# JMIR Research Protocols

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## Protocols

## Original Paper

Protocol

# A Novel Smoking Cessation Smartphone App Integrated With a Mobile Carbon Monoxide Checker for Smoking Cessation Treatment: Protocol for a Randomized Controlled Trial

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## *Abstract*

**Background:** Smoking cessation treatment programs have been widely available for patients with nicotine dependence. Despite intensive programs, the continuous abstinence rate (CAR) from weeks 9-12 is still about 50%. Recently, a smartphone app emerged as a novel tool for therapeutic interventions, including nicotine dependence. In this study, we developed "CureApp Smoking Cessation" (CASC), which consists of a smartphone app for patients and a Web-based patient management software for doctors with a mobile carbon monoxide (CO) checking device to improve the efficacy of the smoking cessation treatment.

**Objective:** This study aims to evaluate whether the CASC app is effective for individuals with nicotine dependence in addition to standard smoking cessation programs.

**Methods:** This will be a randomized, sham-controlled, open-label, multicenter trial. We will recruit participants with nicotine dependence, but are otherwise healthy adults. We will randomize and allocate participants 1:1 to the CASC treatment group or a control app group. Both groups will receive a 12-week standard smoking cessation program with pharmacotherapy and counseling. In addition, participants in the treatment group will have the CASC app installed on their smartphone, which will provide video tutorials, advice from an artificial intelligence nurse, a digital diary, and measure daily exhaled CO concentration. In contrast, the control group will have the control app installed on their smartphone, where all the functions that can potentially effect smoking cessation are removed. The primary outcome will be the biochemically validated CAR from weeks 9-24. The success of smoking cessation will be defined as self-reported continuous abstinence from weeks 9-24 and exhaled CO concentration ≤10 ppm both at weeks 12 and 24. The main secondary outcomes will be the CAR from weeks 9-12, weeks 9-52, and 7-day point prevalence abstinence at weeks 4, 8, 12, 24, and 52.

**Results:** We will recruit 580 participants with nicotine dependence from October 2017 to September 2018 or until the recruitment process is complete. The final 52-week follow-up will be completed in October 2019. We expect all trial results to be available by the end of 2019. The trial is funded by CureApp, Inc.

**Conclusions:** This is the first randomized controlled trial to evaluate the efficacy of CASC. We expect that CASC, in addition to standard smoking cessation programs, has a significantly higher CAR during weeks 9-24 than the control app.

## Introduction

Smoking is a risk factor that causes various diseases such as malignant tumors, heart disease, cerebrovascular disease, and chronic obstructive pulmonary disease [1]. It has been estimated that there are 22 million (approximately 18% of the total Japanese population) of adult smokers in Japan, and the number of deaths attributable to smoking is approximately 129,000 per year, indicating that smoking is the most common extrinsic cause of death among noninfectious diseases [2]. In addition, excess medical expenses owing to smoking are up to 1.5 trillion yen (US $13 billion) [3]. Therefore, reducing smoking prevalence could contribute to not only prevent the onset of these lifestyle-related diseases and cancer but also decrease future medical costs [4].

Smoking cessation treatment programs have been widely available for patients with nicotine dependence supported by the Japanese national insurance system [5]. This program consists of 5 visits spanning 12 weeks providing counseling by health care professionals and pharmacotherapy, including nicotine patch and varenicline. Despite this intensive treatment program, the continuous abstinence rate (CAR) from weeks 9-12 has still been 40%-65% [6-8]. Moreover, it significantly decreases after the program finishes and is around 40% at 1-year follow-up [7]. To improve both in-program and long-term CAR, we need additional and more effective treatment interventions both during the regular outpatient clinic visits and after the completion of the 12-week program [6].

Medical apps for smartphones are emerging as "therapeutic" intervention tools to ameliorate diabetes mellitus [9,10], depression [11], and nicotine dependence [12,13]. Because they cover interoutpatient visit blank periods (ie, intervals between clinic visits during which patients normally cannot obtain any clinical guidance from medical staffs), these apps are useful to continuously monitor, promote, and encourage the treatment program from medical staff, as well as by patients themselves. In this regard, Free et al [13] reported that smoking cessation support with daily or weekly text messages during the program doubled smoking quit rates. Although smartphone apps for nicotine dependence are already available in the United States, it remains unclear whether the app with a mobile carbon monoxide (CO) checker device is safe and effective in patients with nicotine dependence.

Recently, we developed "CureApp Smoking Cessation" (CASC), which consists of the latest version of CureApp Smoking Cessation smartphone app for patients and a Web-based patient management software for primary physicians with a mobile CO checking device to improve the success of the smoking cessation treatment. The CASC provides users with accurate knowledge of nicotine dependence, clues to change their behaviors, and measurements of their own exhaled CO concentration levels at home. In addition, patients can share these data remotely with their primary physicians. Masaki et al reported that, in the previous prospective studies with participants using prototypes of CASC smartphone app without a mobile CO checker, the results showed the feasibility and usability in the phase I study [14] and demonstrated a higher CAR from weeks 9-24 than the national surveys in the phase II study [15].

Therefore, this study aims to evaluate whether the latest version of CASC in addition to a standard smoking cessation program is effective in treating individuals with nicotine dependence.

## Methods

### Overall Trial Design

Figure 1 shows the flowchart of the trial. This trial will be a randomized, sham-controlled, open-label, multicenter trial. Table 1 shows trial centers. This trial aims to assess the efficacy of CASC in patients with nicotine dependence when added to a standard smoking cessation program. The treatment group will use the CASC smartphone app integrated with a mobile CO checker and a Web-based patient management software for 24 weeks. Table 2 shows the overall follow-up schedule. The primary outcome of this study will be the CAR from weeks 9-24. We hypothesize that the CASC treatment group will have a higher CAR than the control app group from weeks 9-24. The CAR is defined as the percentage of individuals continuously not smoking even a puff during the specified period. We will conduct this trial in compliance with the Declaration of Helsinki, Medical Device Good Clinical Practice, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable laws and guidelines in Japan. This protocol and informed consent forms were approved by the Institutional Review Board at Keio University School of Medicine and affiliated institutions. Furthermore, we will use the latest version of the approved documents. This study is registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000031589).

**Figure 1.** Flowchart of the trial protocol. CASC: CureApp Smoking Cessation.
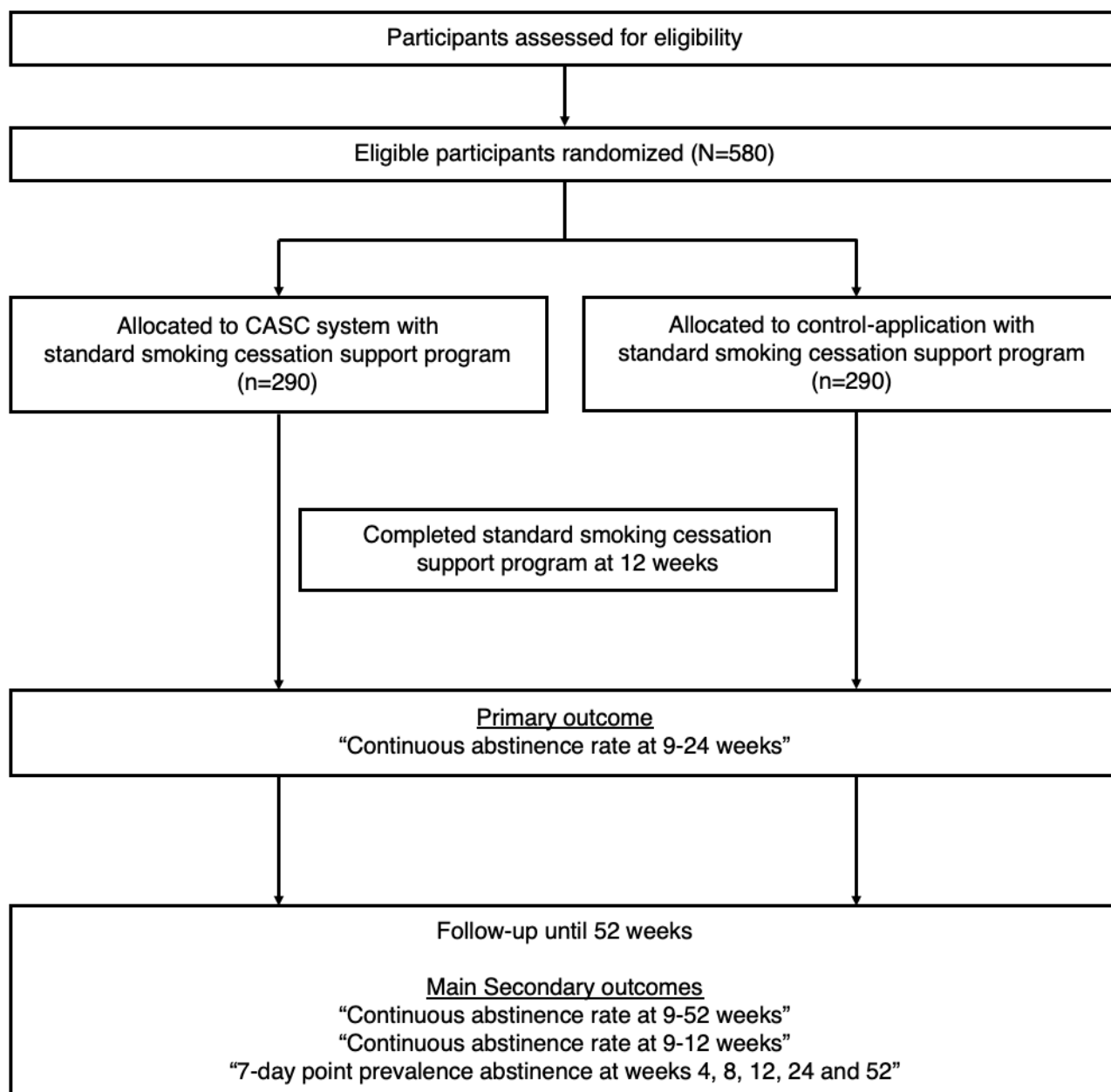


## Trial Participants

We will recruit nicotine-dependent adult participants from October 2017 to September 2018 or until the recruitment process completes; we plan to follow them until October 2019. Participants who meet all inclusion criteria will be included in the trial and those fulfilling the exclusion criteria will be removed from this trial (Textbox 1). We will obtain written informed consent from all trial participants. Participants should understand the content of the consent form sufficiently before their acceptance. Consent forms must be dated and signed both by trial participants and researchers. When consent is obtained, the first copy of the form will be kept in each institution, while the other part will be kept by participants and will not be collected even after the trial is over. In addition, we will inform all participants that their medical care will not be affected if they refuse to enroll in this trial. Participants will be able to leave the trial whenever they want to discontinue it. All participants will receive a compensation of 10,000 yen per clinic visit (7 visits in total).

## Randomization

Randomization will be performed for eligible participants. They will be allocated 1:1 to both arms—the CASC treatment group and the control app group. Randomization will be performed by a computer-generated random sequence with stratification for smoking cessation medications.

**Table 1.** The list of trial centers.

| Number | Institution | Prefecture |
|---|---|---|
| 1 | Ankou Medical Clinic | Tokyo |
| 2 | Ayano Clinic | Saitama |
| 3 | BOOCS Clinic Fukuoka | Fukuoka |
| 4 | Chuo Naika Clinic | Tokyo |
| 5 | Ebisu Garden Place Clinic | Tokyo |
| 6 | Higashi-hie Naika | Fukuoka |
| 7 | Hosoda Shinryojo (clinic) | Tokyo |
| 8 | Inoue Naika Clinic | Ibaraki |
| 9 | Kanda Clinic | Tokyo |
| 10 | Keio University Hospital | Tokyo |
| 11 | Kimura-Shiro Clinic | Fukuoka |
| 12 | Kita Shin-Yokohama Naika Clinic | Kanagawa |
| 13 | Mashiba Iin (clinic) | Saitama |
| 14 | Maekawa Medical Clinic | Kanagawa |
| 15 | Miyazaki RC Clinic | Tokyo |
| 16 | Motosumiyoshi Kokoromi Clinic | Kanagawa |
| 17 | Nakameguro Atlas Clinic | Tokyo |
| 18 | National Center for Global Health and Medicine | Tokyo |
| 19 | Nemoto Geka-Seikeigeka (clinic) | Saitama |
| 20 | Nihonbashi Naika-Allegy Clinic | Tokyo |
| 21 | Nomura Iin (clinic) | Tokyo |
| 22 | Odayaka Life Naika Clinic | Saitama |
| 23 | Saitama City Hospital | Saitama |
| 24 | Sawayama Naika-Sougoushinryou Clinic | Fukuoka |
| 25 | Segawa Hospital | Saitama |
| 26 | Shimizu Clinic Fusa | Saitama |
| 27 | Shinjuku Research Park Clinic | Tokyo |
| 28 | Sone Clinic Shinjuku | Tokyo |
| 29 | Tajima Clinic | Tokyo |
| 30 | Tenjin Sogo Clinic | Fukuoka |
| 31 | Ueda Naika Clinic | Fukuoka |

## Intervention and Control

In addition to the 12-week standard treatment procedure for smoking cessation [5], we will prescribe the CASC to the treatment group. On the other hand, a control app will be prescribed to the control group. The standard 12-week smoking cessation treatment protocol provides 5 on-site examinations and in-person counseling by a primary physician at each outpatient clinic within 3 months.

CASC consists of a CureApp Smoking Cessation smartphone app based on a cloud system paired with a mobile CO checker for participants and a Web-based patient management software for primary care physicians. Participants in the treatment group will install the app in their smartphones and then begin taking a few minutes every day for watching a video tutorial regarding smoking cessation; in addition, participants from the treatment group will keep a digital diary of quitting smoking, chat with artificial intelligence (AI) nurse, and check their exhaled CO concentration by the mobile CO checker at least once a day. Physicians will be able to follow participants' exhaled CO concentration data and physical conditions through a secure cloud system and review them during the clinic visits (Figure 2).

**Table 2.** The trail assessment and evaluation schedule.

| Assessments | Observational period | | | | | | | At withdrawal |
|---|---|---|---|---|---|---|---|---|
| | Day of registration (Day 1) | 2 weeks (Day 15) | 4 weeks (Day 29) | 8 weeks (Day 57) | 12 weeks (Day 85) | 24 weeks (Day 169) | 52 weeks (Day 366) | |
| Patients' background | ✓ | | | | | | | |
| Tobacco Dependence Screener | ✓ | | | | | | | |
| Brinkman Index[a] | ✓ | | | | | | | |
| Fagaström Test for Nicotine Dependence | ✓ | | | | | | | |
| 12-item French version of the Tobacco Craving Questionnaire | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Kano Test for Social Nicotine Dependence | ✓ | | | ✓ | ✓ | ✓ | ✓ | |
| Mood and Physical Symptoms Scale | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Exhaled carbon monoxide concentration | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Status of nonsmoking | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Status of device use | | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ |
| Adverse events | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

[a]Brinkman index=(number of cigarettes per day)×(number of smoking years).

**Textbox 1.** Inclusion and exclusion criteria.

Inclusion:

- Participants diagnosed with nicotine dependence (Tobacco Dependence Screener≥5 points)

- Participants with Brinkman index≥200

- Participants who wish to quit smoking immediately

- Participants who agree to receive the smoking cessation treatment program and sign the written consent form

- Participants who can use a smartphone (operating system: Android 5.0 and above or iPhone 8.0 and above)

Exclusion:

- Participants with severe mental illness

- Participants who cannot come to their follow-up clinic visits during the 1 year

- Participants who have started taking a smoking cessation medication within 1 year before the registration

- Participants who plan to use any smoking cessation aids and participate in any kind of smoking cessation activities (not limited to smoking cessation therapy) outside the trial

- Participants whose investigator or clinical trial doctor judged them to be unsuitable for participation in this trial owing to other reasons

On the other hand, participants from the control app group will be able to perform only 6 basic functions in their app as follows: (1) show the user guide (how to use the app); (2) enter their profile and set the start date of smoking cessation; (3) display the course of 5 visits during the 12-week treatment with a summary of objectives of each visit; (4) show the date of next appointment; (5) get the contact form for technical support; and (6) display an app version, privacy policy, and other administrative information. The other functions of the CASC app will not be incorporated in the control app. The control app will not include the mobile CO checker either. Note that exhaled CO concentrations will be measured by the medical staff at each clinic visit regardless of the study groups, and these CO data at the clinic will be used in the analysis of study outcomes.

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**Figure 2.** Overview of the "CureApp Smoking Cessation". CO: carbon monoxide; IoT: Internet of Things.
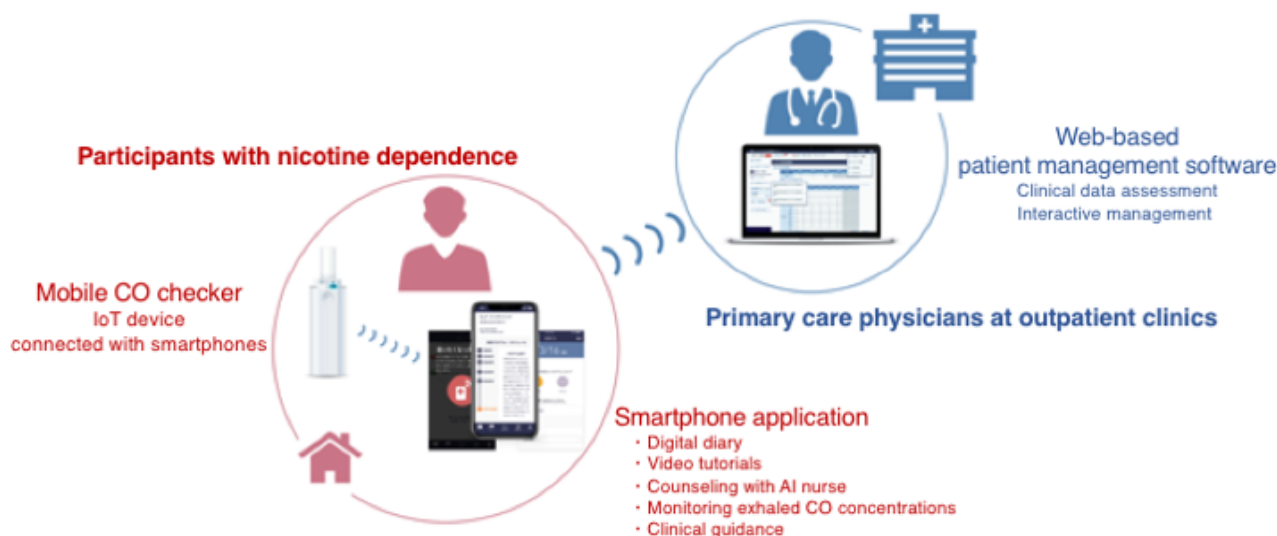


The CASC, control app, and mobile CO checker delivered by CureApp Inc. (Tokyo, Japan) should be carefully managed to ensure they are not used outside the clinical trial at each medical institution. A prescription code will be required to activate the investigational device, and the control group app will be issued by sponsors specific to each practicing medical institution; these sponsors regularly (at least once a year) perform inventory confirming there will be no usage of the app outside the trial.

## Overview of the "CureApp Smoking Cessation" Smartphone app

The CASC smartphone app was developed at CureApp Inc. supervised by the Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine. The app runs on both iOS and Android smartphones. Primary physicians will provide the app prescription code to participants at their outpatient clinics. Participants will download the app through their smartphones, activate the app entering the code, and enter their baseline data including age, sex, years of smoking, number of cigarettes per day, prescribed medications (nicotine patch or varenicline), and motivation and self-confidence regarding smoking cessation. These data will be securely sent to the cloud storage, and the AI of our system will assemble tailor-made smoking cessation programs suitable to each participant based on their personal information. Personal data stored on the cloud can be reviewed by primary physicians. The CASC app has the following 4 main components to maximize the therapeutic effects of pharmacological therapy and counseling provided by health care professionals: (1) keeping a smoking cessation diary (once a day); (2) lectures and educational videos helping its users quit smoking; (3) interactive counseling by chat-bot (AI nurse); and (4) daily measurement and recording of exhaled CO concentration levels at home through a mobile CO checker.

Regarding a Web-based personal computer software for primary doctors, it provides a data management app from patients' CASC mobile apps and advice for physicians to follow the national clinical guidelines appropriately.

## Outcomes

The primary outcome of this study will be the biochemically validated CAR from weeks 9-24. The success of smoking cessation has been defined as (1) self-reported continuous abstinence from weeks 9-24 and (2) exhaled CO concentration no more than 10 ppm at both weeks 12 and 24. In current smoking cessation programs, the CAR from weeks 13-24 drastically decreases, whereas our investigational device is expected to prevent this reduction by covering "treatment gaps" to promote the retention of appropriate recognition and behavioral changes. A single-arm prospective pilot study showed that a CASC app, even without a mobile CO checker, had a significantly higher CAR from weeks 9-24 than the historical cohort that had received standard smoking cessation program [16,17].

In addition, we will evaluate the following secondary outcomes: (1) 7-day point prevalence abstinence at weeks 4, 8, 12, 24, and 52; (2) the CAR from weeks 9-12 and from weeks 9-52; (3) changes in several scores related to smoking cessation, including the Mood and Physical Symptoms Scale (MPSS) [18], 12-item French version of the Tobacco Craving Questionnaire translated into Japanese (FTCQ-12) [19], Kano Test for Social Nicotine Dependence (KTSND) [20], and time to first lapse after initial visit; (4) usage rates of smartphone apps; and (5) the presence of product problems or adverse events.

## Follow-Up Schedule

Table 2 shows the overall follow-up schedule of this trial. At registration, patients' background profile, exhaled CO concentration, nicotine dependence, and smoking status will be assessed using instruments such as the Tobacco Dependence Screener [21], Brinkman index (multiplied by cigarettes per day and years of smoking), Fagerström Test for Nicotine Dependence (FTND), FTCQ-12, KTSND, and MPSS. The background profile includes age, sex, body weight, years of smoking, cigarettes per day, and medical history at the initiation of device use. Regular follow-up visits will be scheduled at 2 weeks (±7 days), 4 weeks (±7 days), 8 weeks (±14 days), 12 weeks (±14 days), 24 weeks (±28 days), and 52 weeks (±28 days); during these follow-up visits, we will examine patients'

scores regarding FTCQ-12, KTSND (after 8 weeks), and MPSS, as well as exhaled CO concentration, status of nonsmoking, status of device use, and adverse events. Adverse events and concomitant pharmacological therapy will be recorded through the trial.

An independent monitoring staff will conduct on-site data monitoring. In addition, the staff will review trial database to confirm whether principal and subinvestigators at each clinic perform the clinical trial according to the research proposal and standard operation procedures, and data queries will be asked if necessary.

### Participant Withdrawal Criteria

Participants will be discontinued from follow-up visits for this trial when they meet either of the following criteria: (1) participants request discontinuation; (2) researchers consider discontinuation is necessary owing to severe adverse effects, for example; (3) the eligibility criteria was violated; (4) significant deviation from the protocol occurred; (5) study institution terminated trial participation because of good clinical practice violation, for example; (6) participants' further follow-up visits are considered very difficult to accomplish; (7) continuing smoking even at the 9th week or participant no longer intends to continue the smoking cessation program; (8) sponsor cannot continue the trial; and (9) any other cause in which researchers decide discontinuation is appropriate.

### Sample Size

The primary endpoint will be the CAR from weeks 9-24. We estimated conservatively 52.8% in the CASC treatment group and 40.8% in the control group as the primary endpoint (CARs from weeks 9-24) based on the survey of smoking cessation [22]. Regarding the effect size, we referred data from a clinical trial of maintenance therapy with varenicline [7], which indicated that 24 weeks of varenicline therapy showed 12% of additional abstinence rate than placebo in the total population. Thus, we estimated that 24 weeks of the CASC intervention could obtain additional effect of 12% on abstinence rate compared with the control group. A sample size of 290 in each treatment group will have 80% power using a chi-square test with a 2-sided significance level of .05 (nQuery Advanced 8.2.1).

### Statistical Analysis

All statistical analyses will be performed according to the intention-to-treat principle and using 2-sided at a .05 significance level. The baseline characteristics will be described by the mean and SD, median and quantiles (continuous variables), or proportion (categorical variables). We will examine the outcomes using the full analysis set. For the primary outcome, we will compare CARs from weeks 9-24 comparing the CASC treatment group and the control group using a logistic regression model adjusted for prescribed smoking cessation medications. In addition, secondary outcomes at each defined period will be evaluated with logistic regression analysis adjusted for appropriate covariates between the groups. We will provide descriptive statistics, odds ratios, 95% CIs, and P values for each outcome. A statistical analysis plan detailing all statistical computations will be completed prior to the lock of the database.

SAS statistical software, version 9.4 or upper version (SAS Institute Inc), will be used for all the analyses.

## Results

A total of 580 participants with nicotine dependence will be recruited from October 2017 to September 2018 or until recruitment is complete. The final 52-week follow-up will be completed in October 2019. We expect that all trial results will be available by the end of 2019.

## Discussion

This is the first randomized controlled trial to evaluate the long-term efficacy of CASC, a smoking cessation support app for participants, which also includes a Web-based software for doctors and a mobile CO checker. We expect that participants in the CASC treatment group, in addition to a 12-week standard smoking cessation program, will exhibit a significantly higher CAR from weeks 9-24 than participants in the control app group.

In recent years, several medical apps for smartphones have shown better clinical outcomes compared with conventional treatment [10-12]. These smartphone apps have also been approved by the US Food and Drug Administration being used in daily clinical practice. In terms of smoking cessation, individuals who used CASC smartphone app without a mobile CO checker achieved 63% of the CAR from weeks 9-24 compared with those who did not use the app (historical control) [15]. Clickotine, another smartphone app for smoking cessation, also reached 30% of the abstinence rate at 8 weeks [23]. However, it remains unclear whether CASC including a mobile CO checker (which provides exhaled CO concentrations for the user), evidence-based behavioral support, education, and counseling programs for smoking cessation is effective for maintaining long-term abstinence rates in patients with nicotine dependence.

We developed and used a mobile Internet of Things (IoT) device to measure an exhaled CO concentration level in this trial. A level of exhaled CO concentration is a useful biomarker for patients with nicotine dependence [5]. It helps them understand how much harmful CO is accumulated in their body and how steadily the harm is decreasing after smoking cessation. They might feel guilty for a high exhaled CO concentration level and try to start quitting, and in another case, they could be encouraged to keep quitting by seeing the decline of their CO level [24]. These experiences could continuously motivate them and improve adherence to the standard smoking cessation program [25].

There are several benefits to including smartphone apps with an IoT device to clinical settings. First, a mobile app covers treatment gaps between the outpatient clinic visits. It is beneficial to continuously contact participants and keep providing effective treatment programs, which could be one of the most important points for the program success [10,13]. Second, medical IoT devices enable us to easily gather biometric information remotely. Patients no longer need to access their outpatient clinics for testing; this might improve patients' total adherence to the treatment program and could contribute to

construct and promote "telemedicine." Third, the total development costs of the app are much lower than that of medical drugs or medical devices. These apps are highly cost-effective and might reduce burgeoning medical costs [3].

Improving nicotine dependence treatment programs with therapeutic smartphone apps and IoT devices is important in terms of preventing chronic obstructive pulmonary disease, cardio- and cerebrovascular diseases, and malignant tumors. In addition, these mobile apps and devices can contribute to preventing secondhand smoke, which kills approximately 15,000

people every year in Japan [3]. In addition, our device can be a pioneer of the stand-alone programmed medical device with better treatment outcomes. Improving medical outcomes with mobile apps and devices is challenging; however, it can become a highly cost-effective treatment option in the near future. We believe that CASC, which is a combination of a smartphone app, a Web-based patient management software, and a mobile CO checker, will be able to improve the CAR, decrease smoking prevalence and passive smoking, and reduce future total medical costs, while preventing smoking-related diseases in the world.

## Acknowledgments

## Conflicts of Interest

This trial is supported by CureApp, Inc. AN has received consulting fees from CureApp, Inc. HT and KF have received honoraria from CureApp, Inc. TM is an employee of CureApp, Inc. KS and SS are the founders and shareholders of CureApp, Inc. and patent holders of the CASC. EH has a consultation contract as a biostatistician with CureApp, Inc. KM has nothing to disclose.

## References

1. Ikeda N, Inoue M, Iso H, Ikeda S, Satoh T, Noda M, et al. Adult mortality attributable to preventable risk factors for non-communicable diseases and injuries in Japan: a comparative risk assessment. PLoS Med 2012 Jan;9(1):e1001160 [FREE Full text] [doi: 10.1371/journal.pmed.1001160] [Medline: 22291576]

2. Ikeda N, Saito E, Kondo N, Inoue M, Ikeda S, Satoh T, et al. What has made the population of Japan healthy? Lancet 2011 Sep 17;378(9796):1094-1105. [doi: 10.1016/S0140-6736(11)61055-6] [Medline: 21885105]

3. Nakamura M. Promoting Tobacco Control for Preventing Passive Smoking: Summary Report (Japanese). 2016. URL: https://mhlw-grants.niph.go.jp/niph/search/NIDD02.do?resrchNum=201608009A [accessed 2018-12-07] [WebCite Cache ID 74U5DtNpT]

4. Igarashi A, Takuma H, Fukuda T, Tsutani K. Cost-utility analysis of varenicline, an oral smoking-cessation drug, in Japan. Pharmacoeconomics 2009;27(3):247-261. [doi: 10.2165/00019053-200927030-00007] [Medline: 19354344]

5. The Standard Procedure Book for Smoking Cessation, 6th edition (Japanese). 2014 Apr. URL: https://www.jrs.or.jp/uploads/uploads/files/information/non-smoking_06.pdf [accessed 2018-12-10] [WebCite Cache ID 74ZVOvjoU]

6. Ministry of Health, Labour and Welfare (Japan). 2017. Report on the Efficacy of Smoking Cessation Treatment Based on Nicotine Dependency Management Fee URL: https://www.mhlw.go.jp/file/05-Shingikai-12404000-Hokenkyoku-Iryouka/0000192293.pdf [accessed 2018-12-07] [WebCite Cache ID 74U5NcjPx]

7. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR, Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006 Jul 05;296(1):64-71. [doi: 10.1001/jama.296.1.64] [Medline: 16820548]

8. Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves KR. Efficacy and tolerability of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. Clin Ther 2007 Jun;29(6):1040-1056. [doi: 10.1016/j.clinthera.2007.06.012] [Medline: 17692720]

9. Quinn CC, Clough SS, Minor JM, Lender D, Okafor MC, Gruber-Baldini A. WellDoc mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. Diabetes Technol Ther 2008 Jun;10(3):160-168. [doi: 10.1089/dia.2008.0283] [Medline: 18473689]

10. Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL. Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. Diabetes Care 2011 Sep;34(9):1934-1942 [FREE Full text] [doi: 10.2337/dc11-0366] [Medline: 21788632]

11. Ebert DD, Zarski A, Christensen H, Stikkelbroek Y, Cuijpers P, Berking M, et al. Internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. PLoS One 2015;10(3):e0119895 [FREE Full text] [doi: 10.1371/journal.pone.0119895] [Medline: 25786025]

12. Bricker JB, Mull KE, Kientz JA, Vilardaga R, Mercer LD, Akioka KJ, et al. Randomized, controlled pilot trial of a smartphone app for smoking cessation using acceptance and commitment therapy. Drug Alcohol Depend 2014 Oct 1;143:87-94. [doi: 10.1016/j.drugalcdep.2014.07.006] [Medline: 25085225]

13. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet 2011 Jul 2;378(9785):49-55 [FREE Full text] [doi: 10.1016/S0140-6736(11)60701-0] [Medline: 21722952]

14. Masaki K. Preliminary Report of a Smartphone Application "CureApp" for Smoking Cessation. 2017 Presented at: American Thoracic Society; 05/24/2017; Washington, USA.

15. Masaki K, Tateno H, Kameyama N, Morino E, Watanabe R, Sekine K, et al. Impact of a Novel Smartphone Application "CureApp Smoking Cessation" on Nicotine Dependence: Prospective Single-arm Interventional Pilot Study. JMIR mHealth uHealth 2018. [doi: 10.2196/preprints.12694] [Medline: 30181109]

16. Masaki K, Tateno H, Morino E. Multi-center, Single-Arm Study to Evaluate Efficacy of Smartphone Application "CureApp" for Smoking Cessation: Interium Report. 2017 Presented at: The 634th Kanto Reginal Meeting, Japanese Society of Internal Medicine; 07/09/2017; Tokyo, Japan.

17. Masaki K, Tateno H, Kameyama N. A Multi-center, Single-Arm Study to Evaluate Efficacy of Smartphone Application "CureApp" for Smoking Cessation. 2018 Presented at: The Japanese Society of Internal Medicine, Annual Scientific Meeting; April 2018; Kyoto, Japan.

18. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology (Berl) 2004 Dec;177(1-2):195-199. [doi: 10.1007/s00213-004-1923-6] [Medline: 15179542]

19. Berlin I, Singleton EG, Heishman SJ. Validity of the 12-item French version of the Tobacco Craving Questionnaire in treatment-seeking smokers. Nicotine Tob Res 2010 May;12(5):500-507 [FREE Full text] [doi: 10.1093/ntr/ntq039] [Medline: 20335281]

20. Otani T, Yoshii C, Kano M, Kitada M, Inagaki K, Kurioka N, et al. Validity and reliability of Kano Test for Social Nicotine Dependence. Ann Epidemiol 2009 Nov;19(11):815-822. [doi: 10.1016/j.annepidem.2009.03.016] [Medline: 19457683]

21. Kawakami N, Takatsuka N, Inaba S, Shimizu H. Development of a screening questionnaire for tobacco/nicotine dependence according to ICD-10, DSM-III-R, and DSM-IV. Addict Behav 1999;24(2):155-166. [Medline: 10336098]

22. Ministry of Health, Labour and Welfare (Japan). 2008. Survey on the actual status of smoking cessation rate in medical institutions calculating insurance fee for nicotine dependence management URL: https://www.mhlw.go.jp/shingi/2008/07/dl/s0709-8k.pdf [accessed 2018-12-07] [WebCite Cache ID 74U5umcPo]

23. Iacoviello BM, Steinerman JR, Klein DB, Silver TL, Berger AG, Luo SX, et al. Clickotine, A Personalized Smartphone App for Smoking Cessation: Initial Evaluation. JMIR Mhealth Uhealth 2017 Apr 25;5(4):e56 [FREE Full text] [doi: 10.2196/mhealth.7226] [Medline: 28442453]

24. Herbeć A, Perski O, Shahab L, West R. Smokers' Views on Personal Carbon Monoxide Monitors, Associated Apps, and Their Use: An Interview and Think-Aloud Study. Int J Environ Res Public Health 2018 Dec 07;15(2) [FREE Full text] [doi: 10.3390/ijerph15020288] [Medline: 29414907]

25. Jamrozik K, Vessey M, Fowler G, Wald N, Parker G, Van Vunakis H. Controlled trial of three different antismoking interventions in general practice. Br Med J (Clin Res Ed) 1984 May 19;288(6429):1499-1503 [FREE Full text] [Medline: 6426618]

## Abbreviations

**AI:** artificial intelligence
**CAR:** continuous abstinence rate
**CASC:** CureApp Smoking Cessation
**CO:** carbon monoxide
**FTCQ-12:** 12-item French version of the Tobacco Craving Questionnaire
**IoT:** Internet of Things
**KTSND:** Kano Test for Social Nicotine Dependence
**MPSS:** Mood and Physical Symptoms Scale

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Protocol

# Discussing Weight Management With Type 2 Diabetes Patients in Primary Care Using the Small Talk Big Difference Intervention: Protocol for a Randomized Controlled Trial

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## *Abstract*

**Background:** Guidelines for the management of type 2 diabetes universally recommend that adults with type 2 diabetes and obesity be offered individualized interventions to encourage weight loss. Yet despite the existing recommendations, provision of weight management services is currently patchy around the United Kingdom and where services are available, high attrition rates are often reported. In addition, individuals often fail to take up services, that is, after discussion with a general practitioner or practice nurse, individuals are referred to the service but do not attend for an appointment. Qualitative research has identified that the initial discussion raising the issue of weight, motivating the patient, and referring to services is crucial to a successful outcome from weight management.

**Objective:** Our aim was to evaluate the effectiveness of an Internet-based training program and practice implementation toolkit with or without face-to-face training for primary care staff. The primary outcome is the change in referral rate of patients with type 2 diabetes to National Health Service adult weight management programs, 3 months pre- and postintervention.

**Methods:** We used the Behavior Change Wheel to develop an intervention for staff in primary care consisting of a 1-hour Internet-based eLearning package covering the links between obesity, type 2 diabetes, and the benefits of weight management, the treatment of diabetes in patients with obesity, specific training in raising the issue of weight, local services and referral pathways, overview of weight management components/ evidence base, and the role of the referrer. The package also includes a patient pamphlet, a discussion tool, a practice implementation checklist, and an optional 2.5-hour face-to-face training session. We have randomly assigned 100 practices in a 1:1 ratio to either have immediate access to all the resources or have access delayed for 4 months. An intention-to-treat statistical analysis will be performed.

**Results:** Recruitment to the study is now complete. We will finalize follow-up in 2018 and publish in early 2019.

**Conclusions:** This protocol describes the development and randomized evaluation of the effectiveness of an intervention to improve referral and uptake rates of weight management programs for adults with type 2 diabetes. At a time when many new

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dietary and pharmacological weight management interventions are showing large clinical benefits for people with type 2 diabetes, it is vital that primary care practitioners are willing, skilled, and able to discuss weight and make appropriate referrals to services.

**KEYWORDS**

obesity; primary care; medical education

## Introduction

Scottish Intercollegiate Guideline Network guidance recommends that "obese adults with type 2 diabetes should be offered individualized interventions to encourage weight loss (including lifestyle, pharmacological or surgical interventions) in order to improve metabolic control" [1]. Despite the existing recommendations, provision of weight management services is currently patchy around the United Kingdom [2,3]. Where services are available, high attrition rates are often reported [4]. In addition, individuals often fail to take up services even after having seemingly agreed to do so. That is, after discussion with a general practitioner (GP) or practice nurse, individuals are referred to the service but do not attend for an appointment [5].

In the National Health Service (NHS) Greater Glasgow and Clyde Health Board area of Scotland, there are currently 25,109 patients with type 2 diabetes and a body mass index (BMI) ≥30 kg/m$^2$, yet only 5855 patients with type 2 diabetes were referred to Glasgow and Clyde Weight Management Service from 2005-2014. Of those, only 1537 attended at the assessment session and only 336 completed the program and lost at least 5 kg [4].

The Glasgow and Clyde Weight Management Service delivers a specialist multidisciplinary, multicomponent, weight management program throughout the Glasgow and Clyde area of the United Kingdom. In an evaluation of the service, the authors highlighted that 27% of the patients who are referred to the program do not opt into the service [6]. This describes patients who are referred via their GP practice and do not contact the service to opt into an initial assessment. Similarly, Brook et al [7] described initial uptake and engagement of a small weight management program of 502 patients. In addition to completing an extensive questionnaire, patients were requested to call to make an appointment with the service personally. Of those referred to the program, 46% did not opt in. Engaging patients in a weight management program is especially difficult, even when the intervention is provided via the primary care route. For example, the Counterweight Project, a weight management program delivered via a GP practice, has been taken up by several practices in Scotland. However, after 2 years, one fifth of enlisted practices failed to enroll patients into the program [8].

An explorative focus group study concentrated on patients' experience of GP management of their weight problems and highlighted how patients would prefer the GP to broach the subject of weight management [9]. Patients were keen to have weight management discussed even when it made them feel embarrassed and they appeared reluctant. Participants highlighted a lack of engagement from GPs regarding weight in addition to poor knowledge regarding service resources for obesity treatment. The authors highlighted the need for GPs to acknowledge the efforts required for long-term lifestyle change while shifting attention from shame to coping. Again, obesity stigma was reported, and the authors highlighted that vulnerable feelings of failure could easily be reinforced by well-intentioned advice. Judgmental attitudes were considered to be particularly demeaning when they came from doctors. In fact, in a recent study of public perceptions of weight-related language used by health providers, 19% of participants highlighted that they would avoid further contact and 21% would seek a new doctor if they felt stigmatized about their weight from their doctor [10].

In fact, GPs may avoid discussion of weight management and lifestyle change altogether as they may feel that they have not received appropriate training to provide effective counseling [11], or they do not approach the subject if patients appear ambivalent about behavior change [12]. Studies also highlight the presence of system-level barriers such as a lack of time during consultations [13]. Even when GPs do address matters of weight-related behavior, there is often disagreement from the patient that the topic has been raised. In a sample of 456 patients, 39% of patients disagreed with GPs' reporting about the content of the discussion during consultations regarding weight, diet, and physical activity. In particular, GPs reported more occasions of discussing weight than patients in 12.5% of consultations [14]. Patients' likeliness to engage in a weight management program is also influenced by practice endorsement and opinion of the GP of the intervention available in addition to other factors: clear understanding of the program, clear understanding of the program goals, structured proactive follow-up, and perception of positive outcomes [14].

Given the importance of weight management for type 2 diabetes, we sought to develop and evaluate an intervention to improve referral rates and uptake of weight management programs for patients with type 2 diabetes and co-existent obesity (Textbox 1).

**Textbox 1.** PICOS summary.

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Participants

Primary care practices in National Health Service Greater Glasgow and Clyde, United Kingdom (at least 1 clinician per practice)

Intervention

A 1-hour eLearning program covering the benefits of weight management in type 2 diabetes, communication skills for raising the issue of weight with patients, and safe management of diabetes during weight loss; patient information pamphlets; patients discussion aid; an implementation toolkit

Comparator

Primary care practices that did not get access to the intervention

Outcomes

Primary – the ratio of referrals over 3 months before and after the Small Talk Big Difference intervention (allowing 1 month for completion)

Secondary – change in referral: uptake ratio; local enhanced service template completion (weight management discussed); change in local enhanced service template completion; completion of lifestyle weight management phase (completion defined as 80% attendance); weight change (kg and %) in lifestyle weight management phase for those attending >1 session; weight change (kg and %) at 1 year for all patients (data from annual diabetes review)

Tertiary – diabetes medications at time of referral: % on weight gaining medications (sulphonylureas, thiazolidinediones, insulin); % on weight neutral/reducing medications (GLP-1 agonists, metformin, DPP-IV inhibitors, SGLT2 inhibitors)

Exploratory – the effect of completion of training; change in referral rate analysis of those who completed Internet-based training only; when training done was completed by GP only, by practice nurse only or both; change in referral rate in those where one practice member completed Internet-based plus face-to-face training

Study Design

Individually randomized controlled trial

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# Methods

## Intervention Development

The Behavior Change Wheel [15] was used as a framework to guide the development of the intervention. It provides a systematic approach to better understand the behaviors and effectively target them. It describes 8 separate steps from defining the problem through to mode of delivery [16].

### Step 1: Define the Problem in Behavioral Terms

Low numbers of patients with type 2 diabetes are currently being referred to weight management [4]. Low numbers of those who were referred take up the offer of a place in the intervention and complete it. Referral would usually be by a GP or practice nurse in a primary care setting. As patients with type 2 diabetes

have an annual review appointment where behavioral change is meant to be discussed, it is likely that this would be the main setting for a weight management referral.

### Step 2: Selecting the Target Behavior

This step was informed by work carried out locally in Glasgow by Rhonda Wilkie (MSc project, unpublished). Eleven patients who had not taken up the offer of a place in weight management were interviewed about their reasons for not doing so. A major theme was the initial discussion with a primary care health professional about weight and weight management (Textbox 2). Other issues that were raised by the patients such as service issues (eg, time and place of the intervention) and administrative issues (eg, not receiving invitations) were deemed outside the control of the working group and were the subject of other development work within the Health Board.

**Textbox 2.** Health professionals' behaviors identified as potential targets and supporting quotes.

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**Not raising the issue of weight during a consultation or not doing so sensitively**

- "I avoid going to my GP [general practitioner] as the first thing I hear is [that] I should lose weight, which upsets me as my GP knows how much I've struggled...I have given up asking for help"

**Not informing patients they had been referred to weight management or what that involved (accurate information given)**

- "Ahh, she [GP] told me that I would be expected to attend for 2 years, every 2 weeks and eh, I wouldn't be allowed to drop out, I had to guarantee that I would stay on the program for 2 years...she did tell me it was a class of 16 or 17 people all discussing it." (incorrect information)

- "One bus, two trains and whatever transport I required from Queens park station to unit...if I had been referred nearer to home, (ie) Johnstone or Paisley, I certainly would have made the effort. Only I felt it ridiculous that a 71-year-old woman with health problems would be expected to travel to a different place to get to from her residence" (incorrect information)

- "Em, I think they [GP] just described Orlistat or whatever the drug is called and gave me a letter away with me. He didn't go into what the service was or what you could do..."

**Not supporting and encouraging patients to attend weight management and lose weight**

- "Lack of support from GP – I felt it was a way of dismissing my weight concerns, he delegated his responsibility by giving me a phone number...I have no support from my GP"

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The target behavior selected was making "informed" referrals to weight management of patients with type 2 diabetes and high BMI ($\geq 25$ kg/m$^2$) during annual diabetes review and supporting patients thereafter. It was felt that the impact of any behavior change is high, and there is a promising likelihood of being able to modify the behavior. There is also the additional benefit of spill-over to patients who have obesity but not type 2 diabetes and to other behavior change conversations such as smoking cessation. The ability to measure such a behavior change is high as the Glasgow and Clyde Weight Management Service uses electronic referrals meaning it is possible to see how many referrals are made, and "informed" can be inferred through uptake and attendance.

## Step 3: Specify the Target Behavior

The target behavior, making "informed" referrals to weight management of patients with type 2 diabetes in primary care, needs to be performed by GPs and practice nurses, in the GP practice, during annual diabetes reviews, and during routine appointments if appropriate. The clinicians need to make more referrals to weight management, approach the subject sensitively and discuss it more often, encourage patients to take up referral and attend, and bring up the topic with patients more than once if required. They need to do this with every relevant patient (once a year per patient), working as a team between GP and nurse to decide who will do it.

## Step 4: Identify What Needs to Change

This step was informed by qualitative interviews carried out as part of a health needs assessment by Public Health, NHS Greater Glasgow and Clyde, between October and December 2012. A total of 25 individuals were interviewed face to face and 2 by telephone. Participants included General Practice (Practice Nurses), Dietetics, Diabetes, Occupational Health, Cardiac Rehabilitation, Community Health (Health Improvement Team), Carers Service, Leisure Providers, and Rehabilitation. Table 1 outlines the components of the Capability, Opportunity, Motivation, and Behavior (COM-B) model with representative supporting quotations from the interviews where relevant.

**Table 1.** The components of the Capability, Opportunity, Motivation, and Behavior (COM-B) model, identified behaviors, and the need for change.

| COM-B components | What needs to happen for the target behavior to occur? | Is there a need for change? | Supporting quote(s) |
|---|---|---|---|
| Physical capability | i. None | i. No change needed | i. N/A[a] |
| Psychological capability | i. Know local pathways and what else needs to be done prior to referral (eg, medication checks)<br>ii. To inform the patient of what is going to happen to them, referrers should know components of effective weight management | i. Yes, our qualitative research shows that referrers do not know local pathways or the components of effective weight management.<br>ii. N/A | i. "I don't feel I've got the skills...it is such a specialist field...to lose weight is a big change. Sometimes the only enjoyment these people have in their life is actually food and to try and turn that on its head and see how they can support themselves, I don't feel...I have the skills to do that effectively."<br>ii. "I think further training would be better, even going to weight management classes to see what's involved so I could then tell the patient...it's alright me sitting with a patient and saying 'you've got to lose weight'...just more about healthy eating, more in depth and if I was referring someone more information so I could then tell the patient, the more information the better." |
| Physical opportunity | i. Have access to relevant patient materials to supplement referral discussions<br>ii. Have access to referral forms for weight management<br>iii. Have time to discuss the topic and make referral | i. Yes, currently such materials do not exist locally.<br>ii. No, referrals are done electronically via the standard referral system. Personal computers with this system are available in all consulting rooms in primary care and referrers will be used to using this system.<br>iii. Yes, make the discussion format as simple as possible to decrease the time required. Referral system is already quick and simple to use. | i. N/A<br>ii. N/A<br>iii. "Often patients I deal with have so many issues at one point in time, they couldn't possibly think about dealing with weight management. I think that maybe means that we end up forgetting about it." |
| Social opportunity | i. Make it part of the routine diabetes consultation carried out by all the practice team and the wider diabetes network<br>ii. Triggers to prompt discussion about weight and referral | i. Yes, would need to get everyone who sees patients with type 2 diabetes in the practice all discussing weight and making referrals. Ideally other practices (eg, within the quality improvement clusters) will also be doing this.<br>ii. No, there is already a prompt in the diabetes Chronic Disease Management Framework for behavior change, which includes recording discussions on weight management and referral to services. | i. N/A<br>ii. N/A |
| Reflective motivation | i. To want to discuss weight management and refer patients, feel that it is an essential part of their job, having confidence that they can discuss weight, and that it would be good for their patients | i. Yes, our qualitative research shows that there are issues with referrers' motivation based on their beliefs towards weight management, their perceived role and belief in their abilities. | i. "I have no idea, that's the truth…I'm limited in what I know. I can sit and discuss diet but priority in my role, I don't know." |
| Automatic motivation | i. Develop a habit of doing it | i. Yes, given referral rates are so low, it is clearly not yet a habit to discuss weight and refer patients during annual diabetes review. | i. N/A |

| COM-B components | What needs to happen for the target behavior to occur? | Is there a need for change? | Supporting quote(s) |
|---|---|---|---|
| Behavioral diagnosis of the relevant COM-B components | i. Psychological capability and reflective motivation are deemed to be the most important, with some changes required in physical opportunity, social opportunity and automatic motivation. Getting to the point where GPs and nurses want to discuss weight management and know how to discuss it and how to refer patients is key to addressing the problem | i. N/A | i. N/A |

aN/A: not applicable.

### Step 5: Identify Intervention Functions

The affordability, practicability, effectiveness/cost-effectiveness, acceptability, side-effects/safety, equity (APEASE) criteria were considered to select intervention functions. It was considered that education and training, and to a lesser degree environmental restructuring, would cover the range of behaviors identified in Step 4. Education was considered affordable, practical, and acceptable with a history of this intervention working in similar contexts. There are practical skills on the discussion of weight management that can be taught, and it is possible to develop patient materials that the referrers could have easily available.

### Step 6: Identify Policy Categories

Using APEASE criteria, policy categories were considered for each of the selected intervention functions. Communication/ marketing and service provision (education), guidelines and service provision (training), and guidelines and environmental/ social planning (environmental restructuring) all fulfilled APEASE criteria.

### Step 7: Identify Behavior Change Techniques

We identified five behavior change techniques matching the three intervention functions that were deemed necessary to improve the making of "informed" referrals to weight management of patients with type 2 diabetes in primary care: (1) information about health consequences, (2) prompts/cues, (3) demonstration of the behavior, (4) instruction on how to perform a behavior, and (5) adding objects to the environment.

### Step 8: Mode of Delivery

Individual level and group face-to-face training and an individually accessed e-learning website were the only modes of delivery that met APEASE criteria. E-learning websites would allow the intervention to be delivered to many people and is a commonly used, acceptable mode of delivery in a health care setting. Face-to-face training allows for more in-depth skills training to be given.

