite Cache ID 7440GWHr4]
7. Mustanski BS, Garofalo R, Emerson EM. Mental health disorders, psychological distress, and suicidality in a diverse sample of lesbian, gay, bisexual, and transgender youths. Am J Public Health 2010 Dec;100(12):2426-2432. [doi: 10.2105/AJPH.2009.178319] [Medline: 20966378]
8. Mustanski B, Garofalo R, Herrick A, Donenberg G. Psychosocial health problems increase risk for HIV among urban young men who have sex with men: preliminary evidence of a syndemic in need of attention. Ann Behav Med 2007 Aug;34(1):37-45 [FREE Full text] [doi: 10.1080/08836610701495268] [Medline: 17688395]
9. Garofalo R, Hotton A, Kuhns L, Gratzer B, Mustanski B. Incidence of HIV Infection and Sexually Transmitted Infections and Related Risk Factors Among Very Young Men Who Have Sex With Men. J Acquir Immune Defic Syndr 2016 May 01;72(1):79-86 [FREE Full text] [doi: 10.1097/QAI.0000000000000933] [Medline: 26745827]
10. Garofalo R, Mustanski BS, McKirnan DJ, Herrick A, Donenberg GR. Methamphetamine and young men who have sex with men: understanding patterns and correlates of use and the association with HIV-related sexual risk. Arch Pediatr Adolesc Med 2007 Jun;161(6):591-596 [FREE Full text] [doi: 10.1001/archpedi.161.6.591] [Medline: 17548765]
11. Perdue T, Hagan H, Thiede H, Valleroy L. Depression and HIV risk behavior among Seattle-area injection drug users and young men who have sex with men. AIDS Educ Prev 2003 Feb;15(1):81-92. [Medline: 12627745]
12. O'Cleirigh C, Newcomb M, Mayer K, Skeer M, Traeger L, Safren S. Moderate levels of depression predict sexual transmission risk in HIV-infected MSM: a longitudinal analysis of data from six sites involved in a "prevention for positives" study. AIDS Behav 2013 Jun;17(5):1764-1769 [FREE Full text] [doi: 10.1007/s10461-013-0462-8] [Medline: 23605154]
13. Clerkin EM, Newcomb ME, Mustanski B. Unpacking the racial disparity in HIV rates: the effect of race on risky sexual behavior among Black young men who have sex with men (YMSM). J Behav Med 2011 Aug;34(4):237-243. [doi: 10.1007/s10865-010-9306-4] [Medline: 21107898]
14. Jeffries WL, Marks G, Lauby J, Murrill CS, Millett GA. Homophobia is associated with sexual behavior that increases risk of acquiring and transmitting HIV infection among black men who have sex with men. AIDS Behav 2013 May;17(4):1442-1453. [doi: 10.1007/s10461-012-0189-y] [Medline: 22569942]
15. Wong CF, Weiss G, Ayala G, Kipke MD. Harassment, discrimination, violence, and illicit drug use among young men who have sex with men. AIDS Educ Prev 2010 Aug;22(4):286-298 [FREE Full text] [doi: 10.1521/aeap.2010.22.4.286] [Medline: 20707690]
16. Raffaelli M, Torres Stone RA, Iturbide MI, McGinley M, Carlo G, Crockett LJ. Acculturation, gender, and alcohol use among Mexican American college students. Addict Behav 2007 Oct;32(10):2187-2199. [doi: 10.1016/j.addbeh.2007.02.014] [Medline: 17408871]
17. Wilson H, Widom C. An examination of risky sexual behavior and HIV in victims of child abuse and neglect: a 30-year follow-up. Health Psychol 2008 Mar;27(2):149-158. [doi: 10.1037/0278-6133.27.2.149] [Medline: 18377133]
18. Albarracin J, Plambeck CR. Demographic factors and sexist beliefs as predictors of condom use among Latinos in the USA. AIDS Care 2010 Aug;22(8):1021-1028. [doi: 10.1080/09540121.2010.487089] [Medline: 20677032]
19. Warren JC, Fernández MI, Harper GW, Hidalgo MA, Jamil OB, Torres RS. Predictors of unprotected sex among young sexually active African American, Hispanic, and White MSM: the importance of ethnicity and culture. AIDS Behav 2008 May;12(3):459-468 [FREE Full text] [doi: 10.1007/s10461-007-9291-y] [Medline: 17721725]
20. Kubicek K, McDavitt B, Carpineto J, Weiss G, Iverson E, Kipke MD. “God Made me Gay for a Reason”: Young Men who have Sex with Men's Resiliency in Resolving Internalized Homophobia from Religious Sources. Journal of Adolescent Research 2009 Sep 01;24(5):601-633 [FREE Full text] [doi: 10.1177/0743558409341078] [Medline: 20160996]
21. Pulsipher C, Montoya J, Plant A, Curtis P, Holloway I, Leibowita A. California HIV AIDS Research Program September. 2016. Addressing PrEP disparities among young gay and bisexual men in California URL: https://aplahealth.org/wp-content/uploads/2016/09/APLA_PrEP_FullReport_WEB.pdf [accessed 2018-11-20] [WebCite Cache ID 74417SwDc]
22. Siegler A, Mouhanna F, Giler R. Distribution of active PrEP prescriptionsthe PrEP-to-need ratio, US. In: Conference on Retroviruses Opportunistic Infections. 2017 Presented at: 25th Conference on Retroviruses Opportunistic Infections (CROI); 2018; Boston, MA.
23. Lelutiu-Weinberger C, Golub SA. Enhancing PrEP Access for Black and Latino Men Who Have Sex With Men. J Acquir Immune Defic Syndr 2016 Dec 15;73(5):547-555 [FREE Full text] [doi: 10.1097/QAI.0000000000001140] [Medline: 27454250]
24. Strauss BB, Greene GJ, Phillips G, Bhatia R, Madkins K, Parsons JT, et al. Exploring Patterns of Awareness and Use of HIV Pre-Exposure Prophylaxis Among Young Men Who Have Sex with Men. AIDS Behav 2017 May;21(5):1288-1298 [FREE Full text] [doi: 10.1007/s10461-016-1480-0] [Medline: 27401537]

25. Kuhns LM, Hotton AL, Schneider J, Garofalo R, Fujimoto K. Use of Pre-exposure Prophylaxis (PrEP) in Young Men Who Have Sex with Men is Associated with Race, Sexual Risk Behavior and Peer Network Size. AIDS Behav 2017 May;21(5):1376-1382 [FREE Full text] [doi: 10.1007/s10461-017-1739-0] [Medline: 28238119]
26. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull 2003 Sep;129(5):674-697 [FREE Full text] [doi: 10.1037/0033-2909.129.5.674] [Medline: 12956539]
27. Tobias C, Cunningham WE, Cunningham CO, Pounds MB. Making the connection: the importance of engagement and retention in HIV medical care. AIDS Patient Care STDS 2007;21 Suppl 1:S3-S8. [doi: 10.1089/apc.2007.9992] [Medline: 17563287]
28. Hightow-Weidman L, LeGrand S, Choi SK, Egger J, Hurt CB, Muessig KE. Exploring the HIV continuum of care among young black MSM. PLoS One 2017;12(6):e0179688 [FREE Full text] [doi: 10.1371/journal.pone.0179688] [Medline: 28662170]
29. Zanoni B, Mayer K. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS 2014 Mar;28(3):128-135 [FREE Full text] [doi: 10.1089/apc.2013.0345] [Medline: 24601734]
30. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. J Acquir Immune Defic Syndr 2011 Oct 01;58(2):193-197. [doi: 10.1097/QAI.0b013e31822d7564] [Medline: 21826014]
31. Menke TJ, Giordano TP, Rabeneck L. Utilization of health care resources by HIV-infected white, African-American, and Hispanic men in the era before highly active antiretroviral therapy. J Natl Med Assoc 2003 Sep;95(9):853-861. [Medline: 14527053]
32. del Rio C. Latinos and HIV care in the Southeastern United States: new challenges complicating longstanding problems. Clin Infect Dis 2011 Sep;53(5):488-489. [doi: 10.1093/cid/cir440] [Medline: 21844032]
33. Rosenberg E, Millett G, Sullivan P, Del Rio C, Curran J. Understanding the HIV disparities between black and white men who have sex with men in the USA using the HIV care continuum: a modeling study. Lancet HIV 2014 Dec;1(3):e112-e118 [FREE Full text] [doi: 10.1016/S2352-3018(14)00011-3] [Medline: 25530987]
34. Skarbinski J, Rosenberg E, Paz-Bailey G, Hall HI, Rose CE, Viall AH, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA Intern Med 2015 Apr;175(4):588-596. [doi: 10.1001/jamainternmed.2014.8180] [Medline: 25706928]
35. Christopoulos KA, Das M, Colfax GN. Linkage and retention in HIV care among men who have sex with men in the United States. Clin Infect Dis 2011 Jan 15;52 Suppl 2:S214-s222 [FREE Full text] [doi: 10.1093/cid/ciq045] [Medline: 21342910]
36. Brennan J, Kuhns LM, Johnson AK, Belzer M, Wilson EC, Garofalo R, Adolescent Medicine Trials Network for HIV/AIDS Interventions. Syndemic theory and HIV-related risk among young transgender women: the role of multiple, co-occurring health problems and social marginalization. Am J Public Health 2012 Sep;102(9):1751-1757 [FREE Full text] [doi: 10.2105/AJPH.2011.300433] [Medline: 22873480]
37. Bruce D, Harper GW, Adolescent Medicine Trials Network for HIV/AIDS Interventions. Operating without a safety net: gay male adolescents and emerging adults' experiences of marginalization and migration, and implications for theory of syndemic production of health disparities. Health Educ Behav 2011 Aug;38(4):367-378 [FREE Full text] [doi: 10.1177/1090198110375911] [Medline: 21398621]
38. Mustanski B, Phillips G, Ryan DT, Swann G, Kuhns L, Garofalo R. Prospective Effects of a Syndemic on HIV and STI Incidence and Risk Behaviors in a Cohort of Young Men Who Have Sex with Men. AIDS Behav 2017 Mar;21(3):845-857 [FREE Full text] [doi: 10.1007/s10461-016-1607-3] [Medline: 27844298]
39. Stall R, Mills TC, Williamson J, Hart T, Greenwood G, Paul J, et al. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. Am J Public Health 2003 Jun;93(6):939-942. [Medline: 12773359]
40. Wilson PA, Nanin J, Amesty S, Wallace S, Cherenack EM, Fullilove R. Using syndemic theory to understand vulnerability to HIV infection among Black and Latino men in New York City. J Urban Health 2014 Oct;91(5):983-998 [FREE Full text] [doi: 10.1007/s11524-014-9895-2] [Medline: 25155096]
41. Centers for Disease Control and Prevention. 2008. Syndemics Overview URL: https://www2.cdc.gov/syndemics/models.htm [accessed 2018-11-20] [WebCite Cache ID 7441VrDgJ]
42. Dyer TP, Shoptaw S, Guadamuz TE, Plankey M, Kao U, Ostrow D, et al. Application of syndemic theory to black men who have sex with men in the Multicenter AIDS Cohort Study. J Urban Health 2012 Aug;89(4):697-708 [FREE Full text] [doi: 10.1007/s11524-012-9674-x] [Medline: 22383094]
43. Wong CF, Schrager SM, Holloway IW, Meyer IH, Kipke MD. Minority stress experiences and psychological well-being: the impact of support from and connection to social networks within the Los Angeles House and Ball communities. Prev Sci 2014 Feb;15(1):44-55 [FREE Full text] [doi: 10.1007/s11121-012-0348-4] [Medline: 23412944]
44. Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: from cascade to continuum to control. Clin Infect Dis 2013 Oct;57(8):1164-1171. [doi: 10.1093/cid/cit420] [Medline: 23797289]
45. Cheever LW. Engaging HIV-infected patients in care: their lives depend on it. Clin Infect Dis 2007 Jun 01;44(11):1500-1502. [doi: 10.1086/517534] [Medline: 17479949]

46. Ford WL, Weiss G, Kipke MD, Ritt-Olson A, Iverson E, Lopez D. The Healthy Young Men's Study: Sampling Methods to Recruit a Random Cohort of Young Men Who Have Sex with Men. J Gay Lesbian Soc Serv 2009 Oct 01;21(4):357-373 [FREE Full text] [doi: 10.1080/10538720802498280] [Medline: 20823947]
47. MacKellar D, Valleroy L, Karon J, Lemp G, Janssen R. The Young Men's Survey: methods for estimating HIV seroprevalence and risk factors among young men who have sex with men. Public Health Rep 1996;111 Suppl 1:138-144 [FREE Full text] [Medline: 8862170]
48. Kissinger P, Rice J, Farley T, Trim S, Jewitt K, Margavio V, et al. Application of computer-assisted interviews to sexual behavior research. Am J Epidemiol 1999 May 15;149(10):950-954. [Medline: 10342804]
49. Ross MW, Tikkanen R, Månsson SA. Differences between Internet samples and conventional samples of men who have sex with men: implications for research and HIV interventions. Soc Sci Med 2000 Sep;51(5):749-758. [Medline: 10975234]
50. Johnston L, O'Malley P, Bachman J, Schulenberg J. Monitoring the Future national survey results on drug use, 1975-2008: Volume I. Secondary school students. Bethesda, MD: National Institute on Drug Abuse; 2010. URL: http://www.monitoringthefuture.org/pubs/monographs/vol1_2008.pdf [accessed 2018-11-20] [WebCite Cache ID 7441iH3Xv]
51. Cone EJ. New developments in biological measures of drug prevalence. NIDA Res Monogr 1997;167:108-129. [Medline: 9243559]
52. Chesney MA, Koblin BA, Barresi PJ, Husnik MJ, Celum CL, Colfax G, EXPLORE Study Team. An individually tailored intervention for HIV prevention: baseline data from the EXPLORE Study. Am J Public Health 2003 Jun;93(6):933-938. [Medline: 12773358]
53. Koblin BA, Chesney MA, Husnik MJ, Bozeman S, Celum CL, Buchbinder S, EXPLORE Study Team. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. Am J Public Health 2003 Jun;93(6):926-932. [Medline: 12773357]
54. Brafford LJ, Beck KH. Development and validation of a condom self-efficacy scale for college students. J Am Coll Health 1991 Mar;39(5):219-225. [doi: 10.1080/07448481.1991.9936238] [Medline: 1783705]
55. Forsyth AD, Carey MP, Fuqua RW. Evaluation of the validity of the condom use self-efficacy scale (CUSES) in young men using two behavioral simulations. Health Psychol 1997 Mar;16(2):175-178 [FREE Full text] [Medline: 9269889]
56. Wingood G, DiClemente R. Gender-related correlates and predictors of consistent condom use among young adult African-American women: a prospective analysis. Int J STD AIDS 1998 Mar;9(3):139-145. [doi: 10.1258/0956462981921891] [Medline: 9530898]
57. Kalichman SC, Johnson JR, Adair V, Rompa D, Multhauf K, Kelly JA. Sexual sensation seeking: scale development and predicting AIDS-risk behavior among homosexually active men. J Pers Assess 1994 Jun;62(3):385-397. [doi: 10.1207/s15327752jpa6203_1] [Medline: 8027907]
58. Centers for Disease Control and Prevention. 2015. Youth Risk Behavior Survey Questionnaire, 2015 URL: https://www.cdc.gov/healthyyouth/data/yrbs/questionnaires.htm [accessed 2018-11-20] [WebCite Cache ID 7442kvLFK]
59. Harris K, Halpern C, Whitsel E. Carolina Population Center. 2009. The National Longitudinal Study of Adolescent to Adult Health: Research Design URL: https://www.cpc.unc.edu/projects/addhealth/design [accessed 2018-11-20] [WebCite Cache ID 74423XiiQ]
60. Rose A, Peters N, Shea J, Armstrong K. Development and testing of the health care system distrust scale. J Gen Intern Med 2004 Jan;19(1):57-63 [FREE Full text] [Medline: 14748861]
61. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials 2004;5(2):74-79. [doi: 10.1310/JFXH-G3X2-EYM6-D6UG] [Medline: 15116282]
62. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugyenyi P, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. J Acquir Immune Defic Syndr 2004 Aug 15;36(5):1100-1102. [Medline: 15247564]
63. Asner-Self KK, Schreiber JB, Marotta SA. A cross-cultural analysis of the Brief Symptom Inventory-18. Cultur Divers Ethnic Minor Psychol 2006 Apr;12(2):367-375. [doi: 10.1037/1099-9809.12.2.367] [Medline: 16719583]
64. Schalet BD, Pilkonis PA, Yu L, Dodds N, Johnston KL, Yount S, et al. Clinical validity of PROMIS Depression, Anxiety, and Anger across diverse clinical samples. J Clin Epidemiol 2016 Dec;73:119-127 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.08.036] [Medline: 26931289]
65. Delaney C. The Spirituality Scale: development and psychometric testing of a holistic instrument to assess the human spiritual dimension. J Holist Nurs 2005 Jun;23(2):145-67; discussion 168. [doi: 10.1177/0898010105276180] [Medline: 15883463]
66. Scheier M, Carver C, Bridges M. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994 Dec;67(6):1063-1078. [Medline: 7815302]
67. Connor KM, Davidson JRT. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18(2):76-82. [doi: 10.1002/da.10113] [Medline: 12964174]
68. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol 2003 Apr;84(4):822-848. [Medline: 12703651]

69. Gratz K, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. Journal of Psychopathology and Behavioral Assessment 2004;26(7):41-54 [FREE Full text]
70. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4(1):92-100. [doi: 10.1207/s15327558ijbm0401_6] [Medline: 16250744]
71. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry 1997 Mar;36(3):340-348. [doi: 10.1097/00004583-199703000-00012] [Medline: 9055514]
72. Ross M, Rosser BR. Measurement and correlates of internalized homophobia: a factor analytic study. J Clin Psychol 1996 Jan;52(1):15-21. [doi: 10.1002/(SICI)1097-4679(199601)52:1<15::AID-JCLP2>3.0.CO;2-V] [Medline: 8682906]
73. Straus M, Hamby S, Boney-McCoy S, Sugarman D. The Revised Conflict Tactics Scales (CTS2). Journal of Family Issues 2016 Jun 30;17(3):283-316. [doi: 10.1177/019251396017003001]
74. Ayala G, Bingham T, Kim J, Wheeler DP, Millett GA. Modeling the impact of social discrimination and financial hardship on the sexual risk of HIV among Latino and Black men who have sex with men. Am J Public Health 2012 May;102 Suppl 2(Supp 2):S242-S249. [doi: 10.2105/AJPH.2011.300641] [Medline: 22401516]
75. Díaz RM, Ayala G, Bein E, Henne J, Marin BV. The impact of homophobia, poverty, and racism on the mental health of gay and bisexual Latino men: findings from 3 US cities. Am J Public Health 2001 Jun;91(6):927-932. [Medline: 11392936]
76. Wills TA. Stress and coping in early adolescence: relationships to substance use in urban school samples. Health Psychol 1986;5(6):503-529. [Medline: 3492372]
77. Wong MD, Sarkisian CA, Davis C, Kinsler J, Cunningham WE. The association between life chaos, health care use, and health status among HIV-infected persons. J Gen Intern Med 2007 Sep;22(9):1286-1291 [FREE Full text] [doi: 10.1007/s11606-007-0265-6] [Medline: 17597350]
78. Canty-Mitchell J, Zimet GD. Psychometric properties of the Multidimensional Scale of Perceived Social Support in urban adolescents. Am J Community Psychol 2000 Jun;28(3):391-400. [doi: 10.1023/A:1005109522457] [Medline: 10945123]

Abbreviations

AA/L-YMSM: black or African American (AA) and Hispanic or Latino (L) YMSM
ART: antiretroviral therapy
CAB: community advisory board
HIV−: HIV negative
HIV+: HIV positive
HYM: Healthy Young Men's cohort study
MSM: men who have sex with men
PEP: postexposure prophylaxis
PrEP: pre-exposure prophylaxis
PROMIS: Patient-Reported Outcomes Measurement Information System
STI: sexually transmitted infection
VAS: visual analog scale
VL: viral load
YAB: youth advisory board
YMSM: young men who have sex with men

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Protocol

Role or Synergistic Interaction of Adenosine and Vitamin D3 Alongside High-Intensity Interval Training and Isocaloric Moderate Intensity Training on Metabolic Parameters: Protocol for an Experimental Study

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Abstract

Background: Obesity is known as one of the major causes of epidemiologic diseases worldwide; therefore, the introduction of treatment strategies by medical professionals, such as the use of various medicines and exercise programs to reduce fat or prevent obesity, is on the rise. Recently, researchers have shown special interest in assessing the effect of lipolytic adenosine and vitamin D deficiency, as well as the effect of exercise, on decreasing body fat percentage.

Objective: This study has been designed to examine the effect of adenosine and vitamin D3 injections, in conjunction with high-intensity interval training and isocaloric moderate-intensity training, on the metabolic parameters of obesity induced by a high-fat diet.

Methods: This is an experimental study using 92 Wistar rats. At 6 weeks of age, the rats' weights will be recorded, after which they will have 1 week to adapt to their new environment before being divided into 12 groups. The rats will participate in a 2-stage experimental intervention, including a 13-week fattening diet phase followed by a 12-week exercise training phase consisting of an exercise program and the injection of adenosine and vitamin D3. Groups 1 and 2 will have a normal diet, and the other groups will have a diet of 40% fat, with free access to food and water up to the second half of the second stage of the study (end of the sixth week of training). After termination of the interventions, tissue collection and molecular assessments (blood for biochemical, tissues for gene expression analyses, and anthropometrical indexes) will be performed.

Results: The project was initiated in April 2017 and completed in December 2017. Data analysis is under way, and the first results are expected to be submitted for publication in November 2018.

Conclusions: We hypothesize that weight loss–induced molecular changes and upregulation will be observed in line with an increase in lipolysis and beta oxidation in muscle and fat tissue as a result of performing isocaloric training in drug-receiving rats and groups on a high-fat diet.

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KEYWORDS

high-fat, diet-induced obesity; high-intensity interval training; isocaloric moderate-intensity training; vitamin D3; adenosine; metabolic parameters; weight loss

Introduction

Background

Obesity is a main health risk factor [1,2] and the major cause of diseases, including metabolic syndrome [3], type 2 diabetes, high blood pressure, and cardiovascular incidence worldwide. The high intake of energy within the body results in abnormal accumulation of fat in adipose tissues [4], which has deteriorating effects on health, life quality, and aging [5]. Thus, the damage of glucose and fat metabolism pathways and the disturbance in metabolic balance of these interrupted conditions [6-8] result in the incidence or development of fat-related diseases [9].

Plant-based substances [4,10,11] and medicines [12-16] have been proposed as strategic treatment and preventive measures for obesity. Presently, one of the most challenging issues in the field of pharmacy is discovering the most effective antiobesity intervention with the least negative side effects on humans. Recently, researchers have focused on the effect of the most active forms of vitamin D and have shown fatty acid oxidation [17] and its controlling role in the incidence of obesity [13,18-23]. On the other hand, while some studies have shown that adipogenesis [24,25] continues through different mechanisms, others have focused on identifying intervention factors that can lead to weight loss, particularly, fat weight, with the researchers revealing the undetected effects of adenosine molecules driven from adenosine triphosphate (ATP) [26].

Depending on the type and dependency of adenosine on specific G proteins, it has a link with one of the 4 receptors—A1, A2A, A2B, and A3—in different tissues showing different functions [27-31]. In contrast to the clinical findings, exercise science training experts rely on the effective and preventive effects of different types of exercise programs on obesity that are relatively consistent without any harmful side effects. On the other hand, considering the significance of intensity and duration of exercise training programs [32-41], high-intensity interval training (HIIT) programs have been identified as a fat controlling intervention [33]. The control of weight increase due to the high-fat content of diet [34] compared with stable aerobic activity, improvement in fat distribution, and insulin with similar energy cost [35], has an effect on obesity. Regardless of the benefits of physical activity on the improvement of obesity, there are inconsistent findings with regard to the decrease in fat indices through participation in physical activity without calorie restriction. In addition, there are a limited number of studies on the significance of calorie consumption based on exercise training volume in contrast to response to different types of training, leading to the same changes in metabolic conditions of obesity-induced high-fat diet with participation in HIIT and isocaloric moderate-intensity training as observed earlier [36].

Thus, considering the significance of finding an antiobesity medicine to reduce weight with less harmful side effects and the undeniable effect of exercise as medicine [14,37] for health and longevity, it seems necessary to examine and compare the effect of medicine, exercise, and their interaction on health. Therefore, due to the inadequate knowledge of introducing harmless medicine to control the increase of the volume and size of fat cells and enhance fat-burning activities in high-fat diets, it seems adenosine (by activating adenosine receptors in response to the density and release of adenosine within the cell that leads to different processes of fat burning) and vitamin D injections, in conjunction with isocaloric sport training, may play a significant role in the reduction of fat accumulation, lipolysis regulation, and insulin sensitivity in vital metabolic organs including the liver, muscles, and different fat tissues, which may eventually lead to weight loss.

Study Objective

The aim of this study is to examine the interaction of adenosine and vitamin D3 alongside HIIT and isocaloric moderate-intensity training on anthropometric, thermogenic, and metabolic gene parameters in high-fat diet–induced obese rats.

Methods

Animals

In this experimental protocol, 92 male Wistar rats will be prepared by the Shahid Mirghani Research Institute. This study has been reviewed by the research ethics committee of Sports Science Research Institute and was approved with the code IR.SSRI.REC.1395.115. The rats will be kept in similar laboratory environment conditions at 22°C±3°C in a 12-hour day-night cycle. All rats will be fed a normal diet until 5 to 6 weeks to gain 182.32 grams of weight. After 1 week of adaptation to a new environment, the 92 rats will be divided into 12 groups to participate in the 2 stages of the experimental intervention, including a 13-week fattening diet plan (they will consume 40% fat) followed by a 12-week exercise program. All the rats in the normal diet (except groups 1 and 2) will have free access to food and water up to the second half of the second stage (end of the sixth week of training). In the beginning of the seventh week, the amount of food given to all the groups will be prepared based on a gram scale (based on the mean value of food in groups 3 and 6) for 6 weeks in an identical scale. This process will continue until the end of the training stage. Anthropometric measures will be assessed for all groups, including weight per week, body mass index (BMI), waist and chest size and ratio, height, Lee index, calories consumed, the ratio of weight gain to the total amount of food consumed, the ratio of weight gain to the total calories consumed monthly, and the amount of food consumed daily by every rat.

Diet

Normal diet will contain 4.30 kcal per gram including 3.87% fat (soy oil), 17.46% casein protein, 68.7% carbohydrates, 8.97% minerals, and 1% vitamins. High-fat diet will contain 5.81 kcal per gram with 40% fat (20% soy oil and 20% [animal fat]

subcutaneous fat oil), 14.1% casein protein, 36.58% carbohydrates, 8.4% minerals, and 0.72% vitamins.

Experimental Groups

Before any intervention, all 92 rats will be assigned randomly to 12 groups while matched for their weights. Moreover, 2 of these groups will serve as the control group and receive a normal diet. The remaining groups will go through 2 treatment stages; in the first stage, they will consume a 40% fat content diet for 13 weeks. In the second stage of the protocol (training phase), 1 of the control groups (n=5), Group 1, will be slaughtered. The 11 remaining groups will include Group 2, the second control group (n=5), which will still be fed a normal diet; Group 3 will continue on a high-fat diet (n=5); Group 4 will continue on a high-fat diet and vitamin D3 injection (n=5); Group 5 will continue on a high-fat diet and adenosine injection (n=8); Group 6 will continue on a high-fat diet and placebo injection (n=8); Group 7 will continue on a high-fat diet and undergo HIIT (n=11); Group 8 will continue on a high-fat diet and undergo HIIT and placebo injection (n=10); Group 9 will continue on a high-fat diet and undergo moderate-interval training (MIT) and adenosine injection (n=11); Group 10 will continue on a high-fat diet and undergo MIT and placebo injection (n=10); Group 11 will continue on a high-fat diet and undergo MIT with D3 injection (n=7); and Group 12 will continue on a high-fat diet and undergo HIIT with D3 injection (n=7; Figures 1-4).

Anthropometric Assessments

The abdominal circumference (immediate anterior to the forefoot), thoracic circumference (immediate behind the foreleg), and body length (nose-to-anus or nose-anus length) will be determined in all the rats every month. The measurements will be done on anaesthetized rats (0.1 mL intraperitoneally of 1% sodium barbiturate). The body weight and body length will be determined with the following anthropometrical parameters [42]:

BMI = body weight in g/length^2 (cm^2)

Lee index = cube root of body weight in grams/nose-to-anus length (cm)

Specific rate of body mass gain will be determined by: g/kg = dM/Mdt, where dM represents the gain of body weight during dt = t2−t1, and M is the rat body weight at t1.

Body Mass and Food Intake

Body mass and food intake (difference between the feed offered and the remaining feed) of each animal will be measured daily throughout the experimental period by precision balance (Gehaka, model BG 2000, Brazil). Feed efficiency and energy efficiency will be calculated using the following formulas:

Feed efficiency = Body mass gain (g)/Total food intake (g)

Energy efficiency = Body mass gain (g)/Total caloric intake (kcal)

Drug Treatment

A total of 190 doses of 3mg/mL adenosine packs and vitamin D3 with 300,000 IU/mL will be purchased from the College of Pharmacy, Tehran University of Medical Sciences. The dosage of adenosine drugs was calculated based on weight and will be prepared in 1 cc of saline. During the first 6 weeks of the training phase, every rat will be injected intraperitoneal (IP), 0.2 mg/mL/kg adenosine dose and vitamin D3 with 10,000-unit dose per rat. After 6 weeks of training, to assess the rate of the effectiveness of the drug, a crossover design will be employed by introducing a dose of 0.4/mg/mL/kg adenosine injection per day and increased unit dose of vitamin D3 to 20,000 IU/ml once in the beginning of the second 6-weeks training period. These doses will undergo no further changes up to the end of the protocol.

Adenosine Intraperitoneal Injection Aspects

The adverse effects of adenosine, however, limit the usefulness of this agent as a systemically (intravenously or intra-arterially) administered drug. When so administered, adenosine can cause heart block, asystole, arrhythmias, bradycardia, hypotension, bronchoconstriction, and a stress reaction consisting of flushing, headache, dyspnea, chest pressure, and nausea. This is done via single application or intermittent or continuous peritoneal lavage, which induces beneficial effects on the intestines of a subject. This approach can achieve pharmacologically active levels of adenosine in the intestinal wall of a mammal (including humans) without producing significant levels of adenosine in the systemic circulation of the subject.

However, there is a possibility that the metabolic barrier to adenosine absorption by the gastrointestinal tract, that is, intestinal adenosine deaminase [43] would be so effective in limiting the bioavailability of peritoneally administered adenosine that active levels of adenosine in the gastrointestinal tract could only be achieved with concentrations of adenosine in the peritoneal cavity so high that absorption at other sites in the peritoneal cavity would result in overwhelming systemic levels of adenosine. When administered to a subject by peritoneal lavage, adenosine dilates the splanchnic circulation and increases adenosine levels in the mesenteric vein, without affecting systemic hemodynamics or increasing adenosine levels in the arterial circulation. This invention, therefore, establishes that therapeutically effective levels of adenosine can be achieved in the peritoneal cavity in a subject without attaining pharmacologically active levels in the subject's systemic circulation [44]. Thus, according to the side effects of intravenous injection, the authors will use IP injection in this study. Moreover, considering the high lethal dose (LD50) of the adenosine and its half-life of 0.6 to 10 seconds and also prolonged absorption through IP injection, we will select 0.2 and 0.4 mg/mL/kg.

Figure 1. Experimental groups' timeline and procedures: Part 1. Group 1 is the control group and will be slaughter after the first stage (n=5); Group 2 is the second control group (n=5), which will still be fed a normal diet; Group 3 will continue on a high-fat diet (n=5); Group 4 will continue on a high-fat diet and vitamin D3 injection (n=5); Group 5 will continue on a high-fat diet and adenosine injection (n=8); Group 6 will continue on a high-fat diet and placebo injection (n=8). ND: normal diet, FPh: fatten phase, ETPh: exercise training phase, HFD: high-fat diet.

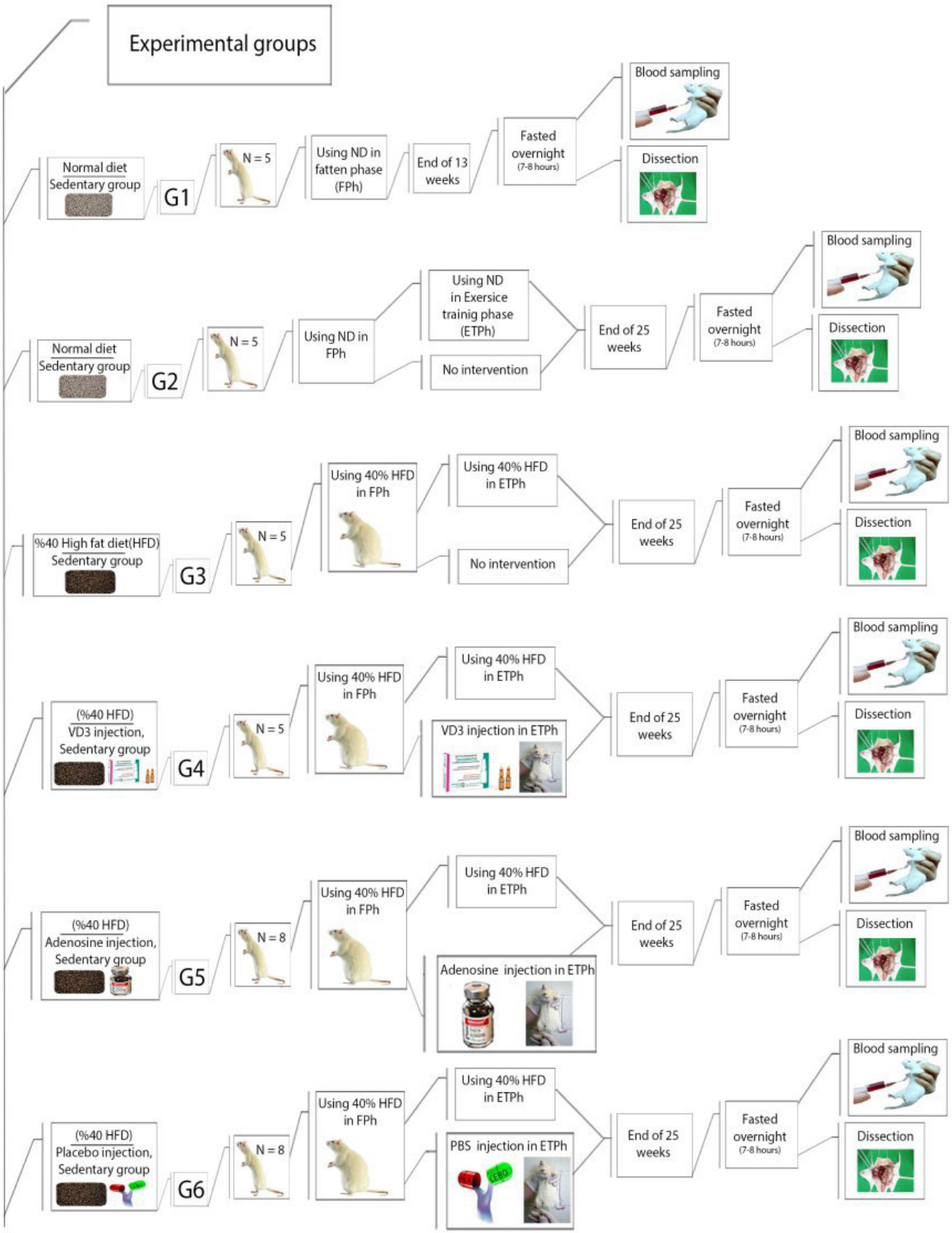


Figure 2. Experimental groups' timeline and procedures: Part 2. Group 7 will continue on a high-fat diet and undergo HIIT (n=11); Group 8 will continue on a high-fat diet and undergo HIIT and placebo injection (n=10); Group 9 will continue on a high-fat diet and undergo moderate-interval training (MIT) and adenosine injection (n=11); Group 10 will continue on a high-fat diet and undergo MIT and placebo injection (n=10). HFD: high-fat diet, FPh: fatten phase, HIIT: high intensity-interval training, ETPh: exercise training phase, MIT: moderate-intensity training.

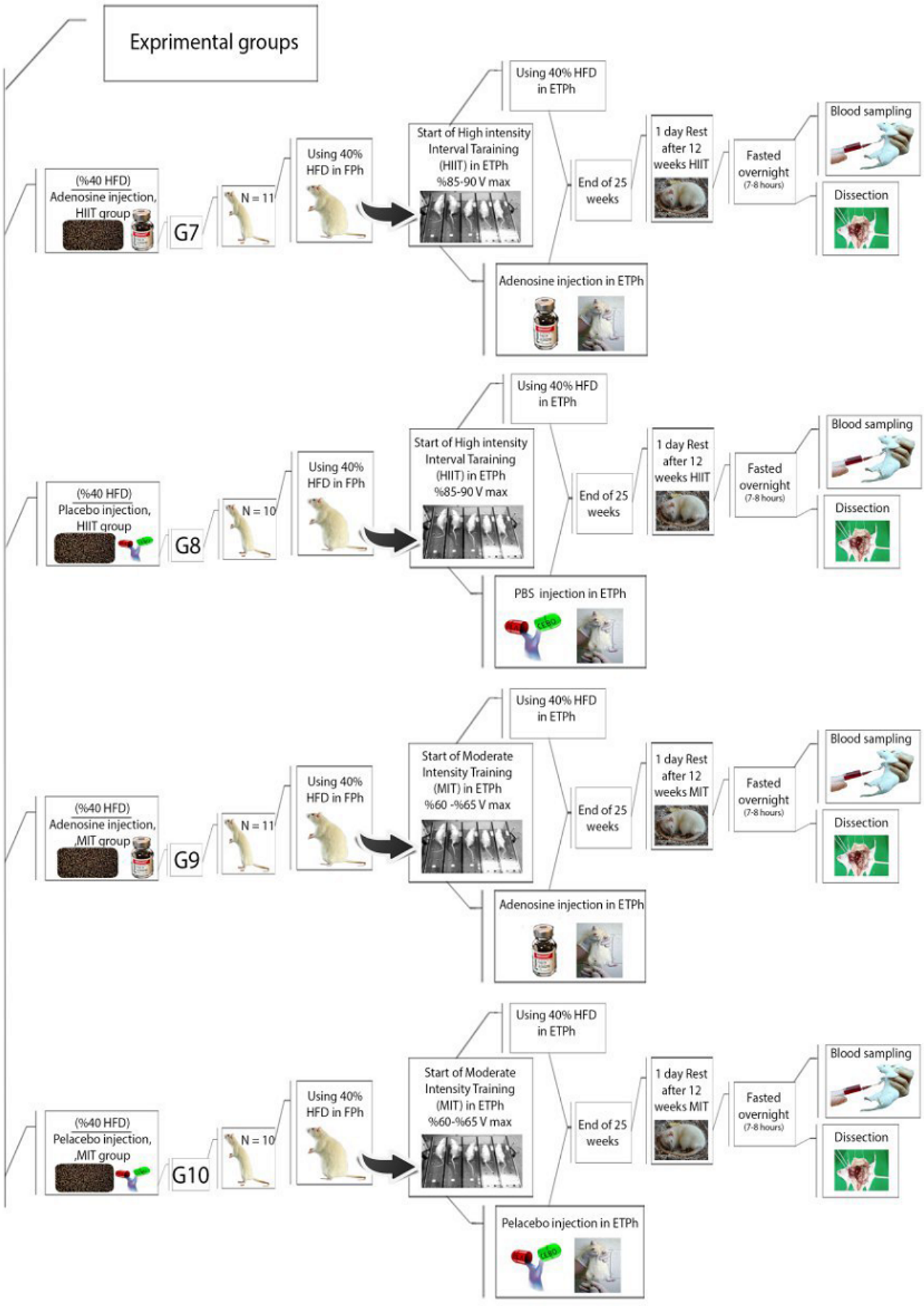


Figure 3. Experimental groups' timeline and procedures: Part 3. Group 11 will continue on a high-fat diet and undergo MIT with D3 injection (n=7); Group 12 will continue on a high-fat diet and undergo HIIT with D3 injection. HFD: high-fat diet, ETPh: exercise training phase, MIT: moderate-intensity training, HIIT: high intensity-interval training.

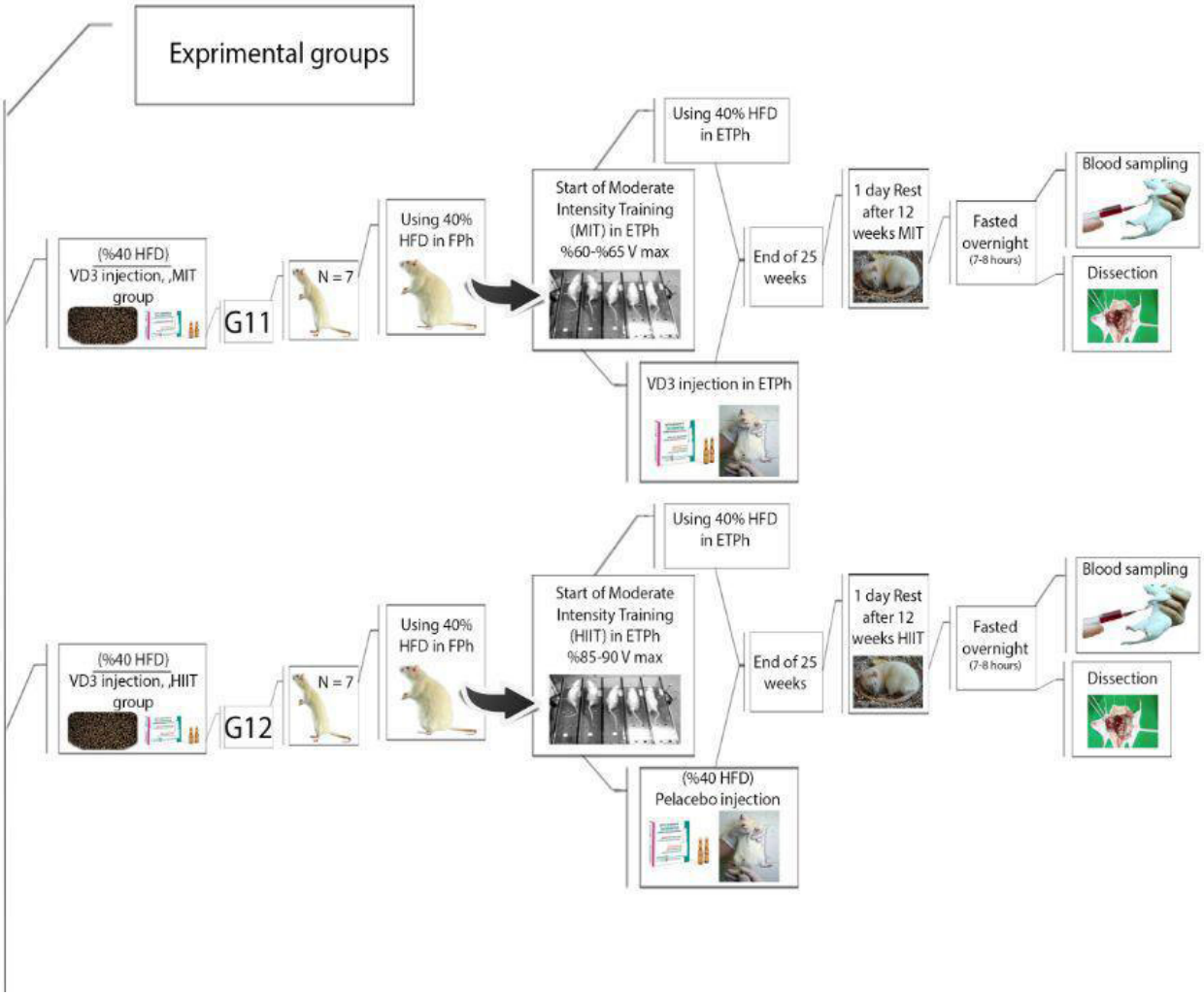
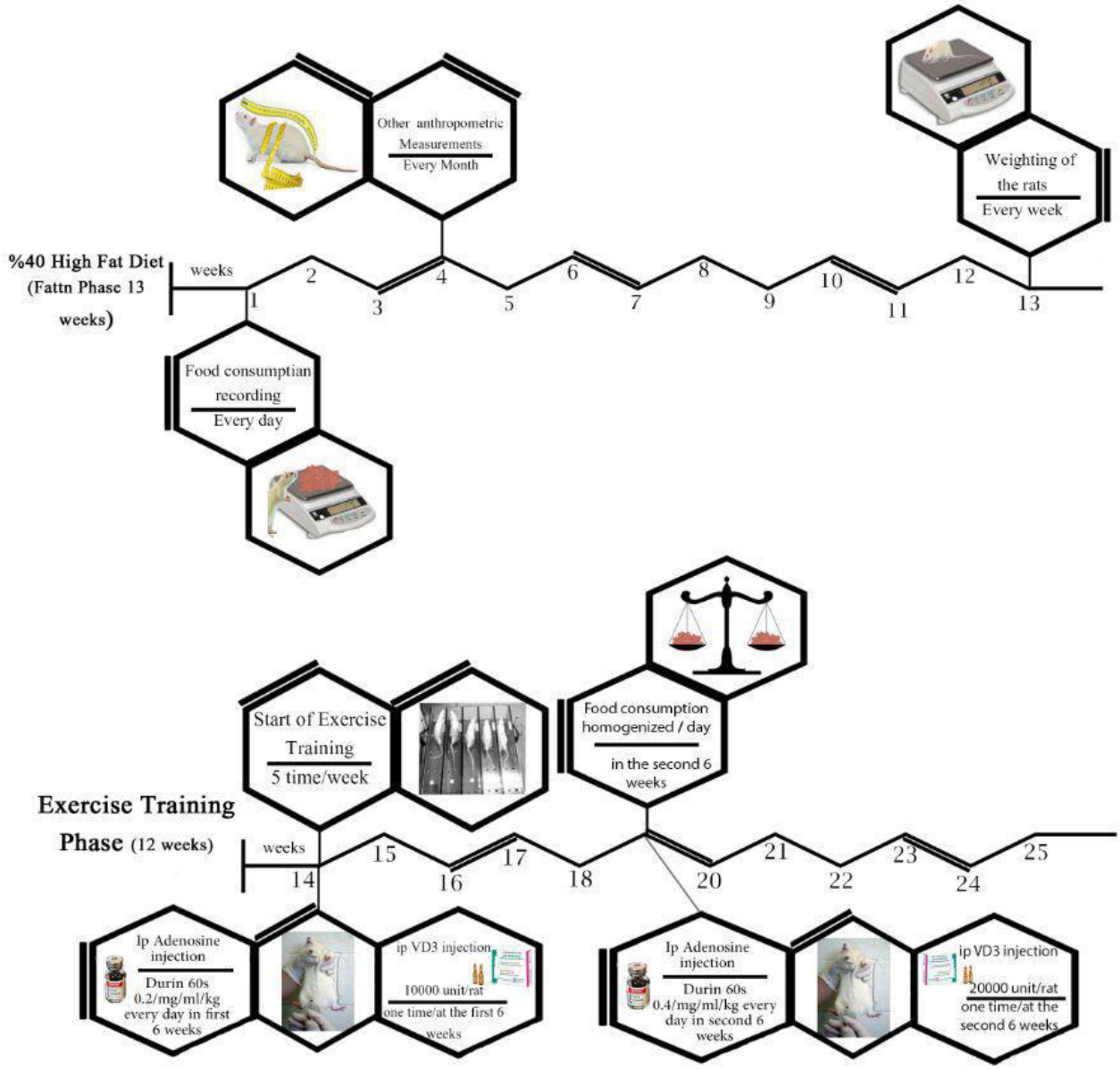


Figure 4. Experimental outline: Fatten Phase. IP: intraperitoneal.



Exercise Protocol

The rats in the training groups will be placed on an animal treadmill to run at various speeds of 6, 8, and 10 m per min in a trial period of a week before the main exercise protocol to become acquainted with the procedures. Then, every rat will be placed on the treadmill to continue running at maximum speed up to the exhaustion point. Following the recording of the maximum speed during exhaustion for every rat [38], the mean value of speed of the exercising rats will be calculated. Then, the exercise protocol will be designed [39] (Tables 1 and 2). The designed program will be based on the data obtained through the pilot phase. The HIIT will include an 85% to 90% V_{max} intensity, whereas, the MIT will be set at 60% to 65% V_{max} level. The warm-up period included comprises 3 min of running at a speed of 10 m per min and cool-down period of 2 min of running at a speed of 15 m per min. Both exercise protocols will be matched for the training volume (consumed calories) to determine the effect of types of exercise programs (isocaloric exercise).

Outcomes

After selecting the rats based on inclusion criteria (weight, age, and species of rats), we will record anthropometrical parameters each week to monitor the changes and use of the dose of drugs and exercise variables. Finally, metabolic, thermogenic, and lipogenesis genes in metabolic tissue (adipose tissues, muscles, liver, and heart, respectively) will be measured and compared to understand the possibility of changes resulting from each intervention in each group that can lead to weight loss, especially fat.

Table 1. High-intensity interval training (HIIT) protocols; 12 weeks high-intensity interval training and 12 weeks isocaloric moderate training; HIIT will be performed 5 times a week with 1 min active/rest ratio.

Week	Bouts, n	Load, meters/minute	Time, minutes	Active rest, minute	Bouts, n	Load, meters/minute	Distance, meters/minute
1	7	31	1	1	6	15	402
2	8	31	1	1	7	15	448
3	8	35	1	1	7	17	494
4	9	36	1	1	8	17	555
5	9	41	1	1	8	19	616
6	9	45	1	1	8	20	660
7	10	45	1	1	9	22	743
8	10	47	1	1	9	22	763
9	10	49	1	1	9	23	792
10	10	50	1	1	9	24	811
11	10	52	1	1	9	24	831
12	10	55	1	1	9	25	870

Table 2. Isocaloric moderate-intensity training (MIT); 12 weeks high-intensity interval training (HIIT) and 12 weeks isocaloric moderate training; MIT will be performed 5 times a week with same distance of HIIT as an isocaloric exercise training.

Week	Bouts, n	Load, meters/minute	Time, minute	Distance, meters/minute
1	1	20	15:21	402
2	1	20	17:39	448
3	1	21	19	494
4	1	21	21:54	555
5	1	22	23:41	616
6	1	23	24:34	660
7	1	24	27	743
8	1	24	27:50	763
9	1	24	29:3	792
10	1	24	29:50	811
11	1	24	30:38	831
12	1	25	31	870

Tissue Collection

After 24 hours of rest and 8 hours of fasting, the rats will be anesthetized by applying pentobarbital sodium (40 mg/kg; IP). Then, after reaching a complete anesthetics condition, blood samples will be drawn directly from the heart and transferred into tubes for serum separation by centrifugation. The samples will be frozen up to −80°C for fat and fat-burning marker analysis. The white fat samples (kidney circumference and visceral), mesenteric (visceral), thigh fat (subcutaneous), interscapular (brown fat), epicardial fat, liver (from the inferior right lobe), gastrocnemius and plantaris muscles, heart epics, and superior part of the thigh will be isolated in 2×2 mm size. All sample collection will be performed from 2 to 4 pm after 7 to 8 hours of fasting. After placing the samples in nitrogen for RNA extraction and gene analysis, they will be transferred to a temperature of −80°C.

Quantitative Polymerase Chain Reaction

Adipose tissue samples will be homogenized in TRIzol solution using a tissue homogenizer (Tissue-Lyser LT; Qiagen, Valencia, CA). Total RNA will be assayed using a NanoDrop spectrophotometer (Thermo Scientific, Wilmington, DE) to assess purity and concentration. First-strand complementary DNA (cDNA) will be synthesized from total RNA using the high-capacity cDNA reverse transcription kit (Applied system; Applied Biosystems). Primer sequences (available upon request) will be designed using the National Center for Biotechnology Information primer design tool. All primers will be purchased from Pishgam (Pishgam, Iran). A 20 µL reaction mixture containing 10 µL SYBR Green Mastermix (Amplicon) and appropriate concentrations of gene-specific primers plus 1000 ng/µL of cDNA template will be loaded in each well of a 96-well plate. All polymerase chain reactions (PCRs) will be performed in duplicates. PCR will be performed with thermal conditions

as follows: 95°C for 10 min, followed by 40 cycles of 95°C for 15 seconds, and 60°C for 45 seconds. A dissociation melt curve analysis will be performed to verify the specificity of the PCR products. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primers will be used to amplify the endogenous control product. Messenger RNA expression values will be presented as 2_ΔΔCT. Data will be expressed as the fold difference relative to GAPDH. Candidate variables include lipolytic, lipolysis, and thermogenesis genes in the visceral, subcutaneous, and brown adipose tissue (BAT), gastrocnemius and soleus muscles, heart muscle, and liver tissues.

For examination of the gene expression in every group, real-time PCR will be employed by ABI Applied Biosystems, Real-Time PCR Systems, (StepOne, Hettich Centrifuges, UNIVERSAL 320, Capacity: 4×100 mL | 32×15 mL), Relative Centrifugal Force/revolutions per minute (RPM/RCF): 15,000/21,382, Temperature Control: −20 to +40°C, cDNA Synthesis Kits—Thermo Scientific, Revert Aid First Strand cDNA Synthesis Kit.

Western Blot Analysis

Radioimmunoprecipitation assay buffer cell lysates will be used to produce western blot-ready samples. Samples will be separated by sodium dodecyl sulfate-polyacrylamide gel analysis transferred to polyvinylidene difluoride membranes, and will be incubated with primary antibodies. Horseradish peroxidase-conjugated mouse or rabbit secondary antibody will be used to detect primary antibodies and will be stained with 3,3'-diaminobenzidine (Sigma-Aldrich, USA). Protein loading will be measured by Bradford (Sigma) staining to determine total protein concentration. The total protein will be loaded in each lane and quantified. These values will be used to adjust for any difference in protein loading or transfer of all band densities. Individual protein bands will be quantified using image J software (National Institutes of Health, USA), and data will be expressed relative to rabbit polyclonal beta actin antibody. Antibodies will be purchased from Abcam (Abcam, Germany).

Biochemical Analysis

The concentrations of glucose, total triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol in serum will be determined by the clinical pathology laboratory using an automated analyzer (Alpha Classic–tajhizatsanjesh). Glycerol, insulin, and free fatty acids will be measured respectively with rat-specific enzyme-linked immunosorbent assay kits (cat No: ZB-GCL48A. Lot.No: ZB-OC717210, cat No: 10-1250-01; Lot No. 25692 ZB-A1515818) according to the manufacturer's instructions. Quantitative insulin sensitivity check index (QUICKI) and homeostatic model assessment for insulin resistance will be calculated as described previously using the equation: QUICKI51/(log [I0] 1 log [G0]), where I0 is fasting insulin (lU/mL) and G0 is fasting glucose (mg/dL)2.

Statistical Analysis

The sample size for this research protocol will be estimated based on the effect size that was effective in previous research, and G*power software will be used to determine the required number. For the descriptive results, mean and SD will be calculated and reported in appropriate tables. For any variable showing nonsymmetry or lack of normality, median, 25, and 75 percentiles will be calculated. For determination of the interaction effect, the mean differences and CIs will be calculated, and for estimation of the effect size, Cohen method will be employed to calculate the standardized mean differences. Each intervention will be evaluated by 2-way analysis of variance.

Results

The project was founded in April 2017 and data collection is expected to be conducted until December 2017. Data analysis will start once the data collection is completed, and the first results are expected to be submitted for publication in November 2018.

Discussion

Summary

The rise in obesity has contributed to increasing numbers of people who need to and attempt to lose weight [45]. Thus, most studies have focused on strategies such as caloric restriction [46], intensity of exercise training, and diet combined with exercise [47-49] and antiobesity drugs [50,51]. However, gene expression profiling of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), BAT, and other tissues, including the liver and skeletal muscle [52], in the same individual after significant weight loss will allow us to delineate biological processes most likely related to weight loss. Moreover, it is observed that significant weight loss is associated with significant changes in blood pressure, TGs, HDL-C, and adiponectin. The multiple significant changes in glucose and lipid metabolism, as well as adipose tissue function in response to weight loss, are significant confounding factors, which may confound the observed gene expression changes, either in a concerted mode or as single factors [53]. To follow up the lipolysis and metabolic statues in VAT, SAT, BAT, and hepatocyte, biochemical variables related to metabolism will be measured in blood samples. In addition, to control for the energy expenditure, we will homogenize food intake for all groups. However, it is necessary that scientists should introduce beneficial interventions with high effectiveness and low side effects. To our knowledge, adenosine is present in adipose tissue after breakdown by ectoenzymes of ATP released as a cotransmitter from sympathetic nerves and adipocytes [19]. Adenosine has been shown to regulate hamster BAT respiration at an early metabolic step of the stimulus- thermogenesis sequence [54]. Adenosine increased lipolysis and induced thermogenesis in brown adipocytes via adenosine A2A receptors, and A2A agonists were shown to counteract high-fat diet–induced obesity in mice [55]. Thus, in this study, adenosine as an exogenous intervention will be used in terms of antiobesity-induced high-fat diet, and also synergistic impact of adenosine will be evaluated with combination of the type of exercise following high-fat diet. Moreover, lower serum 25-hydroxyvitamin D concentrations have been consistently

linked to increasing BMI [56]. Prior studies also demonstrated that the loss of adiposity is associated with a proportional increase in circulating vitamin D levels [57]. Moreover, the stimulation of whole-body fat oxidation and the increase in fecal energy loss are 2 established mechanisms by which vitamin D is changing energy balance and may affect weight loss [58]. In this regard, another aspect of this study is the investigation of vitamin D3 injection as an inhibitor of obesity-induced high-fat diet. In addition, vitamin D3 injection will be evaluated along with the combination of type of exercise related to the exercise volume along with food and tap water ad libitum for the first 6 weeks of the exercise training phase, and after that, food will be homogenized in the next 6 weeks of the exercise training phase.

Expected Results

The researcher expects to observe a decrease in anthropometric indices, such as weight of the rats, as apparent changes due to the isocaloric exercise training, drug injection, and food intake following the received high-fat diet. In addition, exercise related to energy consumption, vitamin D3, and adenosine, separately or interacting 2 interventions, may have effectiveness on molecular and biochemical changes in each metabolic tissue, which will result in weight loss. In addition, it is likely that biochemical and molecular changes and upregulation will be observed in line with the increase in lipolysis and beta oxidation in muscle and fat tissue as a result of performing isocaloric training in drug-receiving rats and groups on a high-fat diet.

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Conflicts of Interest

None declared.

References

1. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. J Am Med Assoc 2003 Jan 01;289(1). [doi: 10.1001/jama.289.1.76]
2. James PT, Rigby N, Leach R, International Obesity Task Force. The obesity epidemic, metabolic syndrome and future prevention strategies. Eur J Cardiovasc Prev Rehabil 2004 Feb;11(1):3-8. [Medline: 15167200]
3. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis 2016 Mar;5:2048004016633371 [FREE Full text] [doi: 10.1177/2048004016633371] [Medline: 26998259]
4. Huang L, Chen J, Cao P, Pan H, Ding C, Xiao T, et al. Anti-obese effect of glucosamine and chitosan oligosaccharide in high-fat diet-induced obese rats. Mar Drugs 2015 Apr 30;13(5):2732-2756 [FREE Full text] [doi: 10.3390/md13052732] [Medline: 25942093]
5. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005 Mar 17;352(11):1138-1145. [doi: 10.1056/NEJMsr043743] [Medline: 15784668]
6. Li P, Oh DY, Bandyopadhyay G, Lagakos WS, Talukdar S, Osborn O, et al. LTB4 promotes insulin resistance in obese mice by acting on macrophages, hepatocytes and myocytes. Nat Med 2015 Mar;21(3):239-247 [FREE Full text] [doi: 10.1038/nm.3800] [Medline: 25706874]
7. Lu B, Bridges D, Yang Y, Fisher K, Cheng A, Chang L, et al. Metabolic crosstalk: molecular links between glycogen and lipid metabolism in obesity. Diabetes 2014 Sep;63(9):2935-2948 [FREE Full text] [doi: 10.2337/db13-1531] [Medline: 24722244]
8. Shimizu N, Maruyama T, Yoshikawa N, Matsumiya R, Ma Y, Ito N, et al. A muscle-liver-fat signalling axis is essential for central control of adaptive adipose remodelling. Nat Commun 2015 Apr 01;6:6693 [FREE Full text] [doi: 10.1038/ncomms7693] [Medline: 25827749]
9. Bilski J, Mazur-Bialy A, Brzozowski B, Magierowski M, Jasnos K, Krzysiek-Maczka G, et al. Moderate exercise training attenuates the severity of experimental rodent colitis: the importance of crosstalk between adipose tissue and skeletal muscles. Mediators Inflamm 2015;2015:605071 [FREE Full text] [doi: 10.1155/2015/605071] [Medline: 25684862]
10. Keenan MJ, Zhou J, Hegsted M, Pelkman C, Durham HA, Coulon DB, et al. Role of resistant starch in improving gut health, adiposity, and insulin resistance. Adv Nutr 2015 Mar;6(2):198-205 [FREE Full text] [doi: 10.3945/an.114.007419] [Medline: 25770258]
11. Si X, Strappe P, Blanchard C, Zhou Z. Enhanced anti-obesity effects of complex of resistant starch and chitosan in high fat diet fed rats. Carbohydr Polym 2017 Feb 10;157:834-841. [doi: 10.1016/j.carbpol.2016.10.042] [Medline: 27987997]
12. Asher WL. Mortality rate in patients receiving “diet pills”. Curr Ther Res Clin Exp 1972 Aug;14(8):525-539. [Medline: 4629314]
13. Fink KB, Göthert M. 5-HT receptor regulation of neurotransmitter release. Pharmacol Rev 2007 Dec;59(4):360-417 [FREE Full text] [doi: 10.1124/pr.107.07103] [Medline: 18160701]
14. Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. Handb Exp Pharmacol 2012(209):433-466. [doi: 10.1007/978-3-642-24716-3_20] [Medline: 22249827]

15. White MA, Grilo CM. Bupropion for overweight women with binge-eating disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2013 Apr;74(4):400-406 [FREE Full text] [doi: 10.4088/JCP.12m08071] [Medline: 23656848]
16. Pooyandjoo M, Nouhi M, Shab-Bidar S, Djafarian K, Olyaeemanesh A. The effect of (L-)carnitine on weight loss in adults: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2016 Dec;17(10):970-976. [doi: 10.1111/obr.12436] [Medline: 27335245]
17. Marcotorchino J, Tourniaire F, Astier J, Karkeni E, Canault M, Amiot M, et al. Vitamin D protects against diet-induced obesity by enhancing fatty acid oxidation. J Nutr Biochem 2014 Oct;25(10):1077-1083. [doi: 10.1016/j.jnutbio.2014.05.010] [Medline: 25052163]
18. Abbas MA. Physiological functions of Vitamin D in adipose tissue. J Steroid Biochem Mol Biol 2017 Dec;165(Pt B):369-381. [doi: 10.1016/j.jsbmb.2016.08.004] [Medline: 27520301]
19. Chang E, Kim Y. Vitamin D decreases adipocyte lipid storage and increases NAD-SIRT1 pathway in 3T3-L1 adipocytes. Nutrition 2016 Jun;32(6):702-708 [FREE Full text] [doi: 10.1016/j.nut.2015.12.032] [Medline: 26899162]
20. Lee H, Bae S, Yoon Y. Anti-adipogenic effects of 1,25-dihydroxyvitamin D3 are mediated by the maintenance of the wingless-type MMTV integration site/β-catenin pathway. Int J Mol Med 2012 Nov;30(5):1219-1224. [doi: 10.3892/ijmm.2012.1101] [Medline: 22922938]
21. Sakuma S, Fujisawa J, Sumida M, Tanigawa M, Inoda R, Sujihera T, et al. The involvement of mitogen-activated protein kinases in the 1α,25-dihydroxy-cholecalciferol-induced inhibition of adipocyte differentiation in vitro. J Nutr Sci Vitaminol (Tokyo) 2012;58(1):1-8 [FREE Full text] [Medline: 23007060]
22. Vu D, Ong JM, Clemens TL, Kern PA. 1,25-Dihydroxyvitamin D induces lipoprotein lipase expression in 3T3-L1 cells in association with adipocyte differentiation. Endocrinology 1996 May;137(5):1540-1544. [doi: 10.1210/endo.137.5.8612483] [Medline: 8612483]
23. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract 2003 May;57(4):258-261. [Medline: 12800453]
24. Narvaez CJ, Simmons KM, Brunton J, Salinero A, Chittur SV, Welsh JE. Induction of STEAP4 correlates with 1,25-dihydroxyvitamin D3 stimulation of adipogenesis in mesenchymal progenitor cells derived from human adipose tissue. J Cell Physiol 2013 Oct;228(10):2024-2036. [doi: 10.1002/jcp.24371] [Medline: 23553608]
25. Nimitphong H, Holick MF, Fried SK, Lee M. 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 promote the differentiation of human subcutaneous preadipocytes. PLoS One 2012 Dec;7(12):e52171 [FREE Full text] [doi: 10.1371/journal.pone.0052171] [Medline: 23272223]
26. Zabielska MA, Borkowski T, Slominska EM, Smolenski RT. Inhibition of AMP deaminase as therapeutic target in cardiovascular pathology. Pharmacol Rep 2015 Aug;67(4):682-688. [doi: 10.1016/j.pharep.2015.04.007] [Medline: 26321268]
27. Fredholm BB, IJzerman AP, Jacobson KA, Linden J, Müller CE. International Union of Basic and Clinical Pharmacology. LXXXI. Nomenclature and classification of adenosine receptors--an update. Pharmacol Rev 2011 Mar;63(1):1-34 [FREE Full text] [doi: 10.1124/pr.110.003285] [Medline: 21303899]
28. Eisenstein A, Carroll SH, Johnston-Cox H, Farb M, Gokce N, Ravid K. An adenosine receptor-Krüppel-like factor 4 protein axis inhibits adipogenesis. J Biol Chem 2014 Jul 25;289(30):21071-21081 [FREE Full text] [doi: 10.1074/jbc.M114.566406] [Medline: 24928509]
29. Johnston-Cox H, Eisenstein AS, Koupenova M, Carroll S, Ravid K. The macrophage A2B adenosine receptor regulates tissue insulin sensitivity. PLoS One 2014 Jun;9(6):e98775 [FREE Full text] [doi: 10.1371/journal.pone.0098775] [Medline: 24892847]
30. Johnston-Cox H, Koupenova M, Yang D, Corkey B, Gokce N, Farb MG, et al. The A2b adenosine receptor modulates glucose homeostasis and obesity. PLoS One 2012 Jul;7(7):e40584 [FREE Full text] [doi: 10.1371/journal.pone.0040584] [Medline: 22848385]
31. Barankiewicz J, Cohen A. Purine nucleotide metabolism in resident and activated rat macrophages in vitro. Eur J Immunol 1985 Jun;15(6):627-631. [doi: 10.1002/eji.1830150618] [Medline: 2408899]
32. Chambliss HO. Exercise duration and intensity in a weight-loss program. Clin J Sport Med 2005;15(2):113-115. [doi: 10.1097/01.jsm.0000151867.60437.5d]
33. Perry CG, Heigenhauser GJ, Bonen A, Spriet LL. High-intensity aerobic interval training increases fat and carbohydrate metabolic capacities in human skeletal muscle. Appl Physiol Nutr Metab 2008 Dec;33(6):1112-1123. [doi: 10.1139/H08-097] [Medline: 19088769]
34. da Rocha GL, Crisp AH, de Oliveira MR, da Silva CA, Silva JO, Duarte AC, et al. Effect of high intensity interval and continuous swimming training on body mass adiposity level and serum parameters in high-fat diet fed rats. ScientificWorldJournal 2016;2016:2194120 [FREE Full text] [doi: 10.1155/2016/2194120] [Medline: 26904718]
35. Trapp EG, Chisholm DJ, Freund J, Boutcher SH. The effects of high-intensity intermittent exercise training on fat loss and fasting insulin levels of young women. Int J Obes (Lond) 2008 Apr;32(4):684-691. [doi: 10.1038/sj.ijo.0803781] [Medline: 18197184]

36. Martins C, Kazakova I, Ludviksen M, Mehus I, Wisloff U, Kulseng B, et al. High-intensity interval training and isocaloric moderate-intensity continuous training result in similar improvements in body composition and fitness in obese individuals. Int J Sport Nutr Exerc Metab 2016 Jun;26(3):197-204. [doi: 10.1123/ijsnem.2015-0078] [Medline: 26479856]
37. Vina J, Sanchis-Gomar F, Martinez-Bello V, Gomez-Cabrera MC. Exercise acts as a drug; the pharmacological benefits of exercise. Br J Pharmacol 2012 Sep;167(1):1-12 [FREE Full text] [doi: 10.1111/j.1476-5381.2012.01970.x] [Medline: 22486393]
38. Pereira MG, Ferreira JC, Bueno CR, Mattos KC, Rosa KT, Irigoyen MC, et al. Exercise training reduces cardiac angiotensin II levels and prevents cardiac dysfunction in a genetic model of sympathetic hyperactivity-induced heart failure in mice. Eur J Appl Physiol 2009 Apr;105(6):843-850. [doi: 10.1007/s00421-008-0967-4] [Medline: 19125280]
39. Ferreira J, Rolim N, Bartholomeu J, Gobatto C, Kokubun E, Brum P. Maximal lactate steady state in running miceffect of exercise training. Clin Exp Pharmacol Physiol 2007 Aug 22;34(8):760-765. [doi: 10.1111/j.1440-1681.2007] [Medline: 17600553]
40. Muniyappa R, Chen H, Muzumdar RH, Einstein FH, Yan X, Yue LQ, et al. Comparison between surrogate indexes of insulin sensitivity/resistance and hyperinsulinemic euglycemic clamp estimates in rats. Am J Physiol Endocrinol Metab 2009 Nov;297(5):E1023-E1029 [FREE Full text] [doi: 10.1152/ajpendo.00397.2009] [Medline: 19706785]
41. Vilchis-Gil J, Klünder-Klünder M, Flores-Huerta S. Effect on the metabolic biomarkers in schoolchildren after a comprehensive intervention using electronic media and in-person sessions to change lifestyles: community trial. J Med Internet Res 2018 Feb 05;20(2):e44 [FREE Full text] [doi: 10.2196/jmir.9052] [Medline: 29402762]
42. Bernardis LL. Prediction of carcass fat, water and lean body mass from Lee's “nutritive ratio” in rats with hypothalamic obesity. Experientia 1970;26(7):789-790. [Medline: 4914444]
43. Phillis JW. Adenosine and adenine nucleotides as regulators of cerebral blood flow: roles of acidosis, cell swelling, and KATP channels. Crit Rev Neurobiol 2004;16(4):237-270. [Medline: 15862108]
44. Jackson EK. Intraperitoneal administration of adenosine inhibits formation of abdominal adhesions. Dis Colon Rectum 2004 Aug;47(8):1390-1396. [Medline: 15484355]
45. Bish CL, Blanck HM, Serdula MK, Marcus M, Kohl HW, Khan LK. Diet and physical activity behaviors among Americans trying to lose weight: 2000 Behavioral Risk Factor Surveillance System. Obes Res 2005 Mar;13(3):596-607 [FREE Full text] [doi: 10.1038/oby.2005.64] [Medline: 15833946]
46. Hill C, Weir BW, Fuentes LW, Garcia-Alvarez A, Anouti DP, Cheskin LJ. Relationship between weekly patterns of caloric intake and reported weight loss outcomes: retrospective cohort study. JMIR Mhealth Uhealth 2018 Apr 16;6(4):e83 [FREE Full text] [doi: 10.2196/mhealth.8320] [Medline: 29661750]
47. Meckling KA, O'Sullivan C, Saari D. Comparison of a low-fat diet to a low-carbohydrate diet on weight loss, body composition, and risk factors for diabetes and cardiovascular disease in free-living, overweight men and women. J Clin Endocrinol Metab 2004 Jun;89(6):2717-2723. [doi: 10.1210/jc.2003-031606] [Medline: 15181047]
48. Donnelly JE, Hill JO, Jacobsen DJ, Potteiger J, Sullivan DK, Johnson SL, et al. Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: the Midwest Exercise Trial. Arch Intern Med 2003 Jun 09;163(11):1343-1350. [doi: 10.1001/archinte.163.11.1343] [Medline: 12796071]
49. Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, et al. Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. Obesity (Silver Spring) 2012 Aug;20(8):1628-1638 [FREE Full text] [doi: 10.1038/oby.2011.76] [Medline: 21494229]
50. Kim GW, Lin JE, Blomain ES, Waldman SA. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther 2014 Jan;95(1):53-66 [FREE Full text] [doi: 10.1038/clpt.2013.204] [Medline: 24105257]
51. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. BMC Med 2016 Nov 29;14(1):191 [FREE Full text] [doi: 10.1186/s12916-016-0735-y] [Medline: 27894343]
52. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004 Dec;114(12):1752-1761 [FREE Full text] [doi: 10.1172/JCI21625] [Medline: 15599400]
53. Mardinoglu A, Heiker JT, Gärtner D, Björnson E, Schön MR, Flehmig G, et al. Extensive weight loss reveals distinct gene expression changes in human subcutaneous and visceral adipose tissue. Sci Rep 2015 Oct 05;5:14841 [FREE Full text] [doi: 10.1038/srep14841] [Medline: 26434764]
54. Schimmel RJ, McCarthy L. Role of adenosine as an endogenous regulator of respiration in hamster brown adipocytes. Am J Physiol 1984 Mar;246(3 Pt 1):C301-C307. [doi: 10.1152/ajpcell.1984.246.3.C301] [Medline: 6199983]
55. Gnad T, Scheibler S, von Kügelgen I, Scheele C, Kilić A, Glöde A, et al. Adenosine activates brown adipose tissue and recruits beige adipocytes via A2A receptors. Nature 2014 Dec 18;516(7531):395-399. [doi: 10.1038/nature13816] [Medline: 25317558]
56. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev 2015 Apr;16(4):341-349. [doi: 10.1111/obr.12239] [Medline: 25688659]

57. Pannu PK, Zhao Y, Soares MJ. Reductions in body weight and percent fat mass increase the vitamin D status of obese subjects: a systematic review and metaregression analysis. Nutr Res 2016 Mar;36(3):201-213. [doi: 10.1016/j.nutres.2015.11.013] [Medline: 26923506]
58. Gonzalez JT, Rumbold PL, Stevenson EJ. Effect of calcium intake on fat oxidation in adults: a meta-analysis of randomized, controlled trials. Obes Rev 2012 Oct;13(10):848-857. [doi: 10.1111/j.1467-789X.2012.01013.x] [Medline: 22708505]

Abbreviations

ATP: adenosine triphosphate
BAT: brown adipose tissue
BMI: body mass index
cDNA: complementary DNA
GAPDH: glyceraldehyde-3-phosphate dehydrogenase
HDL-C: high-density lipoprotein cholesterol
HIIT: high-intensity interval training
IP: intraperitoneal
MIT: moderate-interval training
PCR: polymerase chain reaction
QUICKI: quantitative insulin sensitivity check index
SAT: subcutaneous adipose tissue
TG: total triglyceride
VAT: visceral adipose tissue

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Original Paper

Neurological Disorders in Central Spain, Second Survey: Feasibility Pilot Observational Study

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Abstract

Background: The Neurological Disorders in Central Spain, second survey (NEDICES-2) is a population-based, closed-cohort study that will include over 8000 subjects aged ≥55 years. It will also include a biobank.

Objective: The objective of this study was to evaluate all major aspects of the NEDICES-2 (methods, database, screening instruments, and questionnaires, as well as interexpert rating of the neurological diagnoses) in each one of the planned areas (all of them in central Spain) and to test the possibility of obtaining biological samples from each participant.

Methods: A selection of patients and participants of the planned NEDICES-2 underwent face-to-face interviews including a comprehensive questionnaire on demographics, current medications, medical conditions, and lifestyle habits. Biological samples (blood, saliva, urine, and hair) were also obtained. Furthermore, every participant was examined by a neurologist.

Results: In this pilot study, 567 study participants were enrolled (196 from hospitals and 371 from primary care physician lists). Of these 567, 310 completed all study procedures (questionnaires and the neurological evaluation). The study was time-consuming for several primary care physicians. Hence, a few primary care physicians from some areas refused to participate, which led to a reconfiguration of study areas. In addition, the central biobank needed to be supplemented by the biobanks of local Spanish National Health System hospitals.

Conclusions: Population-based epidemiological surveys, such as the NEDICES-2, require a pilot study to evaluate the feasibility of all aspects of a future field study (population selection, methods and instruments to be used, neurological diagnosis agreement, and data collection).

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KEYWORDS

dementia; essential tremor; headache; longitudinal study; mild cognitive impairment; NEDICES; observational study; Parkinson's disease; pilot study; population-based study; stroke

Introduction

A pilot study is usually recommended before undertaking epidemiological research in large populations to study neurological, psychiatric, or aging-related diseases [1-9]. Surveys investigating neurological diseases are especially difficult because of the need for an expert diagnosis, as a sizable proportion of neurological disorders do not have diagnostic biomarkers [10]. The difficulty increases when epidemiological surveys require upfront screening to obviate the workload of a 2-phase survey [2]. In this type of neurological research, pilot studies prior to the field survey become mandatory.

The original *Neurological Disorders in Central Spain*, first survey (NEDICES-1) was a closed population-based study, which followed a cohort over 13 years [2,3,11,12]. The NEDICES has produced high-quality epidemiological research on different neurological disorders with >70 peer-reviewed publications regarding stroke, dementia, parkinsonism, tremor, and various aspects of aging and mortality. The main limitation of the NEDICES-1 was the few laboratory data we obtained from participants; to overcome this limitation, we have established a new observational survey, the *Neurological Disorders in Central Spain*, second survey (NEDICES-2).

The main differences between the NEDICES-1 and NEDICES-2 are the following. First, in the NEDICES-2, we selected participants through primary care physicians, instead of using the census as in the NEDICES-1. Currently, the Spanish National Health System includes virtually all Spanish legal residents and immigrants. We used computerized data of citizens assigned to primary care physicians because they perform their clinical work at Spanish National Health System centers. Second, this new cohort of participants comprises subjects aged >54 years. The younger cohort was not included in the original survey. Third, a tissue bank (biobank) of participants was created. Fourth, the study areas were not the same as those of the previous NEDICES survey, although similarly located in central Spain. Finally, in the NEDICES-2, the computerized registry of clinical and biological data is centralized in a specific website.

The main objective of our pilot study was to evaluate all major aspects of the NEDICES-2 survey (methods, database, screening instruments, and questionnaires, as well as interexpert rating of neurological diagnoses) and to test the possibility of obtaining biological samples from each participant. Another important objective of this pilot study was to assess the levels of cooperation among potential participants and identify and resolve newly arising problems.

Methods

Design

The coordinating center (Research Institute of the University Hospital "12 Octubre" in Madrid) of the NEDICES-2 designed all aspects of the survey during 2011-2012, advised by participating primary care physicians. The methods and protocols were analogous to the NEDICES-1 survey [2,3,11,12].

Objectives

The NEDICES-2 survey aims to establish a population-based cohort to investigate major age-related neurological disorders (essential tremor, Parkinsonism, stroke, mild cognitive impairment [MCI], and dementia), including the risk factors and possible biomarkers for such neurological diseases. In addition, we aim to confirm the general findings of the NEDICES-1 survey with a new larger cohort, including persons in late adulthood (age 55-64 years) and to assess the possible changes in the neurological diseases incidence over time. Finally, one important aim of this study is to obtain biological samples (blood, urine, hair, and saliva).

Population and Study Areas (Pilot Study Selection)

The NEDICES-2 survey aims for a baseline cohort population of approximately 8000 participants; this number was calculated to adequately detect Parkinson disease, which has the lowest prevalence and incidence of all neurological disorders studied in this research [13,14]. We expect a similar attrition as happened in the NEDICES-1 survey [12]. The areas were selected to represent rural, semirural, and urban populations.

The composition by age reflects the general Spanish population aged >54 years (30% in the strata of 55-64 years); this age composition is like other European cohorts such as the Rotterdam study [15]. The NEDICES-2 population will be selected from primary care physicians' lists to obtain a random group (400-600 subjects per primary care physician's list) representative for age (5-year strata) and sex of subjects aged 55-84 years and of all subjects aged >84 years.

The coordinating center of the NEDICES-2 set up the pilot field study and selected the study protocol (questionnaires, scales, and examinations) with few differences from the NEDICES-1 survey. Furthermore, it developed the telematic utilities for the survey—specific email, Skype conferences, information website, and an electronic platform—to collect study data with privacy requirements. The coordinating center also conducted the pilot study.

The coordinating center selected 7 areas to survey participants for the pilot study: Fuentelarreina and Comillas (central Madrid), Las Margaritas (Getafe, peripheral Madrid), Arganda del Rey (suburban Madrid, semirural area), Cantalejo (Segovia, rural area), Burgos county (rural area), Arévalo (Ávila, semirural area), and Pizarrales (Salamanca, urban area). The participants were randomly selected (choosing 5 of 20) and stratified by sex and age (in 5-year age spans) to be evaluated by 7 primary care physicians. Participants were considered eligible if they had lived in rural or urban areas for >6 months and did not anticipate a serious illness that could cause death within the next year. In addition, for this pilot study, we recruited patients from the outpatient neurology clinics of both the University Hospital "12 de Octubre" in Madrid and the Burgos University Hospital in Burgos. These comprised patients diagnosed with the following neurological disorders: essential tremor, Parkinsonism, stroke, headache, MCI, and dementia.

Questionnaires and Screening Methods

We administered 3 different types of questionnaires. First, lay interviewers (mostly students, not in medicine) administered general questionnaires, including information on the demographic and social aspects of participants. In addition, these questionnaires included screening questions (see below) or brief neuropsychological batteries for detecting or confirming neurological diseases, such as essential tremor [16-18], Parkinsonism [13,14,19], stroke [20,21], or MCI or dementia (37-item version of the Mini-Mental State Examination, clock drawing test, 11-item version of the Pfeffer Functional Activities Questionnaire, Word Accentuation test, verbal fluency [animals and fruits], Trail-Making test, delayed late memory tests, logical memory, and nomenclature and images) [22-27], which had been used in the NEDICES-1. Second, primary care physicians also administered a questionnaire with anthropometric data, general health status, cardiovascular risk factors, previous illnesses, clinical comorbidity [28], and current medications. Furthermore, primary care physicians took standard biochemical specimens (blood and urine) for registration and for the biobank (in some cases, hair and saliva were also included). Finally, a self-reported questionnaire was also completed by each study participant, providing personal data, professional background, education and studies, measurements of subjective health (global, age-comparative, and time-comparative self-rated health) [29], generic health-related quality of life (European Quality of Life Scale) [30], Epworth sleepiness scale [31], physical activity [32], headaches [33], the Beck Depression Inventory scale [34], social relationships of participants, and information about their lifestyle (drugs, tobacco, coffee, and alcohol consumption).

Screening methods for the main neurological disorders were like those used in the NEDICES-1 survey [2,3,11,12]. A random sample of approximately 4% of those who had screened negative in the NEDICES-1 was selected and contacted to assess the performance of these screening methods [1]. Of 205 subjects who were contacted, 183 were successfully scheduled for a neurological examination by a senior neurologist [1]; they all were examined, and none was found to have essential tremor, parkinsonism, or stroke; however, 1.1% (2/183) of subjects were found to have "mild dementia" (95% CI 0.3%-3.9%) [1].

In the NEDICES-1, we included a question for essential tremor ("have you ever suffered from tremor of the head, hands, or legs that has lasted longer than several days?") [17,18]. In addition, 3 questions were administered to screen for parkinsonism (questions about the previous diagnosis of Parkinson disease, tremor, and bradykinesia) [13,14]. Furthermore, we used a validated 9-item questionnaire aimed at identifying parkinsonism-related symptoms [19]. The screening instrument for stroke was a Spanish adaptation of the questionnaire used for screening in the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular disease project [35]. The main screening instruments for MCI or dementia included the Spanish adaptation of a cognitive test (a 37-item version of the Mini-Mental State Examination) and an instrumental activity of daily living scale (11-item version of the Pfeffer Functional Activities Questionnaire) [22,24]. The sensitivities of both the 37-item version of the Mini-Mental State Examination and the Pfeffer Functional Activities Questionnaire Scale are >90% [36].

Ethical Aspects

All participants included in the study gave their written informed consent after full explanation of the procedure. The study, which was conducted in accordance with the principles of the 1975 Declaration of Helsinki, was approved by the ethical standards committee on human experimentation at the University Hospital "12 de Octubre" (Madrid). Written (signed) informed consent was obtained from all enrollees. The data collection and biobank procedures conformed to the Spanish law.

Statistical Analyses

Statistical analyses were performed using SPSS Version 21.0 (IBM Corp). All tests were 2-sided, and the significance was accepted at the 5% level (alpha=.05). Continuous variables were compared using Mann-Whitney *U* test because they were all nonnormally distributed. Furthermore, chi-square test was used to analyze categorical variables.

Results

Population

Figure 1 shows the flowchart of the study. The originally selected population for the pilot study was of 567 participants. Of them, 34.6% (196/567) were recruited from the outpatient neurology clinics of both the University Hospital "12 de Octubre" in Madrid, which provided 168 patients with neurological diseases and 22 patients without them after a careful examination, and the Burgos University Hospital in

Burgos, which provided 6 patients with neurological diseases. The remaining 65.4% (371/567) participants were selected from primary care physicians' lists of the study areas.

Of the subjects recruited from hospitals, 13.3% (26/196) refused to participate; meanwhile, 86.7% (170/196) were adequately evaluated (complete data and assessment by a neurologist). Of the 371 participants selected from primary care physicians' lists, 8.3% (31/371) were excluded because of change of primary care physician, change of address, and deaths. Of the remaining 340 who were eligible by the primary care physician assessment, 15.9% (54/340) were excluded because of inadequate evaluation (institutionalization, unreachable, refusals, and severe diseases). The remaining 286 fulfilled or were administered the questionnaires, but 15.4% (44/286) were excluded because of incomplete data. Finally, 242 participants had complete data; however, only 57.9% (140/242) participants were eligible for the final analyses because neurologists could not evaluate 42.1% (102/242) for several reasons.

Thus, the final sample consisted of 310 participants (61.3%, 190/310, with neurological diseases and 38.7%, 120/310, without them) who presented all the required data (3 questionnaires, neurological evaluation, and biobank donation; Table 1). A higher proportion of participants with neurological diseases were more likely to have depression or depressive symptoms, cataracts, and score worse on screening tests for cognitive disorders (37-item version of the Mini-Mental State Examination and 11-item version of the Pfeffer Functional Activities Questionnaire). In addition, as expected, they scored higher in the Parkinson disease screening test and rated their health as bad or very bad. On the other hand, they were more likely to be more sedentary. Table 2 shows the final sample of participant distribution according to neurologists' diagnosis.

Figure 1. Flow chart of the Neurological Disorders in Central Spain, second survey (NEDICES-2), feasibility pilot study.

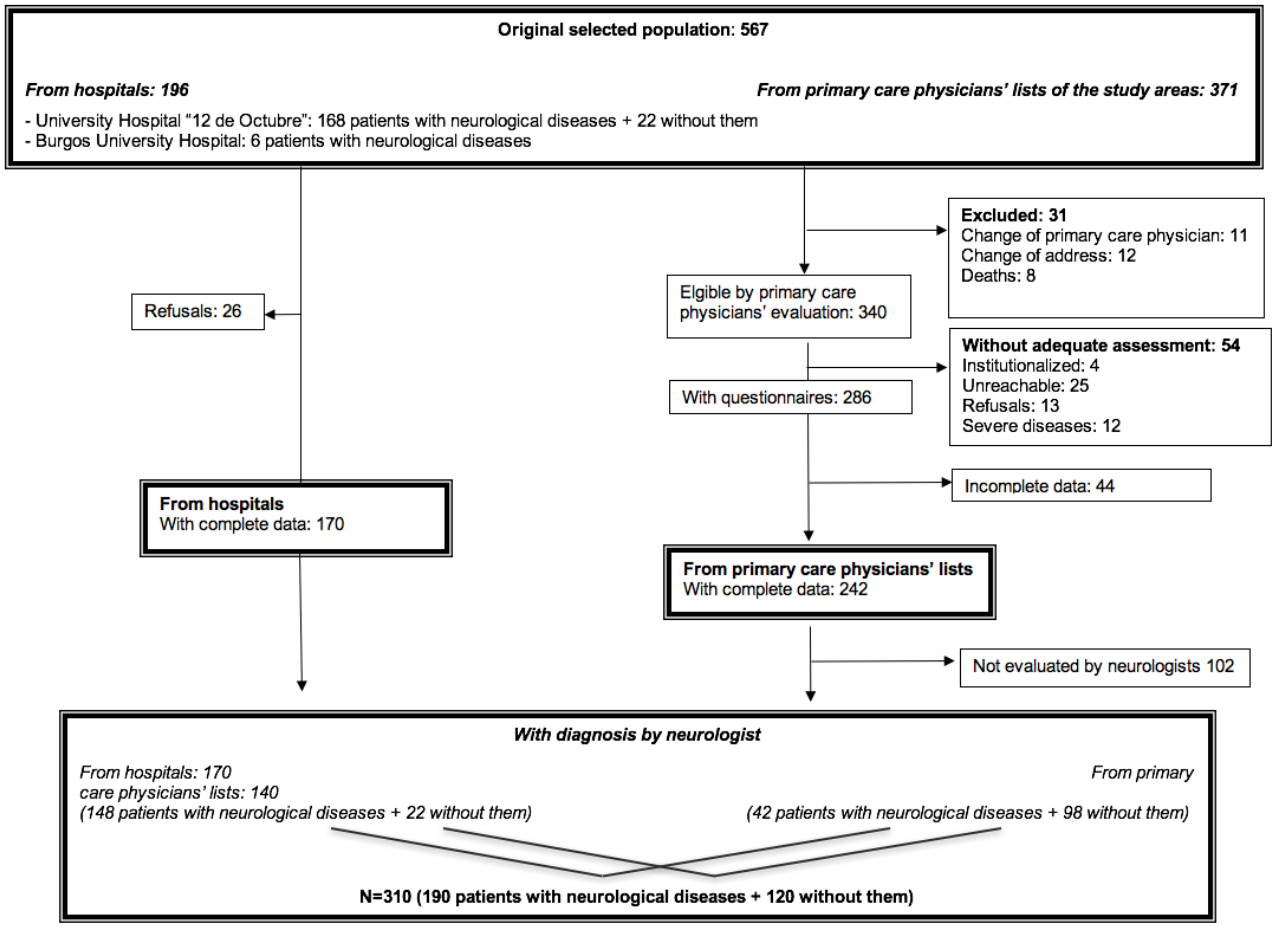

Table 1. Baseline demographics and a selection of clinical characteristics of the final sample of participants (N=310).

Characteristics	Without neurological diseases (n=120[a])	With neurological diseases (n=190[b,c])	*P* value[d]
Age (years), mean (SD); median	70.7 (9.4); 69	71.7 (9.4); 73	.28
Sex, n (%)			.92
Men	55 (45.8)	86 (45.3)	
Women	65 (54.2)	104 (54.7)	
Years of education in years[e], mean (SD); median	9.9 (5.6); 8.0	8.4 (5.2); 8.0	.52
Main nonneurological disorders[e], n (%)			
Diabetes	21 (18.4)	38 (20.7)	.64
Arterial hypertension	62 (53.9)	99 (53.5)	.95
Hypercholesterolemia	56 (48.3)	87 (47.0)	.83
Heart diseases	20 (20.4)	34 (22.2)	.73
Osteoarthritis	59 (51.8)	95 (52.5)	.90
Cancer	18 (16.1)	22 (12.2)	.35
Cataracts	30 (26.3)	74 (41.8)	.007
Chronic pulmonary disease	16 (14.3)	25 (13.7)	.90
Depression	17 (14.9)	50 (27.6)	.011
Deafness	17 (15.2)	57 (31.5)	.002
Lifestyle variables[e]			
Sleeping hours, mean (SD); median	7.0 (1.4); 7.0	7.2 (1.6); 7.0	.47
Ever smoker (ex-smoker plus current smoker), n (%)	1 (11.3)	11.0 (8.9)	.12
Ever drinker (ex-drinker plus current drinker), n (%)	67 (57.3)	103 (54.8)	.67
Physical activity, n (%)			.004
Inactive	60 (52.2)	130 (69.1)	
Moderately inactive	6 (5.2)	15 (8.0)	
Moderately active	22 (19.1)	20 (10.6)	
Active	27 (23.5)	23 (12.2)	
Self-rated health[e], n (%)			.01
Very good	15 (12.8)	8 (4.2)	
Good	55 (47.0)	72 (38.1)	
Fair	41 (35.0)	94 (49.7)	
Poor	5 (4.3)	13 (6.9)	
Very poor	1 (0.9)	2 (1.1)	
Screening tests for cognitive disorders[e], mean (SD); median			
37-item version of the Mini-Mental State Examination	32.2 (4.8); 33.0	30.7 (5.7); 32.0	.02
11-item version of the Pfeffer Functional Activities Questionnaire	1.1 (4.0); 0	3.2 (6.0); 0	<.001
Parkinson disease screening test, mean (SD); median	1.0 (1.2); 1.0	2.8 (2.4); 2.0	<.001
Headache (yes vs no), n (%)	29 (27.4)	57 (34.3)	.26
Beck Depression Inventory scale, mean (SD); median	7.1 (5.6); 6.0	9.7 (6.3); 9.0	<.001

[a]98 from hospitals + 22 from primary care physicians' lists.

[b]148 from hospitals + 42 from primary care physicians' lists.

[c]15 patients had more than one disorder.

[d]Continuous variables were compared using the Mann-Whitney *U* test because they were all nonnormally distributed. Furthermore, the chi-square test

was used to analyze categorical variables.

[e]Data on some participants were missing.

Table 2. Final participant sample (N=310) distribution according to neurologists' diagnosis.

Characteristics	Without neurological diseases (n=120)	With neurological diseases[a] (n=190)					
		Headache (n=37)	Dementia (n=28)	Parkinson disease (n=35)	Stroke (n=43)	Mild cognitive impairment (n=23)	Essential tremor (n=39)
Age (years), mean (SD)	70.1 (9.6)	66.4 (10.5)	78.2 (6.8)	71.5 (10.2)	71.1 (8.4)	75.6 (6.5)	71.4 (8.1)
Gender, n (%)							
Men	55 (45.8)	14 (37.8)	11 (39.3)	21 (60.0)	23 (53.5)	12 (52.2)	14 (35.9)
Women	65 (54.2)	23 (62.2)	17 (60.7)	14 (40.0)	20 (46.5)	11 (47.8)	25 (64.1)

[a]Fifteen participants had more than one disorder.

All selected areas participated in the survey (participant evaluation and acquisition of biological samples), but the quality of the information obtained and the clinical workload for primary care physicians was quite varied, as was the biobank established in each local area. Primary care physicians of Arganda del Rey, Las Margaritas (Madrid), and Pizarrales (Salamanca) had difficulties carrying out the survey because of high clinical load, and therefore, they refused to participate in this pilot study; these areas were then replaced by La Alamedilla (Salamanca, urban area), Calesas, (urban area, Madrid), Valladolid (urban area), and Cantalejo (rural area, Segovia).

Development of the Pilot Study

Each primary care physician invited selected subjects from among his or her patient list to join in the survey through a phone call or a letter. The duration of the interviews with participants was variable (10-20 minutes). Most participants signed the informed consent for both clinical participation and donation to biobanks. The pilot study showed that the central biobank faced practical difficulties such as shortage of staff, high costs, and difficulties with sample arrangements in the University Hospital "12 de Octubre" biobank. The coordinating center overcame this problem by changing the initial survey design to use local biobanks as supplements to the central biobank (except for Madrid, Ávila, and Segovia).

The training of interviewers was satisfactory. Interviewer questionnaires were digitized and sent to the central website. Most of the participants' self-report questionnaires had to be completed on paper and sent to the coordinating center in this format. Evaluations by lay interviewers lasted approximately 1 hour and 15 minutes, sometimes up to 3 hours, with a break. Participants with possible neurological disorders received a second evaluation performed by a neurologist.

The comprehension of questionnaires was generally adequate, with some exceptions. The Beck Depression Inventory scale [34] was difficult to understand for many participants, and the coordinating center replaced it by the Center for Epidemiologic Studies Depression Scale [37] for the future field study. The 37-item version of the Mini-Mental State Examination, 11-item version of the Pfeffer Functional Activities Questionnaire, Word Accentuation test, verbal fluency, Trail-Making test, delayed late memory tests, logical memory, and nomenclature and images [22-25] allowed us to establish the psychometric cuts for screening for dementia, obtaining sensitivity >95% with high specificity.

Once the pilot study was completed, it was decided to compile each subject's evaluations; these summary sheets were sent to each primary care physician for them to discuss with each subject, explain the results obtained, and thank them for their collaboration.

Interrater Agreement in the Clinical Diagnosis of Neurologists Who Will Participate in the Field Study

The interrater agreement of cognitive status and tremor disorders have been published elsewhere [16,38]. Briefly, to assess the diagnostic agreement of cognitive status (dementia, MCI, and normal cognition) among neurologists, medical histories of 30 individuals were provided to 27 neurologists (19 consultant neurologists and 8 neurology residents) [38]. Overall, the interrater agreement on cognitive status was κ=.76 (95% CI 0.65-0.86), being slightly higher among junior neurologists (κ=.85, 95% CI 0.73-0.95) than among seniors (κ=.71, 95% CI 0.59-0.83) and residents (κ=.69, 95% CI 0.54-0.81), but without statistical significance among groups [38]. Dementia severity showed an overall kappa of .34, .44, and .64 for mild, moderate, and severe dementia, respectively [38]. Furthermore, clinical histories and standardized videotaped neurological examinations of 26 individuals (11 with essential tremor, 7 with Parkinson disease, 3 diagnostically unclear, 4 normal, and 1 with a tremor disorder other than essential tremor) were provided to 7 consultant neurologists, 6 neurology residents, and 5 neurology research fellows. For each of the 26 individuals, neurologists were asked to assign a diagnosis of "essential tremor" or "no essential tremor" using the diagnostic criteria proposed by the Movement Disorders Society [39]. The overall kappa was .61 (substantial agreement), with no differences among consultant neurologists (κ=.60), neurology residents (κ=.61), and neurology research fellows (κ=.66) in subgroup analyses [16].

Discussion

A pilot study is the first step in many types of epidemiological studies such as cross-sectional and longitudinal surveys [2-5,9], case-control studies [40], and research investigations [41]. It is unwise to establish a complex survey without an adequate pilot study, as was demonstrated by this study.

Participants, in general, were more cooperative than expected. The main difficulties in the study were unexpected. Specifically, the study was time consuming for primary care physicians, as they had to explain it to participants, obtain informed consents, and complete a summary of their medical history. However, during the design of the NEDICES-2 survey, the coordinating center had erroneously considered that the 3 tasks could be performed in 10 minutes because the lay interviewer had given written information to participants and because there was a specific website with an explanation of the study.

Primary care physicians have a heavy workload in Spain. Many participants required a lengthy explanation of the survey, despite the good explanation on the website. With the public funds that we obtained, we could pay external collaborators as interviewers, but the Spanish National Health System research policy does not permit payment to primary care physicians, even if they devote extra time beyond their working hours. All this caused 3 primary care physicians' teams to leave this study. Thus, the coordinating center had to replace these primary care physicians' study areas by others, even in other geographical areas, to overcome this problem.

Another important difficulty was obtaining biological samples to establish the central biobank at the University Hospital "12 de Octubre" in Madrid. The pilot study showed that the only possible way to address this problem was to send all biological samples to each local Spanish National Health System hospital laboratory (for registration and to establish a local biobank). Otherwise, the pilot study was successful, partly because the methods were analogous to the NEDICES-1. Only a few changes in the screening questionnaires and scales were made after the pilot survey. Moreover, several tests were established for the detection of MCI and dementia.

Substantial agreement was demonstrated for the diagnosis of cognitive status (dementia, MCI, and normal cognition) among neurologists of different levels of experience [38]. The agreement rate was lower in the diagnosis of dementia severity. With respect to tremor disorders, substantial agreement was also demonstrated for the diagnosis of essential tremor among neurologists of different levels of expertise [16]. However, the agreement was lower than that previously reported using the Washington Heights–Inwood Genetic Study of Essential Tremor criteria [42].

In conclusion, we feel that it is impossible to undertake a large and complex neuroepidemiology survey, such as the NEDICES-2, without a pilot study. It is mandatory first to test the feasibility of all aspects of a future field study—population selection, methods, instruments to be used, neurological diagnosis agreement, and data collection. This pilot study reveals some serious deficiencies in the selected areas (the ability of overburdened primary care physicians to collaborate) and the biological bank configuration that could be solved by the coordinating center.

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Conflicts of Interest

None declared.

References

1. Anderson DW, Rocca WA, Rosário JA. Pitfalls in neuroepidemiologic research. Neuroepidemiology 1998;17(2):55-62. [doi: 10.1159/000026153] [Medline: 9592780]
2. Bermejo F, Gabriel R, Vega S, Morales JM, Rocca WA, Anderson DW, Neurological Disorders in Central Spain (NEDICES) Study Group. Problems and issues with door-to-door, two-phase surveys: an illustration from central Spain. Neuroepidemiology 2001 Oct;20(4):225-231. [doi: 10.1159/000054794] [Medline: 11684897]
3. Morales JM, Bermejo FP, Benito-León J, Rivera-Navarro J, Trincado R, Gabriel SR, NEDICES Study Group. Methods and demographic findings of the baseline survey of the NEDICES cohort: a door-to-door survey of neurological disorders in three communities from Central Spain. Public Health 2004 Sep;118(6):426-433. [doi: 10.1016/j.puhe.2003.10.007] [Medline: 15313596]
4. Katsarava Z, Kukava M, Mirvelashvili E, Tavadze A, Dzagnidze A, Djibuti M, et al. A pilot methodological validation study for a population-based survey of the prevalences of migraine, tension-type headache and chronic daily headache in the country of Georgia. J Headache Pain 2007 Apr;8(2):77-82 [FREE Full text] [doi: 10.1007/s10194-007-0367-x] [Medline: 17497261]
5. Bower JH, Mwendo E, Walker R, Maro V, Enquosellasie F, Ali S. Validity of a screening instrument for neurologic disability in resource-poor African communities. J Neurol Sci 2012 Sep 15;320(1-2):52-55 [FREE Full text] [doi: 10.1016/j.jns.2012.06.007] [Medline: 22795389]

6. Rodríguez LA, Urdaneta AE, de la Fuente Sánchez M, Galindo ME, Yanguas LJJ, Rodríguez RV. [Analysis of selection bias in the pilot study of a longitudinal study on aging in Spain]. Gac Sanit 2013;27(5):425-432 [FREE Full text] [doi: 10.1016/j.gaceta.2012.11.008] [Medline: 23291032]
7. Boden-Albala B, Edwards DF, St Clair S, Wing JJ, Fernandez S, Gibbons MC, et al. Methodology for a community-based stroke preparedness intervention: the Acute Stroke Program of Interventions Addressing Racial and Ethnic Disparities Study. Stroke 2014 Jul;45(7):2047-2052 [FREE Full text] [doi: 10.1161/STROKEAHA.113.003502] [Medline: 24876243]
8. Exley K, Aerts D, Biot P, Casteleyn L, Kolossa-Gehring M, Schwedler G, et al. Pilot study testing a European human biomonitoring framework for biomarkers of chemical exposure in children and their mothers: experiences in the UK. Environ Sci Pollut Res Int 2015 Oct;22(20):15821-15834. [doi: 10.1007/s11356-015-4772-4] [Medline: 26036586]
9. Dai J, Chiu HFK, Xiang Y, Chan SSM, Yu X, Hou Z, et al. The prevalence of insomnia and its socio-demographic and clinical correlates in older adults in rural China: a pilot study. Aging Ment Health 2013;17(6):761-765. [doi: 10.1080/13607863.2013.781117] [Medline: 23547946]
10. Nelson LM, Tanner CM, Van Den Eeden SK, McGuire VM. Neuroepidemiology: From Principles to Practice. New York: Oxford University Press; 2004:019513379.
11. Bermejo-Pareja F, Benito-León J, Vega- Q, Díaz-Guzmán J, Rivera-Navarro J, Molina JA, et al. The NEDICES cohort of the elderly. Methodology and main neurological findings. Rev Neurol 2008;46(7):416-423 [FREE Full text] [Medline: 18389461]
12. Vega S, Benito-León J, Bermejo-Pareja F, Medrano MJ, Vega-Valderrama LM, Rodríguez C, et al. Several factors influenced attrition in a population-based elderly cohort: neurological disorders in Central Spain Study. J Clin Epidemiol 2010 Feb;63(2):215-222. [doi: 10.1016/j.jclinepi.2009.03.005] [Medline: 19473811]
13. Benito-León J, Bermejo-Pareja F, Rodríguez J, Molina J, Gabriel R, Morales J, Neurological Disorders in Central Spain (NEDICES) Study Group. Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. Mov Disord 2003 Mar;18(3):267-274. [doi: 10.1002/mds.10362] [Medline: 12621629]
14. Benito-León J, Bermejo-Pareja F, Morales-González JM, Porta-Etessam J, Trincado R, Vega S, Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. Neurology 2004 Mar 09;62(5):734-741. [Medline: 15007123]
15. Hofman A, Brusselle GGO, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, et al. The Rotterdam Study: 2016 objectives and design update. Eur J Epidemiol 2015 Aug;30(8):661-708 [FREE Full text] [doi: 10.1007/s10654-015-0082-x] [Medline: 26386597]
16. Sierra-Hidalgo F, Romero JP, Bermejo-Pareja F, Sánchez-Ferro A, Hernández-Gallego J, Posada IJ, et al. Inter-Rater Agreement in the Clinical Diagnosis of Essential Tremor: Data from the NEDICES-2 Pilot Study. Tremor Other Hyperkinet Mov (N Y) 2014;4 [FREE Full text] [doi: 10.7916/D8JD4TQ0] [Medline: 24587969]
17. Benito-León J, Bermejo-Pareja F, Morales J, Vega S, Molina J. Prevalence of essential tremor in three elderly populations of central Spain. Mov Disord 2003 Apr;18(4):389-394. [doi: 10.1002/mds.10376] [Medline: 12671944]
18. Benito-León J, Bermejo-Pareja F, Louis ED, Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence of essential tremor in three elderly populations of central Spain. Neurology 2005 May 24;64(10):1721-1725. [doi: 10.1212/01.WNL.0000161852.70374.01] [Medline: 15911798]
19. Sevillano MD, de Pedro-Cuesta J, Duarte J, Clavería LE. Field validation of a method for population screening of parkinsonism. Mov Disord 2002 Mar;17(2):258-264. [Medline: 11921110]
20. Díaz-Guzmán J, Bermejo-Pareja F, Benito-León J, Vega S, Gabriel R, Medrano MJ, Neurological Disorders in Central Spain (NEDICES) Study Group. Prevalence of stroke and transient ischemic attack in three elderly populations of central Spain. Neuroepidemiology 2008;30(4):247-253. [doi: 10.1159/000135643] [Medline: 18515974]
21. Martínez-Salio A, Benito-León J, Díaz-Guzmán J, Bermejo-Pareja F. Cerebrovascular disease incidence in central Spain (NEDICES): a population-based prospective study. J Neurol Sci 2010 Nov 15;298(1-2):85-90. [doi: 10.1016/j.jns.2010.08.003] [Medline: 20817180]
22. Contador I, Bermejo-Pareja F, Fernández-Calvo B, Boycheva E, Tapias E, Llamas S, et al. The 37 item Version of the Mini-Mental State Examination: Normative Data in a Population-Based Cohort of Older Spanish Adults (NEDICES). Arch Clin Neuropsychol 2016 May;31(3):263-272. [doi: 10.1093/arclin/acw003] [Medline: 26860862]
23. Contador I, Bermejo-Pareja F, Del Ser T, Benito-León J. Effects of education and word reading on cognitive scores in a community-based sample of Spanish elders with diverse socioeconomic status. J Clin Exp Neuropsychol 2015;37(1):92-101. [doi: 10.1080/13803395.2014.989819] [Medline: 25686369]
24. Louis ED, Benito-León J, Vega-Quiroga S, Bermejo-Pareja F, Neurological Disorders in Central Spain (NEDICES) Study Group. Cognitive and motor functional activity in non-demented community-dwelling essential tremor cases. J Neurol Neurosurg Psychiatry 2010 Sep;81(9):997-1001. [doi: 10.1136/jnnp.2009.202838] [Medline: 20547612]
25. Serna A, Contador I, Bermejo-Pareja F, Mitchell AJ, Fernández-Calvo B, Ramos F, et al. Accuracy of a Brief Neuropsychological Battery for the Diagnosis of Dementia and Mild Cognitive Impairment: An Analysis of the NEDICES Cohort. J Alzheimers Dis 2015;48(1):163-173. [doi: 10.3233/JAD-150086] [Medline: 26401937]

26. Bermejo-Pareja F, Benito-León J, Vega S, Olazarán J, de Toledo M, Díaz-Guzmán J, et al. Consistency of clinical diagnosis of dementia in NEDICES: A population-based longitudinal study in Spain. J Geriatr Psychiatry Neurol 2009 Dec;22(4):246-255. [doi: 10.1177/0891988709335794] [Medline: 19417217]
27. Bermejo-Pareja F, Benito-León J, Vega S, Medrano MJ, Román GC, Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence and subtypes of dementia in three elderly populations of central Spain. J Neurol Sci 2008 Jan 15;264(1-2):63-72. [doi: 10.1016/j.jns.2007.07.021] [Medline: 17727890]
28. Carey IM, Shah SM, Harris T, DeWilde S, Cook DG. A new simple primary care morbidity score predicted mortality and better explains between practice variations than the Charlson index. J Clin Epidemiol 2013 Apr;66(4):436-444 [FREE Full text] [doi: 10.1016/j.jclinepi.2012.10.012] [Medline: 23395517]
29. Fernández-Ruiz M, Guerra-Vales JM, Trincado R, Fernández R, Medrano MJ, Villarejo A, et al. The ability of self-rated health to predict mortality among community-dwelling elderly individuals differs according to the specific cause of death: data from the NEDICES cohort. Gerontology 2013;59(4):368-377 [FREE Full text] [doi: 10.1159/000348781] [Medline: 23615509]
30. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [Medline: 10109801]
31. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991 Dec;14(6):540-545. [Medline: 1798888]
32. Puig RA, Peña CO, Romaguera BM, Duran BE, Heras TA, Solà GM, et al. [How to identify physical inactivity in primary care: validation of the Catalan and Spanish versions of 2 short questionnaires]. Aten Primaria 2012 Aug;44(8):485-493 [FREE Full text] [doi: 10.1016/j.aprim.2012.01.005] [Medline: 22463945]
33. Yoon M, Obermann M, Fritsche G, Slomke M, Dommes P, Schilf C, et al. Population-based validation of a German-language self-administered headache questionnaire. Cephalalgia 2008 Jun;28(6):605-608. [doi: 10.1111/j.1468-2982.2008.01560.x] [Medline: 18422724]
34. Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of general psychiatry Jun 1961:4-71. [Medline: 13688369]
35. Asplund K. What MONICA told us about stroke. Lancet Neurol 2005 Jan;4(1):64-68. [doi: 10.1016/S1474-4422(04)00967-6] [Medline: 15620858]
36. Baldereschi M, Amato MP, Nencini P, Pracucci G, Lippi A, Amaducci L, et al. Cross-national interrater agreement on the clinical diagnostic criteria for dementia. WHO-PRA Age-Associated Dementia Working Group, WHO-Program for Research on Aging, Health of Elderly Program. Neurology 1994 Feb;44(2):239-242. [Medline: 8309565]
37. Soler J, Pérez-Sola V, Puigdemont D, Pérez-Blanco J, Figueres M, Alvarez E. Validation study of the Center for Epidemiological Studies-Depression of a Spanish population of patients with affective disorders. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1997;25(4):243-249. [Medline: 9412163]
38. Llamas-Velasco S, Sierra-Hidalgo F, Llorente-Ayuso L, Herrero-San MA, Villarejo GA, Bermejo PF. Inter-Rater Agreement in the Clinical Diagnosis of Cognitive Status: Data from the Neurological Disorders in Central Spain 2 Pilot Study. Neuroepidemiology 2016;47(1):32-37. [doi: 10.1159/000447699] [Medline: 27398595]
39. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 1998;13 Suppl 3:2-23. [Medline: 9827589]
40. Beghi E, Logroscino G, Chiò A, Hardiman O, Millul A, Mitchell D, et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: results of a population-based pilot case-control study. Amyotroph Lateral Scler 2010 May 03;11(3):289-292 [FREE Full text] [doi: 10.3109/17482960903384283] [Medline: 20433412]
41. Sewell DA, Hammersley VS, Devereux G, Robertson A, Stoddart A, Weir C, et al. Investigating the effectiveness of the Mediterranean diet in pregnant women for the primary prevention of asthma and allergy in high-risk infants: protocol for a pilot randomised controlled trial. Trials 2013 Jun 14;14:173 [FREE Full text] [doi: 10.1186/1745-6215-14-173] [Medline: 23768094]
42. Louis ED, Ford B, Bismuth B. Reliability between two observers using a protocol for diagnosing essential tremor. Mov Disord 1998 Mar;13(2):287-293. [doi: 10.1002/mds.870130215] [Medline: 9539343]

Abbreviations

MCI: mild cognitive impairment
NEDICES-1: The Neurological Disorders in Central Spain, first survey
NEDICES-2: The Neurological Disorders in Central Spain, second survey

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Original Paper

Accelerating Research With Technology: Rapid Recruitment for a Large-Scale Web-Based Sleep Study

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Abstract

Background: Participant recruitment can be a significant bottleneck in carrying out research studies. Connected health and mobile health platforms allow for the development of Web-based studies that can offer improvement in this domain. Sleep is of vital importance to the mental and physical health of all individuals, yet is understudied on a large scale or beyond the focus of sleep disorders. For this reason and owing to the availability of digital sleep tracking tools, sleep is well suited to being studied in a Web-based environment.

Objective: The aim of this study was to investigate a method for speeding up the recruitment process and maximizing participant engagement using a novel approach, the Achievement Studies platform (Evidation Health, Inc, San Mateo, CA, USA), while carrying out a study that examined the relationship between participant sleep and daytime function.

Methods: Participants could access the Web-based study platform at any time from any computer or Web-enabled device to complete study procedures and track study progress. Achievement community members were invited to the study and assessed for eligibility. Eligible participants completed an electronic informed consent process to enroll in the study and were subsequently invited to complete an electronic baseline questionnaire. Then, they were asked to connect a wearable device account through their study dashboard, which shared their device data with the research team. The data were used to provide objective sleep and activity metrics for the study. Participants who completed the baseline questionnaires were subsequently sent a daily single-item Sleepiness Checker activity for 7 consecutive days at baseline and every 3 months thereafter for 1 year.

Results: Overall, 1156 participants enrolled in the study within a 5-day recruitment window. In the 1st hour, the enrollment rate was 6.6 participants per minute (394 per hour). In the first 24 hours, the enrollment rate was 0.8 participants per minute (47 participants per hour). Overall, 1132 participants completed the baseline questionnaires (1132/1156, 97.9%) and 1047 participants completed the initial Sleepiness Checker activity (1047/1156, 90.6%). Furthermore, 1000 participants provided activity-specific wearable data (1000/1156, 86.5%) and 982 provided sleep-specific wearable data (982/1156, 84.9%).

Conclusions: The Achievement Studies platform allowed for rapid recruitment and high study engagement (survey completion and device data sharing). This approach to carrying out research appears promising. However, conducting research in this way requires that participants have internet access and own and use a wearable device. As such, our sample may not be representative of the general population.

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KEYWORDS

connected health; engagement; health; mHealth; mobile health; mobile phone; recruitment; sleep; sleep quality; wearables

Introduction

Participant recruitment can be a significant rate-limiting step to the implementation of research studies [1]. A study found that less than one-third of publicly funded multicenter trials met recruitment targets within the planned timeframe [2]. Another study found that 40% of studies underenrolled participants, with 11% failing to enroll a single participant [3]. Study recruitment can take several months and consume up to 30% of study timelines, which can delay scientific progress and incur substantial additional costs. Another related study found the estimated cost of recruiting and retaining participants for clinical trials alone to be US $2.3 billion annually [4].

The study recruitment process is often underfunded and underresourced. Internet-based technologies have the potential to offer improvement in this domain [5] or, at least, supplement existing approaches. Lessons are being learned from Web-based trials where these processes can be shifted to a less resource-intensive Web-based connected platform. This allows for carrying out faster, cheaper, and more demographically and geographically diverse medical research [4,6,7].

Connected research platforms allow research to be brought out of the traditional lab setting and directly to participants through mobile devices and computers. This approach is part of the larger emerging trend of connected health [8] and mobile health (mHealth) [9]. These platforms may provide a way for participants to be accessed through their mobile devices, through research apps that can be used to monitor health in near real time. Examples of underlying platforms and frameworks that these mobile research apps have been developed based upon include Open mHealth [10], Apple ResearchKit [11], and Android ResearchStack [12]. Apps utilizing these platforms allow survey questionnaires and assessments to be administered to participants quickly and easily. The apps also make it possible to sample consumer wearable data over long periods of time, garnering a great deal of useful data in domains ranging from activity to sleep. The Achievement Studies platform (Evidation Health, Inc, San Mateo, CA, USA) is an example of one such connected platform that is Web-based and, therefore, allows access to participants who are not mobile-enabled or prefer nonmobile Web access; in other words, the platform enables users of any connected device (phone, tablet, laptop, or desktop) to participate in research. This platform has been used to run a wide variety of digital studies [13-15].

There is emerging evidence in support of the myriad ways that these apps and platforms are improving certain aspects of the research process. They have significantly increased the speed and ease of recruiting participants for certain kinds of research studies [13-18], made studies accessible to a larger audience [19], and evidence from prior studies suggests that these app-based interventions promote positive health outcomes in patients with a variety of chronic conditions [15,20-23]. As such, they appear promising for future research studies, but their long-term value remains to be seen.

The motivation for this study was to take advantage of the technological and methodological advancements in the field of connected health or mHealth and apply them to a large-scale research study on sleep. Sleep is an essential biological function of vital importance for many aspects of physical and mental health [24]. The Centers for Disease Control have termed insufficient sleep “a public health epidemic” [25], yet large-scale studies of sleep patterns, quality, and associated characteristics that are substantiated by objective data collection are lacking. Given the importance of sleep health for individuals across demographics and health statuses, the population of interest is maximal. Utilizing a novel platform, the aim of the study was to gain further insights into the relationship between participant sleep and daytime functioning while simultaneously speeding up the recruitment process and maximizing data completeness. The Achievement SleepHealth study was adapted from the SleepHealth Mobile App Study, a mobile research study built on the Apple ResearchKit framework [26], and is considered a substudy of the larger study. The SleepHealth Mobile App Study was limited to iPhone users, whereas the Achievement Study is a Web application-based study that can be accessed by any Web-enabled computer or mobile device.

Methods

Study Design and Overview

The Achievement SleepHealth study was implemented using a Web-based platform to screen, consent, and enroll eligible individuals from across the United States to participate in this 1-year long observational study (Achievement Studies, Evidation Health Inc). Participants could access the Web-based study platform at any time from any Web-enabled device to track progress and complete various study-required procedures. While all participants took part in the study remotely, research staff were available by phone or email to answer questions and otherwise provide support at any time during and after the study period.

Participants and Enrollment

Prospective participants were recruited over a 5-day period using a Web-based strategy within the Achievement community. Members of Achievement can connect their activity trackers and fitness and health apps to the program; as members log activities and use their activity trackers, they accumulate points that are redeemable for monetary rewards. Members can also receive targeted offers to participate in various research opportunities and studies. Members with relevant connected activity trackers were invited through email to participate in the Achievement SleepHealth study. Participants were prompted to visit a website to learn more about the study and verify their eligibility by answering a few Web-based screening questions. If eligible, they completed an electronic informed consent (eConsent) process to enroll in the study. The eConsent document specified that the only data that would be included in the study dataset from their personal device would be from smartphone apps that they specifically permissioned as part of study procedures (eg, Fitbit data). They then went on to complete baseline questionnaires and were invited to connect a wearable activity tracker account if they had not already done so. Participants who completed the baseline questionnaires were subsequently sent a single-item Sleepiness Checker on a daily basis for 7 consecutive days.

Follow-Up

After the initial study procedures described above, participants were asked to track daily alertness levels for 7 consecutive days every 3 months and track sleep and activity with their wearable devices throughout the 1-year study period.

Measurements

Study questionnaires and the Sleepiness Checker activity from the SleepHealth Mobile App Study were replicated on the Achievement Studies platform. Most questions were multiple-choice type, with a small number of numeric entry questions (eg, participant age, weight, caffeine, and alcohol consumption).

Baseline Questionnaires

Six one-time questionnaires were administered to participants sequentially upon enrollment in the Achievement SleepHealth study. The questionnaires were named as follows: About Me, My Health, My Family, Research Interest, Sleep Habits, and Sleep Assessment. The About Me survey was designed to obtain general background information about study participants (eg, gender, age, weight, socioeconomic status, etc). The My Family questionnaire was composed of questions specific to participant households and contained questions such as primary language spoken at home, household size, and the number of minors living at home. The My Health survey included questions related to participants' physical health. It focused on participants' beliefs about the likelihood of developing specific health conditions, and how these health conditions and sleep might be related to one another. The Research Interest Questionnaire comprised a series of questions that were intended to gauge the extent of participants' previous research exposure, as well as their interest in future research. The final 2 questionnaires were sleep-specific. Sleep Habits focused on questions involving participant sleep routines (average time in minutes taken to fall asleep, the number of naps taken during the day, whether a participant was a morning or evening person), whereas the Sleep Assessment contained questions that were specific to sleep quality and included potential problems arising during sleep, as well as symptoms that could potentially be related to various sleep disorders. A common theme of the surveys was that participants were asked questions about their levels of daytime activity, lifestyle, and other factors that could influence their sleep duration and sleep quality.

Figure 1. Sleepiness Checker, SleepHealth app.

Other Study Measures

Sleepiness Checker

Each time the Sleepiness Checker activity was administered to participants (both immediately following the initial questionnaire set and then every 3 months for the 1-year study), it was administered daily for a total of 7 days, sent at the same time of day that the baseline questionnaires were completed. It was adapted from the Karolinska Sleepiness Scale [27], a single-item Likert-type scale anchored by 1 (extremely alert) and 9 (very sleepy, fighting sleep). Figure 1 shows the screenshot of the full range of possible responses.

Sleep- and Activity-Specific Data

As the vast majority of participants used the Fitbit wearable, it was considered the study's primary source of sleep and activity data.

Data Analysis

This paper focuses on baseline characteristics, but future work will share results from longitudinal data and trends over the course of the 1-year study. All analyses were performed in SPSS Statistics v23 (IBM, Armonk, NY, USA). Descriptive statistics were performed on the remaining valid data. All data reported as mean (SD; range) unless indicated otherwise. All enrollment time data are in Coordinated Universal Time (UTC).

Results

Participant Enrollment

Participants were first recruited by email around 9:00 am per Pacific Time Zone on March 24, 2017 (16:00 pm as per UTC). The study was closed to further enrollment on March 29, 2017. The first 100 participants were enrolled in less than 20 minutes. Enrollment reached 1000 participants within about 9 hours. Figure 2 provides a detailed bar graph of enrollment by date and time interval; blue bars represent the number of participants recruited at each time interval, and the red line indicates cumulative study enrollment. During the first 1 hour, the enrollment rate was 6.6 participants per minute (394 per hour). In the first 24 hours, the enrollment rate was 0.8 participants per minute (47 participants per hour).

In total, 1156 participants were enrolled in the study within the recruitment window, but 1 withdrew shortly after enrollment, yielding 1155 participants. Complete study flow with the total number of participants at each step is documented in Figure 3. White boxes indicate steps of the enrollment process, with number and percentage of total valid participants; gray boxes indicate the numbers lost between each step.

In addition, the Web-based recruitment strategy attracted participants from a wide geographic distribution. Using telephone area codes as a proxy for location (which does not guarantee that participants live in these locations), at least 1 participant from all 50 states was enrolled in this study. A graphical representation of proxy geographic location is shown in Figure 4, with point size scaled by the number of participants per area code (range 1-12) and points located at the corresponding latitude and longitude centroid for each represented area code. Alaska and Hawaii area codes corresponded to 6 and 9 participants, respectively, but are not depicted. Furthermore, 12.0% (138/1153) of the participants had area codes from the 15 most rural states, defined by having >50% of the population residing in designated US Census Bureau rural settings [28].

Figure 2. Participant enrollment rate by date and time interval.

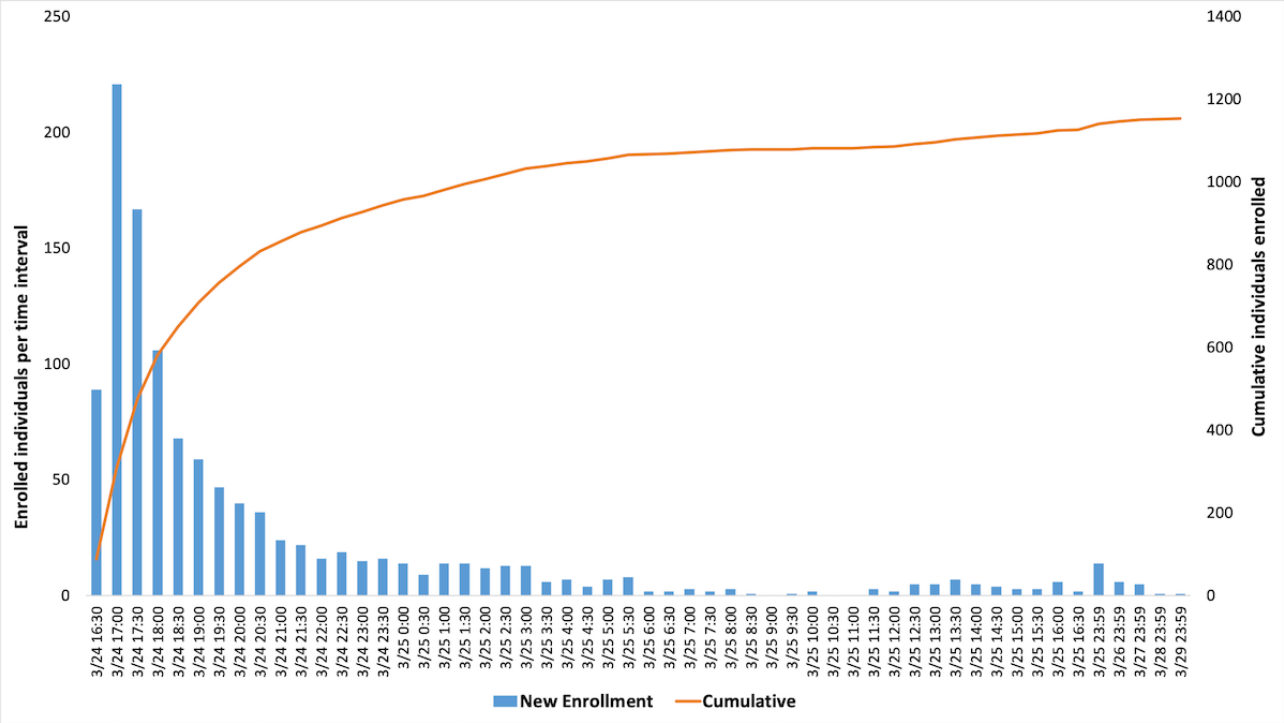
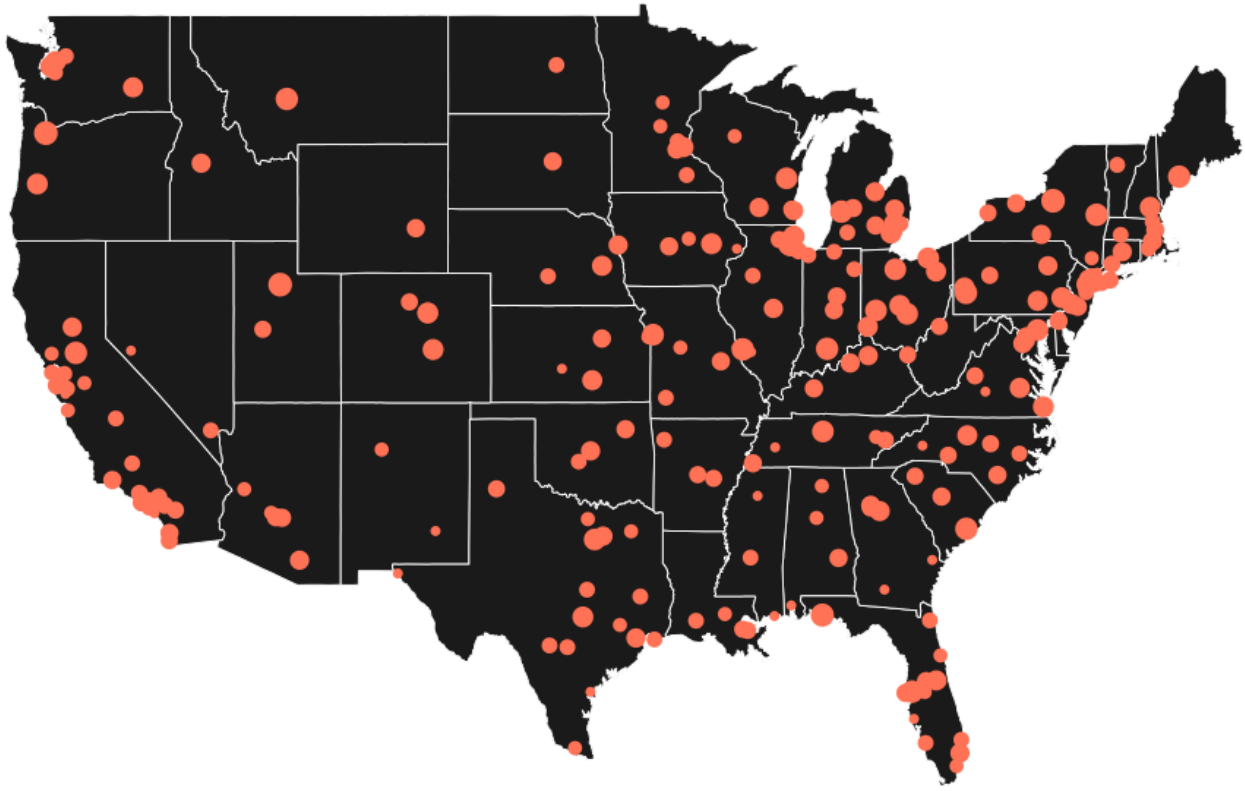


Figure 3. Study participant flow.

Figure 4. Geographic distribution of participants (point size scaled by the number of participants per area code).



Questionnaire Engagement and Characteristics

Overall, 1132 participants completed the baseline questionnaires (1132/1156, 97.9%). Relevant participant demographic information is summarized in Table 1. Additional participant data are presented in Multimedia Appendix 1.

Mean participant age was 34.6 (9.4; 18-67) years. The mean participant weight was 183.4 (51.8; 94-425) pounds. The majority of the participants were women (1053/1132, 93.0%). Note that while Hispanic individuals were not specifically assessed in this study, participants had the opportunity to select "Other" and enter their race; 18 participants reported that they were Hispanic individuals.

Sleepiness Checker Engagement

In this study, 1047 participants completed the baseline Sleepiness Checker activity (1047/1156, 90.5%). Mean days of the Sleepiness Checker completed per participant were 5.7 (1.7; 1-7). Overall, 51.8% (542/1047) of those who completed the baseline Sleepiness Checker completed it on all 7 days. A complete breakdown of the number of days that participants completed the Sleepiness Checker activity is outlined in Table 2.

Objective Activity and Sleep Metrics

Overall, 1000 participants provided activity-specific Fitbit data (1000/1156, 86.5%), and 982 (982/1156, 84.9%) participants provided sleep-specific Fitbit data. Participants shared data from their Fitbits, and these data were used to provide objective sleep and activity metrics for the study.

Table 1. Sample characteristics.

Characteristic	Participants, n (%)		
	Total, n=1132	Females, n=1053	Males, n=79
Education			
High school or general educational development	80 (7.1)	75 (7.1)	5 (6.3)
Some college or 2-year degree	454 (40.1)	429 (40.7)	25 (31.6)
4-year college degree	330 (29.2)	312 (29.6)	18 (22.8)
More than 4-year college degree	265 (23.4)	238 (22.6)	26 (32.9)
Household income in US $			
<10,000	47 (4.2)	44 (4.2)	3 (3.7)
10,000-49,999	361 (31.9)	341 (32.4)	19 (24.1)
50,000-99,999	406 (35.9)	384 (36.5)	22 (27.8)
100,000-149,000	164 (14.5)	145 (13.8)	19 (24.1)
150,000-199,999	45 (4.0)	39 (3.7)	6 (7.6)
200,000-249,999	15 (1.3)	15 (1.4)	0 (0.0)
250,000+	8 (0.7)	8 (0.8)	0 (0.0)
Race			
White	979 (86.5)	923 (87.7)	56 (70.9)
Black or African American	50 (4.4)	45 (4.3)	5 (6.3)
Asian	36 (3.2)	28 (2.7)	8 (10.1)
Other	29 (2.6)	25 (2.4)	4 (5.1)
American Indian or Alaska Native	21 (1.9)	20 (1.9)	1 (1.3)
Pacific Islander	9 (0.8)	5 (0.5)	4 (5.1)
Marital status			
Married	570 (50.3)	531 (50.4)	39 (49.4)
Never married	300 (26.5)	276 (26.2)	23 (29.1)
Unmarried and living with partner	152 (13.4)	146 (13.9)	6 (7.6)
Divorced	84 (7.4)	78 (7.4)	6 (7.6)
Widowed	12 (1.1)	12 (1.1)	0 (0.0)
Separated	11 (1.0)	11 (1.0)	0 (0.0)

Table 2. Participants' Sleepiness Checker engagement (n=1047).

Day	Participants, n (%)
7	542 (51.8)
6	174 (16.6)
5	116 (11.1)
4	67 (6.4)
3	70 (6.7)
2	37 (3.5)
1	41 (3.9)

Discussion

Principal Results

This study resulted in several key findings in speeding up research enrollment while maintaining a high rate of engagement with the study protocol. The study enrolled 1156 participants within a 5-day window, with the majority being enrolled within the first day. Of the original 1156, only 1 withdrew from the study within the first week, indicating that the study was able to achieve a very low rate of initial dropout, which is important in conducting Web-based, eConsent studies. Finally, the rate of initial data collection was quite high for this type of research study as well, with 97.9% (1132/1156) of participants completing initial baseline questionnaires, 90.6% (1047/1156) completing the daytime Sleepiness Checker, and 84.9% (982/1156) sharing their wearable data.

Comparison With Prior Work

Recruitment through the Achievement Studies platform yielded a remarkably high rate of enrollment, which can be attributed to (1) its Web-based methods and (2) its broad potential patient population. Compared with traditional cohort studies of sleep, which in line with previously introduced literature may take many months to enroll fully, Web-based methods of recruitment and enrollment can accelerate this process by orders of magnitude. The emerging Web-based study literature has many examples of this benefit in different patient populations. For instance, Web-based mental health studies with a similar number of participants reached targets in 5 months [29], 3 months [30], and 4 days [31]. A review of 12 studies utilizing Web-based recruitment methods calculated an average of 5 months spent on recruiting, ranging from 7 weeks to 7 months [32]. In comparison, our recruitment approach reached these targets within hours of the first email solicitation. Importantly, this study of sleep health had minimal inclusion and exclusion criteria and barriers to entry, as the study's research focus is relevant to all individuals regardless of demographics or comorbidities. Such broad relevance, in addition to the convenient and predominantly passive means of data collection, additionally affects the observed recruitment timeframe.

It should be noted that one of the original ResearchKit studies (Health eHeart) reportedly enrolled over 10,000 new participants in its first 24 hours of study launch. However, several unique characteristics to its study launch were as follows: (1) the study team was able to work on the open-source platform for nearly a year before launch; (2) the launch was coordinated with the release of 4 other ResearchKit studies; and (3) it was announced by Apple at a major event.

While there are clear advantages to this method of participant recruitment and enrollment, some authors assert that significant drawbacks are involved in Web-based studies such as low levels of engagement and retention [32,33]. Long-term retention and engagement metrics for this study will be reported in subsequent publications; however, results demonstrate promisingly high levels of daily participant engagement, and other studies run on the Achievement Studies platform have yielded high completion rates [14,15]. Furthermore, Web-based recruitment methods are not subject to significant geographic restrictions and are limited only by access to the internet.

Limitations

One limitation of this study is that it was conducted only with members of a Web-based community. While similar studies on the Achievement Studies platform can extend recruitment beyond just existing Achievement community members, to supplement with recruitment on other Web-based channels, on the occasion that the Achievement community is not deemed representative of the desired population, conducting research in this manner does require participants to have internet access. Additionally, the data sources required for this study limited participants to those who owned and used wearable devices. Another limitation is the sample's limited demographic representativeness of the overall population. Participants were predominantly white women (largest subset married with children, educated, income >50k). Screening for the study was not implemented toward specific demographic targets; the inclusion criteria were those aged 18 years and above, residing in the United States, and able to read and understand English. A more diverse sample could have been quickly recruited through the Web by proportionally targeting subgroups using specific criteria, and this approach has been successfully used in other studies on the Achievement Studies platform. Furthermore, it is understood that objective data provided by consumer wearable devices may not accurately agree with clinically acquired measures, such as those obtained using actigraphy and polysomnography, although there is a growing body of recent literature pursuing validation efforts against gold standard, suggesting that consumer wearables may provide useful information about sleep and activity, especially with regards to intrauser trends [34,35]. Clearly, more research is required in the domain of consumer wearables [36-39]. Additional limitations involved in carrying out research in this manner are selection biases, the potential for low retention, and the possibility of privacy and security issues [40,41]. Moreover, participant geographical location was obtained through a proxy measure (telephone area code). This may not always reflect the geographic location where participants currently reside.

Conclusions

The Achievement Studies platform is a useful framework for carrying out longitudinal research from which a large number of participants with wearable and other behavioral data can be rapidly recruited for research studies. In addition, initial participant retention and engagement appear promising. Carrying out community-based research in which individuals can be targeted for studies using specific criteria is an innovative approach to carrying out research. As is the case with large datasets, the data quality will need to be carefully examined. In addition, the representativeness of the sample of the overall population will need to be evaluated and long-term retention and engagement remains to be seen.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplemental data (n=1132).