The Small Talk Big Difference (STBD) intervention comprises:

- a 1-hour Internet-based eLearning package covering the links between obesity, type 2 diabetes, and the benefits of weight management, the treatment of diabetes in patients with obesity, specific training in raising the issue of weight, local services and referral pathways, overview of weight management components/ evidence base, and the role of the referrer (Figures 1-4)
- training on raising the issue, with focus on three key components:
  1. Ask: seeking permission from the patient to discuss their weight
  2. Assess: determine if the patient thinks it important they manage their weight and how confident they feel about achieving weight loss; if the patient does not think it important or is not confident, provide further support and information and aim to discuss again in future
  3. Assist: make a referral to weight management and provide the patient with details of what will happen next and any requirements from the patient at this stage

- Internet-based training, which includes reference to recently published studies, case studies, and an interactive conversation with multiple choice questions to select the appropriate responses; learning will be assessed using end of module multiple choice questions
- a patient pamphlet covering the benefits of weight management in diabetes and what to expect during a weight management program
- a discussion tool with helpful facts and charts that can be used to guide a discussion about weight in a patient with type 2 diabetes
- a practice implementation checklist
- optional 2.5-hour face-to-face training building on the Internet-based module by using experiential learning to teach motivational interviewing techniques

**Figure 1.** Welcome page from Small Talk Big Difference module showing the 4 available modules.
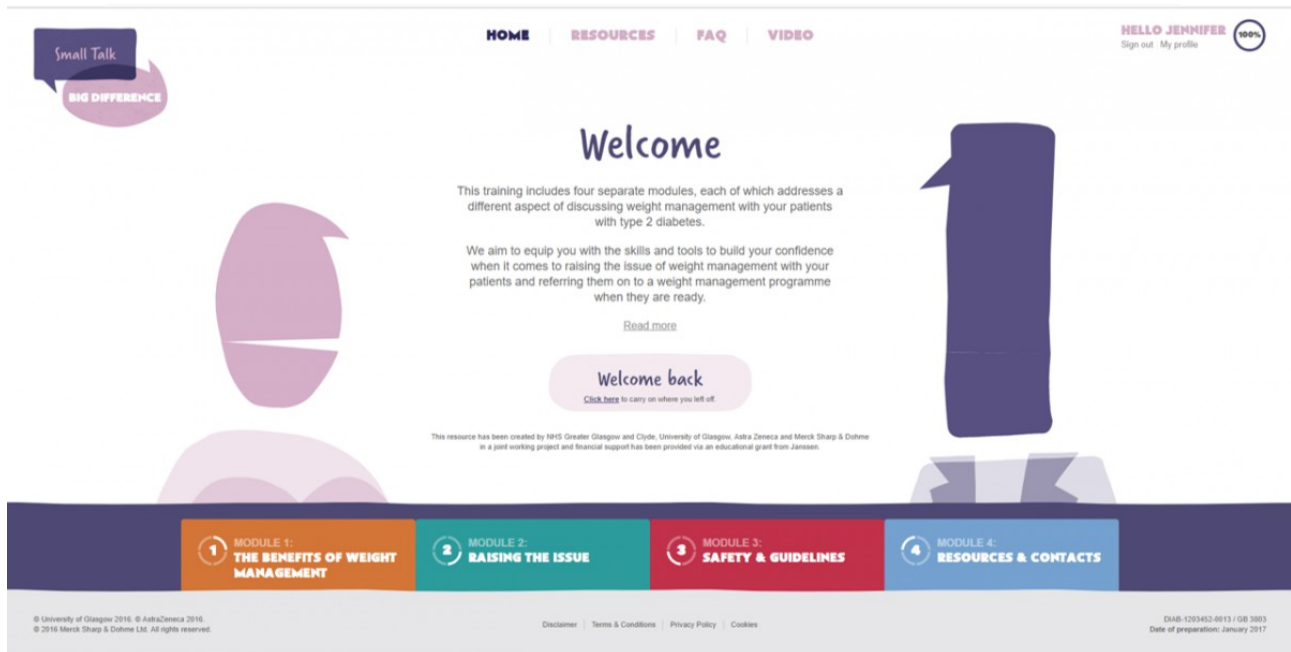


**Figure 2.** Screenshot from welcome video on Small Talk Big Difference eLearning platform.

**Figure 3.** Screenshot from module on benefits of weight management in Small Talk Big Difference eLearning platform.
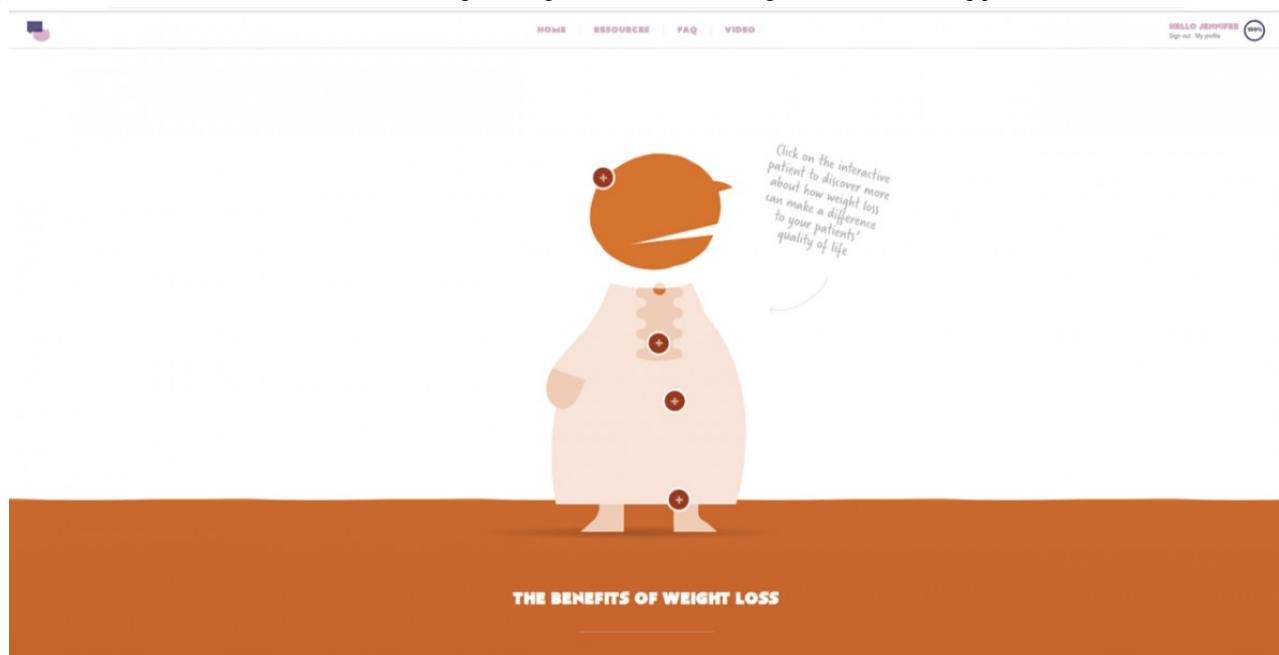


**Figure 4.** Screenshot from interactive video on communication skills in Small Talk Big Difference eLearning platform.
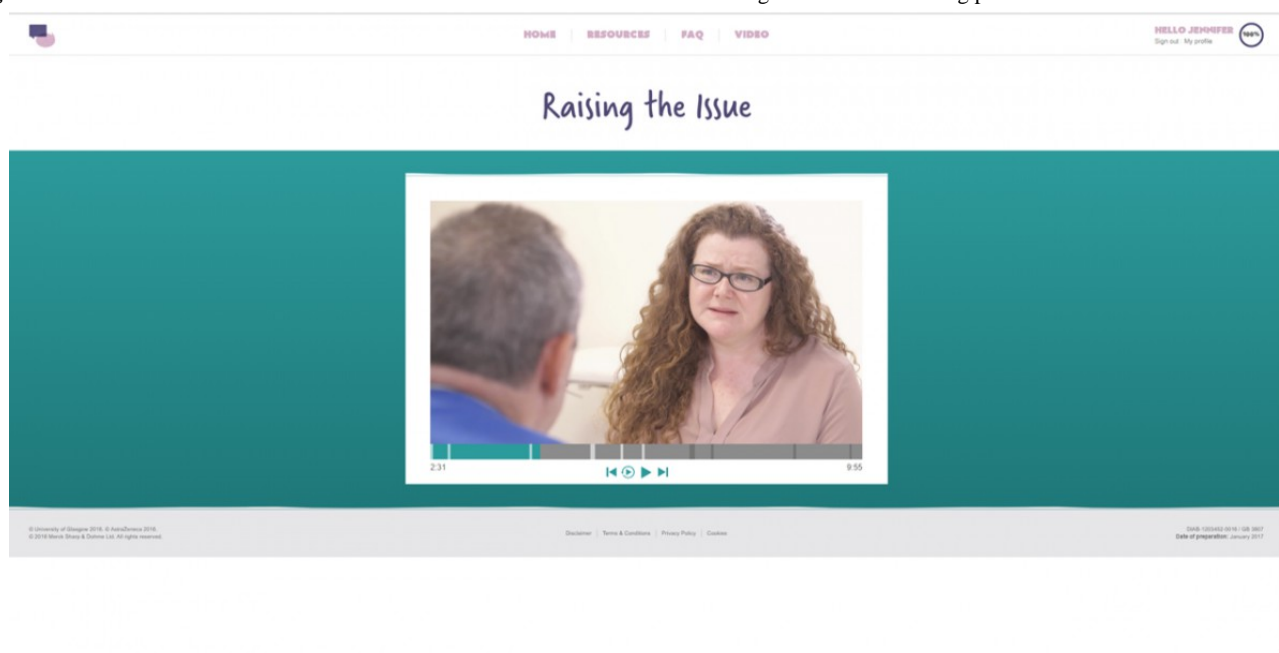


## Trial Objectives

Our aims are to (1) evaluate the effectiveness of an Internet-based training program and practice implementation toolkit with or without face-to-face training for primary care staff in terms of patient attendance at NHS-funded adult weight management services, and (2) gain clinician feedback about an Internet-based training program, practice implementation toolkit, and face-to-face training on raising the issue of weight management with patients with type 2 diabetes.

## Trial Design

A randomized trial design will be used for this evaluation with GP practices randomly assigned to one of the two arms described. We will notify clinicians of the STBD package and evaluation through primary care management, training forums, and communications. If interested, the practices will be able to opt in to the STBD evaluation via email. Once a practice has expressed interest, they will then be randomized to one of the two arms and either receive immediate access to the Internet-based training and print materials or receive access 4 months later (with awareness that their referral rates will be monitored).

The inclusion criteria for participants requires that they be GP practices in NHS Greater Glasgow and Clyde that have a contract for local enhanced services for long-term conditions (ie, diabetes) and have a unique clinical database (ie, not shared with another practice). Practices classified as "17c" (those with a separate NHS contract for long-term conditions) and those

practices with a database shared with another practice (8 practices in area) are excluded.

## Identification of Participants and Consent

As this is an evaluation study of a voluntary training program offered to GP practices as part of the usual program of NHS Health Improvement training, individual consent will not be required. By logging in to the Internet-based training website, practices will be agreeing to participate in the evaluation of the effectiveness of the training. No practices, staff, or patients will be identified during the evaluation. This information is in the letter instructing practices how to log into the training website. Patient data will be used to evaluate the outcomes of the training program, but this will be at the level of the intervention (ie, by GP practice) using health record linkage. The patient data and practice ID will be anonymized and accessed via the NHS Greater Glasgow and Clyde IT Safe Haven, so no individual patient consent will be sought.

All practices will be informed about the available training via communications from clinical directors and other routine NHS communication sources, which will explain the purpose of STBD and provide contact details to use if they are interested in completing the training. Those practices that do opt in will be randomized to one of the two arms of the evaluation. Practices gaining immediate access to the Internet-based training

will be emailed with instructions on how to access the site (Arm 1). They will also be sent a practice kit containing the print materials designed to support implementation of STBD within their practice. Those practices randomized to Arm 1 will be sent options for the supplementary face-to-face training sessions and instructions on how to book a place through NHS Greater Glasgow and Clyde Health Improvement. Practices that express an interest and are randomized to Arm 2 (ie, delayed access to the STBD training), will be notified by email that their instructions for access will be available in 4 months. They will be made aware that their referral data over the next 4 months will be analyzed as part of the evaluation. A reminder letter/email/ phone call will be sent/made to any practice that opts in and does not access or complete the Internet-based training module after 4 weeks.

It will be made clear within correspondence with practices that completion of the training is entirely voluntary and that data for referrals, weight management, and diabetes outcomes will be examined to evaluate the impact of the new Internet-based training, but neither individual practitioners nor practices will be identified in any output.

## Trial Schedule

The schedule and timeline for the trial are outlined in Table 2.

**Table 2.** Trial schedule and timeline.

| Activity | Owner | Outcome | Estimated timeline |
|---|---|---|---|
| Ad placed within primary care communication channels and forums | University of Glasgow and NHS[a] Greater Glasgow and Clyde | Notify practice of training. Opt-in of practices to evaluation | Oct 2017 |
| Randomization | University of Glasgow | Randomized practices that opt in to Arm 1 or 2 using Castor Electronic Data Capture | Oct 2017-Apr 2018 |
| Practices notified of arm for evaluation | University of Glasgow | Practices informed if they are immediate or delayed access to training by email | Oct 2017-Apr 2018 |
| Arm 1: Practices sent patient materials, posters, and invited to complete Internet-based training with or without face-to-face training | NHS Greater Glasgow and Clyde Health Improvement | Practices randomized to Arm 1 or 2 invited to complete training | Oct 2017-May 2018 |
| Notification of completion of Internet-based training (Arm 1) | University of Glasgow | Website analytics notifies research team of Internet-based training completion by practice code | Oct 2017-Sept 2018 |
| Reminder notice/phone call | University of Glasgow | Practices not having completed the Internet-based training will be sent a reminder and also the practice will be phoned once | Nov 2017-May 2018 |
| Provision of face-to-face training (Arm 1) | NHS Greater Glasgow and Clyde Health Improvement | Notification of attendees provided to NHS team | A study-specific face-to-face training session available every 2 months Oct 2017-Jun 2018 |
| Access to referral data | NHS Safe Haven | Statistician has remote access to anonymized data via a virtual private network | Oct 2018 |
| Comparison of change in referral rate (Arms 1 vs 2) | Statistician | Report of results | Dec 2018 |

[a]NHS: National Health Service.

## Randomization

Practices will be randomized to immediate or delayed intervention using the Internet-based random allocation software (Castor Electronic Data Capture) using permuted random block sizes of 4.

## Outcome Measures

The primary outcome is change in primary care referral rate to an adult NHS weight management service. Using data from the weight management database held by NHS Greater Glasgow and Clyde, the ratio of referrals over 3 months before and after the STBD intervention (allowing 1 month for completion) will be calculated. Secondary outcome measures include change in referral, including uptake ratio, local enhanced service template completion (weight management discussed); change in local enhanced service template completion; completion of lifestyle weight management phase (completion defined as 80% attendance); weight change (kg and %) in lifestyle weight management phase for those attending >1 session; and weight change (kg and %) at 1 year for all patients (data from annual diabetes review). Tertiary outcomes include diabetes medications at time of referral, that is percentage on weight gaining medications (sulphonylureas, thiazolidinediones, insulin), and percentage on weight neutral/reducing medications (GLP-1 agonists, metformin, DPP-IV inhibitors, SGLT2 inhibitors). Exploratory analyses (before and after) will be carried out to look at the effect of completion of training; change in referral rate analysis of those who completed Internet-based training only; when training done was completed by GP only, by practice nurse only or both; and change in referral rate in those where one practice member completed Internet-based plus face-to-face training.

## Sample Size

A feasibility study was completed during which five practices (from a range of current referral rates to weight management services and deprivation areas in NHS Greater Glasgow and Clyde) were provided with access to the STBD e-learning program in June 2016. A GP and practice nurse from each attended a 2.5-hour face-to-face training session, and the practices were provided with the implementation toolkit. The referral rate to uptake was assessed for the 3 months prior to the STBD training (March-May 2016), 3 months post- STBD training (October-December 2016), and the same 3 months in 2015 (October-December 2015). We saw an increase in referrals of 50% compared to same period the year before (n=8 and 15 referrals respectively) and 88% compared to previous 3 months (n=10 and 15 referrals respectively) after the STBD intervention. Two practices did not make any referrals in the immediate time period analyzed prior to the intervention. As a result of this, together with the small number of feasibility practices, it was difficult to make a formal power calculation. The effect compared to same period 12 months before was 1.5 (SD 1.21); effect compared to 3 months previous was 1.88 (SD 0.38). A sample size of 80 per group would give 80% power to detect a difference of 0.5 in the change in referral rate based on a hypothetical SD of 1.12.

## Statistics

Comparisons between study arms will be by independent two-sample $t$ tests or appropriate nonparametric equivalents using the prespecified comparisons.

## Study Closure

The evaluation will end 15 months after the practices are invited to participate, to allow time for training, changes in practice, and patient attendance at services.

## Data Handling

We have prepared a custom electronic case report form for the purposes of randomizing the practices to immediate or delayed access to STBD training at the point of opting in. The remaining data for use in this evaluation will be from routine health records (ie, weight management and diabetes care). Access to these data will be via the NHS Greater Glasgow and Clyde Safe Haven (already approved by the Local Privacy Advisory Committee). The data will be fully anonymized and accessed via a virtual private network. Access will be only for the duration of the analysis of the data for the evaluation.

## Review of the E-Learning, Patient Materials, and Evaluation

The STBD training and patient materials packages were developed over 2 years. The contents of the materials were developed by the NHS clinical team including a consultant physician, a GP, a consultant psychologist, specialist dietitian, and a health improvement specialist. Review has been extensive with patient materials reviewed by 7 patient volunteers (with type 2 diabetes and co-existing obesity), the training materials were reviewed by 3 specialist dietitians and 3 health improvement specialists, and then by 8 GPs who are based outside of NHS Greater Glasgow and Clyde. All materials were extensively reviewed by medical and marketing staff from AstraZeneca and Merck Sharp & Dohme to ensure they complied with the Association of British Pharmaceutical Industry code of practice. Evaluation plans had oversight from the evaluation team within NHS Greater Glasgow and Clyde Public Health. After the pilot study was conducted, the e-learning was independently reviewed and approved for continuous professional development points from both the Royal College of Nursing and the Royal College of General Practitioners.

## Approvals

Favorable ethical opinion was received from London – Bromley Research Ethics Committee. Sponsorship and management approval were received from NHS Greater Glasgow and Clyde. NHS Greater Glasgow and Clyde and Glasgow University Insurance and Indemnity will apply.

## Results

The first invitations for this evaluation were emailed in October 2017. Recruitment for this trial closed in April 2018. As there was an extremely large response to the single invitation email from the Primary Care Diabetes Lead sent in March 2018, to avoid discouraging willing practices we decided to extend the

trial to include 100 practices (50 per arm). Follow-up is ongoing and linkage of practice data with referral data was completed by October 2018. It is expected that the trial will report in early 2019.

## Discussion

### Principal Considerations

While the concept of providing training in behavior change techniques and of promoting referrals to services such as weight management to staff working in primary care is not new, to date there have been no interventions that have been evaluated to assess if they are effective at improving rates of referrals and clinical outcomes for patients [17]. While the primary outcomes will be change in referral rates to weight management, secondary outcomes will include weight change and diabetes medications outcomes for referred patients, obtained via health record linkage and de-anonymized. This trial comes at a time when there is strong interest both in weight management for people with type 2 diabetes and in reducing weight stigma in health care interactions and more widely. New interventions for weight management and type 2 diabetes show very promising results [9,18,19]; however, they are Phase 2 and 3 trials with recruited volunteers. The challenge occurs when moving these interventions to real-world settings. To access the benefits of such new interventions, the patients' usual care providers, normally primary care, will have to raise the issue and discuss weight, weight management, and know how and where to refer patients to. Unless this becomes universal, there will be inequity of access to these promising new treatments.

The trial is an evaluation of an intervention that has been developed and delivered by the health care teams usually responsible for delivering practitioner education. All email communications inviting practices to participate were sent by the usual primary care communication channels in the usual weekly newsletters. There was no separate consent process and no research visits or assessments. The entire process has been true to how it would be delivered outside of the intervention. By including 100 of 260 practices in the area, we believe it will be representative of primary care, rather than just an interested few practices.

### Limitations

One current limitation is the lack of a detailed process evaluation. We have some useful data available such as details of who has accessed the website and completed each of the modules, records of any requests for additional patient pamphlets or other materials, and full details of referral, uptake, and completion of weight management alongside electronic diabetes care records. If the intervention is not shown to be effective, it will be important to better understand what contributed to that lack of success, probably requiring interviews with practitioners and patients and even observation or recording of consultations.

### Conclusion

We hope that if this evaluation shows that the Small Talk Big Difference intervention is effective, it will be shared with other health bodies across the United Kingdom and beyond for wide dissemination. It is locally editable and easy to update, meaning that it could be modified to fit other health systems if required.

### Conflicts of Interest

None declared.

### References

1.  Healthcare Improvement Scotland. Management of Diabetes 116 - A National Clinical Guideline. Vol 115. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2010. URL: http://www.sign.ac.uk/pdf/sign116.pdf [accessed 2018-12-03] [WebCite Cache ID 74OKt86TS]
2.  Public Health England. National mapping of weight management services. 2015. URL: https://www.gov.uk/government/publications/weight-management-services-national-mapping [accessed 2018-12-02] [WebCite Cache ID 74NEXAZ2x]
3.  Read S, Logue J. Variations in weight management services in Scotland: a national survey of weight management provision. J Public Health (Oxf) 2016 Dec;38(3):e325-e335. [doi: 10.1093/pubmed/fdv132] [Medline: 26386909]
4.  Botha S, Forde L, MacNaughton S, Shearer R, Lindsay R, Sattar N, et al. Effect of non-surgical weight management on weight and glycaemic control in people with type 2 diabetes: A comparison of interventional and non-interventional outcomes at 3 years. Diabetes Obes Metab 2018 Dec;20(4):879-888. [doi: 10.1111/dom.13171] [Medline: 29178635]
5.  Blane DN, McLoone P, Morrison D, Macdonald S, O'Donnell CA. Patient and practice characteristics predicting attendance and completion at a specialist weight management service in the UK: a cross-sectional study. BMJ Open 2017 Nov 20;7(11):e018286 [FREE Full text] [doi: 10.1136/bmjopen-2017-018286] [Medline: 29162575]
6.  Morrison DS, Boyle S, Morrison C, Allardice G, Greenlaw N, Forde L. Evaluation of the first phase of a specialist weight management programme in the UK National Health Service: prospective cohort study. Public Health Nutr 2012 Jan;15(1):28-38. [doi: 10.1017/S1368980011001625] [Medline: 21806868]

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7.  Brook E, Cohen L, Hakendorf P, Wittert G, Thompson C. Predictors of attendance at an obesity clinic and subsequent weight change. BMC Health Serv Res 2014 Feb 20;14:78 [FREE Full text] [doi: 10.1186/1472-6963-14-78] [Medline: 24552252]

8.  Counterweight Project Team. Evaluation of the Counterweight Programme for obesity management in primary care: a starting point for continuous improvement. Br J Gen Pract 2008 Aug;58(553):548-554 [FREE Full text] [doi: 10.3399/bjgp08X319710] [Medline: 18682018]

9.  Tan D, Zwar NA, Dennis SM, Vagholkar S. Weight management in general practice: what do patients want? Med J Aust 2006 Jul 17;185(2):73-75. [Medline: 16842059]

10. Puhl R, Peterson JL, Luedicke J. Motivating or stigmatizing? Public perceptions of weight-related language used by health providers. Int J Obes (Lond) 2013 Apr;37(4):612-619. [doi: 10.1038/ijo.2012.110] [Medline: 22777543]

11. Forman-Hoffman V, Little A, Wahls T. Barriers to obesity management: a pilot study of primary care clinicians. BMC Fam Pract 2006 Jun 06;7:35 [FREE Full text] [doi: 10.1186/1471-2296-7-35] [Medline: 16756673]

12. Laidlaw A, McHale C, Locke H, Cecil J. Talk weight: an observational study of communication about patient weight in primary care consultations. Prim Health Care Res Dev 2015 May;16(3):309-315. [doi: 10.1017/S1463423614000279] [Medline: 25075809]

13. Mercer SW, Tessier S. A qualitative study of general practitioners' and practice nurses' attitudes to obesity management in primary care. Health Bull (Edinb) 2001 Jul;59(4):248-253. [Medline: 12664735]

14. Greiner KA, Born W, Hall S, Hou Q, Kimminau KS, Ahluwalia JS. Discussing weight with obese primary care patients: physician and patient perceptions. J Gen Intern Med 2008 May;23(5):581-587 [FREE Full text] [doi: 10.1007/s11606-008-0553-9] [Medline: 18322760]

15. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011 Apr 23;6:42 [FREE Full text] [doi: 10.1186/1748-5908-6-42] [Medline: 21513547]

16. Michie S, Atkins L, West R. The Behaviour Change Wheel. Great Britain: Silverback Publishing; 2014.

17. Blane DN, Macdonald S, Morrison D, O'Donnell CA. Interventions targeted at primary care practitioners to improve the identification and referral of patients with co-morbid obesity: a realist review protocol. Syst Rev 2015 May 01;4:61 [FREE Full text] [doi: 10.1186/s13643-015-0046-y] [Medline: 25927993]

18. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet 2018 Dec 25;392(10148):637-649. [doi: 10.1016/S0140-6736(18)31773-2] [Medline: 30122305]

19. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018 Dec 10;391(10120):541-551. [doi: 10.1016/S0140-6736(17)33102-1] [Medline: 29221645]

## Abbreviations

**APEASE:** affordability, practicability, effectiveness/cost-effectiveness, acceptability, side-effects/safety, equity
**BMI:** body mass index
**COM-B:** Capability, Opportunity, Motivation, and Behavior
**GP:** general practitioner
**NHS:** National Health Service
**STBD:** Small Talk Big Difference

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Protocol

# Improving Nutrition and Activity Behaviors Using Digital Technology and Tailored Feedback: Protocol for the Tailored Diet and Activity (ToDAy) Randomized Controlled Trial

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**Related Article:**

This is a corrected version. See correction statement: https://www.researchprotocols.org/2020/12/e25940

## *Abstract*

**Background:** Excess weight is a major risk factor for chronic diseases. In Australia, over 60% of adults are overweight or obese. The overconsumption of energy-dense nutrient-poor (EDNP) foods and low physical activity (PA) levels are key factors contributing to population obesity. New cost-effective approaches to improve population diet and PA behaviors are needed.

**Objective:** This 1-year randomized controlled trial (6-month intervention and 6-month follow-up) aims to investigate whether a tailored intervention using mobile technology can improve diet and PA behaviors leading to weight loss in adults (aged 18-65 years) who are overweight or obese and recruited through a social marketing campaign (LiveLighter).

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**Methods:**  All eligible participants will provide data on demographics and lifestyle behaviors online at baseline, 6 months, and 12 months. Using two-stage randomization, participants will be allocated into one of three conditions (n=200 per group): tailored feedback delivered via email at seven time points, informed by objective dietary (mobile food record app) and activity (wearable activity monitor) assessment; active control receiving no tailored feedback, but undergoing the same objective assessments as tailored feedback; and online control receiving no tailored feedback or objective assessments. Primary outcome measures at 6 and 12 months are changes in body mass, EDNP food and beverage consumption, and daily moderate-to-vigorous PA (measured via accelerometry). Secondary outcomes include change in fruit and vegetable consumption, daily sedentary behaviors, and cost effectiveness.

**Results:**  Enrolment commenced in August 2017. Primary outcomes at 12 months will be available for analysis from September 2019.

**Conclusions:**  Tailored email feedback provided to individuals may deliver a cost-effective strategy to overcome existing barriers to improving diet and PA. If found to be successful and cost effective, upscaling this intervention for inclusion in larger-scale interventions is highly feasible.

**Trial Registration:**   Australian New Zealand Clinical Trials Registry ACTRN12617000554369; https://www.anzctr.org.au /Trial/Registration/TrialReview.aspx?id=371325&isReview=true

**International Registered Report Identifier (IRRID):**  DERR1-10.2196/12782

## Introduction

### Background

Excess weight is a major risk factor for chronic disease. Recent data indicate that more than 63% of Australian adults are overweight or obese, with higher rates observed in men than in women (68% versus 55%) [1]. The five leading attributable risk factors for burden of disease in Australia are poor diet, high body mass index (BMI), tobacco smoking, high blood pressure, and insufficient physical activity (PA) [2]. Of these factors, diet and PA are recognized as key factors for achieving energy balance in the complex development of overweight and obesity [3]. The 2011-2012 National Nutrition Survey reported that just over half of the adults met the recommendations for two serves of fruit, and only 7% met the recommended intake of five serves of vegetables [4]. Furthermore, 35% of the daily energy intake consumed was from "discretionary foods" (foods considered to be of little nutritional value; often high in saturated fats, added sugar, and salt; and alcohol or "junk" foods) [4]. With respect to PA, in 2011-2012, just 40% of adults met the recommended 30 minutes of daily moderate-to-vigorous PA (MVPA), and only 19% of adults achieved the recommended 10,000 steps per day [5]. Equally concerning, given the link between sedentary behavior, chronic disease, and obesity, 30% of adults reported engaging in more than 5 hours of sedentary leisure activity each day [5].

### Interventions in Overweight and Obese Populations

Key components of effective nutrition and PA behavioral change interventions include self-monitoring, feedback on performance, and goal setting [6-11]. More recently, there has been a move towards digital interventions utilizing mobile technology (eg, mobile apps and short message service [SMS] messaging) to improve population reach, real-time data collection, and feedback delivery [12]. Cost efficiency is a major potential strength of such interventions, and the challenge of ensuring design and implementation is supported by strong theoretical constructs. Although a plethora of healthy eating and weight-loss apps have become available, many lack behavioral strategies in their design [13]. A qualitative review of effective technology-based weight-loss interventions identified five key features related to effectiveness: self-monitoring, positive feedback, social support, controlled program content, and individually tailored feedback [14].

Tailored nutrition and PA interventions have shown promise for behavioral change; nonetheless, the effect size has been small, and most interventions thus far lack objective measures of PA [15-18]. Typically, feedback on behavior change is taken from self-report questionnaires, limiting the scope and relevance of individual diet and PA feedback. With the rapid advances in digital technologies, alternative mediums for delivery of information are now possible, including the use of images and other visual elements [19]. Therefore, interventions incorporating digital features provide a platform to test this concept and address concerns raised about the lack of models to inform the design of digital behavioral interventions [20,21]. For instance, a 6-month tailored intervention using the mobile food record (mFR) app for dietary assessment and tailored feedback improved the diet of young adults [22]. Features such as usability and willingness to continue to use apps may contribute to greater engagement and motivation enhancement by participants [20]. To date, few digital interventions have addressed both diet and PA behaviors together in an overweight population [9,23,24]. A unique aspect of this study is the detailed assessment of dietary intake and PA behaviors to inform tailored feedback.

### Aim

This study will use mobile technologies to undertake detailed assessment of dietary intake and PA behaviors and use these

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data to formulate personalized tailored feedback for study participants. The overall aim of this 1-year randomized controlled trial (RCT) is to investigate whether a tailored intervention using mobile technology can improve diet and PA behaviors in adults with overweight or obesity, recruited through the LiveLighter social marketing campaign in Perth, Western Australia.

## Methods

### Study Design

This study is a 1-year RCT with a 6-month intervention and 6-month follow-up. Individuals who enroll via the LiveLighter website [25] will be invited to participate and, if eligible, will be randomized to one of three groups: (1) tailored feedback delivered via email at seven time points informed by objective dietary intake (mFR app) and activity (wearable activity monitor); (2) active control receiving no tailored feedback, but undergoing the same objective dietary and activity assessment as tailored feedback; and (3) online control receiving no tailored feedback or objective assessments (Figure 1). All groups will have access to publically available resources via the LiveLighter website. The inclusion of the online control group will distinguish monitoring and tailoring effects from those elicited by exposure to the LiveLighter social marketing campaign and website materials. The project protocol has been approved by the Curtin University Human Research Ethics Committee (approval number HR61/2016) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000554369).

### Recruitment

Participants in the Perth metropolitan area will be recruited using the LiveLighter website [25], LiveLighter social media campaigns, letter-box drops, and radio interviews directing interested individuals to further information and study registration on the LiveLighter website (Western Australia). Potential participants will complete an online consent and screening questionnaire. Staggered recruitment will take place over a 12-month period. To be eligible, participants must be aged 18-65 years, have a BMI $\geq$ 25 but <40 kg/m$^2$, own a mobile telephone (iPhone or Android phone), be able to engage in regular PA, have internet access, and be available to visit a study center in metropolitan Perth. Participants will be excluded on the basis of serious illness or medical conditions including diabetes requiring insulin, renal disease, liver disease; weight loss > 4 kg in the previous 2 months; appetite suppressant use, weight loss, or hormone-replacement medication use; pregnancy or current breastfeeding; current tobacco smoking; daily alcohol consumption > 5 standard drinks; prior or planned weight loss surgery; and regular use of an activity monitor in the previous 12 months.

**Figure 1.** Study design with randomization to three groups. TF: tailored feedback; AC: active control; OC: online control.
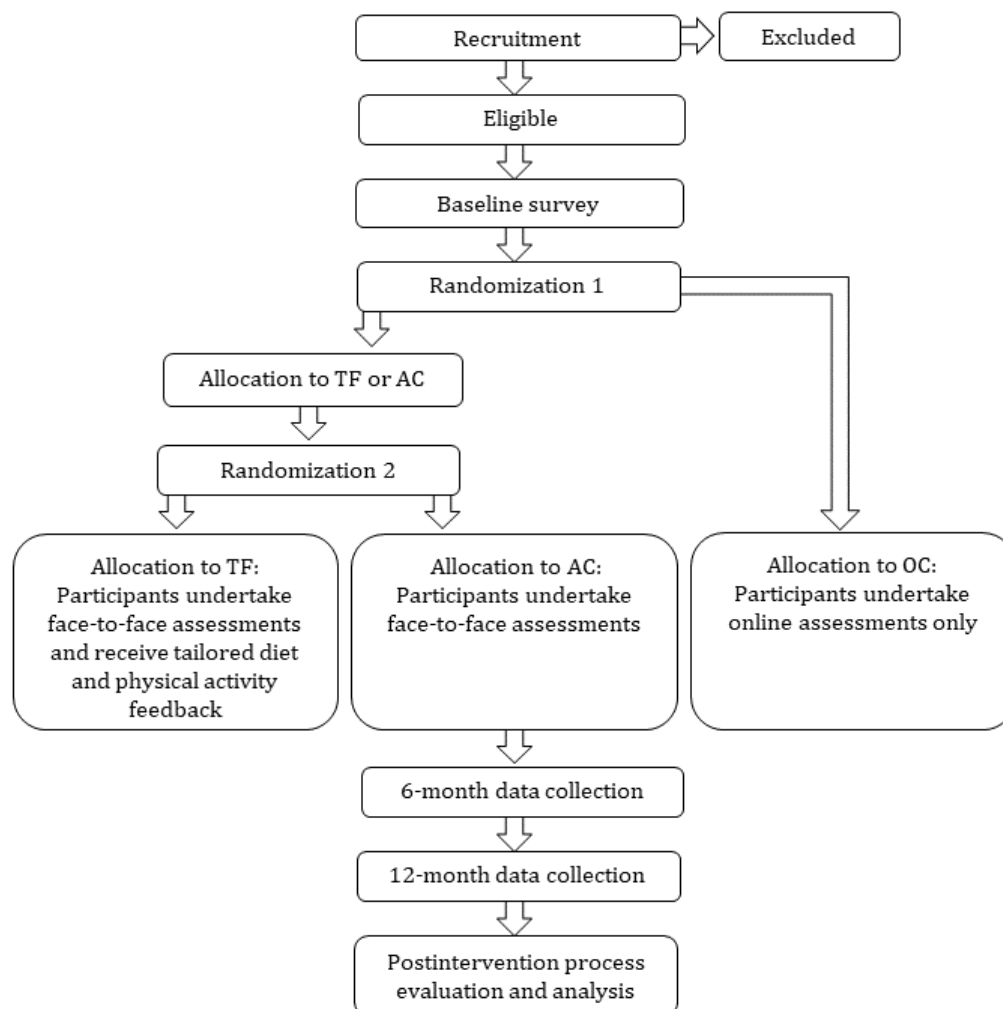


## Randomization

A two-staged block randomization will be used with allocation concealment from the active research team via the use of sealed opaque envelopes. The first randomization will be in blocks of six, with separate sex randomization. Second randomization will be in blocks of four, again with separate sex randomization. Eligible participants will be notified via email and invited to complete an online demographic and lifestyle behaviors questionnaire, as detailed in Table 1, prior to stage 1 randomization to either online control (n=200) or face-to-face (n=400) groups. Stage two randomization will occur at the second study visit to assign face-to-face participants to either tailored feedback or active control. Due to the nature of the intervention, it is not possible to blind participants or researchers to the intervention group postallocation. Sequence generation will be conducted by a biostatistician not involved in the implementation of the trial on site using a randomization table created in Stata (version 15, StataCorp, College Station, TX). The electronic file will be kept in a secure password-protected server by the statistician.

## Data-Collection Procedures

Following stage 1 randomization, tailored feedback and active control participants will be invited to attend two data-collection sessions with the research team, approximately 1 week apart. At the first baseline visit, participants will receive training in the use of the 4-day mFR [26-28] and hip-worn GT3X+ accelerometer (Actigraph, Pensacola, FL). During the second study visit, participants will return their accelerometer and be interviewed to clarify the content of their mFR images. At this visit, height, body mass, waist, and hip girth will be measured according to the standard protocol [29], and an aerobic fitness test (6-minute walk test) will be conducted [30]. The same assessments will be repeated at 6 and 12 months, along with additional online assessments for all groups (Table 1) at the same time points. All participants will have access to the LiveLighter website resources throughout the intervention and will be encouraged to use the materials that include evidence-based healthy recipes and meal plans [25].

## Research Study Database

A purpose-built research study database will be developed based on findings from prior research [44] using a Microsoft Access database platform to track the progress of the study participants

at time points outlined in Tables 1 and 2. The database will have the functionality of sending autogenerated emails containing study information and links. To track progress of the tailored feedback group requiring face-to-face visits, information regarding upcoming appointment date and time and relevant survey URLs will be sent using autogenerated emails. To remind participants of upcoming appointments, email and mobile SMS prompts will be sent from the study database using "Email to SMS" technology.

An online survey tool (Qualtrics) will be used to capture demographic information as outlined in Table 1. The study database will have the functionality of importing data to automatically update participant status with respect to their study compliance. The system will prompt reminders via email and SMS for participants who have not yet completed their tasks.

## Dietary Assessment

For the face-to-face (active control and tailored feedback) groups, diet will be recorded using the mFR app with inclusion of a fiducial marker (an object of known shape, size, and color) [26] in the image to aid in portion size estimation. "Before eating" and "after eating" images of all foods and beverages consumed over four consecutive days, including one weekend day, will be captured at baseline, 6 months, and 12 months for each participant. In addition, at 6, 12, 18, and 24 weeks, the tailored feedback group will complete a 1-day mFR to encourage self-monitoring of food intake to facilitate feedback. All images will be automatically uploaded to a secure cloud server residing on the Curtin University Bentley campus via Wi-Fi or 3G/4G network. All images will be assessed by a research dietitian for serves of fruits, vegetables, and energy-dense nutrient-poor (EDNP) foods and beverages according to the Australian Guide to Healthy Eating standard serves (one serve=600 kJ) [45].

## Physical Activity Assessment

Physical activity and sedentary behavior will be assessed with a hip-worn Actigraph GT3X+ accelerometer to quantify change in average MVPA and sedentary time for the face-to-face (active control and tailored feedback) groups. The accelerometer will also enable the assessment of sleep. The participants will be instructed to wear the accelerometer on their right hip 24/7 for 7 consecutive days. Commonly used cut-off points will be used to classify each minute of accelerometer data as sedentary (<100 counts per minute) [46], light intensity (100-1951 counts per minute), moderate intensity (1952-5724 counts per minute), or vigorous intensity (>5724 counts per minute) [47].

A wrist-worn activity monitor (Fitbit Charge 2) will be provided to the tailored feedback group to enable 24/7 continuous self- and researcher monitoring of step count, MVPA, and hourly movement to inform PA feedback. Participants will be asked to wear the monitor at night to enable the assessment of sleep. With informed consent, activity monitor data will be automatically imported into a back-end research platform (Fitabase) to facilitate PA behavior data monitoring, extraction, and analysis by researchers.

## Intervention Content

Intervention content for diet and PA will be informed by evidence-based guidelines [48-50] to support weight loss through reduced energy intake and increased PA. The behavioral intervention technology framework Capability, Opportunity, Motivation, and Behaviour (COM-B) model; self-determination theory; and previous research will guide the development of intervention behavior-change strategies [20,22,51,52]. These include self-monitoring, goal setting, motivation enhancement (including positive reinforcement in tailoring communications and incentives), and feedback to increase likelihood of engagement [52]. To refine the intervention features and content, formative focus group studies with 56 consumers and health professionals were conducted prior to the intervention.

**Table 1.** Frequency of assessment of variables in the ToDAy study for the tailored feedback, active control, and online control groups.

| Variables | Group | Baseline | 6 months | 12 months |
|---|---|---|---|---|
| Health status EQ-5D[a], a 5-item scale to assess utility and health-related quality of life [31] | TF[b], AC[c], OC[d] | Yes | Yes | Yes |
| Height and body mass (self-report) | TF, AC, OC | Yes | Yes | Yes |
| Height, body mass, body mass index, waist, and hip girth[e] | TF, AC | Yes | Yes | Yes |
| Sociodemographics and personal characteristics assessed via questions on sex, age, eating behavior, educational level, country of birth, ethnicity, socioeconomic status, and financial status | TF, AC, OC | Yes | Yes | Yes |
| Australian eating survey, an online food frequency questionnaire with options for automated dietary feedback previously validated in adults [32] | TF, AC, OC | Yes | Yes | Yes |
| Dietary intake assessed by 4-day mFR[f] | TF, AC | Yes | Yes | Yes |
| Mobile food record usability to assess user feedback and method preference [33,34] | TF, AC | Yes | Yes | Yes |
| Three-factor eating survey to measure factors associated with eating behavior: cognitive restraint of eating, disinhibition, and hunger [35] | TF, AC | Yes | __[g] | — |
| Self-reported physical activity assessed via The International Physical Activity Questionnaire (short form) [36] | TF, AC, OC | Yes | Yes | Yes |
| Cardiorespiratory fitness determined by distance covered in the 6-minute walk test to assess change in submaximal exercise capacity [30] | TF, AC | Yes | Yes | Yes |
| Physical activity and sedentary behavior assessed with GT3X+ Actigraph accelerometer to quantify change in average minutes of moderate-to-vigorous physical activity and sedentary time | TF, AC | Yes | Yes | Yes |
| Sleep-quality assessment using the Pittsburgh Sleep Quality Index seven-component evaluation of sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the previous month [37] | TF, AC | — | Yes | Yes |
| Depression, anxiety, stress scale, with 21 self-report items to assess severity of depression, anxiety, and stress [38] | TF, AC, OC | Yes | Yes | Yes |
| Fear of negative evaluation, with twelve 5-point items to assess concern about being perceived unfavorably [39] | TF, AC | Yes | — | — |
| Social desirability to measure social approval and acceptance [40] | TF, AC | Yes | — | — |
| Habit Index Score [41] | TF, AC | Yes | Yes | Yes |
| Weight-loss history, an 8-item tool to assess previous weight-loss history [42] | TF, AC, OC | — | — | — |
| Technology use questionnaire to assess duration and frequency of technology use indicative of sedentary behaviors [43] | TF, AC, OC | Yes | Yes | Yes |
| Feedback evaluation questionnaire for activity-monitor usability, physical activity, and dietary feedback evaluation | TF | — | Yes | Yes |

[a]EQ-5D: EuroQol-5D.

[b]TF: tailored feedback.

[c]AC: active control.

[d]OC: online control.

[e]Height measured in centimeters via stadiometer using stretch stature method, body mass measured in kilograms via weighing scale in minimal clothing at similar time of the day, body mass index calculated as kilogram per meter squared, waist measured in in centimeters via tape at the narrowest point between the lower costal border and iliac crest, and hip girth measured via tape at the level of the greatest posterior protuberance.

[f]mFR: mobile food record.

[g]Not assessed.

**Table 2.** Overview of frequency, content, and technique of tailored email feedback for diet and physical activity behaviors.

| Feedback frequency | Feedback content | | Behavior-change techniques [52] |
|---|---|---|---|
| | Diet | Physical activity | |
| 2 weeks | • 4-d summary (average + range) from mFR[a] showing average daily serves (kilojoule equivalent) for EDNP[b] foods, sugary drinks, and alcohol<br>• Example ADG[c] serves for EDNP foods, sugary drinks, and alcohol<br>• mFR food images showing participants the source of their EDNP foods, sugary drinks, and alcohol serves<br>• Tailored feedback + goals based on key messages: avoid EDNP foods, avoid sugary drinks, avoid alcohol | • Introduction of movement goals and wearable activity monitor guide<br>• 7-d summary (average + range) for step count, MVPA[d], and hourly movement<br>• Tailored feedback + guidance based on movement goal achievement (not met, almost met, and met) | • Instruction on how to perform the behavior<br>• Feedback on behavior<br>• Tailored personalized message<br>• Prompt self-monitoring of behavior<br>• Goal setting<br>• Discrepancy between current behavior and recommendations |
| 4 weeks | • Weight loss goal of 10%<br>• 4-d summary (average + range) from mFR showing average daily serves for fruit and vegetables<br>• Example ADG serves for fruit and vegetables<br>• mFR food images showing participants the source of their fruit and vegetable intake<br>• Tailored feedback against recommended serves + goals to increase fruit and vegetable serves | • 7-d visual summary of challenge movement goal, with comparison to goal target<br>• Activity tips to assist with weight loss linked to movement goals | • Review behavior goal<br>• Feedback on behavior<br>• Action planning<br>• Prompt self-monitoring of behavior<br>• Discrepancy between current behavior and recommendations |
| 6 weeks | • 1-d summary from 6-wk mFR showing daily serves of EDNP foods, sugary drinks, alcohol, and fruits and vegetables<br>• Comparison against baseline diet<br>• mFR food images showing participants the source of their EDNP foods, sugary drinks, alcohol, fruits, and vegetables<br>• Tailored feedback against recommended serves + goals targeting:<br>• Avoid or limit EDNP foods, sugary drinks and alcohol<br>• Eat less at meals or snacks (except for fruit and vegetables)<br>• Eat less often (eg, limit snacking) | • Review of the movement goals<br>• 7-d summary (average + range) for step count, MVPA, and hourly movement<br>• Comparison with baseline activity for each movement goal<br>• Tailored feedback + guidance based on movement goal achievement (not met, almost met, and met) | • Review behavior goals<br>• Self-comparison<br>• Feedback on behavior<br>• Tailored personalized message<br>• Prompt self-monitoring of behavior<br>• Goal setting<br>• Discrepancy between current behavior and recommendations |
| 12 weeks | • 1-d summary from 12-wk mFR showing daily serves of EDNP foods, sugary drinks, alcohol<br>• mFR food images showing participants the examples of meal or snack behaviors<br>• Tailored feedback + goals targeting:<br>• Eat less at meals or snacks (except for fruits and vegetables)<br>• Avoid or limit snacking | • Reiteration of energy deficit goal + instruction on how to create an energy deficit via energy output<br>• 7-d summary (average + range) of MVPA goal<br>• Tailored feedback + guidance based on movement goal achievement (not met, almost met, and met)<br>• Translation of MVPA into energy output | • Review of outcome goal<br>• Review behavior goal<br>• Feedback on behavior<br>• Tailored personalized message<br>• Prompt self-monitoring of behavior<br>• Goal setting<br>• Discrepancy between current behavior and recommendations |

| Feedback frequency | Feedback content | | Behavior-change techniques [52] |
|---|---|---|---|
| | Diet | Physical activity | |
| 18 weeks | • Reiteration of dietary goals + instruction on how to create an energy deficit from diet (eg, reduction in EDNP food serves)<br>• Reiteration of "what's a serve of EDNP foods"<br>• Reminder of dietary goals + suggestions on how to achieve them:<br>• Avoid or limit EDNP foods, sugary drinks, and alcohol<br>• Eat less at meals or snacks (except for fruit and vegetables)<br>• Eat less often (eg, limit snacking) | • Reiteration of energy-deficit goal + instruction on how to create an energy deficit via energy output<br>• 7-d summary (average + range) of MVPA goal<br>• Tailored feedback + guidance based on movement goal achievement (not met, almost met, and met)<br>• Translation of MVPA into energy output<br>• Reminder of movement goal targets linked to creating an energy deficit | • Review of outcome goal<br>• Review behavior goals<br>• Feedback on behavior<br>• Tailored personalized message<br>• Goal setting<br>• Discrepancy between current behavior and recommendations |
| 6 months | • 4-d summary from 6-mo mFR showing daily serves with comparison against baseline diet<br>• mFR food images showing participants the source of their EDNP foods, sugary drinks, alcohol, fruits, and vegetables<br>• Tailored feedback against recommended serves + goals targeting:<br>• Avoid or limit EDNP foods, sugary drinks, and alcohol<br>• Eat less at meals or snacks (except for fruit and vegetables)<br>• Eat less often (eg, limit snacking)<br>• Tailored support for unhelpful behaviors: Emotional/restrained/uncontrolled eating (identified in the three-factor eating questionnaire)<br>• Tailored feedback on how to make a healthy diet habitual based on habit index score | • Face-to-face visit summary: comparison with baseline (body mass and aerobic fitness)<br>• 7-d visual summary (average) for step count, MVPA, and hourly movement + comparison with baseline for each movement goal<br>• Future goal setting for translation phase<br>• Tailored guidance on how to make PA habitual based on habit index score | • Review behavior goals<br>• Self-comparison<br>• Feedback on behavior<br>• Tailored personalized message<br>• Prompt self-monitoring of behavior<br>• Goal setting<br>• Discrepancy between current behavior and recommendations |
| 12 months | • 4-d summary from 12-mo mFR showing daily serves with<br>comparison against baseline<br>• Tailored feedback against recommended serves + target goals | • Face-to-face visit tabulated summary: comparison with baseline and 6 mo (body mass and aerobic fitness)<br>• 7-d visual summary (average) for step count, MVPA, and hourly movement + comparison with baseline and 6 mo for each movement goal<br>• Future goal setting for translation phase | • Review behavior goals<br>• Self-comparison<br>• Social comparison with study participants<br>• Feedback on behavior<br>• Tailored personalized message<br>• Prompt self-monitoring of behavior<br>• Goal setting<br>• Discrepancy between current behavior and recommendations |

[a]mFR: mobile food record.

[b]EDNP: energy-dense nutrient poor.

[c]ADG: Australian Dietary Guidelines.

[d]MVPA: moderate-to-vigorous physical activity.

At randomization, tailored feedback participants will be informed of feedback email frequency and content and that they may opt out of correspondence at any time by informing the research team. Email templates will be developed for each of the seven time points, containing personalized dietary and PA feedback content for each participant. Feedback will be consistent with communications from the LiveLighter campaign, Australian Dietary Guidelines, and the Australian PA and Sedentary Behavior Guidelines [48-50]. The content will address each participant's personal barriers to changing key diet and PA behaviors, reinforce motivation, and guide the adoption of health-enhancing habits. Tailored feedback on diet and PA behaviors will commence within 2 weeks of baseline and continue at 4, 6, 12, 18 weeks and 6 and 12 months thereafter. The feedback emails will be sent from Monday to Friday during business hours (9 AM to 5 PM). Components used in tailoring will include self-comparison, preference for autonomy support,

intention, motivation, confidence informed by self-determination theory, and motivational interviewing (Table 2) [52,53].

## Message Tailoring

Tailoring involves creating communications in which information about an individual is used to determine specific content he or she receives [15,54]. Positive effects of tailoring have been demonstrated in changing diet and PA behaviors [15-17,55]. The intention of tailoring, which uses characteristics unique to the individual, is to improve behavioral outcomes by altering processing or making the message more acceptable [54,56]. These characteristics can include personal behaviors, psychosocial characteristics, and dietary and PA behaviors. Specific strategies for message tailoring include personalization, feedback, and content matching [54]. This study will focus on personalized feedback (exemplified in Table 3) using information obtained on diet and PA behaviors at baseline and specific time points throughout the intervention. Digital elements (food and beverage images and graphical presentation of PA data) will be included to enable evaluation of these components.

## Tailored Dietary Feedback

Tailored dietary feedback will be formulated by the research dietitian based on food group analysis of the 4-day mFR. Feedback will focus on key messages encouraging daily energy reduction of 2000 kJ by avoiding or limiting EDNP foods, sugar-sweetened beverages, and alcohol; eating less at meals or additional snacks (except for salad and vegetables); and eating less often. Food group serves will be categorized for each participant based on three defined target zones (not achieved, almost achieved, and achieved). A template will be used for each dietary feedback email, modified according to the results of each participants' dietary analysis. For EDNP serves, the template will be modified according to dietary intake to indicate average daily serves of "junk" foods, sugary drinks, and alcohol and kilojoule intake. Participants will be shown an image of their dietary sources of EDNP food and beverages. For fruit and vegetable serves, a scripted message will be devised for three levels of intake: (1) low: 0 to <3.5 serves of fruits and vegetables, (2) medium: 3.5 to <7 serves of fruits and vegetables, and (3) meeting the recommendation: at least 2 serves of fruits and 5 serves of vegetables per day. Individual mFR images will be incorporated into email templates to illustrate the sources of EDNP foods, fruits, and vegetable serves. Two to three suggested modifications will be provided to each participant to support them in achieving the daily energy-reduction goal.

## Tailored Activity Feedback

Individual activity data will inform PA feedback based on activity monitor recordings 1 week prior to the feedback time point. The data will be automatically imported into a research platform (Fitabase) to facilitate monitoring and analysis of continuous back-end data. Messages will focus on the three movement goals: "move more" (step count; toward ≥10,000 steps), "move harder" (minutes spent in MVPA; towards ≥30 active minutes), and "move more often" (hourly movement; towards ≥250 steps per hour). Participants will receive tailored email feedback regarding their current activity, and guidance on goal progression to classify goal achievement (not achieved, almost achieved, or achieved).

## Control Groups

The online control group will complete online self-report questionnaires only, while the active control group will also undertake face-to-face data collection and record dietary intake (mFR app) and PA behaviors (accelerometery) at baseline, 6 months, and 12 months. Neither group will receive tailored messaging or feedback on their dietary intake or PA. As an incentive for retention, active control participants will be advised that they will receive feedback upon study completion, and the online control group will be entered into a 6-monthly prize draw to encourage ongoing participation.

## Economic Evaluation

An economic evaluation will be conducted to consider the relative costs and outcomes of the intervention. To facilitate a cost-utility analysis, the EuroQol-5D will be administered. This is a widely used instrument specifically designed to capture quality of life for health economics [57]. This study will use the five-level version of the instrument to identify sensitive and small, but important, changes in health-related quality of life [58]. Quality-adjusted life years will be estimated for intervention and control groups. Concerning costs, we will collect the time needed to provide tailored advice to participants, medication and supplement use (name, dose, and frequency), and family expenditure on groceries. This will allow economic evaluation from the perspective of the health system (by considering only the cost of the intervention and medication) and a broader society (by considering all costs). Univariate and multivariate sensitivity analyses will be undertaken. In particular, the impact of different methods of extrapolating costs and outcomes beyond the horizon of the trial will be assessed. The costing model will include resources required to assess ongoing maintenance of the mFR and wearable activity monitors, including changes as a result of upgrades to operating systems. We will also record minor costs of ongoing use (SMS messages and email communication). The major cost of the intervention is likely to be provision of tailored advice based on data received (research personnel and research platform costs). This will be estimated by recording time spent deconstructing the mobile app data, the Web app, and objective measures and then interpreting data and constructing appropriate feedback.

**Table 3.** Examples of tailored feedback intervention strategies.

| Type[a] | Example | Processing and goals |
|---|---|---|
| Descriptive (what is known) | Hi Jane, it's the team with your feedback. So how did you score? Ave fruit serves = 1.5, ave veg serves = 3. What's the goal again? 2 fruit & 5 veg every day. You are halfway there! | Effortful processing and self-referencing |
| Comparative (contrasts with others) | Hi Jane, so how did you score? Ave fruit serves = 1.5, veg serves = 3.5. Your fruit serves varied from 0 - 3.5, veg from 1.5 - 5.5 over 4 days. So how does your intake compared to others? Ave fruit serves = 1, veg serves = 2. | Effortful processing, self-referencing, and normative beliefs and attitudes |
| Evaluative (interpretation) | Hi Jane, it's the team with feedback on your PA. So how did you score? Ave steps a day = 5,500. What's your goal again? 10,000 steps a day. You are over halfway there! | Effortful processing, self-referencing, and normative beliefs and attitudes |

[a]Adapted from [54].