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References

1. Newington L, Metcalfe A. Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. BMC Med Res Methodol 2014 Jan 23;14:10 [FREE Full text] [doi: 10.1186/1471-2288-14-10] [Medline: 24456229]
2. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, STEPS group. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. Health Technol Assess 2007 Nov;11(48):iii, ix-iii,105 [FREE Full text] [Medline: 17999843]
3. New Research from Tufts Characterizes Effectiveness and Variability of Patient Recruitment and Retention Practices. 2013. URL: https://csdd.tufts.edu/s/02-Jan-15-2013-Recruitment-Retention.pdf [accessed 2019-01-15] [WebCite Cache ID 75S5UCsK1]
4. Covington D, Veley K. The remote patient-centered approach in clinical research. 2014 Nov 17. URL: http://www.appliedclinicaltrialsonline.com/remote-patient-centered-study-approach-clinical-research [accessed 2018-11-27] [WebCite Cache ID 74Fi74HTq]
5. Marks L, Power E. Using technology to address recruitment issues in the clinical trial process. Trends Biotechnol 2002 Mar;20(3):105-109. [Medline: 11841861]
6. Clinical Research Trends. How New Virtual Clinical Trials Have Improved Patient Recruitment. 2016 Nov 21. URL: https://www.clinicalresearchtrends.com/index.php/2016/11/21/virtual-clinical-trials-improved-recruitment/ [accessed 2018-11-27] [WebCite Cache ID 74Fj60ZRb]
7. Jadhav S. Virtual clinical trials: the future of patient engagement. 2016 Jul 12. URL: http://www.appliedclinicaltrialsonline.com/virtual-clinical-trials-future-patient-engagement [accessed 2018-11-27] [WebCite Cache ID 74FigvDnN]
8. Kvedar J, Coye MJ, Everett W. Connected health: a review of technologies and strategies to improve patient care with telemedicine and telehealth. Health Aff (Millwood) 2014 Feb;33(2):194-199. [doi: 10.1377/hlthaff.2013.0992] [Medline: 24493760]
9. Park Y. Emerging New Era of Mobile Health Technologies. Healthc Inform Res 2016 Oct;22(4):253-254 [FREE Full text] [doi: 10.4258/hir.2016.22.4.253] [Medline: 27895955]
10. Open mHealth.: GitHub, Inc; 2011. URL: https://github.com/openmhealth [accessed 2018-04-23] [WebCite Cache ID 6yvUNGpar]
11. Apple ResearchKit.: Apple, Inc; 2015. URL: https://www.apple.com/researchkit [accessed 2018-04-22] [WebCite Cache ID 6yvRUInN8]
12. ResearchStack. 2016. URL: http://researchstack.org/ [accessed 2018-04-24] [WebCite Cache ID 6yvTDOxLV]
13. Bott N, Kumar S, Krebs C, Glenn JM, Madero EN, Juusola JL. A Remote Intervention to Prevent or Delay Cognitive Impairment in Older Adults: Design, Recruitment, and Baseline Characteristics of the Virtual Cognitive Health (VC Health) Study. JMIR Res Protoc 2018 Aug 13;7(8):e11368 [FREE Full text] [doi: 10.2196/11368] [Medline: 30104186]
14. Morawski K, Ghazinouri R, Krumme A, Lauffenburger JC, Lu Z, Durfee E, et al. Association of a Smartphone Application With Medication Adherence and Blood Pressure Control: The MedISAFE-BP Randomized Clinical Trial. JAMA Intern Med 2018 Jun 01;178(6):802-809. [doi: 10.1001/jamainternmed.2018.0447] [Medline: 29710289]
15. Kumar S, Moseson H, Uppal J, Juusola JL. A Diabetes Mobile App With In-App Coaching From a Certified Diabetes Educator Reduces A1C for Individuals With Type 2 Diabetes. Diabetes Educ 2018 Dec;44(3):226-236. [doi: 10.1177/0145721718765650] [Medline: 29575982]
16. Webster DE, Suver C, Doerr M, Mounts E, Domenico L, Petrie T, et al. The Mole Mapper Study, mobile phone skin imaging and melanoma risk data collected using ResearchKit. Sci Data 2017 Dec 14;4:170005 [FREE Full text] [doi: 10.1038/sdata.2017.5] [Medline: 28195576]
17. Zens M, Woias P, Suedkamp NP, Niemeyer P. "Back on Track": A Mobile App Observational Study Using Apple's ResearchKit Framework. JMIR Mhealth Uhealth 2017 Feb 28;5(2):e23 [FREE Full text] [doi: 10.2196/mhealth.6259] [Medline: 28246069]

18. Bot BM, Suver C, Neto EC, Kellen M, Klein A, Bare C, et al. The mPower study, Parkinson disease mobile data collected using ResearchKit. Sci Data 2016 Mar 03;3:160011 [FREE Full text] [doi: 10.1038/sdata.2016.11] [Medline: 26938265]
19. Jardine J, Fisher J, Carrick B. Apple's ResearchKit: smart data collection for the smartphone era? J R Soc Med 2015 Aug;108(8):294-296 [FREE Full text] [doi: 10.1177/0141076815600673] [Medline: 26268915]
20. Chouvarda IG, Goulis DG, Lambrinoudaki I, Maglaveras N. Connected health and integrated care: Toward new models for chronic disease management. Maturitas 2015 Sep;82(1):22-27. [doi: 10.1016/j.maturitas.2015.03.015] [Medline: 25891502]
21. Colorafi K. Connected health: a review of the literature. Mhealth 2016;2:13 [FREE Full text] [doi: 10.21037/mhealth.2016.03.09] [Medline: 28293591]
22. Fiordelli M, Diviani N, Schulz PJ. Mapping mHealth research: a decade of evolution. J Med Internet Res 2013 May 21;15(5):e95 [FREE Full text] [doi: 10.2196/jmir.2430] [Medline: 23697600]
23. Kumar S, Jones Bell M, Juusola JL. Mobile and traditional cognitive behavioral therapy programs for generalized anxiety disorder: A cost-effectiveness analysis. PLoS One 2018;13(1):e0190554 [FREE Full text] [doi: 10.1371/journal.pone.0190554] [Medline: 29300754]
24. Mukherjee S, Patel SR, Kales SN, Ayas NT, Strohl KP, Gozal D, American Thoracic Society ad hoc Committee on Healthy Sleep. An Official American Thoracic Society Statement: The Importance of Healthy Sleep. Recommendations and Future Priorities. Am J Respir Crit Care Med 2015 Jun 15;191(12):1450-1458 [FREE Full text] [doi: 10.1164/rccm.201504-0767ST] [Medline: 26075423]
25. Center for Disease Control and Prevention. Insufficient Sleep Is a Public Health Epidemic. 2015. URL: https://www.cdc.gov/features/dssleep/ [accessed 2018-11-26] [WebCite Cache ID 74E5RXEKo]
26. American Sleep Apnea Association. SleepHealth Mobile App Study. URL: https://itunes.apple.com/us/app/sleephealth/id1059830442?mt=82016 [accessed 2018-04-24] [WebCite Cache ID 6yvPDcyR6]
27. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci 1990 May;52(1-2):29-37. [Medline: 2265922]
28. Bishop B. How rural are the states?. 2012. URL: https://www.dailyyonder.com/how-rural-are-states/2012/04/03/3847/ [accessed 2018-04-25] [WebCite Cache ID 6yx0mMpvE]
29. Anguera JA, Jordan JT, Castaneda D, Gazzaley A, Areán PA. Conducting a fully mobile and randomised clinical trial for depression: access, engagement and expense. BMJ Innov 2016 Jan;2(1):14-21 [FREE Full text] [doi: 10.1136/bmjinnov-2015-000098] [Medline: 27019745]
30. Batterham PJ. Recruitment of mental health survey participants using Internet advertising: content, characteristics and cost effectiveness. Int J Methods Psychiatr Res 2014 Jun;23(2):184-191. [doi: 10.1002/mpr.1421] [Medline: 24615785]
31. Leach LS, Butterworth P, Poyser C, Batterham PJ, Farrer LM. Online Recruitment: Feasibility, Cost, and Representativeness in a Study of Postpartum Women. J Med Internet Res 2017 Dec 08;19(3):e61 [FREE Full text] [doi: 10.2196/jmir.5745] [Medline: 28274906]
32. Lane TS, Armin J, Gordon JS. Online Recruitment Methods for Web-Based and Mobile Health Studies: A Review of the Literature. J Med Internet Res 2015 Jul 22;17(7):e183 [FREE Full text] [doi: 10.2196/jmir.4359] [Medline: 26202991]
33. Mathieu E, McGeechan K, Barratt A, Herbert R. Internet-based randomized controlled trials: a systematic review. J Am Med Inform Assoc 2013 May 01;20(3):568-576 [FREE Full text] [doi: 10.1136/amiajnl-2012-001175] [Medline: 23065196]
34. Beattie Z, Oyang Y, Statan A, Ghoreyshi A, Pantelopoulos A, Russell A, et al. Estimation of sleep stages in a healthy adult population from optical plethysmography and accelerometer signals. Physiol Meas 2017 Oct 31;38(11):1968-1979. [doi: 10.1088/1361-6579/aa9047] [Medline: 29087960]
35. de Zambotti M, Goldstone A, Claudatos S, Colrain IM, Baker FC. A validation study of Fitbit Charge 2™ compared with polysomnography in adults. Chronobiol Int 2018 Apr;35(4):465-476. [doi: 10.1080/07420528.2017.1413578] [Medline: 29235907]
36. 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]
37. Cadmus-Bertram L. Using Fitness Trackers in Clinical Research: What Nurse Practitioners Need to Know. J Nurse Pract 2017 Jan;13(1):34-40 [FREE Full text] [doi: 10.1016/j.nurpra.2016.10.012] [Medline: 28603469]
38. Majumder S, Mondal T, Deen M. Wearable Sensors for Remote Health Monitoring. Sensors (Basel) 2017 Jan 12;17(1):130 [FREE Full text] [doi: 10.3390/s17010130] [Medline: 28085085]
39. Piwek L, Ellis DA, Andrews S, Joinson A. The Rise of Consumer Health Wearables: Promises and Barriers. PLoS Med 2016 Feb;13(2):e1001953 [FREE Full text] [doi: 10.1371/journal.pmed.1001953] [Medline: 26836780]
40. Dorsey ER, Yvonne Chan YF, McConnell MV, Shaw SY, Trister AD, Friend SH. The Use of Smartphones for Health Research. Acad Med 2017 Dec;92(2):157-160. [doi: 10.1097/ACM.0000000000001205] [Medline: 27119325]
41. Chan YY, Wang P, Rogers L, Tignor N, Zweig M, Hershman SG, et al. The Asthma Mobile Health Study, a large-scale clinical observational study using ResearchKit. Nat Biotechnol 2017 Apr;35(4):354-362 [FREE Full text] [doi: 10.1038/nbt.3826] [Medline: 28288104]

Abbreviations

eConsent: electronic informed consent
mHealth: mobile health
UTC: Coordinated Universal Time

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Corrigenda and Addenda

Metadata Correction: A Decision Support System to Enhance Self-Management of Low Back Pain: Protocol for the selfBACK Project

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Correction of: https://www.researchprotocols.org/2018/7/e167/

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The authors of the paper "A Decision Support System to Enhance Self-Management of Low Back Pain: Protocol for the selfBACK Project" (JMIR Res Protoc 2018;7(7):e167) wish to amend the authors listed on the paper.

In the "Authors" section, the collaborators were not included and only the two main authors were listed in the authorship information. The selfBACK Consortium has been added as a group author, and the names of the contributors have now been listed in the Acknowledgments section. The full list of collaborations associated with the selfBACK Consortium can be found in Multimedia Appendix 1 of this correction notice.

The correction will appear in the online version of the paper on the JMIR website on January 3, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article also has been resubmitted to those repositories.

Multimedia Appendix 1

Collaborators and their affiliations.

[PDF File (Adobe PDF File), 30KB - resprot_v8i1e12180_app1.pdf]

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Corrigenda and Addenda

Metadata Correction: Epidemiology of Surgical Site Infections With Staphylococcus aureus in Europe: Protocol for a Retrospective, Multicenter Study

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Related Article:

Correction of: https://www.researchprotocols.org/2018/3/e63/

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The authors of the paper “Epidemiology of Surgical Site Infections With Staphylococcus aureus in Europe: Protocol for a Retrospective, Multicenter Study” (JMIR Res Protoc 2018;7(3):e63) made a mistake in the final stage of proofreading. In the affiliations list, Dr Liss’s affiliation was incorrectly listed as “Department I of Internal Medicine, University Hospital of Cologne, University of Cologne, Cologne, Germany”. Instead, his affiliation should read “Department I of Internal Medicine, Helios University Hospital Wuppertal, Wuppertal, Germany”.

The correction will appear in the online version of the paper on the JMIR website on January 7, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article also has been resubmitted to those repositories.

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Protocol

A Social Media Website (Supporting Our Valued Adolescents) to Support Treatment Uptake for Adolescents With Depression and/or Anxiety and Their Parents: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Few adolescents who experience depression or anxiety connect to mental health treatment. Supporting Our Valued Adolescents (SOVA) is a stakeholder-informed technology intervention that consists of 2 blog-format websites—one for adolescents and another for parents. SOVA is designed to intervene on targets, which may increase the mental health treatment uptake when adolescents with depression or anxiety are identified in primary care settings.

Objective: This study aims to describe the protocol for a pilot randomized controlled trial designed to refine recruitment and retention strategies, document intervention fidelity and implementation outcomes, and assess changes in health beliefs and knowledge, emotional or informational support, and parent-adolescent communication quality in adolescents and their parents.

Methods: Adolescents identified with symptoms of depression or anxiety, for which a health care provider recommends treatment, and their parents will be recruited from clinics where adolescents are seen for primary care. Adolescent-parent dyads will be randomized at 1:1 to both receive the SOVA websites and enhanced usual care or enhanced usual care alone. Baseline measures and 6-week and 3-month outcomes will be collected by Web-based self-report surveys and electronic health record review. The main pilot outcome is the 6-week study retention rate. Analyses will also assess changes in health beliefs and knowledge, emotional support, and parent-adolescent communication in both adolescents and their parents.

Results: The project was funded in 2017. Recruitment commenced in April 2018 and enrollment is ongoing, with completion anticipated at the end of 2019 with subsequent plans for data analysis and publication submission in early 2020.

Conclusions: The findings of this research will inform the design of a multisite hybrid effectiveness-implementation randomized controlled trial examining the effectiveness and optimal implementation strategies for using SOVA in community primary care settings.

Trial Registration: ClinicalTrials.gov NCT03318666; https://clinicaltrials.gov/ct2/show/NCT03318666

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KEYWORDS

adolescent; adolescent health services; anxiety; depression; technology

Introduction

Adolescents are experiencing depression and anxiety in growing numbers, but few connect to mental health care. Almost 12% of adolescents have major depression or dysthymia and up to a third have an anxiety disorder [1]. A third of depressed adolescents experience suicidality, and 11% attempt suicide [2], resulting in US $12 billion in hospital costs [3]. Yet, only one-third of depressed adolescents receive treatment [4], and initial treatment delays average 10 years [5]. Unmet treatment needs are even more concerning for anxiety, with less than one-fifth of adolescents using mental health services [6]. Although research shows positive effects of antidepressants and cognitive behavioral therapy [7], these treatments are underused in adolescence [8,9], contributing to higher health care utilization as adults [10].

One approach to increasing access and use of mental health treatment is implementing integrated behavioral health models. These models may increase the number of adolescents receiving treatment by actively engaging patients, enabling consultation with and access to mental health professionals within primary care settings, and increasing evaluation and management by primary care providers (PCPs) [11]. By standardizing evaluation through routine screening, providing access to services, and nurturing active engagement in care [12], these models can improve adolescent depression treatment outcomes in primary care [12], where one-third of child mental health is managed [13]. However, these in-person patient engagement techniques may fail to be implemented owing to being resource intense and requiring trained professionals and practice-level changes. More commonly, depression screening is attempted without an approach to increase engagement resulting in low treatment initiation [8,14,15]. One explanation is adolescents identified through routine screening, and their parents may not be seeking mental health services [16,17], leading to a mismatch between evaluated (ie, screening results and PCP evaluation) and perceived need (ie, parent and adolescents' views on whether they need services).

Models of mental health service use can be used to examine factors contributing to the underuse of mental health treatment [17]. The Andersen behavioral model explains how (1) predisposing characteristics (eg, age, gender, race, health beliefs, and knowledge); (2) enabling resources (eg, health insurance, income, and emotional support); and (3) need for services (both evaluated and perceived) can predict service use [18,19]. Parents' and adolescents' perceptions of the adolescents' need for mental health services are known predictors of service use [16,20-23] but difficult for PCPs to address [24].

Negative health beliefs about biological explanations for mental illness and lack of confidence in treatment lead to a decreased perceived need for treatment in young adults [25] and parents [26]. A systematic review found the most important barriers in young people are lack of mental health knowledge [27] and negative beliefs about treatment [28]. Independent of access to care or cost, negative health beliefs strongly correlate with the persistent unmet need of adults who developed mental health problems in childhood [23,29].

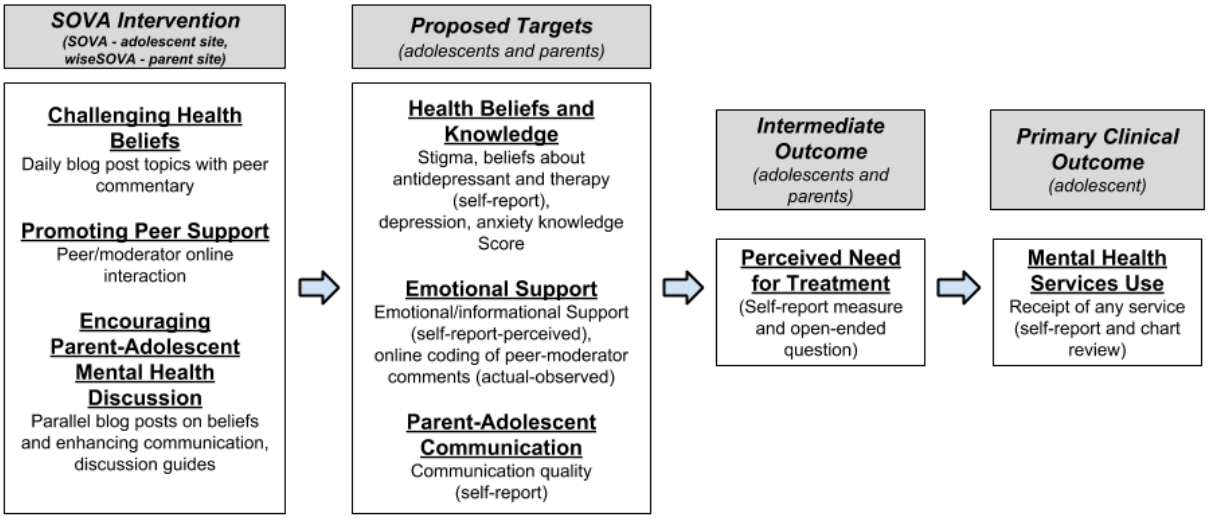
Emotional support increases mental health services use [18,28,30] and may be important for both adolescents and their parents. Peers contribute to mental health interventions by providing hope through self-disclosure, role modeling positive behavior, and using empathy and acceptance [31]. Peer social support is influential in adolescent decision making [32]. For both adolescents and parents, social support can improve treatment expectations [33,34] and increase antidepressant acceptance [35]. By comparing their child's emotional problems with other children, parents consider whether symptoms are developmentally normal [36]. Parents who are peer advocates help other families by sharing knowledge and addressing attitudes toward treatment [37].

Parents' role in facilitating an adolescent to engage with mental health services is gravely important [16,20]. Impaired parent-adolescent communication may decrease help seeking for mental health problems [38,39]. Adolescents' developmental goals of establishing autonomy in decision making and becoming independent can make communication around mental health difficult [40], especially for internalized disorders, like depression, for which adolescents may not express their symptoms aside from displaying irritability—and this can be interpreted as normalized adolescent defiance or "teen angst." Externalizing disorders with behavioral symptoms that parents can readily observe, such as in attention deficit hyperactivity disorder, are more likely to lead to the parent requesting treatment for their adolescent [41]. Few studies that have examined communication around mental illness show evidence for silence and stigma [42], with parents feeling least comfortable discussing suicidal thoughts [43].

The conceptual model in Figure 1 displays how the abovementioned factors may be related. The Supporting Our Valued Adolescents (SOVA) intervention, described below, was designed to address these proposed targets by challenging health beliefs, promoting peer support, and encouraging parent-adolescent mental health discussion. Further details of the design and development of this intervention [44] and its usability testing [45] are available elsewhere.

This protocol aims to use a pilot randomized controlled trial (RCT) of SOVA compared with enhanced usual care (EUC) provided to adolescents with symptoms of depression or anxiety being referred to treatment to refine recruitment and retention strategies, document intervention fidelity and other implementation outcomes, and assess changes in health beliefs and knowledge, emotional or informational support, parent-adolescent communication quality, and explore whether there are differences in mental health service use, the proposed future main outcome. The main pilot outcome is the retention rate, with other feasibility metrics also being described.

Figure 1. Conceptual model. SOVA: Supporting Our Valued Adolescents.



Methods

Study Overview

We will conduct a 6-week pilot, single-blind RCT of SOVA in parent-adolescent dyads identified by their clinician in the course of routine medical care with symptoms of depression or anxiety and referred for a new treatment episode (no treatment in the past 3 months defined as having filled and begun taking an antidepressant and seeing a mental health therapist for at least 3 sessions). This will be a parallel treatment arm study with 1:1 allocation comparing SOVA and EUC to EUC alone. We will examine the feasibility of recruitment and retention strategies, intervention implementation, acceptability by providers, measures appropriateness, rates of missing data, and adequacy of the human subjects' plan. In addition, we will test randomization procedures and measure mental health service use after 3 months. We will also describe changes in target mechanisms (Figure 1) as an embedded proof-of-concept study. For this study, by "retention," we mean assessing whether recruited participants are retained in the study (as opposed to retained in treatment) and complete 6-week outcome measures as estimating the loss to follow-up will help us to plan the sample size needed for a larger effectiveness trial.

Participants and Setting

The University of Pittsburgh Medical Center Children's Hospital of Pittsburgh Center for Adolescent and Young Adult Health (CAYAH) has 4 clinical sites (2 urban academic and 2 suburban community) staffed by 17 adolescent health care providers (AHCPs), including pediatricians specializing in adolescent medicine, nurse practitioners, physician assistants, and pediatric/adolescent gynecologists. AHCPs provide primary care and adolescent consultative services (eg, reproductive health, chronic disease management, and mental health concerns) for young people aged up to 26 years. Patients are routinely screened for depressive symptoms with PHQ-2 [46]; if positive, AHCPs use more extensive screening tools for depression (Patient Health Questionnaire, PHQ-9) [47,48] and anxiety (Generalized Anxiety Disorder, GAD-7) [49] and a brief clinical interview to aid with diagnosis. With an integrated behavioral health care model, licensed social workers and psychologists are available to provide therapy in clinic and work in an integrated fashion with social workers who provide brief counseling and care management. Owing to the availability of on-site mental health services and the focus of the SOVA intervention on addressing attitudinal and not access barriers, this setting was chosen for this initial pilot study. To enhance recruitment, an additional affiliated academic pediatric primary care clinic, which also has access to therapists and conducts routine screening for depression, will also be included. Throughout this manuscript, AHCP will also refer to these affiliated pediatric PCPs. Some individuals who initially accept a PCP referral do not follow through with the referral [15], and a dyad who initially refuses may eventually accept treatment. Hence, recruitment will not distinguish between treatment refusers and engagers, and dyads will be recruited based on the provider determination for the need for treatment.

Recruitment

The research team (RT) will notify AHCPs about the study through an announcement during a regularly scheduled faculty and staff meeting. Patients and parents seeking clinical services are routinely informed that they may be approached about research studies during their visit. In the waiting room and clinic rooms, recruitment posters will be visible, and a recruitment postcard will be available for patients and parents to enter their information and indicate interest in the study, as well as coloring bookmarks and colored pencils. AHCPs will receive the recruitment postcard from their patient, or they may be reminded about the study by a clinical social worker or an RT member. The back of the recruitment postcard will remind the AHCP (1) about the study inclusion criteria, that is "If you are referring this patient for depression or anxiety treatment of any kind (even a follow-up with you) and if they are between the ages of 12-19, they may qualify for the Stress and Worry study;" (2) to include a Stress and Worry patient education information in the electronic depart summary, that is a meaningful use requirement of the electronic health record (EHR) for the CAYAH clinical team; and (3) to ask the patient and parent if they want to stay after the visit to be screened. If they do want to stay to assess eligibility for the study, the AHCP can indicate the research assistant (RA) to come to the patient room, and if they do not

want to stay, they can enter the research postcard in a lockbox, and the patient and parent will be contacted at a later time. Recruitment goals are to recruit about 12 adolescents per month based on the clinic volume and projected number of adolescents who should be offered treatment from other clinical studies on adolescent depression.

Study Procedure

An RT member will use the EHR to prescreen patients, which will involve examining the EHR to confirm the inclusion or exclusion criteria that can be retrieved (see Textbox 1 for full inclusion or exclusion criteria). If criteria are met, then the RT member will proceed to contact interested patients or their parent. If in the clinic, the RT member will discuss this inclusion criteria with the referring AHCP prior to interacting with the patient and parent. Adolescents only up to 19 years are included, as the goal of the SOVA intervention is to encourage earlier initiation of treatment for depression or anxiety.

A waiver of parental permission was obtained from the Institutional Review Board for screening and study enrollment; this was asked for as the target population of the intervention includes adolescents who may have poor communication with their parent and, therefore, do not want to disclose symptoms of depression or anxiety, which would need to occur during the consent process during explanation of study purpose. For adolescents who wish to enroll in the study without their parent, all the same procedures below will be followed for the adolescent alone.

The RT member will then contact the patient and their parent if enrolled (if the RT member is available in the clinic, this will be done in-person, if not, it will be carried out over the phone). RT members will ask the adolescent screening questions from PHQ-9 and GAD-7 or obtain this information from the EHR. If an adolescent scores ≥5 on one or both PHQ-9 and GAD-7, consistent with mild symptoms, then the RT member will ask further inclusion and exclusion criteria. All study data will be collected in the Research Electronic Data Capture (REDCap), a secure Web application used to build and manage secure databases and includes capabilities, such as Web-based surveys, with branching logic and automatic scheduling, as well as randomization modules [50]. If an adolescent scores in the severe category (15-21) on the GAD-7 or severe (20-27) on the PHQ-9, the RT will contact the AHCP to assure that clinical care is in place.

If adolescents wish to enroll with their parent, the RT member will then obtain parental consent, and permission from the parent for the adolescent to participate in the study and assent from the adolescent (or consent from an adolescent aged ≥18 years) documented in REDCap. If adolescents wish to enroll without their parent, the RT member will obtain only adolescent assent. The RT member will notify participants regarding information for compensation, and the RT will ask them to provide a username they would like to use if they are randomized to SOVA. Then, participants will receive a baseline survey emailed from REDCap. Once the adolescent completes the baseline survey, the Principal Investigator or main RA will use the REDCap software to conduct permuted block randomization stratified by patient gender (male vs other owing to a lower number of males attending CAYAH) to randomize to one arm of the study SOVA+EUC or EUC alone. For each adolescent, if their parent is also enrolled, the parent will be assigned to the study arm the adolescent was randomized to. The randomization scheme has been generated by the statistician YL and will not be viewed by the rest of the RT. The AHCP and the RT member conducting 6-week and 3-month EHR data collection will be blinded to the study arm. Figure 2 shows a schema of the RCT design.

Control Arm

All study participants will receive EUC. EUC will include routine follow-up by one of the clinic social workers as is standard practice at CAYAH. The social worker tracks the treatment adherence (therapy attendance) and assists AHCPs with medication monitoring. The social worker offers to assist patients with an appointment, a process shown to increase the first appointment show rate but not increase the uptake rate (ie, the number of patients who schedule out of those referred) [51], but if patients are no longer interested in services, or multiple unsuccessful phone attempts are made (a frequent scenario), then the social worker communicates this with the referring medical provider.

As there is variability in the number of routine follow-ups each patient receives from the clinic social worker due to limited time or availability as well as due to enrolling from a pediatric primary care clinic with a slightly different procedure of following up with patients, we will further standardize EUC. In addition, each patient will receive an informational email from the secure research study email and a phone call from a team Moderator. Moderators are RT members who are volunteer graduate students with a background in social work or psychology who are supervised by the principal investigator (AR). They check for emails to the study account (emails are sent whenever there is new website activity), at least, every 3 hours. The informational email and phone call will be to convey the treatment that the AHCP recommended and ask the adolescent or parent if they are enrolled, if they have questions regarding this treatment, as well as how to contact their clinical team and crisis resources. If the adolescent or parent have questions, the Moderator will securely message the AHCP and CAYAH social worker the question and ask them to contact the adolescent or parent.

Intervention Arm

In addition to EUC, those participants (adolescents and parents) randomized to SOVA will receive a Web-based intervention. The websites for adolescents [52] and parents [53] are 2 separate websites where some content is public (the text of blog posts), but all social content (commenting on blog posts, creating a user profile) requires a username and log-in. All users will receive a separate username and password and adolescents will only log on to the adolescent site, and parents will only log on to the parent site. Every day, there is a new blog post published on the site. While some are written by the RT, others are written by SOVA Peer Ambassadors. These Peer Ambassadors are 14-26-year-old young people recruited to a separate study to understand the effects of blogging on psychological outcomes and resilience. Peer Ambassadors have a history of depression

or anxiety and are willing to anonymously share their personal experiences on the SOVA website. All content written by Ambassadors is screened, scheduled, and edited if need be by the RT. Peer Ambassadors are also encouraged to regularly comment on others' blog posts.

Textbox 1. Inclusion and exclusion criteria.

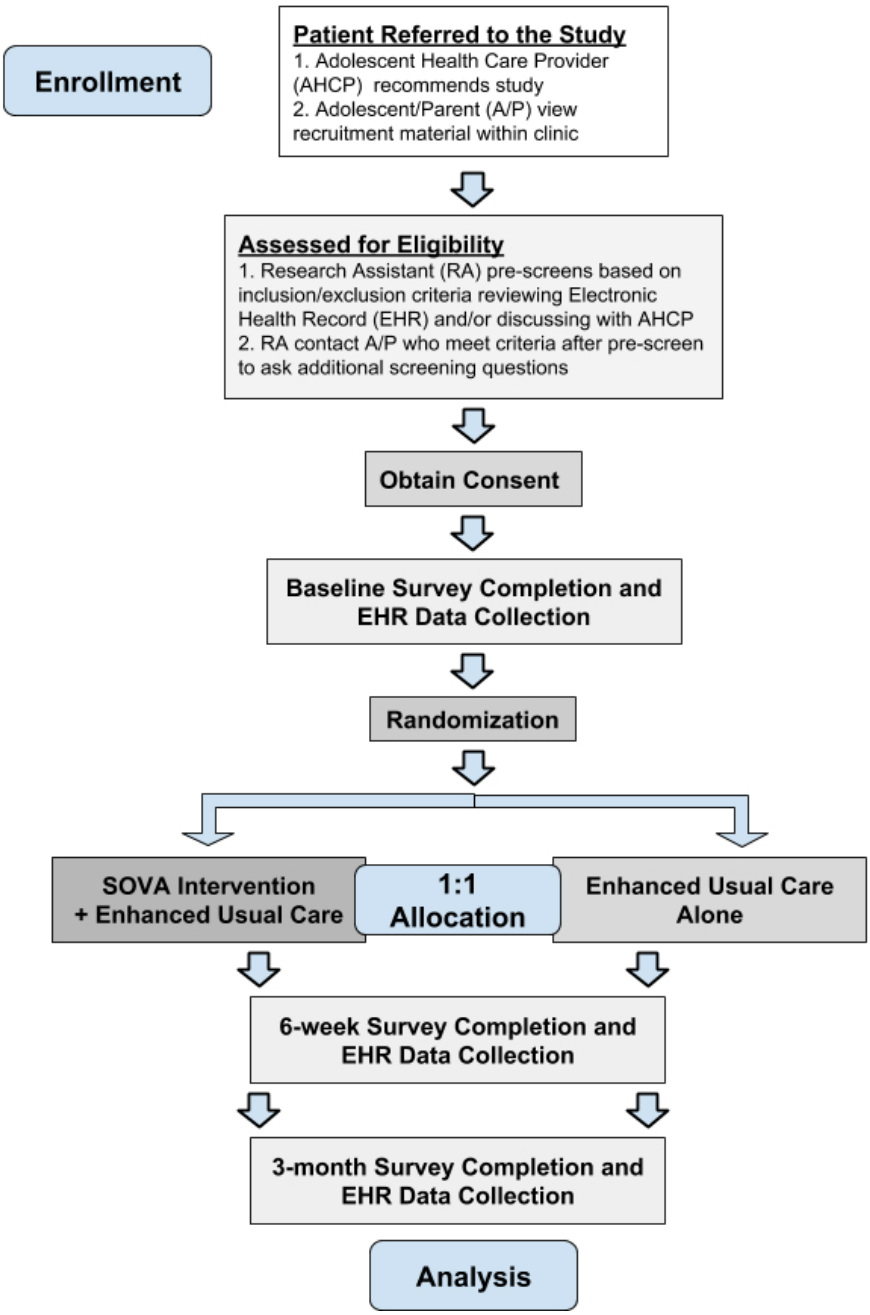
Inclusion criteria

- Adolescents
  - Aged 12-19 years
  - Adolescent health care provider (AHCP) identifies depressive and/or anxiety symptoms
  - Scores at least 5 or greater on the Patient Health Questionnaire (depression) and/or Generalized Anxiety Disorder 7-item scale (anxiety) consistent with at least mild symptoms
  - AHCP recommends adolescent to initiate a new treatment episode (no treatment in the past 3 months)
  - Can read and write in English
  - Has completed the 6th grade
  - Assent (<18 years of age) or consent to study (18 or 19 years of age)
- Parents
  - Adolescent child meets the inclusion and exclusion criteria and agrees to enroll in the study
  - Can read and write in English
  - Has completed the 6th grade
  - Consents to study
- ACHPs
  - Health care provider (physician, nurse practitioner, and physician assistant) providing clinical services
  - Consents to study

Exclusion criteria

- Adolescents
  - Actively suicidal requiring crisis or hospitalization defined as currently having suicidal thoughts and a plan and AHCP recommends immediate crisis services or evaluation for hospitalization
  - History of receiving a psychiatric medication and/or psychotherapy at least 3 times within 2 months for depression and/or anxiety in the past 3 months
  - No access to the internet
  - No active email account
- Parents
  - No access to the internet
  - No active email account
- ACHPs
  - None

Figure 2. Randomized controlled trial study design. SOVA: Supporting Our Valued Adolescents.



Each day of the work week is designated a blog topic theme—positive posts such as uplifting quotes or stories (Monday, eg, "A Kind Word"—a post about how it feels to hear something kind from someone else), psychoeducational posts that also address negative health beliefs (Tuesday, Wednesday, eg, "How to Discuss Hard Topics with Parents" and "When I Grow Up, I Don't Want to Be Like You"—an article discussing the impact of family mental health on whether you plan to seek help for your own), social media education posts (Thursday, eg, "Losing Sleep over FOMO"), and posts which describe other existing resources (Friday, eg, "Circle of 6"—a safety mobile app). Figure 3 presents an example of blog posts. The content on the adolescent website has a corresponding article of the same topic but modified for a parent audience on the parent website on the same day. This is to promote parent-adolescent conversation about the same type of content. Even Peer Ambassador posts are also published by the RT on the parent website so that parents may have insight into young people's perspectives.

Every week, each participant receives an email update with blurbs of the previous week's new posts. Currently, apps are available for Android devices of both websites that parents and adolescents can download. iPhone apps are in progress and may become available during the trial. Those who open the website regularly on the same computer or download the mobile app will also receive daily notifications of new blog post topics. On the adolescent site, users can only make comments under blog posts. If someone replies to their comment they can be notified. On the parent website, in addition to commenting, there is a discussion board feature as well, and again users are notified if

there are replies to their comments on blog posts or the discussion board.

During the Moderator phone call, in addition to the information provided as part of EUC, the Moderator will ask about whether adolescents or parents have tried out and any problems experienced using the websites, explain the purpose of and content available on the websites, the role of SOVA Peer Ambassadors, encourage participation, and explain the role of the Moderator, the ground rules or community guide, and reiterate that adolescent and parent sites are separate.

Figure 3. Examples of blog posts (source: SOVA, University of Pittsburgh).

For adolescents who enroll separately without their parent, we will still provide them with information to share about the wiseSOVA websites that they may provide to their parent; for EUC, adolescents will receive a letter they can provide to their parent listing the information described in the email. In this way, we will encourage parent-adolescent communication without artificially requiring it through the study consent process.

Measures

Pilot Study Main Outcome: Study Retention

The study retention rate, the proportion of adolescents who access the 6-week survey in proportion to those who access the baseline survey, will be the main pilot outcome. This pilot outcome will help for planning recruitment and retention goals for a larger future RCT.

Implementation Outcomes

We will also examine a crude implementation outcome to understand the AHCP fidelity to the intervention by measuring the overall number of adolescents receiving information about "Stress and Worry" in their depart summary and, if possible, compare with the overall International Classification of Diseases, 10th Revision, codes of depression or anxiety made for patients seeing providers at CAYAH. This templated "depart summary" is already a part of AHCPs' workflow as a quality measure [54] with 85% completion on average; AHCP's will be informed about the "Stress and Worry" patient education information, which AHCP's can elect to insert into their depart summaries. This patient education information has psychoeducation materials [55-57], a place to enter treatment recommendations, and information about the study. We will also determine the proportion of adolescents who show interest in the study compared with the number who receive "Stress and Worry" information in the depart summary. We will conduct posttrial interviews with AHCPs about the intervention acceptability.

Proposed Main Outcome: Mental Health Service Use

In this pilot study, multiple measures will be used to determine mental health service use, to determine which measure(s) to choose for a larger future trial. For this, we will conduct an EHR review to determine whether the medication was prescribed or filled and whether a therapist or PCP follow-up appointment(s) was attended. As some information may not be available in the EHR available to the hospital system—for example, a therapist who does not belong to the hospital system may have been seen—we will also use parent and adolescent self-report to determine services accessed by simply asking, "Have you (your child) received any treatment for depression or anxiety since the start of this study (this could include starting a new medication, seeing a professional to talk to, or follow up with your adolescent healthcare provider to talk about depression or anxiety)?" and, if yes, what treatment was received. This will be combined into one measure and mental health services accessed (yes or no) will be determined based on a positive response by either parent or adolescent, or as indicated by the EHR [14].

As multiple types of providers may be accessed when seeking help, we will use the General Help-Seeking Questionnaire [58] at the baseline to determine intention to seek help and the Actual Help-Seeking Questionnaire [59] at follow-up and after 3-months to determine what help was sought from whom.

Table 1 provides an overview of the measures, and Multimedia Appendix 1 provides a detailed description of the study measures. The proposed target mechanisms—health beliefs and knowledge about depression or anxiety, as well as peer emotional and informational support—will be measured in both adolescents and their parents. Furthermore, health beliefs will be elicited through measuring stigma and beliefs about antidepressants and therapy.

Planned Analysis

The main summary statistic sample size is based on the retention rate; a 95% CI will be calculated. Descriptive statistics (the percentage for proportions and means and SDs for continuous measures) will be presented for all feasibility (retention and site usage) and implementation measures. Outcome measures (listed in Multimedia Appendix 1) will be summarized by the study arm and evaluated for change (from the baseline to 6 weeks) in proposed target mechanisms using the chi-square test (for dichotomous outcomes) and 2-sample *t* tests (for continuous measures) separately for adolescents and parents. The number and percentage missing will be reported for each survey item. In addition, study arms will be assessed for balance across all covariates. Content analysis will be used to code Web-based peer-peer or peer-moderator interactions for social support (emotional, empathy, positive emotional self-disclosure, and expressions of concern) [67]. Furthermore, survey data regarding communication and relationship quality will be used to explore temporal associations between parents' and adolescents' change scores in communication quality by the arm using correlational analyses.

At CAYAH, 3845 unique patients aged 12-19 years were seen in 2017. If up to 29.9% (1153/3845) may be identified with symptoms of depression or anxiety [1,74] and 66.9% (2576/3845) may have not had treatment in the past 3 months [4], 20.0% (772/3845) would be eligible for the study over 1 year.

The main outcome is the study retention rate. We predict it will be at least 90%; with an estimated sample size of 150 adolescents (75 per arm), the 95% CI will be 85.2%-94.8%. This would be feasible as only one-fifth of eligible patients would need to enroll. We selected this sample size as the target for this pilot because this number may also facilitate meaningful Web-based peer interaction (ie, having sufficient users online at one time). This target sample size may be reduced based on the study timeline and actual recruitment rates, as this number would not be required for determining pilot outcomes.

Table 1. Measures to be obtained and proposed target mechanisms adolescents and parents.

Construct and method of operationalization	Measure	Timepoint		
		Baseline	6 weeks	3 months
Health beliefs				
1. Stigma	1. Depression Stigma Scale [60]	1, 2, 3	1, 2, 3	N/A[a]
2. Beliefs about antidepressants	2. Resistance to Antidepressant Use Questionnaire, Antidepressant Meanings Scale [61]	1, 2, 3	1, 2, 3	N/A
3. Beliefs about therapy	3a. Adolescent: Barriers to Adolescents Seeking Help [62,63]; 3b. Parent: Parental Barriers to Help Seeking Scale [64]	1, 2, 3	1, 2, 3	N/A
Mental health knowledge				
1. Depression knowledge	1. Depression Literacy Questionnaire [65]	1, 2	1, 2	N/A
2. Anxiety knowledge	2. Anxiety Literacy Questionnaire [65]	1, 2	1, 2	N/A
Peer emotional /informational support				
1. Perceived emotional/informational support	1. Emotional/Informational Subscale from the Medical Outcomes Study Social Support Survey [66]	1	1, 2	N/A
2. Actual/observed emotional/informational support	2. Online coding of peer and moderator comments for types of social support [67]	1	1, 2	N/A
Communication quality				
1. Parent-adolescent communication quality	1. Parent-Adolescent Communication Scale [68]	1	1	N/A
Perceived need for treatment				
1. Perceived need for treatment	1a. Open-ended question about whether adolescent/child needs any mental health service [21]; 1b. the General-Practice Users Perceived-Need Inventory [69]	1a, 1b	1a, 1b	N/A
Proposed main outcome: mental health service use				
1. Intention to seek services	1. General Help Seeking Questionnaire [58]			
2. Receipt of any mental health treatment	2a. Combined measure using Electronic Health Record Chart Review and parent/adolescent self-report [14]; 2b. Actual Help Seeking Questionnaire [58,59]	1	2a, 2b	N/A
Exploratory clinical outcomes				
1. Depressive Symptoms	1. Adolescent: Depressive Symptoms: Patient Health Questionnaire-9 item [47]	1, 2, 3, 5	1, 2, 3, 4a, 4b, 5	4a, 4b
2. Anxiety Symptoms	2. Adolescent: Anxiety Symptoms: Generalized Anxiety Disorder Scale-7 item [49]	1, 2, 3, 5	1, 2, 3, 4a, 4b, 5	4a, 4b
3. Functioning	3a. Adolescent: Multidimensional Adolescent Functioning Scale [70]; 3b. Parent: Columbia Impairment Scale-Parent [71]	1, 2, 3, 5	1, 2, 3, 4a, 4b, 5	4a, 4b
4. Continued mental health service use	4a. Combined measure using Electronic Health Record Chart Review and parent/adolescent self-report [14]; 4b. Actual Help Seeking Questionnaire [58,59]	1, 2, 3, 5	1, 2, 3, 4a, 4b, 5	4a, 4b
5. Relationship quality	5. Parent-child connectedness [72]			
Descriptive covariates				
1. Demographics	1. Age, gender, sexuality (adolescent only), race, ethnicity, education, health insurance (parent only – asked of child), transportation, socioeconomic status	1, 2, 3, 4a, 4b	4b	N/A
2. Treatment history	2. History of medication/therapy in adolescent [73]	1, 2, 3, 4a, 4b	4b	N/A
3. Treatment provider recommends	3. Chart review for treatment recommendation	1, 2, 3, 4a, 4b	4b	N/A
4a. Parental mental health history; 4b. Parental receipt of mental health treatment	4a. Parent: Parental self-report mental health history [14]; 4b. Parent: Actual Help Seeking Questionnaire [58,59]	1, 2, 3, 4a, 4b	4b	N/A

[a]N/A: not applicable.

Results

We expect to determine (1) the feasibility of retaining 90% of individuals for follow-up; (2) implementation outcomes estimating the intervention fidelity; (3) intervention engagement; (4) provider acceptability; (5) appropriateness of measures, amount of missingness; (6) adequacy of human subjects' plan; (7) change in target mechanisms; and (8) extent of Web-based social support achieved, measured by coded Web-based communications.

The University of Pittsburgh Human Research Protection Office provided ethics approval for this study (PRO17070601). It has been registered with ClinicalTrials.gov Protocol Registration and Results System (#NCT03318666).

The project was funded in 2017. Recruitment commenced in April 2018 and enrollment is ongoing, with completion anticipated at the end of 2019 with subsequent plans for data analysis and publication submission in early 2020.

Discussion

This paper describes the protocol for a pilot RCT of the SOVA intervention to refine recruitment and retention strategies, document intervention fidelity and implementation outcomes, and assess changes in health beliefs and knowledge, emotional or informational support, parent-adolescent communication quality, and perceived need for treatment. The findings of this research will inform the study design of a larger multisite hybrid effectiveness-implementation RCT examining the effectiveness of and optimal implementation strategies for using SOVA in community primary care settings. The main outcome measured in this larger trial will be whether SOVA increases the mental health service use compared with usual care. This research will help inform strategies to increase service use of evidence-based depression and anxiety treatments in adolescents and provide PCPs with a tool to address adolescent and parent concerns and attempt to increase their perceived need for treatment.

We considered several iterations of this study design with regards to setting and timing of the intervention. This study will be conducted in a clinical setting that already has an integrated behavioral health model in place. Hence, EUC may also have a strong effect on the proposed main outcome, mental health service use. As a pilot, this study was not designed to determine the effectiveness of SOVA. The specific setting was chosen because of the higher prevalence of primary care and consultative care patients seen with depression and anxiety symptoms who are referred for treatment, as this will facilitate recruitment and is not thought to influence measuring change in the target outcomes. Concurrently, we are conducting preimplementation focus groups in community pediatric primary care settings to inform how PCPs may want to introduce SOVA in that setting. This data will inform how to measure implementation outcomes and conduct a future large hybrid effectiveness-implementation trial in community primary care settings.

Another consideration of the study design was the timing of the intervention with relation to a clinic appointment. Ideally, patients and their parent should receive the intervention immediately after the clinic appointment, but due to requirements to screen, consent, and complete baseline surveys for both the parent and adolescent prior to randomization, this timing may be delayed. Our desire was to use a more pragmatic study design that would simulate how the intervention may be introduced in routine practice, but then place less burden on clinicians seeing patients and on parents and adolescents (eg, not requiring in-person completion of study measures and consent). Another design would have been prescreening or consenting patients prior to scheduled appointments. We will gather data on timing of intervention administration to clinician visit and use this to inform the study design of the larger RCT.

These pilot data are expected to inform the planning of a hybrid effectiveness-implementation study of a technology intervention that should facilitate the more rapid translation of study results into practice.

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Authors' Contributions

AR wrote the manuscript with guidance from the other authors. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed description of measures.
[PDF File (Adobe PDF File), 78KB - resprot_v8i1e12117_app1.pdf]

References

1. Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry 2010 Oct;49(10):980-989 [FREE Full text] [doi: 10.1016/j.jaac.2010.05.017] [Medline: 20855043]
2. Avenevoli S, Swendsen J, He J, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. J Am Acad Child Adolesc Psychiatry 2015 Jan;54(1):37-44.e2 [FREE Full text] [doi: 10.1016/j.jaac.2014.10.010] [Medline: 25524788]
3. Torio CM, Encinosa W, Berdahl T, McCormick MC, Simpson LA. Annual report on health care for children and youth in the United States: national estimates of cost, utilization and expenditures for children with mental health conditions. Acad Pediatr 2015;15(1):19-35. [doi: 10.1016/j.acap.2014.07.007] [Medline: 25444653]
4. Substance Abuse Mental Health Services Administration, National Survey on Drug Use and Health. 2009 Apr 28. The NSDUH Report: Major Depressive Episode Treatment among Adolescents URL: https://namirensco.files.wordpress.com/2015/01/x244x-adolescentdepressionhtml.pdf [accessed 2018-12-10] [WebCite Cache ID 74Z1JpCfP]
5. Wang PS, Berglund PA, Olfson M, Kessler RC. Delays in initial treatment contact after first onset of a mental disorder. Health Serv Res 2004 Apr;39(2):393-415 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00234.x] [Medline: 15032961]
6. Merikangas KR, He J, Burstein M, Swendsen J, Avenevoli S, Case B, et al. Service utilization for lifetime mental disorders in U.S. adolescents: results of the National Comorbidity Survey-Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry 2011 Jan;50(1):32-45 [FREE Full text] [doi: 10.1016/j.jaac.2010.10.006] [Medline: 21156268]
7. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004 Aug 18;292(7):807-820. [doi: 10.1001/jama.292.7.807] [Medline: 15315995]
8. O'Connor BC, Lewandowski RE, Rodriguez S, Tinoco A, Gardner W, Hoagwood K, et al. Usual Care for Adolescent Depression From Symptom Identification Through Treatment Initiation. JAMA Pediatr 2016 Apr;170(4):373-380 [FREE Full text] [doi: 10.1001/jamapediatrics.2015.4158] [Medline: 26832387]
9. Merikangas KR, He J, Rapoport J, Vitiello B, Olfson M. Medication use in US youth with mental disorders. JAMA Pediatr 2013 Feb;167(2):141-148. [doi: 10.1001/jamapediatrics.2013.431] [Medline: 23403911]
10. Keenan-Miller D, Hammen CL, Brennan PA. Health outcomes related to early adolescent depression. J Adolesc Health 2007 Sep;41(3):256-262 [FREE Full text] [doi: 10.1016/j.jadohealth.2007.03.015] [Medline: 17707295]
11. Richardson LP, Ludman E, McCauley E, Lindenbaum J, Larison C, Zhou C, et al. Collaborative care for adolescents with depression in primary care: a randomized clinical trial. JAMA 2014 Aug 27;312(8):809-816 [FREE Full text] [doi: 10.1001/jama.2014.9259] [Medline: 25157724]
12. Asarnow JR, Rozenman M, Wiblin J, Zeltzer L. Integrated Medical-Behavioral Care Compared With Usual Primary Care for Child and Adolescent Behavioral Health: A Meta-analysis. JAMA Pediatr 2015 Oct;169(10):929-937. [doi: 10.1001/jamapediatrics.2015.1141] [Medline: 26259143]
13. Anderson LE, Chen ML, Perrin JM, Van Cleave J. Outpatient Visits and Medication Prescribing for US Children With Mental Health Conditions. Pediatrics 2015 Nov;136(5):e1178-e1185 [FREE Full text] [doi: 10.1542/peds.2015-0807] [Medline: 26459647]
14. Breland DJ, McCarty CA, Zhou C, McCauley E, Rockhill C, Katon W, et al. Determinants of mental health service use among depressed adolescents. Gen Hosp Psychiatry 2014;36(3):296-301 [FREE Full text] [doi: 10.1016/j.genhosppsych.2013.12.003] [Medline: 24417955]
15. Hacker K, Arsenault L, Franco I, Shaligram D, Sidor M, Olfson M, et al. Referral and follow-up after mental health screening in commercially insured adolescents. J Adolesc Health 2014 Jul;55(1):17-23. [doi: 10.1016/j.jadohealth.2013.12.012] [Medline: 24525226]
16. Tanielian T, Jaycox LH, Paddock SM, Chandra A, Meredith LS, Burnam MA. Improving treatment seeking among adolescents with depression: understanding readiness for treatment. J Adolesc Health 2009 Nov;45(5):490-498. [doi: 10.1016/j.jadohealth.2009.03.005] [Medline: 19837356]
17. Van Voorhees BW, Cooper LA, Rost KM, Nutting P, Rubenstein LV, Meredith L, et al. Primary care patients with depression are less accepting of treatment than those seen by mental health specialists. J Gen Intern Med 2003 Dec;18(12):991-1000 [FREE Full text] [Medline: 14687257]
18. Dhingra SS, Zack M, Strine T, Pearson WS, Balluz L. Determining prevalence and correlates of psychiatric treatment with Andersen's behavioral model of health services use. Psychiatr Serv 2010 May;61(5):524-528. [doi: 10.1176/ps.2010.61.5.524] [Medline: 20439377]
19. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav 1995 Mar;36(1):1-10. [Medline: 7738325]
20. Wahlin T, Deane F. Discrepancies between parent- and adolescent-perceived problem severity and influences on help seeking from mental health services. Aust N Z J Psychiatry 2012 Jun;46(6):553-560. [doi: 10.1177/0004867412441929] [Medline: 22441205]
21. Wu P, Hoven CW, Cohen P, Liu X, Moore RE, Tiet Q, et al. Factors associated with use of mental health services for depression by children and adolescents. Psychiatr Serv 2001 Feb;52(2):189-195. [doi: 10.1176/appi.ps.52.2.189] [Medline: 11157117]

22. Breland DJ, McCarty CA, Zhou C, McCauley E, Rockhill C, Katon W, et al. Determinants of mental health service use among depressed adolescents. Gen Hosp Psychiatry 2014;36(3):296-301 [FREE Full text] [doi: 10.1016/j.genhosppsych.2013.12.003] [Medline: 24417955]
23. Mojtabai R, Olfson M, Sampson NA, Jin R, Druss B, Wang PS, et al. Barriers to mental health treatment: results from the National Comorbidity Survey Replication. Psychol Med 2011 Aug;41(8):1751-1761 [FREE Full text] [doi: 10.1017/S0033291710002291] [Medline: 21134315]
24. Radovic A, Reynolds K, McCauley HL, Sucato GS, Stein BD, Miller E. Parents' Role in Adolescent Depression Care: Primary Care Provider Perspectives. J Pediatr 2015 Oct;167(4):911-918 [FREE Full text] [doi: 10.1016/j.jpeds.2015.05.049] [Medline: 26143382]
25. Van Voorhees BW, Fogel J, Houston TK, Cooper LA, Wang N, Ford DE. Attitudes and illness factors associated with low perceived need for depression treatment among young adults. Soc Psychiatry Psychiatr Epidemiol 2006 Sep;41(9):746-754. [doi: 10.1007/s00127-006-0091-x] [Medline: 16896516]
26. Owens PL, Hoagwood K, Horwitz SM, Leaf PJ, Poduska JM, Kellam SG, et al. Barriers to children's mental health services. J Am Acad Child Adolesc Psychiatry 2002 Jun;41(6):731-738. [doi: 10.1097/00004583-200206000-00013] [Medline: 12049448]
27. Johnson EM, Coles ME. Failure and delay in treatment-seeking across anxiety disorders. Community Ment Health J 2013 Dec;49(6):668-674. [doi: 10.1007/s10597-012-9543-9] [Medline: 23054147]
28. Gulliver A, Griffiths KM, Christensen H. Perceived barriers and facilitators to mental health help-seeking in young people: a systematic review. BMC Psychiatry 2010 Dec 30;10:113 [FREE Full text] [doi: 10.1186/1471-244X-10-113] [Medline: 21192795]
29. Goldstein RB, Olfson M, Martens EG, Wolk SI. Subjective unmet need for mental health services in depressed children grown up. Adm Policy Ment Health 2006 Nov;33(6):666-673. [doi: 10.1007/s10488-006-0082-y] [Medline: 16823630]
30. Sawyer MG, Borojevic N, Ettridge KA, Spence SH, Sheffield J, Lynch J. Do help-seeking intentions during early adolescence vary for adolescents experiencing different levels of depressive symptoms? J Adolesc Health 2012 Mar;50(3):236-242. [doi: 10.1016/j.jadohealth.2011.06.009] [Medline: 22325128]
31. Davidson L, Bellamy C, Guy K, Miller R. Peer support among persons with severe mental illnesses: a review of evidence and experience. World Psychiatry 2012 Jun;11(2):123-128 [FREE Full text] [Medline: 22654945]
32. Blakemore S, Robbins TW. Decision-making in the adolescent brain. Nat Neurosci 2012 Sep;15(9):1184-1191. [doi: 10.1038/nn.3177] [Medline: 22929913]
33. Buckley GI, Malouff JM. Using modeling and vicarious reinforcement to produce more positive attitudes toward mental health treatment. J Psychol 2005 May;139(3):197-209. [Medline: 15945515]
34. Perlick DA, Nelson AH, Mattias K, Selzer J, Kalvin C, Wilber CH, et al. In our own voice-family companion: reducing self-stigma of family members of persons with serious mental illness. Psychiatr Serv 2011 Dec;62(12):1456-1462. [doi: 10.1176/appi.ps.001222011] [Medline: 22193793]
35. Berkowitz SA, Bell RA, Kravitz RL, Feldman MD. Vicarious experience affects patients' treatment preferences for depression. PLoS One 2012;7(2):e31269 [FREE Full text] [doi: 10.1371/journal.pone.0031269] [Medline: 22363603]
36. McMiller WP, Weisz JR. Help-seeking preceding mental health clinic intake among African-American, Latino, and Caucasian youths. J Am Acad Child Adolesc Psychiatry 1996 Aug;35(8):1086-1094. [doi: 10.1097/00004583-199608000-00020] [Medline: 8755806]
37. Kelleher KJ, Hoagwood K. Beyond Blame: Parents as Partners. J Pediatr 2015 Oct;167(4):795-796 [FREE Full text] [doi: 10.1016/j.jpeds.2015.07.039] [Medline: 26276224]
38. Williams KA, Chapman MV. Unmet health and mental health need among adolescents: the roles of sexual minority status and child-parent connectedness. Am J Orthopsychiatry 2012 Oct;82(4):473-481. [doi: 10.1111/j.1939-0025.2012.01182.x] [Medline: 23039345]
39. Logan DE, King CA. Parental identification of depression and mental health service use among depressed adolescents. J Am Acad Child Adolesc Psychiatry 2002 Mar;41(3):296-304. [doi: 10.1097/00004583-200203000-00009] [Medline: 11886024]
40. Seiffge-Krenke I. Problem intensity and disposition of adolescents to take therapeutic advice. In: Children at risk: Assessment, Longitudinal Research, and Intervention. Berlin: Walter de Gruyter; 1989.
41. Richardson LP, Russo JE, Lozano P, McCauley E, Katon W. Factors associated with detection and receipt of treatment for youth with depression and anxiety disorders. Acad Pediatr 2010;10(1):36-40 [FREE Full text] [doi: 10.1016/j.acap.2009.09.011] [Medline: 20129479]
42. Mueller J, Callanan MM, Greenwood K. Communications to children about mental illness and their role in stigma development: an integrative review. J Ment Health 2016;25(1):62-70. [doi: 10.3109/09638237.2015.1021899] [Medline: 26207330]
43. Locke J, Eichorn M. JED Foundation. 2008. Mental Health: What do Parents Think? URL: https://www.jedfoundation.org/assets/spectrumarticle-1224277531.pdf [accessed 2018-12-10] [WebCite Cache ID 74Z1NcOyH]

44. Radovic A, DeMand AL, Gmelin T, Stein BD, Miller E. SOVA: Design of a stakeholder informed social media website for depressed adolescents and their parents. J Technol Hum Serv 2018;35(3):169-182 [FREE Full text] [doi: 10.1080/15228835.2017.1347552] [Medline: 29743822]
45. Radovic A, Gmelin T, Hua J, Long C, Stein BD, Miller E. Supporting Our Valued Adolescents (SOVA), a Social Media Website for Adolescents with Depression and/or Anxiety: Technological Feasibility, Usability, and Acceptability Study. JMIR Ment Health 2018 Feb 26;5(1):e17 [FREE Full text] [doi: 10.2196/mental.9441] [Medline: 29483067]
46. Richardson LP, Rockhill C, Russo JE, Grossman DC, Richards J, McCarty C, et al. Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. Pediatrics 2010 May;125(5):e1097-e1103 [FREE Full text] [doi: 10.1542/peds.2009-2712] [Medline: 20368315]
47. 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] [Medline: 11556941]
48. 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 Mar;30(3):196-204. [Medline: 11869927]
49. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
50. 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]
51. Peters KM, Sadler G, Miller E, Radovic A. An Electronic Referral and Social Work Protocol to Improve Access to Mental Health Services. Pediatrics 2018 Nov;142(5). [doi: 10.1542/peds.2017-2417] [Medline: 30282783]
52. Supporting Our Valued Adolescents: A place to learn, share your strength, be positive, and grow. URL: https://sova.pitt.edu/ [accessed 2018-12-12] [WebCite Cache ID 74bVf4O6S]
53. WiseSOVA. URL: https://wisesova.pitt.edu/ [accessed 2018-12-12] [WebCite Cache ID 74bVuW8hb]
54. Reineck LA, Kahn JM. Quality measurement in the Affordable Care Act: a reaffirmed commitment to value in health care. Am J Respir Crit Care Med 2013 May 15;187(10):1038-1039. [doi: 10.1164/rccm.201302-0404ED] [Medline: 23675709]
55. National Institute of Mental Health. Anxiety Disorders URL: https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml [accessed 2018-12-10] [WebCite Cache ID 74Z0Naanx]
56. National Institute of Mental Health. Depression in Children and Adolescents (Fact Sheet) URL: https://www.nimh.nih.gov/health/publications/teen-depression/index.shtml [accessed 2018-12-10] [WebCite Cache ID 74Z0Rn5AN]
57. Psychiatry, American Academy of Child and Adolescent Psychiatry. Anxiety Disorders Resource Center URL: https://www.aacap.org/aacap/families_and_youth/resource_centers/Anxiety_Disorder_Resource_Center/Home.aspx [accessed 2018-12-10] [WebCite Cache ID 74Z0TYitg]
58. Rickwood D, Deane FP, Wilson CJ, Ciarrochi JV. Young people's help-seeking for mental health problems. Australian e-Journal for the Advancement of Mental Health 2005;4(3):34 [FREE Full text]
59. Rickwood DJ, Braithwaite VA. Social-psychological factors affecting help-seeking for emotional problems. Soc Sci Med 1994 Aug;39(4):563-572. [Medline: 7973856]
60. Griffiths KM, Christensen H, Jorm AF, Evans K, Groves C. Effect of web-based depression literacy and cognitive-behavioural therapy interventions on stigmatising attitudes to depression: randomised controlled trial. Br J Psychiatry 2004 Oct;185:342-349. [doi: 10.1192/bjp.185.4.342] [Medline: 15458995]
61. Cohane G. Psychological Barriers to Antidepressant Use in Adolescents, Dissertation for Clinical Psychology. Worcester, MA: Clark University; 2008.
62. Kuhl J, Jarkon-Horlick L, Morrissey R. Measuring Barriers to Help-Seeking Behavior in Adolescents. Journal of Youth and Adolescence 1997 Dec;26(6):637-650. [doi: 10.1023/A:1022367807715]
63. Wilson CJ, Deane FP, Ciarrochi J. Can hopelessness and adolescents' beliefs and attitudes about seeking help account for help negation? J Clin Psychol 2005 Dec;61(12):1525-1539. [doi: 10.1002/jclp.20206] [Medline: 16173086]
64. Bates L. Predictors of Help Seeking Among Early Adolescents: Stages and Factors? Electronic Theses and Dissertations. University of Windsor 2010:490 [FREE Full text]
65. Gulliver A, Griffiths KM, Christensen H, Mackinnon A, Calear AL, Parsons A, et al. Internet-based interventions to promote mental health help-seeking in elite athletes: an exploratory randomized controlled trial. J Med Internet Res 2012 Jun 29;14(3):e69 [FREE Full text] [doi: 10.2196/jmir.1864] [Medline: 22743352]
66. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med 1991;32(6):705-714. [Medline: 2035047]
67. Wang Y, Kraut RE, Levine JM. Eliciting and receiving online support: using computer-aided content analysis to examine the dynamics of online social support. J Med Internet Res 2015 Apr 20;17(4):e99 [FREE Full text] [doi: 10.2196/jmir.3558] [Medline: 25896033]
68. Barnes H, Olson DL. Family inventories: Inventories used in a national survey of families across the family life cycle. In: Olson DH, editor. Parent-adolescent communication scale. St Paul: Family Social Science, University of Minnesota; 1982:33-48.

69. McNab C, Meadows G. Brief assessment of perceived need for mental health care - development of an instrument for primary care use. In: National Depression Initiative. Australia: Monash University; 2004.
70. 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 Feb;52(2):195-200. [doi: 10.1016/j.jadohealth.2012.06.021] [Medline: 23332484]
71. Bird HR, Canino G, Rubio-Stipec M, Ribera JC. Further measures of the psychometric properties of the Children's Global Assessment Scale. Arch Gen Psychiatry 1987 Sep;44(9):821-824. [Medline: 3632256]
72. Lezin N, Rolleri LA, Bean S, Talor J. Parent-child connectedness: Implications for research, interventions and positive impacts on adolescent health. ETR Associates 2004 [FREE Full text]
73. Carlton PA, Deane FP. Impact of attitudes and suicidal ideation on adolescents' intentions to seek professional psychological help. J Adolesc 2000 Feb;23(1):35-45. [doi: 10.1006/jado.1999.0299] [Medline: 10700370]
74. SAMSHA. The NSDUH Report: Substance Use Mental Health Estimates from the 2013 National Survey on Drug Use Health: Overview of Findings. Substance Abuse Mental Health Services Administration Center or Behavioral Health Statistics Quality 2014 [FREE Full text]

Abbreviations

AHCP: adolescent health care provider
CAYAH: Center for Adolescent and Young Adult Health
EHR: electronic health record
EUC: enhanced usual care
GAD-7: Generalized Anxiety Disorder Scale 7-item
PCP: primary care provider
PHQ-9: Patient Health Questionnaire 9-item
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RT: research team
SOVA: Supporting Our Valued Adolescents

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Original Paper

The Development and Testing of a Relationship Skills Intervention to Improve HIV Prevention Uptake Among Young Gay, Bisexual, and Other Men Who Have Sex With Men and Their Primary Partners (We Prevent): Protocol for a Randomized Controlled Trial

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Abstract

Background: Young gay, bisexual, and other men who have sex with men (YMSM) continue to be the group most heavily impacted by HIV in the United States. Substantial evidence indicates that up to two-thirds of new HIV infections occur in the context of a main partnership. Couples HIV testing and counseling (CHTC) has been shown to be a promising and effective strategy for increasing HIV prevention uptake among male couples; however, YMSM who are new to relationships may not have yet developed the efficacy, negotiation, and communication skills to navigate HIV testing in their relationship and communicate around developing a prevention plan.

Objective: This study aims to develop and test a relationship skills–focused HIV prevention intervention for YMSM and their partners. The intervention consists of two telehealth-delivered sessions: the first focuses on relationship skills and the second consists of CHTC and prevention planning. Both sessions are attended by both members of the dyad.

Methods: This protocol describes the development of the proposed intervention (*We Prevent*) and pilot test to examine its feasibility and preliminary efficacy. The intervention will include two motivational interviewing–based sessions: session one is a relationship skills–building session, focused on techniques to explore and build communication skills in a relationship, to help YMSM develop and enhance necessary skills for their current and future relationships; the second session is a CHTC session with YMSM and their partners, to help them develop an HIV prevention plan. Through qualitative data collection and a one-arm pilot with YMSM, we will develop and refine a developmentally appropriate relationship skills session as an addition to the current CHTC intervention. We will then conduct a pilot randomized controlled trial (RCT), comparing the acceptability, feasibility, and preliminary efficacy of the adapted two-session telehealth intervention for YMSM versus a control group receiving one session only—a CHTC session delivered via telehealth.

Results: The *We Prevent* intervention is designed to increase uptake of HIV prevention, shown through self-reported reductions in condomless sex and increases in knowledge and uptake of pre-exposure prophylaxis. In addition, the intervention is designed

to increase HIV and sexually transmitted infection (STI) testing. STI incidence is examined as a secondary outcome. A cost-input analysis will examine the costs associated with intervention delivery to inform future scale-up of the intervention.

Conclusions: Drawing on theory and existing CHTC protocols delivered with video-based counseling, this proposed intervention affords the opportunity to empower YMSM with the skills necessary to communicate with their partners and protect themselves from HIV in their current and future relationships.

Trial Registration: Clinicaltrials.gov NCT03551938; https://clinicaltrials.gov/ct2/show/NCT03551938 (Archived by WebCite at http://www.webcitation.org/73omJCz1a)

International Registered Report Identifier (IRRID): RR1-10.2196/10370

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KEYWORDS

HIV; telehealth; men who have sex with men; adolescents; couples

Introduction

Background

Young gay, bisexual, and other men who have sex with men (YMSM) continue to be the group most heavily affected by HIV/AIDS in the United States [1,2], with increasing incidence of HIV identified among YMSM of color, specifically African-American and Latino youth [1]. Approximately 14% of youth living with HIV are estimated to be unaware of their serostatus, of whom 52% are those assigned a male sex at birth and have sex with men [1].

A number of individual and social factors (eg, substance use, mental health, poverty, stigma, incarceration, and homelessness) have been associated with increased HIV incidence among YMSM [3]. Notably, epidemiological evidence illustrates that up to 80% of new HIV infections occur from primary partners among YMSM [4,5], highlighting the urgent need to attend to the relationship context of HIV transmission in this population [6].

Numerous studies suggest that individuals are more likely to have condomless anal sex (CAS) with their primary partner as compared with casual partners [4,7], and relationship factors such as intimacy, closeness, and trust have been identified as powerful motivators for CAS in relationships [8-10]. For many individuals, there might be an underlying belief that condoms are antithetical to intimacy and that having condomless sex with their partners connotes an act of intimacy [11,12]. However, increased HIV transmission risk among YMSM may occur when a partner lacks knowledge of their own or their partner's serostatus before engaging in CAS [13-18]. For example, studies have estimated that more than 80% of HIV-negative YMSM practice CAS within their relationships [14,18]. Furthermore, some of these young men also engage in CAS outside of their relationship (ie, concurrent CAS). Engagement in CAS (monogamous or concurrent) combined with low rates of testing for HIV and other sexually transmitted infections (STIs), without confirming one's own or a partner's HIV serostatus as negative, heightens YMSM's vulnerability to HIV and other STIs [14,15,18,19].

Despite mounting evidence that dyadic approaches are generally efficacious in promoting safer sex behaviors in adult populations [20-22], few dyadic HIV prevention interventions exist for YMSM in relationships [20,23]. To date, couples HIV testing and counseling (CHTC) represents one of the very few effective couples-focused HIV prevention interventions for male couples. CHTC has been used as an HIV prevention for heterosexual couples in Africa for over 20 years [24] and was adapted for male couples in the United States [25-27]. CHTC has been shown to be effective for male couples in promoting the formation and adherence to prevention planning. It is now endorsed by the Centers for Disease Control and Prevention (CDC) as an effective HIV prevention strategy and is being used across the United States [25,28]. In contrast to individual HIV testing and counseling, CHTC includes both partners in 1 session where they receive counseling and testing together at the same time. Specifically, in the single 30- to 60-min CHTC session, the counselor learns about the couples' relationship and provides tailored counseling and prevention recommendations based on the relationship and serostatus results [24,26].

Although CHTC holds promise in reducing HIV incidence among male couples in general, young male couples may lack the behavioral skills necessary to undergo HIV testing with their partner. YMSM report infrequent HIV testing, even when CAS has occurred with outside partners [29,30]. With few exceptions [31], the majority HIV prevention strategies aimed at YMSM have focused in large part on reducing condomless sex with casual partners [32], effectively ignoring the role of relationships in shaping HIV risk. Thus, YMSM may not perceive themselves to be at risk of HIV acquisition from their primary partner and may lack skills, such as assertive and effective communication, around negotiating relationship dynamics [33]. These factors may limit their uptake of CHTC.

HIV prevention interventions are beginning to recognize the role of relationship factors in shaping HIV risk, although they remain largely focused on adult men who have sex with men (MSM). One example is the 2GETHER intervention that was developed and pilot tested with same-sex male couples aged 18 to 29 years [31]. The 2GETHER intervention involved in-person group format and in-person couples sessions, providing relationship and HIV prevention education to adult male couples in an effort to increase knowledge, motivation, and behavioral skills among male dyads. The 2GETHER intervention demonstrated preliminary efficacy in reducing sexual risk behaviors [31]. 2GETHER focused on building behavioral skills

within relationships among 18 to 29-year-old male dyads and, although perhaps still considered young adults, 18- to 29-year-olds have more relationship and life experiences than younger adolescents. Youth, aged 15 to 19 years, the target for the *We Prevent* intervention, are often just beginning to explore relationships; they thus have a very different set of informational, behavioral, and developmental needs. 2GETHER did not consider the unique developmental needs of MSM below the age of 18 years. *We Prevent* aims to fill this intervention gap through an intervention tailored to the specific needs of 15- to 19-year-old male dyads. By providing a web-based intervention, unlike the in-person format of 2GETHER, *We Prevent* also aims to allow young male couples to receive interventions in an environment in which they feel comfortable, surmounting structural barriers to accessing services.

Accumulating evidence also supports the efficacy of motivationally focused behavioral interventions to reduce HIV transmission risk among YMSM who may not perceive themselves to be at risk for HIV [34,35]. Therefore, motivational interviewing (MI) techniques may be particularly helpful alongside relationship and HIV prevention education to help YMSM develop the skills necessary to navigate the complexities of HIV prevention in their romantic relationships. In addition, the reach of in-person interventions may be restricted by general barriers to dissemination and implementation (eg, cost and highly skilled counselors) [36] as well as the social context of YMSM (eg, fears of being *outed* in their immediate geographical locale) [35,37]. Given the promise of brief technology-delivered interventions (eg, Keep It Up!) [38] and the transitory nature of relationships at this age, younger MSM may benefit from brief online interventions designed to address their relationship and HIV prevention needs.

The proposed intervention, *We Prevent*, will be delivered to young male dyads. The intervention itself, however, is conceptualized as an individual intervention, whereby the aim is to examine how the experience of testing with a male partner, along with relationships-specific skills building, can promote the development of relationship skills that have a long-term influence on the individual's relationships and, subsequently, their engagement in HIV prevention and care. That is, the intervention is intended to create behavioral change at the individual level; although participants receive the intervention as a dyad, it is expected that many relationships in this age group are relatively short in length. The *We Prevent* intervention thus aims to equip individuals with relationship skills to use in their current and future relationships.

As described above, YMSM often rely on online technologies to build their social and sexual networks, receive social support, and obtain relevant health information. In general, internet use among youth and young adults aged 15 to 29 years is nearly universal, at 99% in 2016 [37,39]. Thus, telehealth offers the opportunity to disseminate HIV prevention strategies to YMSM who might otherwise not have this opportunity. Telehealth aims to circumvent traditional impediments to health care access. Over the past decade, telehealth formats have been adapted for use in MSM populations where stigma and a lack of lesbian, gay, bisexual, transgender, queer (LGBTQ)–friendly health care providers contribute to reduced access to care [40]. Online interventions are seen as convenient for youth users and allow for home-based access to health messaging, thereby reducing fears of embarrassment or *outing* by connecting with local resources [36,41]. Recently, CHTC was adapted and is currently being tested using telehealth, specifically videoconferencing software, with preliminary evidence showing high feasibility and acceptability [26]. Both sessions of the *We Prevent* intervention will be delivered virtually via a Health Insurance Portability and Accountability Act (HIPAA)–compliant remote video chat service.

Theoretical Framework For We Prevent

We Prevent draws on the Relationship-Oriented Information-Motivation-Behavioral Skills (RELO-IMB) model [42], which is premised on the IMB model [43]. RELO-IMB was developed for YMSM communities [31]. The *Information* component of the RELO-IMB model is addressed by targeting YMSM-specific knowledge (eg, risk within dyads and with outside partners), *Motivation* is targeted by addressing attitudes and peer norms about HIV prevention in relationships, and *Behavioral Skills* is targeted by addressing risk-reduction skills relevant to YMSM and their partners (eg, discussion about safer sex, HIV testing, and negotiating safety in one's sexual agreement).

We Prevent uses MI techniques and includes 2 sessions: session one—a motivational interview-guided session that provides a facilitated discussion between YMSM and their partner, in which they explore and come to understand their own HIV risk and learn behavioral skills to improve communication—and session two—a CHTC session between the same YMSM and their partner, which facilitates the development of a prevention plan that meets the goals of both partners. In contrast to existing couples-based HIV prevention interventions, *We Prevent* is conceptualized as an individual intervention, whereby the aim is to promote development of relationship skills that can have a long-term influence on the individual's relationships and, subsequently, their engagement in HIV prevention and care.

Accordingly, we hypothesize that YMSM and their partners who engage in *We Prevent* will demonstrate reductions in sexual risk (eg, STI incidence) and greater knowledge and awareness of different prevention options (eg, knowledge of pre-exposure prophylaxis [PrEP] and the importance of repeat STI and HIV testing). We also hypothesize that YMSM who engage in *We Prevent* will demonstrate greater communication skills to use in their relationship, which will provide them with greater self-efficacy for developing an HIV prevention plan with their partner.

Aims and Objectives

The aim of this paper was to describe the protocol for the refinement, pilot testing, and pilot randomized controlled trial (RCT) to examine the acceptability and feasibility of the *We Prevent* intervention.

We Prevent will work closely with the innovative technology (iTech) cores on the development, testing, and analysis elements of each of the 3 phases of research activities described below. Although recruitment is not restricted to the iTech subject recruitment venues (SRVs), the iTech technology core (TC) will provide guidance on the technology necessary for

recruitment and retention strategies as well as technology-related ethical issues for conducting the project with YMSM and their partners. The iTech analytic core (AC) will provide oversight for qualitative and quantitative analyses, including cost affordability analyses. The iTech management core will provide assistance with recruitment and regulatory compliance.

Methods

Trial Registration, Ethics, Consent, and Institutional Board Approval

This study has been reviewed and approved by the University of North Carolina Institutional Review Board (IRB# 18-0200). Reliance agreements were established for each SRV. A certificate of confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent/assent will be obtained for participants aged 15 to 17 years. The study will also be registered on ClinicalTrials.gov.

Overview of Study Design

The study includes 3 phases. Phase I will collect qualitative data from YMSM and feedback from technical experts to develop and refine the 2 sessions the intervention comprises. Phase II involves a one-arm pilot of *We Prevent*, where we will examine the feasibility and acceptability of the intervention as well as its impact on self-reported HIV and STI testing and PrEP knowledge and uptake. We will also analyze the intervention's impact on STI and condomless sex incidence. Phase II will enroll 20 YMSM couples (40 individuals) using online recruitment strategies. Phase III involves a pilot RCT of *We Prevent* (experimental condition) compared with the existing CHTC intervention only (control condition). The pilot RCT will recruit 160 YMSM and their partners (ie, 320 individuals), randomized 1:1 to the intervention and control groups. Primary outcomes of the pilot RCT include uptake of HIV prevention, defined as self-reported routine HIV and STI testing, increased PrEP knowledge and use, and reductions in condomless sex. STI incidence is examined as a secondary outcome, with biomarkers of STIs collected through self-samples that are mailed in by participants. Data on costs associated with the delivery of the intervention are collected to allow a cost analysis to inform the future scale-up of the intervention.

Participants

For all phases, participants must be (1) between the ages of 15 and 19 years; however, the age of recruitment will vary by state because of variations in state consent law such that in some states we will not be able to recruit participants who are as young as 15 years; (2) identify that they are in an emotional and/or sexual relationship with another male (assessed through multiple questions); (3) born male and identify as male; (4) report that they engaged in CAS in their lifetime; (5) are willing to have HIV and STI testing kits delivered to an address that they provide (for phases II and III); (6) have access to a computer with internet access within their home (or the home of one partner); and (7) self-report being HIV negative or unknown serostatus. Male partners must meet the same criteria with the exception of the age restriction and HIV status. We will exclude those who report a recent (within the past 6 months) history of any intimate partner violence, using methods specifically designed for use with male couples, which involves continuously monitoring the presence of intimate partner violence at each assessment point [44]. Partners' age criteria will vary by state laws regarding age of consent laws and statutory rape laws such that we will not be able to recruit some partners who are as young as 15 years in some states (eg, California) or 2 years older than a participant in other states (eg, Colorado).

Recruitment

For all phases, participants will be recruited from across the United States via online advertisements placed on key social media websites (eg, Facebook) and social media sites aimed specifically at MSM (eg, Grindr). Working with iTech TC, the online ads will show visual representations of young male couples in a range of races/ethnicities and will be titled *We Prevent*.

YMSM who click on the advertisement will be taken to a Web page that provides basic information on the study. YMSM proceed to an assent Web page and provide an electronic assent/consent. After assent/consent, YMSM will complete a short screener to assess eligibility and will provide their and their partner's contact information. YMSM who do not provide assent/consent, meet the eligibility criteria, or provide complete contact information will be excluded from the study and be redirected to the online CDC HIV toolkit.

Eligible YMSM will continue by registering. During the registration process, they will provide their contact information and a nickname or name of choice. YMSM who register will be provided with a link via email to allow them to continue to set up an account by selecting a username, password, and security questions. Once the index case (the YMSM who initially clicks on the advertisement) and their partner have both completed the assent forms and the screening questionnaire, both partners have proven eligible for the study, and both have registered on the study website, emails will be sent to the participants detailing the information for their next steps of project participation. For phases II and III, couples' eligibility will be verified post hoc by assessing concordance in both partners' responses to items in the eligibility screener. These post hoc verification procedures have been successfully used in other studies with male couples [45]. Study staff will follow up with a phone call to go over study logistics and will confirm the contact information for each participant. We have been granted a waiver of parental consent for youth aged 15 to 17 years. During the call, the study staff member will review the consent process to ensure they understood their rights and the details of their participation. For phases II and III of the study, participants will be asked to provide a mailing address to receive HIV testing kits (for the second intervention session) and STI testing kits (for the assessment of STI incidence as a secondary outcome). Participants are informed that they can choose any address other than a post office box. In a recent feasibility of home-based HIV testing and remote video counseling with transgender youth aged 15 to 24 years, 100% of the 201 participants provided a delivery address for HIV testing kits,

100% received the kits, and 98% reported their HIV test results [46]. Tests kits are delivered in unmarked boxes, and participants are informed of their delivery date. We will use similar procedures to ensure the safety of participants in phases II and III of the activities.

Phase I Study Procedures

The first phase involves in-depth interviews (IDIs) with YMSM, technical expert group (TEG) reviews, and theater testing and cognitive review of the intervention. These data will be used to revise the content and study procedures in preparation for implementation.

In-depth Interviews With Young Men Who Have Sex With Men

For this task, 40 YMSM will be recruited to participate in IDIs using the recruitment methodology and eligibility criteria outlined above. Partners of index participants will not be recruited or engage in phase I activities. The 40 YMSM will be stratified by race: 10 white, 15 Latino, and 15 black. The IDI will be conducted via VSee, a HIPAA secure video chat software that will also be used to deliver the intervention and that has been used in prior studies [26].

One way that participants can actively guide a qualitative interview process is through the use of activities in which participants are given guidelines or instructions by the researcher but then take control of the activity in a flexible and participant-centered approach. Qualitative data collection involving visualizations can be useful to convey depth and detail that expand beyond verbal expression [47].

The IDI will adopt such a participatory methods approach. During the IDI, participants will create a visual relationship timeline using virtual stickers to develop an overview of their dating and sexual history. The IDI follows a step-by-step process where participants place stickers on the timeline in response to questions about relationship dynamics, desires, and communication. To construct the timeline, participants will add nonidentifying nicknames for up to 5 "sexual and/or romantic partners" who were "significant or memorable" to the participant in some way; participants will define for themselves what "significant or memorable" means.

The timeline begins when the participant first met the earliest partner and ends at the present time. Lines are added to show when and how long each relationship occurred. Participants are given flexibility on how to draw the lines to best represent the timeline of their relationship history (eg, participants could choose to use different types of lines to represent different parts of the relationship, lines could stop and start again, and lines for different people could overlap over the same time period).

Participants then answer a series of questions on each relationship through an action-oriented process that involves applying stickers with predetermined labels to the timelines. Participants will first use "relationship tag" stickers with definition terms (eg, partner, boyfriend, and friends with benefits). Follow-up questions examine why terms were chosen, definitions of terms, relationship development and transitions, and relationship rules (eg, monogamous vs open relationship). Participants then answer the question, "How did you feel about this person when you were together?" by adding up to 5 positive and/or negative "emotion tags" for each partner (eg, trusting, loved, disrespected, and not myself).

The timeline provides an anchor for discussion around relationship communication, negotiation, and desires. Using the timeline, participants will be asked to define what a relationship is, their definition of a successful relationship, and their desires for future relationships. Participants will be asked to describe positive and negative experiences they have had in communicating within relationships. The IDI will ask participants to outline the communication skills they believe they have and the communication skills they desire to have. It will end by asking the participants to describe their desired content and quality for a relationship skills–focused facilitated session. The goals and suggested outline of the session will be described, and participants will be asked to make suggestions for specific content areas.

Adaptation and Technical Expert Review

On the basis of findings from the IDI, the content of the relationship skills session will be developed, and the adaptation of the existing CHTC session will occur. The adaptation of the intervention is to ensure that the content is developmentally appropriate (eg, language and content) and the relationship skills building session meets the needs of YMSM aged 15 to 19 years. A TEG will be formed, consisting of members who engage with diverse communities of YMSM and have experience in the provision of HIV and LGBTQ clinical and social services.

After modifying the intervention content, a series of meetings will be scheduled individually with the TEG members to (1) review the intervention content and training protocols for the 2 counseling sessions and (2) explore existing screening and assessment tools that are culturally and linguistically appropriate for use with diverse groups of YMSM and their partners. VSee video chat will be used for TEG discussions focused on the adaptation of intervention assessments and content as well as the development or provision of feedback associated with the counseling components of the intervention.

In addition, a youth advisory board (YAB) of approximately 8 YMSM who meet the same eligibility criteria as for research participants will be convened. The YAB will be involved in providing feedback on the adaptation of the intervention and study protocols. They will be asked to meet the investigative team 2 to 3 times during the adaptation phase as well as provide feedback on different aspects of the project, including feedback on logo and recruitment materials, website design, website content, and intervention language.

Theatre Testing and Cognitive Review

To develop, refine, and standardize the intervention's content, we will use best practices in usability testing to examine the preliminary intervention. Individual usability interviews with YMSM (n=10) will be conducted using the same recruitment procedures outlined in the IDI stage above. During usability interviews, the moderator will walk the participant through each portion of the intervention manual. Similar to cognitive interviews, they will be asked to think aloud as they navigate

through the intervention. The moderator will note the participant's behavior and any questions that they have regarding the content and flow. As they navigate through the intervention, recordings will be made of any nonverbal behavior that could be important to take into consideration (eg, frowns, sighs, or fidgeting). Recordings will be made of valuable data related to how they respond to each module (eg, how long does it take participants to understand and respond to different modules?). These data will be used as exploratory indicators of content difficulty, attentiveness, and task difficulty. After participants have completed the assessment, they will be asked to reflect on whether the intervention met or exceeded their expectations and their HIV prevention and relationship needs. These data will be used to revise content and study procedures in preparation for implementation.

Phase I Data Analyses

All video interviews will be audio-recorded and transcribed verbatim. With guidance from the iTech AC, we will use framework analyses for all qualitative analyses [48]. Framework analyses are systematic and dynamic in their approach to qualitative data, resulting in the ability to produce accessible analyses focused on specific research questions. The thematic framework will be refined for coding by reading and rereading the data, identifying themes that emerge, and writing analytical memos about those themes. Next, specific sections will be identified that corresponded to particular themes. Finally, we will refine the relationship between indexed data and the original thematic framework, interpreting the resulting themes. Reliability among the coders will be checked by having each coder code a subset of transcripts, with acceptable agreement defined as ≥90% reliability. Disagreements will be resolved through discussion with a third party. Qualitative analyses will involve identifying and summarizing patterns of experiences related to the intervention manual and identifying how to improve the intervention. The study team will review the analysis of qualitative data and assess the strengths and weaknesses of each of the components of the intervention manual based on the findings. The research team will meet TEG and YAB to share results and discuss how best to improve the intervention modules, exercises, and process.

Phase II Study Procedures

We will conduct a one-arm pilot of *We Prevent* to examine the acceptability and feasibility of the intervention and examine the impact of the intervention on increasing self-reported HIV and STI testing and PrEP knowledge and use. We will also examine the feasibility and acceptability of home STI collection kits for laboratory-confirmed STI incidence. These study findings will be used to inform any necessary modifications to phase III RCT. Phase II will be a prospective study, enrolling a sample of 20 YMSM couples (40 individuals). Recruitment and eligibility screening will mirror the procedures for phase I. As described above, couples' eligibility to enroll in the study will be verified post hoc by assessing both partners' responses to items in the eligibility screener for phases II and III. After the completion of the second intervention session, both participants will complete an immediate self-administered follow-up survey and qualitative exit interview as well as 3-month follow-up surveys and STI home tests.

Recruitment, Registration, and Retention

After registering, assented participants will complete a 25-min baseline questionnaire. For interventions to be evaluated as potential *best evidence* –based interventions through CDC's Prevention Synthesis Research activity, data must be available for at least a single follow-up time point for at least 70% of participants. We will use best practices to retain participants (eg, comprehensive locator information that includes participants' cell phone numbers and email), while being sensitive to the risk of undue disclosure of YMSM participating in the study. A certificate of confidentiality will be obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent/assent will be obtained for participants aged 15 to 17 years. In addition, we allow participants to specify the day of the week and time of day when they would like to receive electronic follow-up surveys. Depending on the participant's preferences provided upon registration, contacts will be made initially with the preferred mode of recontact (eg, by short message service text message); if still unresponsive, other available modes (eg, phone call) will be used.

Recruitment and retention activities will be monitored through a participant management system that maintains electronic lists of participants' retention status and automatically creates notification lists for retention staff to ensure that a systematic process is followed and carefully documented for retention. We will follow YMSM for 3 months. The short time frames between assessments help us to respond quickly to retention concerns. Incentives for completing the baseline and follow-ups will be US $40 per assessment.

Index participants and their partners will first complete the baseline survey and then be taken to an online calendar asking them to schedule their first intervention session. The calendar will be populated by study staff per their availability and will reflect local time zones. The page will explain the 2-session intervention format, will provide detailed instructions on downloading the VSee video chat software, and will contain a list of instructions for receiving the intervention (ie, both partners must be together, audio and visual privacy). The VSee software can be used on a personal computer, tablet, or any mobile platform [26]. After the first session, the index participant and their partner will be mailed an HIV testing kit to be used in their second session.

Intervention Condition

The intervention consists of 2 45-min sessions, timed approximately 2 weeks apart. The first session will focus on defining healthy and unhealthy characteristics of relationships, teaching and practicing effective communication skills, reviewing couples-based sexual health information (ie, negotiated safety, PrEP, and HIV and STI testing), and preparing for engaging in CHTC as a couple. The second session—the CHTC session—will follow a similar format to the existing CHTC counseling protocols, the same format as provided to couples in the control condition (ie, pretest counseling, HIV

testing, discussion of HIV risks, delivery of test results, and posttest counseling). Specifically, both *We Prevent* sessions are designed to help YMSM and their partners learn and practice communication skills and set goals regarding HIV prevention and care that can be used throughout their lives.

Participants who receive an HIV-positive result will be counseled on the need for timely linkage to care. The counselor will arrange a time within 1 week of the initial session to conduct a second video session for couples in which one or both of them have preliminary positive results. During this session, new preliminary positives will be directly linked to medical care in their local area. Study staff will follow up with them on the next business day to ensure that contact was made with a local facility closest to where the participant lives or with a medical care agency. The participant would be contacted at least three times to (1) confirm an appointment was scheduled, (2) confirm the appointment was attended, and (3) report confirmatory results.

Team Review and Data Analyses

All sessions and qualitative exit interviews will be audiotaped (with participant consent). Audiotapes will be reviewed by the investigative team, TEG, and members of the iTech AC. This team will conduct a conference call every other week to assess the strengths and weaknesses of the intervention components and indicate revisions to the preliminary protocol. At the completion of intervention for each dyad, the review will focus on potential changes to the protocol (eg, content and timing of interventions and sessions) that will be implemented before the next set of participants starting the intervention. This process will lead to a finalized version of the *We Prevent* manual. We will then examine the impact of the *We Prevent* intervention condition on feasibility, acceptability, and preliminary promise in reducing HIV risk (see phase III for a detailed description of measures, benchmarks, and analyses).

Phase III Study Procedures

We will conduct a pilot two-arm prospective RCT to compare the preliminary efficacy of *We Prevent* versus CHTC alone, both delivered through video counseling, on increasing self-reported HIV and STI testing and PrEP knowledge and uptake. Our secondary outcomes will compare the incidence of laboratory-confirmed STI between the 2 arms. This pilot RCT will enroll a sample of 160 YMSM and their partners (a total of 320 individuals). Self-completed assessments will be conducted online, and self-collected samples for STI testing will be collected every 3 months across the intervention and control arms, with a total follow-up period of 9 months. Recruitment and eligibility screening will mirror the procedures for the prior phases.

Registration and Randomization

Study procedures will mirror phase II. After registering, assented participants will complete a 25-min baseline questionnaire and will then be randomly assigned in a 1:1 ratio into the intervention or control condition. Participants in the intervention condition will be mailed HIV test kits immediately after their first session and those in the control condition will be mailed HIV test kits immediately after their baseline assessments are complete.

Control Condition

The index participant and their partner who are randomized to the control condition will engage in only 1 telehealth session: the existing CHTC intervention delivered via video counseling. In the existing CHTC session, couples receive all elements of counseling and testing together: pretest counseling, HIV testing, discussion of HIV risks, delivery of test results, and posttest counseling. Sessions are future focused: participants are not asked to reveal recent risk behaviors/exposures. Instead, the focus is on the couple learning their serostatus together and building a prevention plan that reflects their relationship goals and serostatus. Foundational to CHTC is the couple talking about and forming a prevention plan together using effective communication skills.

Approximately 1 week before the scheduled session, a box containing 2 home HIV testing kits will be mailed to an address provided by the participants. The participants will be instructed to have the kits with them at the time of the scheduled session but not to use them before the session. During the session, the remotely located counselor will instruct the couple on how to self-test using the kits. The counselor will observe the testing and ensure they can read and interpret the results correctly, and prevention planning will be centered on the results of the HIV testing.

Intervention Condition

The *We Prevent* intervention will be delivered as outlined in phase II.

Primary Outcomes

Our primary outcomes relate to the uptake of HIV prevention, conceptualized as self-reported condomless sex, HIV and STI testing, and PrEP knowledge and use. In addition, our secondary outcome will be laboratory-confirmed STIs (syphilis, gonorrhea, and chlamydia), whereby we will provide participants with kits to self-collect samples that will be mailed back and laboratory tested for STIs.

HIV testing: The baseline survey will include questions on lifetime HIV testing history. Follow-up surveys will assess HIV testing in the prior 3-month period and will include self-reported test results. The primary HIV testing outcome will be the proportion of YMSM tested for HIV 2 or more times, at least 3 months apart, in the 9-month follow-up period. As an additional analysis, we will also examine the proportions of participants who receive at least one HIV test.

STIs and STI testing: The STI testing outcome is defined as the proportion of YMSM tested for STIs at least once in the 9-month follow-up period. At baseline, we will assess lifetime STI testing history and knowledge about STIs. We will ask participants what STIs they have been tested for, the date of their most recent STI test (if known), and whether a medical provider had diagnosed them with an STI. In the follow-up assessments, participants will be mailed a box containing sample self-collection kits at each study assessment point (0, 3, 6, and 9 months). The box contains instructions on how to collect the

samples and how to mail them back to the study site. The samples will be laboratory tested for syphilis, gonorrhea, and chlamydia. We will calculate the incidence of any STI in the 9-month follow-up period.

PrEP awareness and intentions: Surveys will assess participants' knowledge of PrEP, willingness to use PrEP, and uptake of PrEP. PrEP awareness will be a single item measure of whether the participant has heard of PrEP [45]. PrEP willingness will be measured with an existing 8-item scale (alpha=.84) developed for YMSM to gauge likelihood of PrEP use across different conditions (eg, partner types and experiencing potential side effects) [49]. At each follow-up assessment, PrEP-eligible HIV-negative YMSM will be asked whether they have begun using PrEP, and self-reported adherence to PrEP will be assessed at each follow-up visit.

Sexual risk behavior: Sexual risk behavior will be assessed using the Sexual Practices Assessment Schedule [26,50] to capture the number of occasions of sex acts with different partner types, use of condoms during the past 3 months, and knowledge about partners' HIV status and PrEP use. At-risk sex will be defined as any anal intercourse without condoms or PrEP that occurs with a person of known positive or unknown serostatus during the follow-up period.

Dyadic Measures

We will use the 27-item RELO-IMB scale, which was developed with items from the Health and Relationships Survey [42,43]. Information will be assessed with 5 items that gauge beliefs about HIV prevention within relationships (eg, if 2 people have sex only with each other, they really do not have to practice safer sex). Motivation will be assessed with 3 scales assessing participants' attitudes, social norms, and intentions of using different prevention strategies for sexual risk reductions. Behavioral skills include self-efficacy to engage in preventive behaviors in different contexts and communication with partners.

Linkage to HIV Care

For any incident HIV-positive individuals, we will also collect the following outcomes as indicators of linkage to care, per the recent recommendations of the Institute of Medicine [51]. These are measured within 3 months of HIV diagnosis via self-report: (1) attending at least one clinical care appointment, (2) having at least one CD4 test performed, and (3) having at least one viral load test performed. Onset of antiretroviral therapy (ART) initiation, self-reported adherence to ART, and viral suppression are exploratory indicators, as we recognize that our follow-up period may not be a sufficient amount of time to see these changes.

Feasibility and Acceptability

In addition to the outcomes above, the pilot RCT will assess feasibility by examining (1) time to recruit 160 YMSM to the intervention and (2) rate of recruitment per 100 YMSM expressing interest in participation. Adequate feasibility will entail recruiting and enrolling at least five to six YMSM and their partners per month and ensuring at least 80% to 90% retention rate. In addition, we will examine the feasibility and acceptability of mailing home STI kits to participants. Acceptability of the intervention will be determined by analysis of data from a satisfaction survey on the intervention's acceptability. In addition, the percentages of YMSM who do not complete either of the intervention sessions will be assessed. We will also administer a break-up survey in the event that couples break up over the course of the study. The break-up survey will assess reasons for relationship dissolution, including whether the study had an impact on their relationship.

Phase III Data Analysis

We hypothesize that the opportunity to learn relationship skills, the experience of HIV testing with a partner, and developing a prevention plan will encourage YMSM to continue utilizing these skills throughout their relationship and in future relationships. With guidance from the iTech AC, we will analyze data at the individual level, not at the dyadic level—we expect behavioral shifts over the 9-month period among individual YMSM. Therefore, our sample for analysis will be 320 participants. We will also conduct exploratory dyadic analysis to examine how partner effects shape HIV prevention uptake among coupled YMSM.

We will examine differences between the treatment groups for the index participants using *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. We will conduct analyses of our primary and secondary HIV and STI testing behavior outcomes using regression to compare each active treatment group with the control in pairwise comparison tests. The proportion of index participants who obtain at least two tests at least 3 months apart within the follow-up period will be calculated and presented with corresponding 95% exact binomial CIs.

The ability of the intervention to increase PrEP knowledge and willingness to use PrEP over time will be examined using 2 separate outcomes. Scores at baseline and all follow-ups will be analyzed using generalized linear models (GLMs), with properly chosen (based on the distribution of dependent variable) link functions to analyze longitudinal PrEP outcome data. The GLMs will be estimated using generalized estimating equations (GEEs) with robust SE estimates, which provide an extension of regression analysis to the case of correlated or repeated observations with appropriate modeling of the covariance structure. Models will control for demographic characteristics and study arm and will explore interactions between treatment arm and individual characteristics.

The incidence of at-risk sex acts will be calculated as an incidence density, with the numerator being the number of individual at-risk sex acts and the denominator being person-years of follow time. Comparisons of the incidence of at-risk sex acts and incidence of STIs will be made by comparing incidence densities across the arms. Period incidence rates (3-monthly incidence density rates) of at-risk sex will be estimated by performing a GEE Poisson regression analysis of the 3-monthly counts, implemented using SAS PROC GENMOD. GEE models will control for demographic characteristics, baseline HIV testing history and relationship dynamics, and hypothesized mediators. GEE models will also examine interactions between relationship dynamics and sexual risk-taking. In addition, analysis will consider differences in

changes in information, motivation, and behavioral skills in accordance with the RELO-IMB model.

Cost Analysis

To inform the future development and potential scale-up of *We Prevent*, a cost analysis will be conducted for the intervention. Data on costs associated with the delivery of the intervention will be recorded over time. Capital equipment cost (eg, computers), staffing (eg, interventionists time), and facility cost (eg, rent and telephone) that are attributable to our intervention will be obtained from accounting records. No costs associated with research data collection (surveys and biomarkers) will be included. These components of cost will be summed over the 12-month study period for each participant, to generate an estimated per person cost for intervention delivery.

Results

The *We Prevent* protocol was launched in June 2017, with phases I and II expected to be complete by mid-2019. It is expected that the pilot RCT will be launched at the end of 2019, with results finalized by mid-2021.

Discussion

This paper describes the development of *We Prevent*, a theory-based intervention that seeks to adapt existing CHTC protocols and pair them with relationship skills counseling, both delivered through a telehealth platform, to provide the behavioral skills to reduce HIV risk in YMSM's current and future relationships. We will draw on theory and our phase I qualitative data and phase II one-arm pilot to develop and test a dyadic intervention that will empower and enable YMSM to communicate with their partners about HIV and develop a prevention plan.

This project offers several innovations in advancing HIV prevention for YMSM in relationships. First, this intervention seeks to empower adolescent and younger MSM aged 15 to 19 years to choose goals other than 1 specific HIV prevention strategy (eg, repeat HIV testing, PrEP, or establishing sexual agreements). Existing dyadic HIV interventions, such as CHTC, have addressed sexual agreement building. However, to our knowledge, only the 2GETHER pilot intervention has incorporated relationship and HIV prevention education to produce skill building among young same-sex male couples. *We Prevent* builds on this premise and uses MI techniques to enhance motivation and allow for goal flexibility in prevention options among adolescent and younger men in their first relationships. Couples-focused interventions that build on existing brief, motivational-focused interventions may appeal to a wider audience by offering more goal choices, especially for adolescent and younger MSM in their teens. Importantly, *We Prevent* is designed to help YMSM set HIV prevention goals within their relationships, which are likely to be transferred to other relationships over time. CHTC holds promise when delivered using video-based counseling for MSM [26]; therefore, this project will build on this work to adapt the telehealth intervention for YMSM. Intervention research using mobile technology is urgently needed with YMSM communities at risk for HIV who may not have access to services (eg, rural areas). Thus, we believe that *We Prevent* has the potential to reduce HIV and other STIs among YMSM by providing young men with the motivation and skills necessary to manage their relationships throughout their lifetime.

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Conflicts of Interest

None declared.

References

1. Singh S, Song R, Johnson AS, McCray E, Hall I. HIV incidence, prevalence, and undiagnosed infections in men who have sex with men. 2017 Presented at: Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Boston, MA.
2. Centers for Disease Control and Prevention. 2012. Estimated HIV incidence in the United States, 2007-2010 URL: https://www.cdc.gov/hiv/pdf/statistics_hssr_vol_17_no_4.pdf [accessed 2018-11-10] [WebCite Cache ID 73onqu6w0]
3. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS 2014 Mar;28(3):128-135 [FREE Full text] [doi: 10.1089/apc.2013.0345] [Medline: 24601734]
4. Sullivan PS, Salazar L, Buchbinder S, Sanchez TH. Estimating the proportion of HIV transmissions from main sex partners among men who have sex with men in five US cities. AIDS 2009 Jun 1;23(9):1153-1162. [doi: 10.1097/QAD.0b013e32832baa34] [Medline: 19417579]
5. Goodreau SM, Carnegie NB, Vittinghoff E, Lama JR, Sanchez J, Grinsztejn B, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? PLoS One 2012;7(11):e50522 [FREE Full text] [doi: 10.1371/journal.pone.0050522] [Medline: 23209768]

6. Mustanski B, Newcomb ME, Clerkin EM. Relationship characteristics and sexual risk-taking in young men who have sex with men. Health Psychol 2011 Sep;30(5):597-605 [FREE Full text] [doi: 10.1037/a0023858] [Medline: 21604883]
7. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV incidence in the United States, 2006-2009. PLoS One 2011;6(8):e17502 [FREE Full text] [doi: 10.1371/journal.pone.0017502] [Medline: 21826193]
8. Golub SA, Starks TJ, Payton G, Parsons JT. The critical role of intimacy in the sexual risk behaviors of gay and bisexual men. AIDS Behav 2012 Apr;16(3):626-632 [FREE Full text] [doi: 10.1007/s10461-011-9972-4] [Medline: 21630012]
9. Cusick L, Rhodes T. Sustaining sexual safety in relationships: HIV positive people and their sexual partners. Cult Health Sex 2000;2(4):473-487. [doi: 10.1080/13691050050174468]
10. Darbes LA, Chakravarty D, Neilands TB, Beougher SC, Hoff CC. Sexual risk for HIV among gay male couples: a longitudinal study of the impact of relationship dynamics. Arch Sex Behav 2014 Jan;43(1):47-60 [FREE Full text] [doi: 10.1007/s10508-013-0206-x] [Medline: 24233329]
11. Rhodes T, Cusick L. Love and intimacy in relationship risk management: HIV positive people and their sexual partners. Sociol Health Illn 2000;22(1):1-26 [FREE Full text] [doi: 10.1111/1467-9566.00189]
12. Diaz R, Ayala G. Love, passion and rebellion: ideologies of HIV risk among Latino gay men in the USA. Cult Health Sex 1999 Jan;1(3):277-293 [FREE Full text] [doi: 10.1080/136910599301021]
13. Bohl DD, Raymond HF, Arnold M, McFarland W. Concurrent sexual partnerships and racial disparities in HIV infection among men who have sex with men. Sex Transm Infect 2009 Sep;85(5):367-369. [doi: 10.1136/sti.2009.036723] [Medline: 19773457]
14. Mitchell JW, Harvey SM, Champeau D, Seal DW. Relationship factors associated with HIV risk among a sample of gay male couples. AIDS Behav 2012 Feb;16(2):404-411 [FREE Full text] [doi: 10.1007/s10461-011-9976-0] [Medline: 21614560]
15. Parsons JT, Starks TJ, Gamarel KE, Grov C. Non-monogamy and sexual relationship quality among same-sex male couples. J Fam Psychol 2012 Oct;26(5):669-677. [doi: 10.1037/a0029561] [Medline: 22906124]
16. Newcomb ME, Ryan DT, Garofalo R, Mustanski B. The effects of sexual partnership and relationship characteristics on three sexual risk variables in young men who have sex with men. Arch Sex Behav 2014 Jan;43(1):61-72 [FREE Full text] [doi: 10.1007/s10508-013-0207-9] [Medline: 24217953]
17. Davidovich U, de Wit JB, Stroebe W. Assessing sexual risk behaviour of young gay men in primary relationships: the incorporation of negotiated safety and negotiated safety compliance. AIDS 2000 Apr 14;14(6):701-706. [Medline: 10807193]
18. Hoff CC, Chakravarty D, Beougher SC, Darbes LA, Dadasovich R, Neilands TB. Serostatus differences and agreements about sex with outside partners among gay male couples. AIDS Educ Prev 2009 Feb;21(1):25-38 [FREE Full text] [doi: 10.1521/aeap.2009.21.1.25] [Medline: 19243229]
19. Gomez AM, Beougher SC, Chakravarty D, Neilands TB, Mandic CG, Darbes LA, et al. Relationship dynamics as predictors of broken agreements about outside sexual partners: implications for HIV prevention among gay couples. AIDS Behav 2012 Aug;16(6):1584-1588. [doi: 10.1007/s10461-011-0074-0] [Medline: 22020757]
20. Burton J, Darbes LA, Operario D. Couples-focused behavioral interventions for prevention of HIV: systematic review of the state of evidence. AIDS Behav 2010 Feb;14(1):1-10 [FREE Full text] [doi: 10.1007/s10461-008-9471-4] [Medline: 18843530]
21. Crepaz N, Tungol-Ashmon MV, Vosburgh HW, Baack BN, Mullins MM. Are couple-based interventions more effective than interventions delivered to individuals in promoting HIV protective behaviors? A meta-analysis. AIDS Care 2015;27(11):1361-1366 [FREE Full text] [doi: 10.1080/09540121.2015.1112353] [Medline: 26608175]
22. LaCroix JM, Pellowski JA, Lennon CA, Johnson BT. Behavioural interventions to reduce sexual risk for HIV in heterosexual couples: a meta-analysis. Sex Transm Infect 2013 Dec;89(8):620-627. [doi: 10.1136/sextrans-2013-051135] [Medline: 23918756]
23. Mitchell JW. The use of technology to advance HIV prevention for couples. Curr HIV/AIDS Rep 2015 Dec;12(4):516-522 [FREE Full text] [doi: 10.1007/s11904-015-0290-8] [Medline: 26412083]
24. Sullivan PS, Stephenson R, Grazter B, Wingood G, Diclemente R, Allen S, et al. Adaptation of the African couples HIV testing and counseling model for men who have sex with men in the United States: an application of the ADAPT-ITT framework. Springerplus 2014;3:249 [FREE Full text] [doi: 10.1186/2193-1801-3-249] [Medline: 24877036]
25. Bazzi AR, Fergus KB, Stephenson R, Finneran CA, Coffey-Esquivel J, Hidalgo MA, et al. A dyadic behavioral intervention to optimize same sex male couples' engagement across the HIV care continuum: development of and protocol for an innovative couples-based approach (Partner Steps). JMIR Res Protoc 2016 Aug 25;5(3):e168 [FREE Full text] [doi: 10.2196/resprot.6271] [Medline: 27562905]
26. Stephenson R, Freeland R, Sullivan SP, Riley E, Johnson BA, Mitchell J, et al. Home-based HIV testing and counseling for male couples (Project Nexus): a protocol for a randomized controlled trial. JMIR Res Protoc 2017 May 30;6(5):e101 [FREE Full text] [doi: 10.2196/resprot.7341] [Medline: 28559225]
27. Neme S, Goldenberg T, Stekler JD, Sullivan PS, Stephenson R. Attitudes towards couples HIV testing and counseling among Latino men who have sex with men in the Seattle area. AIDS Care 2015;27(10):1354-1359. [doi: 10.1080/09540121.2015.1058894] [Medline: 26272715]

28. Stephenson R, Grabbe KL, Sidibe T, McWilliams A, Sullivan PS. Technical assistance needs for successful implemention of couples HIV testing and counseling (CHTC) interventions for male couples at US HIV testing sites. AIDS Behav 2016 Apr;20(4):841-847. [doi: 10.1007/s10461-015-1150-7] [Medline: 26253221]
29. Mitchell JW, Petroll AE. Patterns of HIV and sexually transmitted infection testing among men who have sex with men couples in the United States. Sex Transm Dis 2012 Nov;39(11):871-876 [FREE Full text] [doi: 10.1097/OLQ.0b013e3182649135] [Medline: 23060078]
30. Chakravarty D, Hoff CC, Neilands TB, Darbes LA. Rates of testing for HIV in the presence of serodiscordant UAI among HIV-negative gay men in committed relationships. AIDS Behav 2012 Oct;16(7):1944-1948 [FREE Full text] [doi: 10.1007/s10461-012-0181-6] [Medline: 22460227]
31. Newcomb ME, Macapagal KR, Feinstein BA, Bettin E, Swann G, Whitton SW. Integrating HIV prevention and relationship education for young same-sex male couples: a pilot trial of the 2Gether intervention. AIDS Behav 2017 Aug;21(8):2464-2478. [doi: 10.1007/s10461-017-1674-0] [Medline: 28083833]
32. Mustanski BS, Newcomb ME, Du Bois SN, Garcia SC, Grov C. HIV in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions. J Sex Res 2011 Mar;48(2-3):218-253 [FREE Full text] [doi: 10.1080/00224499.2011.558645] [Medline: 21409715]
33. Kubicek K. Setting an agenda to address intimate partner violence among young men who have sex with men: a conceptual model and review. Trauma Violence Abuse 2018 Oct;19(4):473-487. [doi: 10.1177/1524838016673599] [Medline: 27756778]
34. Parsons JT, Lelutiu-Weinberger C, Botsko M, Golub SA. A randomized controlled trial utilizing motivational interviewing to reduce HIV risk and drug use in young gay and bisexual men. J Consult Clin Psychol 2014 Feb;82(1):9-18 [FREE Full text] [doi: 10.1037/a0035311] [Medline: 24364800]
35. Lelutiu-Weinberger C, Pachankis JE, Gamarel KE, Surace A, Golub SA, Parsons JT. Feasiblity, acceptability, and preliminary efficacy of a life-chat social media intervention to reduce HIV risk among young men who have sex with men. AIDS Behav 2015 Jul;19(7):1214-1227 [FREE Full text] [doi: 10.1007/s10461-014-0911-z] [Medline: 25256808]
36. Kelly JA, Spielberg FE, McAuliffe TL. Defining, designing, implementing, and evaluating phase 4 HIV prevention effectiveness trials for vulnerable populations. J Acquir Immune Defic Syndr 2008 Mar 01;47(Suppl 1):S28-S33 [FREE Full text] [doi: 10.1097/QAI.0b013e3181605c77] [Medline: 18301131]
37. Hightow-Weidman LB, Muessig KE, Bauermeister J, Zhang C, LeGrand S. Youth, technology, and HIV: recent advances and future directions. Curr HIV/AIDS Rep 2015 Dec;12(4):500-515. [doi: 10.1007/s11904-015-0280-x] [Medline: 26385582]
38. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev 2012;3:CD009756. [doi: 10.1002/14651858.CD009756] [Medline: 22419345]
39. Muessig KE, Nekkanti M, Bauermeister J, Bull S, Hightow-Weidman LB. A systematic review of recent smartphone, Internet and Web 2.0 interventions to address the HIV continuum of care. Curr HIV/AIDS Rep 2015 Mar;12(1):173-190 [FREE Full text] [doi: 10.1007/s11904-014-0239-3] [Medline: 25626718]
40. Chiasson MA, Shaw FS, Humberstone M, Hirshfield S, Hartel D. Increased HIV disclosure three months after an online video intervention for men who have sex with men (MSM). AIDS Care 2009 Sep;21(9):1081-1089. [doi: 10.1080/09540120902730013] [Medline: 20024766]
41. Mustanski B, Parsons JT, Sullivan PS, Madkins K, Rosenberg E, Swann G. Biomedical and behavioral outcomes of Keep It Up!: an ehealth HIV prevention program RCT. Am J Prev Med 2018 Aug;55(2):151-158. [doi: 10.1016/j.amepre.2018.04.026] [Medline: 29937115]
42. Macapagal K, Greene GJ, Andrews R, Mustanski B. Evaluating the relationship-oriented information, motivation, and behavioral skills model of HIV preventive behaviors in young men who have sex with men. AIDS Educ Prev 2016 Apr;28(2):165-179 [FREE Full text] [doi: 10.1521/aeap.2016.28.2.165] [Medline: 27459167]
43. Misovich SJ, Fisher JD, Fisher WA. Close relationships and elevated HIV risk: Behaviorvidence and possible underlying psychological processes. Rev Gen Psychol 1997;1(1):72-107 [FREE Full text]
44. Stephenson R, Finneran C. The IPV-GBM scale: a new scale to measure intimate partner violence among gay and bisexual men. PLoS One 2013;8(6):e62592 [FREE Full text] [doi: 10.1371/journal.pone.0062592] [Medline: 23755098]
45. Stephenson R, Suarez N, Garofalo R, Hidalgo M, Hoehnle S, Thai J, et al. Project Stronger Together: protocol to test a dyadic intervention to improve engagement in HIV care among sero-discordant male couples in three US cities. JMIR Res Protoc 2017 Aug 31;6(8):e170 [FREE Full text] [doi: 10.2196/resprot.7884] [Medline: 28860107]
46. Stephenson R, Metheny N, Sharma A, Sullivan P, Riley E. Providing home-based HIV testing and counseling for transgender youth (Project Moxie): protocol for a pilot randomized controlled trial. JMIR Res Protoc 2017 Nov 28;6(11):e237 [FREE Full text] [doi: 10.2196/resprot.8562] [Medline: 29183868]
47. Guest G, Namey E, Mitchell M. Collecting qualitative data. London: Sage; 2013.
48. Srivastava A, Thompson S. Framework analysis: a qualitative methodology for applied policy research. J Admin Gov 2009;42(2):72-79.
49. Bauermeister JA, Meanley S, Pingel E, Soler JH, Harper GW. PrEP awareness and perceived barriers among single young men who have sex with men. Curr HIV Res 2013 Oct;11(7):520-527 [FREE Full text] [Medline: 24476355]

50. Stephenson R, White D, Darbes L, Hoff C, Sullivan P. HIV testing behaviors and perceptions of risk of HIV infection among MSM with main partners. AIDS Behav 2015 Mar;19(3):553-560 [FREE Full text] [doi: 10.1007/s10461-014-0862-4] [Medline: 25081599]
51. Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. AIDS Res Ther 2016;13:35 [FREE Full text] [doi: 10.1186/s12981-016-0120-0] [Medline: 27826353]

Abbreviations

AC: analytic core
ART: antiretroviral therapy
CAS: condomless anal sex
CDC: Centers for Disease Control and Prevention
CHTC: couples HIV testing and counseling
GEE: generalized estimating equation
GLM: generalized linear model
HIPAA: Health Insurance Portability and Accountability Act
IDI: in-depth interview
iTech: innovative technology
LGBTQ: lesbian, gay, bisexual, transgender, queer
MI: motivational interviewing
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RELO-IMB: Relationship-Oriented Information-Motivation-Behavioral Skills
RCT: randomized controlled trial
STI: sexually transmitted infection
SRV: subject recruitment venue
TC: technology core
TEG: technical expert group
YAB: youth advisory board
YMSM: young gay, bisexual, and other men who have sex with men

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Protocol

A Mobile-Based App (MyChoices) to Increase Uptake of HIV Testing and Pre-Exposure Prophylaxis by Young Men Who Have Sex With Men: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: HIV incidence is growing most rapidly in the United States among young men who have sex with men (YMSM). Overwhelming evidence demonstrates that routine testing and expanded use of pre-exposure prophylaxis (PrEP) would dramatically reduce the population burden of HIV; however, uptake of both interventions is suboptimal among young adults. The use of mobile phone apps by YMSM is ubiquitous and may offer unique opportunities for public health interventions. MyChoices is a theory-driven app to increase HIV testing and PrEP uptake. It was developed by an interdisciplinary team based on feedback from a diverse sample of YMSM.

Objective: The aim of this paper is to describe the protocol for the refinement, beta testing, and pilot randomized controlled trial (RCT) to examine the acceptability and feasibility of the MyChoices app.

Methods: This 3-phase study includes 4 theater testing groups for app refinement with a total of approximately 30 YMSM; for beta testing, including quantitative assessments and exit interviews, with approximately 15 YMSM over a 2-month period; and for a pilot RCT with 60 YMSM. The pilot will assess feasibility, acceptability, and preliminary efficacy of the MyChoices app, compared with referrals only, in increasing HIV testing and PrEP uptake. All participants will be recruited at iTech clinical research sites in Boston, MA, and Bronx, NY.

Results: App refinement is underway. Enrollment for the pilot RCT began in October 2018.

Conclusions: MyChoices is one of the first comprehensive, theory-driven HIV prevention apps designed specifically for YMSM. If MyChoices demonstrates acceptability and feasibility in this pilot RCT, a multicity, 3-arm randomized controlled efficacy trial of this app and another youth-optimized app (LYNX) versus standard of care is planned within iTech. If shown to be efficacious, the app will be scalable, with the ability to reach YMSM across the United States as well as be geographically individualized, with app content integrated with local prevention and testing activities.

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KEYWORDS

adolescents; HIV; men who have sex with men; mHealth; mobile phone; pre-exposure prophylaxis

Introduction

Background

In the United States, HIV incidence is growing most rapidly among young men who have sex with men (YMSM). More than 20% of all new HIV infections in the United States are among young people aged 13-24 years, and 92% of these new infections are diagnosed in YMSM, making them one of the largest risk groups for HIV [1]. Men who have sex with men (MSM) of color are disproportionately impacted by the epidemic; in 2015, significantly more black MSM were diagnosed with HIV than white MSM, despite the relatively lower numbers of black MSM overall. HIV diagnoses among young Latino MSM have increased by 14% [1]. Importantly, it is estimated that compared with the general population, a higher proportion of YMSM (13% vs 44%, respectively) living with HIV do not know that they are infected [2,3] and, thus, will incur a delay seeking effective treatment, making it more likely that they will transmit HIV to others.

Overwhelming evidence demonstrates that routine testing, resulting in early identification, and therefore, early treatment, of HIV infection, and expanded use of pre-exposure prophylaxis (PrEP) would dramatically reduce the population burden of HIV as well as improve health outcomes for those who are infected [4-8]. However, HIV testing and use of PrEP among young adults is suboptimal. While at least biannual HIV testing is recommended for sexually active MSM, data suggest that approximately 60% of YMSM do not get even annual HIV tests [9]. Moreover, uptake of PrEP has remained low [10], particularly among young people. In a national Web-based survey of MSM, only 6% of those aged 18-24 years had ever used PrEP compared with 18% of those in the 30+ age group [11].

The normal developmental trajectory of adolescence and young adulthood involves behavioral experimenting, risk taking, and confronting a host of difficult choices with regard to identity formation [12]. These age-appropriate behaviors, beliefs of invincibility, and still-developing cognitive processes may play a role in increasing HIV risk taking behaviors and in placing a low priority on HIV testing and uptake of prevention strategies, particularly PrEP, which requires taking a daily pill to be effective [13].

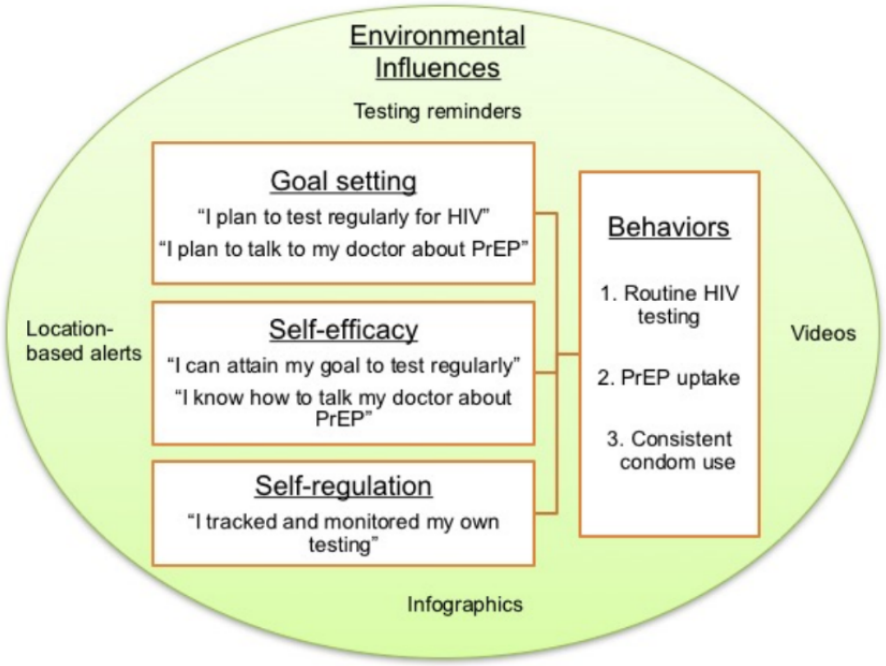
The ongoing and growing HIV risk for YMSM highlights the need to reach younger individuals using developmentally appropriate, innovative methods and modalities. In addition to expanding access to effective prevention modalities, innovative methods to reach YMSM “where they are” must be developed. Smartphone use is nearly universal among youth in the United States [14]. Younger adults, racial and ethnic minorities, and socioeconomically disadvantaged populations have been identified as having high rates of smartphone use, reducing concerns of inequitable access to the technology [15]. The use of mobile phone apps is ubiquitous and is a common way in which youth interact, get information, and meet sex partners. Mobile apps offer unique opportunities for public health interventions, including efforts to increase HIV testing and PrEP uptake, particularly for YMSM, who may be open to receiving information in a familiar and discreet environment.

Although the popularity of mobile health apps is growing, there are limited data on the efficacy of app-based interventions to enhance HIV prevention and increase HIV testing among MSM, particularly YMSM. However, formative research suggests that Web-based, mobile, or social media outlets are acceptable and feasible means to increase the uptake of prevention services and HIV testing among MSM [16-20]. Informed by extensive formative research, Dr. Patrick Sullivan of Emory University (one of iTech’s Principal Investigators), together with app developers from Keymind, developed and tested an HIV testing promotion app for adult MSM (HealthMindr) [21]. Our initial formative research with YMSM [22] suggested interest in the basic functionalities of an HIV testing app like HealthMindr, but the youth felt that it would not be culturally and developmentally appropriate for their peers without further development. As a result, MyChoices incorporates youth feedback to realize an app that draws on the HIV testing functionality of HealthMindr but has been significantly redesigned in the following ways: (1) sexual health information presented in a simple, streamlined, and integrated fashion; (2) designed with attention to having a youth-friendly, social media style appeal; and (3) reduction of text by employing icons, graphics interchange formats (GIFs), and videos.

Theoretical Framework for Intervention

The MyChoices app is informed by the social cognitive theory (SCT), which specifies goal setting, self-efficacy, and self-regulation as essential influences of health behavior [23,24]. SCT holds that cognition, behavior, and environmental influences interact with one another and reinforce one another to impact health behavior (Figure 1).

Figure 1. Theoretical model for the MyChoices app development. PrEP: pre-exposure prophylaxis.



For example, self-regulatory functions (eg, self-monitoring one's HIV testing through development of testing plans) and self-efficacy (eg, belief that one can attain the goal to test regularly) are enhanced by facilitative environmental conditions [23,24] such as reminder systems. MyChoices uses multimedia capabilities and environmental influences to support self-regulation and self-efficacy by enhancing the feeling of control over one's ability to get tested regularly for HIV and use PrEP. Brief surveys about sexual risk and protective health behaviors within the app are used to assist users in tracking and self-monitoring their behaviors and creating a personalized HIV testing plan. Quizzes, videos, and infographics as well as "Help me Choose" (a quiz to help recommend a preferred setting for HIV testing), "Ordering" (a Web-based store to order free condoms, condom-compatible lubricant, and at-home HIV test kits), and geofencing (using global positioning system [GPS] to notify users when they are near a test site and due for testing) functions are used to maximize self-efficacy around HIV prevention and uptake of PrEP.

Aims and Objectives

The aim of this paper is to describe the protocol for the refinement of an HIV prevention mobile app, beta testing it, and conducting a pilot randomized controlled trial (RCT) to examine the acceptability and feasibility of the MyChoices app for YMSM. We hypothesize that participants who are randomized to use the MyChoices app will report that the app is highly acceptable and will use the main functions of the app over the follow-up period. We also hypothesize that while not powered to detect significant differences, MyChoices users will report taking more HIV tests and increasing PrEP uptake compared with YMSM receiving the control condition.

Methods

Phase 1: App Refinement

To refine and enhance the MyChoices app for HIV testing and PrEP uptake among YMSM, we will conduct 4 theater testing groups with approximately 30 YMSM. Testing will take place at 2 iTech subject recruitment venues (SRVs; Boston, MA, and Bronx, NY), and groups will provide suggestions and feedback to improve app acceptability and feasibility as well as approaches to HIV prevention [25]. We aim to have 5-8 participants per group in order to balance the need to have an intimate enough group to share insights, yet large enough to ensure diversity of opinions [26,27]. Participants will be HIV-uninfected YMSM aged between 15 and 24 years who have not had a recent HIV test. For 15-17-year olds, participants must also self-report any anal sex with a male or transfemale partner. For 18-24-year olds, participants must self-report at least one of the following in the past 6 months:

1. ≥1 episode of condomless anal sex with an HIV-positive or unknown HIV status male or transfemale partner
2. Anal sex with ≥2 male or transfemale partners
3. Exchange of money, gifts, shelter, or drugs for anal sex with a male or transfemale partner
4. Sex with a male or transfemale partner and having had a sexually transmitted infection (STI)
5. Sexual partner of an HIV-positive man or transfemale with whom condoms were not consistently used

From our prior experience in recruiting YMSM, we found that it is necessary to include YMSM who engage in lower sexual risk (eg, anal sex with condoms) for the younger age group. Given that risk changes over time, we will still be enrolling an at-risk population who could benefit from the app and who should be testing for HIV regularly.

Prior to theater testing, participants will complete a brief demographic and behavioral questionnaire in order to contextualize the group data. During theater testing, participants will be asked to interact with the MyChoices app, and feedback will be elicited on the overall appearance and functionality of the app interface, appeal, and usability; ways to maximize acceptability (eg, update language, improve flow, etc); components they like and/or dislike; and areas for improvement. Guided by the SCT model, we will specifically obtain insight into the functionalities and content aimed at impacting self-regulation, self-efficacy, and environmental influences as they relate to HIV prevention.

Theater testing groups will last 60-90 minutes, and discussions will be audiorecorded and transcribed verbatim. Facilitators will also take notes and complete standardized debriefing forms immediately following the visit. These data will allow us to make final refinements to the app, as well as the intervention protocol and assessment battery, prior to initiation of the open technical evaluation and RCT pilot.

Phase 2: Beta Testing

After refinement as described above, the MyChoices app will undergo beta testing with a small group of YMSM participants (up to 15 YMSM at 2 iTech SRVs: Boston, MA, and Bronx, NY) over a 2-month period. Using the same criteria as Phase 1, participants will be HIV-uninfected young cisgender MSM aged between 15 and 24 years who have not had a recent HIV test and self-report evidence of risk for acquiring HIV infection. For this phase, participants will also be required to own or lease an Android phone, as MyChoices will only be available on an Android platform during beta testing until it is coded by the same developers in iOS for the pilot RCT. This delay is meant to reduce the cost of recoding multiple versions of the edited app. Besides the slight native differences and system-specific limitations between the two platforms, the app was designed in such a way that the visual elements, capabilities, and interactions would be as similar as possible across both platforms.

All participants will be given brief instructions on the purpose of the MyChoices app and an overview of how to use it. Because the primary objective of the beta testing phase is to test instruments and procedures to be used in the pilot RCT, participants will complete the same assessments and processes to be used in the pilot RCT (see pilot RCT section for details). In brief, we will assess acceptability of the MyChoices app using the System Usability Scale (SUS) [28], and feasibility will be assessed using app analytics to determine whether the app was used and what functionalities were most likely and least likely to be opened. Participants will also be asked to provide feedback during Web-based exit interviews conducted by study staff using a Health Insurance Portability and Accountability Act-compliant videoconferencing software (VSee; VSee Lab, LLC, Sunnyvale, CA) technology. Feedback will be requested on functionality, technical performance, errors and software bugs encountered, overall experiences using the app, feedback for further refinement, and subjective impact of the app on HIV testing and PrEP uptake.

A rapid analysis of the data from the exit interviews will be conducted using the detailed notes taken on the debrief forms [29]. The study team will meet to discuss themes that emerged in the qualitative exit interviews, usage patterns, and acceptability ratings. We will triangulate the findings in order to refine the app, intervention protocol, and assessment tools prior to the pilot RCT [30].

Phase 3: Pilot Randomized Controlled Trial

Study Design

A pilot RCT will be conducted at 2 iTech SRVs (Boston, MA, and Bronx, NY) to evaluate the feasibility and acceptability of the MyChoices app and examine the preliminary efficacy of the app in increasing HIV testing and PrEP uptake compared with a standard of care control group. This information will determine whether MyChoices moves forward to be tested in a full-scale efficacy trial planned with iTech. We will enroll 60 YMSM across 2 iTech SRVs who will be randomized to receive either the MyChoices app or standard of care. Participants will be followed for 6 months and will complete a Web-based assessment every 3 months (Figure 2).

Trial Registration, Ethics, Consent, and Institutional Board Approval

The research and ethics presented in this study have been reviewed and approved by the University of North Carolina at Chapel Hill Institutional Review Board (17-0256). A Certificate of Confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent will be obtained for participants who are 15-17 years old. The study is also registered on ClinicalTrials.gov (NCT03179319). All participants will undergo screening in a private room at the clinical research site. If eligible (see below), the informed consent discussion will be conducted at this time. The informed consent documents will include detailed information on all study procedures and answer questions concerning the study and assent or consent process.

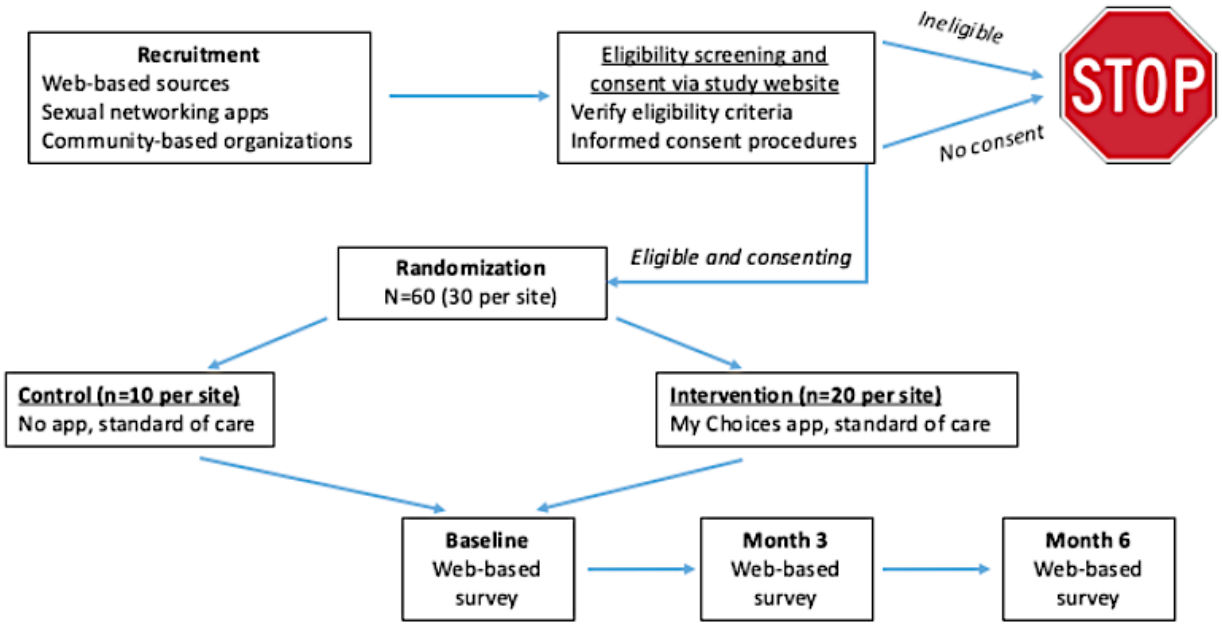
Participants

Study participants (N=60) will be assessed for eligibility by completing a brief screener. Inclusion criteria are identical to those in Phase 2 (beta testing), except that participants must own and be willing to download the app to a phone running either an Android or iOS platform. YMSM of color will be oversampled in order to reach a target enrollment of approximately 50% and to ensure sufficient representation of the population with the most need.

Recruitment

Active recruitment will be carried out by study staff at the SRVs by recruiting individuals from organizations and venues where YMSM attend. This may include community-based organizations for sexual and gender minority youth, youth Pride events, etc. Additionally, passive approaches for recruitment will include posting study information at these venues via flyers, posters, and palm cards describing the study. Web-based recruitment will be conducted by placing banner advertisements on popular Web-based social media outlets (eg, Facebook, Grindr, etc).

Figure 2. The MyChoices pilot randomized controlled trial schema.



Randomization

Only participants who express interest in using MyChoices for HIV prevention, meet eligibility criteria, provide informed consent, and complete a baseline assessment will be eligible for randomization (see Figure 2). Randomization will be stratified by SRV [31] and will occur in a 2:1 ratio with 40 YMSM randomized to the experimental condition (20 at each SRV) and 20 randomized to the control condition (10 at each SRV). This allocation will allow us to efficiently gather additional data on app utilization. Randomization will be based on a pregenerated list created by the iTech Analytic Core statisticians, with random blocks of size 3 or 6, and will be accessed through a Web portal.

Men who are randomized to receive MyChoices will be given brief instructions on the purpose of the app, how to access it, and an overview of how to use it. Participants will be encouraged to explore all components of the app and use it routinely.

Incentives

Participants in the pilot RCT will receive US $50 compensation for the in-person screening or baseline assessment and US $25 compensation for each completed Web-based follow-up assessment.

Intervention

Standard of Care Condition

Following completion of the baseline assessment via computer-assisted self-interviewing (CASI), participants in both conditions will receive written prevention material including recommendations for HIV testing and referrals to local HIV testing sites and prevention services.

MyChoices Intervention Condition

The main functions of the app coincide with the core elements of the SCT of behavior change and are described below (see Figure 3).

Self-Regulation of HIV Risk

Brief surveys within the app are used to assess individual behavior patterns, particularly around sexual relationships. This information is used to customize the users' app experience. For example, users who report having a main partner will be informed about couples counseling and users who report difficulties using condoms will be provided information about PrEP and links to HIV prevention services at local clinical sites. Users will be asked to complete these brief surveys monthly, which will allow recommended prevention activities to be updated based on recent behaviors. Users are also able to enter HIV and STI test results to keep track of past testing dates and results.

Self-Efficacy for HIV Testing and HIV Prevention

A number of components target self-efficacy by empowering YMSM to be confident that they can effectively manage engaging in HIV testing, PrEP uptake, and condom use. For example, quizzes, infographics, and GIFs that focus on the promotion of HIV prevention and regular HIV testing and that appeal to YMSM have been incorporated. Links to videos related to PrEP (eg, what is PrEP and talking to your doctor about PrEP), reasons for routine HIV testing, and the importance of engaging in care if one tests positive are included. The MyChoices app also allows users to order home-testing kits for HIV and STIs (syphilis and rectal and urethral gonorrhea and chlamydia) and different types of condoms and lubricants that can be shipped directly to them or to another more confidential location of their choosing via an arrangement with Amazon. Additionally, the app includes information on and links to testing sites and local PrEP clinics (eg, contact number, address, and

testing hours) as determined using GPS technology, allowing men to locate clinics that are nearby their current location.

Figure 3. The MyChoices home screen.

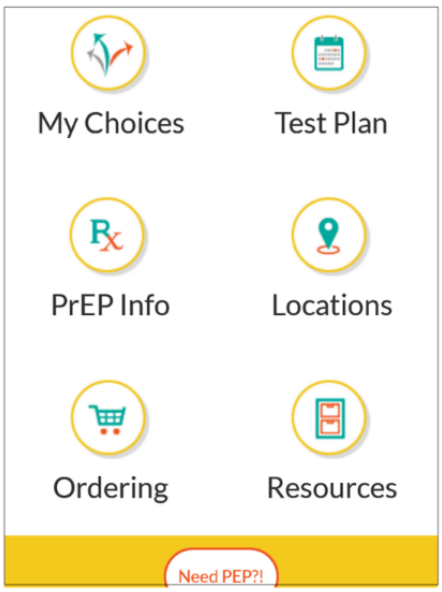
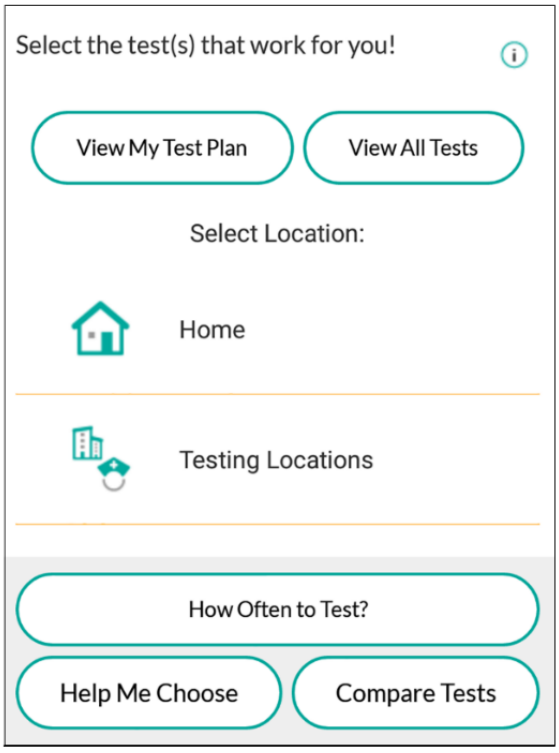


Figure 4. The MyChoices test plan.