## Process Evaluation

Process evaluation will assess to what extent the intervention reached the target audiences. A brief questionnaire will be used to evaluate participants' perception of the tailored feedback (ie, message persuasiveness, message tone, readability, ease of understanding, usefulness of advice, suitability, and relevance to age group) and to comment on features they like/dislike about the program. Usability feedback will also be obtained for the mFR (tailored feedback and active control groups) and activity monitor (tailored feedback group only). Impact evaluation will consist of exit interview surveys via telephone at 14 months to assess intervention impact as well as perceptions of various strategies and materials. Selected program completers and noncompleters (tailored feedback and active control groups) will be invited to participate in one-on-one interviews concerning their perceptions of the ToDAy intervention.

## Statistical Analysis

The following primary outcome variables will be measured at baseline and 12 months of the intervention: changes in body mass, EDNP food and beverage consumption (sugar-sweetened beverages, alcohol, and take away and other "junk" foods), and daily minutes spent in MVPA. Secondary outcome variables include changes in fruit and vegetable serves and daily minutes spent in sedentary activity. Outcomes will identify characteristics of responders who remained engaged and reported improvements in key behaviors and quantify resource use associated with each arm of the study, which will be used in an economic evaluation of tailored feedback. Data on change in outcome variables in each of the two groups will be compared using analysis of covariance. Assumptions of the analyses will be assessed by examining residuals. Data will be transformed if assumptions of the analyses are not satisfied. Possible covariates considered will include age, sex, country of birth, ethnicity, highest education level, socioeconomic index for area, and baseline value of the variable analyzed. $P$-values < .05 will be considered statistically significant. Effect size of differences between treatment and control will be expressed as adjusted mean difference and associated 95% CIs. Data on change in outcome variables postintervention and follow-up time points will be converted into binary categorical variables and analyzed using multivariable logistic regression and generalized estimating equations. Odds ratio and associated 95% CIs will be reported. The analyses will identify characteristics of

participants who are least likely to change their consumption of EDNP foods, PA, and BMI, thereby identifying target groups for future health promotion interventions.

## Power

A sample size of 600 participants (n=200 per group) will have sufficient power to detect a change in the primary outcome variable of at least 0.6 median serves/day of EDNP (discretionary) foods (or equivalent to a 360 kJ/day reduction) between groups at 90% power and 5% level of significance. Assuming a drop-out rate of 20%, a total of 600 participants will be recruited.

## Results

Enrollment commenced in August 2017. Primary outcomes at 12 months will be available for analysis from September 2019.

## Discussion

### Overview

Improving participation and reach is a challenge for population-based obesity interventions. Worldwide participation rates in population studies are declining [59], and while enrollment in studies involving face-to-face recruitment is somewhat higher [59], there is a need to evaluate the effectiveness of digital interventions that include multiple strategies to improve engagement [60]. Interventions utilizing digital technologies may have greater appeal in overweight and obese populations, as participants may feel more comfortable completing self-reported questionnaires in a more anonymous setting [61].

Reasons for the lack of adherence to lifestyle recommendations are poorly understood. One contributing dietary factor may be that many adults incorrectly believe their diet to be healthy when it is not [62]. This mismatch between perceived and actual intake may be corrected by more accurate, objective dietary assessment; comparison with national recommendations; and clear, relatable tailored feedback. Furthermore, despite sustained public health efforts, the majority of Australian adults are "inactive," failing to meet the recommended PA guidelines [63]. Thus, focus on the most-effective messaging strategy (both content and delivery) to target these behaviors is needed. A systematic review of tailored interventions and the identified

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lack of objective measurements in studies on dietary and PA behaviors are key limitations of tailored interventions [17]. This, in part, is due to difficulty in undertaking more objective methods of dietary and PA assessment on a large scale. Exploring digital methods of assessment may allow more cost-effective approaches to be implemented.

Tailoring focuses on characteristics unique to the person with the intention of improving behavioral outcomes by making the message more acceptable to each individual. Characteristics of messages and feedback that can be tailored include personal behaviors, psychosocial characteristics, and diet and PA behaviors [54]. Personal relevance is key, and dynamic (ongoing assessment) tailoring versus static tailoring (one baseline assessment) has stronger effects over time [15]. Effective tailoring strategies include multiple intervention contacts and iterative feedback [19]. Of note, tailoring may be more effective for men than women [64].

Numerous behavioral theories have been used as a basis for tailored interventions, including the Stages of Change Model and Precaution Adoption Process Model [19]. However, there is increasing support for self-determination theory in weight control, diet, and tailored PA interventions to address autonomous motivation and self-regulation [52,53,65-68]. Central to the self-determination theory is an emphasis on autonomous behaviors (originating from one's-self), as opposed to pressure or coercion into a particular course of action when delivering advice [67]. This provides a framework for the style of communication to be used in tailored interventions but does not address approaches used in digital technology interventions. Researchers have raised concerns about the lack of models to inform design of technology-based behavioral interventions [20,21]. In response, Mohr et al [20] proposed a behavioral intervention technology framework for interventions that use a range of technologies, including mobile phones, the Web, and sensors aimed at changing behavior. Features such as usability and willingness to continue to use the app may contribute to enhanced participant engagement and motivation [20]. Michie et al [68] developed the COM-B model, which guides researchers to identify behavioral targets and subsequent psychological theories for behavior-change interventions. The COM-B model identifies capability, opportunity, and motivation as the three core categories to perform a behavior. This means that to perform a behavior, individuals must be capable with physical and mental ability (eg, nutrition knowledge and cooking skills) as well as practical and social opportunities (eg, access to affordable and healthy food). Motivation includes automatic drivers like habits as well as goals, beliefs, plans, and impulses. Assessing these determinants is the first step to identify interventions and theories that can help change behavior.

With respect to PA, wearable technology is being rapidly adopted, with over one-third of the Australian population using activity monitors to record PA and sedentary behaviors [69]. These devices are becoming vital in the context of research to facilitate monitoring of activity in real-time and under free-living conditions. Nonetheless, a gap exists between recording/self-monitoring and behavioral change. Furthermore, there is a lack of strongly designed studies that have considered the combination of behavioral theory with activity monitors to improve health behaviors. New-generation activity monitors allow for critical information to be harnessed from large-scale research studies. In this study, activity monitors will be used to record 24/7 behavior, specifically active and sedentary minutes; exercise intensity; nonsedentary hours; and step count in overweight adults. Together with dietary analysis, curation of these data will enable provision of detailed, richer feedback to participants and may therefore be more effective in helping change diet and PA behaviors. If found successful, the approach used in this study could be incorporated into larger-scale health campaigns.

## Conclusions

The current obesity epidemic is occurring against a background of a decline in PA participation and increasingly poor dietary choices, with the incidence of both obesity and prevalence of inactivity worsening with age. Promoting and maintaining healthy diet and PA behaviors through personalized tailored feedback is feasible, novel, and potentially cost effective. Personalized feedback with comparison to recommendations and guidance in forming healthy habits is essential to overcome existing barriers to lifestyle change. Digital technologies (mobile apps, email, and web) have the potential to reach larger populations of healthy adults and those at risk of chronic disease but to date have not been fully explored. The outcomes of this intervention may have the potential to positively impact health at a boarder population level, with findings informing translation of "best practice" lifestyle intervention aimed at overweight adults.

## Authors' Contributions

The study was conceived and designed by DK, CP, JJ, JAS, ISP, SD, RN, LS, CB, ED, AH, MS, JM, BM, CC, and RH. The paper was drafted by RH, DK, and CS. The paper was revised for intellectual content by DK, CP, CB, LS, JM, KE, JJ, SM, and JS. All authors approved the final content of the paper.

## Conflicts of Interest

None declared.

## References

1. Profiles of Health, Australia, 2011-13. Canberra, Australia: Australian Bureau of Statistics; 2011. URL: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4338.0~2011-13~Main%20Features~Overweight%20and%20obesity~10007 [accessed 2018-11-14] [WebCite Cache ID 73un7bvI2]

2. Institute for Health Metrics and Evaluation. Seattle, WA: IHME; 2010. Global Burden of Disease Profile: Australia URL: http://www.healthdata.org/australia [accessed 2018-11-14] [WebCite Cache ID 73umtO4If]

3. Australian Government Department of Health, National Health and Medical Research Council. Clinical Practice Guidelines for the Management of Overweight and Obesity for Adults, Adolescents and Children in Australia. Canberra, ACT: Commonwealth of Australia; 2013. URL: https://nhmrc.gov.au/about-us/publications/clinical-practice-guidelines-management-overweight-and-obesity [accessed 2019-02-07] [WebCite Cache ID 760BJX4o0]

4. Australian Bureau of Statistics. Canberra, Australia: ABS; 2011. Australian Health Survey: Nutrition First Results - Foods and Nutrients, 2011-12 URL: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4364.0.55.007Main+Features12011-12 [accessed 2018-11-14] [WebCite Cache ID 73uoVjWZb]

5. Australian Bureau of Statistics. Canberra, Australia: ABS; 2011. Australian Health Survey: Physical Activity, 2011-12 URL: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4364.0.55.004Chapter1002011-12 [accessed 2018-11-14] [WebCite Cache ID 73uoe0Oj2]

6. 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]

7. Straker LM, Howie EK, Smith KL, Fenner AA, Kerr DA, Olds TS, et al. The impact of Curtin University's activity, food and attitudes program on physical activity, sedentary time and fruit, vegetable and junk food consumption among overweight and obese adolescents: a waitlist controlled trial. PLoS One 2014;9(11):e111954 [FREE Full text] [doi: 10.1371/journal.pone.0111954] [Medline: 25375109]

8. Morgan PJ, Lubans DR, Collins CE, Warren JM, Callister R. The SHED-IT randomized controlled trial: evaluation of an Internet-based weight-loss program for men. Obesity (Silver Spring) 2009 Nov;17(11):2025-2032. [doi: 10.1038/oby.2009.85] [Medline: 19343018]

9. Turk MW, Elci OU, Wang J, Sereika SM, Ewing LJ, Acharya SD, et al. Self-monitoring as a mediator of weight loss in the SMART randomized clinical trial. Int J Behav Med 2013 Dec;20(4):556-561 [FREE Full text] [doi: 10.1007/s12529-012-9259-9] [Medline: 22936524]

10. Eckerstorfer LV, Tanzer NK, Vogrincic-Haselbacher C, Kedia G, Brohmer H, Dinslaken I, et al. Key Elements of mHealth Interventions to Successfully Increase Physical Activity: Meta-Regression. JMIR Mhealth Uhealth 2018 Nov 12;6(11):e10076 [FREE Full text] [doi: 10.2196/10076] [Medline: 30425028]

11. Burke L, Lee AH, Pasalich M, Jancey J, Kerr D, Howat P. Effects of a physical activity and nutrition program for seniors on body mass index and waist-to-hip ratio: a randomised controlled trial. Prev Med 2012 Jun;54(6):397-401. [doi: 10.1016/j.ypmed.2012.03.015] [Medline: 22503646]

12. Michie S, Yardley L, West R, Patrick K, Greaves F. Developing and Evaluating Digital Interventions to Promote Behavior Change in Health and Health Care: Recommendations Resulting From an International Workshop. J Med Internet Res 2017 Jun 29;19(6):e232 [FREE Full text] [doi: 10.2196/jmir.7126] [Medline: 28663162]

13. Pagoto S, Schneider K, Jojic M, DeBiasse M, Mann D. Evidence-based strategies in weight-loss mobile apps. Am J Prev Med 2013 Nov;45(5):576-582. [doi: 10.1016/j.amepre.2013.04.025] [Medline: 24139770]

14. Khaylis A, Yiaslas T, Bergstrom J, Gore-Felton C. A review of efficacious technology-based weight-loss interventions: five key components. Telemed J E Health 2010 Nov;16(9):931-938 [FREE Full text] [doi: 10.1089/tmj.2010.0065] [Medline: 21091286]

15. Krebs P, Prochaska JO, Rossi JS. A meta-analysis of computer-tailored interventions for health behavior change. Prev Med 2010;51(3-4):214-221 [FREE Full text] [doi: 10.1016/j.ypmed.2010.06.004] [Medline: 20558196]

16. Kroeze W, Werkman A, Brug J. A systematic review of randomized trials on the effectiveness of computer-tailored education on physical activity and dietary behaviors. Ann Behav Med 2006 Jun;31(3):205-223. [doi: 10.1207/s15324796abm3103_2] [Medline: 16700634]

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17. Broekhuizen K, Kroeze W, van Poppel MNM, Oenema A, Brug J. A systematic review of randomized controlled trials on the effectiveness of computer-tailored physical activity and dietary behavior promotion programs: an update. Ann Behav Med 2012 Oct;44(2):259-286 [FREE Full text] [doi: 10.1007/s12160-012-9384-3] [Medline: 22767052]

18. Short CE, James EL, Plotnikoff RC, Girgis A. Efficacy of tailored-print interventions to promote physical activity: a systematic review of randomised trials. Int J Behav Nutr Phys Act 2011 Oct 17;8:113 [FREE Full text] [doi: 10.1186/1479-5868-8-113] [Medline: 21999329]

19. Noar SM, Benac CN, Harris MS. Does tailoring matter? Meta-analytic review of tailored print health behavior change interventions. Psychol Bull 2007 Jul;133(4):673-693. [doi: 10.1037/0033-2909.133.4.673] [Medline: 17592961]

20. 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;16(6):e146 [FREE Full text] [doi: 10.2196/jmir.3077] [Medline: 24905070]

21. 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]

22. Kerr DA, Harray AJ, Pollard CM, Dhaliwal SS, Delp EJ, Howat PA, et al. The connecting health and technology study: a 6-month randomized controlled trial to improve nutrition behaviours using a mobile food record and text messaging support in young adults. Int J Behav Nutr Phys Act 2016 Apr 21;13:52 [FREE Full text] [doi: 10.1186/s12966-016-0376-8] [Medline: 27098449]

23. Wang J, Cai C, Padhye N, Orlander P, Zare M. A Behavioral Lifestyle Intervention Enhanced With Multiple-Behavior Self-Monitoring Using Mobile and Connected Tools for Underserved Individuals With Type 2 Diabetes and Comorbid Overweight or Obesity: Pilot Comparative Effectiveness Trial. JMIR Mhealth Uhealth 2018 Apr 10;6(4):e92 [FREE Full text] [doi: 10.2196/mhealth.4478] [Medline: 29636320]

24. Jakicic JM, Davis KK, Rogers RJ, King WC, Marcus MD, Helsel D, et al. Effect of Wearable Technology Combined With a Lifestyle Intervention on Long-term Weight Loss: The IDEA Randomized Clinical Trial. JAMA 2016 Sep 20;316(11):1161-1171. [doi: 10.1001/jama.2016.12858] [Medline: 27654602]

25. LiveLighter. 2018. URL: https://livelighter.com.au/ [accessed 2018-08-29] [WebCite Cache ID 721f8bzFZ]

26. Zhu F, Bosch M, Woo I, Kim S, Boushey CJ, Ebert DS, et al. The Use of Mobile Devices in Aiding Dietary Assessment and Evaluation. IEEE J Sel Top Signal Process 2010 Aug;4(4):756-766 [FREE Full text] [doi: 10.1109/JSTSP.2010.2051471] [Medline: 20862266]

27. Zhu F, Bosch M, Khanna N, Boushey CJ, Delp EJ. Multiple hypotheses image segmentation and classification with application to dietary assessment. IEEE J Biomed Health Inform 2015 Jan;19(1):377-388. [doi: 10.1109/JBHI.2014.2304925] [Medline: 25561457]

28. Ahmad Z, Kerr DA, Bosch M, Boushey CJ, Delp EJ, Khanna N, et al. A Mobile Food Record For Integrated Dietary Assessment. In: MADiMa16 (2016). USA: ACM; 2016 Oct Presented at: 2nd International Workshop on Multimedia Assisted Dietary Management; 15 - 19 October 2016; Amsterdam, The Netherlands p. 53-62 URL: http://europepmc.org/abstract/MED/28691119 [doi: 10.1145/2986035.2986038]

29. Stewart A, Marfell-Jones M, Olds T, de Ridder JH. International standards for anthropometric assessment. Adelaide: International Society for the Advancement of Kinanthropometry; 2011.

30. Rikli RE. Reliability, validity, and methodological issues in assessing physical activity in older adults. Res Q Exerc Sport 2000 Jun;71(2 Suppl):S89-S96. [Medline: 10925830]

31. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001 Jul;33(5):337-343. [Medline: 11491192]

32. Collins CE, Boggess MM, Watson JF, Guest M, Duncanson K, Pezdirc K, et al. Reproducibility and comparative validity of a food frequency questionnaire for Australian adults. Clin Nutr 2014 Oct;33(5):906-914. [doi: 10.1016/j.clnu.2013.09.015] [Medline: 24144913]

33. Boushey CJ, Harray AJ, Kerr DA, Schap TE, Paterson S, Aflague T, et al. How willing are adolescents to record their dietary intake? The mobile food record. JMIR Mhealth Uhealth 2015;3(2):e47 [FREE Full text] [doi: 10.2196/mhealth.4087] [Medline: 26024996]

34. Kerr DA, Dhaliwal SS, Pollard CM, Norman R, Wright JL, Harray AJ, et al. BMI is Associated with the Willingness to Record Diet with a Mobile Food Record among Adults Participating in Dietary Interventions. Nutrients 2017 Mar 07;9(3) [FREE Full text] [doi: 10.3390/nu9030244] [Medline: 28272343]

35. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 1985;29(1):71-83. [Medline: 3981480]

36. 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]

37. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res 2002 Sep;53(3):737-740. [Medline: 12217446]

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38. Sinclair SJ, Siefert CJ, Slavin-Mulford JM, Stein MB, Renna M, Blais MA. Psychometric evaluation and normative data for the depression, anxiety, and stress scales-21 (DASS-21) in a nonclinical sample of U.S. adults. Eval Health Prof 2012 Sep;35(3):259-279. [doi: 10.1177/0163278711424282] [Medline: 22008979]

39. Tooze JA, Subar AF, Thompson FE, Troiano R, Schatzkin A, Kipnis V. Psychosocial predictors of energy underreporting in a large doubly labeled water study. Am J Clin Nutr 2004 May;79(5):795-804. [doi: 10.1093/ajcn/79.5.795] [Medline: 15113717]

40. Marlowe D, Crowne DP. Social desirability and response to perceived situational demands. J Consult Psychol 1961 Apr;25:109-115. [Medline: 13766997]

41. Allom V, Mullan B, Cowie E, Hamilton K. Physical Activity and Transitioning to College: The Importance of Intentions and Habits. Am J Health Behav 2016 Mar;40(2):280-290. [doi: 10.5993/AJHB.40.2.13] [Medline: 26931760]

42. Myers VH, McVay MA, Champagne CM, Hollis JF, Coughlin JW, Funk KL, et al. Weight loss history as a predictor of weight loss: results from Phase I of the weight loss maintenance trial. J Behav Med 2013 Dec;36(6):574-582 [FREE Full text] [doi: 10.1007/s10865-012-9450-0] [Medline: 22907176]

43. Hands BP, Chivers PT, Parker HE, Beilin L, Kendall G, Larkin D. The associations between physical activity, screen time and weight from 6 to 14 yrs: the Raine Study. J Sci Med Sport 2011 Sep;14(5):397-403. [doi: 10.1016/j.jsams.2011.03.011] [Medline: 21531620]

44. Harray AJ, Boushey CJ, Pollard CM, Delp EJ, Ahmad Z, Dhaliwal SS, et al. A Novel Dietary Assessment Method to Measure a Healthy and Sustainable Diet Using the Mobile Food Record: Protocol and Methodology. Nutrients 2015;7(7):5375-5395 [FREE Full text] [doi: 10.3390/nu7075226] [Medline: 26151176]

45. Australian Government - Department of Health and Aging, National Health and Medical Research Council. Eat for Health - Educator Guide: Information for nutrition educators. Canberra, ACT: Commonwealth of Australia; 2013. URL: https://www.eatforhealth.gov.au/sites/default/files/files/the_guidelines/n55b_eat_for_health_educators_guide.pdf [accessed 2019-02-07] [WebCite Cache ID 760D7SFfa]

46. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. Am J Epidemiol 2008 Apr 1;167(7):875-881 [FREE Full text] [doi: 10.1093/aje/kwm390] [Medline: 18303006]

47. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998 May;30(5):777-781. [Medline: 9588623]

48. Australian Government Department of Health. Australia's Physical Activity and Sedentary Behavior Guidelines for Adults (18-64 years). Canberra, ACT: Commonwealth of Australia; 2017. URL: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines#apaadult [accessed 2019-02-07] [WebCite Cache ID 760EH2cX9]

49. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: US Department of Health & Human Services; 2018. URL: https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf#page=55 [accessed 2019-02-07] [WebCite Cache ID 760FitnI6]

50. Australian Government - Department of Health and Aging, National Health and Medical Research Council. Australian dietary guidelines - providing the scientific evidence for healthier Australian diets. Canberra, ACT: NHMRC; 2013. URL: https://www.eatforhealth.gov.au/sites/default/files/content/n55_australian_dietary_guidelines.pdf [accessed 2019-02-07] [WebCite Cache ID 760CiE3a8]

51. Pollard CM, Howat PA, Pratt IS, Boushey CJ, Delp EJ, Kerr DA. Preferred Tone of Nutrition Text Messages for Young Adults: Focus Group Testing. JMIR Mhealth Uhealth 2016 Jan 19;4(1):e1 [FREE Full text] [doi: 10.2196/mhealth.4764] [Medline: 26787115]

52. 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]

53. Resnicow K, Davis RE, Zhang G, Konkel J, Strecher VJ, Shaikh AR, et al. Tailoring a fruit and vegetable intervention on novel motivational constructs: results of a randomized study. Ann Behav Med 2008 Apr;35(2):159-169. [doi: 10.1007/s12160-008-9028-9] [Medline: 18401673]

54. Hawkins RP, Kreuter M, Resnicow K, Fishbein M, Dijkstra A. Understanding tailoring in communicating about health. Health Educ Res 2008 Jun;23(3):454-466 [FREE Full text] [doi: 10.1093/her/cyn004] [Medline: 18349033]

55. Wright JL, Sherriff JL, Dhaliwal SS, Mamo JCL. Tailored, iterative, printed dietary feedback is as effective as group education in improving dietary behaviours: results from a randomised control trial in middle-aged adults with cardiovascular risk factors. Int J Behav Nutr Phys Act 2011;8:43 [FREE Full text] [doi: 10.1186/1479-5868-8-43] [Medline: 21595978]

56. Kreuter MW, Skinner CS. Tailoring: what's in a name? Health Educ Res 2000 Feb;15(1):1-4 [FREE Full text] [Medline: 10788196]

57. Brooks R, Rabin R, de Charro F. The measurement and valuation of health status using EQ-5D: a European perspective. Dordrecht: Kluwer Academic Press. The Netherlands: Springer; 2013.

58. Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Appl Health Econ Health Policy 2013 Jun;11(3):287-298. [doi: 10.1007/s40258-013-0035-z] [Medline: 23649892]

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59.  Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007 Sep;17(9):643-653. [doi: 10.1016/j.annepidem.2007.03.013] [Medline: 17553702]

60.  Warner ET, Glasgow RE, Emmons KM, Bennett GG, Askew S, Rosner B, et al. Recruitment and retention of participants in a pragmatic randomized intervention trial at three community health clinics: results and lessons learned. BMC Public Health 2013;13:192 [FREE Full text] [doi: 10.1186/1471-2458-13-192] [Medline: 23496916]

61.  Méjean C, Szabo DEF, Touvier M, Kesse-Guyot E, Julia C, Andreeva VA, et al. Motives for participating in a web-based nutrition cohort according to sociodemographic, lifestyle, and health characteristics: the NutriNet-Santé cohort study. J Med Internet Res 2014 Aug 07;16(8):e189 [FREE Full text] [doi: 10.2196/jmir.3161] [Medline: 25135800]

62.  Glanz K, Brug J, van Assema P. Are awareness of dietary fat intake and actual fat consumption associated?--a Dutch-American comparison. Eur J Clin Nutr 1997 Aug;51(8):542-547. [Medline: 11248880]

63.  Australian Bureau of Statistics. Canberra, Australia: ABS; 2007. Physical Activity in Australia: A Snapshot, 2007-08 URL: http://www.abs.gov.au/ausstats/abs@.nsf/mf/4835.0.55.001 [accessed 2018-09-07] [WebCite Cache ID 72FQpXKR7]

64.  Robertson C, Avenell A, Boachie C, Stewart F, Archibald D, Douglas F, et al. Should weight loss and maintenance programmes be designed differently for men? A systematic review of long-term randomised controlled trials presenting data for men and women: The ROMEO project. Obes Res Clin Pract 2016;10(1):70-84. [doi: 10.1016/j.orcp.2015.04.005] [Medline: 25937165]

65.  Teixeira PJ, Palmeira AL, Vansteenkiste M. The role of self-determination theory and motivational interviewing in behavioral nutrition, physical activity, and health: an introduction to the IJBNPA special series. Int J Behav Nutr Phys Act 2012 Mar 02;9:17 [FREE Full text] [doi: 10.1186/1479-5868-9-17] [Medline: 22385644]

66.  Friederichs SAH, Oenema A, Bolman C, Guyaux J, van Keulen HM, Lechner L. I Move: systematic development of a web-based computer tailored physical activity intervention, based on motivational interviewing and self-determination theory. BMC Public Health 2014 Feb 28;14:212 [FREE Full text] [doi: 10.1186/1471-2458-14-212] [Medline: 24580802]

67.  Miller W, Rollnick S. Motivational Interviewing: Preparing People For Change, 2nd Edition. New York: The Guilford Press; 2002.

68.  Michie S, Abraham C, Eccles MP, Francis JJ, Hardeman W, Johnston M. Strengthening evaluation and implementation by specifying components of behaviour change interventions: a study protocol. Implement Sci 2011;6:10 [FREE Full text] [doi: 10.1186/1748-5908-6-10] [Medline: 21299860]

69.  Alley S, Schoeppe S, Guertler D, Jennings C, Duncan MJ, Vandelanotte C. Interest and preferences for using advanced physical activity tracking devices: results of a national cross-sectional survey. BMJ Open 2016 Dec 07;6(7):e011243 [FREE Full text] [doi: 10.1136/bmjopen-2016-011243] [Medline: 27388359]

## Abbreviations

**BMI:** body mass index
**COM-B:** Capability, Opportunity, Motivation, and Behaviour
**EDNP:** energy-dense nutrient-poor foods
**mFR:** mobile food record
**MVPA:** moderate-to-vigorous physical activity
**OC:** online control
**PA:** physical activity
**RCT:** randomized controlled trial
**SMS:** short message service
**TF:** tailored feedback

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Protocol

# National Survey of Morbidity and Risk Factors (EMENO): Protocol for a Health Examination Survey Representative of the Adult Greek Population

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## Abstract

**Background:** Main causes of death in Greece are cardiovascular diseases (CVDs), malignant neoplasms, respiratory diseases, and road traffic crashes. To assess the population health status, monitor health systems, and adjust policies, national population-based health surveys are recommended. The previous health surveys that were conducted in Greece were restricted to specific regions or high-risk groups.

**Objective:** This paper presents the design and methods of the Greek Health Examination Survey EMENO (National Survey of Morbidity and Risk Factors). The primary objectives are to describe morbidity (focusing on CVD, respiratory diseases, and

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diabetes), related risk factors, as well as health care and preventive measures utility patterns in a random sample of adults living in Greece.

**Methods:**   The sample was selected by applying multistage stratified random sampling on 2011 Census. Trained interviewers and physicians made home visits. Standardized questionnaires were administered; physical examination, anthropometric and blood pressure measurements, and spirometry were performed. Blood samples were collected for lipid profile, glucose, glycated hemoglobin, and transaminases measurements. The survey was conducted from May 2013 until June 2016.

**Results:**   In total, 6006 individuals were recruited (response rate 72%). Of these, 4827 participated in at least one physical examination, 4446 had blood tests, and 3622 spirometry, whereas 3580 provided consent for using stored samples for future research (3528 including DNA studies). Statistical analysis has started, and first results are expected to be submitted for publication by the end of 2018.

**Conclusions:**   EMENO comprises a unique health data resource and a bio-resource in a Mediterranean population. Its results will provide valid estimates of morbidity and risk factors' prevalence (overall and in specific subdomains) and health care and preventive measures usage in Greece, necessary for an evidence-based strategy planning of health policies and preventive activities.

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## Introduction

### Background

Noncommunicable diseases account for 68% of all deaths worldwide [1], with cardiovascular diseases (CVDs), cancers, chronic respiratory diseases, and diabetes being among the top 10 leading causes. According to the World Health Organization [2], cardiovascular events were the world's leading causes of death in 2015 (approximately 26.6% of deaths). In addition, about 14.4% of deaths worldwide are because of respiratory diseases [2].

Apart from age, gender and, family history, modifiable risk factors and their interactions account for about 60% of the CVD deaths. The main modifiable CVD risk factors are (1) behavioral factors such as unhealthy diet, sedentary lifestyle, smoking, and alcohol abuse; (2) cardiometabolic factors such as hypertension, hypercholesterolemia, diabetes, and increased body mass index; and (3) exposure to environmental pollutants and socioeconomic risk factors [2-6]. In addition, mental disorders, such as depression and anxiety, account for around 6.2% of the total disease burden [1], affecting approximately 10% of the population [7] and have also been associated with increased cardiovascular risk [8,9]. Over the past 30 years, following national preventive programs, age-standardized mortality rates have fallen in most countries, albeit to different degrees [10]. However, during the same period, initial increases followed by relatively small reductions in the incidence of CVD were observed in Eastern European countries as well as in Greece [10]. It is assumed that adoption of a modern lifestyle increased the prevalence of several CVD risk factors that contributed to the rising mortality rates.

In Greece, according to data from the Hellenic Statistical Authority [11], 50% of persons aged 15 years and over suffer from a chronic disease (25.2% increase compared with 2009). The financial crisis and austerity policies implemented in Greece in 2009 have various detrimental consequences on Greeks' daily lives as well as on their health [12], including increase in heart attacks (50.0%), strokes (23.5%), and depression (80.8%), related also to rise in unemployment [11,13].

To design and implement prevention strategies for chronic diseases, national population representative baseline data on their prevalence are necessary. Nationwide health examination surveys (HES) combining information collected by interviews with participants' physical examination consist the gold standard method to provide such data. HES have a long history in the United States [14,15] and since the 1990s, they have been widely introduced in Europe [16,17]. Setting up and implementation of a nationwide HES entail several difficulties and challenges, some of which are country or region specific.

In Greece, until recently, no such HES had ever been performed at the national level to record the prevalence of frequent chronic diseases and risk factors in a large, randomly selected sample, representative of the general population. Several health surveys have been conducted, which, however, were either restricted to specific regions or to high-risk groups [18-20] or were conducted within focused European projects [21,22].

### Objectives

Valid estimates of population morbidity and risk factor patterns, use of preventive measures, and health services and barriers in accessing health care are necessary to plan and implement effective prevention programs; however, such data are not available in Greece. The National Survey of Morbidity and Risk Factors (EMENO), a population-based health survey, was set up not only focusing on cardiovascular and respiratory diseases and related risk factors but also on assessing population well-being and use of health services, medicines, and preventive measures in a randomly selected sample of adults living in Greece. Combining health data with health examinations and blood sample testing and collection for future use, EMENO constitutes a unique health information tank and bio-resource. This paper presents the design and methodology of EMENO

and discusses the challenges associated with organizing and implementing epidemiological HES using the *door-to-door* approach in a large representative sample.

## Methods

### Study Design

EMENO is a cross-sectional health examination survey combining health data collected by trained interviewers using standardized questionnaires and medical examinations conducted by trained physicians in a randomly selected sample of all adult people (aged ≥18 years) living in Greece, excluding those in supervised care or custody in institutional settings. It was funded by the European Union structural funds and National resources, coordinated by the Department of Hygiene, Epidemiology, and Medical Statistics of the National and Kapodistrian University of Athens Medical School, and implemented in cooperation with all the other Greek Medical Schools and the Institute of Epidemiology, Preventive Medicine, and Public Health. EMENO was initiated in May 2013 and completed in June 2016. The survey was delivered by *door-to-door* interviews using a computer-assisted personal interview (CAPI), augmented with data and physical examinations collected by trained physicians at scheduled appointments. Study physicians visited interviewed participants at their homes. In some small rural areas, interviewed participants were invited to visit local health care units where study physicians examined them. The *door-to-door* approach is common in health screening surveys, and it has been applied in some large scale, well-established surveys such as the National Health and Nutrition Exam Survey (NHANES) [23].

### Sampling Strategy

As a centralized person registry does not exist in Greece, the 2011 census constituted the sampling frame. Multistage stratified random sampling [24,25] based on 2011 Census was applied to select the sample. The sampling procedure consisted of 4 stages: (1) initial sampling units (specific regions), (2) building blocks, (3) households, and (4) individuals.

Stage 1: The whole country was stratified by geographical region (9 regions plus the Greater Attica Area and the Greater Thessaloniki Area) and by degree of urbanization (urban: ≥10,000, semi-urban: 2000-9999, and rural: up to 1999 inhabitants) resulting in 33 strata. As Greater Athens and Thessaloniki Areas account for approximately 45.62% (4,937,936/10,823,686) of the total population, and to increase the precision of estimates for the geographical region subdomain, sampling fraction was allowed to differ by stratum, over-representing smaller strata, and under-representing larger strata, provided that the minimum sampling fraction per region (0.042% in Attica) does not get more than treble the maximum one (0.116% in Ionian islands). Table 1 displays the sampling fraction per stratum.

Given that it was not possible to visit each prefecture in each geographical area, apart from Ionian Islands' region where 1

island (Corfu) was selected, in all other geographical regions, 2 prefectures were randomly selected (Table 1 and Figure 1). Greater Athens area was further divided into 4 regions: Athens, East Attica, West Attica, and Piraeus. Thus, the total primary sampling units (PSUs) were 66 (22 regions multiplied by 3 degrees of urbanization).

Stage 2: Within each PSU, area segments comprising census blocks or combination of blocks were randomly selected (sampling points). From each sampling point, 12 households in urban and semi-urban and 8 in rural areas should be available for interview. Assuming a 50% response rate, the needed number of households per sampling point was 18 for urban and semi-urban and 12 for rural areas. The target sample size was 6000 adults (1 per household). On the basis of the population size of each PSU and considering the corresponding sampling fraction as well as the average number of households per PSU, the total number of sampling points per PSU was determined. In total, 577 sampling points were selected (295 in urban, 89 in semi-urban, and 193 in rural areas). Hellenic Statistical Authority provided the coordinates (latitude and longitude) of each building block within each sampling point, and then these were transferred to maps through Geographic Information Systems to become available to the interviewers.

Stage 3: Within each sampling point, eligible households were selected via systematic sampling. All interviewers were provided with the maps of the selected sampling points. Standardized operating procedures (available on request) were developed on how to select the eligible households within each sampling point (eg, starting from the top left corner of the map, in blocks of flats starting from the top floor and moving clockwise, spiraling downwards). One household of every $x$ households was selected, with the step x ranging from 4 (ie, leaving 4 households and selecting the fifth) to 2, depending on population density. Each map was accompanied by its corresponding step. Interviewers had to describe all followed steps in a specific database. Only residential houses were eligible. If there was no reply in the first attempt, interviewers had to visit the household 2 more times in different hours (eg, once in the morning and once in the evening and one time during weekends). If there was information that a house was not inhabited for a long period or that it was a vacation place, it was considered as noneligible. Similarly, if after 3 attempts nobody replied, the household was also considered as noneligible. If there was a reply but the inhabitants refused to receive information about the study, this was considered as nonresponse.

Stage 4: All eligible (ie, adults ≥18 years) individuals within a household were listed and 1 individual per household was randomly selected (the one who had a birthday last, also known as *most recent birthday* method [26]). If the selected individual agreed to participate, an appointment was arranged for interview. People who refused (counted as nonresponders) were substituted by responders from the next eligible household, until the target number of individuals per sampling point (12 or 8) was met. Response rate was estimated as the number of interviews over the number of eligible households reached.

**Table 1.** Sampling plan and response rates (N=10,823,686).

| Area and urbinity | Distribution of the required sample (n=6000) by urbanity | Sampling fraction (%) | Response rate (%) |
|---|---|---|---|
| **Thrace (N=371,208)** | **n=303** | | |
| Urban | 154 | 0.8157 | 65.8 |
| Semi-urban | 66 | 0.8163 | 75.0 |
| Rural | 83 | 0.8170 | 81.1 |
| **Macedonia (N=1,290,404)** | **n=666** | | |
| Urban | 257 | 0.5165 | 76.6 |
| Semi-urban | 141 | 0.5179 | 82.2 |
| Rural | 268 | 0.5149 | 77.2 |
| **Thessaloniki (N=1,110,312)** | **n=585** | | |
| Urban | 451 | 0.5263 | 50.8 |
| Semi-urban | 106 | 0.5291 | 73.8 |
| Rural | 28 | 0.5283 | 80.0 |
| **Thessaly (N=734,754)** | **n=464** | | |
| Urban | 240 | 0.6309 | 52.7 |
| Semi-urban | 79 | 0.6317 | 71.7 |
| Rural | 145 | 0.6321 | 82.9 |
| **Central Greece (N=758,192)** | **n=479** | | |
| Urban | 147 | 0.6317 | 75.0 |
| Semi-urban | 139 | 0.6353 | 83.8 |
| Rural | 193 | 0.6293 | 95.4 |
| **Epirus (N=336,856)** | **n=291** | | |
| Urban | 104 | 0.8621 | 45.2 |
| Semi-urban | 58 | 0.8718 | 83.3 |
| Rural | 129 | 0.8621 | 95.2 |
| **Ionian (N=207,855)** | **n=242** | | |
| Urban | 50 | 1.1696 | 47.2 |
| Semi-urban | 54 | 1.1669 | 71.8 |
| Rural | 138 | 1.1614 | 76.2 |
| **Aegean (N=507,167)** | **n=355** | | |
| Urban | 129 | 0.7013 | 78.1 |
| Semi-urban | 98 | 0.7008 | 79.3 |
| Rural | 128 | 0.6978 | 90.1 |
| **Attica (N=3,827,624)** | **n=1615** | | |
| Urban | 1529 | 0.4218 | 73.1 |
| Semi-urban | 74 | 0.4252 | 61.8 |
| Rural | 12 | 0.4299 | 88.9 |
| **Peloponnese (N=1,049,347)** | **n=596** | | |
| Urban | 238 | 0.5682 | 82.7 |
| Semi-urban | 120 | 0.5688 | 89.5 |
| Rural | 238 | 0.5672 | 98.4 |
| **Crete (N=629,967)** | **n=404** | | |

| Area and urbinity | Distribution of the required sample (n=6000) by urbanity | Sampling fraction (%) | Response rate (%) |
|---|---|---|---|
| Urban | 192 | 0.6406 | 82.9 |
| Semi-urban | 89 | 0.6456 | 70.6 |
| Rural | 123 | 0.6398 | 68.1 |

**Figure 1.** Final sample mapping.
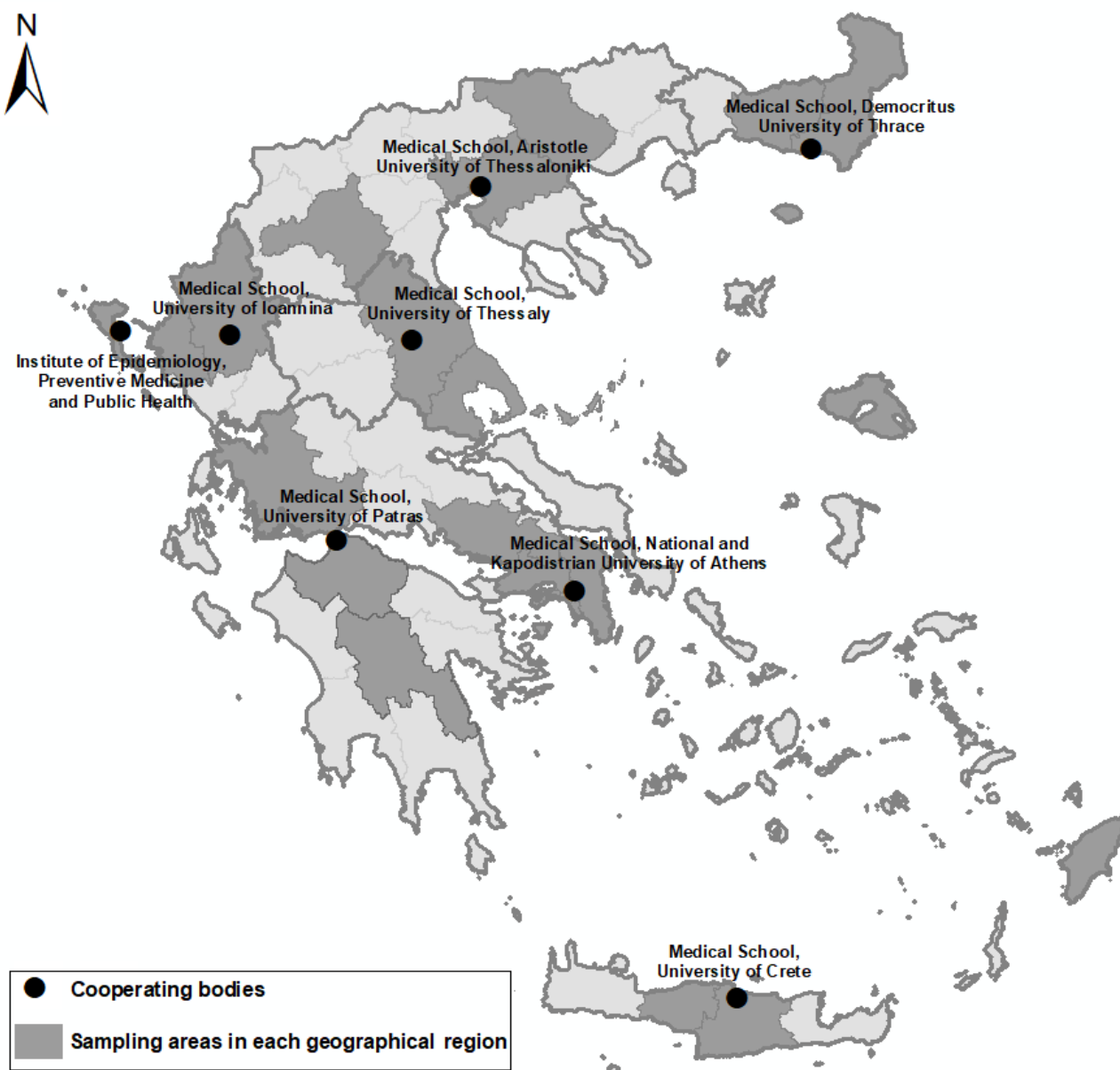


## Sample Size

On the basis of the ATTICA study results [27], the overall prevalence of hypercholesterolemia (total serum cholesterol levels >200 mg/dL or use of lipid lowering agents), hypertension (average blood pressure levels >140/90 mmHg or receiving antihypertensive medication), and of diabetes mellitus (fasting blood glucose >125 mg/dL or receiving antidiabetic medication) was about 40%, 32%, and 7%, respectively. Calculating sampling errors using the corresponding formula for stratified sampling [25] and with a target sample size of 6000 individuals, the above-mentioned prevalence could be estimated with 1.28%, 1.22%, and 0.66% precision, respectively.

## Variables and Questionnaire Development

A scientific committee (SC), which included experts in epidemiology, medical statistics, internal medicine, hypertension, cardiology, respiratory medicine, and psychology, was formed to act as an expert panel tasked with reaching consensus on survey instrument development. For questionnaires' forming, where possible, questionnaire items from existing survey instruments were adapted. For that, a

systematic literature review of international and Greek bibliography and a review of the large epidemiological studies' websites (eg, NHANES; Survey of Health, Ageing and Retirement in Europe; and European Health Examination Survey) were conducted. New questions were drafted by the core research team and scientific committee. Two different questionnaires were formed for interviewers and doctors.

The final interviewers' questionnaire was divided into the following sections: (1) sociodemographic data, including data for insurance coverage, (2) health status (general health, depression and anxiety screening, self-reported chronic diseases, subquestionnaires for coronary and peripheral artery disease, chronic pulmonary obstructive disease (COPD) and asthma, sleep, menstruation, and personal well-being), (3) health care system (use and satisfaction, health expenditures, medicines use, screening, and vaccinations), and (4) factors affecting health (self-reported height and weight, physical activity, adherence to Mediterranean diet, alcohol consumption, nutrition insecurity, smoking, environmental exposure, and household economic characteristics). The sources of the questionnaire items are shown in Multimedia Appendix 1. The total number of items was 142, but through skipping and filters, some respondents answered much fewer items. Although participants were interviewed by CAPI, there were self-administered laminated cards either to most sensitive questions (eg, psychological well-being, health care system, and self-reported chronic diseases) or to questions required visual presentation for a better understanding (to indicate the exact point of pain in chest in the coronary heart disease sub questionnaire or leg pain in the arteriopathy questionnaire). The vast majority of the questions were *close ended*.

Physicians' questionnaire included general information about physical examinations (consultation outcome, place, physical examinations, date, and duration) and sections according to the physical measurements and their exclusion criteria: (1) somatometry (height, weight, waist circumference, and left and right arm circumference); (2) blood pressure and presence of atrial fibrillation (the latter for those aged ≥65years); (3) spirometry; and (4) blood sampling. Collected blood samples were analyzed for total cholesterol, high-density lipoprotein, low-density lipoprotein, glucose, glycated hemoglobin, triglycerides, and transaminases. Standardized instruments (see Multimedia Appendix 2) were used across the country for physicians' measurements, whereas standardized operating procedures (SOPs) were developed by the EMENO SC for each measurement, spirometry, and blood samples' collection. A researchers' manual was developed containing information about health surveys; sampling procedure; interview techniques; detailed guidelines on filling each questionnaire item; the SOPs for physicians' measurements; description of the used instrument; and management of collected blood samples.

Survey questionnaires were tested and validated (time and clarity of questions) in 30 volunteers from urban, semi-urban, and rural areas and different ages. According to Sudman [28], "it usually takes no more than 12-25 cases to reveal the major difficulties and weaknesses in a pretest questionnaire" and "20-50 cases is usually sufficient to discover the major flows in a questionnaire." All research teams participated in this phase.

After questionnaires' pretesting, additions and/or corrections were made, if necessary.

## Clinical and Biochemical Measurements

Detailed SOPs were developed, but here, we briefly summarize methodology for clinical and biochemical measurements. Height and weight were measured without shoes and in light clothes. Arterial blood pressure was measured in sitting position after at least 5 min of rest; 3 valid consecutive measurements were taken with 1-min interval between them. Spirometry was performed in a standardized manner in eligible individuals (sitting position after at least 15 min at rest; participants should not have received any inhaled medicine or smoke within 1 hour before spirometry and should not have consumed any food during the previous 30 min). Portable spirometers (Multimedia Appendix 2) compatible with American Thoracic Society and European Respiratory Society requirements were used [29]. In total, 8 hours fasting serum samples were collected for determining cholesterol, glucose, glycated hemoglobin, triglycerides, and transaminases levels. For glucose, serum samples were collected in special sodium fluoride tubes. Additional samples were stored for future research if consent was provided. Upon specific consents, additional plasma samples for future molecular analyses and whole blood samples for DNA extraction were collected.

## Ethics

EMENO study was approved by the Ethics and Deontology Committee of the National and Kapodistrian University of Athens (date: November 8, 2012, protocol: 1742) and by the Hellenic Data Protection Authority (date: December 7, 2012, protocol: ΓΝ/ΕΞ/1069-1/07-12-2012). A modified version of the informed consent form (ICF) was approved by the Ethics and Deontology Committee of the National and Kapodistrian University of Athens (date: March 6, 2013, protocol: 6315). All participants were given enough time to read carefully the ICF and to ask relevant questions before they signed it. Apart from the ICF for participating in the EMENO, separate ICFs were provided for storing leftover samples and for taking additional samples for research not including or including DNA analysis.

Barcodes were prepared with unique individual codes. These codes were a combination of digits demonstrating the region, the interviewer, and serial number of the participant. Barcodes were given to interviewers and physicians and attached to all forms and questionnaires as well as referral form for blood examinations and blood tubes. Specific deep freeze barcodes were printed and used to store aliquots till blood testing or preservation for future research (if relevant ICFs were signed). Personal data were stored in a separate safely stored file and were linked by code with the rest of the participants' information. Access to personal data was limited to each region's principal investigator and was only used to contact participants for sending thank your letters, the medical report, and for future follow-up, if they had consented to it.

## Researchers' Training

Training materials were developed by the SC on data collection through questionnaire, sampling, blood collection, and physical measurements protocols. All training materials were available

on electronic database, accessible by all researchers. A 2-days training program was organized on September 12, 2013, to September 13, 2013 and lasted 16 hours acknowledged by the Pan-Hellenic Medical Association. All selected (by the time of training implementation) field study staff (30 individuals) attended it. Training sessions included a practical session, where field researchers completed questionnaires in groups of 3 to 5 people and under the supervision of a member of the scientific committee, whereas physicians did medical examinations in volunteers. All participants completed a training program evaluation form. After the core training, a train-the-trainer approach was used to decentralize training in each region. The trained staff, under supervision of the principal investigator of each region, was in charge for training the new staff entering the group throughout the study implementation.

## Pilot Study

We piloted the whole study in a sample of 160 people from urban and rural areas in 7 regions of Greece (Athens, Thessaloniki, Thessaly, Peloponnese, Crete, Epirus, and Thrace). The main objectives or the pilot study were to (1) determine feasibility of the study protocol, (2) check adequacy of research tools, (3) test the performance of measurement instruments, (4) assess the effectiveness of the sampling approaching method, (5) identify potential logistical problems or deficiencies, (6) collect preliminary data for the survey, and (7) check the competence of investigators' and physicians' training.

Although field researchers followed the provided instructions and protocols (they had been provided with special identities and letters of information, whereas local police station was informed about the survey), the response rates were very low, ranging from 27% to 50%. However, among those who consented to EMENO, a particularly high percentage (ranged from 90%-100%) also participated in the physical examinations, indicating that the main difficulty was to gain the trust of eligible households to open the door. This was a function of field researchers lacking prior experience and of limited study promotion. The issue was extensively discussed by the SC and additional ways to effectively promote the study were identified (see Study Dissemination section). Experienced field researchers (mainly working in surveys run by the Hellenic Statistical Authority) were invited to provide additional guidance to EMENO researchers. Women's participation was particularly high (3447, 57.50%), revealing the importance of strictly following the sampling method. Following pilot study's data quality control, mistakes in the Web-based database (skip mistakenly) were detected and corrected, whereas further explanations were provided for specific questions (eg, what we mean by *intense physical exercise*). Further adjustments to the questionnaire were made wherever this was deemed necessary.

## Implementation of the Main Field Study

The principal investigator of each collaborating School of Medicine had the field study of the nearby regions under his or her responsibility (Figure 1). Before starting the filed study, researchers and physicians signed a confidentiality form and vaccination for hepatitis B was recommended. In addition, they were provided with study identities with their photo and personal information. In EMENO's website, apart from information

about the study, the photos, and key curriculum vitae information of the researchers were posted. Field researchers were provided with maps of each sampling point, a laptop with the database, and all necessary printed material. For obviation of participants' mistrust, an informative letter was sent to the local police departments informing about the study. In addition, in case of blocks of flats, an official notification letter was given to the apartment manager to facilitate the entry of field researchers in the eligible flats.

Blood samples were kept in cold environment (at 4°C) until transported, latest within 12 to 18 hours, to collaborating local laboratories for centrifugation. Centrifugal aliquots were stored in the collaborating laboratories at −80 °C until they were sent to the central laboratory (National Retrovirus Reference Center, Laboratory of Hygiene, Epidemiology and Medical Statistics of the Medical School of the University of Athens) for testing.

The ideal blood sampling procedure was determined according to local circumstances: In urban and semi-urban areas, physicians made home visits at scheduled appointments. In rural areas, and in agreement with the participants, blood sampling and medical examinations were performed at nearby health centers.

## Study Dissemination

Study informational brochures were developed and distributed to eligible houses. Additional promotion actions included:

1. Informing meetings with local authorities (mayors and deputies of social policy). The study was conducted with the cooperation of local authorities. The collaboration included (1) an invitation to the study through a letter from the municipality. The researchers' names were mentioned in the letter, (2) announcement of the study on municipality's site, (3) information brochures distribution at infrastructures under the responsible person of the Municipality (such as elderly protection centers, social welfare, and pharmacies), (4) phone calls to eligible households, if these were available in the municipality structures, (5) studies' posters suspension at key point areas of the municipality, and (6) escorting the field researcher by an employee of the Municipality, where feasible.
2. Request and approval of study information letter by the Ministry of education. The Ministry sent a letter of approval to all schools of primary and secondary education, so that promotion functions would be welcome.
3. Request and approval of a letter to promote the study by the Holy Synod. The Holy Synod sent a letter of approval to all orthodox churches of Greece, so that the congregation would be encouraged to participate in the survey.
4. Events in central locations adjacent to sampling points. These events were attended both by the scientific leaders of each region as well as the field researchers and volunteers (mainly students of medical schools).
5. Central and local press conferences in all study regions, where the study objectives and its expected benefits were presented.

## Sending Medical Results to the Participants

Each participant received the following for his or her participation: (1) appreciation letter, (2) results of the medical examinations, (3) medical report (with recommendations) based on the personal medical findings, (4) pyramid of the Mediterranean diet, and (5) National Organization for the Provision of Healthcare Services' recommendations for preventive measures and adult vaccination. A network of specialized physicians was established to which participants identified with urgent previously undiagnosed conditions (eg, hypertension and COPD) were administered at no cost for the participant.

## Information System

The central database was hosted on a central server, located in the Laboratory of Hygiene, Epidemiology and Medical Statistics of the Medical School of the National and Kapodistrian University of Athens. Actions were taken for data security. All data related operations were made through secure transactions encrypted with 128-bit encryption, and both the databases were Atomicity Consistency Isolation Durability-compliant to ensure that all the previously described operations are unique, consistent, isolated, and durable. During field study, data quality assessments were conducted regularly, and adjustments were made when necessary.

## Statistical Analysis

EMENO has a complex study design, with varying selection probabilities across regions. Thus, for the statistical analysis, sampling weights, being the reciprocal of the selection probabilities, should be applied. Although analyses using the sampling weights should give representative estimates, departures in the age and sex distribution from the respective ones based on the 2011 census are expected as women and older individuals are usually over-represented in this kind of surveys. To adjust for such discrepancies, auxiliary information from the 2011 census to reflect Greek population's distribution of age and gender by geographical region was used (poststratification weighting). Thus, the initial weights are multiplied by a correcting factor $f_{PSi}$ as shown below:



Where, $w_{(base)i}$ is the sampling weight, $N_m$ the population's total in the poststratum, $m_i$ and $n_m$ is the corresponding sample's size. Thus, the final weights are $w_{PSi} = w_{(base)i} f_{Psi}$.