Goal Setting and Environmental Influences

The MyChoices app allows users to create an individually tailored HIV testing plan by having them compare and choose different options (eg, antigen-antibody testing to identify very recent infection vs rapid testing at home or in a clinic for convenience and quick answers) and provides answers to questions about HIV transmission behaviors and testing history (Figure 4).

After an HIV testing plan is developed, users have the option to customize the timing and content of testing reminders (eg, users can select from a list of phrases or create their own reminder to ensure privacy). Geofencing technology provides users with notifications to test if in the vicinity of a testing location (based on their GPS location) during the testing timeframe.

Data Collection

Baseline assessments will be conducted at the enrolling clinical site using CASI, with all follow-up assessments at 3 and 6 months conducted off-site and through Web. At each major assessment, participants will complete a CASI-based assessment battery via a secure Web-based data entry system. Outcome domains and measures are described in Table 1.

Table 1. Outcomes and measures for MyChoices pilot randomized controlled trial.

Domain	Description or scale
Primary outcomes	
App acceptability	System Usability Scale [28,32]
App feasibility	Proportion using the app ≥1 time
Secondary outcomes	
HIV testing	Proportion testing at least once during study
PrEP[a] uptake	Proportion of those with a behavioral indication for PrEP who are prescribed and utilize PrEP
Social cognitive theory model constructs outcomes	
Self-regulation	Frequency of use of relevant app components, perceived HIV or STI[b] risk [33]
Self-efficacy	HIV testing self-efficacy [34], PrEP use self-efficacy [35], condom use self-efficacy [36]
Goal setting	Frequency of use of HIV testing plan
Environmental influences	Frequency of use of reminders, frequency of testing due to geofencing technology
Covariates (based on ecosocial model) [37]	
Individual	
Demographics, socioeconomic position	Age, race or ethnicity, student status, education, income, family structure, employment, insurance status
Sexual behavior (# sex partners, condom use, partner selection)	Adapted from the AIDS Risk Behavior Assessment [38]
Drug use behavior (ie, alcohol, cocaine, meth)	Alcohol, Smoking, and Substance Involvement Screening Test [39]
Mental health (depression, anxiety)	Personal Health Questionnaire Depression 8-Item Scale [40], Generalized Anxiety Disorder 7-Item Scale [41], sexual minority stress [42]
Trauma and abuse	Startle, Physically Upset, Anger, and Numbness Posttraumatic Stress Scale [43]
Social	
Social support	Patient-Reported Outcomes Measurement Information System [44]
Peer norms for condom use	Questions regarding peer's use and perceptions for condoms [45,46]
Structural	
SRV[c] or city	Geographic location of study participant
Incarceration history	Recent history and frequency
Structural discrimination	External homophobia [42], racism [47]
Stigma	HIV-related, PrEP-related
Other covariates	
Mobile phone and technology use	Pew research technology use questionnaire [48,49]
Mobile app use over the study period	Log in attempts, HIV testing and PrEP use, proportion complete HIV testing plans, proportion requesting HIV or STI home-test kits
HIV Negative Cascade	HIV or STI testing history, PrEP awareness, barriers to PrEP uptake, PrEP adherence [50], barriers to PrEP use

[a]PrEP: pre-exposure prophylaxis.

[b]STI: sexually transmitted infection.

[c]SRV: subject recruitment venues.

Primary Outcome Measures

To measure acceptability of the MyChoices app, we will use the SUS, a validated 10-item measure that assesses subjective usability of a system, or, in this case, an app [28]. It is scored from 0 to 100, and a score of ≥50 indicates that the app is acceptable [32]. To determine feasibility, we will use app analytics to determine whether at least 60% of individuals randomized to the intervention condition opened the My Choices app at least once after their initial introduction to the app by research staff. We will also assess the proportion of participants who complete their HIV testing plan (regardless of planned testing intervals)—a primary function of the app.

Secondary Outcome Measures

While this pilot study is not powered to examine the efficacy of behavioral outcomes, at each major assessment, participants will be asked to self-report on HIV testing in the previous 3-month interval. We will also assess self-report accuracy by obtaining medical release for HIV test results. Additionally, at each assessment, participants will self-report whether, in the past 3 months, they made and attended a clinic appointment for PrEP initiation, whether they were prescribed PrEP, and whether they utilized PrEP.

Tertiary Outcome Measures

All measures are outlined in detail in Table 1. In brief, congruent with our theoretical model, we will assess the following: (1) Self-regulation: perceived HIV and STI risk and transmission knowledge; (2) Self-efficacy: HIV testing, PrEP use, and condom use self-efficacy; and (3) Environmental influences: perceived utility of reminders for HIV testing. Each of these variables will mirror the content of the app, and we will adapt validated scales when available [51]. We will also assess individual (eg, sexual behavior and mental health), social (eg, social support), and structural (eg, incarceration and stigma) covariates. Finally, among those randomized to the MyChoices condition, we will use app analytic data to assess the frequency and duration of app use, content and functionalities most and least utilized, and requests for HIV or STI testing kits, condoms, and lube.

Statistical Analyses

The primary analyses will summarize acceptability (mean score on the SUS) and feasibility (participants utilizing the app at least once during follow-up) of the app, overall for the intervention arm, with asymptotic normal 95% CIs. Point estimates for mean acceptability ≥50 and for proportion accessing the app >0.60 will be considered the minimum criteria for acceptability and feasibility, consistent with industry standards [28,32].

The primary efficacy analysis will compare HIV testing (defined by the proportion that self-reports at least 1 HIV test result during follow-up) between the study arms at 3- and 6-month follow-ups. Group differences in self-reported PrEP-related appointments and documented HIV test results will also be examined at each time point. Moreover, group differences in measures related to the SCT model constructs (eg, HIV testing self-efficacy) will be assessed. The distribution of all variables will be assessed, and appropriate tests will be conducted (ie, parametric chi-square test vs nonparametric Fisher's exact test).

All analyses will use two-tailed tests of significance, with significance at alpha=.05. We will follow an intent-to-treat approach [52], analyzing participants in the study arm to which they were assigned. We will examine the equivalence of random assignment to groups with regards to key baseline characteristics, including sociodemographics, prior HIV testing patterns, and sexual risk-related variables. In the event that randomization does not work to balance these characteristics, we will assess whether baseline differences may account for differences in outcomes.

Results

Recruitment for the RCT began in October 2018, with study follow-up complete by June 2019.

Discussion

Advances in mobile phone technologies have enabled YMSM to have immediate access to broad social and sexual networks. The proposed project responds to the increasingly widespread use of mobile technology in the United States. MyChoices is a theory-driven app that was developed by our interdisciplinary team of HIV clinicians, epidemiologists, behavioral scientists, and app developers based on feedback from a diverse sample of YMSM and will be refined and tested using scientifically rigorous research methods. Therefore, to our knowledge, MyChoices will be one of the first comprehensive, theory-driven HIV prevention apps designed specifically for YMSM. We anticipate that MyChoices will increase HIV testing and linkage to prevention services because it is developmentally appropriate and meets YMSM where they are, in an environment that is familiar and discrete.

Anticipated limitations of this protocol include the self-reported outcomes for HIV testing and PrEP uptake. We will explore obtaining more objective measures of HIV testing and PrEP uptake, including obtaining photographs of test results and PrEP prescriptions. Relatedly, by answering questions about their HIV testing history at follow-up assessments, self-reported outcomes may be influenced that could bias the results. However, the follow-up survey covers a number of topics, including mental health, stigma, and sexual behaviors, and the HIV testing questions are limited. As a result, we do not anticipate substantial misclassification. There is also a risk that participants in the intervention group may discuss with or even show the MyChoices app to participants in the standard of care group (eg, if friends or partners both enroll in the study). To reduce the risk of contamination, study staff will remind the participants at baseline not to discuss the app with peers who might be in the study.

If MyChoices demonstrates acceptability and feasibility in this pilot study, a multicity, 3-arm RCT of this app and another youth-optimized app (LYNX) versus standard of care will be conducted through iTech. If shown to be efficacious, the MyChoices app could be a scalable technology-based solution, with the ability to reach YMSM across the United States, while

maintaining a "geographically individualized" feel with app content integrated with local prevention and testing activities.

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Conflicts of Interest

None declared.

References

1. Centers for Disease Control and Prevention. 2016 Nov. HIV Surveillance Report: Diagnoses of HIV Infection in the United States and Dependent Areas, 2015 URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2015-vol-27.pdf [accessed 2018-11-04] [WebCite Cache ID 73fi1m6i9]
2. Centers for Disease Control and Prevention. 2015 Jul. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data – United States and 6 dependent areas? 2013 URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillancereport_vol20_no2.pdf [accessed 2018-11-04] [WebCite Cache ID 73fiKJpgd]
3. Wejnert C, Hess KL, Rose CE, Balaji A, Smith JC, Paz-Bailey G, NHBS Study Group. Age-Specific Race and Ethnicity Disparities in HIV Infection and Awareness Among Men Who Have Sex With Men--20 US Cities, 2008-2014. J Infect Dis 2016 Mar 01;213(5):776-783. [doi: 10.1093/infdis/jiv500] [Medline: 26486637]
4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 Aug 11;365(6):493-505 [FREE Full text] [doi: 10.1056/NEJMoa1105243] [Medline: 21767103]
5. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-Analysis of High-Risk Sexual Behavior in Persons Aware and Unaware They are Infected With HIV in the United States. JAIDS Journal of Acquired Immune Deficiency Syndromes 2005;39(4):446-453. [doi: 10.1097/01.qai.0000151079.33935.79]
6. Severe P, Jean Juste MA, Ambroise A, Eliacin L, Marchand C, Apollon S, et al. Early versus Standard Antiretroviral Therapy for HIV-Infected Adults in Haiti. N Engl J Med 2010 Jul 15;363(3):257-265. [doi: 10.1056/nejmoa0910370]
7. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010 Dec 30;363(27):2587-2599 [FREE Full text] [doi: 10.1056/NEJMoa1011205] [Medline: 21091279]
8. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016 Jan 02;387(10013):53-60 [FREE Full text] [doi: 10.1016/S0140-6736(15)00056-2] [Medline: 26364263]
9. Sanchez TH, Sineath RC, Kahle EM, Tregear SJ, Sullivan PS. The Annual American Men's Internet Survey of Behaviors of Men Who Have Sex With Men in the United States: Protocol and Key Indicators Report 2013. JMIR Public Health Surveill 2015;1(1):e3 [FREE Full text] [doi: 10.2196/publichealth.4314] [Medline: 27227126]
10. Krakower DS, Mimiaga MJ, Rosenberger JG, Novak DS, Mitty JA, White JM, et al. Limited Awareness and Low Immediate Uptake of Pre-Exposure Prophylaxis among Men Who Have Sex with Men Using an Internet Social Networking Site. PLoS One 2012;7(3):e33119 [FREE Full text] [doi: 10.1371/journal.pone.0033119] [Medline: 22470438]
11. Mayer K, Biello K, Novak D, Krakower D, Mimiaga M. PrEP uptake disparities in a diverse on-line sample of US men who have sex with men. 2017 Feb Presented at: Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Seattle, Washington.
12. Arnett J. Emerging Adulthood: The Winding Road from the Late Teens Through the Twenties. New York, NY: Oxford University Press; 2014.
13. Gruber HE, Voneche JJ, editors. The essential Piaget. London: Routledge & Kegan Paul PLC; 1977.
14. Anderson AM, Higgins MK, Ownby RL, Waldrop-Valverde D. Changes in neurocognition and adherence over six months in HIV-infected individuals with cocaine or heroin dependence. AIDS Care 2015;27(3):333-337 [FREE Full text] [doi: 10.1080/09540121.2014.985183] [Medline: 25484035]
15. Fjeldsoe BS, Marshall AL, Miller YD. Behavior change interventions delivered by mobile telephone short-message service. Am J Prev Med 2009 Feb;36(2):165-173. [doi: 10.1016/j.amepre.2008.09.040] [Medline: 19135907]
16. Blas MM, Alva IE, Carcamo CP, Cabello R, Goodreau SM, Kimball AM, et al. Effect of an online video-based intervention to increase HIV testing in men who have sex with men in Peru. PLoS One 2010 May 03;5(5):e10448 [FREE Full text] [doi: 10.1371/journal.pone.0010448] [Medline: 20454667]
17. Blas MM, Menacho LA, Alva IE, Cabello R, Orellana ER. Motivating men who have sex with men to get tested for HIV through the internet and mobile phones: a qualitative study. PLoS One 2013;8(1):e54012 [FREE Full text] [doi: 10.1371/journal.pone.0054012] [Medline: 23320116]

18. Hirshfield S, Chiasson MA, Joseph H, Scheinmann R, Johnson WD, Remien RH, et al. An online randomized controlled trial evaluating HIV prevention digital media interventions for men who have sex with men. PLoS One 2012;7(10):e46252 [FREE Full text] [doi: 10.1371/journal.pone.0046252] [Medline: 23071551]
19. Ko N, Hsieh C, Wang M, Lee C, Chen C, Chung A, et al. Effects of Internet popular opinion leaders (iPOL) among Internet-using men who have sex with men. J Med Internet Res 2013 Feb 25;15(2):e40 [FREE Full text] [doi: 10.2196/jmir.2264] [Medline: 23439583]
20. Muessig KE, Pike EC, Legrand S, Hightow-Weidman LB. Mobile phone applications for the care and prevention of HIV and other sexually transmitted diseases: a review. J Med Internet Res 2013 Jan 04;15(1):e1 [FREE Full text] [doi: 10.2196/jmir.2301] [Medline: 23291245]
21. Sullivan PS, Driggers R, Stekler JD, Siegler A, Goldenberg T, McDougal SJ, et al. Usability and Acceptability of a Mobile Comprehensive HIV Prevention App for Men Who Have Sex With Men: A Pilot Study. JMIR Mhealth Uhealth 2017 Mar 09;5(3):e26 [FREE Full text] [doi: 10.2196/mhealth.7199] [Medline: 28279949]
22. Biello K, Coffey-Esquivel J, Hosek S, Belzer M, Sullivan P, Oleson S. Development of a mobile-based application to increase uptake of HIV testing among young US men who have sex with men. 2016 Jul Presented at: 2016 International AIDS Conference; July 18-22, 2016; Durban, South Africa.
23. Bandura A. The anatomy of stages of change. Am J Health Promot 1997;12(1):8-10. [doi: 10.4278/0890-1171-12.1.8] [Medline: 10170438]
24. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
25. Milena ZD, Dainora G, Alin S. Qualitative Research Methods: A comparison between focus-group and in-depth interview. Annals of the University of Ordea, Economic Science Series 2008;17(4):1279-1283 [FREE Full text]
26. Kruger RA, Casey MA. Focus Groups: A Practical Guide For Applied Research. Thousand Oaks, CA: Sage Publications; 2015.
27. Carlsen B, Glenton C. What about N? A methodological study of sample-size reporting in focus group studies. BMC Med Res Methodol 2011 Mar 11;11:26 [FREE Full text] [doi: 10.1186/1471-2288-11-26] [Medline: 21396104]
28. Brooke J. SUS – A quick and dirty usability scale. In: Jordan PW, Thomas B, Weerdmeester BA, McClelland IL, editors. Usability evaluation in industry. London, GB: Taylor & Francis; 1996:189-194.
29. Beebe J. Rapid Assessment Process. In: Kempf-Leonard K, editor. Encyclopedia of social measurement. Atlanta, GA: Elsevier; 2005:285-291.
30. Creswell J. Qualitative Inquiry and Research Design: Choosing among Five Approaches. Los Angeles, CA: Sage Publications; 2012.
31. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999 Jan;52(1):19-26. [Medline: 9973070]
32. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: Adding an adjective rating scale. Journal of Usability Studies 2009;4(3):114-123 [FREE Full text]
33. Napper LE, Fisher DG, Reynolds GL. Development of the perceived risk of HIV scale. AIDS Behav 2012 May;16(4):1075-1083 [FREE Full text] [doi: 10.1007/s10461-011-0003-2] [Medline: 21785873]
34. Jamil M, Guy RJ, Bavinton BR, Fairley C, Grulich A, Holt M, FORTH Investigator Group. HIV testing self-efficacy is associated with higher HIV testing frequency and perceived likelihood to self-test among gay and bisexual men. Sex Health 2017 Apr;14(2):170-178. [doi: 10.1071/SH16100] [Medline: 27883311]
35. Johnson MO, Neilands TB, Dilworth SE, Morin SF, Remien RH, Chesney MA. The role of self-efficacy in HIV treatment adherence: validation of the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES). J Behav Med 2007 Oct;30(5):359-370 [FREE Full text] [doi: 10.1007/s10865-007-9118-3] [Medline: 17588200]
36. Brafford LJ, Beck KH. Development and validation of a condom self-efficacy scale for college students. J Am Coll Health 1991 Mar;39(5):219-225. [doi: 10.1080/07448481.1991.9936238] [Medline: 1783705]
37. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? Soc Sci Med 1994 Oct;39(7):887-903. [Medline: 7992123]
38. Donenberg GR, Emerson E, Bryant FB, Wilson H, Weber-Shifrin E. Understanding AIDS-risk behavior among adolescents in psychiatric care: links to psychopathology and peer relationships. J Am Acad Child Adolesc Psychiatry 2001 Jun;40(6):642-653 [FREE Full text] [doi: 10.1097/00004583-200106000-00008] [Medline: 11392341]
39. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction 2002 Sep;97(9):1183-1194. [Medline: 12199834]
40. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
41. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
42. Hatzenbuehler ML, Nolen-Hoeksema S, Erickson SJ. Minority stress predictors of HIV risk behavior, substance use, and depressive symptoms: results from a prospective study of bereaved gay men. Health Psychol 2008 Jul;27(4):455-462. [doi: 10.1037/0278-6133.27.4.455] [Medline: 18643003]

43. Meltzer-Brody S, Churchill E, Davidson JR. Derivation of the SPAN, a brief diagnostic screening test for post-traumatic stress disorder. Psychiatry Research 1999 Oct;88(1):63-70. [doi: 10.1016/s0165-1781(99)00070-0]
44. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010 Nov;63(11):1179-1194 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.04.011] [Medline: 20685078]
45. Catania JA, Osmond D, Stall RD, Pollack L, Paul JP, Blower S, et al. The continuing HIV epidemic among men who have sex with men. Am J Public Health 2001 Jun;91(6):907-914. [Medline: 11392933]
46. Latkin CA, Forman V, Knowlton A, Sherman S. Norms, social networks, and HIV-related risk behaviors among urban disadvantaged drug users. Social Science & Medicine 2003 Feb;56(3):465-476. [doi: 10.1016/s0277-9536(02)00047-3]
47. Williams DR, Yan Y, Jackson JS, Anderson NB. Racial Differences in Physical and Mental Health: Socio-economic Status, Stress and Discrimination. J Health Psychol 1997 Jul;2(3):335-351. [doi: 10.1177/135910539700200305] [Medline: 22013026]
48. Zickuhr K, Smith A. Pew Research Center. 2012 Apr 13. Digital Differences URL: http://www.pewinternet.org/2012/04/13/digital-differences/ [accessed 2018-11-04] [WebCite Cache ID 73fmbzYmG]
49. Smith A. Pew Research Center. 2015 Apr 01. U.S. Smartphone Use in 2015 URL: http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/ [accessed 2018-11-04] [WebCite Cache ID 73fn2mS2h]
50. Lu M, Safren SA, Skolnik PR, Rogers WH, Coady W, Hardy H, et al. Optimal recall period and response task for self-reported HIV medication adherence. AIDS Behav 2008 Jan;12(1):86-94. [doi: 10.1007/s10461-007-9261-4] [Medline: 17577653]
51. Snead MC, O'Leary AM, Mandel MG, Kourtis AP, Wiener J, Jamieson DJ, et al. Relationship between social cognitive theory constructs and self-reported condom use: assessment of behaviour in a subgroup of the Safe in the City trial. BMJ Open 2014 Dec 30;4(12):e006093 [FREE Full text] [doi: 10.1136/bmjopen-2014-006093] [Medline: 25550295]
52. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. JAMA 2014 Jul 02;312(1):85-86. [doi: 10.1001/jama.2014.7523] [Medline: 25058221]

Abbreviations

CASI: computer-assisted self-interviewing
GPS: global positioning system
GIF: graphics interchange format
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SCT: social cognitive theory
SRV: subject recruitment venues
STI: sexually transmitted infection
SUS: System Usability Scale
YMSM: young men who have sex with men

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Protocol

Acute HIV Infection in Youth: Protocol for the Adolescent Trials Network 147 (ATN147) Comprehensive Adolescent Research and Engagement Studies (CARES) Study

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Abstract

Background: Early treatment studies have shown that prompt treatment of HIV with combination antiretroviral therapy (cART) can limit the size of latent viral reservoirs, thereby providing clinical and public health benefits. Studies have demonstrated that adolescents have a greater capacity for immune reconstitution than adults. Nevertheless, adolescents who acquired HIV through sexual transmission have not been included in early treatment studies because of challenges in identification and adherence to cART.

Objective: This study aimed to identify and promptly treat with cART youth aged 12 to 24 years in Los Angeles and New Orleans who have acute, recent, or established HIV infection, as determined by Fiebig stages 1 to 6 determined by viral RNA polymerase chain reaction, p24 antigen presence, and HIV-1 antigen Western blot. The protocol recommends treatment on the day of diagnosis when feasible. Surveillance and dedicated behavioral strategies are used to retain them in care and optimize adherence. Through serial follow-up, HIV biomarkers and response to antiretroviral therapy (ART) are assessed. The study aims to assess viral dynamics, decay and persistence of viral reservoirs over time, and correlate these data with the duration of viral suppression.

Methods: A total of 72 youth (36 acutely infected and 36 treatment naïve controls) are enrolled across clinical sites using a current community-based strategy and direct referrals. Youth are prescribed ART according to the standard of care HIV-1 management guidelines and followed for a period of 2 years. Assessments are conducted at specific time points throughout these 2 years of follow-up for monitoring of adherence to ART, viral load, magnitude of HIV reservoirs, and presence of coinfections.

Results: The study began enrolling youth in July 2017 across study sites in Los Angeles and New Orleans. As of September 30, 2018, a total of 37 youth were enrolled, 12 with recently acquired, 16 with established HIV infection as determined by Fiebig staging, and 9 pending determination of Fiebig status. Recruitment and enrollment are ongoing.

Conclusions: We hypothesize that the size of the HIV reservoir and immune activation markers will be different across groups treated with cART, that is, those with acute or recent HIV infection and those with established infection. Adolescents treated early who are virally suppressed will have diminished HIV reservoirs than those with established infection. These youth may be potential candidates for a possible HIV vaccine and additional HIV remission intervention trials**.** Our study will inform future studies of viral remission strategies.

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KEYWORDS

HIV; youth; adolescents

Introduction

Background

Of the roughly 40,000 people infected with HIV each year, about 25% are youth aged between 13 and 24 years, and more than half of them are not aware of their status [1,2]. Runaway and homeless youth are particularly susceptible to substance abuse, survival sex (prostitution because of extreme need), contact with the juvenile justice system, and sexually transmitted infections (STIs), putting them at a higher risk of acquiring HIV [3,4]. Specifically, African American males engaging in male-to-male contact continue to have the highest risk of HIV [1,2]. One early study found the seroprevalence of HIV in adolescents aged between 13 and 24 years to be 5.3% [5], whereas more recent estimates from the Centers for Disease Control and Prevention (CDC) have been as high as 6.1% [1].

It is believed that individuals who are acutely infected with HIV play a disproportionate role in the transmission of HIV [6,7]. Acute HIV infection is defined as the 4- to 5-week period [8] that occurs between initial HIV-1 exposure and development of HIV-1-specific antibodies (seroconversion). During this time, there is first a burst of viremia, which allows for the detection of p24 antigen, a core viral protein, and HIV RNA but not HIV-specific antibodies. Many patients experience a variety of nonspecific flu-like symptoms in this phase, which bear resemblance to mononucleosis-like syndrome. During this time, patients have significantly elevated HIV burden in the plasma and genital secretions, thus increasing the likelihood of transmission [9,10]. According to the commonly used Fiebig staging classification system for HIV infection, acutely infected patients do not have any detectable HIV antibodies (Fiebig stages 1-2). Recent infection is defined as the next phase in HIV infection when HIV antibodies become detectable by immunoassays but the HIV-specific Western blot (WB) can range from negative to indeterminate to incomplete (missing p31 band), which corresponds to Fiebig stages 3 to 5. This can last anywhere from 30 to 90 days postinitial infection until a full set of HIV antibodies are present [9,11]. Established infection is considered to be the time in which an immune response is fully mounted and is characterized by a plateau in HIV viremia, also known as Fiebig 6 (Figure 1). Data show that acute HIV infectivity is about 5-fold higher than established HIV infectivity [12,13].

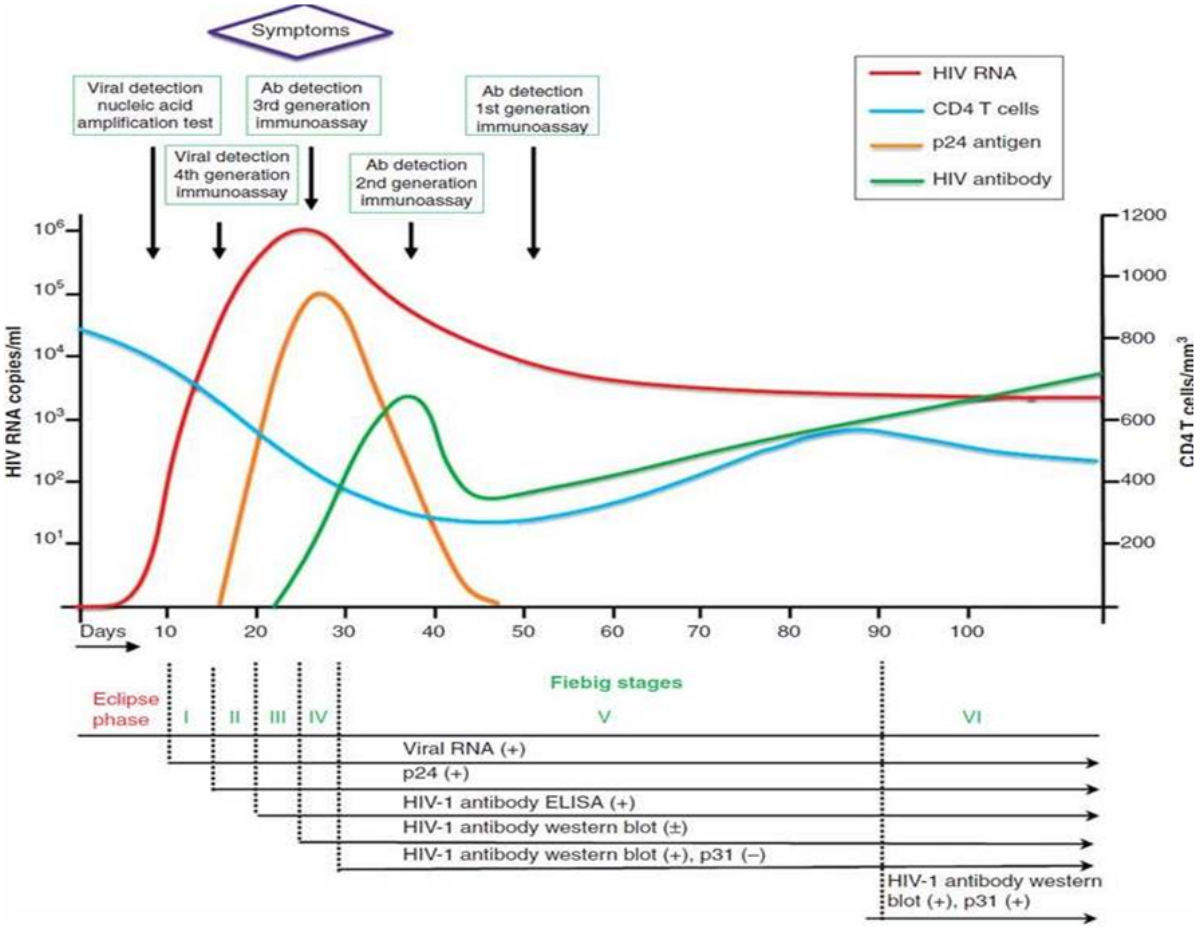
Studies have shown that early detection and treatment of HIV infection have many clinical and public health benefits [14]. Studies of perinatally infected infants have been able to provide important insights about the pathogenesis of acute HIV infection and the need for prompt initiation of antiretroviral therapy. Molecular assays have made it possible to rapidly identify HIV in infants who have been exposed and estimate the duration of infection. On the basis of the time of detection, perinatal transmission of HIV can be classified as in-utero (during gestation), intrapartum (during labor or delivery), or via breastfeeding [15,16]. Studies in which combination antiretroviral therapy (cART) was administered to mothers intrapartum and the newborn shortly after birth showed that HIV perinatal transmission was significantly reduced by two-thirds [17,18]. HIV acquisition was also significantly antiretroviral therapy (ART) was administered to infants in the first 48 hours of life as opposed to previous standards of 3 days or older [18].

To further demonstrate the effectiveness of early antiretroviral therapy on infants, a large multicenter phase 3 trial, National Institute of Child Health and Development HIV Prevention Trials Network 040, conducted by our team of investigators revealed that cART reduced intrapartum HIV transmission by 50% [19] in high-risk HIV-exposed infants whose mothers did not receive cART during pregnancy. A few perinatally infected infants have been able to obtain a period of drug-free remission (plasma HIV undetectable following cessation of cART for more than 1 year). One example is that of a French child born in 1996 who began cART at 3 months of age with treatment for several years and, after drug interruption, experienced long-term drug-free remission that lasted over 12 years [20]. The well-described *Mississippi baby* case began ART 30 hours after birth following high-risk maternal exposure and continued treatment until 18 months of age; this infant experienced drug-free remission for 27 months [21]. Similarly, a recent report of an African child aged 9 years who was treated as an infant for a limited period around 7 weeks of age as part of the Children with HIV Early antiretroviral (CHER) clinical trial has subsequently been in HIV drug-free remission for almost 9 years [22]. These reports provide important information of potential advances in the field in infants and children, whereas little is known about adolescence.

The biggest barrier to HIV remission and cure in children and adults is the presence of latent HIV reservoirs (resting memory T cells and other sites, which contain integrated proviral DNA) [23]. These reservoirs usually reach a set point within the first 2 months of infection and serve as predictors of long-term HIV control [10,24]. When ART is discontinued, these HIV latent reservoirs allow for viral rebound to occur [25,26]. However, if cART is initiated during the acute phase of infection, it is possible to preserve the cluster of differentiation 4 (CD4) T cells and decrease the size of HIV reservoirs [24,27,19]. A period of drug-free remission may then be possible [21]. The French National Agency for Research on AIDS Visconti trial identified 14 adults that were treated during early acute infection and were able to maintain undetectable viral levels for several years after discontinuing cART [28]. Unfortunately, cART initiated after HIV has become established and is not associated with a limit in viral reservoir size or attainment of remission after cessation of cART [29,30].

Traditionally, adolescents who acquired HIV through sexual transmission have not been included in early treatment studies. Identification and adherence to ART and study visits are some of the many challenges associated with enrolling this population. However, data have shown that adolescents retain more residual thymic tissues than adults, giving them a greater capacity for immune reconstitution and CD4 T cell recovery than adults [31,32]. Therefore, it has been suggested that adolescents may be more responsive to early cART than adults with better chances of obtaining drug-free remission [24]. By identifying this population early and promptly initiating potent ART, with adequate surveillance and dedicated behavioral strategies to retain them in care and optimize ART adherence, it may be possible to significantly limit the size of their latent viral reservoirs and preserve their immune systems. This may enable them to better control HIV persistence for long term and allow them the opportunity to participate in additional strategies to induce HIV drug-free remission or become elite posttreatment controllers.

Figure 1. Trajectories of HIV-RNA viremia, CD4 T cells, p24 antigen and HIV antibody over the early phase of HIV infection. Sequence of appearance of different generations of HIV diagnostic assays is presented. Fiebig staging which represents a mean estimation of time from viral acquisition, divided into six phases, has also been superimposed. Eclipse phase is defined by the absence of any marker including p24 and viral RNA. Units for p24 antigen and HIV antibody are not mentioned due to the difference in magnitude. (Routy, J.P., W. Cao, and V. Mehraj, Overcoming the challenge of diagnosis of early HIV infection: a stepping stone to optimal patient management. Expert Rev Anti Infect Ther, 2015. 13(10): p. 1189-93).



Study Aims

This study aimed to identify and promptly initiate potent cART in acutely or recently established HIV-infected youth aged 12 to 24 years in Los Angeles and New Orleans. We hypothesize that the size of the HIV reservoir and immune activation markers will be different across groups treated with cART: those with acute or recent infection and established infection. We predict

that adolescents who are treated early and are virally suppressed during acute or recent infection will have a decreased quantity of HIV reservoirs compared with those with established HIV infection. These youth with low reservoirs and preserved immune systems may be potential candidates for a possible HIV vaccine and additional HIV remission intervention trials.

We expect to recruit youth with acute and recent HIV infection from a large prospective HIV-negative high-risk youth cohort as well as from numerous community clinics. The HIV-negative high-risk youth cohorts are enrolled in a Comprehensive Adolescent Research and Engagement Studies (CARES) partner study, where youth at risk for HIV acquisition are followed periodically for a period of 2 years with point-of-care (POC) periodic HIV testing performed, including fourth generation HIV-1 assays (Alere Determine), GeneXpert qualitative HIV assays (Cepheid), plasma polymerase chain reaction (PCR) assays, and detuned HIV-1/2 enzyme immunoassay. Serial POC testing for syphilis, gonorrhea, and chlamydia are done at the same time points.

On initial identification of HIV infection, following written informed consent, youth are enrolled into the study, with confirmatory HIV RNA performed as well as a standard HIV fourth generation antigen-antibody assays. Study youth have a clinical visit with history, physical examination, and detailed medical or behavioral questionnaire performed. Youth have HIV genotypic susceptibility testing performed and basic hematologic and chemistry panels assessed. They are evaluated for concurrent infections, including syphilis; hepatitis A, B, and C; chlamydia; gonorrhoea; tuberculosis; and cytomegalovirus (CMV). Potent cART is prescribed at the enrollment visit (according to the standard of care procedures or Department of Health and Human Services [DHHS] guidelines and preferably using a single daily pill), and whole blood is collected to perform tests to determine Fiebig staging [11]. Serial follow-up blood samples are obtained in subsequent visits for HIV biomarkers and to monitor response to cART. The aim was to describe and compare viral dynamics, viral decay, and persistence of viral reservoirs in individuals who are acutely, recently, or chronically infected over time, with results correlated with duration of viral suppression. These assays used to measure these parameters include quantitative HIV RNA PCR; measurement of proviral DNA by digital droplet PCR; and studies of HIV-specific immunity, including cellular immunity, cytotoxic T cell responses, immune activation markers, and HIV neutralizing antibody.

Due to the relatively short study duration of 2 years and the need for continuous prolonged viral suppression following cART, we have not included a planned treatment interruption protocol. It is expected that some youth may stop or interrupt therapy because of unanticipated reasons. In these cases, we will strive to reimplement therapy as soon as possible and, meanwhile, will make every effort to closely monitor clinical outcomes and track disease progression. We will definitely strive to re-establish continued cART as soon as possible, particularly to avoid onset of clinical symptoms or presence of detectable plasma viremia >1000 copies/mL. For this purpose, we have a team of counselors and adherence specialists at every visit to encourage ART maintenance. The duration of ART-free HIV remission will be assessed in this subpopulation, and repeat studies of HIV viral reservoirs will be done at baseline and every 2 to 4 months during the ART-free period. Ultimately, in addition to quantifying the viral reservoirs of this unique population, we hope that our overall study will lead to the development of a prolonged HIV remission strategy.

Methods

Design and Population

This is a longitudinal strategic prospective treatment study that identifies, promptly treats, and follows a cohort of adolescent or young adults aged 12 to 24 years who have acute, recent, or established HIV infection. It will measure the effects of early intensive antiretroviral therapy on the establishment and persistence of HIV-1 reservoirs and HIV-1-specific immunity in acutely or recently HIV-infected youth compared with newly diagnosed youth with established infection lasting over 6 months. All youth will be treated according to the standard of care and followed for a period of 24 months.

This study is the first of its kind to enroll a highly at-risk population of HIV-infected adolescents or young adults in the United States. In 2015, among youth aged 13 to 24 years diagnosed in the United States, 81% were gay and bisexual males. Of newly diagnosed male youth, 55% were black, and 24% were Latino [33]. Among youth, an HIV seroprevalence study showed a 5.3% homelessness rate and considered homeless youth to be at highest risk of infection [5]. We have elected to target and enroll youth from 2 HIV epicenters, with large populations of infected and at-risk youth in Los Angeles and New Orleans.

In 2013, a total of 1820 Los Angeles County residents were reported as newly diagnosed with HIV infection, more than that of other urban cities, including Cook County, New York County, Miami-Dade County, and Harris County [34]. Los Angeles contains 6 geographic *hotspots*, which include the following areas: Metro, San Fernando Valley, South Los Angeles, East Los Angeles, San Gabriel, and South Bay [34]. According to a 2015 surveillance report, the New Orleans Metairie area was ranked third based on rate (per 100,000) of HIV diagnosis [33]. The Adolescent Trials Network (ATN) 110 Study in New Orleans screened a total of 200 gay, transgender, and bisexual youth between January and September 2013 and found 9 to be acutely infected, demonstrating the magnitude of the problem in this population [35].

Over a 2-year duration, ATN147 is attempting to enroll a total of 72 youth across clinical sites in Los Angeles and New Orleans. Criteria for study recruitment include (1) age of 12 to 24 years, (2) a positive HIV result (Alere rapid test and GeneXpert HIV qualitative PCR), (3) ability and willingness to provide written informed consent, and (4) willingness to initiate cART. For a physician to treat a participant, they must be willing to follow DHHS guidelines for antiretroviral naïve adolescents and adults [36], including the management of acutely HIV-infected adolescents and adults as outlined in the guidelines.

Youth can be excluded from the study according to the following criteria: (1) prior ART use (>1 week), (2) active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements, (3) any acute, chronic, or recent and clinically significant medical condition that, in the opinion of the site investigator, would interfere with adherence to study requirements or jeopardize the safety or rights of the participant, (4) chronic or recurrent use of medications that modify host immune response, for example, oral or parenteral steroids and cancer chemotherapy, (5) clinical treatment with an ART regimen less effective than those recommended by DHHS HIV clinical guidelines, and (6) enrollment in an experimental ART regimen.

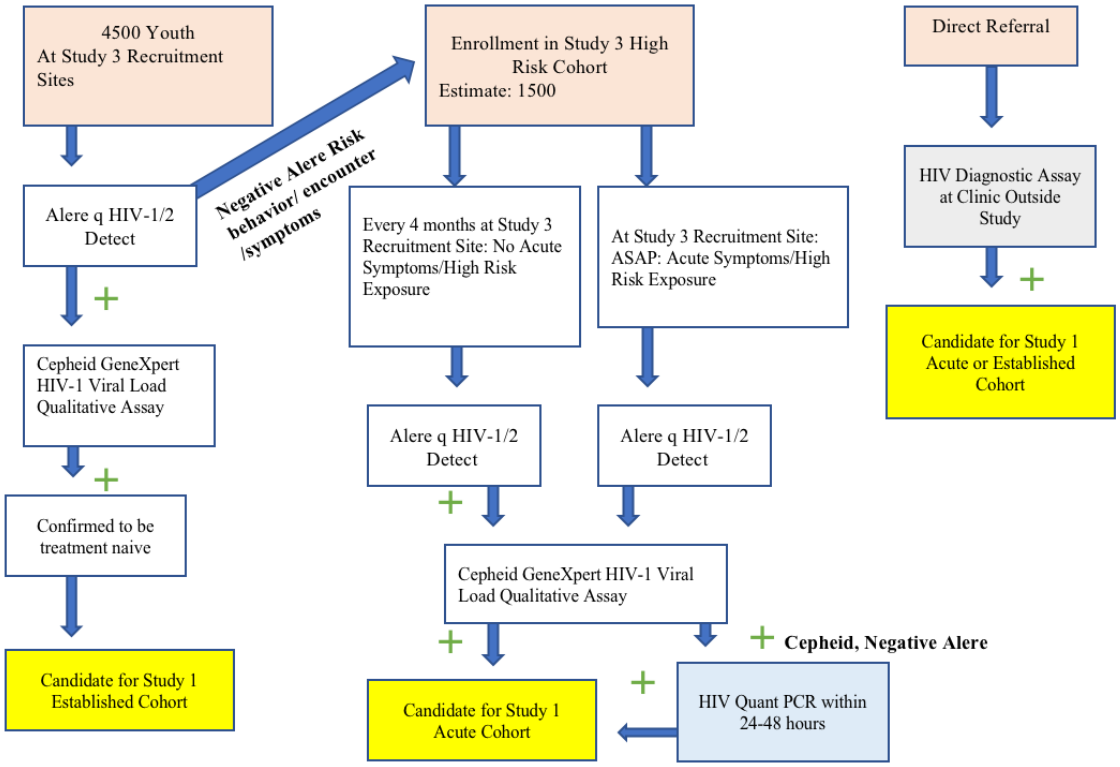
Study Sites and Recruitment

Participating ATN147 study sites include David Geffen University of California at Los Angeles (UCLA) School of Medicine, Department of Pediatrics, Division of Infectious Diseases, the Los Angeles lesbian, gay, bisexual, and transgender (LGBT) Center, and Tulane University School of Medicine, and Department of Adolescent Medicine. Identification and enrollment of acutely or recently infected adolescents are challenging. To address this challenge, we have 2 distinct methods of enrollment: ATN149 CARES and direct referrals as illustrated in Figure 2.

Method 1: Adolescent Trials Network 149: Cost-Efficient Interventions for Youth at Risk for HIV

ATN149 CARES is a study of high-risk HIV seronegative youth who are followed prospectively as part of a community-based strategy conducted by our group of investigators in U19 HD089886-02, a set of coordinated study that concurrently addressed youth living with HIV and seronegative youth. The study initially screens 4500 at-risk youth between the ages of 13 and 24 years at recruitment sites in Los Angeles and New Orleans for clinical and laboratory evidence of HIV using POC testing such as the Alere HIV-1/2 rapid test, which indicates the presence of HIV-1 antibody and/or antigen. In this initial screening phase, if youth are found to have a positive Alere test result and are treatment naïve, they are eligible to enroll in Protocol 147 and are, thus, referred for enrollment. Fiebig staging performed at enrollment will determine the phase of HIV infection these youth are in. Youth who happen to have a positive antigen but a negative antibody test result will undergo additional assessments to determine if they are more acutely infected and will also be referred for enrollment to Protocol 147.

Figure 2. Recruitment study flow. PCR: polymerase chain reaction.



Youth who are found to be seronegative and are assessed as high risk for HIV acquisition based on detailed questionnaires and STI testing are eligible for enrollment into Protocol 149. The estimated sample size of the prospective cohort is 1500 youth who will undergo qualitative and quantitative testing every 4 months for HIV and other STIs over a 2-year period. If

they test positive or report symptoms of acute HIV infection, they become eligible for enrollment into the acute infection Protocol 147.

Method 2: Direct Referrals

Eligible youth referred to the acute infection protocol 147 from urgent care sites, emergency departments, or other clinics can also be enrolled into either the acutely or recently infected cohort or the control cohort based on confirmatory diagnostic testing as long as all eligibility requirements are met.

Diagnosis of HIV Infection and Fiebig Staging

When potential youth are referred for enrollment screening, they may have already tested positive for HIV previously through a POC diagnostic assay. Confirmation of HIV infection is performed with a fourth generation antigen/antibody combo assay followed by a rapid molecular-based test such as the GeneXpert HIV qualitative test and/or Alere q HIV-1/2 Detect along with quantitative HIV RNA and HIV genotypic susceptibility assays. The initial testing algorithm used in the protocol is the same as the one recommended by the CDC for HIV testing, and it encompasses a POC fourth generation HIV antigen/antibody assay. Positive results are confirmed in the study with a quantitative plasma HIV detection nucleic acid assay, also as recommended by the CDC in situations where acute HIV infection is suspected. Normally, 2 HIV nucleic acid assays are not performed per CDC guidelines; however, for study purposes, a qualitative nucleic acid test is first performed in the research laboratory to rule out potentially false-positive fourth generation antigen/antibody combo assay results, particularly as the study aims for same-day treatment initiation. Results for this nucleic acid qualitative assay become available the same day as the clinic visit. An HIV quantitative plasma virus load is also requested in the first study visit; however, results of this laboratory assay take 24 to 48 hours to become available. An HIV WB is performed on stored serum specimens collected on the first clinic visit for determination of Fiebig staging. The study helps inform public health guidelines by rapidly confirming whether plasma HIV viremia is present through the qualitative HIV nucleic acid assays. In this way, patients do not need to wait a few days for virologic confirmation of infection to initiate antiretroviral treatment. This is particularly important in the case of acute infection where HIV antigen/antibody combo assays may not provide definitive results in early infection and is also helpful in situations where false-positive results may occur. Additional diagnostic testing includes CMV PCR of blood; STI testing including gonorrhoea/chlamydia PCR of urine; rapid plasma regain (RPR); Hepatitis panel, which includes hepatitis A, B, and C diagnostic testing; and tuberculosis-Gold quantiFERON testing. Clinical laboratories include a complete blood count with differential and platelets and a chemistry panel, including liver and kidney function tests.

Once enrolled, youth will eventually fall into different categories according to the Fiebig Stage Classification System based on WB results (Table 1), which characterizes the progression of HIV-1 infection from exposure to seroconversion. This staging determines acute or recent or established HIV infection status. Enrollment-visit plasma samples (which are before cART initiation) are used to determine Fiebig staging. On the basis of these stages, youth are placed into 1 of 2 cohorts, which can be further divided into groups as shown in Table 1. We expect to enroll 36 youth in each cohort over a 2-year period. Our acutely or recently infected cohort consists of Fiebig stages 1 to 5 and can be identified based on HIV-1 antibody diagnostic profile. Our control cohort consists of individuals in Fiebig stage 6 who are identified by a positive WB with a p31 band.

Treatment

Starting at the enrollment visit, all youth sign an informed consent, are prescribed cART, and clinically treated according to standard of care HIV-1 management as defined in DHHS guidelines [9]. Genotypic drug resistance testing is performed before initiation of ART to guide the selection of the regimen. Once results of drug resistance testing are available, the treatment regimen can be modified if warranted.

Our study recommends that physicians prescribe fixed-dose combination regimens, favoring once-daily integrase inhibitor–based regimens. Use of complex ART regimens with the inclusion of protease inhibitors may trigger gastrointestinal symptoms and potential loss of adherence by our adolescent or young adult study youth, whereas efficacy of integrase inhibitor (integrase strand transfer inhibitor; INSTI)–based ARTs is successful in suppressing virus more rapidly than non-INSTI-based therapy [37]. By recommending fixed-dose combination once-daily integrase inhibitor–based regimens, we can minimize pill burden and the possibility of ART side effects. We hope that doing so will promote ART adherence and patient satisfaction in a population that is generally not amenable to medication use nor has prior experience with daily medications.

The fixed-dose combination once-daily integrase inhibitor–based regimens recommended may include the single-tablet regimen elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (EVG/COBI/FTC/TAF; Genvoya Foster City, CA: Gilead Sciences, Inc; 2016) [38] or elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil 300 mg (EVG/COBI/FTC/ TDF; Stribild Foster City, CA: Gilead Sciences, Inc; 2016), depending on availability or other similar regimens. EVG/COBI/FTC/TAF has been approved by the US Food and Drug Administration in November 2015 [39] and is similar to the approved single-tablet regimen with TDF but uses the TAF formulation of tenofovir, which appears to have distinct safety advantages. There have been many clinical trials that have included EVG/COBI/FTC/TDF and EVG/COBI/FTC/TAF. One phase-2 study (GS-US-292-0102) treated youth with both regimens and found that, although both groups had increased viral suppression, 88.4% (99/112) of those treated with EVG/COBI/FTC/TAF had HIV-1 RNA less than 50 copies/mL at 48 weeks by snapshot analysis compared with 88% (51/58) in those given EVG/COBI/FTC/TDF [40].

Table 1. Acute, recent, and established HIV infection as per Fiebig staging.

Cohort[a] and group	Fiebig stage	Estmated time from infection (days)	HIV-1 antibody diagnostic profile
Acutely or recently infected (estimated N=36)			
1	1 or 2	0-20	Nonreactive HIV-1 antibody
2	3 or 4	20-30	Reactive HIV-1 antibody; negative or indeterminate results on the Western blot
3	5	30-90	Reactive HIV-1 antibody; positive Western blot without p31 band
Control or established (estimated N=36)			
4	6	90+	Reactive HIV-1 antibody; positive Western blot with p31 band

[a]Adapted from: Fiebig et al study [11].

Table 2. Schedule of evaluations.

Evaluation	Screen	Entry	Week(s)				Month(s)				
			1	2	4	8	4	8	12	18	24
Documentation of acute HIV	X	—[a]	—	—	—	—	—	—	—	—	—
Fiebig staging	—	X	—	—	—	—	—	—	—	—	—
Financial screening	—	X	—	—	—	—	—	—	—	—	—
History	—	X	—	—	—	—	—	—	—	—	—
Physical examination	—	X	X	X	X	X	X	X	X	X	X
Adherence assessment	—	—	X	—	X	—	X	X	X	X	X
Antiretroviral therapy (ART) initiated	—	X	—	—	—	—	—	—	—	—	—
HIV-1/2 enzyme immunoassay fourth generation assay	—	X	—	—	—	—	—	—	—	—	—
HIV-1 genotypic testing	—	X	—	—	—	—	—	—	—	—	—
Urine analysis	—	X	—	—	—	—	—	—	—	—	—
Complete blood count with differential and platelets	—	X	—	X	—	X	X	X	X	X	X
Liver function tests (AST[b], ALT[c], GGT[d])	—	X	—	X	—	X	X	X	X	X	X
Renal function tests (blood urea nitrogen, creatine)	—	X	—	X	—	X	X	X	X	X	X
T cell subsets	—	X	—	X	—	X	X	X	X	X	X
HIV-1 RNA PCR[e] quantitative	—	X	—	X	—	X	X	X	X	X	X
HIV-1 Western blot	—	X	—	—	X	X	—	X	X	X	X
Hepatitis B and C panel	—	X	—	—	—	—	—	—	—	—	—
Rapid plasma regain	—	X	—	—	—	—	—	—	—	—	—
Gonorrhea/chlamydia PCR of urine, oropharynx, and rectum	—	X	—	—	—	—	—	—	—	—	—
Cytomegalovirus PCR blood	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
Pregnancy test	—	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
Reservoir study laboratories (mL)	—	30	10	10	10	10	30	10	30	10	30

[a]Not applicable.
[b]AST: aspartate aminotransferase.
[c]ALT: alanine aminotransferase.
[d]GGT: gamma-glutamyl transferase.
[e]PCR: polymerase chain reaction.
[f]If clinically suspected.
[g]Whenever pregnancy is suspected.

Other potent antiretroviral regimens may be prescribed by the physician based on availability, patient tolerability, and preference. Changes to antiretroviral regimens should be performed when necessary according to HIV management

guidelines [41]. Patients who do not tolerate the ART regimens will be prescribed an alternative ART regimen as clinically indicated. The same will occur with subjects who do not achieve viral load remission, and they may be prescribed an alternative ART regimen as clinically indicated.

Youth will take study medications and come for follow-up visits with physicians at clinic sites for up to 24 months according to the schedule of evaluations (Table 2) for assessment of viral load and HIV reservoir assays, as well as monitoring of coinfections. In addition to the enrollment visit, there will be a total of 9 follow-up visits during which samples will be collected for clinical Laboratoriess and immune reservoir studies. Of the 10 visits, 8 are scheduled during the first 12 months of ART, with 2 subsequent visits performed at 18 and 24 months.

The HIV WB is a part of immune reservoir studies and does not need to be repeated if it shows a full profile Fiebig stage 6 until 1 year. If subjects cannot do both a 2-week and 4-week follow-up visit, it is acceptable to combine the 2 visits into 1 as long as all clinical laboratory assays specified for week 4 are taken. The window periods (not shown in table) are as follows: −7 days for screen; ±7 days for week 1; ±14 days for weeks 2 and 4; ±7 days for week 8; and ±14 days for 4, 8, 12, and 24 months. In the event of virologic failure (not shown in table), HIV-1 genotypic testing will be conducted. In the event of premature study or treatment discontinuation (not shown), our team will try to collect HIV-1 genotypic testing, T cell subsets, HIV RNA quantitative assay, and 30 mL for immune reservoir studies.

Evaluations and Activities

Screening Visit: Day of Diagnosis

During screening, youth are asked a series of questions as part of protocol 147 procedures. If HIV diagnosis is confirmed, a baseline interview will be conducted or if previously completed in study 3, a completed assessment interview will be performed. If youth are referred from other health care providers, the baseline assessment occurs after enrollment into the acute infection Protocol 147 (Table 2).

Study Entry: Day 0

Although screening visit and day 0 may occur on the same day, subjects are enrolled within 48 to 72 hours of an HIV diagnosis, and every attempt is made for treatment initiation to happen on the day of the first study visit. On this day, any necessary confirmatory diagnostic testing is performed, and those who are eligible for the study will provide written informed consent for study participation. Behavioral interventions are provided, and demographic and medical histories are collected and recorded in case report forms. A physical examination is performed, and information regarding clinical signs, symptoms, findings of acute HIV infection, and clinical treatment initiation are recorded. Patients are prescribed antiretrovirals for treatment initiation at this first visit.

If youth newly identified with HIV infection report a partner with unknown or negative HIV serostatus, we invite the study participant to bring their partner to clinic for HIV voluntary testing and counseling and also for pre-exposure prophylaxis (PrEP) initiation as part of overall HIV prevention efforts. If partners are seronegative, they are prescribed PrEP and referred to another ATN companion study (ATN149), where high-risk HIV seronegative youth are followed over time.

A number of clinical laboratory assays are performed and include the following: (1) complete blood count with differential and platelets, (2) liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transferase [GGT]), renal function tests (blood urea nitrogen [BUN] and creatinine), (3) CMV PCR blood if clinically suspected, (4) urine analysis, (5) gonorrhoea/chlamydia PCR of urine (6) RPR, (7) Hepatitis A, B, and C panel, (8) HIV-1 genotypic testing, (9) T cell subsets, and (10) urine pregnancy test (if female) and TB-Gold quantiFERON testing. In addition to these clinical laboratory assays, 30 mL of whole blood is collected for immune reservoir studies. Pregnancy testing is also performed if applicable.

Study Visits Postantiretroviral Therapy Initiation: Day 7, Week 8

A physical examination is performed, and information regarding clinical signs, symptoms, and findings of acute HIV infection or side effects from medication are recorded. Viral load testing, complete blood count, and chemistries are performed. Adherence assessment is performed, and pregnancy testing performed if applicable. In addition, 10 mL of whole blood is collected for immune reservoir studies.

Study Visits Postantiretroviral Therapy Initiation: Weeks 2 and 4

A physical examination is performed, and information regarding clinical signs, symptoms, and findings of acute HIV infection or side effects from medication are recorded. Adherence is assessed, and the following clinical laboratory assays are performed: (1) complete blood count with differential and platelets, (2) liver function tests (AST, ALT, and GGT) and renal function tests (BUN and creatinine), (3) HIV-1 genotypic testing (if clinically indicated or detectable viremia), (4) T cell subsets, (5) HIV-1 RNA PCR quantitative, and (6) urine pregnancy test (if suspected). In addition to these clinical laboratory assays, 10 mL of whole blood is collected for immune reservoir studies. At week 4, an HIV-1 WB is performed unless previous results showed a full profile Fiebig stage 6 (in that case, HIV-1 WB will be conducted at the 1-year mark).

Study Visits Postantiretroviral Therapy Initiation: Months 4, 8, 12, 18, and 24

A physical examination is performed, and information regarding clinical signs, symptoms, and findings of acute HIV infection or side effects from medication are recorded. Adherence is assessed, and the following clinical laboratory assays are performed: (1) complete blood count with differential and platelets, (2) liver function tests (AST, ALT, and GGT) and renal function tests (BUN and creatinine), (3) HIV-1 genotypic testing (if clinically indicated or detectable viremia), (4) T cell subsets, (5) HIV-1 RNA PCR quantitative, and (6) urine pregnancy test (if suspected). In addition to these clinical laboratory assays, 30 mL of whole blood is collected for immune reservoir studies.

Immune Reservoir Studies

At enrollment, collection of 30 mL of (pretreatment) whole blood is collected and used to determine Fiebig staging through the following tests: (1) HIV-1 POC antibody test (fourth generation assay), (2) HIV-1 WB, and (3) HIV-1 quantitative RNA PCR. In addition, digital droplet PCR to measure full-length and partial HIV combination DNA transcripts are performed at enrollment and for each of the 9 subsequent follow-up visits. These tests allow the evaluation of continued reservoir suppression and sustainability of antiretroviral effect while comparing HIV viral dynamics across subject groups. The total amount of blood to be obtained during each study visit should not exceed 30 mL for youth weighing <50 kg.

The primary study endpoint is 24 months following enrollment, when the amount of cell-associated HIV-1 DNA in 5 million total peripheral blood mononuclear cells (assayed by quantitative digital drop PCR) will be compared between individuals initiating ART at different Fiebig stages: 1/2 versus 3/4 versus 5 versus established infection (Fiebig 6 control arm). We will also have HIV reservoir studies assessed at 4, 8, 12, 18, and 24 months. These data will be important to assess for studies of reservoir decay as well if there is drop out or loss to follow-up or evidence of viral rebound.

Statistical Considerations

Descriptive Statistics

The results of this study will be primarily descriptive. In acute cases, the Fiebig score at the time of initiation of ART and the time to suppression of plasma viremia will be summarized over time as mean (SD). The analyses of immune biomarker assessments follow the same analysis.

Regression Analysis

The effects of Fiebig stage on follow-up results will be assessed in these longitudinal analyses using either numerical Fiebig stage or estimated time to initiation of ART as predictors, including stage or stage by time interaction. Drop-out is also important to assess as a binary outcome and will also be assessed with the same approach. Covariates such as STI coinfection, age, race, and behavioral assessments will be considered as potential confounders and included in the regression analysis if they confound the crude analysis. In addition, quantity of provirus over time is a longitudinal analysis. If the data are primarily described as being below detectable limits or not, longitudinal logistic regression will be conducted. If the outcome is numerical, a linear longitudinal analysis to assess the level and time trend will be conducted. Regression analysis will be conducted using the statistical package R (R version 3.0.1; The R Foundation for Statistical Computing).

Strategies for Retention and Adherence

Study youth will be receiving adherence support through a designated case manager and adherence coach, who will already be assigned to the participant to facilitate antiretroviral use, maintenance of appointments, and facilitate overall care. All DHHS guideline recommendations for enhanced adherence will be implemented for study youth. For patients in whom adherence is identified as a major challenge, we will implement directly observed therapy. To facilitate adherence, patients will be offered free transportation to clinic and will receive continuous coaching and encouragement from a designated case manager. In addition, as this study is conducted in partnership with psychiatry and clinical psychologists, they will be available and will provide support and guidance in the management of these patients.

Human Subjects Protection and Ethical Considerations

ATN147 has been reviewed and approved by the institutional review board (IRB) of participating institutions (UCLA IRB registration IRB #16-001819). The study focuses on prompt initiation of antiretroviral treatment on an HIV diagnosis, which is in accordance with current DHHS guidelines. The antiretrovirals that study participants initiate are first-line therapeutic options for HIV. In this way, the study implements recommended standard of care management of newly HIV-diagnosed youth. Study participants are paired with counselors and interviewers or coaches who are available for all subjects. Detailed assessments are made at each study visit of the patient's mental status and outside activities, including the presence of other STIs and substance abuse. Participants are referred to mental health care, and resources for housing and employment are made available to them. As part of our overall HIV youth program, they are also eligible to receive Ryan White's support for medical services. They also have access to a care coordinator and social worker to assist with their needs. Subjects are able to contact a medical provider at any time to address medical questions, including mental health issues. The study provides the background infrastructure with resources and referrals, also through the clinical sites, which are well-seasoned sites in the care of youth with HIV. Study participants are screened for depression at each visit, and if they express intent to harm themselves, they are immediately put in contact with a mental health provider for further assessment. The possibility of participants being victims of violence or participating in criminal activities is thoroughly discussed during their study interviews, with resources put in place to protect and safeguard them under this scenario. Referrals are made to local organizations such as the LGBT Center and Covenant House for support and housing needs.

Results

The study began enrolling youth in July 2017 across study sites in Los Angeles and New Orleans. As of September 30, 2018, a total of 37 youth were enrolled, 12 with recently acquired, 16 with established HIV infection as determined by Fiebig staging, and 9 pending determination of Fiebig status. Recruitment and enrollment are ongoing.

Discussion

Significance of Study

Acute HIV infection in youth is a strategic treatment study aimed to identify and promptly treat recently acquired HIV with ART in youth aged 12 to 24 years who are enrolled in Los Angeles and New Orleans. This population is unique as participants are of an age in which their immune systems are

more mature than that of children, yet have a greater capacity for immune reconstitution and pliability of HIV reservoirs than that of adults [24]. Our study is the first of its kind to characterize reservoirs of an adolescent population, which is generally not amenable to routine clinic visits but is at a high risk of transmission. However, through the use of a multidisciplinary approach taken in collaboration with a group of behavioral scientists, we intend to follow this cohort for 2 years and have all youth enrolled by 2019 to allow for a 2-year follow-up.

Principal Aims

In addition to lowering transmission in this population, our goal is to uncover new data that will inform future remission studies. The inability of cART to eradicate infected cells [42] and the fact that plasma viremia rebounds quickly after treatment discontinuation [43] are reasons why remission as a functional cure is considered a more viable goal [28]. So far, studies have shown that HIV remission is possible in both perinatally infected infants and acutely infected adults [18,28]. We believe that this is definitely possible for acutely infected adolescents as well. We hypothesize that the size of the HIV reservoir and immune activation markers will be different across groups treated with cART, that is, those with an acute or recent HIV infection and those with an established infection. Adolescents treated early who are virally suppressed will have diminished HIV reservoirs than those with established infection. By quantifying viral reservoirs of this unique population, we hope to uncover new data that will be applicable to the general HIV-infected population beyond adolescents and possibly lead to the development of a prolonged HIV remission strategy in the future.

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Conflicts of Interest

None declared.

References

1. Centers for Disease Control and Prevention. 2018. Estimated HIV incidence and prevalence in the United States, 2010-2015 URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-23-1.pdf [accessed 2018-11-23] [WebCite Cache ID 748YQ4vQr]
2. Hall HI, Song R, Tang T, An Q, Prejean J, Dietz P, et al. HIV trends in the United States: diagnoses and estimated incidence. JMIR Public Health Surveill 2017 Feb 03;3(1):e8 [FREE Full text] [doi: 10.2196/publichealth.7051] [Medline: 28159730]
3. Allen DM, Lehman JS, Green TA, Lindegren ML, Onorato IM, Forrester W. HIV infection among homeless adults and runaway youth, United States, 1989-1992. Field Services Branch. AIDS 1994 Nov;8(11):1593-1598. [Medline: 7848596]
4. Greene JM, Ennett ST, Ringwalt CL. Prevalence and correlates of survival sex among runaway and homeless youth. Am J Public Health 1999 Sep;89(9):1406-1409. [Medline: 10474560]
5. Stricof RL, Kennedy JT, Nattell TC, Weisfuse IB, Novick LF. HIV seroprevalence in a facility for runaway and homeless adolescents. Am J Public Health 1991 May;81 Suppl:50-53. [Medline: 2014885]
6. Pilcher CD, Tien HC, Eron JJ, Vernazza PL, Leu S, Stewart PW, Quest Study, Duke-UNC-Emory Acute HIV Consortium. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis 2004 May 15;189(10):1785-1792. [doi: 10.1086/386333] [Medline: 15122514]
7. Pilcher CD, Shugars DC, Fiscus SA, Miller WC, Menezes P, Giner J, et al. HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment and public health. AIDS 2001 May 04;15(7):837-845. [Medline: 11399956]
8. Krebs SJ, Ananworanich J. Immune activation during acute HIV infection and the impact of early antiretroviral therapy. Curr Opin HIV AIDS 2016 Mar;11(2):163-172. [doi: 10.1097/COH.0000000000000228] [Medline: 26599167]
9. AIDSinfo. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents URL: https://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf [accessed 2018-04-05] [WebCite Cache ID 6ySTiR8C6]
10. Robb ML, Ananworanich J. Lessons from acute HIV infection. Curr Opin HIV AIDS 2016 Nov;11(6):555-560 [FREE Full text] [doi: 10.1097/COH.0000000000000316] [Medline: 27716734]
11. Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003 Sep 05;17(13):1871-1879. [doi: 10.1097/01.aids.0000076308.76477.b8] [Medline: 12960819]
12. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. N Engl J Med 2011 May 19;364(20):1943-1954 [FREE Full text] [doi: 10.1056/NEJMra1011874] [Medline: 21591946]
13. Abu-Raddad LJ. Role of acute HIV infection in driving HIV transmission: implications for HIV treatment as prevention. PLoS Med 2015 Mar;12(3):e1001803 [FREE Full text] [doi: 10.1371/journal.pmed.1001803] [Medline: 25781617]

14. Rutstein SE, Ananworanich J, Fidler S, Johnson C, Sanders EJ, Sued O, et al. Clinical and public health implications of acute and early HIV detection and treatment: a scoping review. J Int AIDS Soc 2017 Dec 28;20(1):21579 [FREE Full text] [doi: 10.7448/IAS.20.1.21579] [Medline: 28691435]
15. Oxtoby MJ. Vertically Acquire HIV Infection in the United States. In: Pediatric AIDS: The Challenge of HIV Infection in Infants, Children, and Adolescents. 2 ed. Baltimore, MD: Williams & Wilkins; 1994:3-20.
16. Mofenson L. Current Insights Regarding Vertical Transmission. In: Pediatric AIDS: The Challenge of HIV Infection in Infants, Children, and Adolescents. 2 ed. Baltimore, MD: Williams & Wilkins; 1994:179-203.
17. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994 Nov 03;331(18):1173-1180. [doi: 10.1056/NEJM199411033311801] [Medline: 7935654]
18. Wade NA, Birkhead GS, Warren BL, Charbonneau TT, French PT, Wang L, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 1998 Nov 12;339(20):1409-1414. [doi: 10.1056/NEJM199811123392001] [Medline: 9811915]
19. Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, Pilotto JH, NICHD HPTN 040/PACTG 1043 Protocol Team. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med 2012 Jun 21;366(25):2368-2379 [FREE Full text] [doi: 10.1056/NEJMoa1108275] [Medline: 22716975]
20. Frange P, Faye A, Avettand-Fenoël V, Bellaton E, Descamps D, Angin M, ANRS EPF-CO10 Pediatric Cohortthe ANRS EP47 VISCONTI study group. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. Lancet HIV 2016 Jan;3(1):e49-e54. [doi: 10.1016/S2352-3018(15)00232-5] [Medline: 26762993]
21. Persaud D, Gay H, Ziemniak C, Chen YH, Piatak M, Chun T, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med 2013 Nov 07;369(19):1828-1835 [FREE Full text] [doi: 10.1056/NEJMoa1302976] [Medline: 24152233]
22. Violari A. Viral and host characteristics of a child with perinatal HIV-1 following a prolonged period after ART cessation in the CHER trial. 2017 Presented at: 9th IAS Conference on HIV Science; 2017; Paris, France.
23. Chun TW, Engel D, Berrey MM, Shea T, Corey L, Fauci AS. Early establishment of a pool of latently infected, resting CD4(+) T cells during primary HIV-1 infection. Proc Natl Acad Sci U S A 1998 Jul 21;95(15):8869-8873 [FREE Full text] [Medline: 9671771]
24. Rainwater-Lovett K, Uprety P, Persaud D. Advances and hope for perinatal HIV remission and cure in children and adolescents. Curr Opin Pediatr 2016 Feb;28(1):86-92 [FREE Full text] [doi: 10.1097/MOP.0000000000000304] [Medline: 26709685]
25. Blankson JN, Persaud D, Siliciano RF. The challenge of viral reservoirs in HIV-1 infection. Annu Rev Med 2002;53:557-593. [doi: 10.1146/annurev.med.53.082901.104024] [Medline: 11818490]
26. Chun T, Justement JS, Murray D, Hallahan CW, Maenza J, Collier AC, et al. Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication. AIDS 2010 Nov 27;24(18):2803-2808 [FREE Full text] [doi: 10.1097/QAD.0b013e328340a239] [Medline: 20962613]
27. Williams JP, Hurst J, Stöhr W, Robinson N, Brown H, Fisher M, SPARTACTrial Investigators. HIV-1 DNA predicts disease progression and post-treatment virological control. Elife 2014 Sep 12;3:e03821 [FREE Full text] [doi: 10.7554/eLife.03821] [Medline: 25217531]
28. Sáez-Cirión A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, ANRS VISCONTI Study Group. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog 2013 Mar;9(3):e1003211 [FREE Full text] [doi: 10.1371/journal.ppat.1003211] [Medline: 23516360]
29. Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 1997 Nov 14;278(5341):1295-1300 [FREE Full text] [Medline: 9360927]
30. Katlama C, Deeks SG, Autran B, Martinez-Picado J, van LJ, Rouzioux C, et al. Barriers to a cure for HIV: new ways to target and eradicate HIV-1 reservoirs. Lancet 2013 Jun 15;381(9883):2109-2117 [FREE Full text] [doi: 10.1016/S0140-6736(13)60104-X] [Medline: 23541541]
31. Sandgaard KS, Lewis J, Adams S, Klein N, Callard R. Antiretroviral therapy increases thymic output in children with HIV. AIDS 2014 Jan 14;28(2):209-214. [doi: 10.1097/QAD.0000000000000063] [Medline: 24072195]
32. Mackall CL, Fleisher TA, Brown MR, Andrich MP, Chen CC, Feuerstein IM, et al. Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy. N Engl J Med 1995 Jan 19;332(3):143-149. [doi: 10.1056/NEJM199501193320303] [Medline: 7800006]
33. Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28. 2017 Nov. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2016-vol-28.pdf [accessed 2019-01-08] [WebCite Cache ID 75HBsIrR0]
34. Division of HIV and STD Programs, Los Angeles County Department of Public Health. 2014 Annual HIV/STD Surveillance Report. 2016 Feb. URL: http://publichealth.lacounty.gov/dhsp/Reports/HIV-STDsurveillanceReport2014.pdf

35. Hosek SG, Rudy B, Landovitz R, Kapogiannis B, Siberry G, Rutledge B, Adolescent Trials Network (ATN) for HIVAIDS Interventions. An HIV preexposure prophylaxis demonstration project and safety study for young MSM. J Acquir Immune Defic Syndr 2017 Jan 01;74(1):21-29. [doi: 10.1097/QAI.0000000000001179] [Medline: 27632233]
36. AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV URL: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/11/what-to-start [accessed 2018-11-23] [WebCite Cache ID 748Ubm0W0]
37. Tang Q, Lu H. Latest advances in the efficacy, tolerability, and monotherapy of integrase inhibitors. Biosci Trends 2017;11(4):490-495 [FREE Full text] [doi: 10.5582/bst.2017.01194] [Medline: 28904329]
38. Genvoya [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016. URL: https://www.gilead.com/ [accessed 2018-11-26] [WebCite Cache ID 74E2wqFVK]
39. Administration US Center For Drug Evaluation And Research. Genvoya NDA 207561 Approval Letter. 2015 Nov 5. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207561Orig1s000Approv.pdf [accessed 2018-04-04] [WebCite Cache ID 6ySTvTGhP]
40. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr 2014 Sep 01;67(1):52-58. [doi: 10.1097/QAI.0000000000000225] [Medline: 24872136]
41. AIDSInfo. URL: https://aidsinfo.nih.gov/ [accessed 2018-11-22] [WebCite Cache ID 748Q26fcf]
42. Wong JK, Hezareh M, Günthard HF, Havlir DV, Ignacio CC, Spina CA, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. Science 1997 Nov 14;278(5341):1291-1295 [FREE Full text] [Medline: 9360926]
43. Bongiovanni M, Casana M, Tincati C, d'Arminio MA. Treatment interruptions in HIV-infected subjects. J Antimicrob Chemother 2006 Sep;58(3):502-505. [doi: 10.1093/jac/dkl268] [Medline: 16816398]

Abbreviations

ALT: alanine aminotransferase
ART: antiretroviral therapy
AST: aspartate aminotransferase
ATN: Adolescent Trials Network
BUN: blood urea nitrogen
CARES: Comprehensive Adolescent Research and Engagement Studies
cART: combination antiretroviral therapy
CD4: cluster of differentiation 4
CDC: Centers for Disease Control and Prevention
CMV: cytomegalovirus
COBI: cobicistat
DHHS: Department of Health and Human Services
EVG: elvitegravir
FTC: emtricitabine
GGT: gamma-glutamyl transferase
INSTI: integrase strand transfer inhibitor
IRB: institutional review board
LGBT: lesbian, gay, bisexual, and transgender
PCR: polymerase chain reaction
POC: point-of-care
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
TAF: tenofovir alafenamide
TDF: tenofovir disoproxil
UCLA: University of California at Los Angeles
WB: Western blot

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Protocol

Strategies to Treat and Prevent HIV in the United States for Adolescents and Young Adults: Protocol for a Mixed-Methods Study

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Abstract

Background: Over 20% of HIV diagnoses in the United States are among youth aged 12-24 years. Furthermore, youth have the lowest rates of uptake and adherence to antiretroviral (ARV) medications and are least aware of their HIV status.