Adjustment for nonresponse could also be applied. In the EMENO study, additional data for nonresponders' characteristics were not available. However, response rates were recorded within sampling points. Adjustment for nonresponse could be done by multiplying the initial weights with the reciprocal of the response rate under certain (mostly untested) assumptions. Investigation of the effect of adjusting for nonresponse on study estimates is being planned.

The weighting procedure may lead to weights with extreme values. In such cases, trimming of the weights (usually at the 95th or the 99th centile of their distribution) is suggested, as extreme weights may have a serious impact on the variance of

the estimates. Untrimmed weights are adjusted so that the sum of the weights after trimming to be equal to the sum before trimming. Weights will be graphically investigated to assess the necessity of weight trimming. To determine estimates' variances, we applied the Taylor series linearization method as recommended by National Center for Health Statistics and also used in the NHANES study [30].

Some EMENO participants refused to have physical examinations and/or to provide blood samples. However, those who provided blood samples or had physical exams may differ from those who did not. To adjust for that, we can use either inverse probability weighting or multiple imputation methods. In a preliminary sensitivity analysis we performed [31], we found that these 2 methods provide comparable results; however, this issue needs further investigation.

## Results

### Response Rates

The sampling flowchart is shown in Figure 2. In total, 12,960 households were visited, of which 4620 were noneligible (716 professional use, 1132 uninhabited houses, 1882 no reply at 3 attempts, 372 vacation homes, 365 away from home for more than 2 weeks, and 153 undefined). Among eligible households, the overall response rate for interviewing was 72%. Response rates differed substantially by geographical region and degree of urbanization, being higher in small or rural places and lower in big cities (Table 1). Among interviewed participants, 80.54% (4827) participated in at least one physical examination, 74.20% (4446) had blood tests, and 60.44% (3622) spirometry. In total, 3580 individuals provided signed ICF to use leftover or additionally collected samples for future research, of whom 3528 also allowed for DNA extraction. The number of available samples by sample type were: 3259 serum; 3410 plasma and 3113 whole blood.

### Demographic Characteristics of the Participants

In total, 13 out of the 6006 EMENO participants refused to provide their age. As age is necessary to compute poststratification weights, all results provided are restricted to the 5993 participants with available age. In Table 2, the age and sex distribution of the study population as well as of the reference population are shown. Compared with the reference population (ie, people living in Greece based on the 2011 census), women and older people were over-represented in the sample. However, applying poststratification weighting resolved these discrepancies. Sociodemographic characteristics after poststratification weighting are shown in Table 3. The mean (SD) age of the population was 49.3 (18.6) years; 51.5% (3447) were women; and 46.7% (2597) had graduated secondary or postsecondary school. Over half (3936, 61.0%) were married or in cohabitation. About 12.6% (666) were born in a country other than Greece. Data were gathered during the economic crisis in Greece (2013-2016) and this is reflected in the family income; household monthly income was up to 900€ for 39.8% (2401) of the population, whereas 15.4% (784) were unemployed. The estimated (95% CI) unemployment rate among those aged <65 years was 28.7% (26.9-30.5).

Further statistical analysis of the data is underway, and first results are expected to be submitted by the end of 2018. Main results will concern cardiovascular and respiratory diseases and their corresponding risk factors' prevalence among adult Greek population, assessing the degree of implementation of recommended prevention measures and possible barriers to access to the public health system as well as socioeconomic factors affecting health. In addition, mapping of air pollution levels and investigation of their impact on citizens' health will also be conducted.

**Figure 2.** Sampling flow chart.
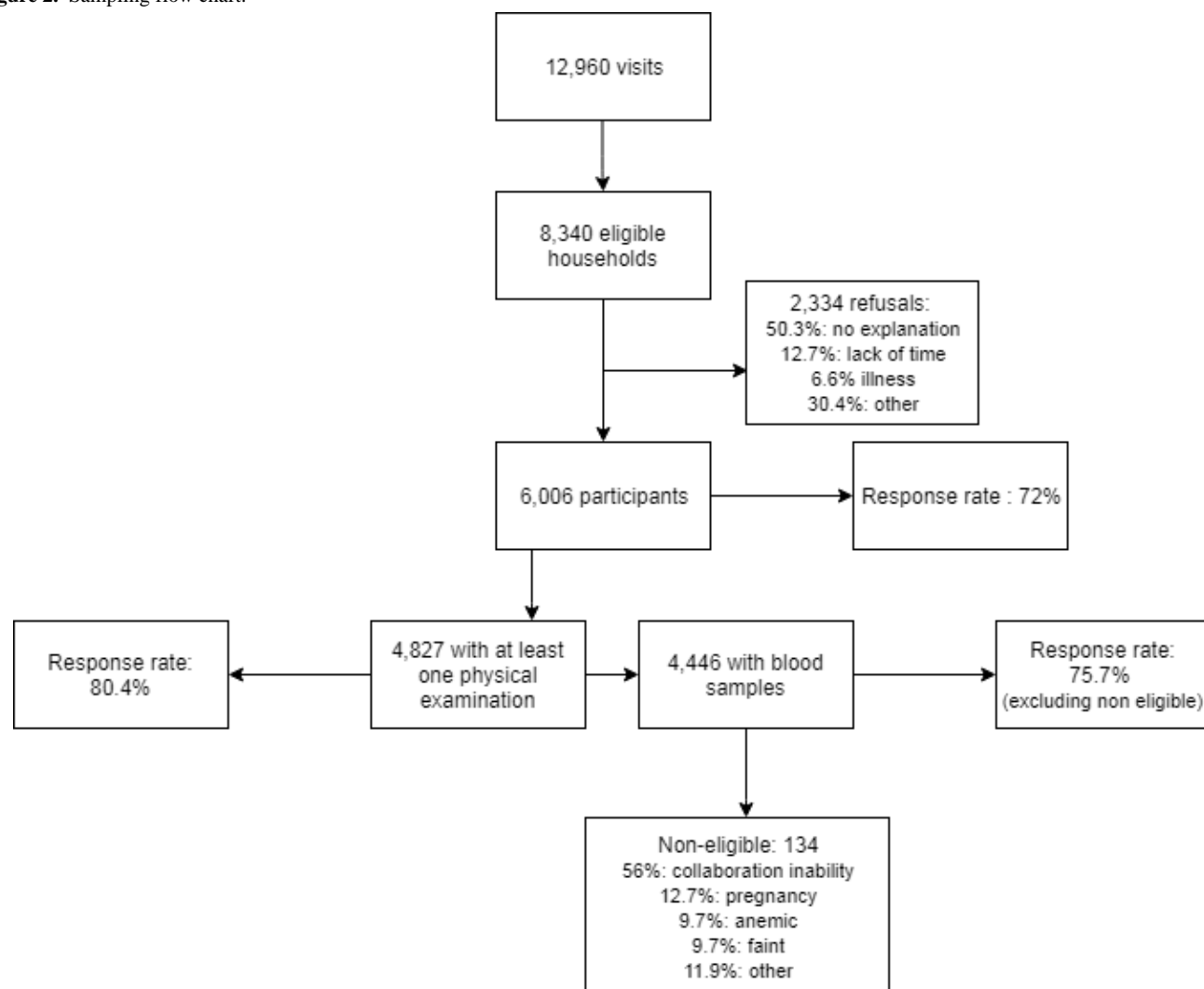


**Table 2.** Age and sex distribution in the National Survey of Morbidity and Risk Factors (EMENO) sample and the corresponding distributions based on the 2011 census.

| Age (years) | Population (Census 2011), n (%) | | Sample (EMENO), n (%) | |
| --- | --- | --- | --- | --- |
| | Male | Female | Male | Female |
| 18-29 | 817,789 (9.16) | 765,498 (8.57) | 298 (4.97) | 336 (5.61) |
| 30-39 | 827,542 (9.27) | 807,762 (9.05) | 350 (5.84) | 469 (7.82) |
| 40-49 | 781,112 (8.75) | 799,983 (8.96) | 406 (6.77) | 614 (10.24) |
| 50-59 | 677,018 (7.58) | 714,836 (8.01) | 425 (7.09) | 688 (11.48) |
| 60-69 | 543,421 (6.09) | 590,624 (6.62) | 484 (8.08) | 627 (10.46) |
| 70-79 | 456,247 9 (5.11) | 560,995 (6.28) | 383 (6.39) | 474 (7.87) |
| 80+ | 231,746 (2.60) | 351,588 (3.94) | 200 (3.34) | 241 (4.02) |
| Total | 4,334,875 (48.56) | 4,591,286 (51.44) | 2546 (42.48) | 3447 (57.52) |

**Table 3.** Demographic characteristics of study participants after poststratification weighting (N=5993).

| Demographic characteristics | Statistics |
| --- | --- |
| **Gender, n (weighted %)** | |
| Male | 2546 (48.5) |
| Female | 3447 (51.5) |
| **Age (years)** | |
| Weighted median (interquartile range) | 47.7 (34-64) |
| **Educational level, n (weighted %)** | |
| Up to primary | 2114 (28.8) |
| Up to secondary or postsecondary | 2575 (46.7) |
| University or higher | 1200 (23.1) |
| Unknown | 82 (1.3) |
| **Family status, n (weighted %)** | |
| Married or in cohabitation | 3936 (61.0) |
| Single | 1995 (38.0) |
| Unknown or no answer | 62 (1.0) |
| **Household Income, n (weighted %)** | |
| Up to 900€ | 2401 (39.8) |
| 900€1700€ | 1658 (28.1) |
| >1700€ | 606 (10.9) |
| No answer | 1328 (21.3) |
| **Employment status, n (weighted %)** | |
| Employed | 2089 (38.7) |
| Retired or household | 2641 (35.4) |
| Unemployed | 784 (15.3) |
| Other or unknown | 479 (10.6) |
| **Country of birth, n (weighted %)** | |
| Greece or Cyprus | 5327 (87.4) |
| Balkans | 297 (5.9) |
| East Europe or Former Soviet Union | 89 (1.7) |
| West Europe or Australia or America | 101 (1.7) |
| Africa | 42 (0.9) |
| Asia | 51 (1.1) |
| Unknown | 86 (1.4) |

# Discussion

## Strengths and Limitations

EMENO is one of the first population-based surveys focused on CVD and chronic respiratory diseases and their risk factors, which also includes anthropometric and physical examinations and blood tests as well as prevention measures uptake, health care facilities, and medicine use for the adult population in Greece. To the best of our knowledge, such data are rarely combined. The main goal or benefit of the EMENO study is that it provides valid estimates of various health indices. Study design and sampling procedure make EMENO one of the most representative of the current general adult population in Greece, thus enabling national authorities to develop tailored and more efficient strategies for disease prevention and management.

Expected benefits at local and international level are multifaceted. Greece will be able to provide European and international agencies with nationwide estimates of the prevalence of chronic diseases and health risks. Moreover, available data will help society with the necessary evidence to rationally monitor health systems and adjust health policies. Participants, local authorities, and nongovernmental organizations will be informed and become aware of health indices, potential inequalities, and impacts of modern lifestyles

and behaviors. This increased awareness will contribute to successfully implement measures to resolve inequalities and to future lifestyle changes. Importantly, some participants have personally benefited already from the diagnosis of previously undiagnosed conditions.

As already mentioned, in EMENO, a blood specimens' storage bank was established providing the opportunity for future studies to estimate the prevalence of other conditions with minimal additional cost. Having also obtained participants' consent for DNA analyses makes EMENO a powerful resource to investigate this study's and future hypotheses relating to environmental, lifestyle, biochemical, and genetic causes of CVD and chronic respiratory diseases in a representative Mediterranean population. EMENO has purposefully adopted harmonized data collection methods that allow data linkage with national or international cohorts or surveys. In case inequalities would be identified, EMENO results will generate new scientific hypotheses prompting to future-focused studies, for example, further studies in specific subpopulations and/or health conditions, explorations of specific diseases, or in specific regions, hazardous environmental exposures.

Study materials (including protocols and questionnaires) will contribute to European and international operators, universities, and research groups aiming to compare and harmonize health surveys and health indices, as the experience gained through studies' implementation will be shared with other European groups conducting health surveys. Scientific reports and papers will be of major interest to other public health scientists.

Within the framework of EMENO, a network of specialists of different disciplines (epidemiologists, statisticians, internal medicine physicians, pneumonologists, microbiologists, public health experts, and database experts) as well as an official collaboration of all Greek schools of medicine has been established. Retaining such a network will be an added value and scientists' mobility and interaction will be boosted. The steering committee will put all its effort to ensure network's sustainability.

Following the successful example of NHANES study, studies such as EMENO could be repeated (possibly with a different focus) in a 5-year time to assess the temporal trends in health indicators and possibly to also investigate health conditions additional to those of the original study health conditions. If such a study would be approved and if adequate funds are ensured, study's participants could be followed up (eg, through telephone interviews) to assess their health progression. The financial burden of such a study will be relatively low, whereas the added values (estimation of diseases' incidence and of life expectancy) will be massive. In such a case, the study will be transformed from a cross-sectional to a cohort one.

Despite the significant benefits of EMENO, there are also some limitations. One major limitation was the sampling methodology and specifically the door-to-door approach for data collection. Although this method is quite common for conducting health screenings [32,33] and is the main approach used by the NHANES [34,35], Hillier et al [23] claimed that "the door-to-door method is too costly for researchers, too intrusive for participants and too dangerous for interviewers." Conducting interviews face-to-face contribute to the quality of data collected but some serious considerations arise, mainly about interviewers' safety. It demands a very well-experienced and trained staff; a good amount of time spent for their training and regular team meetings; however, on the other hand, it also allows for further social observations of the household and neighborhood conditions, which can add valuable information to the studies' main purposes [36]. Another limitation was that for feasibility reasons, we only visited large islands (Rhodes, Corfu, and Lesbos), excluding small ones, which may be more likely to face problems to access to health services.

## Conclusion

The EMENO results will improve thus our understanding on health and health risks of people living in Greece, which will contribute to the evidence-based evaluation of health policies and preventive actions. Using EMENO results as background information, future health burden can be estimated for the main diseases under investigation (CVDs, chronic respiratory diseases, and diabetes). Predictions of future disease burden can be combined with collected data on the use of health services and medicines and with health economics models to estimate future health needs and costs. In conclusion, EMENO comprises a unique health data resource and a valuable bio-resource in a Mediterranean population.

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## Conflicts of Interest

Multimedia Appendix 1
EMENO Questionnaire Sources.
[PDF File (Adobe PDF File), 221 KB - resprot_v8i2e10997_app1.pdf ]

Multimedia Appendix 2
Standardized Instruments.
[PDF File (Adobe PDF File), 120 KB - resprot_v8i2e10997_app2.pdf ]

## References

1. World Health Organization (WHO). 2015. Health in 2015 from MDGs Millennium Development Goals to SDGs Sustainable Development Goals. 2015 URL: http://apps.who.int/medicinedocs/documents/s22230en/s22230en.pdf [accessed 2018-11-27] [WebCite Cache ID 74Ew6mTBg]

2. World Health Organization (WHO). World Health Statistics 2017: Monitoring health for the SDGs (Sustainable Development Goals) URL: http://apps.who.int/iris/bitstream/handle/10665/255336/9789241565486-eng.pdf?sequence=1 [accessed 2018-11-27] [WebCite Cache ID 74EvyxMpy]

3. European Health Network. 2017. European Cardiovascular Disease Statistics 2017 edition URL: http://www.ehnheart.org/images/CVD-statistics-report-August-2017.pdf [accessed 2018-11-27] [WebCite Cache ID 74EwN8pC4]

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. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002 Dec 14;360(9349):1903-1913. [Medline: 12493255]

6. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005 Jan;365(9455):217-223. [doi: 10.1016/S0140-6736(05)17741-1] [Medline: 15652604]

7. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015 Aug 22;386(9995):743-800 [FREE Full text] [doi: 10.1016/S0140-6736(15)60692-4] [Medline: 26063472]

8. Huang KL, Su TP, Chen TJ, Chou YH, Bai YM. Comorbidity of cardiovascular diseases with mood and anxiety disorder: a population based 4-year study. Psychiatry Clin Neurosci 2009 Jun;63(3):401-409 [FREE Full text] [doi: 10.1111/j.1440-1819.2009.01974.x] [Medline: 19566773]

9. Phillips AC, Batty GD, Gale CR, Deary IJ, Osborn D, MacIntyre K, et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. Psychosom Med 2009 May;71(4):395-403. [doi: 10.1097/PSY.0b013e31819e6706] [Medline: 19321850]

10. World Health Organization (WHO). 2017. Cardiovascular diseases (CVDs) URL: http://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [accessed 2018-11-27] [WebCite Cache ID 74ExXOs3v]

11. Hellenic Republic, Greek Statistical Authority. Greek Statistical Authority. [Health Survey: Year 2014] URL: http://www.statistics.gr/documents/20181/1845c3bc-b9d5-41f6-89df-a5436ad3dc23 [accessed 2018-02-26] [WebCite Cache ID 6xWOelvGF]

12. Kondilis E, Giannakopoulos S, Gavana M, Ierodiakonou I, Waitzkin H, Benos A. Economic crisis, restrictive policies, and the population's health and health care: the Greek case. Am J Public Health 2013 Jun;103(6):973-979. [doi: 10.2105/AJPH.2012.301126] [Medline: 23597358]

13. Economou M, Madianos M, Peppou LE, Patelakis A, Stefanis CN. Major depression in the era of economic crisis: a replication of a cross-sectional study across Greece. J Affect Disord 2013 Mar 05;145(3):308-314. [doi: 10.1016/j.jad.2012.08.008] [Medline: 22939388]

14. Alexander CM, Landsman PB, Teutsch SM, Haffner SM, Third National Health and Nutrition Examination Survey (NHANES III), National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003 May;52(5):1210-1214 [FREE Full text] [Medline: 12716754]

15. Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, et al. The decline in blood lead levels in the United States. The National Health and Nutrition Examination Surveys (NHANES). J Am Med Assoc 1994 Jul 27;272(4):284-291. [Medline: 8028141]

16. Tolonen H, Paalanen L, Sääksjärvi K, Koponen P, Palosaari T, Kuulasmaa K. European Health Examination Survey. 2017. Inequalities in availability of health information from national health examination surveys in EU Member States URL: http://www.ehes.info/publications/Report_inequalities_health_information.pdf [accessed 2018-03-01] [WebCite Cache ID 6xajTUNAP]

17. European Health Survey Information Database (EUHSID). European Health Interview & Health Examination Survey Database URL: https://hishes.wiv-isp.be/index.php?hishes=home [accessed 2018-03-01] [WebCite Cache ID 6xajzlkeQ]

18. Panagiotakos DB, Pitsavos C, Chrysohoou C, Risvas G, Kontogianni MD, Zampelas A, et al. Epidemiology of overweight and obesity in a Greek adult population: the ATTICA Study. Obes Res 2004 Dec;12(12):1914-1920 [FREE Full text] [doi: 10.1038/oby.2004.239] [Medline: 15687390]

19. Panagiotakos DB, Pitsavos CH, Chrysohoou C, Skoumas J, Papadimitriou L, Stefanadis C, et al. Status and management of hypertension in Greece: role of the adoption of a Mediterranean diet: the Attica study. J Hypertens 2003 Aug;21(8):1483-1489. [doi: 10.1097/01.hjh.0000084706.87421.7c] [Medline: 12872041]

20. Stergiou GS, Thomopoulou GC, Skeva II, Mountokalakis TD. Prevalence, awareness, treatment, and control of hypertension in Greece: the Didima study. Am J Hypertens 1999 Oct;12(10 Pt 1):959-965. [Medline: 10560781]

21. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in elderly people. Br Med J 1995 Dec 02;311(7018):1457-1460 [FREE Full text] [Medline: 8520331]

22. Naska A, Orfanos P, Chloptsios Y, Trichopoulou A. Dietary habits in Greece: The European Prospective Investigation into Cancer and Nutrition (the EPIC project). Archives of Hellenic Medicine 2005;22(3):259-269 in Greek.

23. Hillier A, Cannuscio CC, Griffin L, Thomas N, Glanz K. The value of conducting door-to-door surveys. Int J Soc Res Methodol 2014;17(3):285-302 [FREE Full text] [doi: 10.1080/13645579.2012.733173]

24. Cochran WG. Sampling Techniques, 3rd edition. New York, USA: Wiley, John & Sons, Incorporated; 1977.

25. Damianou C. Sampling Methodology: Techniques and Applications. Athens: Ethra Publications; 1999.

26. Binson D, Canchola JA, Catania JA. Random selection in a national telephone survey: a comparison of the Kish, Next-Birthday, and Last-Birthday methods. J Off Stat 2000;16(1):53-59 [FREE Full text]

27. Pitsavos C, Panagiotakos DB, Chrysohoou C, Stefanadis C. Epidemiology of cardiovascular risk factors in Greece: aims, design and baseline characteristics of the ATTICA study. BMC Public Health 2003 Oct 20;3:32 [FREE Full text] [doi: 10.1186/1471-2458-3-32] [Medline: 14567760]

28. Sudman S. Applied Sampling. In: Rossi PH, Wright JD, Anderson AB, editors. Handbook of Survey Research. New York, USA: Academic Press; 1983:145-194.

29. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338. [doi: 10.1183/09031936.05.00034805] [Medline: 16055882]

30. Johnson CL, Dohrmann SM, Kerckove VD, Diallo MS, Clark J, Mohadjer LK, et al. National Health and Nutrition Examination Survey: National Youth Fitness Survey Estimation Procedures, 2012. Vital Health Stat 2 2014 Nov(168):1-25 [FREE Full text] [Medline: 25569584]

31. Kalpourtzi N, Touloumi G. Adjusting for unit non-response in the EMENO study: inverse probability and multiple imputation methods. 2017 Presented at: 9th EMR and Italian Region IBS Conference; May 8-12, 2017; Thessaloniki, Greece.

32. Hernandez MT, Klausner JD, McFarland W, Wong E, Bolan G, Molitor F, et al. Hepatitis B prevalence in young women living in low-income areas: the population-based San Francisco Bay area's Young Women's Survey. Sex Transm Dis 2000 Oct;27(9):539-544. [Medline: 11034528]

33. Seña AC, Hammer JP, Wilson K, Zeveloff A, Gamble J. Feasibility and acceptability of door-to-door rapid HIV testing among latino immigrants and their HIV risk factors in North Carolina. AIDS Patient Care STDS 2010 Mar;24(3):165-173 [FREE Full text] [doi: 10.1089/apc.2009.0135] [Medline: 20214484]

34. Centers for Disease Control and Prevention. 2011. National Health and Nutrition Exam Survey: key concepts about survey methodology URL: https://www.cdc.gov/nchs/tutorials/NHANES/SurveyOrientation/SurveyOverview/Info2.htm [accessed 2018-12-02] [WebCite Cache ID 74MXlwj9i]

35. Nieto FJ, Peppard PE, Engelman CD, McElroy JA, Galvao LW, Friedman EM, et al. The Survey of the Health of Wisconsin (SHOW), a novel infrastructure for population health research: rationale and methods. BMC Public Health 2010 Dec 23;10:785 [FREE Full text] [doi: 10.1186/1471-2458-10-785] [Medline: 21182792]

36. Davies K. Knocking on doors: recruitment and enrichment in a qualitative interview‐based study. Int J Soc Res Methodol 2011 Jul;14(4):289-300. [doi: 10.1080/13645579.2010.516645]

## Abbreviations

**CAPI:** computer-assisted personal interview
**COPD:** chronic pulmonary obstructive disease
**CVD:** cardiovascular disease
**EMENO:** National Survey of Morbidity and Risk Factors
**HES:** health examination surveys
**ICF:** informed consent form
**NHANES:** National Health and Nutrition Exam Survey
**PSU:** primary sampling unit
**SC:** scientific committee
**SOP:** standardized operating procedure

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Protocol

# The Safety, Tolerability, and Effects on the Systemic Inflammatory Response and Renal Function of the Human Chorionic Gonadotropin Hormone-Derivative EA-230 Following On-Pump Cardiac Surgery (The EASI Study): Protocol for a Randomized, Double-Blind, Placebo-Controlled Phase 2 Study

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## Abstract

**Background:** The cardiac surgery–induced systemic inflammatory response may induce postoperative hemodynamic instability and impairment of renal function. EA-230, a linear tetrapeptide (A-Q-G-V), is derived from the beta chain of the human chorionic gonadotropin pregnancy hormone. It has shown immunomodulatory and renoprotective effects in several animal models of systemic inflammation. In phase 1 and phase 2a studies, these immunomodulatory effects were confirmed during human experimental endotoxemia, and EA-230 was found to have an excellent safety profile.

**Objective:** The objective of this first in-patient study is to test the safety and tolerability as well as the immunomodulatory and renoprotective effects of EA-230 in a proof-of-principle design in patients with systemic inflammation following on-pump cardiac surgery.

**Methods:** We describe a prospective, randomized, double-blind, placebo-controlled study in which 180 elective patients undergoing on-pump coronary artery bypass grafting, with or without concomitant valve surgery, are enrolled. Patients will be randomized in a 1:1 ratio and will receive either EA-230 (90 mg/kg/hour) or a placebo. These will be infused at the start of the surgical procedure until the end of the use of the cardiopulmonary bypass. The primary focus of this first-in-patient study will be on safety and tolerability of EA-230. The primary efficacy end point is the modulation of the inflammatory response by EA-230 quantified as the change in interleukin-6 plasma concentrations after surgery. The key secondary end point is the effect of EA-230 on renal function. The study will be conducted in 2 parts to enable an interim safety analysis by an independent data monitoring committee at a sample size of 60. An adaptive design is used to reassess statistical power halfway through the study.

**Results:** This study has been approved by the independent competent authority and ethics committee and will be conducted in accordance with the ethical principles of the Declaration of Helsinki, guidelines of Good Clinical Practice, and European Directive 2001/20/CE regarding the conduct of clinical trials. Results of this study will be submitted for publication in a peer-reviewed scientific journal. Enrollment of this study commenced in July 2016, and results are expected at the end of 2018.

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**Conclusions:** This adaptive phase 2 clinical study is designed to test the safety and tolerability of EA-230 in patients undergoing cardiac surgery. In addition, efficacy end points focused on the effect of the systemic inflammatory response and renal function are investigated.

**Trial Registration:** ClinicalTrials.gov NCT03145220; https://clinicaltrials.gov/ct2/show/NCT03145220 (Archived by WebCite at http://www.webcitation.org/74JPh8GNN)

**International Registered Report Identifier (IRRID):** DERR1-10.2196/11441

## Introduction

### Background

The systemic inflammatory response syndrome is characterized by a dysregulated inflammatory reaction in response to conditions such as a severe infection, trauma, and major surgery [1,2]. Although activation of the immune system is essential, a too-pronounced systemic inflammatory response may result in failure of 1 or more organ systems and is associated with morbidity and mortality rates up to 30% [3,4]. Development of acute kidney injury (AKI) represents an early and common manifestation of inflammation-induced organ failure [5-7].

During cardiac surgery, multiple insults, including sternotomy, application of cardiopulmonary bypass (CPB), and aortic cross-clamping are well known to contribute to a systemic inflammatory response [8-11]. The extent of this response is directly associated with impaired patient outcome, as elevated postoperative levels of interleukin (IL)-6 correlate with adverse outcomes and mortality [5,12]. Furthermore, this inflammatory response is believed to play a central role in the pathogenesis of AKI following cardiac surgery [13,14]. In addition, renal impairment is, in turn, independently associated with adverse outcome and impaired patient survival [15,16].

### Immunomodulation

Immunomodulatory strategies until now have failed to demonstrate clear beneficial effects in cardiac surgery patients [17]. For example, large trials on the use of high-dose corticosteroids did not improve overall patient outcome in cardiac surgery patients [18,19], although positive effects on respiratory variables in selected patient groups may be present, as found in post hoc analyses [19]. Nonspecific anti-inflammatory effects and the broad spectrum of side effects of these interventions may have contributed to the lack of overall beneficial effects of these compounds. As a result, current strategies consist of supportive treatment, and novel strategies aimed to attenuate the exaggerated proinflammatory response remain highly warranted.

Of interest, pregnancy is associated with an immune-tolerant adaptation of the immune system, necessary to facilitate the symbiosis of 2 major histocompatibility complex incompatible individuals [20]. Likely related to this effect, a remarkable improvement of several immune-mediated inflammatory diseases is observed during pregnancy [21-23]. Nevertheless, pregnant women are eminently capable of combating infections and often produce antibodies against paternal alloantigens of the fetus, demonstrating that they are fully immunocompetent. These features are suggestive of a selective modulation of the immune system in such a way that harmful immune processes to mother and fetus are suppressed, whereas beneficial immune processes remain unaffected. In this context, an array of oligopeptides related to the primary structure of the human chorionic gonadotropin (hCG) pregnancy hormone was designed and evaluated in experimental animal models of systemic inflammation [24-29]. Of the evaluated oligopeptides, the linear tetrapeptide (sequence: A-Q-G-V), now named EA-230, was shown to exert immunomodulatory effects and to protect against organ failure and associated mortality [25,26,28,30,31]. In particular, the administration of EA-230 resulted in renal function preservation, for example, in ischemia-reperfusion and kidney transplant models [30,31]. It is probable that the profound effects of pregnancy on renal function through increasing renal flow and subsequently increasing glomerular filtration rate (GFR) are causal to these findings [32]. Phase 1 safety studies of EA-230 showed that intravenous administration is well tolerated and has an excellent safety profile [33]. In a phase 2a study during human experimental endotoxemia, a model of controlled systemic inflammation induced by the administration of endotoxin, no safety concerns emerged. Furthermore, subjects treated with the highest dose of EA-230 (90 mg/kg/hour) resulted in less flu-like symptoms, attenuated development of fever, and reduced levels of proinflammatory mediators (among others IL-6 and IL-8) when compared with placebo-treated endotoxemia subjects [34].

### Objectives

A proof-of-principle study is now warranted to (1) investigate the safety profile of EA-230 in patients, (2) investigate whether EA-230 is able to modulate the systemic inflammatory response in patients, and (3) explore whether this translates into a clinical benefit in terms of prevention of organ dysfunction, in particular, renal injury. In this paper, we describe the design of a double-blind, placebo-controlled, randomized, adaptive phase 2 study with EA-230 in patients undergoing elective on-pump cardiac surgery.

## Methods

### Design and Setting

This study is a single-center, prospective, double-blind, placebo-controlled, randomized, single-dose phase 2 study. It has an adaptive design to evaluate the safety and

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immunomodulatory effects of EA-230 in patients undergoing on-pump cardiac surgery for coronary artery bypass grafting (CABG) with or without concomitant valve surgery. A total of 180 eligible patients are planned for inclusion and will be randomized to receive either active or placebo treatment in a 1:1 ratio. The study will be conducted in a tertiary hospital, the Radboud University Medical Center, Nijmegen, the Netherlands. This is the first-in-patient safety and tolerability study, of which the primary efficacy objective is to assess the immunomodulatory effects of EA-230. The key secondary efficacy end point is the effect of EA-230 on renal function. With regard to safety in this first-in-patient study, the study will be conducted in 2 parts. In the first part, 60 patients (40-50 low-risk patients) will be included (see Textboxes 1 and 2 for details) followed by an independent safety analysis by the data monitoring committee (DMC). Patient enrollment will only continue if no safety concerns are raised, and more high-risk patients will be included.

In addition, an adaptive design is used to re-evaluate the statistical power and group size of the study using patient data obtained during the first half of the study. This study is described in accordance with the Standard Protocol Items: Recommendations for Interventional Trial guidelines [35] and registered at ClinicalTrials.gov (identifier: NCT03145220).

## Study Objectives

### Primary Objectives

The primary objectives of the study are to (1) assess the safety and tolerability of EA-230 in patients undergoing on-pump cardiac surgery (related to safety) and (2) assess the immunomodulatory effects of EA-230 in patients with systemic inflammation following on-pump cardiac surgery (related to efficacy).

### Key Secondary Objective

The key secondary objective is to assess the effects of EA-230 on changes in renal function (GFR).

All end points, including other explorative efficacy end points, are described in Table 1.

**Textbox 1.** Inclusion criteria.

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1.  Coronary artery disease, scheduled for elective on-pump coronary artery bypass grafting surgery with or without concomitant valve surgery

2.  Written informed consent to participate in this study before any study-mandated procedure

3.  Patients aged above 18 years, both male and female

4.  Patients have to agree to use a reliable form of contraception with their partners from study entry until 3 months after study drug administration

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**Textbox 2.** Exclusion criteria.

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1.  Immune compromised

    - Solid organ transplantation

    - Known HIV

    - Pregnancy

2.  Use of immunosuppressive drugs (list provided in Web-based supplementary material; see Multimedia Appendix 1)

3.  Nonelective/emergency surgery

4.  Hematological disorders

    - Known disorders from myeloid and/or lymphoid origin

    - Leucopenia

5.  Known hypersensitivity to any excipients of the drug formulations used

6.  Treatment with investigational drugs or participation in any other intervention clinical study within 30 days before study drug administration

7.  Inability to personally provide written informed consent (eg, for linguistic or mental reasons)

8.  Known or suspected of not being able to comply with the study protocol

Additional exclusion criteria to select low-risk patients (for the first 60 patients only)

1.  EuroSCORE II >4

2.  Renal function impairment: serum creatinine >200 μmol/L

3.  Liver function impairment: alanine aminotransferase/aspartate aminotransferase >3 times above upper level of reference range

4.  Left ventricular dysfunction: ejection fraction <35%

5.  Coronary artery bypass grafting procedure with concomitant valve surgery

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**Table 1.** End points.

| Categories and measures | Period |
| --- | --- |
| **Main category** | |
| **Safety and tolerability** | |
| (Serious) adverse events | Signing of informed consent form to day 90 |
| Vital signs (heart rate and blood pressure) | First 24 hours of intensive care unit (ICU) admission |
| Laboratory parameters (hemoglobin, hematocrit, leukocytes, thrombocytes, leukocyte differential blood count, sodium, potassium, creatinine, urea, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, creatine kinase, bilirubin, and C-reactive protein) | Day −1 to day +1 |
| **Efficacy** | |
| Primary: Effect of EA-230 on the inflammatory response quantified by the change in IL[a]-6 plasma concentration over time (AUC[b]). | Surgery day to day 1 |
| Key secondary: Effect of EA-230 on GFR[c] quantified by plasma clearance of iohexol (iGFR[d]) | Day −1 to day +1 |
| **Explorative category** | |
| **Inflammatory** | |
| Effect of EA-230 on the inflammatory response quantified by the change in plasma concentrations over time of IL-6, IL-8, IL-10, tumor necrosis factor-α, IL-1 receptor antagonist, monocyte chemoattractant protein-1, macrophage inflammatory protein 1 (MIP1)[e]-α, MIP1-β, vascular cell adhesion molecule, intercellular adhesion molecule, and IL-17a | Surgery day to day 1 |
| Effect of EA-230 on leukocyte kinetics quantified by change of total cell counts over time | Day −1 to day +1 |
| Effect of EA-230 on changes in body temperature in degree Celsius over time | First 24 hours of ICU admission |
| Effect of EA-230 on required insulin infusion rates | First 24 hours of ICU admission |
| **Renal** | |
| Effect of EA-230 on GFR estimated by modification of diet in renal disease calculation | Day −1 and day +1 |
| Effect of EA-230 on GFR measured by endogenous creatinine clearance using urine and plasma creatinine | Surgery to day +1 |
| Effect of EA-230 on plasma creatinine and proenkephalin | Day −1 to day +1 |
| Effect of EA-230 on changes in urine output | Surgery to day +1 |
| Effect of EA-230 on changes in urinary renal damage markers over time of kidney injury marker-1, neutrophil gelatinase–associated lipocalin, L-fatty acid–binding protein, tissue inhibitor metalloproteinase-2 and insulin-like growth factor binding protein-7, urinary IL-18, and N-acetyl-β-D-glucosaminidase | Surgery to day +1 |
| Effect of EA-230 on changes in urea, sodium, creatinine, and albumin in urine over time | Surgery to day +1 |
| Modulation in need for and duration of renal replacement therapy | Surgery to day 90 |
| Modulation in incidence of different stages of AKI[f] according to the RIFLE[g] criteria | Surgery to day 90 |
| **Cardiovascular** | |
| Modulation in vasopressor use expressed as inotropic score: (dopamine dose × 1 µg/kg/min) + (dobutamine dose × 1 µg/kg/min) + (adrenaline dose × 100 µg/kg/min) + (noradrenaline dose × 100 µg/kg/min) + (phenylephrine dose × 100 µg/kg/min) + (vasopressin (mUnits/kg/min) × 10,000) + (milrinone × 10 mcg/kg/min) [36] | First 24 hours of ICU admission |
| Effect of EA-230 on use of fluid therapy and fluid balance | First 24 hours of ICU admission |
| Effect of EA-230 on creatine kinase and troponin T plasma concentration | Surgery to end of hospital stay |
| Effect of EA-230 on thorax drain production | Surgery to end of ICU admission |
| Pulmonary: Effect of EA-230 on alveolar-arterial gradient $O_2$ gradient | Surgery to end of ICU admission |
| **General outcome** | |

| Categories and measures | Period |
|---|---|
| Effect of EA-230 on change in SOFA[h] score over time | First 24 hours of ICU admission |
| Effect of EA-230 on APACHE[i] IV score at ICU admission | Surgery to ICU admission |
| Effect of EA-230 on major clinical adverse events within 90 days (stroke, myocardial infarction, rethoracotomy, hospital readmission, and pleural and/or pericardial puncture) | Signing of informed consent form to day 90 |
| Effect of EA-230 on length of stay on ICU | Surgery to day 90 |
| Effect of EA-230 on length of hospital stay | Surgery to day 90 |
| Effect of EA-230 on 28 and 90 days mortality | Surgery to day 90 |
| **Pharmacokinetics of EA-230** | |
| Peak blood plasma levels of EA-230 | 10 min before start and stop of CPB[j] |
| Blood plasma levels of EA-230, AUC, maximal concentration, terminal half-life, clearance, and volume of distribution for a limited number of patients receiving active medication (n=15) | During EA-230 administration to 6 hours after stoppage |

[a]IL: interleukin.

[b]AUC: area under the curve.

[c]GFR: glomerular filtration rate.

[d]iGFR: glomerular filtration rate measured by plasma clearance of iohexol.

[e]MIP1: macrophage inflammatory protein.

[f]AKI: acute kidney injury.

[g]RIFLE: risk, injury, failure, loss of kidney function, and end-stage kidney disease classification.

[h]SOFA: sepsis-related organ failure assessment score.

[i]APACHE: acute physiology and chronic health evaluation.

[j]CPB: cardiopulmonary bypass.

## Patient Selection or Eligibility

All adult patients (aged >18 years) scheduled for elective on-pump CABG procedure with or without concomitant valve surgery will be screened for eligibility; see Textboxes 1 and 2 for an overview of all inclusion and exclusion criteria.

## Recruitment

Figure 1 depicts a schematic flowchart of patient recruitment and randomization.

All patients scheduled for elective CABG surgery will be included in a screening log and informed through a detailed informative brochure. After screening for inclusion and exclusion criteria, eligible patients will be personally consulted, and a final inclusion and exclusion check will be performed. After obtaining written informed consent, patients will be enrolled into the study.

## Randomization and Stratification

On the morning of surgery, patients will be randomized by nonblinded independent study personnel for active or placebo treatment. Study personnel will use Good Clinical Practice–approved data management software (Castor EDC, Amsterdam, the Netherlands) in this process. The Castor system applies a stratified randomization to ensure equal distribution between active and placebo treatment of patients with known risk factors for adverse outcomes. Moreover, 3 strata will be included: (1) a CABG procedure with or without concomitant valve surgery; (2) preoperative renal function with an estimated GFR of ≤30, 31 to 90, and >90 mL/min/1.73 m$^2$; and (3) a EuroSCORE II of <4 or ≥4 [37].

## Blinding

Double-blind conditions will be maintained for all patients, the attending physicians, and the medical study team personnel involved in all blinded study procedures, data collection, and/or data analyses. Nonblinded study personnel not involved in any other study procedures will prepare the study medication. Infusion systems and solutions for active and placebo treatment are identical in appearance and texture. The interim safety analysis will be performed by an independent data safety and monitoring board in an unblinded fashion. If it is decided that the study can be continued, all study personnel remain blinded. Unblinding will be authorized by the sponsor after completion of the study, performance of a blinded data review, and locking of the database. A sealed code break envelope is present in case emergency unblinding should be necessary.

## Study Intervention

Intravenous infusion of EA-230, 90 mg/kg/hour, or placebo, will be initiated at the moment of the first surgical incision using an automated infusion pump. Infusion rate is 250 mL/hour, and infusion will be continued until cessation of the CPB or after 4 hours of continuous infusion, whichever comes first.

EA-230 formulation is packed in sterile 5-mL glass vials, containing 1500 mg/vial, dissolved in water for injection at a final concentration of 300 mg/mL with an osmolality of 800 to 1000 mOsm/kg. The placebo formulation consists of sodium chloride diluted in water for injection in identical sterile 5-mL glass vials containing 29 mg/mL to reach a solution with an identical osmolality. EA-230 and placebo will be prepared for continuous intravenous infusion with an osmolality of <400 mOsm/kg by adding the appropriate amount of EA-230 or

placebo to 1000 mL normal saline under aseptic conditions. Placebo and active treatment vials, manufactured by HALIX BV (Leiden, the Netherlands), will be provided by the sponsor.

## Outcome Measures

An overview of the study procedures from inclusion criteria until end of follow-up is depicted in Figure 2. A detailed overview of all outcome measures is also provided in Table 1.

**Figure 1.** Study flowchart. Overview of patient recruitment, randomization, and population analysis procedures from screening to follow-up. CABG: coronary artery bypass grafting.
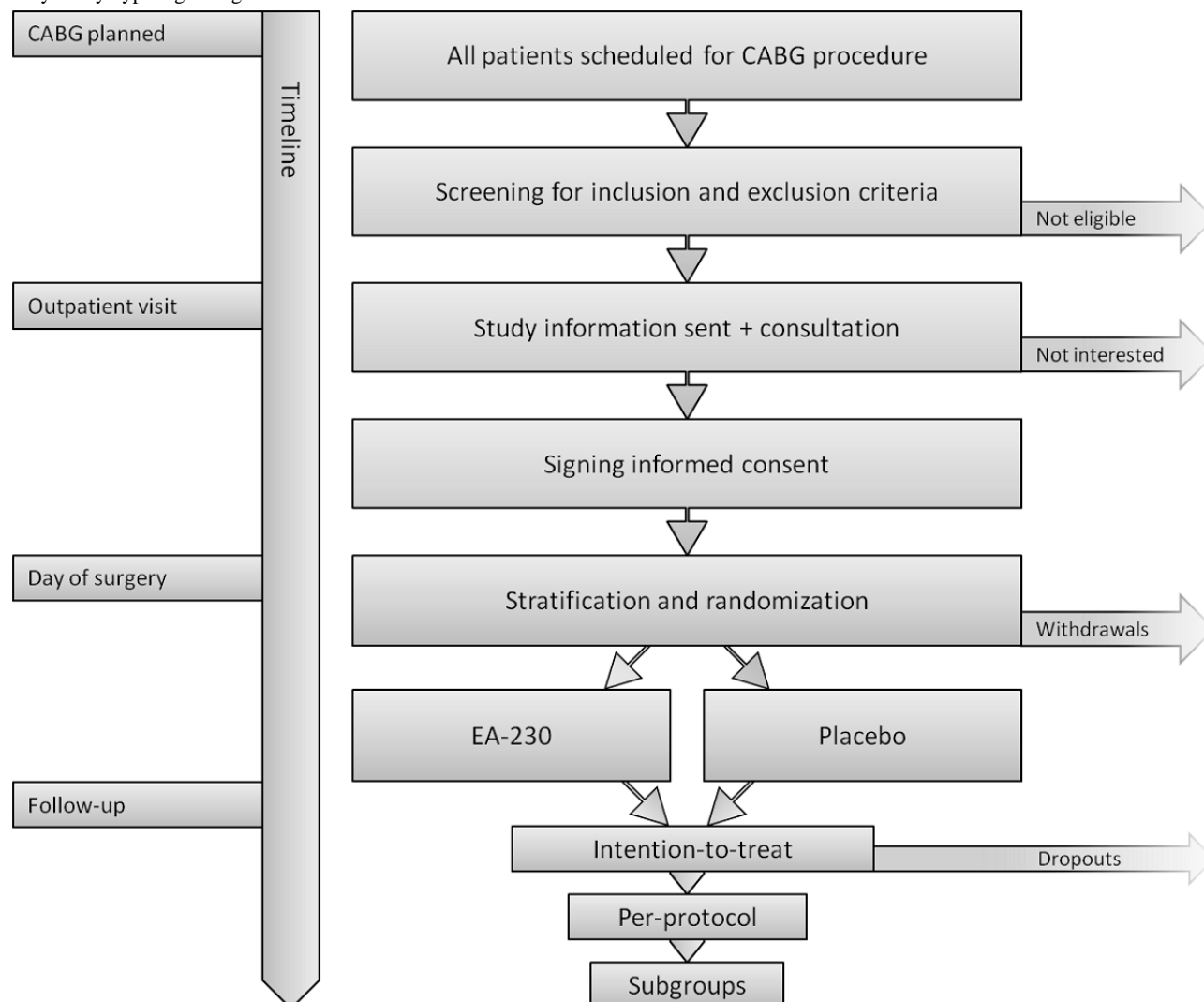


**Figure 2.** Timeline of study procedures. CPB: cardiopulmonary bypass; ICU: intensive care unit; iGFR: glomerular filtration rate measured by plasma clearance of iohexol; OR: Operating Room.
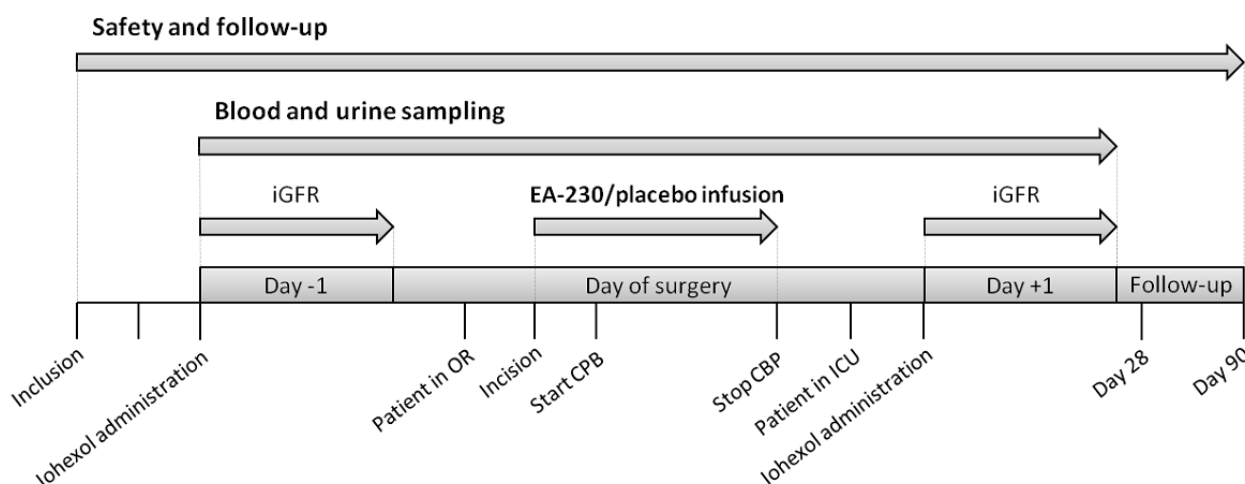
## Primary End Point

The primary focus is the safety and tolerability of EA-230. This is defined by the combination of several safety measurements: the incidence and severity of serious adverse events (SAEs) and serious unexpected suspected adverse reactions (SUSARs), the course of vital signs (heart rate and blood pressure), and the course of routine laboratory parameters. Vital signs and routine laboratory parameters will be registered during the first postoperative day when patients are admitted to the intensive care unit. Safety data will be collected from inclusion in the study until 90 days after the administration of the study drug.

The primary efficacy end point is the modulation of the inflammatory response by EA-230. This will be quantified by the difference in the area under the curve (AUC) plasma IL-6 levels over time from the start of the cardiac procedure until the first postoperative day compared with placebo. Plasma samples will be collected preincision (baseline) at the start of CPB; at 0, 2, 4, and 6 hours after cessation of the CPB; and on the morning of the first postoperative day.

## Key Secondary End Point

Modulation of changes in renal function by EA-230 is defined by changes in the GFR measured before surgery and on the morning of the first postoperative day. For the determination of the GFR, an intravenous bolus of 5 mL iohexol will be administered, and plasma samples will be collected in the following 4 hours. On the day before surgery: 90 and 240 min after iohexol administration and on the postoperative day: 90, 180, and 240 min after iohexol administration. A plasma disappearance curve of iohexol will be constructed to calculate the iohexol GFR (iGFR) according to the methods described by Delanaye et al [38].

All other secondary efficacy end points are exploratory. Data for both parts of the study will be combined to assess both the safety and efficacy of the primary and secondary end points.

## Sample Size Calculation

The primary efficacy end point, AUC of plasma IL-6 levels over time, was used for the power calculation. In the preceding clinical phase 2a study with EA-230, during experimental endotoxemia in healthy volunteers, EA-230 (90 mg/kg/hour) attenuated AUC plasma IL-6 levels by 48% compared with placebo. This first-in-patient proof-of-principle study is powered on a 30% reduction in AUC IL-6, which is deemed a relevant immunomodulatory effect. For the statistical dispersion, AUC IL-6 data from a previous CABG surgery study conducted in the same institute were used (mean 816 pg/mL/hour, SD of 520 pg/mL/hour) [39]. To correct for the nonparametric distribution of these data, the calculated sample size is increased by 15% [40]. With a 2-sided alpha of .05 and a power of 80% (beta of .2), a group size of 82 patients per treatment arm is required. However, selection of low-risk patients in the first part of the study with an expected less pronounced inflammatory response may result in an increased SD of AUC IL-6 in the overall study, and therefore, loss of study power. Hence, the sample size should be adjusted accordingly. In consultation with an independent statistician, a sample size of 90 patients per treatment arm was deemed sufficient to compensate for this

loss in power. Using an adaptive design, sample size will be re-evaluated, and possible early efficacy will be assessed halfway through the study, when 90 patients have been included. A partially unblinded independent statistician and member of the DMC will perform these analyses. For the re-evaluation of the sample size, the pooled SD of the AUC plasma IL-6 levels of the first 90 patients enrolled will be calculated and used to compare with the original sample size according to the method described by Proschan [41]. To demonstrate possible early efficacy, the approach for alpha-spending according to O'Brien-Fleming will be used [42]; a $t$ test will be performed on the collected data with the following alpha $(\alpha 1(t^*)):\alpha 1(t^*)=2-2\phi(Z\ \alpha/2/\sqrt{t^*})$ where $t^*$ represents the information fraction ($t^*=0.5 \times$ original sample size/new sample size). If $P<\alpha 1(t^*)$, the study will be stopped because of early demonstrated efficacy. When no significant differences are found during this interim analysis, the study will continue. For final analysis, an adjusted alpha will be used, corrected for alpha spending.

## Statistical Analysis

The safety parameters will be listed and summarized descriptively according to treatment. No statistical testing on safety end points will be performed. The statistical analysis plan for efficacy end points will be signed before database lock and is provided as online supplementary material (see Multimedia Appendix 2). Data will be presented as mean and SD or SE of the mean or median and interquartile range and analyses performed, depending on their distribution. The primary efficacy end point, the difference in IL-6 plasma concentrations over time (AUC IL-6 plasma levels) between treatment groups, will be analyzed using an unpaired Student $t$ test or Mann-Whitney U test (the latter if data are not normally distributed). In a secondary analysis, the AUC IL-6 plasma levels between treatment groups will also be compared using 2-way analysis of variance (ANOVA; interaction term, on log-transformed data if data are not normally distributed). Differences in the key secondary efficacy end point iGFR between treatment groups over time will be analyzed using 2-way ANOVA, as described above. All other data will be analyzed using unpaired Student $t$ tests or Mann-Whitney U tests for continuous data, 2-way ANOVA for continuous data over time as described above, and chi-square tests for categorical data. A 2-sided $P$ value <.05 is considered significant. For the primary end point, a $P$ value corrected for alpha spending will be used as described earlier. Statistical analyses will be performed using IBM SPSS (IBM, Armonk, NY, USA) and GraphPad Prism (GraphPad Software, La Jolla, CA, USA).

## Withdrawal of Study Patients

Patients may leave the study at any time, for any reason, and without any consequences. The investigator can decide to withdraw a patient from the study for urgent medical reasons or in case of inability to comply with the study protocol.

There is a likely possibility that patients enrolled in the study have their cardiac surgery rescheduled as a result of urgent intervening surgeries or because they meet an exclusion criterion shortly before the start of surgery. Therefore, patients who are withdrawn from the study before investigational medicinal

product administration will be replaced and thus will not be included in any analysis.

## Different Populations to be Analyzed

### Intention-to-Treat Population

The intention-to-treat (ITT) population includes all patients who were randomized and received study treatment, irrespective of satisfying other end point criteria. This population will be used for the analysis of safety and tolerability and all other primary and secondary end points.

### Per-Protocol Population

Analysis of the per-protocol (PP) population will be used as a supplement to the ITT analysis and will be performed for all end points except safety-related end points. The PP includes all ITT patients who have not been excluded from analysis for major protocol deviations.

### Pharmacokinetic Population

Sampling for pharmacokinetic (PK) population analysis will be performed in 30 patients. As EA-230/placebo ratio is 1:1, the PK population will include a subset of approximately 15 patients who received EA-230. For this full PK evaluation, additional blood samples will be obtained during infusion of EA-230 until 6 hours after cessation of administration.

### Subgroup Analyses

Subgroup analyses will be performed on the following predetermined preoperative randomization strata: (1) CABG with or without concomitant valve surgery; (2) preoperative renal function with an estimated GFR of ≤30, 31 to 90, and >90 mL/min/1.73 m$^2$; and (3) EuroSCORE II of <4 or ≥4.