Objective: Our objective was to design a set of interrelated studies to promote completion of each step of the HIV Prevention Continuum by uninfected youth at high risk (YHR), as well as completion of steps in the Treatment Continuum by youth living with HIV (YLH).

Methods: Gay, bisexual, and transgender youth; homeless youth; substance-abusing youth; youth with criminal justice contact; and youth with significant mental health challenges, particularly black and Latino individuals, are being recruited from 13 community-based organizations, clinics, drop-in centers, and shelters in Los Angeles and New Orleans. Youth are screened on the basis of self-reports and rapid diagnostic tests for HIV, drug use, and sexually transmitted infections and, then, triaged into one of 3 studies: (1) an observational cohort of YLH who have never received ARV medications and are then treated—half initially are in the acute infection period (n=36) and half with established HIV infection (n=36); (2) a randomized controlled trial (RCT) for YLH (N=220); and (3) an RCT for YHR (N=1340). Each study contrasts efficacy and costs of 3 interventions: an automated messaging and weekly monitoring program delivered via text messages (short message service, SMS); a peer support intervention delivered via social media forums; and coaching, delivered via text message (SMS), phone, and in-person or telehealth contacts. The primary outcomes are assessing youths' uptake and retention of and adherence to the HIV Prevention or Treatment Continua. Repeat assessments are conducted every 4 months over 24 months to engage and retain youth and to monitor their status.

Results: The project is funded from September 2016 through May 2021. Recruitment began in May 2017 and is expected to be completed by June 2019. We expect to submit the first results for publication by fall 2019.

Conclusions: Using similar, flexible, and adaptable intervention approaches for YLH and YHR, this set of studies may provide a roadmap for communities to broadly address HIV risk among youth. We will evaluate whether the interventions are cost-efficient strategies that can be leveraged to help youth adhere to the actions in the HIV Prevention and Treatment Continua.

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KEYWORDS

gay, bisexual, and transgender youth; HIV/AIDS; homelessness; LGBTQ; mobile phone

Introduction

Adolescents represent over 20% of HIV cases in the United States [1]. Far fewer youth access the biomedical treatments available to prevent transmission and treat HIV infection compared with adults [1]. These treatments include early identification of HIV infection through repeat HIV testing, pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) to prevent infection, and the use of antiretroviral (ARV) medications, or Treatment as Prevention, to reduce the risk of transmitting HIV among those living with HIV [2-4]. To stop HIV infection among adolescents, the Office of AIDS Research at the National Institutes of Health (NIH) [5] has identified a set of broadly implemented innovative intervention strategies that are consistent with the following principles:

1. The biomedical strategies to treat HIV are increasingly similar to those to prevent the acquisition of HIV; similar strategies can be successful with youth of different serostatus.
2. Syntheses of evidence-based HIV intervention programs developed over the last 30 years provide models and practices that can be used in today's interventions.
3. Mobile technologies are an efficient strategy for sharing information, sending messages, engaging youth, and enhancing self-monitoring, regardless of the platform used.
4. Interventions should be the least intensive needed to obtain health-protective behaviors by any individual youth. A Stepped Care approach—which initially provides minimal intervention and only increases the intensity of the intervention if no change occurs—may be more effective and cost efficient than providing the same intervention package to all youth.
5. HIV prevention and treatment must be planned, tailored, and executed at a local level.
6. Our scientific breakthroughs are only relevant if we can recruit, retain, and keep youth living with HIV (YLH) and youth at high risk (YHR) of acquiring HIV engaged in health care and adherent lifelong to prevention and treatment services.

A set of 3 interrelated studies, known as the Comprehensive Adolescent Research and Engagement Studies (CARES), is being mounted to evaluate strategies to increase youth's uptake, maintenance, and retention in the HIV Prevention and Treatment Continua [2-4].

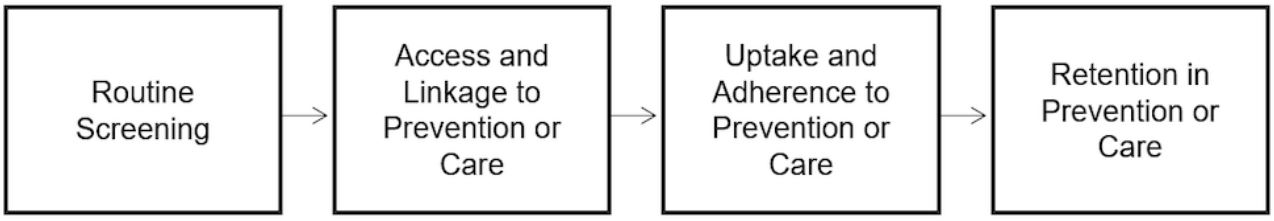
Participants are acutely infected YLH, YLH with established HIV infection, and YHR. This paper summarizes the rationale behind these studies, including the recruitment, retention, assessment, and intervention strategies common across them. Individual protocol papers in this volume outline each specific trial [6-8]. The integrated data analytic protocols [9] and strategies for monitoring sexually transmitted infections (STI) across the studies [10] are concurrently available.

YLH and YHR in the United States are largely gay and bisexual males and transgender youth (GBTY), with black and Latino GBTY accounting for the majority of HIV diagnoses among adolescents [1,11]. In addition, young people with mental health and substance abuse disorders, those who experience homelessness and sexual abuse, and those with histories of incarceration are at increased risk for acquiring HIV [12-15]. These subgroups are overrepresented among black and Latino, low-income youth. YLH in the United States are concentrated in the South and along the West and East Coasts, with the majority of YLH living in urban areas [11]. We selected Los Angeles (LA) and New Orleans—two HIV epicenters diverse in geography, the demographic distribution of HIV, and cultural characteristics—for conducting the 3 studies. By designing and testing interventions in these two cities, we aim to demonstrate the efficacy of the same intervention strategies and principles tailored to substantially different settings.

The intervention strategies for YLH and YHR are increasingly similar. Rather than creating separate programs, one team can implement services for both subgroups. ARV medications have now been demonstrated effective for both: (1) achieving HIV viral suppression, reducing risk of HIV transmission, and increasing the quality and length of life for persons living with HIV and (2) reducing acquisition of HIV among seronegative persons, that is, the success of Treatment as Prevention [2]. These breakthroughs have shifted the loci of almost all prevention and treatment services from community to medical settings. At present, 78% of federal HIV funding is in medical settings compared with 53% in 1998 [16]; this shift has two major implications for HIV prevention for youth.

First, the HIV Prevention Continuum and the HIV Treatment Continuum [2-4,17] are similar in the tasks that are required for youth, as shown in Figure 1. Whether a young person is a YLH or a YHR, each must be linked to medical care, have insurance to cover payments for medical care, and have the transportation and skills to navigate a medical system. In addition, optimal care for both YLH and YHR is to prescribe ARV medications, again, resulting in the need for both to adhere to medical regimens over time, have regular check-ups, and anticipate when their medications need refills. Both YLH and YHR must be monitored for issues like side effects and toxicities over time.

Figure 1. Similarity of the HIV Prevention Continua for seronegative youth at high risk for HIV and the HIV Treatment Continua for youth living with HIV.



Because such a high percentage of YLH and YHR are GBTY, it is typical that youth must cope with stigma from others toward their sexual orientation [18]. The stigma can occur when disclosing their sexual orientation, gender identity, or HIV status to others [18]. These similarities again suggest that the interventions for these youth can be fundamentally similar.

Second, HIV services concentrated in medical settings often do not reach the youth who need them the most. Adolescents and young adults, particularly young men, do not engage in health care visits routinely, and black and Latino adolescents are less likely to utilize medical care than peers of other ethnicities [19]. YLH are more likely than adults living with HIV to be homeless, recently incarcerated, uninsured, or living in a low-income household [1]. These factors can serve as barriers to seeking medical care for HIV prevention and treatment. Street outreach programs, shelters, bars, hook-up settings, or social media sites associated with risk behaviors (eg, Grindr) are the most likely places to access these youth. Furthermore, providers are uncomfortable bringing up sexuality; 40% have difficulty bringing up the human papillomavirus vaccine, even with parents [20]. Thus, community-based recruitment efforts are likely to identify YLH and YHR in need of services, as well as medical clinic-based efforts. Therefore, we are recruiting in both community settings and adolescent medicine sites.

Although evidence-based interventions (EBIs) are difficult to replicate, they share key conceptual components [21-23]. Reviews of manuals of evidence-based adolescent HIV programs have found that all programs (1) frame the prevention message; (2) not only share knowledge regarding HIV but also help youth apply the health knowledge in their daily routines; (3) remove barriers to reaching implementing the health behavior (eg, getting insurance); and (4) build social support to sustain healthy behaviors. Based on these key conceptual components, we are evaluating 3 technology-driven intervention strategies: short message service (SMS) text messaging, peer support via social media, and paraprofessional coaching. Regardless of the delivery strategy, the intervention aims to link youth to medical care, improve access and consistent adherence to ARV medication, and increase routine health monitoring among youth. These studies test whether the strategies are also efficacious and cost effective in shaping healthy, HIV-related routines among youth.

Technology drives our approach because almost all adolescents (92%) go on the Web daily, typically with mobile devices [24]. Smartphones are increasingly available to youth, including black and Latino youth [25] and homeless youth [26]. Texting is particularly important for adolescents; 90% of those with phones text and typically receive and send 30 texts each day [24]. SMS text messages increase ARV medication adherence [27] as well as adherence to medical regimens for other chronic diseases [28]. SMS text messages change both the health-seeking and adherence behaviors of YLH and reduce risky sexual and drug use behaviors of YHR [29]. Much of this Web-based activity is driven by social media, with over 70% of adolescents aged under 18 years using Facebook, Instagram, or Snapchat [25]. Thus, technology is a powerful tool to intervene, scale, and monitor YLH and YHR to enhance HIV prevention and treatment.

A core component of our approach is an Automated Messaging and Monitoring Intervention (AMMI). Youth receive SMS text messages daily and are asked to report on their behaviors weekly. When delivering texts for ARV medication adherence, evidence shows that follow-up phone calls are needed if there is no response to a weekly text, and direct step-by-step instructions are better than vague support [30,31]. Monitoring—that is, asking youth about their lives—is directly related to a 15% change in behavior [31]. All youth in our studies receive AMMI, tailored to their personal risk factors.

Peer support via social media, detailed by Swendeman et al [8], is also used in these studies to engage and support youth. Both AMMI and social media-based peer support are important because they are scalable intervention strategies [32,33].

Paraprofessional coaching is a concept with wide cultural appeal and a more intensive interpersonal strategy to create healthy routines among YLH and YHR [34-36]. In 2 randomized controlled trials (RCTs) in sub-Saharan Africa [35,36], we found benefits lasting 5 years for mothers living with HIV and their children receiving paraprofessional coaching. Similarly, we found that paraprofessional coaching at soccer games is effective in engaging and assisting young men to reduce their HIV risk [37]. Coaches in these studies are community peers that we have trained in the key conceptual components of EBIs and in the skills that can help youth problem-solve hassles of daily living and support engagement and adherence to HIV interventions. Coaching in the CARES interventions has been detailed by Arnold et al [7].

These 3 intervention strategies utilize the same social cognitive model of behavior change. However, each uses different mediators of change. AMMI is aimed at informing, motivating, cueing or reminders, and self-monitoring. The primary change strategies for peer support are rewarding new behaviors and providing positive role models. Coaching relies on a behavior-change analyst who can link to community resources and facilitate goal-setting, problem solving, and building self-regulation skills in a real-world situation with individual youth. The intervention delivery strategies vary in resource

intensity. Therefore, we are using designs that allow us to identify the minimum dosage needed by YLH and YHR to achieve their HIV-related goals. Manual-style interventions that provide the same dose, scripts, and content for all persons in the targeted population are likely to overserve the needs of many youth [23,38]. The Stepped Care model is a cost-effective and patient-centered approach to improve treatment outcomes for chronic illnesses [39]. Rather than everyone getting the same intervention, the dose and type of intervention are linked to the youth's needs. Youth initially receive the least resource-intensive interventions and step up the intensity of the intervention only if not adhering to the medical regimen [40]. Given its clinical and financial benefits, the Stepped Care model has been used widely in the management of mental health problems, diabetes, and obesity [24,41]. We are testing its usefulness for YLH. In contrast, for the study with YHR that has a larger sample than the YLH study, we are using a randomized factorial design of the same intervention strategies to assess the efficacy and cost-effectiveness of each intervention independently and in combination.

YLH and YHR need lifelong health care, with repeated monitoring of their health status. The success of PrEP/PEP as a biomedical prevention strategy and ARV medication for treatment have demonstrated the efficacy of biomedical prevention [2,3]. Yet each of the landmark HIV studies with adults showed that only 50% adhered to the intervention [42]. Youth are typically less adherent than adults [43], especially over a long period. The HIV Prevention Continuum [17] requires regular HIV and STI testing and engagement in prevention strategies such as PrEP, PEP, and condom use. YLH must have their viral load repeatedly tested and must be monitored for concurrent STI, drug use, and other factors that impact adherence as well as for potential ARV medication-related resistance or toxicities. Ongoing counseling, support, and outreach are likely to be required over time for youth to achieve these aims. In these studies, we are recruiting and following a cohort of YHR and cohorts of YLH, linking them to medical care and other interventions, and assessing intervention efficacy at 4-month intervals over 24 months. These studies use the practices outlined by the Centers for Disease Control and Prevention (CDC) for those infected and at risk of acquiring HIV. The one deviation from CDC is that we conduct 3 HIV/STI tests annually (along with other assessments) rather than 4 times per year (due to costs).

Methods

Organizational Structure

Each study and the overall design were approved by review boards of the Adolescent Medicine Trials Network (ATN) and the University of California, LA (IRB#16-001372).

CARES brings together an interdisciplinary team to design, implement, and evaluate every aspect of the 3 studies. A Management Core manages the institutional review board for each study, monitors and reports adverse events; convenes Advisory Boards; manages the activities of the Recruitment, Engagement and Retention Center (RERC); and works across studies to ensure all activities are consistent with the ATN and NIH policies and procedures. The RERC has established collaborative community partnerships and supervises screening, recruitment, and retention of 1340 YHR, 220 YLH, and 72 treatment-naïve YLH who are either acutely infected or have established HIV infection. RERC staff reassess youth at 4-month intervals for 24 months. After randomization, an intervention team delivers the interventions across studies. At weekly cross-team conference calls, data on enrollment, retention, and intervention delivery are reviewed to ensure high-quality implementation. The Management Core leadership and the RERC teams interact with the Public Health and AIDS offices, and community-based and HIV care provider organizations, to provide updates on study activities on an ongoing basis. Figure 2 shows the organizational relationship of the Management Core and the 3 studies.

Study Design

Adolescent Medicine Trials Network Protocol 147

This study encompasses ARV treatment initiation for acutely infected YLH and YLH with established infection. A cohort of treatment-naïve YLH will be aggressively treated with medications that are the current standard in the field and repeatedly assessed at 4-month intervals to examine if the viral reservoirs remain low, which should slow disease progression (Nielsen-Saines and Bryson, Principal Investigators). Youth will be recruited that vary in time since infection. Acute HIV infections are described as stages [44], based on the presence of viral RNA, P24 antigen, and subsequent immunoglobulin (Ig)M/IgG antibody responses. Acute infection is determined using the Fiebig stage determination based on antibody, antigen, polymerase chain reaction, and western blot results. In addition, measures of virus persistence in latent reservoirs, based on digital drop polymerase chain reaction detection of proviral DNA, estimate the replication-competent reservoir size among acutely infected YLH, which is compared with that among treatment-naïve YLH who were infected more than 90 days prior to antiretroviral therapy initiation. Additional details on Protocol 147, including power calculations for sample sizes, have been provided by Nielsen-Saines et al [6].

Adolescent Medicine Trials Network Protocol 148: A Stepped Care RCT for YLH With Established HIV Infection

This study examines whether a Stepped Care approach is better than a Standard Care condition to achieve the viral suppression among treatment-experienced YLH with established infection. The 3 levels of the Stepped Care Intervention are as follows: (1) AMMI; (2) AMMI and peer support via social media; and (3) AMMI, peer support, and coaching. Figure 3 outlines the study design, and Textbox 1 lists the conditions in the Stepped Care condition. YLH in the Stepped Care arm are stepped-up to the next level of intervention if their viral load is >200 copies/mL at any 4-month follow-up assessment.

Figure 2. Organizational relationships between Management Core and the individual study teams, as well as the advisory board of the Comprehensive Adolescent Research and Engagement Studies program project. ATN: Adolescent Medicine Trials Network.

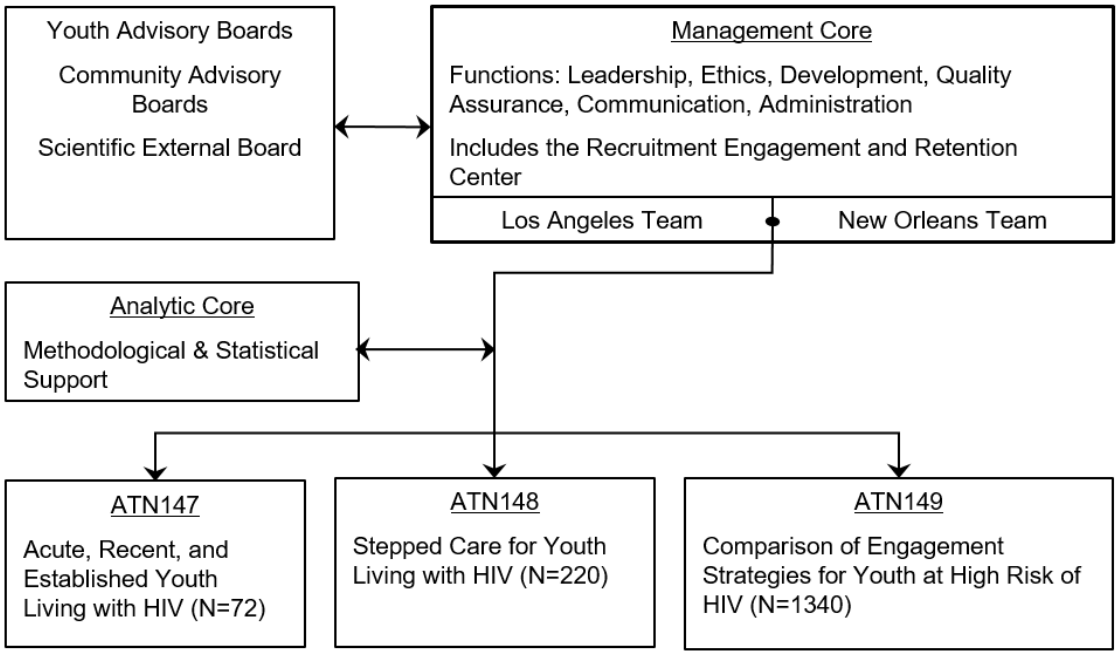
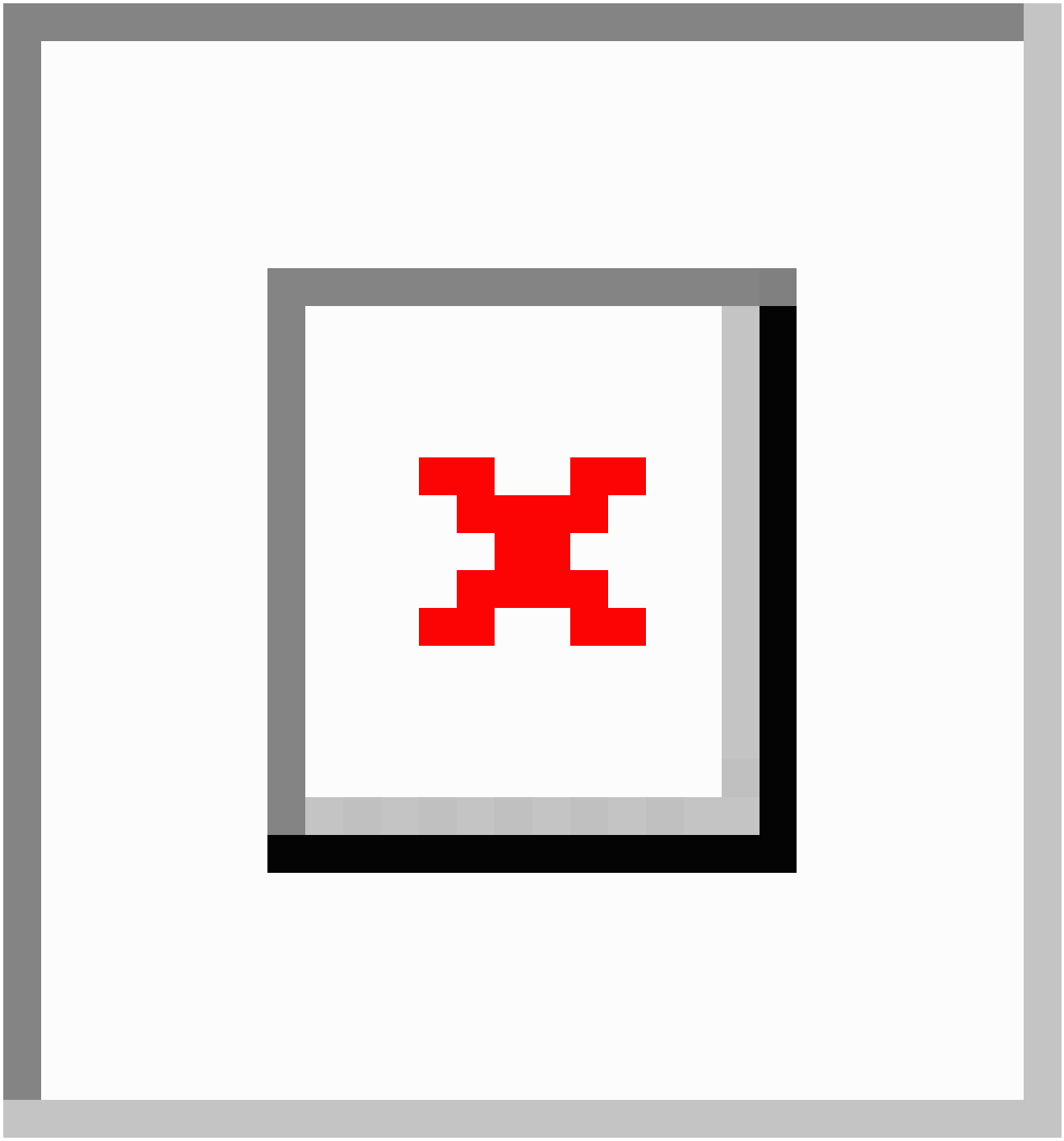


Figure 3. Design of the randomized controlled trial for youth living with HIV (YLH).



Textbox 1. Outline of the components in the Stepped Care Condition for youth living with HIV.

Goals

- Linkage to care
- Adherence to antiretroviral medication
- Manage comorbidities
- Viral suppression

Level 1

- Tailored Automated Messaging Monitoring Intervention (AMMI)
- Repeat assessments for 4 months

Level 2

- Peer support
- Tailored AMMI
- Repeat assessments for 4 months

Level 3

- Coaching
- Peer support
- Tailored AMMI
- Repeat assessments for 4 months

Adolescent Medicine Trials Network Protocol 149: Engaging Seronegative Youth in the HIV Prevention Continuum

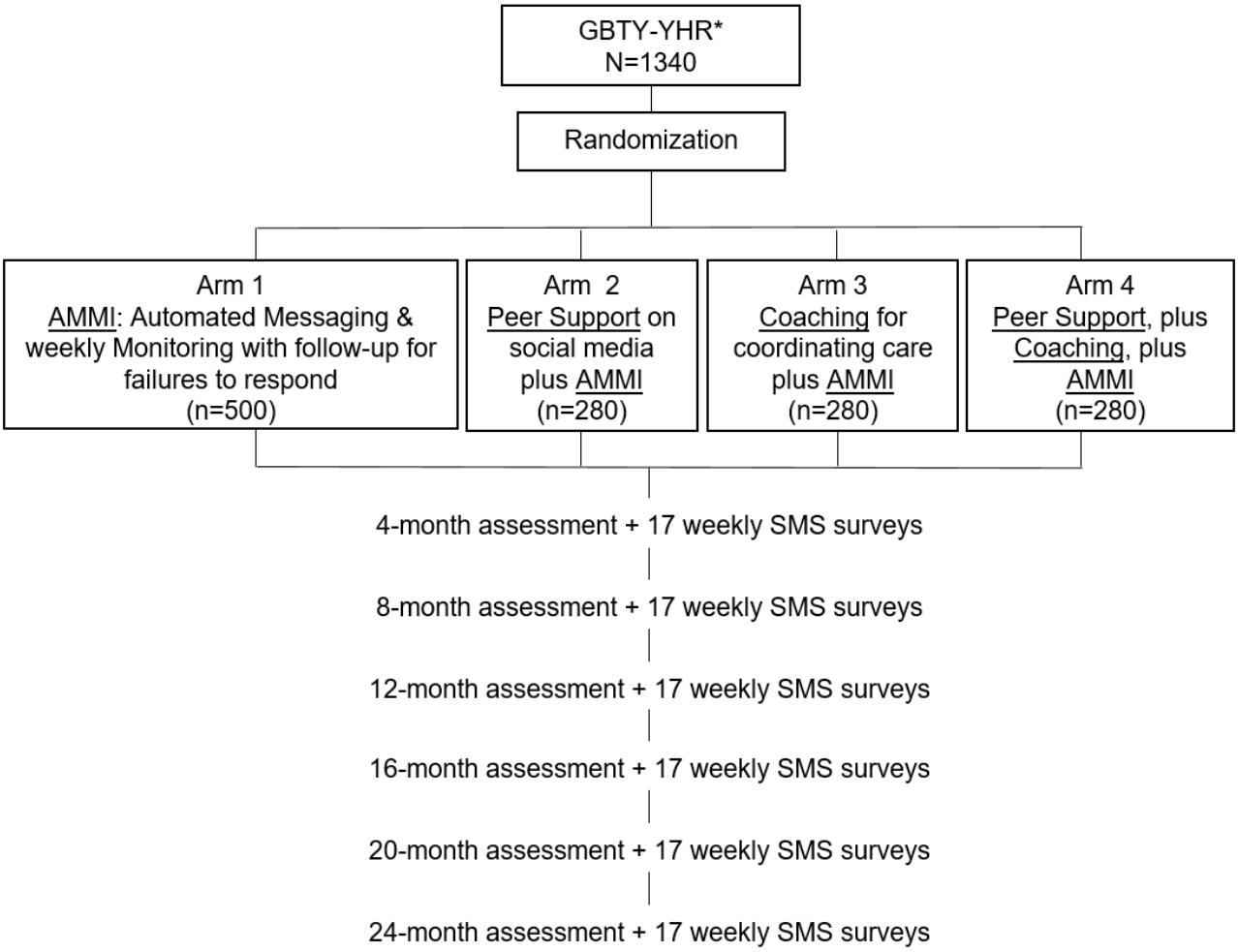
The outcomes for this trial are as follows: staying engaged in medical care, adopting PEP after HIV exposure or PrEP prior to HIV exposure, or using condoms on 100% of sexual acts as well as repeatedly testing for HIV on an ongoing basis every 4 months. Figure 4 summarizes the following 4 active treatment conditions: (1) AMMI alone; (2) AMMI and peer support through social media; (3) AMMI and coaching; or (4) AMMI, peer support, and coaching. Because the challenges are so similar, the staff delivering the interventions—the AMMI, the peer support, and the coaches—are shared across the studies. All coaches are taught basic skills common across EBI, a theory of change based on the social cognitive model and a set of basic intervention messages. Coaches are of the same cultural backgrounds and experiences as the youth in the study, facilitating bonding and shared knowledge of difficult life circumstances. In addition, coaches and participants have access to a clinical supervisor, who is on call 24 hours, 7 days a week in each city. Furthermore, all YHR are offered transportation and an appointment for PrEP.

Recruitment Sites

Sites

We selected LA and New Orleans, two HIV epicenter cities, because of their many differences. With 10.2 million persons spread across 4048 square miles, identifying and engaging YHR and YLH in LA is challenging [45]. Fortunately, LA County's HIV epidemic and HIV-related services are concentrated in 6 communities. For example, there are 9 youth-serving agencies within 1.5 miles in the Hollywood area. However, it may take 2-3 hours to reach these agencies from different parts of LA. While New Orleans has fewer agencies than LA, the city has a better public transportation system and is much smaller, at 170 square miles, and with a population of about 393,000 persons [45]. The demographic distribution of HIV also differs between the two cities. About 70% of new HIV diagnoses in New Orleans are among black men who have sex with men (MSM) and black women [46]. About half of the new diagnoses in LA are among Latino individuals [47]. In addition, MSM account for a larger percentage of HIV diagnoses in LA (84%) [47] than in New Orleans (66%) [46].

Figure 4. Design of the randomized controlled trial for youth at high risk (YHR) of HIV. *GBTY-YHR: Seronegative gay, bisexual, transgender youth at high risk of HIV (homeless youth); SMS: short message service.



In each city, there are collaborating agencies whose staff implement the study protocols, as well as sites at which we place our interviewers. These sites change over time based on the youth population and time of the year. The LA and New Orleans recruitment sites are listed in Textboxes 2 and 3, respectively.

In addition, recruitment is being conducted via social media in both cities. Recruiters use Grindr, Jack'd, and Scruff for targeted recruitment and Instagram, Snapchat, and Facebook to create broader visibility for the study. Recruiters post pictures and send messages via social media in real time, including while at in-person venues and recruitment events to encourage youth to approach the recruiters.

Textbox 2. Los Angeles recruitment sites.

- Los Angeles LGBT Center
- Covenant House California
- The Village Family Services
- Safe Place for Youth (SPY)
- Transitional Age Youth Academy
- The Long Beach Gay and Lesbian Center
- Miller Children's Hospital
- Multiple sites in Inland Empire of Southern California with recruitment coordinated by TruRevolution, a LGBTQ-focused community-based organization: The Riverside County Regional Medical Center, the San Bernardino Public Health Clinic, Borrego Health, Eisenhower Medical Center.

Textbox 3. New Orleans recruitment sites.

- Tulane Adolescent Drop-In Center
- Tulane Adolescent Drop-In Clinic at Covenant House
- Tulane T-Cell Clinic
- University Medical Center Infectious Disease Clinic
- Crescent Care (formerly NO/AIDS Task Force)
- Brotherhood, Inc

Interviewers

The RERC team operates as a single entity with separate supervisors in each city. A minimum of 10 interviewers, reflective of the gender, sexual orientation, ethnicity, and life experiences of our target population, are certified as HIV test counselors and trained for 4-6 weeks on the following: phlebotomy and blood protocols; rapid diagnostic tests (RDTs; Alere, Xpert); coping with adolescents on drugs; suicide and crisis management; interview skills and role playing; HIV 101 education; study protocol; tracking and follow-up of youth; legal and ethical mandates (ie, mandated reporting of HIV and other STIs); cultural competency (GBTY and transgender-specific training); cyber bullying; housing issues; treatment of STIs for gonorrhea and chlamydia; and referral for treatment of syphilis. All contacts are documented in real time on Web-connected tablets or mobile phones using Dimagi's CommCare platform [9]. Supervisors review data and reports from CommCare weekly and use reports in supervision meetings. There are monthly in-service trainings and random field visits to ensure high-quality work.

Screening

Screening for recruitment is scheduled to stagger across the days of the week and time of the day to ensure all youth receive an opportunity for participation. After obtaining verbal consent, youth are screened for study eligibility with an 18-item questionnaire conducted by the interviewer and receive a rapid point-of-care fourth-generation Alere test (Alere, Waltham, MA, USA) for HIV infection and RDT for STI as well as illicit drug use and current alcohol use. The STI testing [10] includes testing for *Chlamydia trachomatis* and *Neisseria gonorrhea* (CT/NG) using the US Food and Drug Administration-approved Xpert CT/NG assay (Cepheid, Sunnyvale, CA, USA). The Xpert CT/NG assay provides test results in 90 minutes and youth are offered same-day treatment and expedited-partner therapy in accordance with CDC recommendations. Screening for syphilis infection occurs using the Clinical Laboratory Improvement Amendments of 1988 waived rapid point-of-care fingerstick whole blood treponemal antibody test Syphilis Health Check (Diagnostics Direct, Stone Harbor, NJ, USA). Persons with reactive rapid syphilis tests are referred for having their venous serum tested for rapid plasma reagin and *Treponema pallidum* particle agglutination determination and clinical treatment.

Youth meeting the eligibility criteria are then triaged to one of the 3 studies based on the results of an initial HIV test. Protocol 147 enrolls all youth with acute or recent HIV infection and treatment-naïve YLH with established HIV infection. YLH enroll in Protocol 148 if they have had ARV medication previously. Among the 1340 YHR in Protocol 149, we anticipate that a small proportion will seroconvert and be detected during the acute infection phase and immediately triaged to enroll in Protocol 147.

Baseline and Follow-Up Assessments

Youth in all 3 studies are assessed every 4 months over 24 months, with the RDTs used at initial screening and with a self-report interview administered face-to-face by interviewers with sensitive questions self-administered by participants using the interviewers tablet or mobile phone-based assessment app. Textbox 4 summarizes the content areas covered in the baseline and follow-up interviews. These interviews are highly similar across studies with only small variations regarding past ARV experience, adherence, and HIV-related stigma for YLH and for YHR questions on PrEP/PEP knowledge and experience.

Textbox 4. Domains repeatedly assessed every 4 months throughout the 24-month follow-up period for all participants in every study.

- Rapid diagnostic tests for HIV, STI, and substance use (youth living with HIV with not be retested for HIV)
- Current health provider?
  - Current access to provider?
  - Current medical appointments?
  - Current antiretroviral (ARV) medication prescription?
  - Relationship with provider?
- Where is ARV medication prescription?
  - Drug? Dose?
  - Pharmacy?
  - Need new drug access card?
- ARV medication adherence?
- Physical health?
- Comorbidities?
  - Homelessness?
  - Mental health symptoms, care & hospitalization?
  - Drug use?
  - Alcohol use or abuse?
  - Illness? Hospitalization?
  - Gang involvement?
  - Criminal justice contact?
  - Sexual partners? Condom use?
  - Social support?
  - Employment? School?
  - Income?
  - Pleasant activities?

Data Collection and Analysis

CommCare (Dimagi, Cambridge, MA, USA) is an open-source support program used by the research team for data collection and monitoring [9]. Automated quality assurance programs review recruitment rate, uptake of testing, HIV/STI results, intervention implementation, and responses to weekly monitoring surveys by SMS text message (or email with a weblink to a RedCap version of the survey if participants do not respond to SMS text message surveys). Reviewing these data weekly as a team across all locations, and with input from interviewers, coaches, coordinators, and principal investigators, allows for continual iterative improvement of all protocols. Senior statisticians meet monthly to review data for each protocol. Furthermore, the central analytic team supports additional researchers on projects using the deidentified data.

In addition, cost-benefit analyses are being performed on the basis of a modified form of the UNAIDS 2010 template [48]. The total costs of each intervention component of each study, as well as the costs of repeatedly assessing a cohort to facilitate engagement are monitored on an ongoing basis. Costs are of 2 types: costs of delivering the intervention and additional costs incurred by participants for their use of health care services and services from other agencies (eg, use of the criminal justice system). Intervention costs are obtained from project records and take into consideration the number of hours worked, the hourly wage, and benefits of staff. Costs to design and deliver the interventions include coaches, supervisors, facility charges, software costs, and SMS text messaging and other social media costs, messaging and mobile app data costs, additional time in coaching and supervision, and server hosting. Staff monitor their time and activity reports one week quarterly via an app to provide accurate estimates of staffing costs. The costs of additional services are derived from respondent reports of health care received, medical records, and are estimated using publicly available data. Research-specific costs (eg, incentive payments, informed consent, screens, and software adaptation for survey tools) are excluded from total costs. All cost data are price-adjusted back to year one of the study, using the medical care component of the consumer price index. These data inform not only the cost-utility analyses for this study but also future modeling studies by other researchers.

Resource Sharing Plan

In accordance with the NIH Data Sharing Policy [49] and the NIH Public Access Policy, data, manuals, tools, and research findings generated from this study will be made publicly accessible in nonproprietary formats, free of charge, with unlimited use and distribution rights. After all data are deidentified, cleaned, and validated and main findings are published, we will make study data available to the scientific community and the general public on the Data and Specimen Hub open-source system of the National Institute of Child Health and Human Development and by the Coordinating Center of the ATN. To adhere to the "open data" quality standards, we will follow Dublin Core International metadata standards [50], following the 5-star open data deployment scheme [51].

Results

The project is funded from September 2016 through May 2021. The study team is currently recruiting and conducting follow-up assessments. Preliminary analyses are underway. We are scheduled to complete recruitment and baseline data collection by June 2019 and expect to analyze baseline data and submit the first results for publication by fall 2019.

As of December 1, 2018, we have recruited 44 participants in Protocol 147, with 14 of these young people in the Fiebig stages 1-5. These are predominately young GBTY who are black and Latino. However, women and young heterosexual men are also included.

In Protocol 148, we have recruited 95 YLH; 68% (65/95) are black and 19% (18/95) are Latino individuals. Over half (48/95, 51%) test positive for an STI at recruitment, 67% (64/95) test positive for recent marijuana use, 10% (10/95) for cocaine, and 2% (2/95) for opiates.

In Protocol 149, 956 YHR have been recruited; 46% (440/956) are GBTY, 59% (564/956) are black, 25% (239/956) are Latino, 54% (516/956) have been homeless in the last year, 34% (325/956) have had contact with the criminal justice system, 34% (325/956) have been hospitalized for mental illness, 55% (526/956) have positive results for RDT for drug use, and 17% (163/956) have a current STI. Both YLH and YHR typically have multiple risk factors placing them at high risk for negative health outcomes.

Discussion

This innovative set of interrelated studies provides a novel, scalable, and flexible technology-based approach for addressing the HIV epidemic among youth in the United States. These studies illustrate how currently available biomedical prevention approaches have built a "bridge" in intervention research with YLH and YHR [52], resulting in comparable intervention approaches for both groups. To achieve our goal of helping youth advance through each step of the Prevention and Treatment Continua, youth must be identified, engaged, and retained in prevention and treatment services and routinely monitored. Together the proposed studies will offer counties, cities, and communities a system for integrating and coordinating prevention and care for YLH and YHR. We expect our results will be broadly applicable to diverse agencies and jurisdictions, including the CDC, National Association of State AIDS Directors, Health Resources and Services Administration, state and local health departments, and heavily impacted communities.

One of the major innovations in this program project is to monitor the outcomes over time for youth identified and treated with ARV soon after HIV infection. Our acute infection research protocol, which has been described in detail elsewhere [6], is based on our team's successful Cure research with pediatric populations [5]. One of the biggest challenges we face is identifying a sufficiently large pool (N=36) of youth in the acute infection phase; in the first 15 months, we have identified 13 youths. The systems that we are implementing (eg, regular HIV/STI testing, weekly automated monitoring of signs and symptoms of HIV infection), if successful, can lay the groundwork for accessing this difficult-to-identify group. Even if we identify biomedical interventions that can reduce the size of the viral reservoir and achieve a functional Cure, clinicians and researchers need a viable, cost-effective approach for identifying and engaging newly infected youth in the acute infection phase. The work we are conducting will advance our knowledge in this important area.

Another contribution of these studies is the use of technology-based approaches that emphasize the function we aim to achieve, rather than a specific platform, such as an app [53]. This approach is based on more than a decade of experience collecting data on mobile phones domestically and in resource-poor settings (South Africa, Uganda, and India), monitoring adherence daily. The technology-based interventions in these studies use off-the-shelf and rapidly deployable and adaptable tools of SMS text messaging, private social media discussion forums, and flexible communication channels for interpersonal coaching.

Cost and cost-benefit analyses are key aspects of our studies as they not only inform policy makers but also facilitate better estimates in the modeling of communities' combination prevention strategies. Across all types of intervention studies, the costs, benefits, cost-utility, and cost-effectiveness are key issues in considering the scalability of each intervention and the value-added per dollar spent on the intervention strategy. For instance, a recent modeling experiment on the HIV Prevention Continuum for MSM in the United States found that the most successful strategy is to test MSM every 3 months for HIV infection [54]. However, the approximate cost for repeatedly testing MSM would be US $5 billion annually, a prohibitive cost and unlikely to be warranted. Unfortunately, these types of data, critical for conducting modeling exercises that can inform policy decisions, are not currently available for youth. Because we are planning to repeatedly test YHR every 4 months to approximate CDC recommendations [55] and to identify acutely infected YLH, this longitudinal dataset will yield information on the combination of risk factors among youth who go on to seroconvert. Not only will it tell us who and how to identify YLH, but it will also provide actual data for conducting modeling exercises. Finally, because no seroprevalence studies have been conducted among homeless GBTY and YHR in many years, this study informs public health

administrators and policy makers whether implementing routine HIV testing in homeless shelters is warranted.

In summary, the United States is challenged to reduce new HIV infections among youth and to broadly implement the preventive interventions (particularly PEP and PrEP) that US scientists have identified. To stop HIV among youth, aggressive programs targeting YHR and YLH must be broadly implemented. This challenge requires modifications of our standard scientific approaches to replication with the fidelity of EBI, utilization of new technologies, and practical strategies for engaging and retaining youth in medical care lifelong. This set of studies examines one approach to achieving this aim.

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Conflicts of Interest

None declared.

References

1. Centers for Disease Control and Prevention. 2018. HIV Among Youth URL: http://www.cdc.gov/hiv/group/age/youth/ [WebCite Cache ID 6yPXNG2E0]
2. Cohen MS, Holmes C, Padian N, Wolf M, Hirnschall G, Lo Y, et al. HIV treatment as prevention: how scientific discovery occurred and translated rapidly into policy for the global response. Health Aff (Millwood) 2012 Jul;31(7):1439-1449. [doi: 10.1377/hlthaff.2012.0250] [Medline: 22778333]
3. Hankins CA, Dybul MR. The promise of pre-exposure prophylaxis with antiretroviral drugs to prevent HIV transmission: a review. Curr Opin HIV AIDS 2013 Jan;8(1):50-58. [doi: 10.1097/COH.0b013e32835b809d] [Medline: 23201856]
4. Kahn JO, Martin JN, Roland ME, Bamberger JD, Chesney M, Chambers D, et al. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: the San Francisco PEP Study. J Infect Dis 2001 Mar 01;183(5):707-714. [doi: 10.1086/318829] [Medline: 11181146]
5. National Institutes of Health: Office of AIDS Research. URL: https://www.oar.nih.gov/ [accessed 2018-04-04] [WebCite Cache ID 6yQlOsiqC]
6. Nielsen-Saines K, Mitchell K, Kerin T, Fournier J, Kozina L, Andrews B, et al. Acute HIV Infection in Youth: Protocol for the Adolescent Trials Network 147 Comprehensive Adolescent Research and Engagement Studies Study. J Med Internet Res 2018 (forthcoming). [doi: 10.2196/10807]
7. Arnold E, Swendeman D, Rotheram-Borus M, Harris D, Fournier J, Kozina L, The ATN CARES Team. Stepped Care Intervention to Suppress Viral Load Among Youth Living with HIV. J Med Internet Res 2018 (forthcoming). [doi: 10.2196/10791]
8. Swendeman D, Arnold E, Harris D, Comulada W, Reback C, Kozina L, The ATN CARES Team. What strategies are enough to protect youth from HIV: Automated messaging, weekly behavioral monitoring, peer social media networks, or interpersonal coaching? J Med Internet Res 2018 (forthcoming). [doi: 10.2196/11165]
9. Comulada W, Tang W, Swendeman D, Cooper A, Wacksman J, Adolescent Medicine Trials Network (ATN) CARES Team. Development of an Electronic Data Collection System to Support a Large-Scale HIV Behavioral Intervention Trial: Protocol for an Electronic Data Collection System. JMIR Res Protoc 2018 Dec 14;7(12):e10777 [FREE Full text] [doi: 10.2196/10777] [Medline: 30552083]
10. Shannon C, Koussa M, Lee S, Fournier J, Abdalian S, Rotheram-Borus M, et al. Community-based, point-of-care sexually transmitted infection screening among high-risk adolescents in Los Angeles and New Orleans: A study protocol, Adolescent Medicine Trials Network. J Med Internet Res 2018 (forthcoming). [doi: 10.2196/10795]
11. Centers for Disease Control and Prevention. HIV in the United States by Region URL: https://www.cdc.gov/hiv/statistics/overview/geographicdistribution.html [WebCite Cache ID 6yPXqN0Hh]
12. Woollett N, Cluver L, Bandeira M, Brahmbhatt H. Identifying risks for mental health problems in HIV positive adolescents accessing HIV treatment in Johannesburg. J Child Adolesc Ment Health 2017 May;29(1):11-26. [doi: 10.2989/17280583.2017.1283320] [Medline: 28287023]
13. Burton P, Ward C, Artz L. Centre for Justice & Crime Prevention. Zurich, Switzerland; 2016 Jun. Sexual victimisation of children in South Africa: Final report of the Optimus Foundation Study URL: http://www.cjcp.org.za/uploads/2/7/8/4/27845461/08_cjcp_report_2016_d.pdfrE [WebCite Cache ID 6yPXyKgJf]

14. Mutumba M, Elkington KS, Bauermeister JA, Bucek A, Dolezal C, Leu CS, et al. Changes in Substance Use Symptoms Across Adolescence in Youth Perinatally Infected with HIV. AIDS Behav 2017 Apr;21(4):1117-1128 [FREE Full text] [doi: 10.1007/s10461-016-1468-9] [Medline: 27371136]
15. Abram KM, Stokes ML, Welty LJ, Aaby DA, Teplin LA. Disparities in HIV/AIDS Risk Behaviors After Youth Leave Detention: A 14-Year Longitudinal Study. Pediatrics 2017 Feb 23;139(2):e20160360 [FREE Full text] [doi: 10.1542/peds.2016-0360] [Medline: 28115541]
16. Kaiser Family Foundation. 2017 Sep. U.S. Federal Funding for HIV/AIDS: Trends Over Time URL: https://www.kff.org/global-health-policy/fact-sheet/u-s-federal-funding-for-hivaids-trends-over-time/ [accessed 2018-10-23] [WebCite Cache ID 73OEps6fZ]
17. McNairy ML, El-Sadr WM. A paradigm shift: focus on the HIV prevention continuum. Clin Infect Dis 2014 Jul;59 Suppl 1:S12-S15 [FREE Full text] [doi: 10.1093/cid/ciu251] [Medline: 24926026]
18. Swendeman D, Rotheram-Borus MJ, Comulada S, Weiss R, Ramos ME. Predictors of HIV-related stigma among young people living with HIV. Health Psychol 2006 Jul;25(4):501-509 [FREE Full text] [doi: 10.1037/0278-6133.25.4.501] [Medline: 16846325]
19. Institute of Medicine. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: The National Academies Press; 2003.
20. Gilkey MB, Malo TL, Shah PD, Hall ME, Brewer NT. Quality of physician communication about human papillomavirus vaccine: findings from a national survey. Cancer Epidemiol Biomarkers Prev 2015 Nov;24(11):1673-1679 [FREE Full text] [doi: 10.1158/1055-9965.EPI-15-0326] [Medline: 26494764]
21. Collins C, Harshbarger C, Sawyer R, Hamdallah M. The diffusion of effective behavioral interventions project: development, implementation, and lessons learned. AIDS Educ Prev 2006 Aug;18(4 Suppl A):5-20. [doi: 10.1521/aeap.2006.18.supp.5] [Medline: 16987085]
22. Cunningham SD, Card JJ. Realities of replication: implementation of evidence-based interventions for HIV prevention in real-world settings. Implement Sci 2014 Jan 06;9:5 [FREE Full text] [doi: 10.1186/1748-5908-9-5] [Medline: 24387142]
23. Rotheram-Borus MJ, Swendeman D, Chorpita BF. Disruptive innovations for designing and diffusing evidence-based interventions. Am Psychol 2012 Sep;67(6):463-476 [FREE Full text] [doi: 10.1037/a0028180] [Medline: 22545596]
24. Stoop CH, Nefs G, Pommer AM, Pop VJM, Pouwer F. Effectiveness of a stepped care intervention for anxiety and depression in people with diabetes, asthma or COPD in primary care: A randomized controlled trial. J Affect Disord 2015 Sep 15;184:269-276. [doi: 10.1016/j.jad.2015.05.063] [Medline: 26118755]
25. Lenhart A. Pew Research Center: Internet & Technology. 2015 Apr 09. Teens, Social Media & Technology Overview 2015 URL: http://www.pewinternet.org/files/2015/04/PI_TeensandTech_Update2015_0409151.pdf [WebCite Cache ID 6yQjcUcxT]
26. Rice E, Barman-Adhikari A. Internet and Social Media Use as a Resource Among Homeless Youth. J Comput Mediat Commun 2014 Jan 01;19(2):232-247 [FREE Full text] [doi: 10.1111/jcc4.12038] [Medline: 25328374]
27. Finitsis DJ, Pellowski JA, Johnson BT. Text message intervention designs to promote adherence to antiretroviral therapy (ART): a meta-analysis of randomized controlled trials. PLoS One 2014;9(2):e88166 [FREE Full text] [doi: 10.1371/journal.pone.0088166] [Medline: 24505411]
28. Mbuagbaw L, Mursleen S, Lytvyn L, Smieja M, Dolovich L, Thabane L. Mobile phone text messaging interventions for HIV and other chronic diseases: an overview of systematic reviews and framework for evidence transfer. BMC Health Serv Res 2015 Jan 22;15:33 [FREE Full text] [doi: 10.1186/s12913-014-0654-6] [Medline: 25609559]
29. Ybarra ML, Prescott TL, Philips GL, Bull SS, Parsons JT, Mustanski B. Iteratively Developing an mHealth HIV Prevention Program for Sexual Minority Adolescent Men. AIDS Behav 2016 Dec;20(6):1157-1172 [FREE Full text] [doi: 10.1007/s10461-015-1146-3] [Medline: 26238038]
30. Ramanathan N, Swendeman D, Comulada WS, Estrin D, Rotheram-Borus MJ. Identifying preferences for mobile health applications for self-monitoring and self-management: focus group findings from HIV-positive persons and young mothers. Int J Med Inform 2013 Apr;82(4):e38-e46 [FREE Full text] [doi: 10.1016/j.ijmedinf.2012.05.009] [Medline: 22704234]
31. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 2010 Nov 27;376(9755):1838-1845. [doi: 10.1016/S0140-6736(10)61997-6] [Medline: 21071074]
32. Swendeman D, Rotheram-Borus MJ. Innovation in sexually transmitted disease and HIV prevention: internet and mobile phone delivery vehicles for global diffusion. Curr Opin Psychiatry 2010 Mar;23(2):139-144 [FREE Full text] [doi: 10.1097/YCO.0b013e328336656a] [Medline: 20087189]
33. Swendeman D, Ramanathan N, Baetscher L, Medich M, Scheffler A, Comulada WS, et al. Smartphone self-monitoring to support self-management among people living with HIV: perceived benefits and theory of change from a mixed-methods randomized pilot study. J Acquir Immune Defic Syndr 2015 May 01;69 Suppl 1:S80-S91 [FREE Full text] [doi: 10.1097/QAI.0000000000000570] [Medline: 25867783]
34. Rotheram-Borus MJ, Swendeman D, Lee S, Li L, Amani B, Nartey M. Interventions for families affected by HIV. Transl Behav Med 2011 Jun;1(2):313-326 [FREE Full text] [doi: 10.1007/s13142-011-0043-1] [Medline: 21765881]

35. Rotheram-Borus MJ, le Roux IM, Tomlinson M, Mbewu N, Comulada WS, le Roux K, et al. Philani Plus (+): a Mentor Mother community health worker home visiting program to improve maternal and infants' outcomes. Prev Sci 2011 Dec;12(4):372-388 [FREE Full text] [doi: 10.1007/s11121-011-0238-1] [Medline: 21850488]
36. Rotheram-Borus M, Richter L, Van Rooyen H, van Heerden A, Tomlinson M, Stein A, et al. Project Masihambisane: a cluster randomised controlled trial with peer mentors to improve outcomes for pregnant mothers living with HIV. Trials 2011 Jan 04;12:2 [FREE Full text] [doi: 10.1186/1745-6215-12-2] [Medline: 21205302]
37. Rotheram-Borus MJ, Tomlinson M, Durkin A, Baird K, DeCelles J, Swendeman D. Feasibility of Using Soccer and Job Training to Prevent Drug Abuse and HIV. AIDS Behav 2016 Dec;20(9):1841-1850 [FREE Full text] [doi: 10.1007/s10461-015-1262-0] [Medline: 26837624]
38. Bower JL, Christensen CM. Harvard Business Review. 1995. Disruptive Technologies: Catching the Wave URL: https://hbr.org/1995/01/disruptive-technologies-catching-the-wave [accessed 2018-11-29] [WebCite Cache ID 74HtPNuuG]
39. Bower P, Gilbody S. Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. Br J Psychiatry 2005 Jan;186:11-17. [doi: 10.1192/bjp.186.1.11] [Medline: 15630118]
40. Von Korff M, Tiemens B. Individualized stepped care of chronic illness. West J Med 2000 Feb;172(2):133-137 [FREE Full text] [Medline: 10693379]
41. Salloum A, Robst J, Scheeringa MS, Cohen JA, Wang W, Murphy TK, et al. Step one within stepped care trauma-focused cognitive behavioral therapy for young children: a pilot study. Child Psychiatry Hum Dev 2014 Feb;45(1):65-77 [FREE Full text] [doi: 10.1007/s10578-013-0378-6] [Medline: 23584728]
42. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 Aug 11;365(6):493-505 [FREE Full text] [doi: 10.1056/NEJMoa1105243] [Medline: 21767103]
43. Agwu AL, Fleishman JA, Korthuis PT, Siberry GK, Ellen JM, Gaur AH, Research Network HIV. Disparities in antiretroviral treatment: a comparison of behaviorally HIV-infected youth and adults in the HIV Research Network. J Acquir Immune Defic Syndr 2011 Sep 01;58(1):100-107 [FREE Full text] [doi: 10.1097/QAI.0b013e31822327df] [Medline: 21637114]
44. Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003 Sep 05;17(13):1871-1879. [doi: 10.1097/01.aids.0000076308.76477.b8] [Medline: 12960819]
45. United States Census Bureau. QuickFacts: New Orleans city, Louisiana; Los Angeles County, California URL: https://www.census.gov/quickfacts/fact/table/neworleanscitylouisiana,losangelescountycalifornia/PST045217 [accessed 2018-10-02] [WebCite Cache ID 72sBVdtMj]
46. Louisiana Department of Health. 2016 STD/HIV Surveillance Report URL: http://ldh.la.gov/assets/oph/HIVSTD/std/STDAnnualReports/2016_STDHIV_SurveillanceReport_Final.pdf [WebCite Cache ID 72sQdMYeu]
47. Division of HIV and STD Programs, Los Angeles County Department of Public Health. County of Los Angeles: Public Health. 2018 Jun. 2016 Annual HIV Surveillance Report URL: http://publichealth.lacounty.gov/dhsp/Reports/HIV/AnnualHIVSurveillanceReport2016.pdf [WebCite Cache ID 72sOvz4bg]
48. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS. 2010 Dec. Getting To Zero: 2011–2015 Strategy URL: http://www.unaids.org/sites/default/files/sub_landing/files/JC2034_UNAIDS_Strategy_en.pdf [WebCite Cache ID 6yPXjlNvN]
49. National Institutes of Health (NIH). NIH Data Sharing Policy URL: http://grants.nih.gov/grants/policy/data_sharing [WebCite Cache ID 6yQnt7IW0]
50. DCMI: Home. 2012 Jun 14. Dublin Core Metadata Element Set, Version 1.1: Reference Description URL: http://dublincore.org/documents/dces/ [accessed 2018-04-04] [WebCite Cache ID 6yQo5mtYu]
51. 5-star Open Data. 2015. URL: https://5stardata.info/en/ [accessed 2018-04-04] [WebCite Cache ID 6yQoKPJES]
52. NYC.gov. The New York City HIV Status Neutral Prevention and Treatment Cycle URL: https://www1.nyc.gov/site/doh/health/health-topics/hiv-status-neutral-prevention-and-treatment-cycle.page [accessed 2018-04-10] [WebCite Cache ID 6yaK8KrB2]
53. Rotheram-Borus MJ, Tomlinson M, Swendeman D, Lee A, Jones E. Standardized functions for smartphone applications: examples from maternal and child health. Int J Telemed Appl 2012;2012:973237 [FREE Full text] [doi: 10.1155/2012/973237] [Medline: 23304136]
54. Delaney KP, Rosenberg ES, Kramer MR, Waller LA, Sullivan PS. Optimizing Human Immunodeficiency Virus Testing Interventions for Men Who Have Sex With Men in the United States: A Modeling Study. Open Forum Infect Dis 2015 Dec;2(4):ofv153 [FREE Full text] [doi: 10.1093/ofid/ofv153] [Medline: 26613096]
55. Branson B, Handsfield H, Lampe M, Janssen R, Taylor A, Lyss S, Centers for Disease ControlPrevention (CDC). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 2006 Sep 22;55(RR-14):1-17; quiz CE1 [FREE Full text] [Medline: 16988643]

Abbreviations

AMMI: Automated Messaging and Monitoring Intervention

ARV: antiretroviral
ATN: Adolescent Medicine Trials Network
CARES: Comprehensive Adolescent Research and Engagement Studies
CDC: Centers for Disease Control and Prevention
CT: Chlamydia trachomatis
EBI: evidence-based interventions
GBTY: gay and bisexual males and transgender youth
LA: Los Angeles
MSM: men who have sex with men
NG: Neisseria gonorrhea
NIH: National Institutes of Health
PEP: postexposure prophylaxis
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
RDT: rapid diagnostic tests
RERC: Recruitment, Engagement, and Retention Center
SMS: short message service
STI: sexually transmitted infection
YHR: youth at high risk
YLH: youth living with HIV

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Protocol

Developing a Mobile App (LYNX) to Support Linkage to HIV/Sexually Transmitted Infection Testing and Pre-Exposure Prophylaxis for Young Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young men who have sex with men (YMSM) in the United States have among the highest incidence of HIV and sexually transmitted infection (STI) and the lowest uptake of HIV and STI testing and pre-exposure prophylaxis (PrEP). Nearly universal mobile phone ownership among youth provides an opportunity to leverage mobile health apps to increase HIV/STI testing and PrEP uptake among YMSM.

Objective: The goals of this project are to develop and refine LYNX, a novel mobile app to support linkage to HIV/STIs testing and PrEP services among YMSM in the United States, and to evaluate the acceptability and feasibility of LYNX in a pilot randomized controlled trial (RCT).

Methods: This research protocol will be conducted in 3 phases: an iterative development phase with a series of 3 focus groups among 20 YMSM to refine the LYNX app; an open technical pilot among 15 YMSM to optimize usability of the app; and then a 6-month pilot RCT among 60 HIV-uninfected YMSM at risk for HIV acquisition. Developed using the Information, Motivation, and Behavioral skills theoretical model, the LYNX app includes an electronic diary to track sexual behaviors (information), a personalized risk score to promote accurate risk perception (information/motivation), testing reminders (motivation/behavioral skills), and access to home-based HIV/STI testing options and geospatial-based HIV/STI testing care sites (behavioral skills). Feasibility and acceptability will be assessed through app analytics of usage patterns and acceptability scales administered via computer-assisted self-interview at 3 and 6 months. We will also evaluate preliminary efficacy by comparing the proportion of YMSM who test at least once during the 6-month pilot and the proportion who successfully link to a PrEP provider in the intervention versus control groups.

Results: Formative work is currently underway. The LYNX pilot RCT will begin enrollment in October 2018, with study results available in 2019.

Conclusions: The LYNX app is one of the first mobile apps designed to increase HIV/STI testing and PrEP uptake among YMSM. As low-perceived risk is a barrier to HIV/STI testing and PrEP use among youth, the personalized risk assessment and interactive sexual diary in LYNX could assist YMSM in better understanding their HIV risk and providing motivation to test for HIV/STIs and initiate PrEP. Coupled with community-based recruitment, this novel mobile app has great potential to reach and engage YMSM not currently involved in care and increase rates of HIV/STI testing and PrEP uptake in this vulnerable population.

Trial Registration: ClinicalTrials.gov NCT03177512; https://clinicaltrials.gov/ct2/show/NCT03177512 (Archived by WebCite at http://www.webcitation.org/73c917wAw)

International Registered Report Identifier (IRRID): PRR1-10.2196/10659

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KEYWORDS

mobile app; HIV testing; sexually transmitted infections; sexually transmitted diseases; pre-exposure prophylaxis; youth; adolescent; men who have sex with men

Introduction

Background

The HIV epidemic has been worsening among young men who have sex with men (YMSM) in the United States. YMSM aged 13 to 24 years had the greatest increase (26%) in diagnosed HIV infections from 2008 to 2011 [1], and infection rates have remained high through 2014. YMSM accounted for over one quarter of new HIV infections among MSM and over three quarters of new HIV diagnoses among youth aged 13 to 24 years in 2015 [2]. YMSM of color are disproportionately affected by HIV, with black YMSM experiencing the largest increase in new infections during this period. In 2015, black and Latino men who have sex with men (MSM) accounted for 55% and 24% of infections among YMSM, respectively. There is an urgent need for ensuring access to effective HIV prevention approaches in this vulnerable population.

HIV testing is critical for ensuring access to timely treatment and preventing ongoing transmission for HIV-infected YMSM and for linkage to effective preventive tools for those who test HIV negative. Although the Centers for Disease Control and Prevention (CDC) recommends at least yearly HIV testing for MSM [3], in a recent national Web-based survey, only 53% of YMSM reported testing in the past year and 33% had never tested in their lifetime [4]. Furthermore, 44% of HIV-infected youth in the United States were unaware of their diagnosis, compared with 13% of the general population [5]. Reasons for not testing can include factors at the individual, social, and structural levels [6-9] such as not having time to test (11%), low perceived risk (42%), and fear of testing positive/stigma (20%) [10]. Bacterial sexually transmitted infections (STIs) have been identified as potential drivers of HIV infection [11-21]. Despite YMSM having the highest annual STI rate among any age group [22], STI screening rates are low, with less than half of YMSM reporting STI testing in the last year [10,23-30]. Low perceived risk, lack of symptoms, and lower access to health care providers have been identified as barriers to HIV/STI testing [31,32].

Pre-exposure prophylaxis (PrEP) has demonstrated high efficacy, but uptake has been low among YMSM. The iPrEx trial, in which half the participants were aged under 25 years, demonstrated an estimated >90% PrEP efficacy among MSM with detectable drug levels in blood [33,34]. Despite these results, there has been a myriad of challenges to increasing PrEP uptake in the United States, including low awareness, concerns about side effects, low risk perception, and PrEP stigma [35-38]. According to national prescription data, youth aged under 24 years are the least likely to initiate PrEP, with only 9% of PrEP initiations in 2015 occurring in this age group [39]. In a recent national survey, only half of YMSM aged 15 to 24 years had heard of PrEP and 1.7% had ever used PrEP [40]. Demonstration projects also highlight challenges with PrEP uptake. In the US Demo Project of 550 MSM, only 20% were age 25 years or less, and PrEP uptake was lower among younger, nonwhite, and less educated persons. Self-perceived risk was low among those declining PrEP, despite high rates of condomless sex and STIs in this group [41]. In the Adolescent Medicine Trials Network for HIV/AIDS interventions (ATN) 110 study of YMSM aged 18 to 22 years, PrEP uptake was only 16%, and PrEP adherence was lower among black YMSM and declined overall during follow-up, particularly with less frequent visits [42]. Taken together, these data point to deficits in self-perceived risk that may result in low PrEP uptake, especially among YMSM of color, and the importance of engaging youth when offering and delivering PrEP.

Mobile technologies have enormous potential to reach and engage YMSM in HIV prevention [43-47]. Mobile phones have nearly reached saturation among youth, making mobile technology a particularly promising tool to reach this population that has been traditionally hard to reach through clinical services. Smartphone adoption is particularly high among young adults, with approximately 86% of those aged less than 30 years owning a smartphone. Youth are more likely to use their mobile devices for more activities such as downloading mobile apps, internet access, social networking, and accessing health information [48,49], and African American and Latinx individuals are more likely to use their phones for accessing health information and educational content [50]. The expansion of smartphones' reach has increased the possibilities of dynamic, mobile phone–based HIV prevention interventions.

Theoretical Framework for Intervention

Using the Information-Motivation-Behavior Skills (IMB) model, we have developed a highly interactive mobile app to promote accurate risk perception and increase HIV/STI testing and linkage to care among YMSM. Key components of the LYNX app will address IMB needs for both increasing HIV/STI testing frequency and PrEP uptake and are shown in Table 1. The sexual health promotion (Sex Pro) tool is an innovative Web-based app [51] that provides a personalized HIV risk score, based on data from several large MSM cohort studies [17,21,52,53]. This score is displayed on a *speedometer* (1-20 scale), with a higher score representing a higher level of protection, and was highly predictive of HIV risk among black MSM in HIV Prevention Trials Network (HPTN) 061, with all HIV infections occurring in individuals with a score below 16 [54]. YMSM found it particularly useful and informative but preferred a mobile app to the Web app format. Sex Pro has been developed into a mobile app, with additional features incorporated, including a sex diary to facilitate accurate data collection; HIV/STI testing information and reminders; access to a home HIV/STI testing kit ordered through a link from the app and delivered to a location of the users' choosing (eg, home or subject recruitment venue [SRV]); and access to geospatial-based testing site and linkage to HIV care information.

Aims and Objectives

This study is part of the UNC/Emory Center for Innovative Technology (iTech), which has the overall goal to develop innovative technology–focused interventions addressing the HIV prevention and care continuum for youth [55]. In this protocol, we will first refine the LYNX app through a series of focus groups (FGs) and optimize usability through a small technical pilot. We will then evaluate the acceptability and feasibility of the LYNX app in a pilot randomized controlled trial (RCT) among YMSM at risk for HIV acquisition in the United States. If found to be feasible and acceptable, LYNX will be tested for efficacy in increasing HIV testing and PrEP linkage in a separate efficacy RCT study (COMPARE) as part of the iTech. A costing analysis to determine overall per participant costs for administering the app and cost per HIV test provided and per PrEP initiation will be performed as part of COMPARE.