## Safety Considerations

### Adverse Events

All adverse events will be judged by the investigators with regard to severity (*mild, moderate, or severe*) according to Common Terminology Criteria for Adverse Events guidelines 4.030 [43] and their perceived relation to the study drug (*definitely, probably, possibly, or unrelated/unlikely to be related*). SAEs or SUSARs include death, life-threatening disease, persistent and/or significant disability and/or incapacity, and hospitalization and/or prolongation of inpatient hospitalization.

The investigator will report all SAEs and SUSARs to the sponsor without undue delay after obtaining knowledge of the events. Monitoring and re-evaluation of the SAE/SUSAR and its relation to the study drug will subsequently be performed by an independent medical doctor with the independent Contract Research Organization QPS (Groningen, the Netherlands) and reported to the Central Committee on Research Involving Human Subjects (CCMO, The Hague, The Netherlands) within a maximum period of 15 days (or 7 days when the event is life threatening or results in death) and to the independent ethics committee of the Radboud University Nijmegen Medical Center (CMO, Arnhem-Nijmegen, the Netherlands).

### Data Monitoring Committee

An independent DMC, consisting of 3 expert members, including 1 biostatistician, will assess safety of the study drug. The first DMC meeting will be held on completion of the first part of the study that includes 40 to 50 low-risk patients. During this interim safety analysis, inclusion will be paused, and an extensive partially unblinded assessment of (S)AEs, vital signs, and routine laboratory parameters will be performed. Inclusion of patients in the study will only continue if no safety concerns are raised by the DMC. A second meeting will be held after 90 patients have been enrolled (including higher risk patients) to reassess all safety parameters. At this point, the DMC will advise on the continuation or termination of the study.

## Ethical Considerations

The regional and central independent ethical committee, CMO Arnhem-Nijmegen, and the CCMO, respectively, have approved the study protocol, amendments, informed consent, and all other study-relevant written information for the patients. The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki ICH E6(R1), the Medical Research Involving Human Subjects Act, guidelines of Good Clinical Practice, and European Directive (2001/20/CE). Informed consent will be obtained before any study-specific procedures are performed. Substantial amendments will be provided to the CMO for approval. Nonsubstantial amendments will be provided to the CMO for notification.

## Data Quality Assurance and Publication

Data will be handled confidentially and anonymously. The study site maintains source documentation and is responsible for accurate data entry in electronic case report form. The Good Clinical Practice–certified data capture system Open Clinica (Waltham, MA, USA) was used in this process. Blinded study personnel are provided with an individual username and password with complete traceability. Quality assurance, data management with full data validation and monitoring of all source documents, study procedures, study data, SAEs, and SUSARs will be performed by the independent Contract Research Organization QPS. The database will be locked after completion of the data review, resolutions to all queries, and the signing of the statistical analysis plan. Following database lock, a study patient identification code list (provided by the Castor data management system, Amsterdam, the Netherlands) will be used to link the stratified interventional treatment (active or placebo) to the patient. Data and body material will be kept in secure storage at the intensive care research department and is accessible by study personnel only. The handling of patient data in this study complies with the Dutch Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens). The principal investigator and the subinvestigators will write the manuscript that will be submitted for publication in a peer-reviewed scientific medical journal after completion of the study, irrespective of results.

## Patient and Public Involvement

Patients and the public were not involved in the design and/or the conduct of the study protocol. Study outcome will be disseminated to all study participants individually. The burden

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of the intervention was assessed by the independent ethics committees CMO and CCMO, which include laymen members.

## Results

Enrollment of this study commenced in July 2016, and results are expected at the end of 2018.

## Discussion

### General

To evaluate the safety, immunomodulatory, and renoprotective effects of EA-230, we designed this single-center, double-blind, randomized, placebo-controlled adaptive phase 2 study in patients undergoing on-pump cardiac surgery. In this study primarily focused on safety, we will also assess the immunomodulatory effects of EA-230. Our key secondary objective is to investigate whether EA-230 prevents a decrease in renal function (which is possibly related to its immunomodulatory effects) in this patient population. Patients undergoing on-pump cardiac surgery represent an ideal study population to evaluate the effects of EA-230 on the systemic inflammatory response in a proof-of-principle study. These cardiac surgery procedures are highly standardized and have a well-characterized sequence of inflammatory insults: release of Danger-Associated Molecular Pathways as a result of tissue damage during incision and sternotomy, leukocyte activation induced by the use of the extracorporeal circuit, ischemia-reperfusion damage following aortic cross-clamping and subsequent declamping, and translocation of endotoxins because of increased gut permeability [8-11]. Due to the elective timing of these insults, the moment of activation of the immune system is well defined, and the following inflammatory response during and after surgery follows a relatively homogenous pattern. Furthermore, the inflammatory response is clinically relevant, as inflammatory mediators IL-6 and IL-8 have been shown to be key orchestrators of the systemic inflammatory response following cardiac surgery and are associated with postoperative adverse outcome, including the occurrence of AKI and long-term mortality [5,12,44]. As EA-230 has attenuated IL-6 and IL-8 in earlier work [34], it has the potential to modulate release of these specific mediators that are associated with organ failure in cardiac surgery patients.

### Design

The inclusion and exclusion criteria of this study are not overly restrictive to facilitate enrollment and to increase generalizability. Although the inflammatory response is relatively comparable among cardiac surgery patients, these permissive criteria might influence study results because patients with known preoperative risk factors may develop a more pronounced inflammatory response and/or have a worse outcome. However, in a randomized study such as this, these interpatient differences are likely to be equally divided between treatment and placebo groups. Nevertheless, we used a stratified randomization procedure to optimize group balance. In addition, 3 major preoperative determinants for outcome, namely baseline renal function, EuroSCORE II [37], and CABG with or without

valve surgery were used to ensure equal distribution between groups of patients with known risk factors.

The 2-part study design facilitates an extensive safety interim analysis by the DMC after the first part and limits potential risks for patients. It also ensures efficient assessment of efficacy by combining data from both parts for all safety and efficacy analyses. Furthermore, with the use of an adaptive design, the trial sample size can be adjusted halfway through the trial by conducting a new power calculation using the variation of IL-6 concentrations of obtained data of the first half of the study, this way guaranteeing adequate statistical power. The use of such an adaptive design has recently been recommended for the design of clinical studies such as this study [45].

To date, no side effects attributed to EA-230 have been observed, which is in sharp contrast to other immunomodulatory drugs. This may be because of the fact that EA-230 is an endogenous, immunological active breakdown product of the pregnancy hormone beta hCG. In addition, the fact that the tolerant immune phenotype during pregnancy is not accompanied with complications related to immunosuppression suggests that targeting this pathway may be of more benefit than the use of other immunomodulatory therapies.

Evaluation of the effects of EA-230 on renal function is of specific interest in this study for several reasons. First, EA-230 exerted potent renal protective effects in animal studies. Second, a significant proportion of these patients suffer from postoperative renal injury [13,14], which is, in turn, related to their clinical outcome [15,16]. This study is unique in terms of accurate assessment of renal function because a gold standard method to measure GFR is used, instead of estimating GFR based on serum creatinine. Although it is well established that serum creatinine and urine output are suboptimal parameters to assess acute deterioration of renal function, they remain to be the most commonly used markers to diagnose AKI clinically and in research settings. Creatinine is unreliable because it is a late marker and is influenced by muscle mass, fluid shifts, immobilization and is partially, but actively, secreted by the kidneys [46-48]. The iGFR method has proven to be as reliable as the inulin clearance (with an $R^2$ of 0.96 [49]) and accurately detects even minor changes [38,50]. Therefore, clinically significant changes in GFR can be reliably assessed in this study. These renal function measurements have not been performed in any large cardiac surgery trial to date and will substantially improve the validity of the data and quality of this study. As a potential downside, the iohexol method does require trained personnel in the collection of multiple blood samples to create a plasma decay curve. As a result of this labor-intensive process, iGFR measurements will be performed only twice in this study: preoperatively, representing a baseline measurement and on the morning of the first postoperative day. As discussed earlier, conventional renal function markers are late and unreliable. Therefore, little is known about the exact postoperative course of renal function deterioration and/or decrease in GFR. As such, there is a chance that the single postoperative iGFR measurement could fail to detect a decrease in GFR following on-pump cardiac surgery.

A limitation of this study is the dose of EA-230. Only one dose is used, based on the fact that only the highest dose was effective in terms of modulating the immune response in the previous experimental human endotoxemia study [34]. As a result, it will remain unknown whether similar efficacy in patients can be attained using a lower dose or higher efficacy can be achieved using a higher dose. Furthermore, whether the use of the artificial extracorporeal circulation affects EA-230's pharmacokinetics or pharmacodynamics is unknown. Along these lines, the fluid balance shift in patients undergoing cardiac surgery may alter distribution of EA-230, with nontherapeutic plasma concentrations as a possible result.

## Summary

The EASI Study is a double-blind, randomized, placebo-controlled phase 2 study of EA-230 in 180 patients undergoing on-pump cardiac surgery. It applies stratification and has an adaptive study design. Apart from safety and tolerability, it is designed to examine the immunomodulatory and renal protective effects of EA-230 in patients with systemic inflammation.

## Acknowledgments

## Authors' Contributions

LTvE and PP primarily designed the study. RB and RvG drafted the manuscript, whereas MM, PP, and JH assisted in its revision. All authors participated in the conception, design, and/or coordination of the study. All authors have critically reviewed and approved the final manuscript for publication.

## Conflicts of Interest

## Multimedia Appendix 1

List of immunosuppressive drugs.

[PDF File (Adobe PDF File), 188KB - resprot_v8i2e11441_app1.pdf ]

## Multimedia Appendix 2

Statistical Analysis Plan.

[PDF File (Adobe PDF File), 868KB - resprot_v8i2e11441_app2.pdf ]

## References

1.  Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. 1992 Jun Presented at: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference; 1991; Northbrook p. 1644-1655 URL: https://journal.chestnet.org/article/S0012-3692(16)38415-X/abstract [doi: 10.1378/chest.101.6.1644]
2.  Balk RA. Systemic inflammatory response syndrome (SIRS): where did it come from and is it still relevant today? Virulence 2014 Jan 01;5(1):20-26 [FREE Full text] [doi: 10.4161/viru.27135] [Medline: 24280933]
3.  Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006 Feb;34(2):344-353. [Medline: 16424713]
4.  Dulhunty JM, Lipman J, Finfer S, Sepsis Study Investigators for the ANZICS Clinical Trials Group. Does severe non-infectious SIRS differ from severe sepsis? Results from a multi-centre Australian and New Zealand intensive care unit study. Intensive Care Med 2008 Sep;34(9):1654-1661. [doi: 10.1007/s00134-008-1160-2] [Medline: 18504549]
5.  Zhang WR, Garg AX, Coca SG, Devereaux PJ, Eikelboom J, Kavsak P, TRIBE-AKI Consortium. Plasma IL-6 and IL-10 concentrations predict AKI and long-term mortality in adults after cardiac surgery. J Am Soc Nephrol 2015 Dec;26(12):3123-3132 [FREE Full text] [doi: 10.1681/ASN.2014080764] [Medline: 25855775]
6.  Rabb H, Griffin MD, McKay DB, Swaminathan S, Pickkers P, Rosner MH, Acute Dialysis Quality Initiative Consensus XIII Work Group. Inflammation in AKI: current understanding, key questions, and knowledge gaps. J Am Soc Nephrol 2016 Feb;27(2):371-379 [FREE Full text] [doi: 10.1681/ASN.2015030261] [Medline: 26561643]

7.  Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015 Aug;41(8):1411-1423. [doi: 10.1007/s00134-015-3934-7] [Medline: 26162677]

8.  Warren OJ, Smith AJ, Alexiou C, Rogers PL, Jawad N, Vincent C, et al. The inflammatory response to cardiopulmonary bypass: part 1--mechanisms of pathogenesis. J Cardiothorac Vasc Anesth 2009 Apr;23(2):223-231. [doi: 10.1053/j.jvca.2008.08.007] [Medline: 18930659]

9.  Rossaint J, Berger C, Van Aken H, Scheld HH, Zahn PK, Rukosujew A, et al. Cardiopulmonary bypass during cardiac surgery modulates systemic inflammation by affecting different steps of the leukocyte recruitment cascade. PLoS One 2012;7(9):e45738 [FREE Full text] [doi: 10.1371/journal.pone.0045738] [Medline: 23029213]

10. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg 2005;3(2):129-140 [FREE Full text] [doi: 10.1016/j.ijsu.2005.04.002] [Medline: 17462274]

11. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest 1997 Sep;112(3):676-692. [Medline: 9315800]

12. Gueret G, Lion F, Guriec N, Arvieux J, Dovergne A, Guennegan C, et al. Acute renal dysfunction after cardiac surgery with cardiopulmonary bypass is associated with plasmatic IL6 increase. Cytokine 2009 Feb;45(2):92-98. [doi: 10.1016/j.cyto.2008.11.001] [Medline: 19128984]

13. Thiele RH, Isbell JM, Rosner MH. AKI associated with cardiac surgery. Clin J Am Soc Nephrol 2015 Mar 06;10(3):500-514 [FREE Full text] [doi: 10.2215/CJN.07830814] [Medline: 25376763]

14. O'Neal JB, Shaw AD, Billings 4th FT. Acute kidney injury following cardiac surgery: current understanding and future directions. Crit Care 2016 Jul 04;20(1):187 [FREE Full text] [doi: 10.1186/s13054-016-1352-z] [Medline: 27373799]

15. Brown JR, Cochran RP, Dacey LJ, Ross CS, Kunzelman KS, Dunton RF, Northern New England Cardiovascular Disease Study Group. Perioperative increases in serum creatinine are predictive of increased 90-day mortality after coronary artery bypass graft surgery. Circulation 2006 Jul 04;114(1 Suppl):I409-I413 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.105.000596] [Medline: 16820609]

16. Liotta M, Olsson D, Sartipy U, Holzmann MJ. Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting. Am J Cardiol 2014 Jan 01;113(1):70-75. [doi: 10.1016/j.amjcard.2013.09.012] [Medline: 24176074]

17. Hall R. Identification of inflammatory mediators and their modulation by strategies for the management of the systemic inflammatory response during cardiac surgery. J Cardiothorac Vasc Anesth 2013 Oct;27(5):983-1033. [doi: 10.1053/j.jvca.2012.09.013] [Medline: 23276596]

18. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015 Sep 26;386(10000):1243-1253. [doi: 10.1016/S0140-6736(15)00273-1] [Medline: 26460660]

19. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. J Am Med Assoc 2012 Nov 07;308(17):1761-1767. [doi: 10.1001/jama.2012.14144] [Medline: 23117776]

20. Munoz-Suano A, Hamilton AB, Betz AG. Gimme shelter: the immune system during pregnancy. Immunol Rev 2011 May;241(1):20-38. [doi: 10.1111/j.1600-065X.2011.01002.x] [Medline: 21488887]

21. Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. J Am Med Assoc 2005 Dec 07;294(21):2751-2757. [doi: 10.1001/jama.294.21.2751] [Medline: 16333011]

22. Raychaudhuri SP, Navare T, Gross J, Raychaudhuri SK. Clinical course of psoriasis during pregnancy. Int J Dermatol 2003 Jul;42(7):518-520. [Medline: 12839599]

23. Hazes JM, Coulie PG, Geenen V, Vermeire S, Carbonnel F, Louis E, et al. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. Rheumatology (Oxford) 2011 Nov;50(11):1955-1968 [FREE Full text] [doi: 10.1093/rheumatology/ker302] [Medline: 21890617]

24. Khan NA, Khan A, Savelkoul HF, Benner R. Inhibition of septic shock in mice by an oligopeptide from the beta-chain of human chorionic gonadotrophin hormone. Hum Immunol 2002 Jan;63(1):1-7. [Medline: 11924526]

25. Khan NA, Vierboom MP, van Holten-Neelen C, Breedveld E, Zuiderwijk-Sick E, Khan A, et al. Mitigation of septic shock in mice and rhesus monkeys by human chorionic gonadotrophin-related oligopeptides. Clin Exp Immunol 2010 Jun;160(3):466-478 [FREE Full text] [doi: 10.1111/j.1365-2249.2010.04112.x] [Medline: 20345979]

26. van den Berg HR, Khan NA, van der Zee M, Bonthuis F, IJzermans JN, Dik WA, et al. Synthetic oligopeptides related to the [beta]-subunit of human chorionic gonadotropin attenuate inflammation and liver damage after (trauma) hemorrhagic shock and resuscitation. Shock 2009 Mar;31(3):285-291. [doi: 10.1097/SHK.0b013e31817fd62a] [Medline: 18654091]

27. van den Berg JW, Dik WA, van der Zee M, Bonthuis F, van Holteen-Neelen C, Dingjan GM, et al. The β-human chorionic gonadotropin-related peptide LQGV reduces mortality and inflammation in a murine polymicrobial sepsis model. Crit Care Med 2011 Jan;39(1):126-134. [doi: 10.1097/CCM.0b013e3181fa3a93] [Medline: 20890188]

28. van der Zee M, Dik WA, Kap YS, Dillon MJ, Benner R, Leenen PJ, et al. Synthetic human chorionic gonadotropin-related oligopeptides impair early innate immune responses to Listeria monocytogenes in mice. J Infect Dis 2010 Apr 01;201(7):1072-1080. [doi: 10.1086/651134] [Medline: 20170375]

29.  Khan NA, Benner R. Human chorionic gonadotropin: a model molecule for oligopeptide-based drug discovery. Endocr Metab Immune Disord Drug Targets 2011 Mar;11(1):32-53. [Medline: 21352093]

30.  Khan NA, Susa D, van den Berg JW, Huisman M, Ameling MH, van den Engel S, et al. Amelioration of renal ischaemia-reperfusion injury by synthetic oligopeptides related to human chorionic gonadotropin. Nephrol Dial Transplant 2009 Sep;24(9):2701-2708. [doi: 10.1093/ndt/gfp369] [Medline: 19633318]

31.  Gueler F, Shushakova N, Mengel M, Hueper K, Chen R, Liu X, et al. A novel therapy to attenuate acute kidney injury and ischemic allograft damage after allogenic kidney transplantation in mice. PLoS One 2015 Jan 24;10(1):e0115709 [FREE Full text] [doi: 10.1371/journal.pone.0115709] [Medline: 25617900]

32.  Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. Clin J Am Soc Nephrol 2012 Dec;7(12):2073-2080 [FREE Full text] [doi: 10.2215/CJN.00470112] [Medline: 22879432]

33.  van Groenendael R, van Eijk LT, Kox M, Pickkers P. Pharmacokinetics, safety and tolerability of the novel beta-hCG derived immunomodulatory compound, EA-230. Br J Pharmacol 2018 Accepted for publication (forthcoming).

34.  van Groenendael R, van Eijk LT, Leijte GP, Koeneman B, Kox M, Pickkers P. Effects of EA-230 during experimental human endotoxemia. 2016 Presented at: ESICM; 2016; Milan, Italy URL: https://icm-experimental.springeropen.com/articles/10.1186/s40635-016-0098-x

35.  Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Br Med J 2013 Jan 08;346:e7586 [FREE Full text] [Medline: 23303884]

36.  Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med 2010 Mar;11(2):234-238. [doi: 10.1097/PCC.0b013e3181b806fc] [Medline: 19794327]

37.  Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012 Apr;41(4):734-44; discussion 744-45. [doi: 10.1093/ejcts/ezs043] [Medline: 22378855]

38.  Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? Clin Kidney J 2016 Oct;9(5):682-699 [FREE Full text] [doi: 10.1093/ckj/sfw070] [Medline: 27679715]

39.  Hoedemaekers CW, Pickkers P, Netea MG, van Deuren M, van der Hoeven JG. Intensive insulin therapy does not alter the inflammatory response in patients undergoing coronary artery bypass grafting: a randomized controlled trial [ISRCTN95608630]. Crit Care 2005;9(6):R790-R797 [FREE Full text] [doi: 10.1186/cc3911] [Medline: 16356228]

40.  Lehmann EL. Nonparametrics: Statistical Methods Based on Ranks. United States: Pearson Education; 1998:76-81.

41.  Proschan MA. Sample size re-estimation in clinical trials. Biom J 2009 Apr;51(2):348-357. [doi: 10.1002/bimj.200800266] [Medline: 19358221]

42.  O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979 Sep;35(3):549-556. [Medline: 497341]

43.  National Institutes of Health. 2009 May 28. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 URL: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [WebCite Cache ID 70AQn01H0]

44.  de Fontnouvelle CA, Greenberg JH, Thiessen-Philbrook HR, Zappitelli M, Roth J, Kerr KF, TRIBE-AKI Consortium. Interleukin-8 and tumor necrosis factor predict acute kidney injury after pediatric cardiac surgery. Ann Thorac Surg 2017 Dec;104(6):2072-2079. [doi: 10.1016/j.athoracsur.2017.04.038] [Medline: 28821332]

45.  Bhatt DL, Mehta C. Adaptive designs for clinical trials. N Engl J Med 2016 Jul 07;375(1):65-74. [doi: 10.1056/NEJMra1510061] [Medline: 27406349]

46.  Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004 Aug;8(4):R204-R212 [FREE Full text] [doi: 10.1186/cc2872] [Medline: 15312219]

47.  Bagga A, Bakkaloglu A, Devarajan P, Mehta RL, Kellum JA, Shah SV, Acute Kidney Injury Network. Improving outcomes from acute kidney injury: report of an initiative. Pediatr Nephrol 2007 Oct;22(10):1655-1658. [doi: 10.1007/s00467-007-0565-4] [Medline: 17665221]

48.  Summary of recommendation statements. Kidney Int Suppl (2011) 2012 Mar;2(1):8-12 [FREE Full text] [doi: 10.1038/kisup.2012.7] [Medline: 25018916]

49.  Erley CM, Bader BD, Berger ED, Vochazer A, Jorzik JJ, Dietz K, et al. Plasma clearance of iodine contrast media as a measure of glomerular filtration rate in critically ill patients. Crit Care Med 2001 Aug;29(8):1544-1550. [Medline: 11505124]

50.  Gaspari F, Perico N, Ruggenenti P, Mosconi L, Amuchastegui CS, Guerini E, et al. Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. J Am Soc Nephrol 1995 Aug;6(2):257-263 [FREE Full text] [Medline: 7579093]

## Abbreviations

**AKI:** acute kidney injury

**ANOVA:** analysis of variance
**AUC:** area under the curve
**CABG:** coronary artery bypass grafting
**CCMO:** Central Committee on Research Involving Human Subjects
**CMO:** independent ethics committee of the Radboud University Nijmegen Medical Center
**CPB:** cardiopulmonary bypass
**DMC:** data monitoring committee
**GFR:** glomerular filtration rate
**hCG:** human chorionic gonadotropin
**ICU:** intensive care unit
**iGFR:** glomerular filtration rate measured by plasma clearance of iohexol
**IL:** interleukin
**ITT:** intention-to-treat
**MIP1:** macrophage inflammatory protein
**PK:** pharmacokinetic
**PP:** per-protocol
**RIFLE:** risk, injury, failure, loss of kidney function, and end-stage kidney disease classification
**SAE:** serious adverse event
**SOFA:** sepsis-related organ failure assessment score
**SUSAR:** serious unexpected suspected adverse reaction

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Protocol

# Transforming Mental Health Delivery Through Behavioral Economics and Implementation Science: Protocol for Three Exploratory Projects

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## Abstract

**Background:** Efficacious psychiatric treatments are not consistently deployed in community practice, and clinical outcomes are attenuated compared with those achieved in clinical trials. A major focus for mental health services research is to develop effective and cost-effective strategies that increase the use of evidence-based assessment, prevention, and treatment approaches in community settings.

**Objective:** The goal of this program of research is to apply insights from behavioral economics and participatory design to advance the science and practice of implementing evidence-based practice (EBP) for individuals with psychiatric disorders across the life span.

**Methods:** Project 1 (Assisting Depressed Adults in Primary care Treatment [ADAPT]) is patient-focused and leverages decision-making heuristics to compare ways to incentivize adherence to antidepressant medications in the first 6 weeks of treatment among adults newly diagnosed with depression. Project 2 (App for Strengthening Services In Specialized Therapeutic Support [ASSISTS]) is provider-focused and utilizes normative pressure and social status to increase data collection among community mental health workers treating children with autism. Project 3 (Motivating Outpatient Therapists to Implement: Valuing a Team Effort [MOTIVATE]) explores how participatory design can be used to design organizational-level implementation strategies to

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increase clinician use of EBPs. The projects are supported by a Methods Core that provides expertise in implementation science, behavioral economics, participatory design, measurement, and associated statistical approaches.

**Results:** Enrollment for project ADAPT started in 2018; results are expected in 2020. Enrollment for project ASSISTS will begin in 2019; results are expected in 2021. Enrollment for project MOTIVATE started in 2018; results are expected in 2019. Data collection had begun for ADAPT and MOTIVATE when this protocol was submitted.

**Conclusions:** This research will advance the science of implementation through efforts to improve implementation strategy design, measurement, and statistical methods. First, we will test and refine approaches to collaboratively design implementation strategies with stakeholders (eg, discrete choice experiments and innovation tournaments). Second, we will refine the measurement of mechanisms related to heuristics used in decision making. Third, we will develop new ways to test mechanisms in multilevel implementation trials. This trifecta, coupled with findings from our 3 exploratory projects, will lead to improvements in our knowledge of what causes successful implementation, what variables moderate and mediate the effects of those causal factors, and how best to leverage this knowledge to increase the quality of care for people with psychiatric disorders.

**Trial Registration:** ClinicalTrials.gov NCT03441399; https://www.clinicaltrials.gov/ct2/show/NCT03441399 (Archived by WebCite at http://www.webcitation.org/74dRbonBD)

**International Registered Report Identifier (IRRID):** DERR1-10.2196/12121

# Introduction

## Background

Worldwide, psychiatric disorders account for more years lived with disability than any other category of disease [1]. The risk of premature mortality of people with severe psychiatric disorders is elevated [2], and the annual burden to the US economy is approximately half a trillion dollars, less than half of which is due to the cost of treatment [3]. Efficacious treatments are not consistently deployed in community practice, and clinical outcomes are attenuated compared with those achieved in clinical trials [4-6]. A major frontier for mental health services research is to develop effective and cost-effective strategies that increase the use of evidence-based assessment, prevention, and treatment approaches in community settings [7]. Although the field of implementation science has offered many new frameworks that identify factors associated with the use of evidence-based practice (EBP) in health and mental health care [8,9], there is still much potential to be realized in developing and testing new approaches that more successfully increase the use of EBP. The goal of our Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (ALACRITY) Center is to apply behavioral economics and participatory design to accelerate the reach and impact of treatments for individuals with psychiatric illness across the life span.

## Gaps in the Field of Implementation Science

On average, it takes 17 years for 14% of research to make its way into practice, with the majority of research findings never deployed in the community [10]. This finding has galvanized the development of implementation science, a discipline that has evolved rapidly, and focuses on the scientific study of methods to increase the adoption, implementation, and sustainment of EBP [11]. Implementation strategies are the interventions of implementation science. Early implementation research tested strategies that primarily involved training clinicians in EBP, based on assumptions that clinicians did not use them because they lacked knowledge and skills. Findings from a number of randomized controlled trials suggested that training improved clinicians' knowledge of and attitudes toward EBP but did not lead to practice change [12-14]. This body of research highlighted contextual factors, such as clinician motivation and organizational culture, typically considered nuisance factors in efficacy trials, as important and understudied variables in their own right [15,16].

Implementation research in both health and mental health care began prioritizing the identification of determinants at clinician, organization, and system levels that affect implementation success or failure. Several heuristic implementation frameworks that attempted to capture constructs at each of these levels supported these studies [8,9,17]. Broadly, these studies used either qualitative methods to elucidate barriers to or facilitators of implementation [18-21] or quantitative methods to test associations between determinants and implementation outcomes such as fidelity to EBPs [22-26]. Furthermore, 3 major gaps have emerged from research that our center aims to address: (1) implementation science has not leveraged the rich literature from behavioral economics, (2) implementation research encourages stakeholder involvement but has not yet operationalized how best to do so, and (3) implementation research lacks causal theory.

## Implementation Science Has Not Leveraged the Rich Literature From Behavioral Economics

Implementation studies historically have been premised on the assumption that clinicians make rational clinical choices that maximize utility for themselves and their patients [27]. A growing body of research from the field of behavioral economics suggests that this is not how clinicians make decisions. Behavioral economics includes a set of models and frameworks that recognize that individuals tend to make decisions under the constraints of bounded rationality [28]. In other words, clinicians do not always make decisions based on complete information,

exhaustive analysis of all potential outcomes, and maximization of expected utility. Instead, individuals are influenced by myriad psychological, social, cognitive, and emotional factors and a wide range of simplifying cognitive heuristics or shortcuts when making decisions. Clinicians likely are influenced in their decision making about which treatment to use and how to use it by heuristics such as availability bias (a case seen recently is particularly salient), hindsight bias (tendency to infer causality from a recent event even if it was not predictable), and status quo bias (the tendency to stick with the approach they usually use even if new and better approaches may now be available) [29,30].

To date, implementation research has not leveraged insights from behavioral economics to design implementation strategies. This approach is promising and has been applied outside of the scope of implementation science with regard to physician and patient behavior in health care [31-34]. The application of this approach necessarily moves the field away from implementation strategies designed to increase knowledge and toward strategies such as changing the environment (ie, choice architecture) to make it easier to do the desired thing, making EBP use the default, and using incentives and rewards to leverage cognitive heuristics. Incentives refer to informing individuals that they will receive rewards if they perform a behavior. Rewards refer to giving an individual money, vouchers, or valued objects or status when the behavior is performed [35].

## Implementation Research Encourages Stakeholder Involvement but Has Not Operationalized How to Do So

Although implementation science underscores the importance of stakeholder involvement in the implementation process [36], there has been little study on how to systematically involve stakeholders, such as patients, providers, administrators, payers, and policy makers, in the development, refinement, and testing of implementation strategies [37]. Engaging stakeholders systematically can increase the specificity, accuracy, and success of implementation strategies. Participatory design approaches, which emphasize active involvement of stakeholders in the design process, can be used to include stakeholder input in the process of designing and refining implementation strategies [38].

## Implementation Science Lacks Causal Theory

Causal theory is largely underdeveloped in implementation science [11,39], and there is a limited understanding of the mechanisms by which implementation strategies work [29,40]. One major rate-limiting step is that randomized controlled trials of implementation strategies rarely incorporate formal tests of mediating mechanisms [40]. This is due in part to the underdevelopment of rigorous statistical methods to test mediating and moderating effects of hypothesized mechanisms in a multilevel context. Implementation trials almost always are clustered, with patients nested within clinicians and clinicians within organizations [8,9,17]. Furthermore, implementation strategies can be directed at patients, clinicians, or organizations, and strategies at 1 level may target behavior and outcomes at other levels. For example, changes in organizational climate may affect clinician behavior and patient outcomes. There are

few validated statistical approaches to test these pathways, sometimes referred to as *complex moderated mediation* or *conditional indirect effects* in a multilevel context, thus limiting the forward movement of the field in understanding how or when implementation strategies are most effective.

A second factor that limits the development of causal theory in implementation science is the lack of standardized and validated measures that assess putative mechanisms that link strategies to outcomes. Important work is currently underway to address this measurement gap in some areas of implementation science [41]; however, constructs from the field of behavioral economics, including measures that assess cognitive heuristics, have been notably absent. This is an important gap given the potential promise of these heuristics as a lever for behavior change.

Even when measures are available to assess putative mediating mechanisms and investigators test these variables as mediators within randomized controlled trials, a third factor that limits the development of causal theory in implementation science is the failure of many implementation strategies to engage the targeted mechanisms [40]. A recent systematic review of 88 randomized controlled implementation trials in mental health service settings found no evidence that any implementation strategy engaged its targeted mechanisms of action [40]. One potentially important reason for this is that, to date, the design of implementation strategies has not incorporated systematic end-user feedback and perspectives. Studies have shown that intervention design is significantly improved when it systematically elicits end-user feedback about behavioral bottlenecks and other barriers to enactment of the targeted behavior and incorporates this feedback into intervention design [42].

The center is funded as part of the National Institute of Mental Health ALACRITY P50 to support the rapid development, testing, and refinement of novel and integrative approaches for optimizing the effectiveness of treatments for and prevention of mental disorders and organizing and delivering mental health services in community settings [43]. The major aim of the Penn ALACRITY center is to accelerate the pace at which effective treatments for mental disorders are deployed in community practice, thereby increasing their impact on improving quality of life for people with these disorders, and to advance the science of implementation. The Penn ALACRITY center is intended to support research that demonstrates high synergy across disciplines and that increases the public health impact of existing and emerging mental health interventions and service delivery strategies. The Penn ALACRITY center addresses these goals with the following objectives:

> Objective 1: Apply innovative, interdisciplinary approaches from behavioral economics to implementation science.

> Objective 2: Apply methods from participatory design to ensure that the stakeholders' voice is included in the development of implementation strategies in a systematic, rigorous, and collaborative manner.

> Objective 3: Develop statistical approaches that allow for the elucidation of mechanisms and causal theory.

## Methods

### Overview

The Methods Core is the foundation of the Penn ALACRITY center. Specifically, it supports 3 incubators related to implementation strategy design, measurement, and statistical methods: (1) optimization of implementation strategy design through our design incubator, (2) refinement of measurement of mechanisms through our measurement incubator, and (3) development of novel approaches to test mechanisms in multilevel implementation trials through our statistical methods incubator. The Methods Core supports 3 exploratory projects that are wide in scope and span the most salient levels at which implementation takes place—the individual in treatment, the clinician, and the organization. Although each project stands alone, they are linked through common methods and measurement tools (see Table 1).

Project 1 (Assisting Depressed Adults in Primary care Treatment [ADAPT]) compares the effectiveness of different schedules of financial incentives to increase medication adherence among adults recently diagnosed with depression in primary care settings. Project 2 (App for Strengthening Services In Specialized Therapeutic Support [ASSISTS]) examines the effectiveness of normative pressure in increasing the use of EBP among frontline clinicians working with children with autism in schools. Project 3 (Motivating Outpatient Therapists to Implement: Valuing a Team Effort [MOTIVATE]) develops and tests the acceptability of organization-focused implementation strategies to increase clinicians' use of EBPs in community mental health clinics. In the section that follows, we will describe the major activities of the Methods Core, followed by more in-depth descriptions of each project.

### Methods Core

#### *Design Incubator: Optimize Implementation Strategy Design*

The design incubator will test several participatory approaches to develop implementation strategies. Here, we describe 4 methods including innovation tournaments, behavioral design, rapid-cycle prototyping, and discrete choice experiments.

Innovation tournaments [44,45] take a collaborative and systematic approach to addressing complex and relatively unstructured problems using ideas from end users. Innovation tournaments begin when a host calls for ideas in an area of interest. End users are invited to submit ideas, which go through sequential stages of screening and evaluation by crowdsourcing

peer review and expert input to filter and shape the raw ideas into the most promising ideas. At the end of the tournament, a few winning ideas are selected. Although innovation tournaments are solution-focused, they have added benefits related to team building and shifting organizational climate to be more egalitarian so that end users have direct input. Innovation tournaments have been successfully used in many contexts to increase stakeholder engagement, including quality improvement in health care [44,45], but have not been used to address challenges of implementing EBP in mental health services. In addition, 2 of our 3 projects (ASSISTS and MOTIVATE) include this approach. In ASSISTS, we use innovation tournaments to engage therapists in designing nonfinancial incentive strategies to improve the use of EBP among one-to-one aides working with school-age children with autism. Although we propose to leverage normative pressure to increase use of 1 EBP, data collection, there are many ways normative pressures can be applied, and there may be other incentives that may be equally or more effective, which we can learn about from our stakeholders. In MOTIVATE, we use innovation tournaments to engage clinicians in identifying the best way for organizations to use financial and nonfinancial incentives to help clinicians implement EBP.

Behavioral design is a systematic approach, informed by engineering and human-centered design principles, to understand human behavior and apply those insights to the design of behavior change interventions [46,47]. In this 5-step approach, designers first define the problem and then diagnose the problem from a behavioral lens, using qualitative and quantitative data about the context of the target behavior. The diagnosis process yields hypotheses informed by behavioral insights about the channels or barriers to the desired behavior. Next, these hypotheses are translated into potential solutions. Design solutions are also informed by behavioral insights. One design approach, developed by the UK Behavioural Insights Team, is the Easy, Attractive, Social, and Timely Framework, which organizes design solutions into factors that make the desired behavior *Easy, Attractive, Social, and Timely* [48]. For example, creating default solutions (which people will naturally stick with) makes a behavior very easy. Providing peer comparisons makes a behavior social, as most of us care how we do relative to peers, and what others think of us. Designed solutions are then tested and scaled through rigorous experiments. Project MOTIVATE employs behavioral design to generate solutions to improve the implementation of EBPs in community mental health settings. The contextual data for diagnosis phase will comprise, in part, the ideas submitted in the innovation tournament.

**Table 1.** Comparisons across the 3 exploratory projects.

| Attributes | Project 1: ADAPT[a] | Project 2: ASSISTS[b] | Project 3: MOTIVATE[c] |
|---|---|---|---|
| Ecological level | Patient | Clinician | Organization |
| Population | Adults with depression | Youth with autism | A wide range of diagnoses and ages |
| Type of incentive | Financial | Social | Mix |
| Outcome | Medication adherence | Data collection | Acceptability of implementation strategies |

[a]ADAPT: Assisting Depressed Adults in Primary care Treatment.

[b]ASSISTS: App for Strengthening Services In Specialized Therapeutic Support.

[c]MOTIVATE: Motivating Outpatient Therapists to Implement: Valuing a Team Effort.

Rapid-cycle prototyping is an industry innovation that has recently been applied to health care and is a complementary approach to behavioral design. The goal of rapid-cycle prototyping is to test potential innovations more efficiently, less expensively, and more reliably than traditional clinical trials [49]. These approaches leverage mini-pilots, or experiments that are integrated within operations, to learn how to best design strategies. Rapid-prototyping does not rely on a finished product to test. Rather, mock-ups or inexpensive versions are tested before completing the product. For example, when IBM wanted to test how users would respond to speech recognition software, it placed a hidden typist in another room who could hear the speaker through a microphone, rather than developing this complex technology first [50]. Rapid-cycle prototyping has been used extensively at the Penn Medicine Center for Health Care Innovation in a variety of clinical contexts as a way to quickly learn from successive iterations of a new technology. We use rapid-cycle prototyping in 1 of our projects. In ASSISTS, our digital tool to collect data and improve implementation will rely heavily on rapid-cycle prototyping to iteratively test the interface, information content, and response to a phone-based data collection app for providers of one-on-one behavioral support for children with autism.

Discrete choice experiments [51,52] are frequently applied in health economics as a way to rate the acceptability of programs. They have not been used to provide input on the design of implementation strategies although they represent another promising approach to increasing stakeholder engagement [53]. Discrete choice experiments are a technique for systematically eliciting individual preferences for options and their specific attributes. By systematically eliciting tradeoffs among constructed outcome combinations, discrete choice experiments generate data that can quantify relative utility or satisfaction for the presented option as well as its specific attributes. This strategy allows for eliciting preferences for treatments that do not currently exist or that individuals have not yet experienced. We use discrete choice experiments in MOTIVATE to evaluate the acceptability of collaboratively developed implementation strategies targeting organizations to increase clinician EBP implementation.

### *Measurement Incubator: Refine Measurement of Mechanisms Related to Clinician Factors*

Implementation science frameworks posit that individual factors such as motivation, self-efficacy, knowledge, and attitudes are important in the implementation process [8,9]. To date, these factors have primarily been described and measured using health behavior theories such as the Theory of Planned Behavior [54] and Social Cognitive Theory [55]. Less explored in implementation research have been the psychological heuristics that shape decision making and characterize our decision-making styles and may both mediate and moderate the impact of implementation strategies. In our 3 exploratory projects, we hypothesize that psychological heuristics affect implementation strategy success. For example, risk aversion describes the human tendency to value losses more than equivalent gains [30] and may shape how a consumer responds to a financial incentive to adhere to an EBP or may make managers reluctant to *take a gamble* on innovative practices that may put quality at risk. Present bias refers to the tendency of individuals to overvalue immediate or current rewards compared with future rewards [56]. Present-biased individuals may be more responsive to financial incentives; present-biased managers may require short-term rewards that provide more immediate feedback than those commonly seen in many pay-for-performance programs that involve incentive disbursement at the end of each year. Regret aversion refers to the tendency of individuals to reduce the possibility of regret when making choices and can be deployed in the design of lotteries or other tangible or intangible rewards systems; response to such designs is likely to vary with underlying heterogeneity in regret aversion. Individuals' sensitivity to conformity and social referents similarly can be leveraged both through descriptive comparisons (eg, "this is how you are using EBP compared with your peers") and injunctive comparisons (eg, "these are your supervisors' expectations of how you will use EBP") [57]. An individual's unique pattern of cognitive biases and decision-making styles can be described as their *behavioral phenotype* [42] and may explain individual variation in responses to implementation strategies.

Implementation science frameworks also posit the importance of organizational factors in explaining implementation success, emphasizing constructs such as organizational culture (the collective sense of how work is done in an organization), organizational climate (the collective sense of how the work environment affects psychological well-being), implementation climate (group perspective on whether use of an innovation is expected, supported, and rewarded), and implementation leadership (group beliefs about how capably a leader supports EBP implementation) [58-62]. These organizational constructs explain much of the variance in implementation outcomes [23]. They are generally measured by aggregating individual

responses within organizations or organizational units following a demonstration of construct validity at the organization level. In addition to defining individual decision-making styles, behavioral phenotypes may be important organizational descriptors, which would require aggregating responses across individuals. As an exploratory objective, we will examine the validity and utility of aggregating individual behavioral phenotypes to the organizational level [63]. In other words, do people with similar behavioral phenotypes cluster in organizations, and do these aggregated phenotypes predict important implementation outcomes? Individual behavioral phenotypes could cluster within organizations if, for example, leaders only hire individuals whose psychological heuristics are consistent with their own or if the organizational culture changes employees' heuristics. If individual behavioral phenotypes translate into an organizational construct, we will also explore questions related to organizational composition, such as how clinicians' behavioral phenotypes compare with those of their administrators and which is more predictive of implementation and clinical outcomes.

We will refine existing, validated measures from the behavioral economics literature for assessing psychological heuristics. Once measured in patients, providers, and administrators, these phenotypes can be evaluated as mediators and moderators of implementation strategy effects.

### Statistical Methods Incubator: Develop Novel Approaches to Test Mediating and Moderating Effects of Mechanisms

Mechanisms refer to *processes that are responsible for change* [64]; they can be considered the *active ingredients* that explain the specific ways in which implementation strategies affect implementation and client outcomes. The identification of mechanisms can lead to more efficient and tailored strategies based on the EBP of interest and the context in which it is implemented. The goals of the statistical methods incubator are to develop methods that quantify the magnitude and statistical significance of cross-level indirect effects in mediation models (the approach needed to test mechanisms) that span patient, clinician, and organizational levels and develop methods and guidelines for designing studies that have adequate statistical power to detect mediation effects in these multilevel trials. These methods are necessary to rigorously test the implementation strategies that are developed through our exploratory projects and pilot studies.

Although some research has begun to identify challenges and propose solutions for addressing mediation in simple 2-level mediation models (patients nested within providers) [65], little is known about the extension of these methods to 3-level models (patients within providers within organizations) or models that incorporate multiple measures over time. For example, questions remain about the extent to which various model specifications result in biased parameter estimates and the most effective strategies for overcoming these biases to obtain accurate parameter estimates and correct tests of statistical significance for indirect effects in 3-level models. Complications arise in these models because of the interdependence of observations within levels and because the relationships among lower-level

variables can vary at different levels [65-67]. Although significant progress has been made in accounting for these design features when modeling direct effects, the modeling of indirect effects is more complicated and has not been examined with as much rigor. This deficit is particularly important in implementation studies of organizations where there can be considerable homogeneity within levels, and interventions at 1 level can have substantial effects on other levels—all of which complicates modeling [23,40,68].

There are no good guidelines to help investigators design multilevel studies so that they have adequate power to detect indirect effects of clinical interest. The importance of designing studies with adequate statistical power to detect meaningful effects is well understood [69] and accepted. Several resources are available to support researchers in ensuring that studies are adequately powered to detect main effects of interventions in both single-level trials and multilevel trials [70-72]. As the field moves to an experimental approach that requires testing of the mediating mechanisms that link implementation strategies to outcomes at multiple levels, we will have to examine indirect effects in studies that have sufficient statistical power to detect these effects, should they be present. Although methods are available to calculate statistical power for main effects in clustered trials, we know of no validated methods to calculate statistical power to detect cross-level indirect effects in multilevel trials. Without this information, investigators are unable to plan studies that are adequately powered to address questions of mechanisms. This work will build on and extend 2 approaches to test indirect effects in multilevel models—multilevel structural equation modeling [73] and the *centered within context with means reintroduced* approach [65]—to address 3-level models with mediators, interventions, and randomization at different levels. This work will result in generalizable instructions and guidelines on how to conduct multilevel mediation analysis in 3-level mediation models applicable to studying mechanisms in a wide range of implementation trials and empirical evidence supporting the need for these approaches to increase the precision and accuracy of indirect effect estimates.

## Exploratory Projects

### Project 1: Assisting Depressed Adults in Primary Care Treatment (Patient-Level)

Improving the management of adult depression is one of the great challenges facing outpatient mental health care. As continuous antidepressant treatment tends to improve symptoms of depression [74-76], quality of life [74], and social functioning [77] as well as reduce health care costs [78], it is a cornerstone of evidence-based treatment for adult depression. Yet adults who initiate antidepressants for depression often discontinue within the first few weeks of treatment, before their medication becomes fully effective [79]. Although patient-level strategies have been highlighted in several implementation frameworks, there has been little empirical study relating to patient-level uptake of EBP [80]. We will conduct a pilot study to test whether modest time-limited escalating or de-escalating daily financial rewards for patient antidepressant use, based on behavioral economic theory, improves medication adherence

and clinical outcomes of adults initiating treatment of depression. This will make a contribution to implementation science by elucidating how patient-facing implementation strategies can be used to increase the manner in which patients engage with EBP.

Tangible financial patient rewards have successfully increased a wide range of health behaviors [31,34,81-84], including medication adherence [85-88]. Financial rewards for medication adherence tend to have their strongest effects when they are provided frequently and close in time to when the medication is taken [88]. In depression, in contrast to many other conditions, it may be necessary to provide financial incentives for antidepressant adherence only during the initial weeks of treatment, when untreated depression makes nonadherence risk greatest and before the patient's mood begins to improve [89,90]. After this point, antidepressants may help lift the patient's mood, providing feedback to become self-reinforcing and facilitate better adherence.

Behavioral economics research has highlighted that the design and delivery of financial incentives significantly influence effectiveness [91,92]. Antidepressant therapy requires continuous medication adherence. However, the therapy's mechanism of action makes early adherence difficult: the rewards of antidepressants (decreased depressive symptoms) do not materialize instantaneously but only after several weeks of use, whereas the costs (inconvenience and side effects) accrue in the present. With this in mind, it is possible that providing larger initial incentives that fade over time may help people to overcome initial inertia and get started. It is also possible, however, that an increasing daily incentive, which people generally prefer [93], may better leverage key behavioral principles, including the use of reference points (people compare with what they have received previously, and the increasing rewards will be thus viewed positively) and loss aversion as patients who initiate treatment face an ever-greater lost opportunity if they discontinue medications as rewards increase [94]. However, it is also possible that an increasing daily incentive, which people generally prefer [93], may better leverage key behavioral principles, including the endowment effect (ascribing more value to things because one owns them) and loss aversion as patients who initiate treatment face an ever-greater lost opportunity if they discontinue medications as rewards increase [94].

We will compare the effects of usual care, escalating, and de-escalating patient financial incentives on daily antidepressant medication adherence and depression symptom control of nonelderly adults with clinical depression (see Table 2). A three-arm pilot study will randomize 120 adults in outpatient treatment who are starting antidepressants for depression to receive either (1) usual care (n=40), (2) usual care and escalating daily financial incentives (n=40), or (3) usual care and de-escalating daily financial incentives (n=40). Participants assigned to the escalating incentive arm will receive US $2 per day, increasing to US $7 per day with daily feedback tied to use of Adheretech wireless medication devices using the Way to Health platform for the first 6 weeks of antidepressant adherence (US $189 maximum). Those assigned to the de-escalating incentive arm will receive an incentive that

decreases from US $7 per day to US $2 per day for daily antidepressant adherence over the 6-week period (US $189 maximum). The study will achieve the following specific aims: (1) compare the effectiveness of usual care, escalating incentives, and de-escalating incentives on improving adherence to antidepressant therapy and reducing depressive symptoms 6 weeks following treatment initiation; (2) determine whether 6 week escalating or de-escalating financial incentives continue to improve antidepressant adherence and depressive symptom control over the 6- to 12-week period following termination of the incentives; and (3) assess the similarity of the study groups with respect to potential negative effects of incentives including regret over study participation. We will also explore potentially moderating effects of 2 psychological biases (present bias and information avoidance) on the effectiveness of the interventions to improve daily antidepressant adherence. Habit formation and decision regret will be evaluated as secondary outcomes. Given that this study is one of the first of its kind to explore financial incentives for medication adherence in individuals with psychiatric disorders, we have paid careful attention to potential ethical concerns [95]. It is of note that we will not prescribe any medication, and we leave the assessment of benefits relative to risks for each patient to that patient's clinician. We have included the Decision Regret Scale [96], which we will monitor regularly to identify potential issues of dissatisfaction with study participation. We also plan to conduct qualitative interviews with participants asking specifically about their perspectives on financial incentives and adherence to antidepressants.

### *Project 2: App for Strengthening Services in Specialized Therapeutic Support (Clinician-Level)*

Elementary school children with autism often need intensive support throughout the day [97]. Concerns about safety, behavioral challenges, and the need for a highly structured environment have resulted in an increased use of one-to-one aides at home, school, and in the community [98,99]. These aides, referred to as therapeutic support staff (TSS) in Philadelphia, usually have a bachelor's or associate's degree and receive limited training and supervision due to the community-based nature of their work, which often requires them to work in settings independent from their supervisors and peers [98,100]. Ideally, aides would use evidence-based interventions in the family of applied behavior analysis to help children reduce problem behaviors and increase adaptive behaviors [101,102].

Philadelphia's Medicaid system spends more than US $80 million a year on TSS, about a third of the children's mental health services budget. Although children with autism comprise 7% of all children served through this system, they account for 40% of TSS services. Administrators, advocates, and parents have decried the poor or unknown quality of care and outcomes associated with it, yet the very nature of the work they do makes it difficult to monitor. Our observations of TSS in the community [98], combined with our interviews with administrators and clinicians, suggest that TSS are not supported in providing high-quality, evidence-based care, in large part because of the isolating nature of their work and limited opportunity for measurement of performance, acknowledgment, and feedback.

**Table 2.** Assisting Depressed Adults in Primary care Treatment (ADAPT) Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flow diagram.

| Stages and time point | Study period | | | | |
| --- | --- | --- | --- | --- | --- |
| | Screening | Baseline | Intervention period (weeks 1-6) | Follow-up | |
| | | | | End of week 6 | End of week 12 |
| **Enrollment** | | | | | |
| Eligibility screen | X[a] | X | —[b] | — | — |
| Verbal informed consent | X | — | — | — | — |
| Randomization | — | X | — | — | — |
| **Interventions** | | | | | |
| Escalating financial incentives | — | — | X | — | — |
| De-escalating financial incentives | — | — | X | — | — |
| Control | — | — | X | — | — |
| **Assessments** | | | | | |
| Patient Health Questionnaire-9 | X | — | — | X | X |
| Generalized Anxiety Disorder-7 | — | X | — | X | X |
| Beck Hopelessness Scale | — | X | — | X | X |
| Theory of Planned Behavior | — | X | — | — | — |
| Information avoidance | — | X | — | — | — |
| Present bias | — | X | — | — | — |
| Decision Regret Scale | — | — | — | X | X |
| Habit formation | — | — | — | X | X |
| Daily antidepressant adherence (automated collection via electronic pill bottle) | — | — | X | X | X |
| Antidepressant prescription (via electronic health record abstraction) | — | — | X | X | X |

[a]X denotes the study period in which each component occurs.

[b]Not applicable.

This project will develop and test strategies to increase TSS's self-efficacy, supervision, and sense of belonging to a professional community, with opportunities for peer comparison and supervisor recognition as mechanisms to increase the use of EBP. The target practice for this study is data collection. We chose data collection because (1) it is a component of every EBP for children with autism and is common to many mental health interventions for other children as well, (2) this foundational practice is essential to measuring and monitoring outcomes and has been associated with more positive outcomes in and of itself, and (3) it makes possible the objective assessment of the effectiveness of implementation strategies and supports iteration and improvement.

Our clinician-focused implementation strategy is based on 3 psychological principles informed by behavioral economics. The first is bounded rationality, defined as limited information, cognitive capacity, and willpower [103]. TSS may find data collection difficult because they are not sure what information to collect or how to collect it easily. The second is perceptions of social norms [57]. On the basis of typical practice, TSS may

believe that their supervisors do not expect them to collect data and that none of their peers collect data. The third is hyperbolic discounting, in which people prefer more immediate gratification (not expending effort to collect data) at the expense of long-term outcomes (data ultimately used to show a child's progress and inform future interventions) [56].

Philadelphia's Department of Behavioral Health is making substantial investments in establishing and enforcing standards for autism intervention. Data collection will be an important part of these new standards. We will use a participatory design approach to build a digital app on the Penn Way to Health platform that allows TSS to (1) receive frequent communication and reminders about how and when to collect data, (2) easily collect and upload data, (3) observe how the child in their care is progressing, (4) observe how they compare with their peers in data collection, and (5) receive positive recognition from their supervisors and employers in response to frequent and accurate data collection.

We will use rapid-cycle prototyping, an iterative development process that involves multiple tests of our intervention's utility,

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feasibility, acceptability, and potential for long-term system-wide implementation. To develop the components of this new tool, we will (1) conduct an innovation tournament among TSS and their supervisors to identify ways to increase TSS's data collection; (2) observe and query 10 TSS workers in the field to examine how they collect data, the functional and structural barriers that impede their ability and willingness to collect data, and their intentions, attitudes, subjective norms, and self-efficacy regarding data collection; (3) use rapid prototyping and testing to create an app through Way to Health that makes data collection easier, more rewarding, and socially desirable and refine the app based on observation and data collection; (4) test the refined app with 30 TSS from 3 agencies; and (5) explore broader applicability of this technology with our partners to determine how use of other EBPs can be objectively and inexpensively measured and rewarded.

### Project 3: Motivating Outpatient Therapists to Implement: Valuing a Team Effort (Organizational-Level)

In project MOTIVATE, we will partner with stakeholders to develop implementation strategies that target organizations and leverage established principles from behavioral economics to improve EBP implementation in community mental health clinics. In our work investigating the implementation of EBP over the past 5 years [23,104], agency administrators and policy makers have repeatedly told us that the most significant barrier to implementing EBP is the need for a significant organizational financial investment, which is challenging in the context of an under-resourced public mental health system [21,105-108].

In response to this challenge, payers, including Philadelphia's Department of Behavioral Health and Intellectual disAbility Services (DBHIDS), are beginning to use financial incentives to motivate organizations to encourage EBP implementation. These efforts are based in part on evidence from a few published studies, which show that pay-for-performance schemes, that is, paying clinicians directly for the implementation of EBPs, result in greater use of EBP and higher fidelity [109-111]. However, studies have also shown that incenting organizations rather than clinicians is not highly effective in changing clinicians' use of EBP [112-115]. This discrepancy highlights the importance of understanding how to help organizations leverage incentives to change clinician behavior most efficiently and effectively.

The limited impact of paying organizations to change clinician behavior may be due to a number of factors ranging from poor incentive design to organizational incentives not being translated into incentives for frontline clinicians [116]. Organizational leaders likely do not have the training in how to design or use flow-through incentive funds effectively nor is there any research (or established implementation strategies) to guide this practice [115]. We address this gap through a participatory design process that integrates stakeholder input from clinicians, administrators, policy makers, and payers to develop incentive-oriented implementation strategies that target organizations [36].

Our participatory design approach incorporates 3 novel and promising methods for systematically eliciting and leveraging

end-user input to design effective interventions. First, we will use an innovation tournament (described previously) to generate ideas from clinicians (the end users) about the best ways for organizations to use financial and nonfinancial incentives to facilitate clinician implementation of EBP (see description above). Second, we will refine the ideas generated through the innovation tournament using a *behavioral diagnosis* process. We will use a structured tool developed by ideas42 to comprehensively analyze the ideas submitted in the tournament and identify specific behavioral barriers impeding the use of EBPs by clinicians. For example, tournament ideas that indicate that clinicians run out of time to implement EBPs during the standard 50-min therapy session may suggest that the planning fallacy (ie, the tendency to consistently underestimate the time needed to complete an action) contributes to incomplete or infrequent use of EBPs in session. The behavioral diagnosis step will yield multiple hypothesized behavioral bottlenecks that, once confirmed or disconfirmed by stakeholders, will inform implementation strategy design.

Third, once a set of implementation strategies have been identified as potentially useful, we will use a discrete choice experiment to systematically elicit and quantify stakeholders' preferences regarding how these strategies should be designed and structured [53]. Discrete choice experiments present potential users of a product or service with a series of forced-choice questions that require them to choose between alternative designs. For example, clinicians might be required to choose between a financial incentive in the form of a large annual bonus for high EBP fidelity or a small monthly payment for fidelity or they might choose to verify fidelity by tape recording all sessions or having 1 in-session observation. By systematically combining various attributes and levels, a discrete choice experiment quantifies the extent to which specific design features are desired. This information will then be used to inform the design of an incentive strategy that targets organizations to improve clinicians' EBP delivery.

## Declarations

### Current Study Status

We have begun recruitment and data collection for Projects 1 and 3; data collection is ongoing for both projects. Project 2 recruitment and data collection will begin in 2019. No publications containing the results of this study have been submitted or published in any journal.

### Ethics Approval and Consent to Participate

The institutional review boards of the University of Pennsylvania and the City of Philadelphia approved all study procedures, and all ethical guidelines were followed. All individuals interested in participating in the research described in this protocol will provide written informed consent.

## Setting

This work is occurring in close collaboration with community stakeholders vested in mental health in the City of Philadelphia. Our major partners include the DBHIDS, the School District of Philadelphia, the nonprofit organizations that serve the mental health needs of Philadelphia residents in the DBHIDS network,

and the University of Pennsylvania Health System. Philadelphia is a city of 1.6 million racially and ethnically diverse communities, approximately a third of who are enrolled in Medicaid. Philadelphia manages the behavioral health care of its Medicaid enrollees through Community Behavioral Health (CBH), a not-for-profit corporation that falls within the organizational structure of DBHIDS. CBH pays for mental health and substance use care for more than 100,000 consumers annually and has more than 250 organizations in network, including approximately 50 CBH centers and other specialized mental health and substance use agencies providing outpatient services.

The School District of Philadelphia serves approximately 140,000 students educated in 214 schools annually, making it the eighth largest school district in the United States. Furthermore, three-quarters of its students are eligible for free or reduced-price lunch. About two-thirds of students are African American and 10% are Latinx, and 107 languages other than English are spoken at home by District students.

The University of Pennsylvania Health System is the largest health system in the Delaware Valley. It includes 6 hospitals and 2 regional medical centers. Last year, the health system accommodated more than 5 million outpatient visits, 135,000 adult hospital admissions, and 350,000 emergency room visits.

All projects are approved by the appropriate institutional review boards.

## Results

Enrollment for project ADAPT started in 2018; results are expected in 2020. Enrollment for project ASSISTS will begin in 2019; results are expected in 2021. Enrollment for project MOTIVATE started in 2018; results are expected in 2019. Data collection had begun for ADAPT and MOTIVATE when this protocol was submitted.

## Discussion

### Summary

Although hundreds of treatments for common psychiatric disorders have demonstrated efficacy, problems persist in optimizing their implementation in community practice [117,118]. When evidence-based interventions are adopted, they are often not implemented in the way they were designed and do not result in the same outcomes observed with highly selected patients under controlled conditions. The 3 projects described in this protocol address the problems of incomplete uptake of selected EBPs in community practice and will result in approaches that could lay the foundation for ways to address

implementation gaps at the levels of individuals in treatment, clinicians, and organizations. Our Methods Core will develop statistical, participatory design, and behavioral phenotyping approaches to increase the specificity and external validity of implementation strategies and the rigor with which and for whom they work.

One innovation of our Penn ALACRITY center is the merging of mental health treatment, implementation science, behavioral economics, and participatory design. Implementation research in mental health has identified important, malleable characteristics of treatments, the individuals using them, and the organizations in which they work that affect their use and outcomes. Behavioral economists have identified a wide range of patterns in human decision making that may contribute to poor health outcomes as well as methods of designing the environment to optimize optimal decision making [91,92,119-127]. These complementary approaches may be helpful when considering the implementation challenges faced in the community. Participatory design actively involves stakeholders in designing new technologies to help ensure that the results meet their needs. Our Penn ALACRITY center activities will introduce a new level of rigor and innovative methods for eliciting and incorporating stakeholder input and will represent the first merging of interdisciplinary perspectives. Future research can test the output of these different participatory design approaches to test their effectiveness in the design of implementation strategies.

### Outcomes and Conclusions

We anticipate that our Penn ALACRITY center will result in the following outcomes. First, through the design, measurement, and statistical methods incubators, the Methods Core will generate guidelines for using participatory design approaches (ie, innovation tournaments, rapid-cycle prototyping, and discrete choice experiments) in the development of implementation strategies; a set of publicly available measures of behavioral phenotypes and a database that pools deidentified patient, provider, and organizational data; and practical statistical tools, guidelines, and information that facilitate the design of the next generation of mechanism-focused randomized trials in implementation science. Second, through our exploratory projects, we will generate data that will seed future implementation science studies that incorporate advances from behavioral economics and participatory design [128]. Third, through our scientific and dissemination activities, we hope both to (a) advance implementation science by integrating new conceptual models and methods to develop implementation strategies and (b) increase the use of EBPs in community settings to improve patient well-being and quality of care.

## Authors' Contributions

All authors contributed to the conceptualization and design of the proposed work (RB, AB, MC, ZC, JF, EBH, AL, DM, SM, MO, MP, RS, KV, NW, and KZ). RB, DM, and KV are principal investigators and are responsible for all center activities. AB, SM, and NW are the project directors for the Methods Core. SM, MO, and KV are project directors for Project 1. DM and MP are project directors for Project 2. RB, RS, and NW are project directors for Project 3. RB and DM drafted the initial manuscript. All authors read, provided critical feedback and editing, and approved the final manuscript.

## Conflicts of Interest

None declared.

## References

1. Patel V, Chisholm D, Parikh R, Charlson FJ, Degenhardt L, Dua T, DCP MNS Author Group. Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. Lancet 2016 Apr 16;387(10028):1672-1685. [doi: 10.1016/S0140-6736(15)00390-6]

2. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015 Apr;72(4):334-341 [FREE Full text] [doi: 10.1001/jamapsychiatry.2014.2502] [Medline: 25671328]

3. Insel TR. Assessing the economic costs of serious mental illness. Am J Psychiatry 2008 Jun;165(6):663-665. [doi: 10.1176/appi.ajp.2008.08030366] [Medline: 18519528]

4. Evans TS, Berkman N, Brown C, Gaynes B, Weber RP. Agency for Healthcare Research and Quality. 2016. Disparities within serious mental illness URL: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/mental-illness-disparities_technical-brief.pdf [accessed 2018-12-08] [WebCite Cache ID 74WOOqIJy]

5. Girlanda F, Fiedler I, Becker T, Barbui C, Koesters M. The evidence-practice gap in specialist mental healthcare: systematic review and meta-analysis of guideline implementation studies. Br J Psychiatry 2017 Jan;210(1):24-30. [doi: 10.1192/bjp.bp.115.179093] [Medline: 27445353]

6. Melendez-Torres GJ, Dickson K, Fletcher A, Thomas J, Hinds K, Campbell R, et al. Systematic review and meta-analysis of effects of community-delivered positive youth development interventions on violence outcomes. J Epidemiol Community Health 2016 Dec;70(12):1171-1177. [doi: 10.1136/jech-2015-206132] [Medline: 27445348]

7. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]

8. Aarons GA, Hurlburt M, Horwitz SM. Advancing a conceptual model of evidence-based practice implementation in public service sectors. Adm Policy Ment Health 2011 Jan;38(1):4-23 [FREE Full text] [doi: 10.1007/s10488-010-0327-7] [Medline: 21197565]

9. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009 Aug 7;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]

10. Balas EA, Boren SA. Managing clinical knowledge for health care improvement. Yearb Med Inform 2000(1):65-70. [Medline: 27699347]

11. Williams NJ, Beidas RS. Annual research review: the state of implementation science in child psychology and psychiatry: a review and suggestions to advance the field. J Child Psychol Psychiatry 2018 Aug 25. [doi: 10.1111/jcpp.12960] [Medline: 30144077]

12. Beidas RS, Edmunds JM, Marcus SC, Kendall PC. Training and consultation to promote implementation of an empirically supported treatment: a randomized trial. Psychiatr Serv 2012 Jul;63(7):660-665 [FREE Full text] [doi: 10.1176/appi.ps.201100401] [Medline: 22549401]

13. Miller WR, Yahne CE, Moyers TB, Martinez J, Pirritano M. A randomized trial of methods to help clinicians learn motivational interviewing. J Consult Clin Psychol 2004 Dec;72(6):1050-1062. [doi: 10.1037/0022-006X.72.6.1050] [Medline: 15612851]

14.  Sholomskas DE, Syracuse-Siewert G, Rounsaville BJ, Ball SA, Nuro KF, Carroll KM. We don't train in vain: a dissemination trial of three strategies of training clinicians in cognitive-behavioral therapy. J Consult Clin Psychol 2005 Feb;73(1):106-115 [FREE Full text] [doi: 10.1037/0022-006X.73.1.106] [Medline: 15709837]

15.  Beidas RS, Kendall PC. Training therapists in evidence-based practice: a critical review of studies from a systems-contextual perspective. Clin Psychol (New York) 2010 Mar;17(1):1-30 [FREE Full text] [doi: 10.1111/j.1468-2850.2009.01187.x] [Medline: 20877441]

16.  Herschell AD, Kolko DJ, Baumann BL, Davis AC. The role of therapist training in the implementation of psychosocial treatments: a review and critique with recommendations. Clin Psychol Rev 2010 Jun;30(4):448-466 [FREE Full text] [doi: 10.1016/j.cpr.2010.02.005] [Medline: 20304542]

17.  Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. Milbank Q 2004;82(4):581-629 [FREE Full text] [doi: 10.1111/j.0887-378X.2004.00325.x] [Medline: 15595944]

18.  Locke J, Wolk CB, Harker C, Olsen A, Shingledecker T, Barg F, et al. Pebbles, rocks, and boulders: the implementation of a school-based social engagement intervention for children with autism. Autism 2017 Nov;21(8):985-994 [FREE Full text] [doi: 10.1177/1362361316664474] [Medline: 28954537]

19.  Palinkas LA, Um MY, Jeong CH, Chor KH, Olin S, Horwitz SM, et al. Adoption of innovative and evidence-based practices for children and adolescents in state-supported mental health clinics: a qualitative study. Health Res Policy Syst 2017 Mar 29;15(1):27 [FREE Full text] [doi: 10.1186/s12961-017-0190-z] [Medline: 28356145]

20.  Stein BD, Celedonia KL, Kogan JN, Swartz HA, Frank E. Facilitators and barriers associated with implementation of evidence-based psychotherapy in community settings. Psychiatr Serv 2013 Dec 1;64(12):1263-1266 [FREE Full text] [doi: 10.1176/appi.ps.201200508] [Medline: 24292731]

21.  Beidas RS, Stewart RE, Adams DR, Fernandez T, Lustbader S, Powell BJ, et al. A multi-level examination of stakeholder perspectives of implementation of evidence-based practices in a large urban publicly-funded mental health system. Adm Policy Ment Health 2016 Nov;43(6):893-908 [FREE Full text] [doi: 10.1007/s10488-015-0705-2] [Medline: 26658692]

22.  Higa-McMillan CK, Nakamura BJ, Morris A, Jackson DS, Slavin L. Predictors of use of evidence-based practices for children and adolescents in usual care. Adm Policy Ment Health 2015 Jul;42(4):373-383. [doi: 10.1007/s10488-014-0578-9] [Medline: 25023894]

23.  Beidas RS, Marcus S, Aarons GA, Hoagwood KE, Schoenwald S, Evans AC, et al. Predictors of community therapists' use of therapy techniques in a large public mental health system. JAMA Pediatr 2015 Apr;169(4):374-382 [FREE Full text] [doi: 10.1001/jamapediatrics.2014.3736] [Medline: 25686473]

24.  Beidas R, Skriner L, Adams D, Wolk CB, Stewart RE, Becker-Haimes E, et al. The relationship between consumer, clinician, and organizational characteristics and use of evidence-based and non-evidence-based therapy strategies in a public mental health system. Behav Res Ther 2017 Dec;99:1-10. [doi: 10.1016/j.brat.2017.08.011] [Medline: 28865284]

25.  Benjamin Wolk C, Marcus SC, Weersing VR, Hawley KM, Evans AC, Hurford MO, et al. Therapist- and client-level predictors of use of therapy techniques during implementation in a large public mental health system. Psychiatr Serv 2016 May 1;67(5):551-557 [FREE Full text] [doi: 10.1176/appi.ps.201500022] [Medline: 26876658]

26.  Brookman-Frazee L, Haine RA, Baker-Ericzén M, Zoffness R, Garland AF. Factors associated with use of evidence-based practice strategies in usual care youth psychotherapy. Adm Policy Ment Health 2010 May;37(3):254-269 [FREE Full text] [doi: 10.1007/s10488-009-0244-9] [Medline: 19795204]

27.  Becker GS. The Economic Approach to Human Behavior. Chicago, IL: The University of Chicago Press; 1978.

28.  Fiske S, Taylor SE. Social Cognition: From Brains to Culture. Thousand Oaks, CA: SAGE Publications; 2013.

29.  Tversky A, Kahneman D. The framing of decisions and the psychology of choice. Science 1981 Jan 30;211(4481):453-458. [Medline: 7455683]

30.  Kahneman D, Tversky A. Prospect theory: an analysis of decision under risk. Econometrica 1979;47:263-291. [doi: 10.2307/1914185]

31.  Volpp KG, Troxel AB, Pauly MV, Glick HA, Puig A, Asch DA, et al. A randomized, controlled trial of financial incentives for smoking cessation. N Engl J Med 2009 Feb 12;360(7):699-709. [doi: 10.1056/NEJMsa0806819] [Medline: 19213683]

32.  Patel MS, Day SC, Halpern SD, Hanson CW, Martinez JR, Honeywell Jr S, et al. Generic medication prescription rates after health system-wide redesign of default options within the electronic health record. JAMA Intern Med 2016 Dec 1;176(6):847-848. [doi: 10.1001/jamainternmed.2016.1691] [Medline: 27159011]

33.  Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, State JJ, et al. A synchronized prescription refill program improved medication adherence. Health Aff (Millwood) 2016 Aug 1;35(8):1504-1512. [doi: 10.1377/hlthaff.2015.1456] [Medline: 27503977]

34.  Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, et al. Randomized trial of four financial-incentive programs for smoking cessation. N Engl J Med 2015;372:2108-2117. [doi: 10.1056/NEJMoa1414293]

35.  Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]

36. Chambers DA, Azrin ST. Research and services partnerships: partnership: a fundamental component of dissemination and implementation research. Psychiatr Serv 2013 Jun;64(6):509-511. [doi: 10.1176/appi.ps.201300032] [Medline: 23728600]

37. Pellecchia M, Mandell DS, Nuske HJ, Azad G, Benjamin Wolk C, Maddox BB, et al. Community-academic partnerships in implementation research. J Community Psychol 2018;46(7):941-952. [doi: 10.1002/jcop.21981]

38. Mitchell V, Ross T, May A, Sims R, Parker C. Empirical investigation of the impact of using co-design methods when generating proposals for sustainable travel solutions. CoDesign 2016;12(4):205-220. [doi: 10.1080/15710882.2015.1091894]

39. Lewis CC, Klasnja P, Powell BJ, Lyon AR, Tuzzio L, Jones S, et al. From classification to causality: advancing understanding of mechanisms of change in implementation science. Front Public Health 2018 May 7;6:136 [FREE Full text] [doi: 10.3389/fpubh.2018.00136] [Medline: 29868544]

40. Williams NJ. Multilevel mechanisms of implementation strategies in mental health: integrating theory, research, and practice. Adm Policy Ment Health 2016 Sep 1;43(5):783-798 [FREE Full text] [doi: 10.1007/s10488-015-0693-2] [Medline: 26474761]

41. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]

42. Kangovi S, Asch DA. Behavioral phenotyping in health promotion: embracing or avoiding failure. J Am Med Assoc 2018 May 22;319(20):2075-2076. [doi: 10.1001/jama.2018.2921] [Medline: 29710244]

43. National Institutes of Health. 2016. Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (ALACRITY) Research Centers (P50) URL: https://grants.nih.gov/grants/guide/pa-files/PAR-16-354.html [accessed 2018-09-05] [WebCite Cache ID 72DRawNxn]

44. Terwiesch C, Ulrich K. Innovation Tournaments: Creating and Selecting Exceptional Opportunities. Boston, MA: Harvard Business Review Press; 2009.

45. Terwiesch C, Mehta SJ, Volpp KG. Innovating in health delivery: the Penn Medicine innovation tournament. Healthc (Amst) 2013 Jun;1(1-2):37-41. [doi: 10.1016/j.hjdsi.2013.05.003] [Medline: 26249638]

46. Tantia P. The new science of designing for humans. Stanford Social Innovation Review 2017;15(2):29-33 [FREE Full text]

47. Datta S, Mullainathan S. Behavioral design: a new approach to development policy. Rev Income Wealth 2014 Feb 4;60(1):7-35. [doi: 10.1111/roiw.12093]

48. Service O, Hallsworth M, Halpern D, Algate F, Gallagher R, Nguyen S, et al. The Behavioural Insights Team. 2014. EAST: Four Simple Ways to Apply Behavioural Insights URL: https://www.behaviouralinsights.co.uk/publications/east-four-simple-ways-to-apply-behavioural-insights/ [accessed 2018-12-08] [WebCite Cache ID 74WOe8fAw]

49. Asch DA, Rosin R. Innovation as discipline, not fad. N Engl J Med 2015 Aug 13;373(7):592-594. [doi: 10.1056/NEJMp1506311] [Medline: 26267619]

50. Zahran S. Software Process Improvement: Practical Guidelines for Business Success. Harlow, UK: Pearson Education Limited; 1998.

51. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics 2008;26(8):661-677. [doi: 10.2165/00019053-200826080-00004] [Medline: 18620460]

52. Louviere JJ, Islam T, Wasi N, Street D, Burgess L. Designing discrete choice experiments: Do optimal designs come at a price? J Consum Res 2008 Aug 1;35(2):360-375. [doi: 10.1086/586913]

53. Salloum RG, Shenkman EA, Louviere JJ, Chambers DA. Application of discrete choice experiments to enhance stakeholder engagement as a strategy for advancing implementation: a systematic review. Implement Sci 2017 Nov 23;12(1):140 [FREE Full text] [doi: 10.1186/s13012-017-0675-8] [Medline: 29169397]

54. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-T]

55. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977;84(2):191-215. [doi: 10.1037/0033-295X.84.2.191]

56. O'Donoghue T, Rabin M. Doing it now or later. Am Econ Rev 1999;89(1):103-124. [doi: 10.1257/aer.89.1.103]

57. Cialdini RB. Influence: Science and Practice. Boston, MA: Allyn & Bacon; 2000.

58. Glisson C, Schoenwald SK, Hemmelgarn A, Green P, Dukes D, Armstrong KS, et al. Randomized trial of MST and ARC in a two-level evidence-based treatment implementation strategy. J Consult Clin Psychol 2010 Aug;78(4):537-550 [FREE Full text] [doi: 10.1037/a0019160] [Medline: 20658810]

59. Proctor EK, Landsverk J, Aarons G, Chambers D, Glisson C, Mittman B. Implementation research in mental health services: an emerging science with conceptual, methodological, and training challenges. Adm Policy Ment Health 2009 Jan;36(1):24-34 [FREE Full text] [doi: 10.1007/s10488-008-0197-4] [Medline: 19104929]

60. Ehrhart MG, Aarons GA, Farahnak LR. Assessing the organizational context for EBP implementation: the development and validity testing of the Implementation Climate Scale (ICS). Implement Sci 2014 Oct 23;9:157 [FREE Full text] [doi: 10.1186/s13012-014-0157-1] [Medline: 25338781]

61. Aarons GA, Ehrhart MG, Farahnak LR, Sklar M. Aligning leadership across systems and organizations to develop a strategic climate for evidence-based practice implementation. Annu Rev Public Health 2014;35:255-274 [FREE Full text] [doi: 10.1146/annurev-publhealth-032013-182447] [Medline: 24641560]

62. Green AE, Albanese BJ, Cafri G, Aarons GA. Leadership, organizational climate, and working alliance in a children's mental health service system. Community Ment Health J 2014 Oct;50(7):771-777 [FREE Full text] [doi: 10.1007/s10597-013-9668-5] [Medline: 24323137]

63. Camerer CF, Malmendier U. Behavioral Economics of Organizations. In: Behavioral Economics and Its Applications. Princeton, NJ: Princeton University Press; 2007:235-290.

64. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol 2007;3:1-27. [doi: 10.1146/annurev.clinpsy.3.022806.091432] [Medline: 17716046]

65. Zhang Z, Zyphur MJ, Preacher KJ. Testing multilevel mediation using hierarchical linear models: problems and solutions. Organ Res Methods 2008;12(4):695-719. [doi: 10.1177/1094428108327450]

66. Scott MA, Simonoff JS, Marx BD, editors. The SAGE Handbook of Multilevel Modeling. London, England: Sage Publications; 2013.

67. Raudenbush SW, Bryk AS. Hierarchical Linear Models: Applications and Data Analysis Methods. Thousand Oaks, CA: Sage Publications; 2001.

68. Williams NJ, Glisson C, Hemmelgarn A, Green P. Mechanisms of change in the ARC organizational strategy: increasing mental health clinicians' EBP adoption through improved organizational culture and capacity. Adm Policy Ment Health 2017 Mar;44(2):269-283 [FREE Full text] [doi: 10.1007/s10488-016-0742-5] [Medline: 27236457]

69. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

70. Cohen J. A power primer. Psychol Bull 1992 Jul;112(1):155-159. [doi: 10.1037/0033-2909.112.1.155] [Medline: 19565683]

71. Scherbaum CA, Ferreter JM. Estimating statistical power and required sample sizes for organizational research using multilevel modeling. Organ Res Methods 2008 Apr 8;12(2):347-367. [doi: 10.1177/1094428107308906]

72. Snijders T. Power and Sample Size in Multilevel Linear Models. In: Everitt B, Howell D, editors. Encyclopedia of Statistics in Behavioral Science. Chichester, UK: Wiley; 2005:1570-1573.

73. Preacher KJ, Zyphur MJ, Zhang Z. A general multilevel SEM framework for assessing multilevel mediation. Psychol Methods 2010 Sep;15(3):209-233. [doi: 10.1037/a0020141] [Medline: 20822249]

74. Demyttenaere K, Andersen HF, Reines EH. Impact of escitalopram treatment on quality of life enjoyment and satisfaction questionnaire scores in major depressive disorder and generalized anxiety disorder. Int Clin Psychopharmacol 2008 Sep;23(5):276-286. [doi: 10.1097/YIC.0b013e328303ac5f] [Medline: 18703937]

75. Charbonneau A, Rosen AK, Owen RR, Spiro 3rd A, Ash AS, Miller DR, et al. Monitoring depression care: in search of an accurate quality indicator. Med Care 2004 Jun;42(6):522-531. [doi: 10.1097/01.mlr.0000127999.89246.a6] [Medline: 15167320]

76. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry 1998 Dec;55(12):1128-1132. [doi: 10.1001/archpsyc.55.12.1128] [Medline: 9862557]

77. Miranda J, Chung JY, Green BL, Krupnick J, Siddique J, Revicki DA, et al. Treating depression in predominantly low-income young minority women: a randomized controlled trial. J Am Med Assoc 2003 Jul 2;290(1):57-65. [doi: 10.1001/jama.290.1.57] [Medline: 12837712]

78. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. Med Care 2006 Apr;44(4):300-303. [doi: 10.1097/01.mlr.0000204287.82701.9b] [Medline: 16565629]

79. Olfson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adults with depression in the United States. Am J Psychiatry 2006 Jan;163(1):101-108. [doi: 10.1176/appi.ajp.163.1.101] [Medline: 16390896]

80. Kreuter MW, Bernhardt JM. Reframing the dissemination challenge: a marketing and distribution perspective. Am J Public Health 2009 Dec;99(12):2123-2127. [doi: 10.2105/AJPH.2008.155218] [Medline: 19833993]

81. Marcus AC, Kaplan CP, Crane LA, Berek JS, Bernstein G, Gunning JE, et al. Reducing loss-to-follow-up among women with abnormal Pap smears. Results from a randomized trial testing an intensive follow-up protocol and economic incentives. Med Care 1998 Mar;36(3):397-410. [Medline: 9520963]

82. Kullgren JT, Troxel AB, Loewenstein G, Asch DA, Norton LA, Wesby L, et al. Individual- versus group-based financial incentives for weight loss: a randomized, controlled trial. Ann Intern Med 2013 Apr 2;158(7):505-514 [FREE Full text] [doi: 10.7326/0003-4819-158-7-201304020-00002] [Medline: 23546562]

83. John LK, Loewenstein G, Troxel AB, Norton L, Fassbender JE, Volpp KG. Financial incentives for extended weight loss: a randomized, controlled trial. J Gen Intern Med 2011 Jun;26(6):621-626 [FREE Full text] [doi: 10.1007/s11606-010-1628-y] [Medline: 21249462]

84. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. J Am Med Assoc 2008 Dec 10;300(22):2631-2637 [FREE Full text] [doi: 10.1001/jama.2008.804] [Medline: 19066383]

85. Volpp KG, Loewenstein G, Troxel AB, Doshi J, Price M, Laskin M, et al. A test of financial incentives to improve warfarin adherence. BMC Health Serv Res 2008 Dec 23;8:272 [FREE Full text] [doi: 10.1186/1472-6963-8-272] [Medline: 19102784]

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86. Kimmel SE, Troxel AB, Loewenstein G, Brensinger CM, Jaskowiak J, Doshi JA, et al. Randomized trial of lottery-based incentives to improve warfarin adherence. Am Heart J 2012 Aug;164(2):268-274 [FREE Full text] [doi: 10.1016/j.ahj.2012.05.005] [Medline: 22877814]

87. Asch DA, Troxel AB, Stewart WF, Sequist TD, Jones JB, Hirsch AG, et al. Effect of financial incentives to physicians, patients, or both on lipid levels: a randomized clinical trial. J Am Med Assoc 2015 Nov 10;314(18):1926-1935 [FREE Full text] [doi: 10.1001/jama.2015.14850] [Medline: 26547464]

88. Petry NM, Alessi SM, Byrne S, White WB. Reinforcing adherence to antihypertensive medications. J Clin Hypertens (Greenwich) 2015 Jan;17(1):33-38 [FREE Full text] [doi: 10.1111/jch.12441] [Medline: 25413264]

89. Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S. Adherence to antidepressant treatment among privately insured patients diagnosed with depression. Med Care 2007 Apr;45(4):363-369 [FREE Full text] [doi: 10.1097/01.mlr.0000254574.23418.f6] [Medline: 17496721]

90. Nierenberg AA, Farabaugh AH, Alpert JE, Gordon J, Worthington JJ, Rosenbaum JF, et al. Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry 2000 Sep;157(9):1423-1428. [doi: 10.1176/appi.ajp.157.9.1423] [Medline: 10964858]

91. Loewenstein G, Asch DA, Volpp KG. Behavioral economics holds potential to deliver better results for patients, insurers, and employers. Health Aff (Millwood) 2013 Jul;32(7):1244-1250. [doi: 10.1377/hlthaff.2012.1163] [Medline: 23836740]

92. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. J Am Med Assoc 2007 Nov 28;298(20):2415-2417. [doi: 10.1001/jama.298.20.2415] [Medline: 18042920]

93. Petry NM, Peirce JM, Stitzer ML, Blaine J, Roll JM, Cohen A, et al. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: a national drug abuse treatment clinical trials network study. Arch Gen Psychiatry 2005 Oct;62(10):1148-1156. [doi: 10.1001/archpsyc.62.10.1148] [Medline: 16203960]

94. Camerer C, Hua Ho T. Experience-weighted attraction learning in normal form games. Econometrica 1999 Jul;67(4):827-874. [doi: 10.1111/1468-0262.00054]

95. Giles EL, Robalino S, Sniehotta FF, Adams J, McColl E. Acceptability of financial incentives for encouraging uptake of healthy behaviours: a critical review using systematic methods. Prev Med 2015 Apr;73:145-158. [doi: 10.1016/j.ypmed.2014.12.029] [Medline: 25600881]

96. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, et al. Validation of a decision regret scale. Med Decis Making 2003;23(4):281-292. [doi: 10.1177/0272989X03256005] [Medline: 12926578]

97. Myers SM, Johnson CP, American Academy of Pediatrics Council on Children With Disabilities. Management of children with autism spectrum disorders. Pediatrics 2007 Nov;120(5):1162-1182. [doi: 10.1542/peds.2007-2362] [Medline: 17967921]

98. Azad GF, Locke J, Downey MM, Xie M, Mandell DS. One-to-one assistant engagement in autism support classrooms. Teach Educ Spec Educ 2015 Nov 1;38(4):337-346 [FREE Full text] [doi: 10.1177/0888406415603208] [Medline: 26807003]

99. Fisher M, Pleasants SL. Roles, responsibilities, and concerns of paraeducators: findings from a statewide survey. Remedial Spec Educ 2011 Feb;33(5):287-297. [doi: 10.1177/0741932510397762]

100. Koegel RL, Kim S, Koegel LK. Training paraprofessionals to improve socialization in students with ASD. J Autism Dev Disord 2014 Sep;44(9):2197-2208 [FREE Full text] [doi: 10.1007/s10803-014-2094-x] [Medline: 24671749]

101. Young HE, Falco RA, Hanita M. Randomized, controlled trial of a comprehensive program for young students with autism spectrum disorder. J Autism Dev Disord 2016 Feb;46(2):544-560. [doi: 10.1007/s10803-015-2597-0] [Medline: 26438637]

102. Odom SL, Boyd BA, Hall LJ, Hume K. Evaluation of comprehensive treatment models for individuals with autism spectrum disorders. J Autism Dev Disord 2010 Apr;40(4):425-436. [doi: 10.1007/s10803-009-0825-1] [Medline: 19633939]

103. Simon HA. Bounded rationality and organizational learning. Organ Sci 1991;2(1):125-134. [doi: 10.1287/orsc.2.1.125]

104. Beidas RS, Aarons G, Barg F, Evans A, Hadley T, Hoagwood K, et al. Policy to implementation: evidence-based practice in community mental health--study protocol. Implement Sci 2013 Mar 24;8:38 [FREE Full text] [doi: 10.1186/1748-5908-8-38] [Medline: 23522556]

105. Stewart RE, Adams DR, Mandell DS, Hadley TR, Evans AC, Rubin R, et al. The perfect storm: collision of the business of mental health and the implementation of evidence-based practices. Psychiatr Serv 2016 Feb;67(2):159-161 [FREE Full text] [doi: 10.1176/appi.ps.201500392] [Medline: 26522680]

106. Chou AF, Wallace N, Bloom JR, Hu TW. Variation in outpatient mental health service utilization under capitation. J Ment Health Policy Econ 2005 Mar;8(1):3-14. [Medline: 15870481]

107. Hadley TR. Financing changes and their impact on the organization of the public mental health system. Adm Policy Ment Health 1996 May;23(5):393-405. [doi: 10.1007/BF02112900]

108. Honberg R, Kimball A, Diehl S, Usher L, Fitzpatrick M. National Alliance on Mental Illness. 2011 Nov. State Mental Health Cuts: The Continuing Crisis URL: https://www.nami.org/getattachment/About-NAMI/Publications/Reports/StateMentalHealthCuts2.pdf [accessed 2018-12-10] [WebCite Cache ID 74Z5ll3Ie]

109. Garner BR, Godley SH, Dennis ML, Hunter BD, Bair CM, Godley MD. Using pay for performance to improve treatment implementation for adolescent substance use disorders: results from a cluster randomized trial. Arch Pediatr Adolesc Med 2012 Oct;166(10):938-944. [doi: 10.1001/archpediatrics.2012.802] [Medline: 22893231]

110. Garner BR, Godley SH, Bair CM. The impact of pay-for-performance on therapists' intentions to deliver high-quality treatment. J Subst Abuse Treat 2011 Jul;41(1):97-103 [FREE Full text] [doi: 10.1016/j.jsat.2011.01.012] [Medline: 21315539]

111. Shepard DS, Calabro JA, Love CT, McKay JR, Tetreault J, Yeom HS. Counselor incentives to improve client retention in an outpatient substance abuse aftercare program. Adm Policy Ment Health 2006 Nov;33(6):629-635. [Medline: 16758330]

112. Song Z, Rose S, Safran DG, Landon BE, Day M, Chernew ME. Harvard Library Office for Scholarly Communication. Payment reform in Massachusetts: effect of global payment on heath care spending and quality 4 years into the alternative quality contract URL: https://dash.harvard.edu/bitstream/handle/1/12407606/ZSong%20Honors%20Thesis%209-22-14%20Redacted%20Version%203%200.pdf?sequence=5 [accessed 2018-12-14] [WebCite Cache ID 74eUeFuqk]

113. McWilliams JM, Chernew ME, Landon BE, Schwartz AL. Performance differences in year 1 of pioneer accountable care organizations. N Engl J Med 2015 May 14;372:1927-1936. [doi: 10.1056/NEJMsa1414929]

114. McWilliams JM, Hatfield LA, Chernew ME, Landon BE, Schwartz AL. Early performance of accountable care organizations in medicare. N Engl J Med 2016 Jun 16;374(24):2357-2366 [FREE Full text] [doi: 10.1056/NEJMsa1600142] [Medline: 27075832]

115. Acevedo A, Lee MT, Garnick DW, Horgan CM, Ritter GA, Panas L, et al. Agency-level financial incentives and electronic reminders to improve continuity of care after discharge from residential treatment and detoxification. Drug Alcohol Depend 2018 Feb 1;183:192-200. [doi: 10.1016/j.drugalcdep.2017.11.009] [Medline: 29288914]

116. Stewart RE, Lareef I, Hadley TR, Mandell DS. Can we pay for performance in behavioral health care? Psychiatr Serv 2017 Feb 1;68(2):109-111. [doi: 10.1176/appi.ps.201600475] [Medline: 27903140]

117. Garland AF, Haine-Schlagel R, Brookman-Frazee L, Baker-Ericzen M, Trask E, Fawley-King K. Improving community-based mental health care for children: translating knowledge into action. Adm Policy Ment Health 2013 Jan;40(1):6-22 [FREE Full text] [doi: 10.1007/s10488-012-0450-8] [Medline: 23212902]

118. Pincus HA, Page AE, Druss B, Appelbaum PS, Gottlieb G, England MJ. Can psychiatry cross the quality chasm? Improving the quality of health care for mental and substance use conditions. Am J Psychiatry 2007 May;164(5):712-719. [doi: 10.1176/ajp.2007.164.5.712] [Medline: 17475728]

119. Volpp KG, Asch DA, Galvin R, Loewenstein G. Redesigning employee health incentives--lessons from behavioral economics. N Engl J Med 2011 Aug 4;365(5):388-390 [FREE Full text] [doi: 10.1056/NEJMp1105966] [Medline: 21812669]

120. Asch DA, Muller RW, Volpp KG. Automated hovering in health care--watching over the 5000 hours. N Engl J Med 2012 Jul 5;367(1):1-3. [doi: 10.1056/NEJMp1203869] [Medline: 22716935]

121. Volpp KG, Pauly MV, Loewenstein G, Bangsberg D. P4P4P: an agenda for research on pay-for-performance for patients. Health Aff (Millwood) 2009;28(1):206-214 [FREE Full text] [doi: 10.1377/hlthaff.28.1.206] [Medline: 19124872]

122. Halpern SD, Asch DA, Volpp KG. Commitment contracts as a way to health. BMJ 2012 Jan 30;344:e522 [FREE Full text] [doi: 10.1136/bmj.e522]

123. Volpp KG, Loewenstein G, Asch DA. Assessing value in health care programs. J Am Med Assoc 2012;307(20):2153-2154. [doi: 10.1001/jama.2012.3619] [Medline: 22618919]

124. Volpp KG, Loewenstein G, Asch DA. Choosing wisely: low-value services, utilization, and patient cost sharing. J Am Med Assoc 2012 Oct 24;308(16):1635-1636 [FREE Full text] [doi: 10.1001/jama.2012.13616] [Medline: 23093160]

125. Loewenstein G, Asch DA, Friedman JY, Melichar LA, Volpp KG. Can behavioural economics make us healthier? BMJ 2012 May 23;344:e3482 [FREE Full text] [Medline: 22623635]

126. Loewenstein G, John LK, Volpp K. Using Decision Errors to Help People Help Themselves. In: Shafer E, editor. The Behavioral Foundations of Public Policy. Princeton, NJ: Princeton University Press; 2012.

127. Volpp KG, Loewenstein G. Using ideas from behavioral economics to promote improvements in health behaviors. In: Kahan S, Gielen AC, Fagan PJ, Green LW, editors. Health Behavior Change in Populations. Baltimore, MD: Johns Hopkins University Press; 2014.

128. Falk-Krzesinski HJ, Börner K, Contractor N, Fiore SM, Hall KL, Keyton J, et al. Advancing the science of team science. Clin Transl Sci 2010 Oct;3(5):263-266 [FREE Full text] [doi: 10.1111/j.1752-8062.2010.00223.x] [Medline: 20973925]

## Abbreviations

**ADAPT:** Assisting Depressed Adults in Primary care Treatment
**ALACRITY:** Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness
**ASSISTS:** App for Strengthening Services In Specialized Therapeutic Support
**CBH:** Community Behavioral Health
**DBHIDS:** Department of Behavioral Health and Intellectual disAbility Services
**EBP:** evidence-based practice
**MOTIVATE:** Motivating Outpatient Therapists to Implement: Valuing a Team Effort
**TSS:** therapeutic support staff

Protocol

# Development of a Web-Based Peer Support Program for Family Caregivers of Ventilator-Assisted Individuals Living in the Community: Protocol for a Pilot Randomized Controlled Trial

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## *Abstract*

**Background:** Across Europe, Canada, Australia, and the United States, the prevalence of home mechanical ventilation (HMV) prevalence is 6.6-12.9 per 100,000. At-home ventilator-assisted individuals (VAIs) are often vulnerable and highly comorbid, requiring complex care. In Canada, most VAI care is provided by family, leading to poor health-related quality of life and increased caregiver burden. No supportive interventions or peer support programs are tailored to VAI caregivers. Owing to the financial, geographic, and time limitations, Web-based support delivery may especially meet VAI family caregiver needs. We have developed a peer mentor training and Web-based peer support program for VAI caregivers including information-sharing, peer-to-peer communication, and peer mentorship.

**Objective:** Study Stage 1 aims to (1) evaluate the face and content validity of the peer mentor training program and (2) investigate participant satisfaction. Study Stage 2 aims to evaluate (1) the feasibility of participant recruitment and Web-based program delivery; (2) acceptability, usability, and satisfactoriness; (3) experiences of caregivers and peer mentors with the Web-based peer support program; and (4) effect of the Web-based peer support program on caregiver health outcomes.

**Methods:** Study Stage 1: We will train 7 caregivers to act as peer mentors for the Web-based peer support program trial; they will complete questionnaires rating the utility of individual training sessions and the training program overall. Study Stage 2: We will recruit 30 caregiver peers for a pilot randomized controlled trial of the 12-week Web-based peer support program using a waitlist control; the program includes private chat, a public discussion forum, and weekly moderated chats. Caregiver peers will be randomized to the intervention or waitlist control group using a 1:1 ratio using Randomize.net. Both groups will complete pre- and postintervention health outcome questionnaires (ie, caregiving impact, mastery, coping, personal gain, positive affect, and depression). Caregiver peers in the intervention arm will only complete a program evaluation and will be invited to participate in an interview to provide insight into their experience. Peer mentors will be invited to participate in a Web-based focus group to provide insight into their experience as mentors. We will judge the feasibility per the number of recruitment and program

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delivery goals met, use analysis of covariance to compare health outcomes between intervention and control groups, and analyze qualitative data thematically.

**Results:** Peer mentor training was completed with 5 caregivers in July 2018. To date, 2 caregivers have beta-tested the website, and the Web-based peer support program trial will commence in September 2018. Results are expected by early 2019.

**Conclusions:** This study will result in the production and initial evaluation of a rigorously developed, evidence- and stakeholder-informed Web-based peer training and peer support program for caregivers of VAIs residing at home.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/11827

## Introduction

### Family Caregivers of Ventilator-Assisted Individuals

Prevalence rates for ventilator-assisted individuals (VAIs) living at home are increasing globally. The 2005 Eurovent Study estimated the prevalence of home mechanical ventilation (HMV) at 6.6 per 100,000 population across 16 European countries [1]. Comparative research from Australia and New Zealand indicated a minimum prevalence of HMV of 9.9 and 12.0 per 100,000, respectively [2]. Recent data from Canada and the United States indicate that 12.9 and 6.6 per 100,000 population, respectively, receive HMV [3,4]. Given the unique and complex care needs of VAIs [3], family caregivers play an essential role in sustaining the stable environment that enables them to live at home [5,6]. If family caregivers are unable to support VAIs to remain in the home, the only alternative is institutionalization [7]. Several studies have highlighted that caregiving can increase the burden and decrease the caregiver health-related quality of life [8]. A study focusing on caregivers of VAIs with progressive neuromuscular disease, a common indication from HMV, described a negative impact on both physical and emotional caregiver health, with the initial transfer home perceived as extremely stressful [5]. These findings emphasize the growing acceptance that family caregiving is a serious public health issue requiring intervention [9].

### Support From Other Caregivers

Peer support comprises (1) emotional support (expressions of caring, empathy. and reassurance); (2) informational support (advice, suggestions, factual input, and feedback); and (3) affirmational support (affirmation of feelings and behaviors, reassurance that frustrations can be managed) [10]. Peers—individuals who have experienced the same health problem and have similar characteristics as the support recipients—can be a key source of support for family caregivers [11]. Peer support improves the health-related quality of life and well-being by decreasing feelings of isolation, improving mood, buffering stress, creating a sense of empowerment, and increasing self-efficacy in various patient and caregiver populations [12-14]. The lack of peer support has been shown to predict distress [15]. Several peer support models exist including in-person, peer-to-peer matching, and online support [16].

### Online Peer Support Provision

Within the broader family caregiver population, geographic limitations, time constraints and a lack of respite have been cited as reasons that caregivers do not utilize in-person support groups [17]. In addition, the economic burden of diseases that leads to mechanical ventilation frequently make attendance at in-person meetings cost-prohibitive [18]. Consequently, many caregivers are turning to the internet as an avenue for social support [19]. Over the past decade, the number of Web-based health interventions providing a broad array of family caregiver supports in a cost-effective, accessible, and convenient fashion have increased exponentially [20]. Within these Web-based programs, peer-to-peer communication is a particularly critical element of support, with qualitative findings indicating that caregivers highly appreciate and benefit from interaction with similar others [20]. Therefore, peer support delivered using Web-based modalities is especially well-tailored to fit the demanding nature of the VAI caregiver role.

### Development of a Web-based Peer Support Program for Caregivers of Ventilator-Assisted Individuals

Rising numbers of VAIs living at home [3], the burden of family caregiving [5,9], the proven benefit of peer support in various caregiving populations, and the lack of existing social support for caregivers of community-based VAIs [6] suggest an urgent need for peer support programs for these family caregivers. Although peer support interventions have been shown to be effective in a number of illness populations, there are currently no studies of family caregivers of VAIs in the home. As peer support can take many forms [16] and multicomponent Web interventions (ie, including several support features— informational links, chat, and discussion forum) tend to be more effective in reducing caregiver burden [21,22], we will develop, validate, and conduct feasibility evaluation of an Web-based peer support program entailing elements of informational support, peer-to-peer interaction, as well as peer-mentoring.

### Overall Study Objective

This study aims to develop a comprehensive Web-based peer support program for VAI caregivers, including peer-mentoring, and explore the feasibility of the program.

## Methods

### Study Stage 1: Peer Mentor Training

#### Objectives

**Primary Objective**

The primary objective is to evaluate the utility of the peer mentor training program.

**Secondary Objective**

The secondary objective is to investigate participant satisfaction with the peer mentor training program.

#### Procedure

We have adapted a peer *training* program developed by St. Jude's Research Hospital (Memphis, TN, USA) for parents caring for a child with cancer [23], also recommended as a valuable resource by an existing peer support tool kit used for parents of technology-dependent children [16]. We selected this training program because of its focus on mentorship skill development (rather than peer-matching process and logistics) and the publicly available recorded training sessions. To ensure that our adapted *training* program has the face and content validity for our home VAI caregiver population, we will ask a minimum of 2 home VAI caregivers and 1 clinician that manages this patient population to review and make suggestions regarding content, structure, and delivery.

The original St. Jude's peer *training* program consists of 4 in-person sessions and our Web-based mentor training program will reflect this. The four 1-hour sessions will cover the following topics: (1) peer mentorship basics (eg, family-centered care, where or how to obtain educational materials specific to HMV); (2) mentoring skills (eg, active listening and sharing stories); (3) boundary-setting (eg, mentor's boundaries and value of boundaries); and (4) mentorship at the end-of-life, emergency situations, and wrap-up (eg, unique end-of-life circumstances, red flags, when to call for help, debriefing about training, and next steps for participating in evaluation). During each of the sessions, the trainer will go over the material and incorporate short "break-out sessions" that will allow participants to pause, reflect, and discuss new concepts and skills.

We will host mentor training sessions using GoToMeeting to facilitate Web-based attendance. GoToMeeting allows for high-definition video and high-quality audio, compatibility with desktops or tablets or phones, screen sharing, and video recording. This latter feature will enable recording of the training sessions and archiving on a secure server to inform future iterations of the training program.

#### Participants

The inclusion criteria for peer mentors are as follows: (1) age ≥18 years; (2) previous or current family caregiver for a community-residing VAI; (3) able to speak and read English; (4) access to a computer (with video and microphone) and a high-speed internet connection; and (5) available for training sessions. The exclusion criteria are as follows: (1) currently experiencing severe depression as indicated by a score of ≥10 on the Centre for Epidemiological Studies Short Depression scale during recruitment screening [24].

#### Recruitment

We will recruit caregivers from the provincial Ventilation Equipment Pool (Kingston, ON, Canada), and the long-term and home ventilation clinics of West Park Healthcare Centre (Toronto, ON, Canada). We will seek snowball referrals from clinician experts, professional societies, patient advocacy groups (eg, Muscular Dystrophy Canada), and through Twitter.

We will recruit 5-10 peer mentors for training. Purposive sampling based on the following criteria will be used to ensure sample diversity: (1) ventilator type (invasive: n=2; noninvasive: n=5); (2) diagnostic category [rapidly progressing disease (amyotrophic lateral sclerosis): n=2; nonrapidly progressing disease (Guillain-Barré syndrome, Myasthenia Gravis, and postpolio syndrome): n=2; variably progressing disease (muscular dystrophy): n=2]; (3) relationship to care-recipient (spouse: n=2; child: n=2; parent: n=1); and (4) sex (male: n=2; female: n=5).

#### Data Collection

Prior to training, we will ask peer mentors to complete a demographic questionnaire and rate their general health status (on a scale of 1-5; 1=very good, 5=Poor). Before and after the training program participation, we will ask peer mentors to complete the Mentoring Skills Inventory [25]; this questionnaire asks peer mentors to indicate whether they are very comfortable ("V"), moderately comfortable ("M"), or uncomfortable ("U") with 12 mentoring skills (eg, brokering relationships; coaching; goal-setting; managing conflict; providing and receiving feedback) [25,26]. After each training session, we will ask peer mentors to complete a short questionnaire rating the extent to which they agree with a series of questions about the design, content, instruction, and utility of the training session on a 5-point Likert scale (1=strongly disagree; 5=strongly agree). In addition, they will be asked to comment on what they benefited from most, what was unclear, and what would benefit from additional content. Any mentor(s) identified as needing clarification or additional training will be followed up with on an individual basis. We will ask peer mentors to complete an end-of-training questionnaire rating their satisfaction with the training overall (eg, objectives clearly defined and trainers knew material) on a 5-point Likert scale (1=strongly agree; 5=strongly disagree). Furthermore, they will be asked to comment on which training sessions they found most or least informative and to provide any suggestions for future iterations of the peer mentor training program.

#### Data Analysis

We will report descriptive statistics from individual training session questionnaires and the end-of-training questionnaires, including counts and proportions for categorical data and means and SDs (or medians and interquartile ranges), depending on the distribution of continuous data.

## Study Stage 2: Web-based Peer Support Program

### *Objectives*

#### Primary Objective

The primary objective is to evaluate the feasibility of trial recruitment and program delivery according to *a-priori* definitions described below and including user ratings of acceptability, usability, and satisfaction.

#### Secondary (Exploratory) Objectives

The secondary objectives are to explore (1) caregiver health outcomes (ie, caregiving impact, mastery, coping, personal gain, positive affect, and depression) before and after participation in the Web-based peer support program and (2) the experiences with the program from the perspective of caregiver peers and peer mentors.

### *Trial Design*

We will conduct a pilot randomized controlled trial (RCT) of the 12-week Web-based peer support program with waitlist control. Research Ethics Board approval was received from the University of Toronto in May 2017, where the research is being conducted.

### *Study Setting*

While the online peer support intervention is Web based, the study is being hosted at the University of Toronto. Recruitment is limited to Canadian caregivers of VAIs.

### *Eligibility Criteria*

The inclusion and exclusion criteria for the peer mentor training also apply to participants for the Web-based peer support program feasibility RCT except needing to be *currently* providing care to a VAI living at home.

### The Web-based Peer Support Program (Intervention)

### *Technical Development*

The end goal for this development project was to create a "social-network" style website (akin to Facebook). This website would also need to digitally capture and record all interactions between participants. To provide all the functionality needed for this study (including interaction data capture), we found that nonproprietary "off-the-shelf" software programs or templates were insufficient. Therefore, we used a hybrid of "existing-base-software" coupled with code or programming designed and integrated into this base software, making the functionality of this website unique.

### *Content and Design*

The content and design of the Web-based peer support program were informed by a scoping review led by the first author [20], a local peer support tool kit [16], and a provincial peer support program [27]. The 12-week Web-based peer support program entails the following: (1) informational resources (links to relevant websites and resources—eg, national disease and caregiving organizations); (2) discussion forum open to caregiver peers and peer mentors enabling asynchronous contact; (3) weekly chat (live 1-hour forum for discussing a specific topics—eg, self-care, illness management moderated by the

research team); and (4) private messaging, including audio, video, or text chat, allowing participants one-on-one or select group interaction with other caregiver peers or peer mentors. Private messaging is hidden from other participants but accessible to the research team for monitoring purposes. Every participant (peer mentors and caregiver peers) will create a personal profile with information about their caregiving situation (eg, who are or were caring for, ie, spouse, child, duration of care, diagnosis, etc). Based on the peer mentor profiles, caregiver peers will have the opportunity to access mentors they believe are well suited to address their support needs, questions, and concerns.