Table 1. LYNX components to increase HIV/STI testing and PrEP uptake, according to the Information-Motivation-Behavior Skills model.

Goal	Information	Motivation	Behavioral skills
Increase HIV/STI[a] testing	Personalized HIV risk assessment; sexual history diary and partner tracking	Personalized testing reminders; HIV/STI-testing diary and personalized HIV risk score	Home-based HIV/STI-testing options and instructions; geospatial-based testing site and linkage to HIV care information
Increase PrEP[b] uptake	PrEP educational materials	Testimonials of peers who decided to take PrEP; impact of PrEP on Sex Pro score	Links to youth clinics offering PrEP; app-based tips for insurance/access issues; PrEP navigation through app chat function

[a]STI: sexually transmitted infection.

[b]PrEP: pre-exposure prophylaxis.

Methods

Trial Registration, Ethics, Consent, and Institutional Board Approval

This study has been reviewed and approved by the University of North Carolina institutional review board (IRB# 17-0170). Reliance agreements were established for each SRV. A certificate of confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent/assent will be obtained for participants who are aged 15 to 17 years. The study is also registered on ClinicalTrials.gov (NCT03177512).

Design

This research protocol will be conducted in 3 phases: an iterative development phase with a series of FGs and in-depth interviews (IDIs) among up to 20 YMSM to refine the LYNX app; an open technical pilot among 15 YMSM to optimize usability of the app; and then a 6-month pilot RCT among 60 HIV-uninfected YMSM at risk for HIV acquisition, in which participants are randomized 2:1 to receive the LYNX app versus standard of care.

Data in the formative phase will include videotaped FGs and IDIs, and data from the technical pilot will include a Web-based qualitative exit interview, a computer-assisted self-interview (CASI), and app analytics (including log-in times, clicks on different app pages, and completion of different app activities). For the pilot RCT, feasibility and acceptability will be assessed through app analytics of usage patterns and acceptability scales administered via CASIs. We will also evaluate preliminary efficacy by comparing the proportion of YMSM who test at least once during the 6-month pilot and the proportion who successfully link to a PrEP provider in the intervention versus control groups. All phases of this study take place in 2 diverse iTech SRV cities: Chicago, IL (study site CORE Center), and Tampa, FL (study site University of South Florida).

Participants

Eligibility criteria with a "*" are only for participants in the technical pilot and pilot RCT. Eligible participants are cisgender men who (1) are aged 15 to 24 years; (2) have not had an HIV test in the past 6 months* (3 months for the pilot RCT); (3) self-report being HIV-uninfected or HIV status unknown at screening; (4) own an iOS or Android mobile phone and willing and able to download the LYNX app; (5) are able to understand, read, and speak English; (6) are not taking PrEP*; (7) have self-reported evidence of being at risk for HIV acquisition,

including at least one of the following in the past 6 months: (a) ≥1 episode of condomless anal sex with an HIV-positive or unknown HIV status male or transfemale partner; (b) anal sex with ≥2 male and/or transfemale partners; (c) exchange of money, gifts, shelter, or drugs for anal sex with a male or transfemale partner; (d) sex with a male or transfemale partner and having had an STI; or (e) if those aged 15 to 18 years who report of any anal sex with a male or transfemale partner; (8) have not received experimental HIV vaccine product with evidence of vaccine-induced seropositivity*; (9) not currently enrolled in another HIV intervention study*; and (10) do not have any health or social condition (eg, cancer requiring frequent hospitalization) that in the judgment of the investigator would make participation unsafe, complicate interpretation of study outcome data, or interfere with achieving study objectives.

To ensure inclusion of youth most impacted by HIV, we will oversample YMSM of color, with a goal of enrolling two-thirds of the cohort YMSM of color and at least one-quarter black YMSM.

Recruitment

Participants will be recruited through a variety of strategies including Web-based and social media strategies (eg, Craigslist, social networking ads, and gay networking mobile apps); distributing posters, flyers, and palm cards about the study; and direct outreach at local venues frequented by YMSM, including community-based organizations, schools, bars, social clubs, beauty parlors and/or barber shops, sports venues, churches, health fairs, balls, and other community events. Clinic-based recruitment may include reviewing medical charts of existing patients for potential eligibility or referrals from other providers in the clinic.

Potential subjects who are recruited or contact the SRV about the study will be followed up and assessed by trained SRV study staff at participating sites by phone, email, or in person. They will be informed of the nature of the study, the information to be collected, and the evaluations and assessments that are involved. Those who express interest in the study will be required to provide signed informed assent/consent and have eligibility criteria confirmed by research staff before enrolling into the study.

Everyone who is contacted for recruitment, has his medical chart reviewed to assess potential eligibility, is referred to the study by a provider, or is consented for study participation will be referred to a Web-based eligibility screener to assess eligibility. Individuals who do not consent to participate will be asked if they are willing to provide their reason for declining participation. Individuals assessed as ineligible for enrollment will have the reasons for ineligibility recorded.

Description of App Intervention

The LYNX app has been developed by Apt Mobility (www.aptmobility.com), the technical team who created the original version of the Sex Pro app and has extensive experience creating health-related apps. As shown in Table 1, the LYNX app was developed using the IMB framework to increase HIV/STI testing and PrEP uptake among YMSM. Upon downloading the LYNX app on to a personal device/phone, the user completes an onboarding process. This process includes creating log-in credentials and setting a password to access the password-protected app, entering basic demographic data, customizing user settings (eg, date, time, content of testing and reminders to use Sex Pro, and configuring *rate your partner* categories), and completing the baseline Sex Pro score. In addition to displaying the score, information will be provided on aspects of the participants' behaviors (eg, number of anal sex partners, condom use, and substance use) that contributed to their score. Participants are then taken to the LYNX landing screen with icons for key functions of the app, including HIV/STI testing and PrEP resources (Information); Sex Pro and earned badges (developed to integrate *gamification* into the app) for completing in-app activities (eg, sexual diary entries and ordering an HIV/STI home testing kit; Motivation); and HIV/STI testing instructions with access to home testing options (Behavioral Skills). All data collected by the app are stored on a secure Web-based cloud environment (Amazon Web Service) that is Health Insurance Portability and Accountability Act (HIPAA)–compliant, with a Business Associates Agreement established for secure data storage. Information is encrypted at rest on the phone and server and during transit to the secure server. Preliminary screenshots of the LYNX app prototype are shown in Multimedia Appendix 1. The LYNX app will be developed for both iOS and Android platforms, the 2 mobile phone platforms that together make up more than 97% of smartphones in the United States [56].

Formative-Phase Focus Groups

To refine the LYNX app, we will use an iterative development design using FG or individual IDI with 8 to 10 YMSM at each SRV, followed over 3 to 6 months (up to 3 iterations). Each FG or IDI will take 1 to 2 hours. Using a discussion guide, a member of the LYNX study team will demonstrate the app and wireframes (screenshots) of new components and elicit perspectives in content, layout, usability, and functionality. The IMB domains described above will guide the development process. We will also elicit feedback on the home HIV/STI testing kit and instructions and investigate preferences for documentation of clinic or home-based HIV/STI testing (release of medical records, upload test results via secure website and through the app). Participants will be asked to download and test iterative versions of the app for 2 weeks before the next FG, where we will gather feedback on the usability, design, and potential impact of the app. Study staff will use an onboarding document to walk participants through the download procedures and use of the app. FGs may be conducted in person or via videoconferencing.

All FGs and IDIs will be video-recorded for transcription and analysis. The goal of the analysis is to identify barriers and facilitators to app usability. If available, members of the app development team will observe the FGs via video conference in case they need more clarification of specific suggestions for improving the app. Analysis of the data will commence immediately after participants leave, in the form of a discussion of salient themes and suggestions. The team will then prioritize changes to the app for the next iteration to be tested and discussed in the next round of FG discussions. If further

transcription is necessary, selected segments of the video and audio interview data will be transcribed.

Technical Pilot

After revisions to the LYNX app are completed based on the formative phase, we will conduct a 2-month, single-arm, pilot study among 12 to 15 YMSM across 2 iTech SRV cities to optimize the technical performance and functionality of LYNX. YMSM who participated in the formative phase may participate in the technical pilot, as their feedback on app revisions will provide useful insights to the development team. At an in-person enrollment visit (approximately 1.5 hours), YMSM will download the LYNX app and answer a Web-based CASI questionnaire on sociodemographics, use of technology, and risk behaviors. Study staff will use an onboarding document to walk participants through the download procedures and use of the app. Participants will then be encouraged to use all app components over the next 2 months, including ordering and using the HIV/STI test kit at least once during the technical pilot.

Upon completion of the technical pilot, all participants will complete a Web-based exit interview with qualitative-trained study staff to provide feedback on functionality, technical performance, errors and bugs encountered, overall experiences using the app, feasibility and acceptability of methods to confirm HIV testing results (eg, upload results via a secure website), and feedback for further refinement. Web-based interviews (approximately 1 hour) will be conducted via a HIPAA-compliant, video chat application (Zoom) that provides strong security components. We will also assess youth satisfaction with the app using the system usability scale (SUS), a validated assessment tool assessing various domains of the app with demonstrated high internal consistency across a number of studies [57]. Participants will be emailed a link to complete a CASI to assess these measures. Each CASI will take approximately 1 hour to complete. All exit interviews will be audio- and video-recorded and transcribed for analysis by the iTech Analytic Core (AC).

Pilot Randomized Controlled Trial

After the LYNX app is refined and optimized through the findings from the formative work and technical pilot, we will evaluate the feasibility, acceptability, and preliminary impact of LYNX through a pilot RCT with 60 HIV-uninfected YMSM at risk for HIV acquisition.

Randomization

Participants who express interest in using LYNX, meet eligibility criteria, provide informed consent, and complete a baseline assessment will be eligible for enrollment and randomization. The enrollment visit will take approximately 1.5 hours. After successful enrollment into the study, subjects will be randomized 2:1 into either the LYNX intervention arm (N=40) or control arm (N=20). The 2:1 allocation will allow us to efficiently gather additional data on app utilization. Randomization will be stratified by age (15 to 18 years and 19 to 24 years) and site and based on a pregenerated list created by the lead iTech AC statistician, with random blocks of size 3 or 6 [58]. After assent/consent and baseline survey completion, the participant will be randomized (assigned to the next available random allocation).

LYNX Intervention Condition

Individuals who receive LYNX will be given brief instructions on the purpose of the app, how to access it, and an overview of how to use it. Participants will be encouraged to explore all components of the app and use it routinely.

Standard of Care Condition

Following screening, participants in both conditions will receive standard of care prevention material consisting of provision of information regarding recommendations for HIV testing and referrals to local HIV testing sites and prevention services.

Intervention

Study staff will assist participants in downloading the LYNX mobile app, provide instruction on its use, and help set up reminders to input sex diary entries. To restrict access to the LYNX app to intervention arm participants only, they will be provided a single-use registration code that will need to be entered to gain access to the app. Study staff will use an onboarding document to walk participants through the download procedures and use of the app. These reminders will be personalized by the user for day, time, and message content at the first visit and can subsequently be updated by participants if desired. Participants will be encouraged to explore and use other components of the app (including the Sex Pro score, PrEP videos, bidirectional chat function with study staff, and geolocation features). Users will receive quarterly HIV/STI testing reminders using the mobile device notification feature. For confidentiality purposes, reminder notifications are nonspecific, but inside the app, the participant is linked to a customizable reminder. Reminders include 2 options for testing: (1) the ability to order a home HIV/STI testing kit to be mailed to a location of their choosing (eg, home or the SRV) free of charge or (2) a geo-located map of the closest HIV/STI testing sites. For participants who test HIV-positive during the study, information about next steps for linkage to care is included in the testing section of the app, including a phone number for an on-call clinician available 24 hours a day. In addition, there is a chat function in which participants can contact LYNX staff for support and assistance with linkage to care. Any participant who enters a positive HIV test result into the app will be contacted by the study team and provided supportive counseling and referral to treatment services.

Control Arm

Participants randomized to the control condition will be instructed to access HIV/STI testing at existing sites in the community. They will be provided with a list of these testing sites, along with an informational brochure about PrEP. All participants will be provided access to Sex Pro (risk assessment tool that is part of LYNX and will be made available on the Web) after completion of the study.

Follow-Up Visits

All enrolled participants will be followed for 24 weeks. After enrollment, all follow-up visits will occur on the Web, with SMS reminders, email, and phone follow-up conducted as

needed to ensure completion of study procedures. Participants will complete a Web-based CASI at 12 and 24 weeks (each approximately 1 hour) and receive a stipend for completion of procedures at each visit. Visit windows will be 14 days before or after the target date.

At the 3-month visit, up to 20 participants randomized to the LYNX arm will be selected for participation in a 1.5-hour exit IDI. The purpose of the exit interviews is to elicit additional feedback on their experiences using the app, any technical difficulties encountered, and how the app could be further improved. Participants will be selected for interview using purposive sampling based on level of engagement with the app, whether participants completed HIV/STI testing and/or initiated PrEP during the study, and to achieve diversity based on sociodemographics (eg, age and race/ethnicity). Additionally, any participant who has a positive HIV test during the study will be offered an interview. By purposively sampling certain participants for the exit interviews, the goal is to select *information-rich* cases from which one can learn a great deal about issues of central importance to the purpose of the research [59]. All interviews will be conducted via Zoom and audio-recorded for transcription and analysis.

Outcomes

Primary and secondary outcomes and moderating variables for the pilot RCT are shown in Table 2.

The primary acceptability outcome will be measured by the SUS, a 10-item, 5-point Likert scale giving an overall view of usability. The SUS is technology-independent and provides a global measure of system satisfaction and subscales of usability and learnability [57]. A score of >50 (out of 100) indicates the app is acceptable [74]. We will also assess interest in future use of LYNX at study completion. For feasibility, we will assess frequency of log-ins and use of various components of LYNX, based on app analytics. If >60% of participants open the app at least once after the initial enrollment visit, it will be considered feasible. We will also assess the proportion of YMSM who complete the personalized risk assessment, a key component of the app, and the number of HIV/STI home testing kits requested and completed. As a secondary outcome, we will evaluate the preliminary efficacy of LYNX in increasing HIV/STI testing and PrEP care linkage. For HIV testing, we will evaluate the proportion who complete at least one HIV test during the 6 months of follow-up. Self-reported HIV/STI testing via CASI will be confirmed by methods that are finalized during the formative phase (eg, medical record review and upload test results via secure website). For PrEP linkage, we will evaluate (1) the proportion of participants reporting interest in PrEP uptake during follow-up using the question "How interested are you in taking PrEP?" with response options "not at all interested, a little interested, somewhat interested, very interested, and extremely interested" compared with baseline; (2) the proportion making and attending a clinic appointment for PrEP evaluation; and (3) the proportion who receive a prescription for PrEP and the proportion who pick up PrEP medication from the pharmacy. We will request participants to sign medical release forms for the release of their HIV/STI testing results and records regarding PrEP initiation. We will also measure sexual behaviors at each quarterly follow-up visit, including numbers of partners and types of sexual behaviors, by HIV serostatus and position (insertive and receptive) in the past 3 months. Finally, we will assess IMB model constructs including HIV/STI testing and PrEP knowledge, attitudes, motivations, and behavioral skills related to HIV/STI testing and PrEP uptake. Given the importance of moderating contextual factors that may influence uptake of prevention strategies in YMSM, we will use the eco-social theoretical model which links individual, social, and structural factors (ie, socioeconomic position, social networks, and stigma) across a hierarchical framework to explore these factors as they relate to HIV/STI testing and PrEP uptake among YMSM [6-9]. Process measures including recruitment, consent, dropout, and missed visit rates will also be assessed.

Statistical Analysis

Response rates to follow-up surveys will be tabulated by recruitment venue and respondent characteristics to help understand potential sources of bias. We will characterize the study population using descriptive statistics and compare the intervention and control groups at baseline using *t* test, Wilcoxon test, and chi-square test. The primary outcomes of the pilot RCT will be acceptability and feasibility of the app. Point estimates for mean SUS score ≥50 and for proportion accessing the app >0.60 will be considered the minimum criteria for acceptability and feasibility, consistent with industry standards [57]. Descriptive statistics will be used to evaluate app analytics, including number of log-in attempts, cumulative time spent using the app, mean session duration, and frequency and duration of use of different components of the app. A secondary feasibility outcome will be achieved if ≥50% of participants who open the app complete their personalized risk score at least once.

The secondary outcomes of preliminary efficacy of the LYNX app to increase HIV/STI testing (any testing over follow-up) and PrEP uptake (as described above) will be evaluated using unadjusted risk ratios for each outcome. If there is evidence of divergence from balance in measured baseline covariates (ie, failure of randomization), post hoc analyses using Poisson regression with robust SEs [75] will be used to estimate adjusted risk ratios. Outcome variables will represent any HIV testing and any PrEP uptake over the follow-up period. Separate models will be estimated for each outcome.

With 60 participants randomized 2:1 to intervention:control and 10% to 20% attrition, we will have 80% power to detect 37% to 42% point increases in HIV testing and PrEP uptake, depending on rates in controls. The lack of precision and large minimum detectable effects, typical of pilot studies, will entail careful interpretation of study results in the light of overall patterns, plausibility, and findings from other mobile health (mHealth) studies.

Incentives

Participants receive incentives consistent with local standards for completing each study visit. This includes the US $50 to US $60 for the baseline visit and US $25 to US $30 for the 3- and 6-month follow-up visits.

Table 2. Outcomes and measures for LYNX.

Domain	Data source	Description/scale
Primary outcomes		
Acceptability	CASI[a]	System Usability Scale [57], Intervention Acceptability Scale [61], and acceptability of app components
Feasibility	App analytics	Frequency of app log-ins and use of different components of LYNX
Secondary outcomes		
HIV testing frequency	CASI, EP[b], MR[c]	Number of HIV tests during study
STI[d] testing frequency	CASI, EP, MR	Number of STI tests during study
HIV testing knowledge, attitudes, and behaviors	CASI	National HIV Behavioral Surveillance men who have sex with men-4 (NHBS-MSM-4)
PrEP[e] knowledge and attitudes; PrEP willingness	CASI	PrEP awareness and willingness scales
PrEP linkage	CASI, MR	HIV-negative cascade measures
Social impacts	CASI	Social benefits and harms of using app
Model constructs		
Information-Motivation-Behavioral Skills (IMB)	CASI	Adapted scales based on content of app [62,63]
Covariates (based on eco-social model)[6-9]		
Individual		
Demographics, socioeconomic position	CASI	Age, race/ethnicity, gender identity, sexual identity, student status, education, income, family structure, employment, insurance status, and food insecurity
Sexual behavior (number of sex partners, condom use, partner selection)	CASI	Numbers and types of partners, HIV-status of partners, sexual position, and condom use
Drug use behavior (ie, alcohol, cocaine, meth)	CASI	Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [64] and Alcohol Use Disorders Identification Test (AUDIT-C) [65]
Self-efficacy	CASI	HIV testing [66], PrEP use [67], condom use [68]
Mental health (depression, anxiety)	CASI	Generalized anxiety disorder 7-item scale and patient health questionnaire
Perceived risk of HIV infection	CASI	Perceived risk of HIV scale [69]
Trauma and abuse	CASI	Startle, Physiological Arousal, Anger and Numbness (SPAN) [70]
Social/sexual network		
Social support	CASI	Patient-Reported Outcomes Measurement Information System (PROMIS) [71]
Peer norms for condom use	CASI	
Structural		
SRV[f]/city	CRF[g]	Geographic location of study participant
Access to health care	CASI	Barriers, frequency of seeing a provider, locations, and comfortability in discussing sex with provider
Incarceration history	CASI	Ever and recent history
Structural discrimination	CASI	Everyday discrimination scale [72], racism, sexual minority stress [73], and medical mistrust
Stigma	CASI	PrEP-related and sexuality-related
Other covariates		
Mobile phone and technology use	CASI	Device types, operating system, and phone plan, sharing of devices, internet use and frequency, and use of social networking sites

Domain	Data source	Description/scale
Mobile app use over study period	App analytics	Login attempts, HIV testing and PrEP use, proportion complete HIV-testing plan, and proportion requesting HIV/STI home test kits

[a]CASI: computer-assisted self-interview.

[b]EP: electronic picture.

[c]MR: medical record confirmation.

[d]STI: sexually transmitted infection.

[e]PrEP: pre-exposure prophylaxis.

[f]SRV: subject recruitment venue.

[g]CRF: case report form.

Results

This pilot RCT will begin enrolling in October 2018, and study results will be available in 2019.

Discussion

The LYNX pilot RCT will evaluate the feasibility and acceptability of one of the first mobile apps designed to increase HIV testing and PrEP uptake among YMSM. A recent review of 285 HIV mobile apps revealed that only 8% specifically addressed MSM and none dealt with PrEP [76]. Furthermore, most were developed by nonacademic, nonpublic health developers, which may be less credible than apps created by university or health department sponsors [77]. LYNX was developed by a multidisciplinary team of public health researchers, HIV physicians, behavioral specialists, and app developers, with input from YMSM at all stages of development. Although most prior mHealth prevention interventions have focused on behavioral risk reduction alone, LYNX will incorporate components to increase HIV/STI testing and linkage to treatment and prevention services, including PrEP, and will be specifically tailored for use in YMSM.

The LYNX app will use a personalized risk assessment to assist YMSM in evaluating their risk of HIV. Internet-based personalized decision support tools have been used successfully to assist users with behavior changes in several diseases including heavy alcohol use, hyperlipidemia, and obesity [78-85]. Currently, no mHealth interventions integrate personalized HIV risk assessment, appeal to YMSM, and incorporate HIV/STI testing and resources to increase PrEP uptake [86-88]. A highly engaging risk assessment tool could assist YMSM better understand their HIV risk, provide motivation to test for HIV/STIs, and help determine when to take PrEP.

Challenges in developing mHealth interventions have been described previously and include coordination and communication with the technology developer; understanding the needs and preferences of the target population, vendors, and researchers having differing values and priorities; and extra time needed for testing and debugging the intervention [89]. To address these potential challenges in the development and testing of the LYNX app, we have established weekly calls with Apt Mobility to discuss development priorities and provide feedback on app development; established a Web-based spreadsheet to track all requests for app builds and modifications; and assigned a study coordinator with extensive experience in developing mHealth apps to manage this project. In addition, as described in this protocol, we have included extensive formative work to elicit feedback from diverse YMSM regarding their preferences and needs for content and features. Finally, we have worked with the iTech core to build realistic timelines, factoring in time required for app testing, debugging, and revisions.

In summary, a technology-based HIV prevention app has great potential in scaling up HIV/STI testing and PrEP use among YMSM. Modeling studies in MSM suggest that substantial coverage of HIV prevention services is needed to reduce population-level incidence [90], yet uptake of these services has been limited in youth. With the high penetration of smartphones among youth, LYNX has great potential to reach large numbers of high-risk YMSM who may not access medical care or traditional testing sites, at marginal incremental costs. If found to be feasible and acceptable in this pilot study, the LYNX app will be evaluated in a head-to-head comparison with the MyChoices app (Biello et al, *ATN 141*, submitted to this issue) in the COMPARE RCT. If effective, these apps could facilitate nationwide scale-up of HIV/STI testing and PrEP use among YMSM.

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Conflicts of Interest

AL has led studies for which Gilead Sciences has donated the study drug. SB has been an investigator on studies for which Gilead Sciences has donated the study drug.

Multimedia Appendix 1

Screenshots of the LYNX app.

[PDF File (Adobe PDF File), 626KB - resprot_v8i1e10659_app1.pdf]

References

1. CDC. Atlanta, GA: Centers for Disease Control And Prevention; 2017. HIV/AIDS Slide Sets URL: https://www.cdc.gov/hiv/library/slidesets/index.html [accessed 2018-11-03] [WebCite Cache ID 73eM6YLx7]
2. CDC. Atlanta, GA: Centers for Disease Control and Prevention; 2016 Nov. HIV Surveillance Report: Diagnoses of HIV Infection in the United States and Dependent Areas URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2015-vol-27.pdf [accessed 2018-11-03] [WebCite Cache ID 73eMSLeSo]
3. DiNenno EA, Prejean J, Irwin K, Delaney KP, Bowles K, Martin T, et al. Recommendations for HIV screening of gay, bisexual, and other men who have sex with men-United States, 2017. MMWR Morb Mortal Wkly Rep 2017 Aug 11;66(31):830-832 [FREE Full text] [doi: 10.15585/mmwr.mm6631a3] [Medline: 28796758]
4. Sanchez TH, Sineath RC, Kahle EM, Tregear SJ, Sullivan PS. The annual American men's internet survey of behaviors of men who have sex with men in the United States: protocol and key indicators report 2013. JMIR Public Health Surveill 2015;1(1):e3 [FREE Full text] [doi: 10.2196/publichealth.4314] [Medline: 27227126]
5. CDC. Atlanta, GA: Centers for Disease Control and Prevention; 2015 Jul. HIV Surveillance Supplemental Report: Monitoring selected national HIV prevention and care objectives by using HIV surveillance data?United States and 6 dependent areas?2013 URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillancereport_vol20_no2.pdf [accessed 2018-11-03] [WebCite Cache ID 73eMzvXUC]
6. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? Soc Sci Med 1994 Oct;39(7):887-903. [Medline: 7992123]
7. Baral S, Logie CH, Grosso A, Wirtz AL, Beyrer C. Modified social ecological model: a tool to guide the assessment of the risks and risk contexts of HIV epidemics. BMC Public Health 2013 May 17;13:482 [FREE Full text] [doi: 10.1186/1471-2458-13-482] [Medline: 23679953]
8. Poundstone KE, Strathdee SA, Celentano DD. The social epidemiology of human immunodeficiency virus/acquired immunodeficiency syndrome. Epidemiol Rev 2004;26:22-35. [doi: 10.1093/epirev/mxh005] [Medline: 15234945]
9. Smith LR, Fisher JD, Cunningham CO, Amico KR. Understanding the behavioral determinants of retention in HIV care: a qualitative evaluation of a situated information, motivation, behavioral skills model of care initiation and maintenance. AIDS Patient Care STDS 2012 Jun;26(6):344-355 [FREE Full text] [doi: 10.1089/apc.2011.0388] [Medline: 22612447]
10. CDC. Atlanta, GA: Centers for Disease Control and Prevention; 2014. HIV Surveillance Special Report: HIV Risk, Prevention, and Testing Behaviors—National HIV Behavioral Surveillance System: Men Who Have Sex With Men, 20 U.S. Cities, 2011 URL: https://www.cdc.gov/hiv/pdf/HSSR_8_NHBS_MSM_PDF-03.pdf [accessed 2018-11-03] [WebCite Cache ID 73eNOQ43O]
11. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nat Rev Microbiol 2004 Jan;2(1):33-42. [doi: 10.1038/nrmicro794] [Medline: 15035007]
12. Berman SM, Cohen MS. STD treatment: how can it improve HIV prevention in the South? Sex Transm Dis 2006 Jul;33(7 Suppl):S50-S57. [doi: 10.1097/01.olq.0000175395.95911.85] [Medline: 16554696]
13. Buchbinder SP, Douglas JM, McKirnan DJ, Judson FN, Katz MH, MacQueen KM. Feasibility of human immunodeficiency virus vaccine trials in homosexual men in the United States: risk behavior, seroincidence, and willingness to participate. J Infect Dis 1996 Nov;174(5):954-961. [Medline: 8896495]
14. Koblin BA, Husnik MJ, Colfax G, Huang Y, Madison M, Mayer K, et al. Risk factors for HIV infection among men who have sex with men. AIDS 2006 Mar 21;20(5):731-739. [doi: 10.1097/01.aids.0000216374.61442.55] [Medline: 16514304]
15. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. J Acquir Immune Defic Syndr 2010 Apr 01;53(4):537-543. [doi: 10.1097/QAI.0b013e3181c3ef29] [Medline: 19935075]
16. Scott KC, Philip S, Ahrens K, Kent CK, Klausner JD. High prevalence of gonococcal and chlamydial infection in men who have sex with men with newly diagnosed HIV infection: an opportunity for same-day presumptive treatment. J Acquir Immune Defic Syndr 2008 May 01;48(1):109-112. [doi: 10.1097/QAI.0b013e318165dc0b] [Medline: 18209679]
17. Koblin BA, Chesney MA, Husnik MJ, Bozeman S, Celum CL, Buchbinder S, EXPLORE Study Team. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. Am J Public Health 2003 Jun;93(6):926-932. [Medline: 12773357]
18. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis 2005 Jul 01;41(1):67-74. [doi: 10.1086/430704] [Medline: 15937765]
19. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999 Feb;75(1):3-17 [FREE Full text] [doi: 10.1136/sti.75.1.3] [Medline: 10448335]

20. Zetola NM, Bernstein KT, Wong E, Louie B, Klausner JD. Exploring the relationship between sexually transmitted diseases and HIV acquisition by using different study designs. J Acquir Immune Defic Syndr 2009 Apr 15;50(5):546-551 [FREE Full text] [doi: 10.1097/QAI.0b013e318195bd2b] [Medline: 19367993]
21. Buchbinder SP, Vittinghoff E, Heagerty PJ, Celum CL, Seage GR, Judson FN, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. J Acquir Immune Defic Syndr 2005 May 01;39(1):82-89. [Medline: 15851918]
22. Centers for Disease Control and Prevention. CDC. Atlanta, GA: Department of Health and Human Services; 2015. Sexually Transmitted Disease Surveillance URL: https://www.cdc.gov/std/stats14/surv-2014-print.PDF [accessed 2018-11-03] [WebCite Cache ID 73eNZvdY7]
23. Bourne C, Knight V, Guy R, Wand H, Lu H, McNulty A. Short message service reminder intervention doubles sexually transmitted infection/HIV re-testing rates among men who have sex with men. Sex Transm Infect 2011 Apr;87(3):229-231. [doi: 10.1136/sti.2010.048397] [Medline: 21296796]
24. Centers for Disease Control Prevention. HIV testing among men who have sex with men—21 cities, United States, 2008. MMWR Morb Mortal Wkly Rep 2011 Jun 03;60(21):694-699 [FREE Full text] [Medline: 21637183]
25. Kellerman SE, Lehman JS, Lansky A, Stevens MR, Hecht FM, Bindman AB, et al. HIV testing within at-risk populations in the United States and the reasons for seeking or avoiding HIV testing. J Acquir Immune Defic Syndr 2002 Oct 01;31(2):202-210. [Medline: 12394799]
26. McDaid LM, Hart GJ. Contact with HIV prevention services highest in gay and bisexual men at greatest risk: cross-sectional survey in Scotland. BMC Public Health 2010 Dec 31;10:798 [FREE Full text] [doi: 10.1186/1471-2458-10-798] [Medline: 21194448]
27. Miller LG, Simon PA, Miller ME, Long A, Yu EI, Asch SM. High-risk sexual behavior in Los Angeles: who receives testing for HIV? J Acquir Immune Defic Syndr 1999 Dec 15;22(5):490-497. [Medline: 10961611]
28. Makulowich GS. HIV and STD prevention update. Multisite HIV prevention trial. AIDS Patient Care STDS 1998 Sep;12(9):725-727. [doi: 10.1089/apc.1998.12.725] [Medline: 15468447]
29. Fuqua V, Chen YH, Packer T, Dowling T, Ick TO, Nguyen B, et al. Using social networks to reach Black MSM for HIV testing and linkage to care. AIDS Behav 2012 Feb;16(2):256-265. [doi: 10.1007/s10461-011-9918-x] [Medline: 21390535]
30. Finlayson TJ, Le B, Smith A, Bowles K, Cribbin M, Miles I, Centers for Disease Control Prevention. HIV risk, prevention, and testing behaviors among men who have sex with men—National HIV Behavioral Surveillance System, 21 U.S. cities, United States, 2008. MMWR Surveill Summ 2011 Oct 28;60(14):1-34 [FREE Full text] [Medline: 22031280]
31. MacKellar DA, Valleroy LA, Secura GM, Behel S, Bingham T, Celentano DD, Young Men's Survey Study Group. Perceptions of lifetime risk and actual risk for acquiring HIV among young men who have sex with men. AIDS Behav 2007 Mar;11(2):263-270. [doi: 10.1007/s10461-006-9136-0] [Medline: 16791527]
32. Dorell CG, Sutton MY, Oster AM, Hardnett F, Thomas PE, Gaul ZJ, et al. Missed opportunities for HIV testing in health care settings among young African American men who have sex with men: implications for the HIV epidemic. AIDS Patient Care STDS 2011 Nov;25(11):657-664. [doi: 10.1089/apc.2011.0203] [Medline: 21923415]
33. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010 Dec 30;363(27):2587-2599 [FREE Full text] [doi: 10.1056/NEJMoa1011205] [Medline: 21091279]
34. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, iPrEx Study Team. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med 2012 Sep 12;4(151):151ra125 [FREE Full text] [doi: 10.1126/scitranslmed.3004006] [Medline: 22972843]
35. Saberi P, Gamarel KE, Neilands TB, Comfort M, Sheon N, Darbes LA, et al. Ambiguity, ambivalence, and apprehensions of taking HIV-1 pre-exposure prophylaxis among male couples in San Francisco: a mixed methods study. PLoS One 2012;7(11):e50061 [FREE Full text] [doi: 10.1371/journal.pone.0050061] [Medline: 23166819]
36. Fuchs JD, Sobieszczyk ME, Madenwald T, Grove D, Karuna ST, Andrasik M, HVTN 505 Protocol Team. Intentions to use preexposure prophylaxis among current phase 2B preventive HIV-1 vaccine efficacy trial participants. J Acquir Immune Defic Syndr 2013 Jul 01;63(3):259-262 [FREE Full text] [doi: 10.1097/QAI.0b013e318296df94] [Medline: 23614998]
37. Krakower DS, Mimiaga MJ, Rosenberger JG, Novak DS, Mitty JA, White JM, et al. Limited awareness and low immediate uptake of pre-exposure prophylaxis among men who have sex with men using an internet social networking site. PLoS One 2012;7(3):e33119 [FREE Full text] [doi: 10.1371/journal.pone.0033119] [Medline: 22470438]
38. Liu A, Cohen S, Follansbee S, Cohan D, Weber S, Sachdev D, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. PLoS Med 2014 Mar;11(3):e1001613 [FREE Full text] [doi: 10.1371/journal.pmed.1001613] [Medline: 24595035]
39. Bush S, Ng L, Magnuson D, Piontkowsky D, Giler R. Significant Uptake of Truvada for Pre-Exposure Prophylaxis (PrEP) Utilization in the US in Late 2014-1Q2015. 2015 Presented at: IAPC IAPAC Treatment, Prevention, and Adherence Conference; June 28-30, 2015; Miami, FL URL: http://www.iapac.org/AdherenceConference/presentations/ADH10_OA74.pdf
40. Sullivan P, Sineath C, Kahle E, Sanchez T. Awareness, willingness and use of oral pre-exposure prophylaxis (PrEP) among a national sample of US men who have sex with men. In: AIDS IMPACT 2015, Abstract 2362. 2015 Presented at: AIDS

Impact; July 28-31,2015; Amsterdam, Netherlands URL: http://www.aidsimpact.com/2015/Academics/Programme/abstract/?id=2362
41. Cohen SE, Vittinghoff E, Bacon O, Doblecki-Lewis S, Postle BS, Feaster DJ, et al. High interest in preexposure prophylaxis among men who have sex with men at risk for HIV infection: baseline data from the US PrEP demonstration project. J Acquir Immune Defic Syndr 2015 Apr 01;68(4):439-448 [FREE Full text] [doi: 10.1097/QAI.0000000000000479] [Medline: 25501614]
42. Hosek SG, Rudy B, Landovitz R, Kapogiannis B, Siberry G, Rutledge B, et al. An HIV Preexposure Prophylaxis Demonstration Project and Safety Study for Young MSM. J Acquir Immune Defic Syndr 2017 Dec 01;74(1):21-29 [FREE Full text] [doi: 10.1097/QAI.0000000000001179] [Medline: 27632233]
43. Gold J, Lim MS, Hocking JS, Keogh LA, Spelman T, Hellard ME. Determining the impact of text messaging for sexual health promotion to young people. Sex Transm Dis 2011 Apr;38(4):247-252. [doi: 10.1097/OLQ.0b013e3181f68d7b] [Medline: 20966830]
44. Holloway IW, Cederbaum JA, Ajayi A, Shoptaw S. Where are the young men in HIV prevention efforts? Comments on HIV prevention programs and research from young men who sex with men in Los Angeles county. J Prim Prev 2012 Dec;33(5-6):271-278 [FREE Full text] [doi: 10.1007/s10935-012-0282-z] [Medline: 23132515]
45. Eyrich-Garg KM. Mobile phone technology: a new paradigm for the prevention, treatment, and research of the non-sheltered "street" homeless? J Urban Health 2010 May;87(3):365-380 [FREE Full text] [doi: 10.1007/s11524-010-9456-2] [Medline: 20397058]
46. Riley WT, Rivera DE, Atienza AA, Nilsen W, Allison SM, Mermelstein R. Health behavior models in the age of mobile interventions: are our theories up to the task? Transl Behav Med 2011 Mar;1(1):53-71 [FREE Full text] [doi: 10.1007/s13142-011-0021-7] [Medline: 21796270]
47. Muessig KE, Pike EC, Fowler B, LeGrand S, Parsons JT, Bull SS, et al. Putting prevention in their pockets: developing mobile phone-based HIV interventions for black men who have sex with men. AIDS Patient Care STDS 2013 Apr;27(4):211-222 [FREE Full text] [doi: 10.1089/apc.2012.0404] [Medline: 23565925]
48. Anderson M. Pew Internet. 2015. Technology Device Ownership: 2015 URL: http://www.pewinternet.org/2015/10/29/technology-device-ownership-2015 [accessed 2018-11-03] [WebCite Cache ID 73ePbSdhO]
49. Smith A. Pew Internet. 2015. US Smartphone Use in 2015 URL: http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/2015/ [accessed 2018-11-03] [WebCite Cache ID 73ePoGy1p]
50. Anderson M. Pew Research Center. 2015. Racial and ethnic differences in how people use mobile technology URL: http://www.pewresearch.org/fact-tank/2015/04/30/racial-and-ethnic-differences-in-how-people-use-mobile-technology/ [accessed 2018-11-03] [WebCite Cache ID 73ePw71wq]
51. Sex Pro. San Francisco, CA: San Francisco Department of Public Health; 2015. Welcome to Sex Pro! URL: https://mysexpro.org/en/home/ [accessed 2018-11-09] [WebCite Cache ID 73nReY8Nt]
52. Bartholow BN, Goli V, Ackers M, McLellan E, Gurwith M, Durham M, et al. Demographic and behavioral contextual risk groups among men who have sex with men participating in a phase 3 HIV vaccine efficacy trial: implications for HIV prevention and behavioral/biomedical intervention trials. J Acquir Immune Defic Syndr 2006 Dec 15;43(5):594-602. [doi: 10.1097/01.qai.0000243107.26136.82] [Medline: 17003693]
53. Koblin BA, Mayer KH, Noonan E, Wang CY, Marmor M, Sanchez J, et al. Sexual risk behaviors, circumcision status, and preexisting immunity to adenovirus type 5 among men who have sex with men participating in a randomized HIV-1 vaccine efficacy trial: step study. J Acquir Immune Defic Syndr 2012 Aug 01;60(4):405-413 [FREE Full text] [doi: 10.1097/QAI.0b013e31825325aa] [Medline: 22421748]
54. Scott H, Vittinghoff E, Irvin R, Liu A, Fields S, Magnus M. Sex Pro: A Personalized HIV Risk Assessment Tool for Men Who Have Sex With Men. 2015 Presented at: CROI 2015; February 23-26, 2015; Seattle, WA URL: http://www.croiconference.org/sessions/sex-pro-personalized-hiv-risk-assessment-tool-men-who-have-sex-men
55. Hightow-Weidman LB, Muessig K, Rosenberg E, Sanchez T, LeGrand S, Gravens L, et al. University of North Carolina/Emory Center for Innovative Technology (iTech) for Addressing the HIV Epidemic Among Adolescents and Young Adults in the United States: Protocol and Rationale for Center Development. JMIR Res Protoc 2018 Aug 03;7(8):e10365 [FREE Full text] [doi: 10.2196/10365] [Medline: 30076126]
56. Statista. 2017. Subscriber share held by smartphone operating systems in the United States from January 2012 to June 2017 URL: https://www.statista.com/statistics/266572/market-share-held-by-smartphone-platforms-in-the-united-states/ [accessed 2018-11-03] [WebCite Cache ID 73eQbwvew]
57. Brooke J. SUS: a quick and dirty usability scale. In: Jordan P, Thomas BW, McClelland I, editors. Usability Evaluation in Industry. London, UK: Taylor and Francis; 1996:189-194.
58. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999 Jan;52(1):19-26. [doi: 10.1016/S0895-4356(98)00138-3] [Medline: 9973070]
59. Patton MQ. Qualitative interviewing. Qual Health Res 2002;3:344-347 [FREE Full text]
60. Rotheram-Borus MJ, Wu Z, Liang L, Li L, Detels R, Guan J, NIMH Collaborative HIV/STD Prevention Trial Group. Reductions in sexually transmitted infections associated with popular opinion leaders in China in a randomised controlled trial. Sex Transm Infect 2011 Jun;87(4):337-343 [FREE Full text] [doi: 10.1136/sti.2010.046243] [Medline: 21278400]

61. Horvath KJ, Oakes JM, Rosser BR, Danilenko G, Vezina H, Amico KR, et al. Feasibility, acceptability and preliminary efficacy of an online peer-to-peer social support ART adherence intervention. AIDS Behav 2013 Jul;17(6):2031-2044 [FREE Full text] [doi: 10.1007/s10461-013-0469-1] [Medline: 23553347]
62. Fisher CM. Are information, motivation, and behavioral skills linked with HIV-related sexual risk among young men who have sex with men? J HIV AIDS Soc Serv 2011;10(1):5-21 [FREE Full text] [doi: 10.1080/15381501.2011.549064] [Medline: 21731473]
63. Misovich S, Fisher W, Fisher J. A measure of AIDS prevention, information, motivation, behavioral skills, and behavior. In: Davis C, Yarber W, Bauserman R, Schreer G, Davis S, editors. Handbook of Sexuality Related Measures. Thousand Oaks, CA: Sage; 1998:328-337.
64. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction 2002 Sep;97(9):1183-1194. [Medline: 12199834]
65. Bradley KA, DeBenedetti A, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res 2007 Jul;31(7):1208-1217. [doi: 10.1111/j.1530-0277.2007.00403.x] [Medline: 17451397]
66. Jamil MS, Guy RJ, Bavinton BR, Fairley CK, Grulich AE, Holt M, FORTH Investigator Group. HIV testing self-efficacy is associated with higher HIV testing frequency and perceived likelihood to self-test among gay and bisexual men. Sex Health 2017 Apr;14(2):170-178. [doi: 10.1071/SH16100] [Medline: 27883311]
67. Erlen JA, Cha ES, Kim KH, Caruthers D, Sereika SM. The HIV Medication Taking Self-efficacy Scale: psychometric evaluation. J Adv Nurs 2010 Nov;66(11):2560-2572 [FREE Full text] [doi: 10.1111/j.1365-2648.2010.05400.x] [Medline: 20722799]
68. Rotheram-Borus M, Murphy D, Coleman C, Kennedy M, Reid H, Cline T, et al. Risk acts, health care,medical adherence among HIV+ youths in care over time. AIDS and Behavior 1997;1(1):43-52 [FREE Full text] [doi: 10.1023/A:1026213905034]
69. Napper LE, Fisher DG, Reynolds GL. Development of the perceived risk of HIV scale. AIDS Behav 2012 May;16(4):1075-1083 [FREE Full text] [doi: 10.1007/s10461-011-0003-2] [Medline: 21785873]
70. Meltzer-Brody S, Churchill E, Davidson JR. Derivation of the SPAN, a brief diagnostic screening test for post-traumatic stress disorder. Psychiatry Res 1999 Oct;88(1):63-70. [doi: 10.1016/s0165-1781(99)00070-0]
71. Hahn EA, Devellis RF, Bode RK, Garcia SF, Castel LD, Eisen SV, et al. Measuring social health in the patient-reported outcomes measurement information system (PROMIS): item bank development and testing. Qual Life Res 2010 Sep;19(7):1035-1044 [FREE Full text] [doi: 10.1007/s11136-010-9654-0] [Medline: 20419503]
72. Williams DR, Yan Y, Jackson JS, Anderson NB. Racial differences in physical and mental health: socio-economic status, stress and discrimination. J Health Psychol 1997 Jul;2(3):335-351. [doi: 10.1177/135910539700200305] [Medline: 22013026]
73. Hatzenbuehler ML, Nolen-Hoeksema S, Erickson SJ. Minority stress predictors of HIV risk behavior, substance use, and depressive symptoms: results from a prospective study of bereaved gay men. Health Psychol 2008 Jul;27(4):455-462. [doi: 10.1037/0278-6133.27.4.455] [Medline: 18643003]
74. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: adding an adjective rating scale. J Usability Stud 2009;4(3):114-123 [FREE Full text]
75. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005 Aug 01;162(3):199-200. [doi: 10.1093/aje/kwi188] [Medline: 15987728]
76. Sullivan PS, Jones J, Kishore N, Stephenson R. The roles of technology in primary HIV prevention for men who have sex with men. Curr HIV/AIDS Rep 2015 Dec;12(4):481-488. [doi: 10.1007/s11904-015-0293-5] [Medline: 26519083]
77. Goldenberg T, McDougal SJ, Sullivan PS, Stekler JD, Stephenson R. Preferences for a mobile HIV prevention app for men who have sex with men. JMIR Mhealth Uhealth 2014 Oct 29;2(4):e47 [FREE Full text] [doi: 10.2196/mhealth.3745] [Medline: 25355249]
78. Sheehan J, Sherman KA. Computerised decision aids: a systematic review of their effectiveness in facilitating high-quality decision-making in various health-related contexts. Patient Educ Couns 2012 Jul;88(1):69-86. [doi: 10.1016/j.pec.2011.11.006] [Medline: 22185961]
79. Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2011(10):CD001431. [doi: 10.1002/14651858.CD001431.pub3] [Medline: 21975733]
80. Doumas DM, Hannah E. Preventing high-risk drinking in youth in the workplace: a web-based normative feedback program. J Subst Abuse Treat 2008 Apr;34(3):263-271. [doi: 10.1016/j.jsat.2007.04.006] [Medline: 17600650]
81. Kypri K, McCambridge J, Cunningham JA, Vater T, Bowe S, De Graaf B, et al. Web-based alcohol screening and brief intervention for Māori and non-Māori: the New Zealand e-SBINZ trials. BMC Public Health 2010;10:781 [FREE Full text] [doi: 10.1186/1471-2458-10-781] [Medline: 21176233]
82. Harle CA, Downs JS, Padman R. Effectiveness of personalized and interactive health risk calculators: a randomized trial. Med Decis Making 2012;32(4):594-605. [doi: 10.1177/0272989X11431736] [Medline: 22247421]

83. Wagener TL, Leffingwell TR, Mignogna J, Mignogna MR, Weaver CC, Cooney NJ, et al. Randomized trial comparing computer-delivered and face-to-face personalized feedback interventions for high-risk drinking among college students. J Subst Abuse Treat 2012 Sep;43(2):260-267. [doi: 10.1016/j.jsat.2011.11.001] [Medline: 22197301]
84. Grover SA, Lowensteyn I, Joseph L, Kaouache M, Marchand S, Coupal L, Cardiovascular Health Evaluation to Improve ComplianceKnowledge Among Uninformed Patients (CHECK-UP) Study Group. Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: the CHECK-UP study: a randomized controlled trial. Arch Intern Med 2007 Nov 26;167(21):2296-2303. [doi: 10.1001/archinte.167.21.2296] [Medline: 18039987]
85. Soureti A, Murray P, Cobain M, Chinapaw M, van Mechelen W, Hurling R. Exploratory study of web-based planning and mobile text reminders in an overweight population. J Med Internet Res 2011 Dec 20;13(4):e118 [FREE Full text] [doi: 10.2196/jmir.1773] [Medline: 22182483]
86. Muessig KE, Pike EC, Legrand S, Hightow-Weidman LB. Mobile phone applications for the care and prevention of HIV and other sexually transmitted diseases: a review. J Med Internet Res 2013;15(1):e1 [FREE Full text] [doi: 10.2196/jmir.2301] [Medline: 23291245]
87. Menza TW, Hughes JP, Celum CL, Golden MR. Prediction of HIV acquisition among men who have sex with men. Sex Transm Dis 2009 Sep;36(9):547-555 [FREE Full text] [doi: 10.1097/OLQ.0b013e3181a9cc41] [Medline: 19707108]
88. Carpenter KM, Stoner SA, Mikko AN, Dhanak LP, Parsons JT. Efficacy of a web-based intervention to reduce sexual risk in men who have sex with men. AIDS Behav 2010 Jun;14(3):549-557 [FREE Full text] [doi: 10.1007/s10461-009-9578-2] [Medline: 19499321]
89. Horvath K, Ecklund AM, Hunt SL, Nelson TF, Toomey TL. Developing internet-based health interventions: a guide for public health researchers and practitioners. J Med Internet Res 2015 Jan 23;17(1):e28 [FREE Full text] [doi: 10.2196/jmir.3770] [Medline: 25650702]
90. Carnegie NB, Goodreau SM, Liu A, Vittinghoff E, Sanchez J, Lama JR, et al. Targeting pre-exposure prophylaxis among men who have sex with men in the United States and Peru: partnership types, contact rates, and sexual role. J Acquir Immune Defic Syndr 2015 May 01;69(1):119-125 [FREE Full text] [doi: 10.1097/QAI.0000000000000555] [Medline: 25942463]

Abbreviations

ATN: Adolescent Medicine Trials Network
CASI: computer-assisted self-interview
CRF: case report form
EP: electronic picture
FG: focus group
IDI: in-depth interview
IMB: Information-Motivation-Behavioral Skills
mHealth: mobile health
MR: medical record confirmation
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
Sex Pro: sexual health promotion
SRV: subject recruitment venue
STI: sexually transmitted infection
SUS: System Usability Scale
YMSM: young men who have sex with men

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Protocol

A Pre-Exposure Prophylaxis Adherence Intervention (LifeSteps) for Young Men Who Have Sex With Men: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: New HIV infections occur at a disproportionately high rate among young men who have sex with men (YMSM). It is, therefore, essential that comprehensive HIV prevention strategies, specifically tailored to their needs and perceptions, are developed, tested, and disseminated. Antiretroviral pre-exposure prophylaxis (PrEP) is effective in decreasing HIV transmission among men who have sex with men; however, adherence is critical to its efficacy. In open-label studies among YMSM, adherence was suboptimal. Hence, behavioral approaches that address the unique challenges to YMSM PrEP adherence are needed.

Objective: This study aims to describe the protocol for intervention refinement and a pilot randomized controlled trial (RCT) of a PrEP adherence intervention, LifeSteps for pre-exposure prophylaxis for young men who have sex with men (LSPY).

Methods: This study includes the following 2 phases: formative qualitative interviews with approximately 20 YMSM and 10 key informants for intervention adaptation and refinement and a pilot RCT of up to 50 YMSM to assess the feasibility, acceptability, and preliminary efficacy of the LSPY, compared with the PrEP standard of care, to improve PrEP adherence. Participants will be recruited at 3 iTech subject recruitment venues in the United States.

Results: Phase 1 is expected to begin in June 2018, and enrollment of phase 2 is anticipated to begin in early 2019.

Conclusions: Few rigorously developed and tested interventions have been designed to increase PrEP adherence among YMSM in community settings, despite this population's high HIV incidence. The long-term goal of this intervention is to develop scalable protocols to optimize at-risk YMSM's PrEP uptake and adherence to decrease the HIV incidence.

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KEYWORDS

adolescents; adherence; antiretroviral pre-exposure prophylaxis; HIV prevention; men who have sex with men

Introduction

Background

In the United States, men who have sex with men (MSM) represent over half of all individuals living with HIV (56%) [1,2] and account for the largest number of new HIV infections each year (70%), with rates of new diagnoses at least 44 times higher than rates among heterosexual men [1,2]. While the incidence of new infections has decreased among other groups (eg, heterosexuals and injection drug users), the annual number of new infections among MSM has consistently increased over the past 20 years [1]. New HIV infections occur at a disproportionately high rate among young men who have sex with men (YMSM) in particular [3,4]. As such, it is essential that comprehensive HIV prevention strategies, specifically tailored to the needs and perceptions of YMSM, are developed, tested, and disseminated.

Pre-exposure prophylaxis (PrEP) is currently the only Food and Drug Administration-approved biomedical prevention method for MSM in the United States. The iPrEx study [5], which recruited 2499 men and transgender women over 11 sites in 6 countries, represented the first proof-of-concept that oral chemoprophylaxis is effective in decreasing the HIV transmission among MSM. However, adherence is critical to PrEP efficacy. In the iPrEx study, among participants with detectable levels of tenofovir in their blood, the risk of acquiring HIV decreased by >90%, and the intent-to-treat efficacy was 86% in 2 subsequent TDF/FTC (emtricitabine/tenofovir disoproxil fumarate, brand name Truvada) PrEP clinical trials of MSM in the United Kingdom and France [6,7]. In addition, pharmacological analyses corroborated the highly protective effects of TDF/FTC for PrEP among individuals who had detectable medication levels in their blood, highlighting the critical role of adherence in PrEP efficacy. This underscores the need for future PrEP interventions to focus on evidence-based strategies to promote adherence, to optimize the benefits that antiretroviral chemoprophylaxis may be able to provide for at-risk MSM.

Although YMSM readily accepted PrEP in several studies, adherence was suboptimal. In an open-label study of PrEP use by YMSM aged 18-22 years (ATN 110), only one-third of the study participants had protective drug levels after 1 year despite intensive adherence counseling, and the HIV incidence in the sample was 3% per year [8]. In addition, adherence was suboptimal in a parallel PrEP study of YMSM aged 15-17 years, and the annualized HIV incidence exceeded 6% [9]. In these studies, adherence tended to decline after 3 months of PrEP use, when the interval between study visits was extended from monthly to every 3 months, despite individualized or group-based behavioral adherence interventions. PrEP adherence might be even lower for YMSM prescribed PrEP in primary care settings, where adherence support may be less intensive than that in clinical trials. Thus, tailored interventions to support PrEP adherence in YMSM are needed.

Interventions to support PrEP adherence have shown promise in adults, but require adaptation to meet the unique needs of adolescents. LifeSteps is an evidence-based HIV medication adherence intervention for HIV-infected individuals, which was developed by Safren et al [10-12]; it has been adapted for diverse populations [13-15], including adolescents in the "Positive STEPS" project [16]. Positive STEPS was successful in improving antiretroviral therapy adherence relative to a standard-of-care comparison group in a pilot randomized controlled trial (RCT) among HIV-infected youth, aged 16-24 years, in the United States and is currently being evaluated in a National Institutes of Health–funded, 2-city efficacy trial (NCT03092531). In addition, LifeSteps has been adapted for PrEP users. In a study of at-risk MSM aged ≥18 years, a 4-session, nurse-delivered version of LifeSteps adapted for PrEP users resulted in excellent PrEP adherence and higher drug levels in the intervention condition compared with a time- and attention-matched control condition [17]. Given the evidence that shows short message service (SMS) text messages can improve antiretroviral medication adherence when integrated with counseling [18-23], especially in adolescents, the use of weekly SMS text messages as motivational and social cues to support adherence was added to LifeSteps [17,24].

Many YMSM may be dealing with a variety of unique psychosocial (eg, sexual identity formation, depression, and substance use) and sociostructural (eg, stigma, bullying, unstable housing, and family trauma) concerns, creating potential barriers to PrEP adherence that require additional support, for them to optimally adhere to and achieve maximal benefit from PrEP. To determine the extent to which these factors might influence PrEP adherence, LifeSteps for PrEP is being further optimized for YMSM through formative interviews with at-risk YMSM and their providers, and with a subsequent pilot study.

Theoretical Framework for Intervention

The adaptation of LifeSteps for PrEP for YMSM (LSPY) is being guided by the Gelberg-Andersen Behavioral Model for Vulnerable Populations; this model posits that health behaviors are influenced by a complex interplay of *environmental* and *patient* factors [25]. For at-risk YMSM, *environmental factors* that may affect adherence include challenges they face in their *external environments* (eg, unstable housing) and those faced in *health care environments* (eg, relying on parents' insurance) [26]. *Patient,* or *individual*, factors that affect PrEP adherence include *predisposing factors* (eg, low health literacy), *enabling factors* (eg, copay assistance), and *perception of need* (eg, HIV risk perception) [27]. The proposed intervention—through the LifeSteps for PrEP modules and daily SMS text messages—aims

to exert its effects on multiple domains of the model to optimize PrEP adherence.

Aims and Objectives

The long-term goal is to develop scalable protocols to optimize at-risk YMSM's PrEP uptake and adherence to decrease the HIV incidence. The first step toward this goal is to revise and refine LifeSteps for PrEP for delivery by nurses specializing in adolescent health so that it is tailored for high-risk, HIV-uninfected YMSM initiating PrEP. This paper aims to describe the protocol for the refinement of LSPY and a pilot RCT to examine the acceptability and feasibility of LSPY. We hypothesize that participants who are randomized to LifeSteps for PrEP will be highly satisfied with the intervention. In addition, we hypothesize that, although not powered to detect significant differences, YMSM randomized to the LifeSteps for PrEP condition will demonstrate better adherence compared with YMSM in the standard-of-care condition.

Methods

Phase 1: LifeSteps for Pre-Exposure Prophylaxis for Young Men Who Have Sex With Men Refinement

To refine the LSPY intervention, we will conduct in-depth, individual qualitative interviews with up to 20 HIV-uninfected, at-risk YMSM who present for bacterial sexually transmitted infection (STI) screening or treatment, or those seeking PrEP at Fenway Health, an iTech subject recruitment venue (SRV) and clinical center, which specializes in the care of sexual and gender minority patients [28]. In addition, we will conduct in-depth qualitative interviews with up to 10 key informants, including PrEP providers and staff, at community-based organizations that work with YMSM. Youth participants will be HIV-uninfected YMSM aged 15-24 years who self-report evidence of high risk for acquiring HIV infection (eg, recent bacterial STI diagnosis). We will use purposive sampling to recruit a diverse sample of YMSM with respect to race and ethnicity, age, and prior PrEP experience. Furthermore, we will recruit YMSM at various points in the PrEP continuum of care, including those who have opted not to initiate PrEP despite recommendations from clinicians, those who are using PrEP and report high levels of adherence, and those who report adherence challenges.

After informed consent and prior to the interview, participants will complete a brief demographic and behavioral questionnaire to contextualize the qualitative data. In the interviews, we will identify potential strategies to optimize PrEP adherence for YMSM and will explore youth perspectives on the use of nurses to deliver the intervention and weekly SMS text messages.

For PrEP-naïve youth, we will also explore youth concerns about adhering to PrEP, how these concerns influence their decisions about whether or not to initiate PrEP, and whether the availability of a structured, supportive intervention that was nurse-delivered or regular SMS text messages would influence these decisions.

For PrEP-experienced youth, we will explore their experiences with medication adherence and strategies used to overcome any barriers, their views on the content of what they might have wanted to discuss with a nurse (eg, potential side effects, lab monitoring, how to discuss PrEP with friends and family, and substance use), and acceptability of SMS text messaging.

Specific topics to be explored are based on the conceptual model described above, including: environmental factors affecting access and PrEP adherence, including structural factors (eg, housing insecurity and lack of transportation), health care factors (eg, inconvenient scheduling of clinical visits and nonaffirming atmosphere for sexual minorities); patient factors that may influence adherence, including predisposing issues (eg, substance use and depression), enabling factors (eg, knowledge of the benefits of PrEP and social supports), and perceived need to use PrEP (eg, self-perception of HIV risk); and perspectives regarding the proposed adherence interventions, including the use of SMS text messaging as reminders and motivational cues (eg, ideal timing and content), and a nurse-led intervention (eg, reasons they would or would not want to discuss adherence with a nurse, the preferred content, and structure of counseling sessions). An open-ended approach will allow us to elicit potentially unexpected considerations that influence initiation of and PrEP adherence among YMSM.

Study visits will last approximately 60-90 minutes, and participants will receive US $50 for this one-time interview. All interviews will be digitally recorded, and interviewers will take detailed notes using debriefing forms. Recordings will be transcribed by members of the iTech Analytic Core who are trained in qualitative methods. The qualitative team will apply rapid qualitative analysis techniques to the analysis of interview data [29]; this approach involves the initial identification of themes and tabulation of frequencies regarding the endorsement of themes across participants. Immediately following each of the interviews, the facilitator team will record observational insights, content, and key themes from the interview; this approach will result in an ongoing set of memos created by the team that rapidly describes and elucidates salient themes. The memos will guide the codebook creation and coding scheme for a more formal content analysis of transcripts [30,31]. These data will inform the adaptation of the youth-tailored LSPY intervention that we will test in the RCT pilot. Specifically, new modules may be developed, other modules removed, or new content added to existing modules. If diverse needs are identified by phase 1 participants, refinements will be made globally given that the intervention is designed to be individually tailored by the interventionists during the sessions based on participants' needs and clinical judgment [32].

Phase 2: Pilot Randomized Controlled Trial

Trial Registration, Ethics, Consent, and Institutional Board Approval

The research and ethics presented in this study have been reviewed and approved by the University of North Carolina at Chapel Hill Institutional Review Board (17-2513). A Certificate of Confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent will be obtained for participants aged 15-17

years. Furthermore, the study is in the process of being registered on ClinicalTrials.gov.

All participants will undergo screening in a private room at the clinical research site. If eligible (see below), informed consent will be conducted at this time. The informed consent documents will include detailed information on all study procedures and answer questions concerning the study and consent process.

Study Design

A 3-site, 2-arm pilot RCT will be conducted to assess the feasibility and acceptability of the LSPY intervention and preliminary efficacy of the intervention to improve PrEP adherence for daily oral PrEP and retention in PrEP care, compared with a standard of PrEP care control group. The inclusion of a control group will allow us to estimate an effect size to sufficiently power a future full-scale efficacy trial. As such, we will enroll up to 50 YMSM in the RCT (randomized 1:1 to the 2 arms) from iTech SRVs in Atlanta (GA), Boston (MA), and Chicago (IL). Participants will be followed for 6 months and will complete biological (ie, renal safety, STI screening, and drug levels) and behavioral assessments every 3 months, including self-reported PrEP adherence, sexual behaviors, and psychosocial health. In addition, we will conduct a brief, 15-minute semistructured exit interview with participants in the LSPY intervention arm to provide an opportunity for more in-depth and open-ended feedback on the intervention satisfaction and acceptability. These data will be used to finalize the intervention manual to enhance participant acceptability. Figure 1 shows the pilot RCT schema.

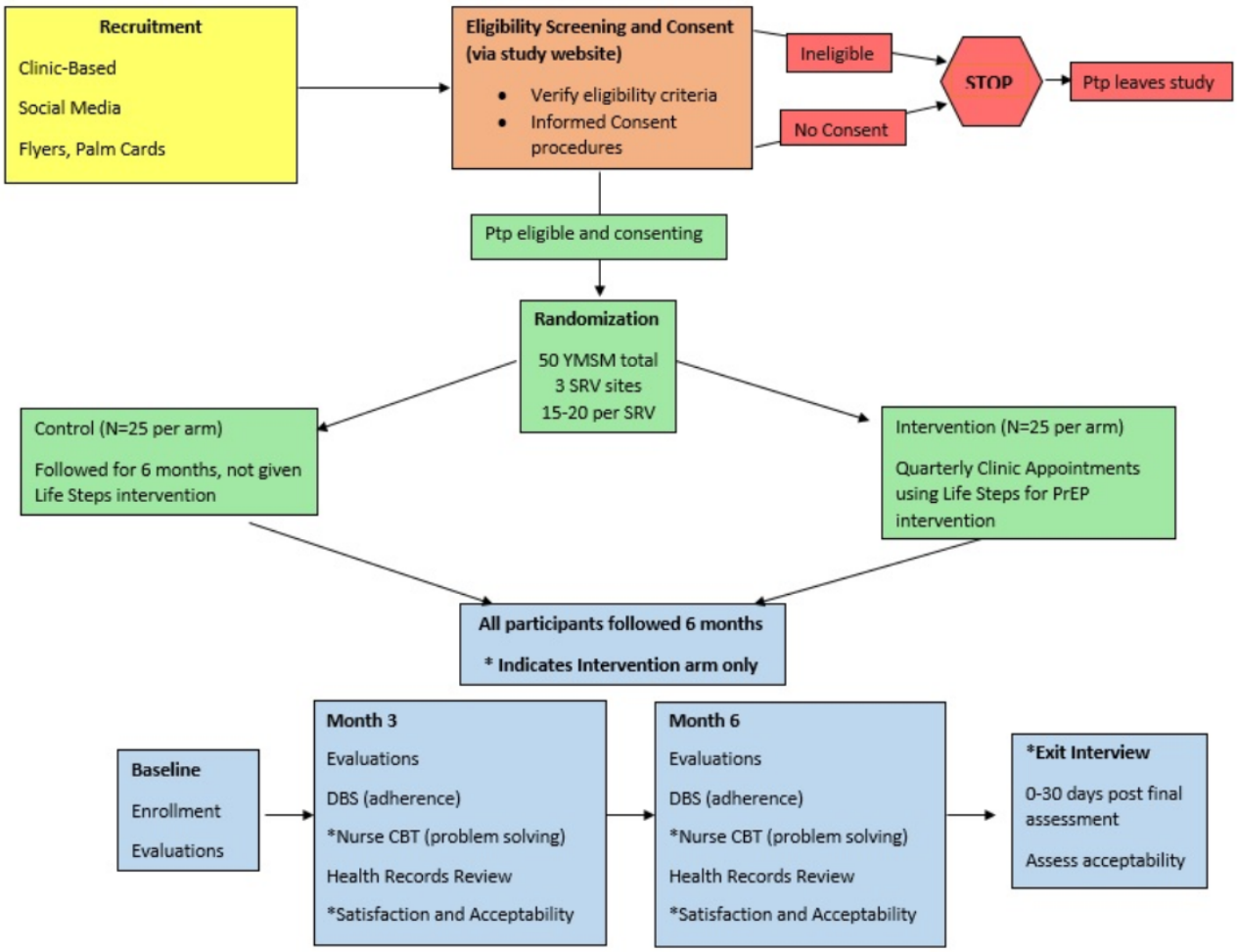
Participants

Study participants (n=50) will be assessed for eligibility by completing a brief screener. The inclusion criteria include the following: age 15-24 years; assigned male sex at birth; identify as male; identified as PrEP candidates by local clinicians because of self-reported risk or presentation with a new bacterial STI; and PrEP-naïve (assessed by self-report). In addition, participants will be able to understand, read, and speak English. For the pilot RCT, we will recruit YMSM prior to their first PrEP prescription, as the interventions are designed to be administered at the time of PrEP initiation.

Recruitment

Active recruitment will be carried out by the study staff at each SRV by recruiting men at the SRVs. In each city, the SRVs represent diverse settings, including an academic research center (Atlanta, GA), a community health center (Boston, MA), and a hospital-based clinic (Chicago, IL). In addition, recruitment will occur at local organizations and venues that YMSM attend, including community-based organizations for lesbian, gay, bisexual, and transgender youth, Youth Pride events, etc.

Figure 1. The pilot randomized controlled trial RCT study schema. Ptp: participant; YMSM: men who have sex with men; SRV: subject recruitment venue; PrEP: pre-exposure prophylaxis; DBS: dried blood spot; CBT: cognitive behavioral therapy.



At recruitment venues, trained staff will approach youth and offer them information about the study (either verbally or by offering them a business card or advertisement flyer), including brief descriptions of the study design and contact information (ie, study email and phone number).

In addition, passive approaches for recruitment will include posting study information through flyers, posters, and palm cards describing the study at these venues. Moreover, Web-based recruitment will be conducted by placing banner advertisements on popular Web-based social media outlets for YMSM (eg, Facebook, Grindr, etc).

Randomization

Only participants who express interest in LSPY to increase PrEP adherence, meet the eligibility criteria, and provide informed consent will be eligible for randomization. Overall, 50 YMSM who are PrEP-naïve and appropriate candidates for antiretroviral PrEP at the 3 iTech SRVs (15-20 per site) will be randomized 1:1. The randomization will be stratified by SRVs [33] and will be based on a pregenerated list created by iTech Analytic Core statisticians and accessed by a Web portal.

Incentives

Participants in the pilot RCT will receive US $50 compensation for the in-person screening or baseline assessment and US $50 compensation for each completed follow-up assessment and the exit interview.

Intervention

Standard-of-Care Condition

Following the completion of baseline assessments, participants in both conditions will receive the standard of care for PrEP initiation and adherence. Each participating SRV will document standard-of-care procedures at their site prior to protocol initiation.