### Primary Outcome

Our primary outcome is the feasibility of trial recruitment and program delivery. The feasibility will be assessed on the basis of compliance with the protocol represented by the following criteria:

1. The proportion of peer mentors participating weekly in any program element (ie, discussion forum, private chat, or live chat) for, at least, 8 out of the 12 program weeks: ≥60% of peer mentors
2. The proportion of caregiver peers participating weekly in any program element (ie, discussion forum, private chat, or live chat) for, at least, 8 out of the 12 program weeks: ≥60% of peer mentors
3. Discussion forum usage: ≥50% participants (peer mentors and caregiver peers) posting each week
4. Live weekly chat usage: ≥50% participants (peer mentors and caregiver peers) joining each week
5. The frequency of weekly mentor contacts: ≥25% of mentors receive, at least, 1 message each week
6. The proportion of peer mentors contacted: ≥50% of mentors contacted, at least, once during the 12-week program
7. The proportion of caregiver peer participants who contacted a mentor: ≥50% of caregiver peer participants during the 12-week program
8. Attrition rates: ≤30% caregiver peer participants withdrawing from the study before completion of postintervention questionnaires

We have selected the following decisions to determine the feasibility [28,29]:

- 0-2/8 criteria met—Stop; study design not feasible.
- 3-5/8 criteria met—Continue with modifications; feasible study design with modifications.
- 6-7/8 criteria met—Continue without modifications but monitor closely; feasible study design with close monitoring.
- 8/8 criteria met—Continue without modifications; feasible study design as is.

### Participant Timeline

We will instruct participants to participate in the discussion forum, at least, twice a week and in each weekly chat. In addition, we will instruct participants to access peer mentors selected per their own preference, at least, once every week. Participants can choose to access only one or several peer mentors, again at their own preference. Caregiver peer

participants will be instructed to respond to messages directed at them from either mentors or other peers through the Web-based peer support site within 48 hours.

We will instruct peer mentors to participate in the discussion forums, at least, 2 times a week and in each weekly chat. In addition, we will instruct peer mentors to contact the research team if they are concerned about the well-being of participants. The research team will then contact those participants to assess the situation and recommend visiting their family doctor to access supports if required. We will instruct peer mentors to respond to messages directed at them through the Web-based peer support site within 48 hours.

## Sample Size

There has been no prior assessment of a peer support intervention for VAI caregivers on which to base our sample size calculations. Using feasibility criteria of 15% dropout and 70% participation in weekly chats, a sample size of 30 would allow us to be 90% confident that estimates are accurate within 22% and 28% percentage points, respectively [30].

## Recruitment

Recruitment procedures for the Web-based peer support program feasibility RCT are the same as those for the peer mentor training. We will aim to recruit 30 participants. We will recruit caregivers until we achieve the following minimum numbers: (1) ventilator subgroup (invasive: n=2; noninvasive: n=8); (2) diagnostic category (rapidly progressing disease: n=3; nonrapidly progressing disease: n=3; restrictive thoracic cage disorders: n=3); (3) relationship to care-recipient (spouse: n=4; child: n=4; parent: n=4); and (4) gender (male: n=5; female: n=7).

## Allocation

We will randomize consenting participants to the peer support intervention or waitlist control using a 1:1 ratio using Randomize.net. No stratification will be applied, and allocation will be concealed using opaque sealed envelopes. Those randomized to the waitlist control will be given access to the peer support program following the 12-week intervention phase. A waitlist control group was chosen as it is believed to be a cost-effective and ethical alternative to no-treatment control groups when primarily studying psychological and behavioral interventions such as the one in this study [31]. Those randomized to the intervention group will receive information through email about the website features (eg, forum, chat) and instructions in their use, log-in and profile instructions, and the weekly chat schedule. We will send weekly email reminders to encourage participants to access website resources, participate in the weekly chat, and draw their attention to active discussion forum threads.

## Data Collection

### At Baseline

A blinded assessor will collect the demographic and health information from participants in both the intervention group and control group and administer the exploratory caregiver-reported measures (listed in Table 1) through email or over the phone (as per the participants' preference). Our research team has previously used this battery of questionnaires identifying that completion takes approximately 30-40 minutes.

### Upon Program Completion

We will ask participants (intervention arm only) to complete a program evaluation (through telephone or email, depending on preference). The program evaluation will assess the acceptability through a series of questions (eg, about the helpfulness of the program, how likable program was; 5-point Likert scale; generally, 1=very unacceptable; 5=very acceptable). The evaluation will assess satisfaction by asking participants the extent to which they agree with a series of questions about the program content, delivery, and outcomes (5-point Likert scale; 1=disagree; 5=agree) [45]. Finally, the evaluation will assess the usability by asking participants the extent to which they agree with a series of questions about the usability of various program features (5-point Likert scale; 1=strongly disagree; 5=strongly agree) [46]. We will invite participants to complete a semistructured qualitative interview to further explore their experience with the peer support program (eg, which features were most beneficial, what aspects were most challenging, what can be improved, what should be kept the same) and their perspectives on the support received from peers (eg, quality of support, influence on their caregiving experience). We will host 1-2 focus groups with the peer mentors using GoToMeeting. Using a semistructured interview guide, we will explore their experiences and perspectives of the Web-based program as trained peer mentors. Furthermore, we will audiorecord interviews and focus groups and transcribe verbatim.

## Statistical Methods

We will report descriptive statistics for demographic or health data, feasibility, and exploratory caregiver outcomes. To compare caregiver-reported outcomes between intervention and control groups, we will use the analysis of covariance with pretest scores as the covariate and group allocation, time, and the interaction between time and group allocation as independent variables. For nonnormally distributed scores, we will use a nonparametric alternative. All quantitative data will be analyzed in Statistical Analysis Software V9.4 (SAS Institute) using an intent-to-treat approach.

We will use the thematic content analysis to analyze interview and focus group transcripts following the framework outlined by Braun and Clark, which entails a line-by-line coding of transcripts, constant comparison, and generation of recurring themes [47]. We will use NVivo 11 software to facilitate the coding process. In collaboration with MBW, LR will analyze 20% of data to reduce bias and enhance the credibility and reliability of the qualitative findings [48].

**Table 1.** Exploratory caregiver-reported outcomes.

| Measure name | Items | Score range | Description | Test-retest reliability (r) | Internal consistency (alpha) |
|---|---|---|---|---|---|
| Caregiving Impact Scale [32,33] | 14 | 0-84 | Higher scores suggest providing care interferes with caregivers' abilities to maintain participation in valued activities | N/A[a] | .88 [32] |
| Barthel Index [34] | 10 | 0-20 | Higher scores indicate more functional independence | 0.89 [35] | .87-.92 [36] |
| Pearlin Mastery Scale [37] | 7 | 7-28 | Higher scores indicate a greater sense of control over life | 0.81 [37] | .75 [38] |
| Brief Coping Orientation to Problems Experienced (COPE) [39] | 28 | 6-24 (problem-based coping); 22-88 (emotion-based coping) | Higher scores on either subscale represent greater use of that coping style | 0.58-0.72 [40] | .57-.90 [39] |
| Personal Gain Scale [41] | 4 | 4-16 | Higher scores indicate caregivers' discovery of inner strengths because of providing care | N/A | .9 [42] |
| Positive and Negative Affect Schedule [43] | 10 | 10-50 | Higher scores indicate more psychological well-being | 0.47-0.68 [43] | .95 [42] |
| Centre for epidemiological studies short depression scale [24] | 10 | 0-30 | Higher scores sores indicate greater depression | 0.41-0.70 [44] | .89 [42] |

[a]N/A: not applicable.

## Results

We recruited 5 caregivers to be trained as mentors. The mentor training was completed in July 2018. We have recruited 4 caregivers to participate in the Web-based peer support program. We anticipate initiating the support program September 2018. Results are expected by early 2019.

Two caregivers have beta-tested the peer support website and issues identified have been addressed. Below are screenshots of the initial log-in page (Figure 1), home page (Figure 2), profile set-up page (Figure 3), and private chat function (Figure 4).

**Figure 1.** Screenshot of the initial log-in page.

**Figure 2.** Screenshot of the home page.
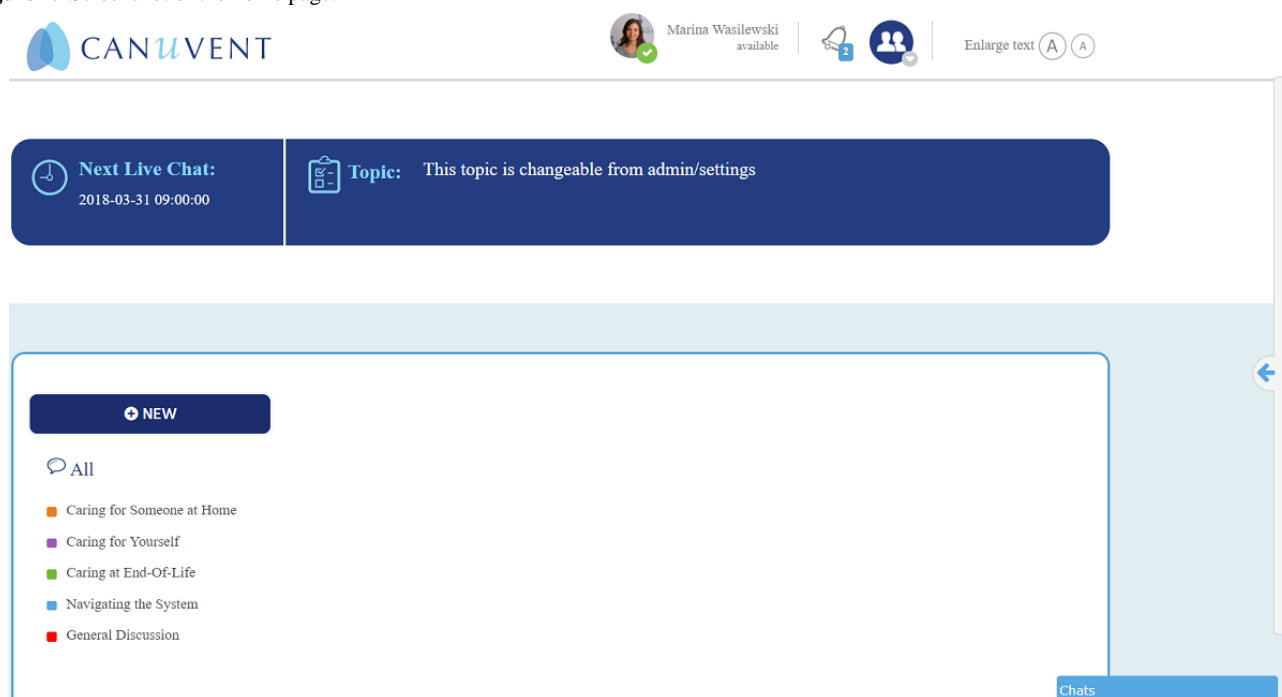
**Figure 3.** Screenshot of the profile set-up page.
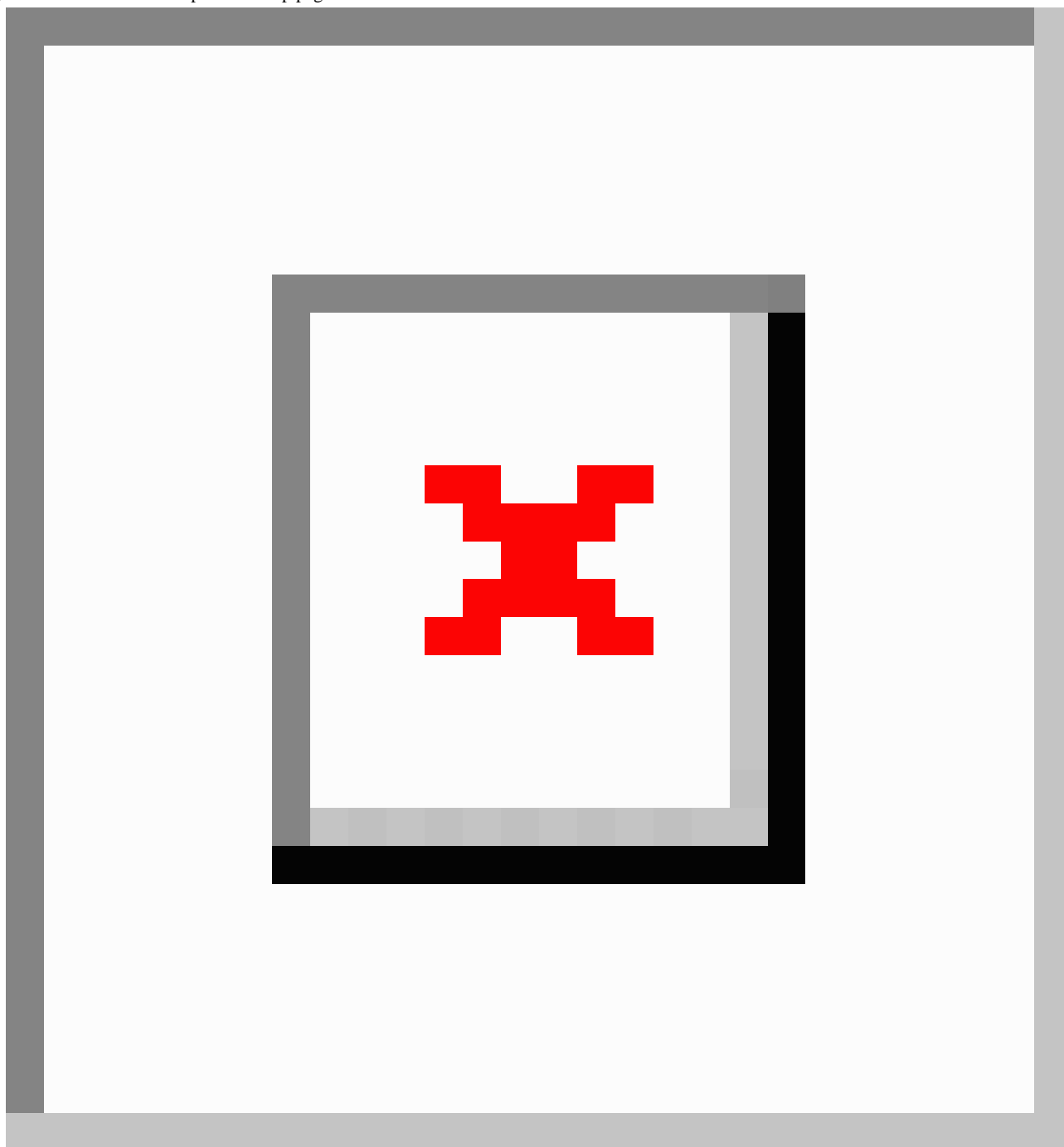
**Figure 4.** Screenshot of the private chat function.
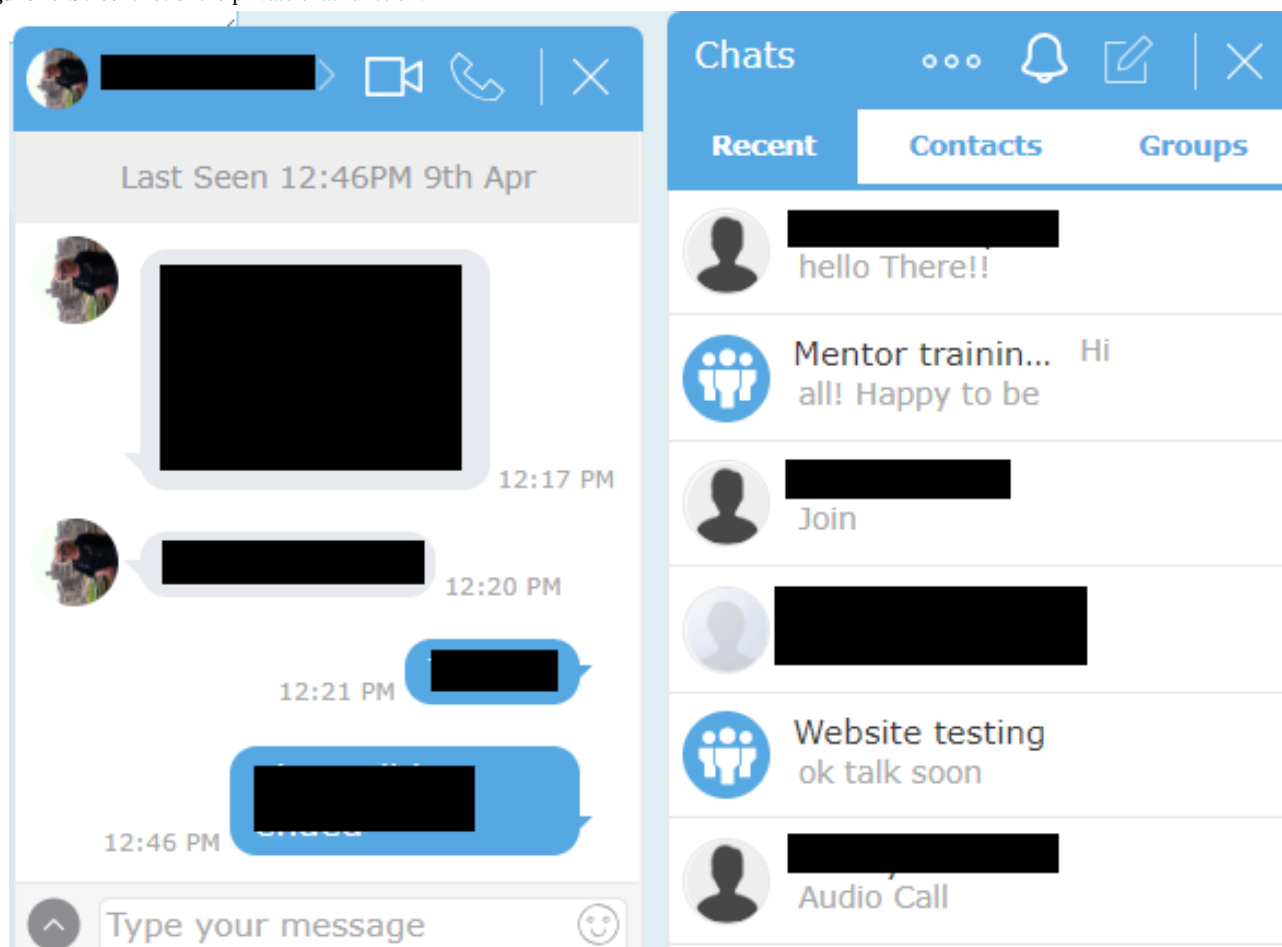


## Discussion

This study will result in the production and initial evaluation of a rigorously developed, evidence- and stakeholder-informed peer training and peer support program for caregivers of VAIs residing at home. Burdened and stressed caregivers may experience significant negative physical and emotional consequences to their own health, which may then impact their ability to care for VAIs who themselves are exceptionally vulnerable. Despite a growing body of evidence supporting the effectiveness of peer support interventions [20], there are currently no support programs of this nature tailored to caregivers of VAIs. The evaluation of the peer support program will highlight whether the inclusion of multiple communication tools is feasible, usable, and effective. The evidence generated will inform future iterations of the program so that it includes only the most valuable tools and optimizes them to enable support exchange.

The Web-based peer support program aims to empower community-residing VAIs and their caregivers to manage diseases necessitating mechanical ventilation. We anticipate that if caregivers have better health and quality of life, they will be better able to care for their loved ones who use ventilators.

This can help VAIs remain in their homes and, thereby, mitigate the declines in health and quality of life associated with residential care placement [7].

Perceived strengths of this study include the intervention's social networking-style interface that is likely to be familiar to participants, thereby enhancing the potential for greater usage and better usability of the peer support program. In addition, we anticipate that having multiple features on the website (eg, private chat, discussion forum, and live weekly chat) will increase the likelihood that participants will engage with and benefit from this peer support hub. Finally, the mixed-method nature of this research will not only provide insight into usage patterns and changes in health outcome scores but will also allow for an in-depth exploration of participants' experiences with the websites and perceptions of how it has influenced their health and caregiving experience. As this is a feasibility study, it is not our objective to test significance. However, we are aware that this limits our ability to comment on the findings' relevance and have identified it as a goal for future evaluations of the peer support program. While the inclusion of multiple Web-based features has the potential to increase engagement, there is still a possibility that the study will be limited by attrition.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Peer review report (for grant funding from Muscular Dystrophy Canada).

[PDF File (Adobe PDF File), 207KB - resprot_v8i2e11827_app1.pdf ]

## References

1. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J 2005 Jun;25(6):1025-1031 [FREE Full text] [doi: 10.1183/09031936.05.00066704] [Medline: 15929957]

2. Garner DJ, Berlowitz DJ, Douglas J, Harkness N, Howard M, McArdle N, et al. Home mechanical ventilation in Australia and New Zealand. Eur Respir J 2013 Jan;41(1):39-45 [FREE Full text] [doi: 10.1183/09031936.00206311] [Medline: 22653765]

3. Rose L, McKim D, Katz S, Leasa D, Nonoyama M, Pedersen C, CANuVENT Group. Home mechanical ventilation in Canada: a national survey. Respir Care 2015 May;60(5):695-704 [FREE Full text] [doi: 10.4187/respcare.03609] [Medline: 25587173]

4. King AC. Long-term home mechanical ventilation in the United States. Respir Care 2012 Jun;57(6):921-30; discussion 930 [FREE Full text] [doi: 10.4187/respcare.01741] [Medline: 22663967]

5. Evans R, Catapano MA, Brooks D, Goldstein RS, Avendano M. Family caregiver perspectives on caring for ventilator-assisted individuals at home. Can Respir J 2012;19(6):373-379 [FREE Full text] [doi: 10.1155/2012/452898] [Medline: 23248801]

6. Dale CM, King J, Nonoyama M, Carbone S, McKim D, Road J, CANuVENT group. Transitions to Home Mechanical Ventilation: The Experiences of Canadian Ventilator-Assisted Adults and Their Family Caregivers. Ann Am Thorac Soc 2017 Dec 28. [doi: 10.1513/AnnalsATS.201708-663OC] [Medline: 29283698]

7. Hill NS. Ventilator management for neuromuscular disease. Semin Respir Crit Care Med 2002 Jun;23(3):293-305. [doi: 10.1055/s-2002-33038] [Medline: 16088622]

8. Kajiyama B, Thompson LW, Eto-Iwase T, Yamashita M, Di Mario J, Marian Tzuang Y, et al. Exploring the effectiveness of an internet-based program for reducing caregiver distress using the iCare Stress Management e-Training Program. Aging Ment Health 2013;17(5):544-554 [FREE Full text] [doi: 10.1080/13607863.2013.775641] [Medline: 23461355]

9. Roth DL, Perkins M, Wadley VG, Temple EM, Haley WE. Family caregiving and emotional strain: associations with quality of life in a large national sample of middle-aged and older adults. Qual Life Res 2009 Aug;18(6):679-688 [FREE Full text] [doi: 10.1007/s11136-009-9482-2] [Medline: 19421895]

10. House J. Work stress and social support. In: Work stress and social support. Reading, Massachusetts: Addison-Wesley Pub Co; 1981.

11. Toseland RW, Rossiter CM. Group interventions to support family caregivers: a review and analysis. Gerontologist 1989 Aug;29(4):438-448. [Medline: 2521101]

12. Hibbard MR, Cantor J, Charatz H, Rosenthal R, Ashman T, Gundersen N, et al. Peer support in the community: initial findings of a mentoring program for individuals with traumatic brain injury and their families. J Head Trauma Rehabil 2002 Apr;17(2):112-131. [Medline: 11909510]

13. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychol Bull 1985 Sep;98(2):310-357. [Medline: 3901065]

14. Pinquart M, Sörensen S. Correlates of physical health of informal caregivers: a meta-analysis. J Gerontol B Psychol Sci Soc Sci 2007 Mar;62(2):P126-P137. [Medline: 17379673]

15. Kenneson A, Bobo JK. The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. Health Soc Care Community 2010 Sep;18(5):520-528. [doi: 10.1111/j.1365-2524.2010.00930.x] [Medline: 20561071]

16. Schippke J, Provvidenza C, Townley A, Kingsnorth S. Holland Bloorview Kids Rehabilitation Hospital. Toronto, Ontario: Evidence to Care; 2015. Peer support best practice toolkit: Section 1.0 Background and models of peer support URL: https://hollandbloorview.ca/Assets/Evidence%20to%20Care/Peer%20support%20toolkit/EtC_PeerSupport_Section1_FA.pdf [accessed 2018-12-13] [WebCite Cache ID 74daTTuTs]

17. O'Connor M, Arizmendi BJ, Kaszniak AW. Virtually supportive: a feasibility pilot study of an online support group for dementia caregivers in a 3D virtual environment. J Aging Stud 2014 Aug;30:87-93 [FREE Full text] [doi: 10.1016/j.jaging.2014.03.001] [Medline: 24984911]

18. Mikkelsen ME, Jackson JC, Hopkins RO, Thompson C, Andrews A, Netzer G, et al. Peer Support as a Novel Strategy to Mitigate Post-Intensive Care Syndrome. AACN Adv Crit Care 2016;27(2):221-229. [doi: 10.4037/aacnacc2016667] [Medline: 27153311]

19. Lewis ML, Hobday JV, Hepburn KW. Internet-based program for dementia caregivers. Am J Alzheimers Dis Other Demen 2010 Dec;25(8):674-679. [doi: 10.1177/1533317510385812] [Medline: 21131674]

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20. Wasilewski MB, Stinson JN, Cameron JI. Web-based health interventions for family caregivers of elderly individuals: A Scoping Review. Int J Med Inform 2017 Jul;103:109-138. [doi: 10.1016/j.ijmedinf.2017.04.009] [Medline: 28550996]

21. Acton GJ, Kang J. Interventions to reduce the burden of caregiving for an adult with dementia: a meta-analysis. Res Nurs Health 2001 Oct;24(5):349-360. [Medline: 11746065]

22. Sörensen S, Pinquart M, Duberstein P. How effective are interventions with caregivers? An updated meta-analysis. Gerontologist 2002 Jun;42(3):356-372. [Medline: 12040138]

23. St. John's Children's Hospital. Mentor Day Training Video URL: https://www.stjude.org/treatment/patient-resources/patient-family-centered-care/mentor-day-training-video.html?vgnextoid=a965d6f6d3487310VgnVCM100000290115acRCRD&vgnextchannel

24. Radloff L. The CES-D Scale. Applied Psychological Measurement 2016 Jul 26;1(3):385-401. [doi: 10.1177/014662167700100306]

25. Student Life. Mentoring Skills Inventory URL: https://www.studentlife.utoronto.ca/system/files_force/Mentoring-Skills-Inventory.pdf?download= [accessed 2018-09-28] [WebCite Cache ID 72mDBFzOd]

26. Zachary L. The Mentor's Guide: Facilitating Effective Learning Relationships. San Francisco, California: Wiley, John & Sons, Incorporated; 2011.

27. Spinal Cord Injury Ontario. Peer Support. 2017. URL: https://sciontario.org/support-services/connect/peer-support/ [WebCite Cache ID 72mDFDZ6u]

28. Als LC, Nadel S, Cooper M, Vickers B, Garralda ME. A supported psychoeducational intervention to improve family mental health following discharge from paediatric intensive care: feasibility and pilot randomised controlled trial. BMJ Open 2015 Dec 29;5(12):e009581 [FREE Full text] [doi: 10.1136/bmjopen-2015-009581] [Medline: 26715482]

29. Kauer S, Buhagiar K, Blake V, Cotton S, Sanci L. Facilitating mental health help-seeking by young adults with a dedicated online program: a feasibility study of Link. BMJ Open 2017 Jul 09;7(7):e015303 [FREE Full text] [doi: 10.1136/bmjopen-2016-015303] [Medline: 28694345]

30. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008 Apr;31(2):180-191. [doi: 10.1002/nur.20247] [Medline: 18183564]

31. Cunningham JA, Kypri K, McCambridge J. Exploratory randomized controlled trial evaluating the impact of a waiting list control design. BMC Med Res Methodol 2013 Dec 06;13:150 [FREE Full text] [doi: 10.1186/1471-2288-13-150] [Medline: 24314204]

32. Cameron JI, Franche R, Cheung AM, Stewart DE. Lifestyle interference and emotional distress in family caregivers of advanced cancer patients. Cancer 2002 Jan 15;94(2):521-527 [FREE Full text] [doi: 10.1002/cncr.10212] [Medline: 11900237]

33. Cameron JI, Cheung AM, Streiner DL, Coyte PC, Stewart DE. Stroke survivors' behavioral and psychologic symptoms are associated with informal caregivers' experiences of depression. Arch Phys Med Rehabil 2006 Feb;87(2):177-183. [doi: 10.1016/j.apmr.2005.10.012] [Medline: 16442969]

34. Morley D, Selai C, Thompson A. The self-report Barthel Index: preliminary validation in people with Parkinson's disease. Eur J Neurol 2012 Jun;19(6):927-929. [doi: 10.1111/j.1468-1331.2011.03592.x] [Medline: 22117585]

35. Granger CV, Dewis LS, Peters NC, Sherwood CC, Barrett JE. Stroke rehabilitation: analysis of repeated Barthel index measures. Arch Phys Med Rehabil 1979 Jan;60(1):14-17. [Medline: 420565]

36. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol 1989;42(8):703-709. [Medline: 2760661]

37. Pearlin LI, Schooler C. The structure of coping. J Health Soc Behav 1978 Mar;19(1):2-21. [Medline: 649936]

38. Aneshensel C, Zarit S, Pearlin L, Whitlatch C, Mullan J. Profiles in Caregiving: The Unexpected Career. San Diego, California: Elsevier Science; 1995.

39. 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]

40. Cooper C, Katona C, Livingston G. Validity and reliability of the brief COPE in carers of people with dementia: the LASER-AD Study. J Nerv Ment Dis 2008 Nov;196(11):838-843. [doi: 10.1097/NMD.0b013e31818b504c] [Medline: 19008735]

41. Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. Gerontologist 1990 Oct;30(5):583-594. [Medline: 2276631]

42. Cameron JI, Herridge MS, Tansey CM, McAndrews MP, Cheung AM. Well-being in informal caregivers of survivors of acute respiratory distress syndrome. Crit Care Med 2006 Jan;34(1):81-86. [Medline: 16374160]

43. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988 Jun;54(6):1063-1070. [Medline: 3397865]

44. González P, Nuñez A, Merz E, Brintz C, Weitzman O, Navas EL, et al. Measurement properties of the Center for Epidemiologic Studies Depression Scale (CES-D 10): Findings from HCHS/SOL. Psychol Assess 2017 Dec;29(4):372-381 [FREE Full text] [doi: 10.1037/pas0000330] [Medline: 27295022]

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45.   Campbell J, Cook JA, Jonikas JA, Einspahr K. Peer Outcomes Protocol Project. Chicago: University of Illinois at Chicago; 2004. Peer Outcomes Protocol (POP): Questionnaire URL: http://www.cmhsrp.uic.edu/download/POP.Questionnaire.pdf [accessed 2018-12-13] [WebCite Cache ID 74dbOo2LD]

46.   Morgan J. ScholarWorks@UMass Amherst.: University of Massachusetts Amherst; 2013. An Evaluation of Methods to Assess Whether Health Information Technology-Based Tools Improve Weight Loss Measures in Bariatric Surgery Patients URL: https://scholarworks.umass.edu/theses/1142/ [accessed 2018-12-13] [WebCite Cache ID 74dbdBsMm]

47.   Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]

48.   Judith G, Nicki T. Qualitative Methods for Health Research. In: Qualitative Methods For Health Research. London, England: Sage Publications Ltd; 2018.

## Abbreviations

**HMV:** home mechanical ventilation
**RCT:** randomized controlled trial
**VAI:** ventilator-assisted individual

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Protocol

# Examining the Effects of Mindful Eating Training on Adherence to a Carbohydrate-Restricted Diet in Patients With Type 2 Diabetes (the DELISH Study): Protocol for a Randomized Controlled Trial

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2020/1/e17226/

## Abstract

**Background:** Diet patterns have a profound influence on glycemic control for individuals with type 2 diabetes mellitus (T2DM), and craving-related eating is an important obstacle to dietary adherence. A growing body of research suggests that carbohydrate-restricted (CR) diets can improve glycemic control and reduce medication dependence in T2DM. However, limited data speak to the effects of long-term adherence to CR diets. Mindful eating training has been shown to reduce craving-related eating in overweight populations but has yet to be examined as a behavioral support for dietary adherence in T2DM. This trial examines behavioral mechanisms, particularly craving-related eating, through which mindful eating training might improve adherence to CR dietary recommendations in T2DM. This will clarify the importance of focusing on craving-related eating in the optimization of dietary adherence interventions.

**Objective:** The aim of this trial is to determine whether providing training in mindful eating increases adherence to a CR dietary recommendation in T2DM.

**Methods:** We are randomizing 60 participants to receive a CR diet with or without mindful eating training (12-week group intervention) and are following participants for 12 weeks after intervention completion. We hypothesize that participants who receive mindful eating training (relative to those who do not) will demonstrate greater adherence to the CR diet.

**Results:** Our primary outcome is change in craving-related eating, as assessed using an ecological momentary assessment mobile phone–based platform. Secondary behavioral pathway outcomes include changes in stress-related eating, impulsivity, glycemic control, weight change, dietary adherence, and resumption of dietary adherence after dietary nonadherence.

**Conclusions:** This theory-driven trial will shed light on the impact of mindfulness training on mechanisms that may impact dietary adherence in T2DM.

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## Introduction

### Background

Type 2 diabetes mellitus (T2DM) is the costliest chronic disease in the United States, afflicting 30.3 million people in the United States (9.4% of the population) and nearly 382 million people worldwide [1-4]. Lowering glycosylated hemoglobin ($HbA_{1c}$), a central measure of glycemic control in T2DM, reduces the risk of complications such as nephropathy and retinopathy [5]. Although lifestyle modification, particularly in the spheres of nutrition and exercise, is a key component of improving glycemic control in T2DM, achieving long-term adherence to lifestyle changes remains a challenge [6].

The American Diabetes Association currently includes carbohydrate-restricted (CR) diets as one of several appropriate diet patterns for people with T2DM [7]. Several trials, reviews, and meta-analyses suggest that lowering carbohydrate intake can improve glucose control, insulin resistance, and body weight [8-14]. In this trial, we will administer a CR diet that restricts carbohydrates to approximately 10% of caloric intake (about 50 g/day) so as to induce *nutritional ketosis*, a low level of ketone production that serves as a biomarker for assessing dietary adherence to carbohydrate restriction.

Food cravings, defined as intense urges or desires to eat specific types of foods [15], as well as emotional and mindless eating, pose challenges to adherence to diet recommendations, especially for people with T2DM [16,17]. Seeing desirable food can induce food cravings [18-20]; hence, it is unsurprising that food cravings are the most commonly cited reason for dietary nonadherence and that reductions in food cravings are associated with long-term weight loss [21-23]. The modern food environment is replete with food cues and opportunities to eat, which can amplify the impact of food cravings on dietary adherence. Effectively treating T2DM and prediabetes, which together affect more than one-third of Americans, requires long-term dietary adherence [24,25].

Mindful eating practices may increase dietary adherence by reducing craving-related eating [26-28], which poses challenges to individuals with T2DM [16,29-31]. Training in mindfulness, which can be defined as "paying attention on purpose, in the present moment, and nonjudgmentally, to the unfolding of experience moment to moment [32]" may equip individuals with skills to recognize and observe their experiences of food cravings without acting on them (ie, eating in response to them). Mindfulness training focuses on reducing self-judgment (*nonjudgment*), which may increase resilience (resumption of dietary adherence) after temporary lapses in dietary adherence [33]. In this trial, we randomize half of participants to receive training in mindful eating to ascertain whether and how such training may impact behavioral pathways that shape dietary adherence in T2DM.

### Objectives

The primary behavioral change we are testing is whether training in mindful eating can reduce craving-related eating as assessed using ecological momentary assessment (EMA). This trial examines behavioral pathways that we hypothesize to be tied to clinical outcomes; it does not center on clinical outcomes themselves such as improvements in glycemic control. We also test whether mindful eating training may contribute to other adaptive behavioral changes, including (1) decreased impulsivity, (2) decreased stress- and emotion-related eating, and (3) improved resilience after dietary nonadherence occurs (resumption of dietary adherence). We will also test whether mindful eating training may improve glycemic control ($HbA_{1c}$, fasting glucose, and insulin resistance) and contribute to weight loss. We also aim to directly assess whether training in mindful eating improves dietary adherence as assessed in blood ketones and 24-hour dietary recall.

## Methods

### Overview

The central goal of this trial is to test whether there is evidence that supports proposed mechanisms through which our behavioral intervention (a particular type of mindful eating training) impacts eating in response to cravings and/or influences one or more of the additional mechanistic pathways we have hypothesized. We designed this trial in response to a National Institute of Health (NIH) grant announcement designed to investigate mechanisms of action that may lead to change in clinical outcomes. This is a randomized controlled, two-group trial that tests group-based 12-week in-person interventions and follows participants for a 12-week postintervention period (24 weeks of trial participation total). We randomly assign participants to 1 of 2 intervention groups; both groups receive training in how to follow a CR diet, but 1 group also receives mindful eating training. We are recruiting 3 waves of approximately 20 participants each (N=60 total). Participants complete 12 weekly in-person sessions followed by 3 monthly in-person maintenance sessions, for a total of 15 sessions over 6 months. Participants complete self-report questionnaires (online and Qualtrics), provide blood specimen assessments (LabCorp [34] location of choice), and respond to mobile phone–based assessments about their current food cravings and emotions using EMA [35] methods, along with other assessments (see Table 1 for the schedule of evaluations). The University of California, San Francisco (UCSF) institutional review board (IRB16-20025) approved of all trial procedures,

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and all participants provide written informed consent before enrollment.

## Recruitment and Eligibility

We recruit participants from several sources, including within UCSF clinics (eg, diabetes clinic, general internal medicine clinic). We work with the UCSF Clinical and Translational Science Institute to send physical letters to potentially eligible participants in the UCSF system who had previously consented to be contacted about research studies for which they may be eligible. We also recruit participants via flyers posted in the community as well as use social media strategies, such as Facebook, Nextdoor, and Craigslist (see Textbox 1 for trial inclusion and exclusion criteria.

## Enrollment Procedures

Potential participants make initial contact with the study by visiting the study website or telephoning a dedicated study phone number. They review the study website and the full-study consent before electronically signing an online consent to be screened for study eligibility. They then complete an eligibility Web-based screener (Qualtrics). If potentially eligible per the Web-based screener, study staff conduct a phone screening to further assess eligibility. In this call, study staff confirm basic

eligibility criteria and review study schedules, procedures, and assessments. If, after this call, potential participants remain eligible and interested, they then complete a short message service (SMS) text message–based assessment (EMA) that involves responding to SMS text messages from their smartphones 3 times per day, on 3 days distributed across a week. Potential participants must respond to at least 7 of 9 messages and must report eating in response to a craving at least 2 times. If potential participants meet these criteria, they then complete an in-person screening and consent visit. This visit includes collecting or administering (1) health history and medication information, (2) information on excluded substance misuses, mental and medical conditions, and medication contraindications, (3) weight and height assessments, (4) computerized cognitive assessments, and (5) a fasting blood draw to assess parameters required for inclusion: $HbA_{1c}$ between 6.5% and 12.0%, thyroid-stimulating hormone in a normal range, and liver and kidney function in a normal range. We conduct enrollment procedures in the 8 weeks before a wave starts. If the EMA or the $HbA_{1c}$ components of enrollment procedures take place more than 4 weeks before the wave start date, we repeat these measures in the week before the wave start date. Participants remain eligible regardless of data collected during repeat measures.

**Table 1.** Schedule of evaluations and intervention phases.

| Time (activity or assessment) | Pre-enrollment (screening and consent visit) | Baseline (preintervention assessment and randomization to intervention arm) | Weeks 0-12 (intervention period) | Week 12 (postintervention assessment) | Weeks 12-24 (maintenance period) | Week 24 (post-maintenance assessment) |
|---|---|---|---|---|---|---|
| Informed consent | ✓ | — | — | — | — | — |
| Health history | ✓ | — | — | — | — | — |
| Demographics and background information | ✓ | — | — | — | — | — |
| Inclusion or exclusion criteria assessment | ✓ | — | — | — | — | — |
| Craving EMA[a] | ✓ | — | ✓ | ✓ | ✓ | ✓ |
| Laboratory-based chemistry testing | ✓ | ✓ | — | ✓ | — | ✓ |
| Online self-report measures | — | ✓ | — | ✓ | — | ✓ |
| 24-hour dietary recall | — | ✓ | — | ✓ | — | ✓ |
| Computerized cognitive assessment | ✓ | — | — | ✓ | — | ✓ |
| Anthropometrics[b] | ✓ | — | — | ✓ | — | ✓ |
| Weekly diet and/or mindful eating classes | — | — | ✓ | — | — | — |
| Monthly diet and/or mindful eating follow-up classes | — | — | — | — | ✓ | — |
| Ketone testing for dietary adherence[c] | — | — | ✓ | ✓ | ✓ | ✓ |
| Home glucose testing for safety[d] | — | — | ✓ | — | ✓ | — |

[a]EMA: ecological momentary assessment, administered over 1 week at each pre-enrollment, baseline, and weeks 7, 13, 19, and 24.

[b]Height at baseline only.

[c]Ketone testing 3 times per week during intervention period and 2 times per week during maintenance period.

[d]Only for individuals using insulin and sulfonylurea medications.

**Textbox 1.** Inclusion and exclusion criteria.

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**Inclusion criteria**

- History of type 2 diabetes

- 6.5%≤glycosylated hemoglobin or $HbA_{1c}<12.0\%$

- Age ≥18 years

- Experience food-related cravings most days of the week and/or eat in response to food cravings more than they wish they did

- On screening ecological momentary assessment (EMA), report eating in response to cravings at least twice over the course of 3 days

- Able to engage in light physical activity

- Have a smartphone and respond to at least 7 of 9 short message service text messages delivered over the course of 3 days during pre-enrollment

- English speaking

- Willing to participate in diet and mindfulness interventions

**Exclusion criteria**

- Unable to provide informed consent

- Substance abuse, mental health, or medical condition that will make it difficult to participate in the intervention or may alter key outcomes or require important diet modifications

- Pregnant or planning to get pregnant in the next 6 months, breastfeeding, or <6 months postpartum

- Current use of weight loss medications or supplements

- History of weight loss (bariatric) surgery in the past 18 months or current plans for bariatric surgery

- Currently enrolled in a weight loss program or have unalterable plans to enroll in one of these programs in the next year

- Vegan or vegetarian

- Unwilling to do home blood ketone monitoring

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## Randomization

We randomize participants in a 1:1 fashion to either group using random permuted blocks with varying sizes and stratifying by body mass index (BMI; above and below BMI of 25) after completion of all screening and baseline assessment steps to enrollment and before initiation of intervention. We randomize participants to intervention group approximately 1 week before the start of classes to minimize postrandomization attrition because of life circumstances that may impact class attendance (eg, job loss or family issue).

## Masking

We do not mask participants to intervention group. Some of our assessments, specifically those done at LabCorp (blood draws; [34]) and those done via Web-based self-report surveys, are masked to intervention group. LabCorp [34] locations have no knowledge of the research design or intervention group. In this trial, 24-hour dietary recall interviews are conducted by research assistants blinded to intervention group. We do not mask other study coordinators to intervention group as the funding and study team is not large enough to support separate assessment and intervention teams. No intervention group information is included on the data collection forms used at follow-up visits (eg, weight measurement), but some staff who are highly involved in administrative aspects of the study classes may be aware of intervention group. Study physicians are not strictly blinded to intervention group, but effort is made to limit

communication of this information to them. For example, they are not provided intervention group information when they make medication reductions or adjustments either at baseline or during the intervention phase. Participants may, however, in the course of their medication management discussions with study physicians, discuss their experience in the trial and could self-reveal their intervention group. A principal investigator might, in the course of responding to a participant with a study concern, learn of his or her intervention group (eg, if a participant has a concern about the mindful eating intervention that is not adequately addressed by the project director or other key study personnel).

## Trial Period

We have defined the trial period as a 3-level variable, including baseline (the period preceding the intervention), 3 months postbaseline (occurring immediately following the end of the intensive intervention period), and 6 months postbaseline (occurring 6 months after baseline and 3 months after the intensive intervention period ends).

## Data Collection

We collect data at several occasions over the course of the 24-week trial period. Table 1 displays a schedule of evaluations.

## Self-Report Measures

We administer self-report measures of mood, eating behavior, and other psychological factors (online, Qualtrics). Table 2 displays self-report measures.

**Table 2.** Self-report and computerized cognitive assessments.

| Type and measure name (acronym; number of items or minutes) | Construct assessed |
|---|---|
| **Online (Qualtrics) self-report measures** | |
| Perceived Stress Scale (PSS; 10 items) [41] | Global perceptions of stress |
| Patient Health Questionnaire (PHQ-8; 8 items) [42] | Depression symptoms |
| Reward-based Eating Drive (RED-9; 9 items) [43] | Reward-based drive to eat (loss of control over eating, lack of satiety, and preoccupation with food) |
| Food Craving Questionnaire-Trait-Reduced (FCQ-T-R; 15 items) [44] | Emotional food craving, preoccupation with food, loss of control over eating, and positive outcome expectancy |
| Midlife in the United States (MIDUS) Stress Eating Items (MIDUS; 2 items) [45] | How one's eating changes in response to a stressful event: eating to feel better and eating more than usual |
| Palatable Eating Motives Scale (PEMS; 19 items) [46] | Social, conformity, enhancement, and coping-based motives for eating tasty food |
| Stress Eating (1 item) [47] | Eating when under moderate stress |
| Weight Efficacy Lifestyle Questionnaire – Short Form (WEL-SF; 8 items) [48] | Ability to adhere to a diet when in challenging situations (eg, socializing and peer pressure) |
| Loss of Control over Eating – Brief (LOCES-Brief; 7 items) [49] | Loss of control over eating |
| Food Acceptance and Action Questionnaire (FAAQ; 10 items) [50] | Acceptance of one's motivations to eat |
| Modified Differential Emotions Scale (MDES; 20 items) [51] | Positive and negative emotions |
| Dutch Eating Behavior Questionnaire, Restrained Eating Subscale (DEBQ-R; 10 items) [52] | Restrained eating behavior |
| Five Factor Mindfulness Questionnaire (FFMQ; 24 items) [53] | Tendencies to be mindful in daily life |
| Promis-29 (29 items) [54] | Multidimensional quality of life measure |
| Self-Compassion Scale Short Form (SCS-SF13; 12 items) [55] | Self-kindness, self-judgment, common humanity, isolation, mindfulness, over-identification |
| Body Responsiveness Questionnaire (BRQ; 7 items) [56] | Responsiveness to bodily sensations |
| **Computerized cognitive measures** | |
| Delayed discounting (DD; 5 trials, 1 min) [57] | Valuation of proximal versus delayed monetary rewards |
| Go/No-Go (GNG; 12 min) [58] | Sustained attention and response inhibition |
| Food Stroop (5 min) [59] | Food preoccupation |
| Relative reinforcing efficacy of food (RRE; 4 min) [60] | Relative reinforcement value of tasty food |
| Dot probe (4 min) [61] | Selective attentional processing for food versus nonfood stimuli |

## Ecological Momentary Assessment

We assess hunger, stress, craving, craving-related eating, and emotions by sending SMS text messages to participants' personal smartphones at different points during the trial, as shown in Table 1. Each SMS text message includes a link that participants tap on in order to access the survey, which is administered on the Qualtrics platform. Participants receive SMS text messages 3 times over the course of the day, and these times have yielded high response rates in our prior work [26]. Before participants respond to these SMS text messages, they are presented with the following definition of food craving: "A food craving is a desire to eat a particular type of food or drink. You might go out of your way for it because only specific foods will satisfy the craving. This is different than hunger, because a variety of foods can satisfy hunger." Our primary outcome is participants' responses to the question regarding craving-related eating. During enrollment, we review the importance of responding to these SMS text message assessments with participants by explaining that it is difficult for us to understand their daily experiences without hearing firsthand from them, in the moment, what they are experiencing. Participants receive EMA at baseline and at weeks 7, 13, 19, and 24 (see Table 3 for EMA questions and administration schedule [35]).

## Laboratory (Clinical) Assessments

We collect several biomarkers of metabolic health and glycemic control (see Table 4 for blood-based biomarker testing conducted at LabCorp [34]).

## Computerized (Cognitive) Assessments

We administer computerized cognitive assessments (Inquisit) that index metrics, including reward-related behavior, behavioral response inhibition, food preoccupation, and attentional processing. Such factors have emerged as meaningful predictors of eating behavior and weight change over time [36-38] (see Table 2 for computerized cognitive assessments).

**Table 3.** Ecological momentary assessment (EMA) questions.

| Time | Questions[a] |
|------|-----------|
| 11:00 am | 1. How physically hungry are you right now? (sliding response: "not at all hungry" to "very hungry") |
| | 2. Since you woke up today, have you craved a particular type of food or drink? (2 choices: "Yes" or "No") |
| | 2a. How strong was that craving? (sliding response: "not strong" to "very strong") |
| | 2b. Did you eat or drink anything in response to that craving (2 choices: "yes" or "no") |
| | 2c. What food or drink did you eat? (open-ended response with a blank text box) |
| | 2d. Once you began eating in response to this craving, did you feel you could stop? (sliding response: "I could stop" to "I could NOT stop") |
| 4:30 pm | 1. How physically hungry are you right now? (sliding response: "not at all hungry" to "very hungry") |
| | 2. Since you last responded to one of our texts, have you craved a particular type of food or drink? (2 choices: "yes" or "no") |
| | 2a. How strong was that craving? (sliding response: "not strong" to "very strong") |
| | 2b. Did you eat or drink anything in response to that craving? (2 choices: "yes" or "no") |
| | 2c. What food or drink did you eat? (open-ended response with a blank text box) |
| | 2d. Once you began eating in response to this craving, did you feel you could stop? (sliding response: "I could stop" to "I could NOT stop") |
| 9:00 pm | 1-2d questions (identical to 4:30 pm) |
| | 3. Today, did you have any other cravings for food or drink that you haven't yet told us about in one of these texts? (2 choices: "yes" or "no") |
| | 3a. How strong was that craving? (sliding response: "not strong" to "very strong") |
| | 3b. Did you eat or drink anything in response to that craving? (2 choices: "yes" or "no") |
| | 3c. What food or drink did you eat? (open-ended response with a blank text box) |
| | 3d Once you began eating in response to this craving, did you feel you could stop? (sliding response: "I could stop" to "I could NOT stop") |
| | 4. Over the entire day, how much have you felt happy/pleased/cheerful? (sliding response: "not at all" to "all the time") |
| | 5. Over the entire day, how much have you felt unhappy/sad/frustrated? (sliding response: "not at all" to "all the time") |
| | 6. Over the course of the entire day, what's the most stressed you've felt? (sliding response: "not at all stressed" to "very stressed") |

[a]The prespecified outcome variable is craving-related eating, as assessed in item 2b (11:00 am, 4:30 pm, and 9:00 pm) and item 3b (11:00 pm only).

**Table 4.** Blood-based chemistry testing (LabCorp).

| Test[a] | Construct assessed and/or rationale | Consent visit: eligibility screening | Assessment: baseline | Assessments: 3 and 6 months |
|------|-----------|-----------|-----------|-----------|
| Glycosylated hemoglobin | Inclusionary test and study variable: level of overall glucose control | ✓ | ✓ | ✓ |
| C-peptide | Inclusionary test[b]: confirms type 2 diabetes among individuals using exogenous insulin | ✓ | — | — |
| Thyroid stimulating hormone | Exclusionary test: rules out an untreated thyroid disorder | ✓ | — | — |
| Comprehensive metabolic panel | Exclusionary test: rules out liver and/or kidney dysfunction; study variable: liver enzymes | ✓ | ✓ | ✓ |
| Glucose, plasma | Study variable: allows for calculation of insulin resistance and fasting glucose | — | ✓ | ✓ |
| Insulin, plasma | Study variable: allows for calculation of insulin resistance and fasting glucose | — | ✓ | ✓ |
| High-sensitivity C-reactive protein | Study variable: biomarker of inflammation | — | ✓ | ✓ |
| NMR LipoProfile | Study variables: triglycerides and detailed cholesterol measures | — | ✓ | ✓ |

[a]All samples are collected from individuals in a fasting state.

[b]We assess C-peptide only among potential participants reporting insulin use or a history of diabetic ketoacidosis.

## Dietary Adherence

We measure adherence to carbohydrate restriction in 2 ways: (1) presence of blood ketones, which provide a biological measure of substantial restriction of carbohydrate intake and (2) 24-hour dietary recall.

### Ketones

In week 4, we provide participants with a home-based blood ketone-monitoring device (Precision Xtra System; Abbott Diabetes Care, Alameda, California) and ketone strips, which participants use with the device to measure β-hydroxybutyrate (BOHB) in the blood. This method was recently used in a CR diet intervention for individuals with T2DM [39]. We teach participants how to use the meter in person and ask them to measure their blood ketones before dinner, 2 to 3 times a week, on alternating days. Participants are asked to report ketone results via online survey on a weekly basis. The meters store data, which staff check at every weekly class (starting in week 5) and every monthly class (starting in week 16) to confirm self-reported measurements. Values collected by meters will be used for analysis; however, if their equipment malfunctions (eg, breakage or loss), we will use available self-reported values. For this trial, we define nutritional ketosis as a BOHB level between 0.3 and 3.0 mmol/L. Although the level of carbohydrate restriction needed to achieve ≥0.3 BOHB varies between individuals, in our experience, most individuals need to restrict carbohydrate intake to below 50 g per day of nonfiber carbohydrate to achieve nutritional ketosis.

### 24-Hour Dietary Recall

Despite limitations of self-report measures in assessing dietary intake, they remain an important tool to assess dietary adherence. The 24-hour dietary recall provides a measure that complements the ketone measure by providing overall diet composition information that cannot be obtained from ketone measures. We use the University of Minnesota's Nutrition Data System for Research (NDSR) software to perform 24-hour dietary recalls via telephone. This is a widely used dietary analysis program that enables the collection of multiple 24-hour dietary recalls and encompasses multiple foods appropriate for diets of T2DM patients. Although the NIH recommends a single 24-hour assessment at each repeated time point, we collected 2 assessments at each time point (1 on a weekday and 1 on a weekend day) [40]. Recalls are entered into the NDSR software immediately after completion. Dietary recalls are conducted without prior notification to avoid changes in diet on the reporting day.