"LifeSteps For Pre-Exposure Prophylaxis For Young Men Who Have Sex With Men" Condition

The experimental intervention, LSPY, was derived from our prior work with individuals living with HIV [12,34] and individuals using PrEP [32], and will be finalized following phase 1 focus groups. LifeSteps was originally designed as a standalone, one-session adherence intervention for individuals living with HIV. The goal of the sessions was to help an individual understand all steps involved in successful adherence to HIV treatment (eg, communicating with the treatment team, medication storage, securing refills, etc). LifeSteps has since been refined for individuals using PrEP [17,32,35]. Phase 1 data may inform the structure of the sessions, the addition of optional modules, and problem-solving material tailored to the unique

challenges of YMSM. Currently, the LSPY intervention consists of 4 weekly sessions at the time of PrEP initiation and 2 booster sessions, which occur 2 and 3 months after PrEP initiation. Overall, the core components of the intervention will focus on medication adherence, sexual behavior, and problem solving to overcome barriers to adherence, using motivational interviewing techniques when needed. Session 1 will include education about PrEP, a discussion involving the psychosocial context in which PrEP use occurs, a brief motivational interviewing exercise, and discussion of establishing a dosing schedule. The session content after session 1 is designed to be flexible, allowing patients to identify their adherence support needs and for the interventionist to choose the material that is most relevant to the individual participant. Session 2 will begin with an adherence "check-in," and will, then, focus on understanding the clients' experiences taking PrEP, and engaging in problem solving to address any reported barriers to adherence. In addition, session 3 will begin with an adherence check-in and will, then, introduce sexual risk behavior education, identifying high-risk activities, and factors that could increase and decrease personal risk for HIV, as well as other STIs. The session will involve a discussion about biological factors associated with the HIV transmission (eg, partners' level of infectiousness and measured by plasma HIV RNA), as well as other STIs, and will discuss ways to reduce their risk in the context of taking PrEP. In the final weekly session, a nurse-counselor will discuss PrEP adherence goals and prior session content, and patients' plans for continued PrEP use upon the intervention completion. Optional modules will provide a framework to help interventionists work with participants experiencing substance abuse or mental health concerns, which were adversely impacting PrEP adherence. For example, if a participant or an interventionist identifies a mental health or substance use-related concern that impacts PrEP adherence in the participant's sexual health promotion plan, the interventionist may use motivational interviewing skills to increase the willingness to discuss this issue as a barrier to adherence or problem-solving strategies for managing it. These optional modules will also include site-specific referral sources (on-site, if relevant) so that more intensive counseling around the barrier may be sought. In addition, an interventionist may introduce a brief relaxation exercise if anxiety is a prominent concern. Booster sessions at months 2 and 3 are designed to offer an opportunity for the trained study nurse to assess PrEP adherence in the absence of weekly support. Study nurses can use booster sessions to review PrEP adherence over a longer time span and address barriers to adherence using problem-solving skills learned during the earlier sessions. For participants who identified no challenges to adherence, the study nurse can use the booster session to review and refine the existing adherence plan and help them identify potential future barriers to adherence.

As part of the LSPY intervention, *weekly SMS text messaging* will be used to support adherence, as well as to understand participants' patterns of behavior. Participants will receive weekly SMS text messages to motivate them to take their medications and assess whether or not they took their medication and had condomless sex. The weekly texts will continue throughout the follow-up period for each participant in the intervention group.

Data Collection

Baseline assessments will be conducted in-person, with follow-up assessments after 3 and 6 months. At each major assessment, participants will complete an assessment battery through a secure Web-based data entry system. As mentioned previously, participants in the LSPY intervention arm will receive a weekly, brief SMS text messaging-based survey to assess whether or not they took their medication and had condomless sex in the past week. By obtaining data on the weekly patterns of medication adherence and HIV risk, the study team will be able to assess whether changes in adherence were associated with the increased, unchanged, or decreased HIV risk.

Primary Outcome Measures

To measure the *acceptability* of the LSPY intervention, participants will self-report the degree to which they find the intervention appropriate and useful using Likert-type agreement scales on factors such as the intervention content, intervention length, and intervention delivery. We will use the System Usability Scale, a validated 10-item measure, which is scored from 0 to 100 [37]. A score of ≥50 indicates that the intervention is acceptable [38].

To assess the *feasibility*, we will track the number of potential participants we screen, the number of potential participants who meet the study inclusion criteria, the number of participants who meet the study criteria and then enroll, and the number of treatment and assessment sessions completed by all enrolled participants (across conditions). In addition, we will track the duration of assessments and reasons for declining enrollment and prematurely leaving the trial.

Although this pilot study is not powered to examine the efficacy of biological and behavioral outcomes, we will assess its impact on adherence to obtain an estimated effect size to power a future full-scale efficacy trial. As such, at each major assessment, dried blood spot drug levels of tenofovir diphosphate and emtricitabine triphosphate will serve as biological correlates of *adherence* [39]. In addition, self-reported PrEP adherence will also be assessed using timeline follow back [36]. Furthermore, we will obtain medical record release forms from participants to determine medical appointment adherence, measured as the proportion of scheduled clinic visits attended by each patient over their study observation period.

Secondary Outcome Measures

To assess the impact of the intervention on potential mediators of adherence, we will use scales developed from our initial study [17,32] with adults. Specifically, *readiness to use PrEP* will be assessed using a series of questions that ask how likely they are to use or continue using PrEP under a variety of circumstances. In addition, *behavioral skills for PrEP use* will be assessed with 12 items that ask how "hard" or "easy" it was for participants to implement a variety of skills, including discussing side effects with medical providers and remembering to take pills on time. The *PrEP taking self-efficacy* will be adapted from the HIV Treatment Adherence Self-Efficacy Scale [40], which assesses

confidence to take medications in various situations. Finally, we will also assess individual (eg, sexual behavior and mental health) and environmental (eg, incarceration, stigma, and health care access) covariates that could impact adherence.

Statistical Analyses

We will use descriptive statistics to characterize the distribution of all study variables. The primary analysis will measure the feasibility of the intervention by the proportion of participants retained in the study at the end of the study period, and we will measure the acceptability by the percentage of participants who rate each intervention as acceptable on their final follow-up survey. Point estimates of ≥.50 for the feasibility and acceptability will be considered the minimum criteria for the acceptability and feasibility, consistent with standards used in similar behavioral health studies.

The primary biological outcome analysis will compare adherence (defined by the percentage of participants with dried blood spot drug levels >700 fmol/punch, a level correlated with high protection from HIV acquisition [36,41]) at the 3- and 6-month visits between the study arms and will be used to estimate the effect size for a future full-scale efficacy trial. In addition, group differences in the proportion of PrEP clinic appointments kept will be compared.

All analyses will use 2-tailed tests of significance with significance at alpha=.05. We will follow an intent-to-treat model [42], analyzing participants in the study arm to which they were assigned. We will examine the equivalence of random assignment to groups with regards to key baseline characteristics, including sociodemographics, prior HIV testing patterns, and sexual risk-related variables. If randomization does not work to balance these characteristics, we will assess whether baseline differences may account for differences in outcomes.

Results

While qualitative interviews are anticipated to begin in June 2018, recruitment for the pilot RCT is anticipated to begin in early 2019, with the study follow-up complete in February 2020.

Discussion

Oral PrEP has the potential to change the HIV prevention landscape and curtail the HIV epidemic dramatically. Adequate adherence levels can reduce HIV acquisition among MSM by >90% [5,6,41,43], and increasing the effective use of PrEP among YMSM—one of the highest-risk groups for new infections—is one of the leading priorities for HIV prevention. However, YMSM face multiple challenges in initiating and adhering to PrEP [44], and, in 2 open-label studies of PrEP use by YMSM aged 15-17 and 18-22 years (ATN 113 and 110) [8,9], adherence was suboptimal after 3 monthly visits, and the HIV incidence was high (6% and 3%, respectively).

At present, few rigorously developed and tested interventions exist for increasing PrEP adherence among YMSM in community settings. Our long-term goal is to develop scalable protocols to optimize the at-risk YMSM's PrEP uptake and adherence to decrease the HIV incidence. In a pilot RCT, LifeSteps for PrEP—a 4-session, nurse-delivered cognitive behavioral therapy-based counseling intervention—improved PrEP adherence compared with a time- and attention-matched controls among at-risk MSM aged ≥18 years [17].

The adaptation for LSPY will be informed, developed, and refined through formative research that involves YMSM at all levels. HIV-uninfected YMSM will inform the intervention and curricular materials through formative qualitative interviews and exit interviews after participating in the pilot RCT. By incorporating information and feedback on the content of the intervention from YMSM, we will ensure content is tailored to their contextual realities in a manner that promotes PrEP adherence skills building and problem solving.

Anticipated limitations of this protocol include potential limits of generalizability of the results of the formative, qualitative interviews given that they will take place in one urban city. While preparing for the pilot RCT, we will present the intervention at iTech-supported Youth Community Advisory Boards at participating SRVs to obtain additional feedback from geographically diverse populations. Similarly, the pilot RCT may have limited generalizability outside the 3 urban settings and may need to be further adapted for settings where access to clinical care is less robust.

If LSPY demonstrates the acceptability and feasibility in this pilot RCT, we plan to test its efficacy in a full-scale, multicity, randomized controlled efficacy trial. If shown to be efficacious, this in-person, nurse-delivered counseling intervention with SMS text messaging for ongoing support will allow for a youth-informed, targeted PrEP adherence intervention for YMSM.

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Conflicts of Interest

DSK has been a consultant to Fenway Health on a research project funded by Gilead Sciences, and has developed and/or presented educational material about HIV-prevention for Medscape, MED-IQ, DKBmed, and UptoDate, Inc.

References

1. Centers for Disease Control and Prevention. Atlanta, GA: CDC; 2017 Feb. HIV/AIDS among gay and bisexual men URL: https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/cdc-msm-508.pdf [accessed 2018-11-14] [WebCite Cache ID 6slHfZ3Jo]
2. Centers for Disease Control and Prevention. Atlanta, GA: CDC; 2008 Aug. Estimates of New HIV Infections in the United States URL: https://www.cdc.gov/nchhstp/newsroom/docs/fact-sheet-on-hiv-estimates.pdf [accessed 2017-08-17] [WebCite Cache ID 6slIBD89d]
3. Centers for Disease Control and Prevention. HIV Surveillance Report, 2015. Atlanta, GA: CDC; 2016 Nov. Diagnoses of HIV infection in the United States and dependent areas, 2015 URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2015-vol-27.pdf [accessed 2018-11-14] [WebCite Cache ID 6slIPO72P]
4. Garofalo R, Hotton AL, Kuhns LM, Gratzer B, Mustanski B. Incidence of HIV infection and Sexually Transmitted Infections and Related Risk Factors among Very Young Men Who Have Sex with Men. J Acquir Immune Defic Syndr 2016 Jan 7. [doi: 10.1097/QAI.0000000000000933] [Medline: 26745827]
5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010 Dec 30;363(27):2587-2599 [FREE Full text] [doi: 10.1056/NEJMoa1011205] [Medline: 21091279]
6. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016 Jan 2;387(10013):53-60 [FREE Full text] [doi: 10.1016/S0140-6736(15)00056-2] [Medline: 26364263]
7. Molina J, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015 Dec 3;373(23):2237-2246. [doi: 10.1056/NEJMoa1506273] [Medline: 26624850]
8. Hosek SG, Rudy B, Landovitz R, Kapogiannis B, Siberry G, Rutledge B, Adolescent Trials Network (ATN) for HIVAIDS Interventions. An HIV Preexposure Prophylaxis Demonstration Project and Safety Study for Young MSM. J Acquir Immune Defic Syndr 2017 Jan 01;74(1):21-29. [doi: 10.1097/QAI.0000000000001179] [Medline: 27632233]
9. Hosek SG, Landovitz RJ, Kapogiannis B, Siberry GK, Rudy B, Rutledge B, et al. Safety and Feasibility of Antiretroviral Preexposure Prophylaxis for Adolescent Men Who Have Sex With Men Aged 15 to 17 Years in the United States. JAMA Pediatr 2017 Nov 01;171(11):1063-1071. [doi: 10.1001/jamapediatrics.2017.2007] [Medline: 28873128]
10. Safren SA, Otto MW, Worth JL. Life-steps: Applying cognitive behavioral therapy to HIV medication adherence. Cognitive and Behavioral Practice 1999 Sep;6(4):332-341. [doi: 10.1016/S1077-7229(99)80052-2]
11. Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther 2001 Oct;39(10):1151-1162. [Medline: 11579986]
12. Safren SA, O'Cleirigh C, Tan JY, Raminani SR, Reilly LC, Otto MW, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. Health Psychol 2009 Jan;28(1):1-10 [FREE Full text] [doi: 10.1037/a0012715] [Medline: 19210012]
13. Shiu C, Chen W, Simoni J, Fredriksen-Goldsen K, Zhang F, Zhou H. The Chinese Life-Steps Program: A Cultural Adaptation of a Cognitive-Behavioral Intervention to Enhance HIV Medication Adherence. Cogn Behav Pract 2013 May;20(2):202-212 [FREE Full text] [doi: 10.1016/j.cbpra.2012.05.005] [Medline: 23667305]
14. Psaros C, Haberer JE, Katabira E, Ronald A, Tumwesigye E, Campbell JD, et al. An intervention to support HIV preexposure prophylaxis adherence in HIV-serodiscordant couples in Uganda. J Acquir Immune Defic Syndr 2014 Aug 15;66(5):522-529 [FREE Full text] [doi: 10.1097/QAI.0000000000000212] [Medline: 24853311]
15. Reisner SL, Hughto JMW, Pardee DJ, Kuhns L, Garofalo R, Mimiaga MJ. LifeSkills for Men (LS4M): Pilot Evaluation of a Gender-Affirmative HIV and STI Prevention Intervention for Young Adult Transgender Men Who Have Sex with Men. J Urban Health 2016 Feb;93(1):189-205 [FREE Full text] [doi: 10.1007/s11524-015-0011-z] [Medline: 26753882]
16. Thurston IB, Bogart LM, Wachman M, Closson EF, Skeer MR, Mimiaga MJ. Adaptation of an HIV Medication Adherence Intervention for Adolescents and Young Adults. Cogn Behav Pract 2014 May;21(2):191-205 [FREE Full text] [Medline: 25452680]
17. Mayer KH, Safren SA, Elsesser SA, Psaros C, Tinsley JP, Marzinke M, et al. Optimizing Pre-Exposure Antiretroviral Prophylaxis Adherence in Men Who Have Sex with Men: Results of a Pilot Randomized Controlled Trial of “Life-Steps for PrEP”. AIDS Behav 2017 May;21(5):1350-1360. [doi: 10.1007/s10461-016-1606-4] [Medline: 27848089]
18. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS 2011 Mar 27;25(6):825-834 [FREE Full text] [doi: 10.1097/QAD.0b013e32834380c1] [Medline: 21252632]
19. Vidrine DJ, Arduino RC, Lazev AB, Gritz ER. A randomized trial of a proactive cellular telephone intervention for smokers living with HIV/AIDS. AIDS 2006 Jan 9;20(2):253-260. [doi: 10.1097/01.aids.0000198094.23691.58] [Medline: 16511419]
20. Ybarra ML, Bull SS. Current trends in Internet- and cell phone-based HIV prevention and intervention programs. Curr HIV/AIDS Rep 2007 Dec;4(4):201-207. [Medline: 18366952]
21. Cole-Lewis H, Kershaw T. Text messaging as a tool for behavior change in disease prevention and management. Epidemiol Rev 2010;32:56-69 [FREE Full text] [doi: 10.1093/epirev/mxq004] [Medline: 20354039]

22. Adler R. Healthcare unplugged. Oakland, CA: California Healthcare Foundation; 2007. The evolving role of wireless technology URL: https://www.chcf.org/wp-content/uploads/2017/12/PDF-HealthCareUnpluggedTheRoleOfWireless.pdf [accessed 2018-11-14] [WebCite Cache ID 73v5rtbnT]
23. Fjeldsoe BS, Marshall AL, Miller YD. Behavior change interventions delivered by mobile telephone short-message service. Am J Prev Med 2009 Feb;36(2):165-173. [doi: 10.1016/j.amepre.2008.09.040] [Medline: 19135907]
24. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. PLoS Med 2013;10(9):e1001511 [FREE Full text] [doi: 10.1371/journal.pmed.1001511] [Medline: 24058300]
25. Gelberg L, Andersen RM, Leake BD. The Behavioral Model for Vulnerable Populations: application to medical care use and outcomes for homeless people. Health Serv Res 2000 Feb;34(6):1273-1302 [FREE Full text] [Medline: 10654830]
26. Pettifor A, Nguyen NL, Celum C, Cowan FM, Go V, Hightow-Weidman L. Tailored combination prevention packages and PrEP for young key populations. J Int AIDS Soc 2015;18(2 Suppl 1):19434 [FREE Full text] [doi: 10.7448/IAS.18.2.19434] [Medline: 25724507]
27. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. AIDS Patient Care STDS 2013 Apr;27(4):248-254 [FREE Full text] [doi: 10.1089/apc.2012.0419] [Medline: 23565928]
28. Mayer K, Appelbaum J, Rogers T, Lo W, Bradford J, Boswell S. The evolution of the Fenway Community Health model. Am J Public Health 2001 Jun;91(6):892-894. [Medline: 11392929]
29. Betancourt TS, Speelman L, Onyango G, Bolton P. A qualitative study of mental health problems among children displaced by war in northern Uganda. Transcult Psychiatry 2009 Jun;46(2):238-256 [FREE Full text] [doi: 10.1177/1363461509105815] [Medline: 19541749]
30. Joffe H, Yardley L. Content and thematic analysis. In: Marks DF, Yardley L, editors. Research methods for clinical and health psychology. London, UK: Sage; 2004.
31. Miles M, Huberman A, Saldana J. Qualitative data analysis. Thousand Oaks, CA: Sage; 2013.
32. Taylor SW, Psaros C, Pantalone DW, Tinsley J, Elsesser SA, Mayer KH, et al. "Life-Steps" for PrEP Adherence: Demonstration of a CBT-Based Intervention to Increase Adherence to Preexposure Prophylaxis (PrEP) Medication Among Sexual-Minority Men at High Risk for HIV Acquisition. Cogn Behav Pract 2017 Feb;24(1):38-49 [FREE Full text] [doi: 10.1016/j.cbpra.2016.02.004] [Medline: 28392673]
33. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999 Jan;52(1):19-26. [Medline: 9973070]
34. Safren SA, Mayer KH, Ou S, McCauley M, Grinsztejn B, Hosseinipour MC, HPTN 052 Study Team. Adherence to Early Antiretroviral Therapy: Results From HPTN 052, a Phase III, Multinational Randomized Trial of ART to Prevent HIV-1 Sexual Transmission in Serodiscordant Couples. J Acquir Immune Defic Syndr 2015 Jun 01;69(2):234-240 [FREE Full text] [doi: 10.1097/QAI.0000000000000593] [Medline: 26009832]
35. Psaros C, Haberer JE, Katabira E, Ronald A, Tumwesigye E, Campbell JD, et al. An intervention to support HIV preexposure prophylaxis adherence in HIV-serodiscordant couples in Uganda. J Acquir Immune Defic Syndr 2014 Aug 15;66(5):522-529 [FREE Full text] [doi: 10.1097/QAI.0000000000000212] [Medline: 24853311]
36. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med 2015 Dec;5(4):470-482 [FREE Full text] [doi: 10.1007/s13142-015-0315-2] [Medline: 26622919]
37. Brooke J. SUS: a quick and dirty usability scale. In: Jordan P, Thomas B, Weerdmeester B, McClelland I, editors. Usability Evaluation in Industry. London, UK: Taylor and Francis; 1996:189-194.
38. Bangor A, Kortum P, Miller J. Determining What Individual SUS Scores Mean: Adding an Adjective Rating Scale. Journal of Usability Studies 2009 May 01;4(3):114-123 [FREE Full text]
39. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med 2012 Sep 12;4(151):151ra125 [FREE Full text] [doi: 10.1126/scitranslmed.3004006] [Medline: 22972843]
40. Johnson MO, Neilands TB, Dilworth SE, Morin SF, Remien RH, Chesney MA. The role of self-efficacy in HIV treatment adherence: validation of the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES). J Behav Med 2007 Oct;30(5):359-370 [FREE Full text] [doi: 10.1007/s10865-007-9118-3] [Medline: 17588200]
41. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014 Sep;14(9):820-829. [doi: 10.1016/S1473-3099(14)70847-3] [Medline: 25065857]
42. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. JAMA 2014 Jul 02;312(1):85-86. [doi: 10.1001/jama.2014.7523] [Medline: 25058221]
43. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis 2015 Nov 15;61(10):1601-1603 [FREE Full text] [doi: 10.1093/cid/civ778] [Medline: 26334052]

44. Miller MK, Wickliffe J, Jahnke S, Linebarger JS, Dowd D. Accessing General and Sexual Healthcare: Experiences of Urban Youth. Vulnerable Child Youth Stud 2014 Jul 1;9(3):279-290 [FREE Full text] [doi: 10.1080/17450128.2014.925170] [Medline: 25101138]

Abbreviations

LSPY: LifeSteps for pre-exposure prophylaxis for young men who have sex with men
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SMS: short message service
SRV: subject recruitment venue
STI: sexually transmitted infection
YMSM: young men who have sex with men

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Original Paper

Primary Prevention of Intimate Partner Violence Among Recently Married Dyads Residing in the Slums of Pune, India: Development and Rationale for a Dyadic Intervention

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Abstract

Background: Intimate partner violence (IPV) is frequently experienced by women of low socioeconomic status in India. It is a human rights violation and associated with negative effects on physical and mental well-being, underscoring the need for effective prevention strategies.

Objective: This study aimed to develop a dyadic intervention for the primary prevention of IPV among newly married couples residing in slum communities in India.

Methods: The intervention was developed using a community-based, mixed-methods design rooted in couple-interdependence theory and guided by the intervention mapping (IM) framework. It used the six critical IM steps to inform the content and delivery of the intervention: (1) needs assessment, (2) preparation of matrices of change objectives, (3) selection of theory-based methods and practical applications, (4) production of intervention components and materials, (5) intervention adoption and implementation, and (6) evaluation planning.

Results: The resulting *Ghya Bharari Ekatra* (*Take a Flight Together*) intervention is intended to be delivered in 6 weekly sessions by a trained pair of male and female lay community educators to groups of 3 to 5 newly married couples in the community in which they reside. It uses games, discussions, self-reflections, and skill-building exercises to cover the following topics: enhancing relationship quality time, self-esteem and resilience, communication and conflict management, goal setting and implementation, sexual communication and sexual health and reproductive health knowledge, and redefining and challenging norms surrounding IPV occurrence. The formative work guided the protocol, including module duration and timing (2-hour sessions of convenience to participants), ordering of modules (based on potential level of interest and sensitivity of the topics), content (ie, informed scripts of role plays and films), intervention delivery methods (ie, interactive activities), and selection of the interventionists (based on capacity to connect with participants) and venue (community-based, convenient, and safe spaces). *Ghya Bharari Ekatra* was piloted between January and May 2018, and evaluation is presently underway.

Conclusions: Ghya Bharari Ekatra is evidence-based, grounded in intervention-mapping, and developed and iteratively refined using a community-based participatory research approach, suggesting it has great potential to be an acceptable and effective solution to preventing IPV among newly married couples.

Trial Registration: ClinicalTrials.gov NCT03332134; https://clinicaltrials.gov/ct2/show/NCT03332134

(JMIR Res Protoc 2019;8(1):e11533) doi:10.2196/11533

KEYWORDS

intimate partner violence; prevention; gender-based violence; domestic violence; intervention

Introduction

The Impact of Intimate Partner Violence in India

Intimate partner violence (IPV), defined by the World Health Organization as "behavior by an intimate partner or ex-partner that causes physical, sexual or psychological harm, including physical aggression, sexual coercion, psychological abuse and controlling behaviors," is experienced by approximately one-third (30%) of women worldwide during their lifetime [1]. The National Family Health Survey data suggest that women in India experience IPV with high frequency as well [2], but Indian women of lower socioeconomic status (SES) suffer substantially greater rates, with prevalence estimates ranging from 21% to 99% [3-8]. In addition to being a violation of basic human rights, IPV is associated with numerous negative mental and physical health outcomes and adoption of maladaptive health behaviors [1]. The high IPV prevalence among low-SES populations in India [2,9] and its associated negative health outcomes underscore the need for effective tailored prevention strategies.

Existing Strategies to Address Intimate Partner Violence

To date, the majority of IPV prevention efforts by the government sector, nongovernmental organizations, and research-based organizations in India has focused on secondary and tertiary IPV prevention [10,11]. However, saturation of legal, mental health, and other IPV support services; high cost and resource limitations hindering expansion of these services; and the high IPV prevalence speak to the need to develop evidence-based affordable, effective, sustainable, and scalable primary prevention strategies to better address the epidemic. Primary prevention in other countries typically begins in schools and colleges and focuses on dating relationships [12]; however, in India, sociocultural barriers, such as social taboos associated with discussing intimacy and sexual relations in schools and colleges [13], and elevated school dropout rates among girls of low SES [14] impede such efforts. The period between engagement and marriage is also not opportune as it is often short and consumed by religious rituals and social and family gatherings for the couple. Fortunately, interventions for primary prevention can be timed later (ie, after marriage) as premarital courtship is still limited (at a nascent stage in the country), 90% of marriages are arranged by parents, and the age of first sexual relationship is often delayed to postmarriage [2,9].

The international literature suggests that most evidence-based IPV prevention interventions engage women alone [10,15,16], men alone [17-21], men and women in parallel gender-concordant groups [22-24], men and women together in large groups [25], or communities (ie, through large-scale community mobilization campaigns) [26,27]. Interdependence theory posits that both intrapersonal and interpersonal dyadic processes serve as determinants of couple's behavior change [28], suggesting IPV prevention may be most effective, working with the couple as a unit. Our search only found 2 IPV prevention efforts that worked with dyads [29,30], both of which demonstrated reductions in IPV but were developed and conducted in resource-rich settings. In India, 3 major evidence-based interventions have been developed or adapted and tested but again worked solely with women [10], men [19], or mother-in-law and daughter-in-law pairs [31]. We herein describe the development of a dyadic intervention for the primary prevention of IPV among newly married couples residing in slum communities. Specifically, we provide the evidence and theoretical basis for the intervention content and delivery.

Methods

Study Overview and Use of the Intervention Mapping Framework

The intervention, *Ghya Bharari Ekatra* (*take a flight together*), was developed using a community-based, mixed-methods design, rooted in couple-interdependence theory and guided by the intervention mapping (IM) framework outlined by Bartholomew et al [32]. IM is a systematic approach to intervention planning, implementation, and evaluation that is driven by evidence, theory, and community participation [32]. It involves 6 critical steps: (1) a needs assessment, (2) preparation of matrices of change objectives, (3) selection of theory-based methods and practical applications, (4) production of intervention components and materials, (5) intervention adoption and implementation, and (6) evaluation planning.

The methods used to develop the intervention include (1) cross-sectional surveys with newly married men and women residing in slums to identify correlates of IPV to inform intervention change objectives, (2) 21 key informant interviews (with individuals who bring expertise in IPV, gender equality, marital health, sexual and reproductive health, or work with slum communities) to inform the content and delivery of the intervention, (3) feedback from gender-based violence (GBV) experts and the Indian Council of Medical Research-National AIDS Research Institute (ICMR-NARI, Pune, India) community advisory board (CAB) on the intervention protocol, and (4) 3 focus group discussions with married men, married women, and parents-in-law (each of 7-10 participants) to assess acceptance of some of the more controversial topics included in the intervention.

The intervention was developed in Pune, India, the second largest city in the western state of Maharashtra. It has a population of 3.1 million, a female:male sex ratio of 0.948, and significant religious diversity (79% [2,449,000/3,100,000] Hindu; 11% [341,000/3,100,000] Muslim; 4% [124,000/3,100,000] Buddhist; 2% [62,000/3,100,000] Jain; and 2% [62,000/3,100,000] Christian). Approximately, a quarter (22% or 690,545 individuals) of Pune resides in slums [33].

Trial Registration, Ethics, Consent, and Institutional Board Approval

The study was approved by the Ethics Committee of ICMR-NARI and the institutional review board of Emory University (Atlanta, USA) and registered at ClinicalTrials.gov (NCT03332134) and the Clinical Trials Registry-India (CTRI/2018/01/011596).

Intervention Mapping Step 1: Needs Assessment

First, we conducted a systematic review of the literature to assess the breadth and depth of IPV in India and to identify high-risk groups (ie, women of low SES) [34]. Confirmation of IPV as a major priority area for the target community came from prior work within the Pune community [9,35], regular reporting on IPV by local media [36,37], and recognition of need for the development and evaluation of an evidence-based IPV intervention by ICMR-NARI CAB.

Afterward, an analysis of IPV causation in Pune slums was undertaken to inform the development of the PRECEDE logic model (Figure 1). This included identification of correlates of IPV perpetration and experience through respective cross-sectional surveys with 100 newly married male and 100 newly married female residents of Pune slums and extraction of themes regarding IPV causation from key informant interviews.

We then assessed the community capacity by exploring services provided by local community-based organizations (CBOs); engaging in informal discussions with community leaders and individuals working in the intervention communities (ie, from *anganwadis* [Integrated Child Development Scheme, ICDS, child care centers] and *mitramandals* [male youth social clubs]); reviewing Indian laws, policies, and government schemes that address IPV; and surveying the physical environment (ie, space to conduct the intervention) and local resources (ie, police stations for safety concerns).

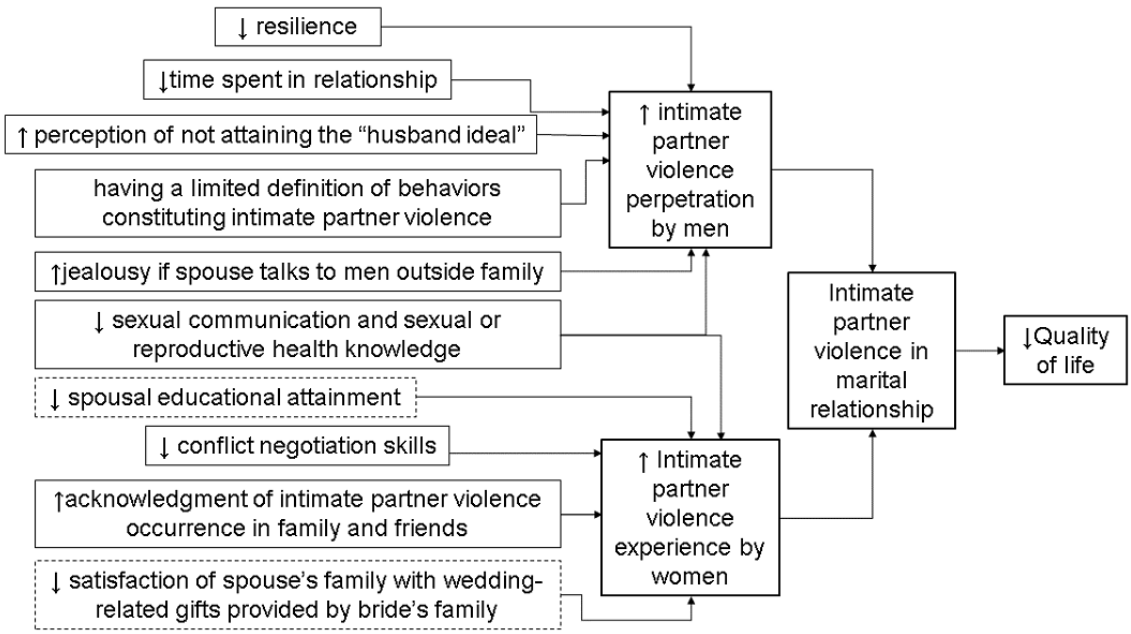
Intervention Mapping Step 2: Preparation of Matrices of Change Objectives

To develop matrices of change objectives (Multimedia Appendix 1, we used the IPV correlates noted in IM step 1 to draw causal pathways for influencing change in IPV perpetration for men and IPV experience for women, defined the desired behavioral outcomes of the intervention, and then subdivided the behavioral outcomes into performance objectives. Afterward, the stated performance objectives were linked with key, changeable determinants informed by behavior change theories [32] to ultimately define and prioritize the change objectives for the intervention.

Intervention Mapping Step 3: Selection of Theory-Based Methods and Practical Applications

Together with the research field team (that brought working knowledge of the needs and interests of individuals residing in Pune slums through years of field experience), we brainstormed ideas for the intervention that would accomplish each of the change objectives. We narrowed the list of applications based on the extent to which we felt they could appeal to and meet the needs of the intervention population and whether the application was justified by a theory-based behavior change method. The selected intervention applications were individually again examined by ASK, SS, and RS to ensure they addressed the respective change objectives.

Figure 1. A logic model of the needs assessment.



Intervention Mapping Step 4: Production of Intervention Components and Materials

The phase II key informant interview data were used to inform the production of the application content and materials. Specifically, we extracted case stories and common marital conflict scenarios, and key informant suggestions about information content, delivery methods (including language considerations), order of module delivery, and duration. We then reviewed and revised the content and delivery for the 6-intervention modules exercise-by-exercise until team consensus was achieved about the material being relevant, stimulating, clear, and appropriate in addressing the change objectives.

Thereafter, the intervention materials and delivery strategy were presented to the ICMR-NARI CAB and regional GBV experts and revised based on their feedback. The content of specific exercises for which there remained uncertainty about participant acceptance or comprehension (ie, exercises related to sexual communication and knowledge, career planning, and government schemes) was presented to the community for feedback through 3 focus group discussions with married men (n=7), married women (n=7), and mothers-in-law and fathers-in-law (n=8). Finally, the research team worked intimately with the module publishers and film producers (for the short films used in module 3 to ensure quality and appropriateness of the final product.

Intervention Mapping Step 5: Intervention Adoption and Implementation

We brainstormed potential adopters of the intervention, consulting recommendations from the qualitative data about existing government and nongovernment programs with whom to partner to enhance future scalability and sustainability of the intervention. The brainstorming included free listing of community gatekeepers who could raise awareness about the intervention and recruit participants, individuals and agencies who could deliver the intervention, and potential intervention venues. Subsequently, we met the individuals and agencies to gauge their interest, capacity, and processes they required to formally establish the partnership. Selected interventionists underwent a 1-week interactive training. Necessary paperwork for partnering agencies was completed.

Intervention Mapping Step 6: Evaluation Planning

To develop the plan for evaluation of intervention effect, we consulted the matrices of change objectives and the scientific literature to find appropriate, validated tools to measure the desired change. In developing the measures of acceptance, feasibility, and safety, we ensured the evaluation included the perspectives of multilevel stakeholders (ie, participants, interventionists, police stations, CBOs, and community members) as is emphasized by Bartholmew et al [32]. Process indicators related to fidelity, dose delivered, dose received, reach, recruitment, and context were developed in consultation with the Consolidated Standards of Reporting Trials guidance for pilot trials [38] and the process evaluation guide by Saunders et al [39].

Results

Summary

The resulting *Ghya Bharari Ekatra* intervention (Figure 2) was a 6-session intervention that was intended to be delivered by a trained pair of male and female community educators to groups of 3 to 5 newly married couples in the slum community in which the participants resided. Community educators were lay people who either belonged to the community in which the intervention was conducted or were members of other communities interested in grassroots-level community work. The intervention employed competitive games, intensive discussions, self-reflections, and skill-building exercises and covered the following topics in 2-hour sessions over 6 weeks: enhancing relationship quality time, self-esteem and resilience, communication and conflict management, goal setting and implementation, sexual communication and sexual health and reproductive health knowledge, and redefining and challenging norms surrounding IPV occurrence. All sessions were delivered to groups of couples with the exception of the sexual communication and sexual and reproductive health module, which was to be delivered in gender-concordant groups of 3 to 5. In this section, we demonstrate how the results of each IM step contributed to the development of the intervention.

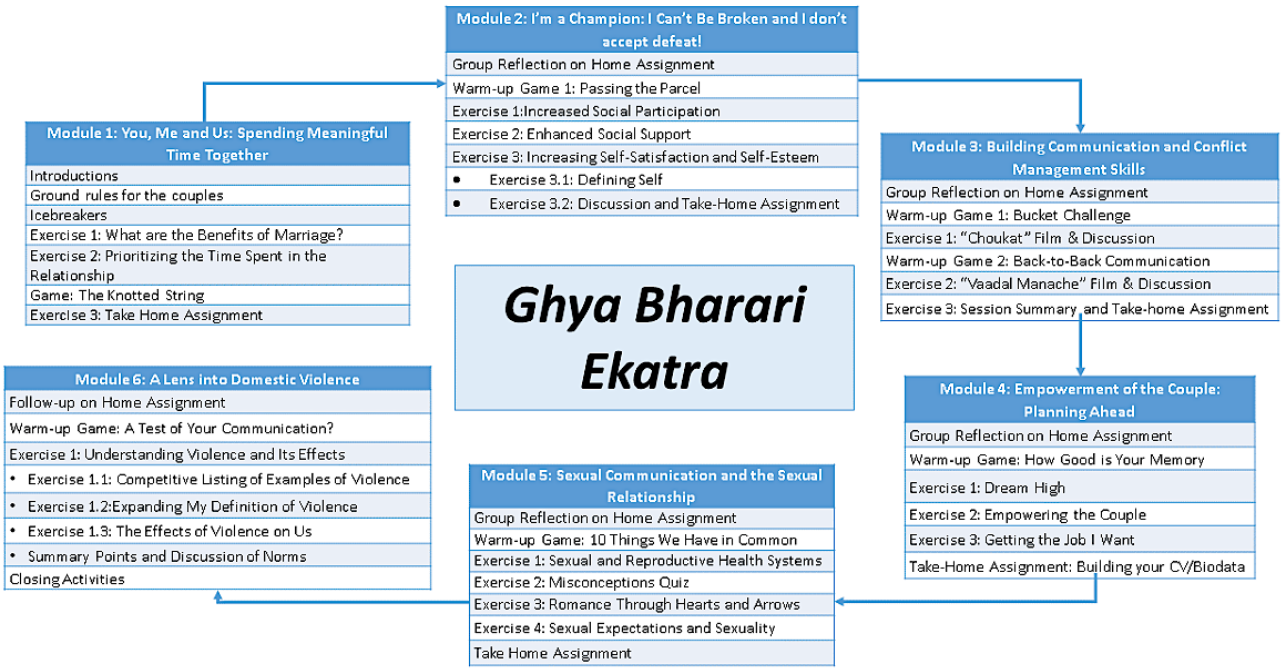
Intervention Mapping Step 1: Needs Assessment

The systematic review [34], formative work [9,35], and NARI CAB meetings identified the need for a targeted primary IPV prevention intervention for low-income, slum communities in India. The cross-sectional surveys and key informant interviews isolated key behavioral factors contributing to IPV in this community and led to the development of the PRECEDE logic model (Figure 1). The assessment of community capacity highlighted that individual slum communities had many resources (ie, venues) to foster implementation of the intervention: community halls, *anganwadis*, *mitramandals*, *mahilabachatghat* groups (women's savings groups), CBOs, and schools.

Intervention Mapping Step 2: Preparing the Matrix of Change Objectives

Figure 1 was used to define and prioritize, based on changeability and importance, the desired behavioral outcomes for each of the 6 intervention modules. Each of the behavioral outcomes became the focus of a session in the 6-session intervention: (1) increased quality time spent in the relationship, (2) increased self-esteem and resilience, (3) enhanced communication and conflict management skills, (4) improved goal setting and goal implementation skills, (5) improved sexual communication and sexual health and reproductive health knowledge, and (6) expansion of definitions of behaviors constituting IPV and challenge subjective norms surrounding IPV occurrence. For each of the 6 sessions, individual matrices of change objectives were developed (Multimedia Appendix 1).

Figure 2. The *Ghya Bharari Ekatra* intervention.



Intervention Mapping Step 3: Selection of Theory-Informed Intervention Methods and Practical Applications

Couple's interdependence theory is the unifying theory in which the intervention is grounded [28]. The Interdependence model [28], which we used to guide intervention development, has 3 major components: (1) *transformation of motivation* or shift in orientation from self- to relationship-centered (ie, the husband internalizing the impact of IPV and poor relationship quality on his spouse and the relationship), (2) *communal coping* in which the dyad has a shared assessment of the threat of IPV and poor relationship quality to their health and quality of life and share a vision of the action plan to reduce IPV and improve relationship quality, and (3) *behavior change* through which the couple together adopts and sustains behaviors to reduce IPV and enhance relationship quality. In addition to couple's interdependence theory, several theoretical behavior change methods along with the change objectives guided the development of the practical applications for each module (Multimedia Appendix 2).

Intervention Mapping Step 4: Development of Intervention Components and Materials

The qualitative data guided the intervention duration, module order, content, and delivery.

Module Duration and Order

Key informant interviews provided guidance on module duration and order of delivery. Participants placed emphasis on the need for intervention timing to be convenient for participants, for interventionists to be respectful of the participant's time, and for sessions to be limited to 2 hours. An HIV researcher with expertise in working with slum communities guided:

> *Many will say "our time is up, we are leaving"…You can give training for 1 hour, at the most 2 hours...Whatever time we tell [them], we should do within that.*

Although key informants had varying suggestions for ordering of modules, most agreed on beginning with relationship building, as it was the foundation of married life. A founder of a marital counseling CBO expanded on the importance of prioritizing this module:

> *Because many times they [participants] don't know...I mean, understanding wife, or understanding husband, usually as marriages are always between the families...they have seen [their respective partner] maybe at the time of marriage or maybe only at the event of meeting the girl, otherwise they don't know what is [a marital relationship]...And then...first 3-4 months, especially in our communities, there are so many festivals and this and that and go to this temple, that temple, and then there is no time to [spend with each other], you know?*

Other common themes about module order included the need for initial intervention sessions to have particularly high appeal (ie, provide information about relevant government services and economic empowerment), delaying the sexual and reproductive health session until group rapport and comfort were established, and ensuring each module built on information provided in the prior sessions. Finally, 1 key informant who works with a CBO that focuses on women's empowerment and gender equality through male engagement highlighted the importance for the session about domestic violence (DV) to occur at the end to minimize attrition:

> *And anyways, when we talk of domestic violence to begin with. Then men think, "these people have this only." [That this is the only agenda this organization is coming to us with]. They get put off by that. We should take that [the issue of violence] up last.*

Intervention Delivery

To engage and retain participants, key informants emphasized the need for the intervention to be fun, interactive, and activity-based and to make use of audio-visual tools:

> *If you just give lectures, nobody will come to you.* [Gynecologist]
>
> *The more audio-visual films you will use, the more impact you will have.* [DV lawyer]
>
> *You need to make it as engaging and as participatory as possible.* [GBV researcher]

Specific delivery methods (ie, competitions, games, role plays, self-reflection, practice with feedback, songs and dance therapy, and quizzes) and audio-visual tools (ie, flip charts, anatomic models, and films) suggested by the key informants were incorporated throughout all 6 sessions. To foster couple interest and engagement in the sessions, a *star points competition* was woven throughout the 6 sessions, wherein couples accumulated points for participation, punctuality, and the games they won, and ultimately, the couple with the most points at the final session was recognized and received an award.

Key informant data also led us to repeatedly evaluate the language used in the modules to ensure it was easy to understand, familiar to the participants, and also scientific. For example, a social worker of a CBO that focused on women's empowerment and gender equality through male engagement advised:

> *Many times to make it palatable for the slum area people, we use many times the words, which are, they use for their body parts. Now, to begin with this is good, but ultimately we should bring them to the real scientific terms of that body part.*

Key informants also provided guidance on which exercises should be performed individually, in couples, and in groups. For example, the input from a counselor of a marital counseling CBO led to the sexual communication and sexual and reproductive health session being delivered in separate gender-concordant groups:

> *First, sexuality you should conduct in a group and separately too. Because, if the participant has to speak openly, then [conducting men and women group sessions], limitations will come for that. Even if you take a couple...if they are husband and wife, even then, to talk to someone else in front of my partner will be difficult for me.*

Content

Individual module content was also informed by key informant data. For example, in response to the advice provided by the director of a CBO that engaged men to promote gender equality below, we designed an activity in module 1 in which couples self-reflected about the time they dedicated to their relationship and strategies to increase that time:

> *This is a relationship program and you can't talk about relationships without emotions and without reflections and without communications…You actually need to bring in the self-reflection.*

As part of the second and fourth sessions, which respectively aimed to build resilience and empower the couple, interactive informational sessions were held with community resource people (ie, social workers, government scheme enrollment officers, and *bhishi group* leaders) to provide relevant information about community resources. These sessions were derived from key informants stressing the need for the intervention to be linked to existing structures and tailored to the needs of and services available in individual slum communities:

> *The needs of one community may not be the needs of the next [community]. So it will also be important to cater it in that sense. As in, "this is our module, and we now have to use this,"—we can't do that.* [DV lawyer]

She further expanded that:

> *...connecting them to government systems becomes important so that it's longstanding.*

The scripts for the module 3 films, used to provoke discussion about effective communication and conflict management strategies, were based on conflict scenarios taken directly from examples provided by our key informants and observations made by our field team. While in the field, our team noted that conflict in the newly married couples often arose from differences in expectations resulting from the newly wed women having moved to the urban slums from surrounding rural areas following marriage, whereas the men had long resided in urban slum environments. This was substantiated by key informant examples. For example, an ICDS project officer, responsible for overseeing *anganwadi* workers explained:

> *Soon after marriage, one girl came...and she was from a rural area. At that time, when that girl came into the slum, and at that time, the boy was from Pune, so accordingly he had many expectations, that "my wife should wear jeans."...But she wasn't used to jeans, because she was from a typical, rural area. "So then how can I do it?" About that they both started arguing.*

Module 5 content was derived from the topics identified by key informants as critical to cover (ie, reproductive health systems, conception and pregnancy, communicating sexual expectations, and creating romance). Items for the module 5 misconceptions quiz were pulled directly from misconceptions reported by key informants (ie, penile length being associated with pleasure, pornography guiding performance of sexual intercourse, and erectile drugs being misused). A marital counselor provided the following:

> *Most of [the men] do sexual abuse in accordance with what they watch in blue films and they perform similar acts on their wives leading to harassment and unnatural sexual acts. This attitude can be changed through proper education.*

We added content about sexuality and creating romance based on a suggestion by a key informant who directed a gender-equality CBO that engaged men:

> *How physical relationships are connected to emotional bonding, we need to focus on this too. Otherwise, if we look at it (marital sexual relationship) only from the perspective of bodily need, then to strengthen the bond in this relationship becomes very difficult.*

Finally, module 6 content was developed in response to key informants emphasizing the need to challenge deep-rooted norms of DV acceptance and to enable participants to expand their definitions of behaviors constituting abuse (taking into account the survivor perspective). A feminist sociologist and a DV lawyer informant, respectively, suggested the means for doing so:

> *What men perceive as violence and what women perceive as violence is very different. I think we need to tease that out.* [Feminist sociologist]

> *To be able to say that you know violence is subjective and that we'll have to understand it from the victim's perspective.* [DV lawyer informant]

The finalization of the intervention name, *Ghya Bharari Ekatra*, involved research team members, in consultation with the community, brainstorming and short listing titles that were memorable, appealing, and best depicted a couple's joint empowerment. Searches of other Indian empowerment programs and interventions were conducted to ensure uniqueness. The title was ultimately determined by vote among research team members.

Intervention Mapping Step 5: Planning for Intervention Adoption, Implementation, and Sustainability

The decision to engage male and female community educators as the primary interventionists, to bring in community resource people to lead specific intervention exercises, to work with *anganwadi* workers in recruiting participants, and to utilize community-based venues was driven by key informant data.

Interventionists

In selecting interventionists, key informants stressed the need to ensure that the candidate was interested in the intervention, had strong oratory and critical thinking skills and gender-equitable attitudes, capacity to make the participants feel safe and secure, and sensitivity (to note when a participant seemed uncomfortable). Many highlighted the need for the interventionists to be of a similar demographic to the participants to best connect with them. For example, a counselor from the marital counseling CBO described who an ideal interventionist would be:

> *[People from] the slum community and the ordinary citizens of the society...those who have led successful lives…those who have brought up kids. Those who think that their lives have been spent happily, you should involve such people, because they are a role model in front of them.*

The director of a CBO that engaged men to promote gender equality further emphasized this:

> *...to whom do people connect? To those whose language they are accustomed, to them they connect.*

He also elaborated on the need for the interventionists to be emotionally engaged with the participants' community:

> *If you are not part of people's life, people are not part of your project, OK? In that community, in that couple, someone in that couple's mothers has died during the period [of the intervention], someone's father has died. It's someone's 10th[10thday death memorial ceremony]...If your intervention team isn't part of their lives, they [the participants] aren't part of our procedures emotionally.*

Key informants emphasized the importance of some sessions to be delivered by content-level experts (ie, legal, health, and social workers and mental health counselors), community resource people (ie, *bachatghat* group leaders and community welfare officers), and engaging *anganwadi* workers to help with recruitment and retention, given their existing rapport with community members and likely interest in the intervention. Two marital counselors separately emphasized the need for some content to be delivered by gender-concordant facilitators:

> *However much you might think that they [the participants] will not feel shy, it is not at all like that. Hence while conducting the husband's sex education, you keep a gents community worker [have a male community worker as the facilitator]...and while conducting for ladies, you keep a lady [have a female community worker as the facilitator].*

> *When a woman tells a man, it remains ineffective but when a man tells another man, about what is DV, and how it is contracted and how should one live in day-to-day lives, then the attitude will change. The attitude of looking at domestic violence should change.*

Thus, we ultimately decided to have the sessions facilitated by a male and female community educator, who demonstrated strong oratory, group facilitation, critical thinking skills, and community involvement during the behavioral interviewing process. Content-level experts (ie, medical officers) and community resource people (ie, social workers and *bachatghat* leaders) were also brought in for the second, fourth, and fifth session, and participants were provided contact information for other services that provided support for IPV, substance abuse, and legal, medical, and mental health. Session 5 was the only session delivered in gender-concordant groups (as opposed to groups of couples) and was delivered by gender-concordant doctors. In addition, the research team met the local ICDS administration to obtain permission for *anganwadi* workers to help facilitate recruitment and retention efforts.

Training

A 6-day training for the community educators was held at ICMR-NARI by the research team. It was conducted in Marathi and Hindi and covered basic research ethics and safety, DV, community educator responsibilities (including need to report

DV and other safety concerns to the study team), and the content of each of the 6 intervention sessions. First, research team members role-played the delivery of each session. Afterward, community educators mock delivered the session with feedback from the research team and other community educators.

Venue

Key informants highlighted the need for the venue to be of choice and convenience to the participants, in a setting where privacy could be maintained, a safe space where participants would feel comfortable sharing, and where discipline could be maintained. A trainer from a CBO, who promoted gender equity and justice, advised that for participants to be engaged, the research team had to dedicate effort to creating a safe space:

> *People would talk to you, if you actually create that space, very safe for sharing—not just between the trainer and trainees, but also amongst the group of participants, right? How safe they would feel in a physical structure, in a room, in a hall...How safe they feel with the gadgets around, mobile phones, audio-recorders, or video camera...You know, it all depends on the way you create that environment.*

Although health care settings were mentioned as optimal spaces for maintaining privacy, they carried associated stigma and fear of infectivity, cost, and challenges of distance and insufficient space. *Outings* (ie, gardens and trips) were also suggested because they could serve as fun, exciting lures for potential participants, and potentially ensure the couples' presence for the entirety of the session, but concerns were raised about time in travel and whether participants would be permitted to leave their community (particularly, if pregnant). Many key informants suggested having the venue in the slum community itself out of convenience, accessibility, and ease of obtaining family member's permission for the couple to attend, but noted that we may encounter difficulty maintaining privacy and finding space in such venues. Suggested community-based venues included *anganwadis*, schools, community halls, and religious venues. Religious venues brought the advantage of being acceptable but were often cited as lacking privacy, having sociopolitical affiliation, challenging secularism, and having limited availability (ie, serving as child care centers by day).

Factoring in the concerns raised by the key informants, we ultimately decided to hold the intervention in the slum community from which the participants were drawn. Venues were selected in partnership with community educators, weighing likelihood of safety and privacy. In addition, community educators and field team members were provided scripts and protocols for handling specific violations of privacy and safety. Finally, community meetings were held before the intervention delivery to help avert community misconceptions and undue stigma associated with the program.

Intervention Mapping Step 6: Planning for Evaluation

The detailed evaluation plan, developed using the Multimedia Appendix 1 matrices of change, is presented in Table 1. It includes both outcome and process indicators and assesses preliminary efficacy, safety, feasibility, and acceptance. Evaluation methods include a preintervention and 3-month postintervention survey administered to participants, postsession open-ended discussions with participants to assess acceptance, postsession open-ended discussions with community educators to assess acceptance and challenges with delivery, research team logging of recruitment and retention numbers and associated facilitators and barriers, and semistructured evaluation of fidelity, dose delivered, and dose received by the research team during each session.

Table 1. Intervention evaluation plan.

Indicator and assessment method	Data source
Outcome indicators	
Participants spend more quality time together in the relationship	
Time spent in relationship	M[a] (S[b])
Satisfaction with time spent in relationship	M (S)
Participants experience enhanced self-esteem and resilience	
Resilience (CD-RISC-10[c])	M (S)
Extent to which feel attained qualities of *ideal husband*	M (S)
Jealousy if spouse talks to other men	M (S)
Self-esteem (RSES[d])	M (S)
Participants develop enhanced communication and conflict management skills	
Conflict negotiation skills (CTS2N[e])	F[f] (S)
Confidence in communicating various scenarios with partner	M/F (S)
Participants develop enhanced confidence in goal setting and goal-implementation skills	
Extent to which feel attained qualities of *ideal husband*	M (S)
Confidence in setting and achieving goals, and listing resources that support achieving goals	M (S)
Participants develop enhanced sexual communication and sexual and reproductive health knowledge	
Confidence in sexual communication	M/F (S)
Reproductive health beliefs	M/F (S)
Participants' definitions of behaviors constituting IPV[g] will expand and will be less accepting of IPV	
Definition of DV[h] (using items from abridged IFVCS[i])	M (S)
Attitudes toward DV acceptance (ATWBS[j])	F (S)
Overall reduced DV	
Past 1-month DV experience (abridged IFVCS)	F (S)
Process indicators	
Fidelity	
Extent to which training provided as planned	RT[k]
Extent to which interventionists delivered each activity as intended	
Difficulty interventionists experienced in delivering intervention content	PE[l]
Dose delivered	
Number of sessions delivered by PE	RT
Extent to which expected content delivered	RT
Extent to which intended intervention material used	RT
Time required to deliver each activity	RT
Dose received (exposure and satisfaction)	
Participant engagement in each session activity	RT
Participant completion of home assignments	RT
Participant understanding of content of each activity	M/F
Participant satisfaction with each session, timing, and duration of intervention	M/F
Family satisfaction with subject's participation in intervention	M/F
Participant satisfaction with interventionists	M/F

Indicator and assessment method	Data source
Participant acceptance of safety measures	F (S)
PE satisfaction with each session	PE
Participant recruitment and retention	
Number approached and number of attempts to reach potential participant pre-enrollment	RT, M/F
Time between initial contact with community gatekeeper and completion of recruitment	RT, M/F
Family presence during permission process	RT, M/F
Number consented and barriers to consenting	RT, M/F
Number assessed for eligibility, and ineligibility reasons	RT, M/F
Number randomized	RT, M/F
Number of barriers to baseline and 3-month survey completion; staff attempts and reminders	RT, M/F
Reach or participation rate	
Number or duration of sessions participant attended and barriers to attendance	RT, M/F
Number terminated, exited from the study and reason	RT, M/F
Number of staff reminders and home visit reminders	RT, M/F
Number of staff calls or home visits for missed sessions	RT, M/F
Context	
Response from police, community leaders, and family members when household approached	RT
Number of community sensitization meetings held, number in attendance, and response to or acceptance of intervention	RT
Barriers or facilitators encountered by the study team in implementing the program	RT
Safety	
How research is being discussed in the community	PE
1-month DV experience	PE; RT; F (S)
Family conflict attributed to intervention	PE; RT; F (S)
DV reported by participants (or noted by staff) at Women's day or during intervention	PE; RT; F (S)
Adverse events	PE; RT; F (S)
Additional feasibility indicators	
Number of potential PE approached and eligible to serve as interventionists and associated barriers	RT
Number of PE completion of training	RT
Number of community key persons, E-seva Kendra officials, and medical officers attending sessions 2, 4, and 5, respectively (and associated barriers)	RT
Venue identification, privacy, and retention	RT
Cost of intervention delivery	RT

[a]M: male participant.

[b]S: pre- and postintervention survey item.

[c]CD-RISC-10: Connor-Davidson Resilience Scale-10 item.

[d]RSES: Rosenberg Self-Esteem Scale.

[e]CTS2N: Conflict Tactics Scale-2 Negotiation Subscale.

[f]F: female participant.

[g]IPV: intimate partner violence.

[h]DV: domestic violence.

[i]IFVCS: Indian Family Violence and Control Scale

[j]ATWBS: Attitudes Toward Wife Beating Scale.

[k]RT: research team.

[l]PE: peer educator.

Discussion

Principal Findings

Primary prevention of IPV in low-SES communities in India is critical, as IPV is not only a human rights violation but also a critical public health problem, with high frequency and significant associated psychosocial and physical morbidity. *Ghya Bharari Ekatra* is evidence-based, developed using theory (ie, couple-interdependence theory as a unifying framework as well as individual behavior change theories to inform intervention methods), grounded in intervention-mapping, and developed and iteratively refined using a community-based participatory research approach, suggesting it has great potential to be an acceptable and effective solution to preventing IPV among newly married couples. The greatest strengths of *Ghya Bharari Ekatra* include that it is peer-led, community-based, interactive, and introduces novel concepts that are of importance to the participants. Furthermore, integration of the intervention into existing community resources and government program infrastructure will foster future sustainability and scalability throughout slum communities in India if it is deemed effective.

Pilot Study Progress

Enrollment into the pilot study to assess the safety, acceptance, feasibility, and preliminary efficacy in 40 couples (20 intervention and 20 control) commenced in January 2018 and was completed in May 2018. Preliminary feedback from participants, community educators, and the research field team suggests the intervention was highly accepted and safe. Three-month follow-up visits have been completed, and pilot results will be available in the spring of 2019. If pilot results are promising, the efficacy of *Ghya Bharari Ekatra* will be tested on a large scale throughout India.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Matrix of change objectives.

[PDF File (Adobe PDF File), 31KB - resprot_v8i1e11533_app1.pdf]

Multimedia Appendix 2

Theory-informed methods and practical applications.

[PDF File (Adobe PDF File), 41KB - resprot_v8i1e11533_app2.pdf]

References

1. Global and Regional Estimates of Violence against Women: prevalence and health effects of intimate partner violence and non-partner sexual violence. Geneva: World Health Organization; 2013. URL: http://www.who.int/reproductivehealth/publications/violence/9789241564625/en/ [WebCite Cache ID 72qcH8Sgs]
2. International Institute for Population Sciences (IIPS). RCHIIPS. 2015. National Family Health Survey, India URL: http://rchiips.org/NFHS/NFHS-4Report.shtml [accessed 2018-10-01] [WebCite Cache ID 72qcEdUit]
3. Shrivastava PS, Shrivastava SR. A study of spousal domestic violence in an urban slum of Mumbai. Int J Prev Med 2013 Jan;4(1):27-32 [FREE Full text] [Medline: 23412398]
4. Rocca C, Rathod S, Falle T, Pande R, Krishnan S. Challenging assumptions about women's empowerment: social and economic resources and domestic violence among young married women in urban South India. Int J Epidemiol 2009 Apr;38(2):577-585 [FREE Full text] [doi: 10.1093/ije/dyn226] [Medline: 18952621]
5. Ruikar M, Pratinidhi AK. Physical wife abuse in an urban slum of Pune, Maharastra. Indian J Public Health 2008;52(4):215-217 [FREE Full text] [Medline: 19189826]

6. Krishnan S, Rocca C, Hubbard A, Subbiah K, Edmeades J, Padian NS. Do changes in spousal employment status lead to domestic violence? Insights from a prospective study in Bangalore, India. Soc Sci Med 2010 Jan;70(1):136-143 [FREE Full text] [doi: 10.1016/j.socscimed.2009.09.026] [Medline: 19828220]
7. Begum S, Donta B, Nair S, Prakasam CP. Socio-demographic factors associated with domestic violence in urban slums, Mumbai, Maharashtra, India. Indian J Med Res 2015 Jun;141(6):783-788 [FREE Full text] [doi: 10.4103/0971-5916.160701] [Medline: 26205021]
8. Solomon S, Subbaraman R, Solomon S, Srikrishnan A, Johnson S, Vasudevan C, et al. Domestic violence and forced sex among the urban poor in South India: implications for HIV prevention. Violence Against Women 2009 Jul;15(7):753-773 [FREE Full text] [doi: 10.1177/1077801209334602] [Medline: 19448166]
9. Kalokhe AS, Stephenson R, Kelley ME, Dunkle KL, Paranjape A, Solas V, et al. The development and validation of the Indian family violence and control scale. PLoS One 2016;11(1):e0148120 [FREE Full text] [doi: 10.1371/journal.pone.0148120] [Medline: 26824611]
10. Saggurti N, Nair S, Silverman J, Naik D, Battala M, Dasgupta A, et al. Impact of the RHANI Wives intervention on marital conflict and sexual coercion. Int J Gynaecol Obstet 2014 Jul;126(1):18-22 [FREE Full text] [doi: 10.1016/j.ijgo.2014.01.015] [Medline: 24795094]
11. Ministry of Women & Child Development. Women Empowerment Schemes URL: http://wcd.nic.in/schemes-listing/2405 [accessed 2018-10-01] [WebCite Cache ID 72qfGZqkV]
12. Foshee VA, Bauman KE, Ennett ST, Linder GF, Benefield T, Suchindran C. Assessing the long-term effects of the Safe Dates program and a booster in preventing and reducing adolescent dating violence victimization and perpetration. Am J Public Health 2004 Apr;94(4):619-624. [Medline: 15054015]
13. Ismail S, Shajahan A, Sathyanarayana Rao TS, Wylie K. Adolescent sex education in India: current perspectives. Indian J Psychiatry 2015;57(4):333-337 [FREE Full text] [doi: 10.4103/0019-5545.171843] [Medline: 26816418]
14. Kalokhe A, Iyer S, Kolhe A, Dhayarkar S, Paranjape A, Del Rio C, et al. Correlates of domestic violence experience among recently-married women residing in slums in Pune, India. PLoS One 2018;13(4):e0195152 [FREE Full text] [doi: 10.1371/journal.pone.0195152] [Medline: 29608581]
15. Pronyk P, Hargreaves J, Kim J, Morison L, Phetla G, Watts C, et al. Effect of a structural intervention for the prevention of intimate-partner violence and HIV in rural South Africa: a cluster randomised trial. Lancet 2006 Dec 02;368(9551):1973-1983. [doi: 10.1016/S0140-6736(06)69744-4] [Medline: 17141704]
16. Gupta J, Falb K, Lehmann H, Kpebo D, Xuan Z, Hossain M, et al. Gender norms and economic empowerment intervention to reduce intimate partner violence against women in rural Côte d'Ivoire: a randomized controlled pilot study. BMC Int Health Hum Rights 2013 Nov 01;13:46 [FREE Full text] [doi: 10.1186/1472-698X-13-46] [Medline: 24176132]
17. Pulerwitz J, Hui W, Arney J, Scott LM. Changing gender norms and reducing HIV and violence risk among workers and students in China. J Health Commun 2015 Aug;20(8):869-878. [doi: 10.1080/10810730.2015.1018573] [Medline: 25950187]
18. Hossain M, Zimmerman C, Kiss L, Abramsky T, Kone D, Bakayoko-Topolska M, et al. Working with men to prevent intimate partner violence in a conflict-affected setting: a pilot cluster randomized controlled trial in rural Côte d'Ivoire. BMC Public Health 2014 Apr 10;14:339 [FREE Full text] [doi: 10.1186/1471-2458-14-339] [Medline: 24716478]
19. Pulerwitz J, Michaelis A, Verma R, Weiss E. Addressing gender dynamics and engaging men in HIV programs: lessons learned from Horizons research. Public Health Rep 2010;125(2):282-292 [FREE Full text] [doi: 10.1177/003335491012500219] [Medline: 20297757]
20. Pulerwitz J, Hughes L, Mehta M, Kidanu A, Verani F, Tewolde S. Changing gender norms and reducing intimate partner violence: results from a quasi-experimental intervention study with young men in Ethiopia. Am J Public Health 2015 Jan;105(1):132-137. [doi: 10.2105/AJPH.2014.302214] [Medline: 25393199]
21. Peacock D, Levack A. The men as partners program in South Africa: reaching men to end gender-based violence and promote sexual and reproductive health. Int J Men's Health 2004;3:173-188 [FREE Full text]
22. Jones D, Peltzer K, Villar-Loubet O, Shikwane E, Cook R, Vamos S, et al. Reducing the risk of HIV infection during pregnancy among South African women: a randomized controlled trial. AIDS Care 2013;25(6):702-709 [FREE Full text] [doi: 10.1080/09540121.2013.772280] [Medline: 23438041]
23. Jewkes R, Gibbs A, Jama-Shai N, Willan S, Misselhorn A, Mushinga M, et al. Stepping Stones and Creating Futures intervention: shortened interrupted time series evaluation of a behavioural and structural health promotion and violence prevention intervention for young people in informal settlements in Durban, South Africa. BMC Public Health 2014 Dec 29;14:1325 [FREE Full text] [doi: 10.1186/1471-2458-14-1325] [Medline: 25544716]
24. Jewkes R, Nduna M, Levin J, Jama N, Dunkle K, Khuzwayo N, et al. A cluster randomized-controlled trial to determine the effectiveness of Stepping Stones in preventing HIV infections and promoting safer sexual behaviour amongst youth in the rural Eastern Cape, South Africa: trial design, methods and baseline findings. Trop Med Int Health 2006 Jan;11(1):3-16 [FREE Full text] [doi: 10.1111/j.1365-3156.2005.01530.x] [Medline: 16398750]
25. Green E, Blattman C, Jamison J, Annan J. Women's entrepreneurship and intimate partner violence: a cluster randomized trial of microenterprise assistance and partner participation in post-conflict Uganda (SSM-D-14-01580R1). Soc Sci Med 2015 May;133:177-188. [doi: 10.1016/j.socscimed.2015.03.042] [Medline: 25875324]

26. Wagman J, Gray R, Campbell J, Thoma M, Ndyanabo A, Ssekasanvu J, et al. Effectiveness of an integrated intimate partner violence and HIV prevention intervention in Rakai, Uganda: analysis of an intervention in an existing cluster randomised cohort. Lancet Glob Health 2015 Jan;3(1):e23-e33 [FREE Full text] [doi: 10.1016/S2214-109X(14)70344-4] [Medline: 25539966]
27. Abramsky T, Devries K, Kiss L, Nakuti J, Kyegombe N, Starmann E, et al. Findings from the SASA! Study: a cluster randomized controlled trial to assess the impact of a community mobilization intervention to prevent violence against women and reduce HIV risk in Kampala, Uganda. BMC Med 2014 Jul 31;12:122 [FREE Full text] [doi: 10.1186/s12916-014-0122-5] [Medline: 25248996]
28. Lewis M, McBride C, Pollak K, Puleo E, Butterfield R, Emmons KM. Understanding health behavior change among couples: an interdependence and communal coping approach. Soc Sci Med 2006 Mar;62(6):1369-1380. [doi: 10.1016/j.socscimed.2005.08.006] [Medline: 16146666]
29. Feinberg M, Jones D, Hostetler M, Roettger M, Paul I, Ehrenthal DB. Couple-focused prevention at the transition to parenthood, a randomized trial: effects on coparenting, parenting, family violence, and parent and child adjustment. Prev Sci 2016 Dec;17(6):751-764. [doi: 10.1007/s11121-016-0674-z] [Medline: 27334116]
30. Rhoades GK. The effectiveness of the within our reach relationship education program for couples: findings from a federal randomized trial. Fam Process 2015 Dec;54(4):672-685. [doi: 10.1111/famp.12148] [Medline: 25787758]
31. Krishnan S, Subbiah K, Khanum S, Chandra P, Padian NS. An intergenerational women's empowerment intervention to mitigate domestic violence: results of a pilot study in Bengaluru, India. Violence Against Women 2012 Mar;18(3):346-370. [doi: 10.1177/1077801212442628] [Medline: 22531083]
32. Bartholomew L, Parcel G, Kok G, Gottlieb N, Fernandez ME. Planning Health Promotion Programs: An Intervention Mapping Approach. San Francisco, CA: Jossey-Bass; 2011.
33. Census 2011. 2011. Pune City Census 2011 data URL: https://www.census2011.co.in/census/city/375-pune.html [accessed 2018-10-01] [WebCite Cache ID 72qasGDda]
34. Kalokhe A, Del Rio C, Dunkle K, Stephenson R, Metheny N, Paranjape A, et al. Domestic violence against women in India: a systematic review of a decade of quantitative studies. Glob Public Health 2017 Dec;12(4):498-513 [FREE Full text] [doi: 10.1080/17441692.2015.1119293] [Medline: 26886155]
35. Kalokhe AS, Potdar RR, Stephenson R, Dunkle KL, Paranjape A, Del Rio C, et al. How well does the World Health Organization definition of domestic violence work for India? PLoS One 2015;10(3):e0120909 [FREE Full text] [doi: 10.1371/journal.pone.0120909] [Medline: 25811374]
36. The Times of India. 2012. Molestation cases, dowry deaths increase in Pune URL: https://timesofindia.indiatimes.com/city/pune/Molestation-cases-dowry-deaths-increase-in-Pune/articleshow/17447188.cms [WebCite Cache ID 72qbqcPMe]
37. Mid-Day. 2014. Pune's Shame: District Records 355 Cases Of Domestic Violence In 365 Days URL: https://www.mid-day.com/articles/pune-s-shame-district-records-355-cases-of-domestic-violence-in-365-days/15283185 [accessed 2018-11-20] [WebCite Cache ID 744I5RcnC]
38. Eldridge S, Chan C, Campbell M, Bond C, Hopewell S, Thabane L, PAFS consensus group. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud 2016;2:64 [FREE Full text] [doi: 10.1186/s40814-016-0105-8] [Medline: 27965879]
39. Saunders R, Evans M, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. Health Promot Pract 2005 Apr;6(2):134-147. [doi: 10.1177/1524839904273387] [Medline: 15855283]

Abbreviations

ATWBS: Attitudes Toward Wife Beating Scale
CAB: community advisory board
CBO: community-based organization
CD-RISC-10: Connor-Davidson Resilience Scale-10 item
CTS2N: Conflict Tactics Scale-2 Negotiation Subscale
DV: domestic violence
F: female participant
GBV: gender-based violence
ICDS: Integrated Child Development Scheme
ICMR-NARI: Indian Council of Medical Research-National AIDS Research Institute
IFVCS: Indian Family Violence and Control Scale
M: male participant
PE: peer educator
IM: intervention mapping
IPV: intimate partner violence
RSES: Rosenberg Self-Esteem Scale
RT: research team

S: pre- and postintervention survey item
SES: socioeconomic status

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