## Resilience Following Dietary Nonadherence

Our measure will be the time from a ketone measure of <0.3 BOHB mmol/L to higher levels of ≥0.3 BOHB mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

## Interventions

### Carbohydrate-Restricted (CR) Diet Classes

We teach participants an *ad libitum* CR eating plan, similar to that in our previously published work, which was developed with clinicians, dieticians, and researchers with expertise in this area [8,62]. For this trial's CR diet, we instruct participants to reduce their carbohydrate intake to between 20 and 35 nonfiber grams of carbohydrates per day (with the goal of remaining under 50 nonfiber grams per day), to eat an adequate amount of protein (as described by the Institute of Medicine [63]), and to eat fat to achieve satiety. This recommendation fits macronutrient profiles that have been demonstrated effective in improving glycemic control among individuals with T2DM in meta-analyses of RCTs [13,64,65]. We advocate a gradual transition toward this CR diet by instructing participants to change different types of meals each week: They change their breakfasts and snacks in the first week, their lunches in the second week, and their dinners in the third week. After approximately 4 weeks, participants are fully implementing CR dietary recommendations. The specific content of participants' diets varies but generally includes green leafy and other nonstarchy vegetables, nuts, seeds, fats (except trans fats), fish, poultry, meats, eggs, cheese, avocados, and low-carbohydrate fruits such as berries. We instruct participants to avoid sugar-sweetened foods (eg, sugar-laden desserts such as cakes, cookies, and ice cream), sugar-sweetened beverages (eg, sugared sodas and sweetened teas and coffees), naturally sweet foods (eg, tropical fruits), and starchy foods (eg, foods made with grain-based flours such as bread, pasta, tortillas, breakfast cereals, and pastas, as well as potatoes and rice). Each week, we provide class participants with CR diet recipes and a lending library of CR diet cookbooks (see Table 5 for core and booster diet curriculum components or weekly topics).

### Teacher

A board-certified internal medicine physician who has transitioned patients with T2DM onto CR diets in her private practice is the primary teacher who leads all diet classes.

### Fidelity Check

We record all class sessions, and a PhD-level clinical health psychologist and a PhD-level social health psychologist, the latter of whom originally developed the diet classes [8], review a randomly selected subset of these recordings to ensure that the diet class does not include content related to mindful eating. The primary teacher meets with one or both psychologists weekly by phone to review events occurring during classes and to review material for the following week. When the primary teacher is unavailable to teach (on rare occasions), one of the psychologists serves as a substitute. Study psychologists observe one-sixth of the CR classes in person.

## Mindful Eating Intervention

We deliver the Eat Right Now (ERN) [26] program, which is a mindful eating intervention in the form of a mobile app. It functions on both iOS and Android platforms, and we administer it in combination with a weekly 1-hour group class.

**Table 5.** Core and booster diet curriculum components.

| Session | Topics |
| --- | --- |
| Week 1 | Introduction to the program; information about insulin, diet, and type 2 diabetes; overview of previous research on very low-carbohydrate diets for adults with type 2 diabetes; what to eat on a very low-carbohydrate diet; how to count net (nonfiber) grams of carbohydrates; sample shopping list; example breakfast and snacks; how to deal with potential side effects of the diet; encouragement to change breakfasts and snacks to be very low-carbohydrate. |
| Week 2 | The history of using a very low-carbohydrate diet for type 2 diabetes; very low-carbohydrate lunch suggestions; ideas for eating at restaurants; suggestions for planning ahead; list of low-carbohydrate vegetables; encouragement to clear noncompliant foods out of their pantries; suggestion to add very low-carbohydrate lunches to their already very low-carbohydrate breakfasts and snacks. |
| Week 3 | Overview of the increase in type 2 diabetes over time; very low-carbohydrate dinner suggestions; encouragement to pick out recipes from cookbooks and online resources; suggestion to keep a favorite foods diary in order to track very low-carbohydrate foods they enjoy; information about non-nutritive sweeteners and sugar alcohols; suggestion to add very low-carbohydrate dinners. |
| Week 4 | The meaning of and how to measure blood ketone levels; how to deal with potential side effects of being in nutritional ketosis; inspirational stories from others trying this approach to help manage their type 2 diabetes. |
| Week 5 | Discussion of participants' perception of testing for ketones over the previous week; discussion about types of fat and encouragement to add fat to their diet; types of lower carbohydrate fruits; the benefits of sleep and information about sleep hygiene. |
| Week 6 | Ways to break through a weight-loss plateau; encouragement to increase food variety; information about alcohol. |
| Week 7 | Very low-carbohydrate travel suggestions; fast food options; snack ideas; problem-solving tips for eating on the meal plan. |
| Week 8 | Coping with peer pressure to not comply with the meal plan; suggestions for very low-carbohydrate party and holiday food; encouragement to safely add in physical activity; information about coping with physical challenges related to physical activity. |
| Week 9 | Reminders of the diet basics; suggestion to pay attention to food sensitivities; information about cholesterol types and health risk; description of the health impact of sugar consumption; reminders for how to order very low-carbohydrate meals at restaurants. |
| Week 10 | Discussion of example restaurant menus; self-assessment of their dietary adherence (technical, psychological, or external struggles). |
| Week 11 | Information about changes in hunger and flavor when following a very low-carbohydrate diet; partnered sharing of the program so far. |
| Week 12 | Ways to recover from slips and stick to their program-related goals; reminders of tricky dietary issues. |
| Week 16 (Maintenance) | Success story of a physician treating his own and others' type 2 diabetes using a very low-carbohydrate diet; how to access recorded presentations given by physicians about using a very low-carbohydrate diet for type 2 diabetes (freely available online); information about how a very low-carbohydrate diet has been used to help other health conditions. |
| Week 20 (Maintenance) | How fruits and vegetables have changed over time; information about online support groups; how to cope with being under the weather/ill and following a very low-carbohydrate meal plan. |
| Week 24 (Maintenance) | Case studies of several long-term adherents to a very low-carbohydrate diet; description of research on the long-term impact of a very low-carbohydrate diet for type 2 diabetes; suggestions for fine-tuning the diet to potentially reduce red and processed meat consumption; encouragement to stick with the program. |

### Mobile App

This 28-module course has been tested in overweight women who report problematic overeating in response to food cravings [26]. Participants in that study experienced reductions in daily craving-related eating (assessed using EMA), as well as reductions in trait-level measures of overeating, including reward-based eating drive, eating to cope with negative emotions, and food cravings. ERN intervention components center on (1) the scientific underpinnings of how food cravings arise and are reinforced, (2) research on the behavioral conditioning processes by which responses to food cravings become habitual, and (3) research showing how mindfulness directly targets cravings to change behavior. ERN modules teach participants to attend to three aspects of eating: why, what,

and how: *Why* they eat, including environmental and emotional triggers unrelated to homeostatic hunger; *What* types of food are most likely to lead to and reinforce cravings; and *How* to eat with awareness and mindful attention to physiological cues. Each module lasts approximately 5 to 10 minutes, and participants can only access one new module per day (after completing the previous module). Participants have unlimited access to previous modules. We ask participants to complete 2 or 3 modules per week during the intervention period, which translates to about 1 module every 2 days. In addition to the modules, participants can access extra tools to aid in mindfully "riding out" food cravings as they occur. Each of these tools targets disruptions in automatic, "mindless" eating in response to cravings and emphasizes attending to physiologic hunger signals. Participants can set reminders within the app that

encourage them to check in with their hunger and emotional state and to use mindfulness skills that help cultivate mindful eating habits. After the 28 modules are complete, all tools and previous modules remain available for the duration of the trial to support ongoing mindful eating and skill use (see Textbox 2 for a description of intervention content and [26] for further details about the ERN intervention).

### Weekly Classes

Each in-person weekly class focuses on participants' experiences in learning and applying mindful eating skills that they learn from the modules. Weekly classes are not didactic in nature but rather center around discussing participants' experiences with mindful eating practices, troubleshooting obstacles, and engaging in and reflecting on group exercises. If randomized to the mindfulness treatment arm, participants attend this class in the hour before attending the CR diet class. If they wish, participants can arrive 30 minutes early to class to watch an ERN module of their choice as a group.

### Teachers

Two mindful eating teachers colead most mindful eating classes, with a single teacher leading the session when the second teacher is not available. Both teachers completed supervised training in the ERN intervention according to a standardized teacher training process led by Dr Judson Brewer, MD, PhD, who developed the ERN mobile intervention.

### Fidelity Check

We audio record all mindful eating classes. An instructor in the Mindful Eating Facilitator Training course reviews a randomly selected subset of these recordings and conducts supervision calls with study teachers. During these calls, the instructor provides feedback on adherence to the ERN model, teaching style, and group facilitation processes. Teachers are aware of the content in the diet classes, and we instruct them to avoid messages that might conflict with the diet class content.

### Interventions: Maintenance Phase

After the weekly intervention phase (12 weeks), participants receive the following maintenance support:

### Monthly Diet Booster Classes

During monthly diet booster classes, the teacher provides supplemental material intended to troubleshoot problems, discusses progress and barriers to progress, and engages participants in motivating conversations geared toward continuation of assigned intervention-related behaviors. Monthly class content features information about how physicians are using CR diets to help their patients with T2DM and other metabolic conditions, the experiences of long-term adherents to a CR diet, and other related topics (see Table 6 for additional detail).

### Weekly Diet Individual Meetings

During these brief (15 min) individual meetings, which are held over the phone, the diet teacher answers any CR diet-related questions and concerns that may be individually specific to the participant. These individual meetings allow teaching to be tailored to individual needs related to several diet-related topics, such as weight loss stalls, lack of food variety, difficulties remaining in ketosis, or poor dietary adherence. The individual meetings are only offered to select participants. Over the course of the 3 planned waves, we test methods of selecting participants for these individual consultations, including the feasibility and acceptability of offering the individual consultations to a subset of participants based on ketone levels at 12 weeks.

**Textbox 2.** Mindful eating training components.

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Modules 1-7: Goals, habit formation, body scan, behavioral management, self-monitoring, existing with cravings

- Modules 1 and 2 allow the participant to set goals and teach them how habits form (eg, positive and negative reinforcement). These modules also introduce the roles of self-monitoring and mindless eating. Module 3 introduces basic mindfulness practices such as the body scan, which targets bodily awareness and momentary concentration. Module 4 defines refined, hyper-processed, calorically dense foods, with an emphasis on how these foods can have addictive qualities. It also defines healthier, nutrient-dense, lower-glycemic foods. Module 5 teaches how to mindfully work with food cues, affective states, and food cravings using the Recognize, Allow, Investigate, Notice (RAIN) exercise. This exercise promotes the dissociation between experiencing food cravings and eating in response to them. Module 6 helps individuals recognize self-judgment and how to be kind to themselves if they feel that they have "screwed up."

Modules 8-14: Noting practice, barriers to change, concept reinforcement

- Modules 8 through 14 emphasize the use of noting practice (the "N" of RAIN). Modules in week 2 encourage participants to note what their hunger, craving, and satiety levels are while eating and when considering eating. Participants view several animations that reinforce their understanding of how people "feed" their cravings by eating.

Modules 15-21: Loving-kindness, curiosity

- Modules 15 through 21 continue to reinforce noting practice and teach users to differentiate emotional eating (eg, due to stress) from physiological, homeostatic hunger (module 15). Modules 16 and 17 reinforce self-kindness (eg, loving-kindness) and curiosity, respectively.

Modules 22-28: Strategizing, reinforcing, next steps

- Modules 22 through 28 introduce how habitual thought patterns can be obstacles, and how we can mindfully observe our thoughts. Week 4 modules also help individuals reflect on their own experience from the previous few weeks of changing their relationship to food cravings. These reflections facilitate participants' awareness of their new habits and a gradual shift away from experiencing (and indulging) food cravings without awareness toward mindfully attending to their food craving triggers. Week 4 gives participants a sense of which modules they might want to review to reinforce certain lessons or tools (eg, excessive self-judgment).

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**Table 6.** Schedule and time commitments of intervention activities.

| Phase and activity | Activity schedule | Total time commitment | CR[a]-only group | CR and mindful eating group |
|---|---|---|---|---|
| **Intervention phase (weeks 1-12)** | | | | |
| Diet classes | Weekly for 1 hour | 12 hours | ✓ | ✓ |
| Mindful eating classes | Weekly for 1 hour | 12 hours | — | ✓ |
| Eat Right Now app | Engage 2 or 3 times per week for 5-10 min | 4 hours for required videos; additional time using app as desires | — | ✓ |
| **Maintenance phase (weeks 13-24)** | | | | |
| Diet booster classes | Monthly for 1 hour | 3 hours | ✓ | ✓ |
| Diet individual meetings (15 min by phone)[b] | Up to weekly, but typically biweekly or less often | 0-3 hours | ✓ | ✓ |
| Mindful eating booster classes | Monthly for 1 hour | 3 hours | — | ✓ |
| Mindful eating Zoom sessions[c] | Weekly for 1 hour, no meetings week of booster classes | 0-8 hours | — | ✓ |
| Total Time | 18 required hours | 37 required hours + 13 optional hours | — | — |

[a]CR: carbohydrate-restricted.

[b]Encouraged but optional; offered to select participants who schedule as they wish up to weekly.

[c]Encouraged but optional.

## Mindful Eating Booster Classes and Weekly Group Internet-Video Meetings (Zoom)

The mindful eating booster classes follow the same interactive format as the in-person weekly classes conducted during the intervention phase. During the intervention phase, these classes are held in-person once a month. During the maintenance phase, these classes are held over Zoom videoconferencing on weeks in which no in-person class is held. During the maintenance phase, in both the monthly in-person classes and the weekly Zoom classes, teachers continue to deliver the ERN intervention and focus on questions and challenges that participants bring up during class. Though we assign modules in-between all classes held during the intervention phase, we do not assign modules during the maintenance phase, as participants will have already completed the full 28-day curriculum.

## Safety Monitoring

### Glucose Monitoring and Medication Adjustment

CR diets often lead to decreases in glucose levels in people with T2DM. This increases the risk of hypoglycemia among individuals using glucose-lowering medications, such as sulfonylureas or insulin, unless appropriate medication adjustments are made. In our previous research [8], we used a medication reduction protocol designed to reduce the risk of hypoglycemia when initiating a CR diet, which resulted in no episodes of clinically significant hypoglycemia. For this trial, we use a similar protocol. Study physicians (medical doctors) who have experience in transitioning people with T2DM onto low-carbohydrate diets (one internal medicine physician, one endocrinologist physician) will serve as study physicians. These study physicians review participants' medications before participants begin the nutritional intervention. Study physicians oversee changes in medications, specifically reductions (or

discontinuations if at a low dose) in an order that typically prioritizes reductions/discontinuations as follows: (1) insulin, (2) sulfonylureas, (3) meglitinides (secretagogues), (4) SGLT-2 inhibitors, (5) GLP-1 agonists and DPP4 inhibitors, and (6) thiazolidinediones (TZD). Biguanides (eg, metformin) are typically continued unless glycosylated hemoglobin levels ($HbA_{1c}$) are consistently below 6.5%. Initial medication adjustments typically involve reducing a medication dose by half and are aimed at preventing hypoglycemia when initiating carbohydrate restriction. The number of medications reduced is calibrated based on initial $HbA_{1c}$ levels, with limited medication reductions in participants with high $HbA_{1c}$ levels and more extensive reductions in participants with $HbA_{1c}$ levels in the low diabetic range. For example, a participant with an $HbA_{1c}$ level greater than 8.0% might have a recommendation to reduce insulin doses in half while continuing other medications, while a participant with an $HbA_{1c}$ level between 6.5% and 7.0% might have a recommendation to stop using all diabetes medications other than biguanides and TZDs. We ask participants using all glucose-lowering medications other than metformin to measure their blood glucose at least once daily (before dinner) to ensure they are not at risk for hypoglycemia. For participants who are on a regimen considered to have additional risks of hypoglycemia (eg, insulin), we ask them to also measure their blood glucose in a fasted state (before breakfast). We review symptoms of hypoglycemia with participants in the initial group meeting and provide the following instructions: any participant who believes that he or she has hypoglycemia should immediately check his or her glucose level (fingerstick), if possible, and should consume carbohydrates if their glucose levels are below 70 mg/dL. If a glucose level cannot be obtained promptly, they should consume carbohydrates. We instruct all participants to report hypoglycemic symptoms to study staff. Study staff notify study

physicians immediately upon learning that a participant has reported hypoglycemic symptoms or glucose levels below 80 mg/dL if on medications other than metformin; hypoglycemic symptoms or glucose levels below 60 mg/dL if using either metformin alone or no glucose-lowering medications; or glucose levels above 220 mg/dL (all participants). Participants can contact study staff by phone call, text message, or email to ask questions and report symptoms or problems, and all study staff can then immediately reach study physicians by mobile phone or pager for urgent problems. Study staff collect regular glucose information from participants weekly (online, Qualtrics). Study physicians review glucose values at least weekly and make medication adjustments based on glucose levels, current medication regimens, and how long the participant has followed the CR diet. Predinner glucose levels below 110 mg/dL typically trigger evaluation of further medication reductions, using the priority list described above, in participants receiving medications other than biguanides. We provide participants' primary care physicians with information about the study before participants begin the study, notify them of any changes to medication regimens, and consult with them as needed.

### Hyperlipidemia

Some clinical trials of CR diets for obesity have demonstrated hyperlipidemia in response to a high-fat diet; hence, we will monitor participants for this possibility by testing serum lipids at baseline as well as at 12 and 24 weeks. Lipid studies include lipid particle size assessment using nuclear magnetic resonance methods (LabCorp, NMR Lipoprofile [34]). Although many people tolerate increases in saturated fat without deleterious changes in blood cholesterol levels on a CR diet, a minority experience increases in low-density lipoprotein (LDL) cholesterol. Participants with significant increases in LDL cholesterol, particularly increases accompanied by an increase in small particle LDL (small particle LDL cholesterol being the most strongly linked to increases in cardiovascular disease risk), receive counseling on how to follow a CR diet that limits saturated fat and increases monounsaturated and polyunsaturated fats, such as those found in olive oil and nuts.

### Minor Side Effects

Minor side effects including constipation, headache, diarrhea, muscle cramping, rash, or general weakness may occur when initiating a CR diet. Most side effects occur at the beginning of the diet transition, are short-lived, and are generally well-treated with adjustments to fluid intake and other diet modifications that are thoroughly addressed at the first diet class and throughout the study. We monitor for and record side effects, and study staff involve the diet teacher and study physicians as needed.

### Data Safety Monitoring Board (DSMB)

We have created a 2-person DSMB. We hold annual DSMB meetings via Zoom videoconference. In the case of a serious adverse event (SAE), we will call for a special closed meeting of the DSMB to review any needed changes or early stopping of the trial (see 2.10.8, Interim Analyses, Stopping Rules). In this trial, an adverse event (AE) is defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. AEs will be recorded regardless of their relationship to the study intervention. An SAE is defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

AEs that are collected as solicited events at study visits include recent hospitalizations or new medical diagnoses or problems. We will also record unsolicited events reported by participants. AE data that are formally assessed at study visits will be compared with existing unsolicited events in participant records to avoid double capture. The study team reviews all potential AEs reported by study participants and determines their relatedness to diet or study intervention, expectedness, and severity.

We monitor hypoglycemia and serum fasting lipid profiles. As shown in Table 7, we use the Common Terminology Criteria for Adverse Events (CTCAE) as follows, with grades 1 to 3 considered AEs, and grades 4 and 5 considered SAEs.

## Statistical Methods

### Preliminary Analyses

We will examine data distributions at baseline using summary statistics and will use graphical methods to visualize data to identify possible outliers and non-normal distributions before proceeding with modeling. Discussions of outliers and of missing data are included below (see "Sensitivity Analyses" and "Missing Data").

**Table 7.** Criteria for adverse events.

| CTCAE[a] term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Cholesterol high | >ULN[b]-300 mg/dL | >300-400 mg/dL | >400-500 mg/dL | >500 mg/dL | — |
| Hypertriglyceridemia | 150 mg/dL-300 mg/dL | >300 mg/dL-500 mg/dL | >500 mg/dL-1000 mg/dL | >1000 mg/dL; life-threatening consequences | Death |
| Hypoglycemia | <LLN[c]-55 mg/dL | <55-40 mg/dL | <40-30 mg/dL | <30 mg/dL life-threatening consequences; seizures | Death |

[a]CTCAE: Common Terminology Criteria for Adverse Events. CTCAE criteria available [66].

[b]ULN: upper limit of normal.

[c]LLN: lower limit of normal.

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**Table 8.** Primary and secondary trial outcomes.

| Measure | Construct assessed | Primary outcome | Secondary outcome | Outcome type |
|---|---|---|---|---|
| Ecological momentary assessment of eating behavior | Craving-related eating | ✓ | — | Behavioral |
| Computerized cognitive assessment: delayed discounting | Impulsivity | — | ✓ | Behavioral |
| Palatable Eating Motives Scale: Coping Subscale | Stress-related eating | — | ✓ | Behavioral |
| 24-hour dietary recall | Dietary adherence | — | ✓ | Behavioral |
| Blood ketone levels | Dietary adherence; dietary adherence after nonadherence | — | ✓ | Clinical |
| Weight | Weight | — | ✓ | Clinical |
| Glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$) | Glycemic control | — | ✓ | Clinical |
| Glucose, plasma | Glycemic control | — | ✓ | Clinical |
| Insulin, plasma | Glycemic control | — | ✓ | Clinical |

### Primary Outcome

As shown in Table 8, the primary outcome is reduction in craving-related eating, as measured through EMA text messages. Participants respond to the EMA question, "Did you eat or drink anything in response to that craving?" as *yes* or *no* (see Table 3). We will use a mixed effects logistic regression model, with random effects for day nested within study period nested within person, and for each of up to 4 possible reports per day (morning, afternoon, evening, and "any other time not previously reported"), to predict the dichotomous primary outcome (yes/no responses to EMA question). Model covariates (fixed effects) include time of day, study period, randomization group, and the interaction of study period by randomization group. This will allow us to estimate the odds of indulging a craving at 3 and 6 months compared with baseline, separately for each arm, as well as allowing for direct comparisons between study arms at each time.

### Secondary Outcomes

Secondary outcomes include changes in impulsivity, stress- and emotion-related eating, glycemic control ($HbA_{1c}$, fasting glucose, and insulin resistance), and weight. We also assess dietary adherence (ketone levels) as a secondary outcome (see Table 8 for all secondary outcome variable descriptions).

To assess changes in impulsivity, stress- and emotion-related eating, glycemic control, and weight (all treated as continuous variables), across groups and over time, we will use ANCOVA and linear mixed methods. In mixed models, we will include a random person effect, as well as fixed effects including study period, randomization group, and their interaction term. We will estimate differences between randomization groups at each time point and differences between time points within each randomization group.

To assess dietary adherence (ketone levels) and resilience following dietary nonadherence, we will first dichotomize ketone data as "ketosis" (values ≥0.3 BOHB mmol/L in fingerstick blood) and "not ketosis" (values <0.3 BOHB mmol/L in fingerstick blood). We have dichotomized ketone levels based

on our use of this level as an indicator that participants are engaging in adequate CR to achieve nutritional ketosis.

To assess overall dietary adherence, we will use a mixed effects logistic regression model with random effects for study period nested within person, as each participant provides ketone data 3 times per week for several weeks within each study period. We will include (as fixed effects) study period, randomization group, and their interaction term. We will estimate differences between randomization groups at each time point and differences between time points within each randomization group. We will also explore models treating ketone data continuously using the same model specifications as described above. This will yield average differences in the ketone levels between randomization groups and within time points.

To assess resilience following dietary nonadherence, we will compare the amount of time that passes between obtaining a ketone value <0.3 BOHB mmol/L (not in ketosis) after having had a prior ketone value of ≥0.3 BOHB mmol/L (in ketosis) between study groups, using a repeated measures analysis to address multiple episodes within participants, if these occur.

### Sensitivity Analyses

If outliers are present in continuous measures, we will rerun models after Winsorizing these data using 3 SDs from the mean cut-off to minimize the impact of extreme values [67].

### Missing Data

An important goal is to achieve high levels of participant retention and to minimize missing data. When consenting and enrolling participants, we emphasize the importance of completing study assessments and explain that missing data negatively impact scientific research. We provide financial compensation for the time participants spend completing study measures, and we devote significant staff resources to allow for careful participant follow-up. Mixed effects models using maximum likelihood (ML) estimation limit the risk of biased results due to missing data [68]. Our analytic approach uses these methods to minimize the impact of missing data.

**Table 9.** Power to detect between-group differences based on one-sided and two-sided tests for a difference in means between groups.

| Power for a one-sided test | Power for a two-sided test | Alpha | Control arm (n) | Mindful eating arm (n) | Days with craving-related eating in control arm (%) | Days with craving-related eating in mindful eating arm (%) | Delta (difference between arms) | SD |
|---|---|---|---|---|---|---|---|---|
| 0.7855 | 0.6786 | .05 | 30 | 30 | 50 | 43 | −7 | 11 |
| 0.8726 | 0.7910 | .05 | 30 | 30 | 50 | 42 | −8 | 11 |
| 0.7855 | 0.6786 | .05 | 30 | 30 | 49 | 42 | −7 | 11 |
| 0.8726 | 0.7910 | .05 | 30 | 30 | 49 | 41 | −8 | 11 |
| 0.7855 | 0.6786 | .05 | 30 | 30 | 48 | 41 | −7 | 11 |
| 0.8726 | 0.7910 | .05 | 30 | 30 | 48 | 40 | −8 | 11 |
| 0.7855 | 0.6786 | .05 | 30 | 30 | 47 | 40 | −7 | 11 |
| 0.8726 | 0.7910 | .05 | 30 | 30 | 47 | 39 | −7 | 11 |

### Data Management

Data are collected by trained research assistants and study coordinators using paper forms and Web-based questionnaires (online, Qualtrics). All surveys and forms are deidentified and coded with a unique subject number.

All data collection forms and laboratory reports are reviewed by the study team and data entry staff, who ensure that they are accurate and complete. A person who has not collected or entered data reviews the entered data for quality assurance. Protocol compliance and monitoring is done via review of records and forms after each participant visit and before data entry. Review is done by a study staff member who is not involved in the data collection for that participant, and any discrepancies or potential problems are reviewed by the Project Director or a senior study coordinator. Protocol deviations are captured by regular review of cases during the enrollment process by the Project Director to ensure that eligibility criteria are met. Key points of review include postconsent visit and baseline lab completion before randomization.

### Sample Size Estimates

Although this study is intended to provide a foundation for future trials of mindfulness and dietary change and the primary focus is not on having adequate power for hypothesis testing, we have performed a statistical power analysis for our primary outcome, which is craving-related eating.

Our preliminary data showed that participants experienced eating in response to a craving on 50% of days at baseline (SD 11%). We aim to assess whether participants who receive the mindful eating intervention experience a decrease in craving-related eating relative to participants who do not receive the mindful eating intervention. Because we anticipate a directionality of effect (we hypothesize greater adherence over time among the participants who receive the mindful eating training), we planned our sample size around a one-sided test but also performed a power analysis using a two-sided test. We estimate that we will have greater than 80% power to detect a difference between study groups if there is a between-group difference in craving-related eating at follow-up of 8 percentage points using a one-sided test and 79% power using a two-sided test (see Table 9).

### Interim Analyses, Stopping Rules

We have not planned any interim analyses, and we do not anticipate stopping the study early. Although our main clinical outcome of interest, $HbA_{1c}$, is a biomarker indicating long-term risk of clinical events due to diabetes (eg, neuropathy, blindness), it is not an outcome that would justify early stopping rules for a trial of this size and duration. The DSMB will review any SAEs related to the intervention or assessment procedures in separately scheduled, closed meetings (if SAEs were to occur) to determine whether the study should be stopped. The DSMB chair will moderate any closed sessions and collect a formal vote from DSMB members as to whether the trial should continue given the occurrence of an AE.

## Results

The project was funded in September of 2016 and final classes ended in March of 2018. Data analysis is currently underway, and we expect to submit results for publication in early 2019.

## Discussion

### Principal Findings

Adhering to dietary recommendations poses challenges for a variety of conditions, including obesity and diabetes [16,21]. This intervention is based upon a model that postulates that for many people, it is difficult to adaptively respond to food cravings in ways that maintain adherence to a dietary prescription. Although previous mindfulness-based interventions have begun to suggest that mindfulness-based interventions may impact obesity-related behaviors (yet, not necessarily weight loss itself) [69-71], we are employing a specific component of mindfulness (ie, mindful eating), which we hypothesize to more specifically impact obesity-related behaviors.

Prior work has documented that decreasing carbohydrate intake in people with T2DM leads to improved glycemic control [14] and that following a low-carbohydrate diet can reduce cravings for carbohydrate-rich foods [23]. Despite this "best case" scenario for limiting cravings for carbohydrate-rich foods, we postulate that adherence to carbohydrate restriction can be challenging for many people because of difficulty coping with

persistent food cravings. The modern food environment facilitates the experience of food cravings and also ensures that inexpensive food to satisfy these cravings is readily available. Prior data on the importance of food cravings in adherence to nutrition recommendations in T2DM leaves some uncertainties. Some studies have reported increases in food cravings during weight loss diets [72], but this type of study does not address persons with T2DM, and the focus on calorie restriction as opposed to diet pattern also differs from this study. Of more direct relevance, a recent study of persons with T2DM has reported that, in general, persons with T2DM put on a weight loss diet with differing proportions of protein and carbohydrate reported reductions in food cravings, which did not differ by diet composition [73]. The overall reduction in food cravings was moderate, however, with a 15% improvement in one measure of food craving, indicating that while cravings improved, they did not go away. Weight was positively correlated with cravings. The authors concluded that "Reductions in the frequency of food cravings and improvements in eating behaviors may encourage compliance and adherence to lifestyle programs which ultimately may enhance diabetes management." Given some uncertainties in existing literature, our study is aimed, in part, at clarifying the role that reductions in eating in response to food cravings may play in improving nutritional adherence in T2DM.

In addition to addressing eating in response to food cravings, we also postulate that other behavioral pathways may be relevant in improving diet adherence in T2DM. For example, resuming dietary adherence following lapses in adherence poses a significant challenge and remains understudied [74]. Our study directly tests mindful eating training as an intervention to strengthen adaptive coping with food-craving experiences and to resume dietary adherence following lapses.

Although we ultimately aim to impact clinical outcomes (eg, $HbA_{1c}$), this trial differs from other trials by focusing on behavioral mechanisms through which our intervention may impact clinical outcomes. Thus, our hypothesized behavioral mechanisms are the primary endpoints at this stage of our research. This study is therefore aligned with models advocated by the Science of Behavior Change (SOBC) model [75] and the Obesity-Related Behavioral Intervention Trials (ORBIT) model [76]. These models advocate identifying and individually testing key mechanisms that may underlie successful behavior changes and then developing and testing interventions that target these mechanisms. These models focus on maximizing potential to optimize intervention potency, efficiency, and effectiveness.

This trial includes several innovative features. First, it focuses on identifying mechanisms that underpin behavioral factors that influence health outcomes, that is, ascertaining if increasing training in mindful eating (mechanism) can increase dietary adherence (behavioral factor) holds implications for dietary interventions in T2DM (clinical health outcomes). Dietary prescriptions can effectively improve glycemic control to the extent that they are followed [13]; hence, developing methods to increase dietary adherence is a critical public health need.

Second, this trial focuses on testing these mechanisms, in part, using a cost-effective hybrid method that can be implemented in a variety of health care settings, including those with greater limitations on in-person services, that is, the didactic portion of the mindful eating training being tested in this trial is currently available for health care providers to prescribe to patients with smartphones, which 77% of US adults own [77]. The smartphone-based administration method ensures that all recipients of this intervention receive the intervention exactly as it was tested (ie, no effects of different intervention instructors). Mobile platforms allow patients to integrate behavioral change components as they go about their daily lives [78]. Third, this trial uses EMA in the form of mobile text messaging, which reduces issues associated with recall [79]. These ambulatory measures are important for both study providers and recipients. Such measures provide behavioral feedback to study staff, who can engage with patients to identify problems (both for intervention development purposes and to assist the patient with solutions), as well as provide actionable feedback directly to the patients, who can self-correct based on data they collect. Fourth, this trial uses both biological (blood ketone testing) and self-report (24-hour dietary recall) methods to assess dietary adherence.

## Limitations

Limitations of this trial include that it is powered to examine behavioral pathways we hypothesize to be tied to clinical outcomes rather than to evaluate clinical outcomes themselves, such as improvements in glycemic control. As described in the ORBIT model for developing behavioral treatments for chronic diseases [76], this trial is situated at phase IIb, which tests for a signal in the behavioral target while using a control group. Previous research has found that greater levels of mindfulness are associated with less stress- and emotion-related eating [29] and suggests that completing the mindfulness intervention administered in this trial leads to reductions in stress- and emotion-related eating, craving intensity, and rate of eating in response to cravings [26]. The next phase of this work will include a larger sample size that will provide better statistical power to examine clinical outcomes. Additionally, future work should test strategies for maintenance of behavioral (and clinical) changes. Moreover, our trial design and control group, although informed by the ORBIT model, does leave open the possibility that the additional content provided to the mindful eating group (eg, mobile app, more class time) may also influence our outcomes above and beyond the mindful eating instruction, as the groups may have differed in terms of time, attention from teachers, and participants' expectations.

We designed this two-group randomized controlled trial to test behavioral pathways through which mindfulness may impact the ability to respond to food cravings in ways that are consistent with a dietary prescription for T2DM. The findings may be relevant for understanding the effects of mindfulness interventions on dietary adherence in the context of diabetes, obesity, and other chronic metabolic diseases.

## Acknowledgments

## Conflicts of Interest

FH is a scientific advisor to Virta Health. All other authors declare no conflicts of interest.

## Multimedia Appendix 1

Peer-reviewer report from the NIH.

[PDF File (Adobe PDF File), 190KB - resprot_v8i2e11002_app1.pdf ]

## References

1. Leung M, Pollack L, Colditz G, Chang S. Life years lost and lifetime health care expenditures associated with diabetes in the U.S., National Health Interview Survey, 1997-2000. Diabetes Care 2015 Mar;38(3):460-468 [FREE Full text] [doi: 10.2337/dc14-1453] [Medline: 25552420]

2. Ozieh M, Bishu K, Dismuke C, Egede L. Trends in health care expenditure in U.S. adults with diabetes: 2002-2011. Diabetes Care 2015 Oct;38(10):1844-1851 [FREE Full text] [doi: 10.2337/dc15-0369] [Medline: 26203060]

3. Seuring T, Archangelidi O, Suhrcke M. The ecomonic costs of Type 2 Diabetes: a global systematic review. Pharmacoeconomics 2015 Aug;33(8):811-831 [FREE Full text] [doi: 10.1007/s40273-015-0268-9] [Medline: 25787932]

4. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2017 Dec;40(Suppl 1):S11-S24. [doi: 10.2337/dc17-S005] [Medline: 27979889]

5. Stratton I, Adler A, Neil H, Matthews D, Manley S, Cull C, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000 Aug 12;321(7258):405-412 [FREE Full text] [Medline: 10938048]

6. Middleton KR, Anton SD, Perri MG. Long-term adherence to health behavior change. Am J Lifestyle Med 2013;7(6):395-404 [FREE Full text] [doi: 10.1177/1559827613488867] [Medline: 27547170]

7. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, American Diabetes Association. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2013 Nov;36(11):3821-3842 [FREE Full text] [doi: 10.2337/dc13-2042] [Medline: 24107659]

8. Saslow LR, Kim S, Daubenmier JJ, Moskowitz JT, Phinney SD, Goldman V, et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. PLoS One 2014;9(4):e91027 [FREE Full text] [doi: 10.1371/journal.pone.0091027] [Medline: 24717684]

9. Santos F, Esteves S, da Costa Pereira A, Yancy JW, Nunes J. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev 2012 Nov;13(11):1048-1066. [doi: 10.1111/j.1467-789X.2012.01021.x] [Medline: 22905670]

10. Nielsen JV, Joensson E. Low-carbohydrate diet in type 2 diabetes. Stable improvement of bodyweight and glycemic control during 22 months follow-up. Nutr Metab (Lond) 2006 Jun 14;3:22 [FREE Full text] [doi: 10.1186/1743-7075-3-22] [Medline: 16774674]

11. Kirk J, Graves D, Craven T, Lipkin E, Austin M, Margolis K. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc 2008 Jan;108(1):91-100. [doi: 10.1016/j.jada.2007.10.003] [Medline: 18155993]

12. Dashti H, Mathew T, Khadada M, Al-Mousawi M, Talib H, Asfar S, et al. Beneficial effects of ketogenic diet in obese diabetic subjects. Mol Cell Biochem 2007 Aug;302(1-2):249-256. [doi: 10.1007/s11010-007-9448-z] [Medline: 17447017]

13. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Res Care 2017;5(1):e000354 [FREE Full text] [doi: 10.1136/bmjdrc-2016-000354] [Medline: 28316796]

14. Feinman R, Pogozelski W, Astrup A, Bernstein R, Fine E, Westman E, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition 2015 Jan;31(1):1-13 [FREE Full text] [doi: 10.1016/j.nut.2014.06.011] [Medline: 25287761]

15. Weingarten H, Elston D. The phenomenology of food cravings. Appetite 1990 Dec;15(3):231-246. [doi: 10.1016/0195-6663(90)90023-2]

16. Schlundt D, Rea M, Kline S, Pichert J. Situational obstacles to dietary adherence for adults with diabetes. J Am Diet Assoc 1994 Aug;94(8):874-879. [doi: 10.1016/0002-8223(94)92367-1]

17. Ogden J, Coop N, Cousins C, Crump R, Field L, Hughes S, et al. Distraction, the desire to eat and food intake. Towards an expanded model of mindless eating. Appetite 2013 Mar;62:119-126. [doi: 10.1016/j.appet.2012.11.023] [Medline: 23219989]

18.   Simmons W, Martin A, Barsalou L. Pictures of appetizing foods activate gustatory cortices for taste and reward. Cereb Cortex 2005 Oct;15(10):1602-1608. [doi: 10.1093/cercor/bhi038] [Medline: 15703257]

19.   Papies EK. Tempting food words activate eating simulations. Front Psychol 2013;4:838 [FREE Full text] [doi: 10.3389/fpsyg.2013.00838] [Medline: 24298263]

20.   Vartanian LR, Herman CP, Wansink B. Are we aware of the external factors that influence our food intake? Health Psychol 2008 Sep;27(5):533-538. [doi: 10.1037/0278-6133.27.5.533] [Medline: 18823179]

21.   Dalton M, Finlayson G, Walsh B, Halseth AE, Duarte C, Blundell JE. Early improvement in food cravings are associated with long-term weight loss success in a large clinical sample. Int J Obes (Lond) 2017 Aug;41(8):1232-1236 [FREE Full text] [doi: 10.1038/ijo.2017.89] [Medline: 28373674]

22.   Hall D, Most M. Dietary adherence in well-controlled feeding studies. J Am Diet Assoc 2005 Aug;105(8):1285-1288. [doi: 10.1016/j.jada.2005.05.009] [Medline: 16182647]

23.   Martin C, Rosenbaum D, Han H, Geiselman P, Wyatt H, Hill J, et al. Change in food cravings, food preferences, and appetite during a low-carbohydrate and low-fat diet. Obesity (Silver Spring) 2011 Oct;19(10):1963-1970 [FREE Full text] [doi: 10.1038/oby.2011.62] [Medline: 21494226]

24.   Beltrán-Sánchez H, Harhay M, Harhay M, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. J Am Coll Cardiol 2013 Aug 20;62(8):697-703 [FREE Full text] [doi: 10.1016/j.jacc.2013.05.064] [Medline: 23810877]

25.   Tabák A, Herder C, Rathmann W, Brunner E, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet 2012 Jun;379(9833):2279-2290. [doi: 10.1016/S0140-6736(12)60283-9]

26.   Mason A, Jhaveri K, Cohn M, Brewer J. Testing a mobile mindful eating intervention targeting craving-related eating: feasibility and proof of concept. J Behav Med 2018 Apr;41(2):160-173. [doi: 10.1007/s10865-017-9884-5] [Medline: 28918456]

27.   Mason A, Epel E, Kristeller J, Moran P, Dallman M, Lustig R, et al. Effects of a mindfulness-based intervention on mindful eating, sweets consumption, and fasting glucose levels in obese adults: data from the SHINE randomized controlled trial. J Behav Med 2016 Apr;39(2):201-213 [FREE Full text] [doi: 10.1007/s10865-015-9692-8] [Medline: 26563148]

28.   Kristeller J, Wolever R. Mindfulness-based eating awareness training for treating binge eating disorder: the conceptual foundation. Eat Disord 2011;19(1):49-61. [doi: 10.1080/10640266.2011.533605] [Medline: 21181579]

29.   Tak S, Hendrieckx C, Nefs G, Nyklíček I, Speight J, Pouwer F. The association between types of eating behaviour and dispositional mindfulness in adults with diabetes. Results from Diabetes MILES. The Netherlands. Appetite 2015 Apr;87:288-295. [doi: 10.1016/j.appet.2015.01.006] [Medline: 25596042]

30.   Cerrelli F, Manini R, Forlani G, Baraldi L, Melchionda N, Marchesini G. Eating behavior affects quality of life in type 2 diabetes mellitus. Eat Weight Disord 2013 Oct 17;10(4):251-257. [doi: 10.1007/BF03327492]

31.   Raymond K, Lovell GP. Food addiction symptomology, impulsivity, mood, and body mass index in people with type two diabetes. Appetite 2015 Dec;95:383-389. [doi: 10.1016/j.appet.2015.07.030] [Medline: 26232140]

32.   Kabat-Zinn J, Hanh T. Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness. New York: Random House LLC; 2009.

33.   Forman E, Butryn M. A new look at the science of weight control: how acceptance and commitment strategies can address the challenge of self-regulation. Appetite 2015 Jan;84:171-180 [FREE Full text] [doi: 10.1016/j.appet.2014.10.004] [Medline: 25445199]

34.   LabCorp. URL: https://www.labcorp.com [accessed 2018-11-05] [WebCite Cache ID 73iLhsqqO]

35.   Shiffman S, Stone AA, Hufford M. Ecological Momentary Assessment. Annu Rev Clin Psychol 2008 Apr;4(1):1-32. [doi: 10.1146/annurev.clinpsy.3.022806.091415]

36.   Stojek M, MacKillop J. Relative reinforcing value of food and delayed reward discounting in obesity and disordered eating: a systematic review. Clin Psychol Rev 2017 Jul;55:1-11. [doi: 10.1016/j.cpr.2017.04.007] [Medline: 28478269]

37.   Nederkoorn C, Houben K, Hofmann W, Roefs A, Jansen A. Control yourself or just eat what you like? Weight gain over a year is predicted by an interactive effect of response inhibition and implicit preference for snack foods. Health Psychol 2010 Jul;29(4):389-393. [doi: 10.1037/a0019921] [Medline: 20658826]

38.   Nijs I, Muris P, Euser A, Franken I. Differences in attention to food and food intake between overweight/obese and normal-weight females under conditions of hunger and satiety. Appetite 2010 Apr;54(2):243-254. [doi: 10.1016/j.appet.2009.11.004] [Medline: 19922752]

39.   Hallberg S, McKenzie A, Williams P, Bhanpuri N, Peters A, Campbell W, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. Diabetes Ther 2018 Apr;9(2):583-612 [FREE Full text] [doi: 10.1007/s13300-018-0373-9] [Medline: 29417495]

40.   NIH National Cancer Institute: Dietary Assessment Primer. Summary Tables: Recommendations on Potential Approaches to Dietary Assessment for Different Research Objectives Requiring Group-level Estimates URL: https://dietassessmentprimer.cancer.gov/approach/table.html [accessed 2018-11-05] [WebCite Cache ID 73iM4xpc2]

41.   Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385. [doi: 10.2307/2136404]

42. Kroenke K, Strine T, Spitzer R, Williams J, Berry J, Mokdad A. 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]

43. Epel E, Tomiyama A, Mason A, Laraia B, Hartman W, Ready K, et al. The reward-based eating drive scale: a self-report index of reward-based eating. PLoS One 2014;9(6):e101350 [FREE Full text] [doi: 10.1371/journal.pone.0101350] [Medline: 24979216]

44. Meule A, Hermann T, Kübler A. A short version of the Food Cravings Questionnaire-Trait: the FCQ-T-reduced. Front Psychol 2014;5(190):190 [FREE Full text] [doi: 10.3389/fpsyg.2014.00190] [Medline: 24624116]

45. Tsenkova V, Boylan JM, Ryff C. Stress eating and health. Findings from MIDUS, a national study of US adults. Appetite 2013 Oct;69:151-155 [FREE Full text] [doi: 10.1016/j.appet.2013.05.020] [Medline: 23747576]

46. Burgess E, Turan B, Lokken K, Morse A, Boggiano M. Profiling motives behind hedonic eating. Preliminary validation of the Palatable Eating Motives Scale. Appetite 2014 Jan;72:66-72. [doi: 10.1016/j.appet.2013.09.016] [Medline: 24076018]

47. Epel E, Jimenez S, Brownell K, Stroud L, Stoney C, Niaura R. Are stress eaters at risk for the metabolic syndrome? Ann N Y Acad Sci 2004 Dec;1032(1):208-210. [doi: 10.1196/annals.1314.022] [Medline: 15677412]

48. Ames G, Heckman M, Grothe K, Clark M. Eating self-efficacy: development of a short-form WEL. Eat Behav 2012 Dec;13(4):375-378. [doi: 10.1016/j.eatbeh.2012.03.013] [Medline: 23121791]

49. Latner J, Mond J, Kelly M, Haynes S, Hay P. The loss of control over eating scale: development and psychometric evaluation. Int J Eat Disord 2014 Sep;47(6):647-659. [doi: 10.1002/eat.22296] [Medline: 24862351]

50. Juarascio A, Forman E, Timko CA, Butryn M, Goodwin C. The development and validation of the food craving acceptance and action questionnaire (FAAQ). Eat Behav 2011 Aug;12(3):182-187. [doi: 10.1016/j.eatbeh.2011.04.008] [Medline: 21741015]

51. Fredrickson BL, Tugade MM, Waugh CE, Larkin GR. What good are positive emotions in crisis? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. J Pers Soc Psychol 2003 Feb;84(2):365-376 [FREE Full text] [doi: 10.1037//0022-3514.84.2.365] [Medline: 12585810]

52. van Strien T, Frijters J, Bergers G, Defares P. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. Int J Eat Disord 1986 Feb;5(2):295-315. [doi: 10.1002/1098-108X(198602)5:2<295::AID-EAT2260050209>3.0.CO;2-T]

53. Tran U, Glück TM, Nader I. Investigating the Five Facet Mindfulness Questionnaire (FFMQ): construction of a short form and evidence of a two-factor higher order structure of mindfulness. J Clin Psychol 2013 Sep;69(9):951-965. [doi: 10.1002/jclp.21996] [Medline: 23784693]

54. 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]

55. Raes F, Pommier E, Neff K, Van Gucht D. Construction and factorial validation of a short form of the Self-Compassion Scale. Clin Psychol Psychother 2011;18(3):250-255. [doi: 10.1002/cpp.702] [Medline: 21584907]

56. Daubenmier J. The relationship of yoga, body awareness, and body responsiveness to self-objectification and disordered eating. Psychol Women Q 2016 Nov 25;29(2):207-219. [doi: 10.1111/j.1471-6402.2005.00183.x]

57. Koffarnus M, Bickel W. A 5-trial adjusting delay discounting task: accurate discount rates in less than one minute. Exp Clin Psychopharmacol 2014 Jun;22(3):222-228 [FREE Full text] [doi: 10.1037/a0035973] [Medline: 24708144]

58. Fillmore M, Rush C, Hays L. Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. Addiction 2006 Sep;101(9):1323-1332. [doi: 10.1111/j.1360-0443.2006.01522.x] [Medline: 16911732]

59. Channon S, Hayward A. The effect of short-term fasting on processing of food cues in normal subjects. Int J Eat Disord 1990 Jul;9(4):447-452. [doi: 10.1002/1098-108X(199007)9:4<447::AID-EAT2260090411>3.0.CO;2-0]

60. Epstein L, Dearing K, Roba L. A questionnaire approach to measuring the relative reinforcing efficacy of snack foods. Eat Behav 2010 Apr;11(2):67-73 [FREE Full text] [doi: 10.1016/j.eatbeh.2009.09.006] [Medline: 20188288]

61. Johansson L, Ghaderi A, Andersson G. The role of sensitivity to external food cues in attentional allocation to food words on dot probe and Stroop tasks. Eat Behav 2004 Jul;5(3):261-271. [doi: 10.1016/j.eatbeh.2004.01.005] [Medline: 15135338]

62. Saslow LR, Mason AE, Kim S, Goldman V, Ploutz-Snyder R, Bayandorian H, et al. An online intervention comparing a very low-carbohydrate ketogenic diet and lifestyle recommendations versus a plate method diet in overweight individuals with type 2 diabetes: a randomized controlled trial. J Med Internet Res 2017 Feb 13;19(2):e36 [FREE Full text] [doi: 10.2196/jmir.5806] [Medline: 28193599]

63. Trumbo P, Schlicker S, Yates A, Poos M, Food and Nutrition Board of the Institute of Medicine, The National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. J Am Diet Assoc 2002 Nov;102(11):1621-1630. [Medline: 12449285]

64. Sainsbury E, Kizirian N, Partridge S, Gill T, Colagiuri S, Gibson A. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2018 May;139:239-252. [doi: 10.1016/j.diabres.2018.02.026] [Medline: 29522789]

65. van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate-compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. Am J Clin Nutr 2018 Aug 01;108(2):300-331. [doi: 10.1093/ajcn/nqy096] [Medline: 30007275]

66. National Cancer Institute. CTEP: Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events (CTCAE) URL: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

67. Vittinghoff E, Glidden D, Shiboski S, McCulloch C. Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models. New York, NY: Springer-Verlag New York, LLC; 2011.

68. Siddiqui O, Hung HM, O'Neill R. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 2009;19(2):227-246. [doi: 10.1080/10543400802609797] [Medline: 19212876]

69. Godfrey K, Gallo L, Afari N. Mindfulness-based interventions for binge eating: a systematic review and meta-analysis. J Behav Med 2015 Apr;38(2):348-362. [doi: 10.1007/s10865-014-9610-5] [Medline: 25417199]

70. Katterman S, Kleinman B, Hood M, Nackers L, Corsica J. Mindfulness meditation as an intervention for binge eating, emotional eating, and weight loss: a systematic review. Eat Behav 2014 Apr;15(2):197-204. [doi: 10.1016/j.eatbeh.2014.01.005] [Medline: 24854804]

71. O'Reilly GA, Cook L, Spruijt-Metz D, Black D. Mindfulness-based interventions for obesity-related eating behaviours: a literature review. Obes Rev 2014 Jun;15(6):453-461 [FREE Full text] [doi: 10.1111/obr.12156] [Medline: 24636206]

72. Weingarten H, Elston D. Food cravings in a college population. Appetite 1991 Dec;17(3):167-175. [doi: 10.1016/0195-6663(91)90019-O]

73. Watson N, Dyer K, Buckley J, Brinkworth G, Coates A, Parfitt G, et al. Reductions in food cravings are similar with low-fat weight loss diets differing in protein and carbohydrate in overweight and obese adults with type 2 diabetes: a randomized clinical trial. Nutr Res 2018 Sep;57:56-66. [doi: 10.1016/j.nutres.2018.05.005] [Medline: 30122196]

74. Forman EM, Schumacher LM, Crosby R, Manasse SM, Goldstein SP, Butryn ML, et al. Ecological momentary assessment of dietary lapses across behavioral weight loss treatment: characteristics, predictors, and relationships with weight change. Ann Behav Med 2017 Oct;51(5):741-753. [doi: 10.1007/s12160-017-9897-x] [Medline: 28281136]

75. NIH Office of Strategic Coordination - The Common Fund. Science of Behavior Change URL: https://commonfund.nih.gov/behaviorchange [accessed 2018-11-05] [WebCite Cache ID 73iNfXHCd]

76. Czajkowski SM, Powell LH, Adler N, Naar-King S, Reynolds KD, Hunter CM, et al. From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. Health Psychol 2015 Oct;34(10):971-982 [FREE Full text] [doi: 10.1037/hea0000161] [Medline: 25642841]

77. Perrin A. Pew Research Center. 2017 Jun 28. 10 facts about smartphones as the iPhone turns 10 URL: http://www.pewresearch.org/fact-tank/2017/06/28/10-facts-about-smartphones/ [accessed 2018-11-05] [WebCite Cache ID 73iNomCkU]

78. Heron K, Smyth J. Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. Br J Health Psychol 2010 Feb;15(Pt 1):1-39 [FREE Full text] [doi: 10.1348/135910709X466063] [Medline: 19646331]

79. Conner TS, Mehl MR. Ambulatory Assessment: Methods for Studying Everyday Life. In: Emerging trends in the social and behavioral sciences: an interdisciplinary, searchable, and linkable resource. Wiley Online Library: John Wiley & Sons, Inc; 2015.

## Abbreviations

**AE:** adverse event
**BMI:** body mass index
**BOHB:** β-hydroxybutyrate
**CR:** carbohydrate-restricted
**DSMB:** Data Safety Monitoring Board
**EMA:** ecological momentary assessment
**ERN:** Eat Right Now
**HbA$_{1c}$:** glycosylated hemoglobin
**hsCRP:** high-sensitivity C-reactive protein
**IRB:** institutional review board
**LDL:** low-density lipoprotein
**ML:** maximum likelihood
**NCCIH:** National Center for Complementary and Integrative Health
**NDSR:** Nutrition Data System for Research
**NIH:** National Institutes of Health
**ORBIT:** Obesity-Related Behavioral Intervention Trials
**SAE:** serious adverse event
**SOBC:** Science of Behavior Change
**T2DM:** type 2 diabetes mellitus

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**TSH:** thyroid stimulating hormone
**TZD:** thiazolidinediones
**UCSF:** University of California, San Francisco

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Protocol

# Comprehensive Lifestyle Improvement Program for Prostate Cancer (CLIPP): Protocol for a Feasibility and Exploratory Efficacy Study in Men on Androgen Deprivation Therapy

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## Abstract

**Background:** Androgen deprivation therapy (ADT) for prostate cancer is associated with adverse cardiometabolic effects such as reduced libido, hot flashes, metabolic syndrome, diabetes, myocardial infarction, and stroke. This reduces quality of life and potentially increases mortality. Several large clinical trials have demonstrated improvements in cardiometabolic risk with comprehensive multimodality lifestyle modification. However, there is a lack of data for such interventions in men on ADT for prostate cancer, and existing studies have used non-standardized interventions or lacked data on metabolic risk factors.

**Objective:** The Comprehensive Lifestyle Improvement Project for Prostate Cancer (CLIPP) is designed to address these gaps by using an intervention modeled on the Diabetes Prevention Program, a standardized multicomponent intervention with demonstrated effectiveness in reducing cardiometabolic risk factors that has been successfully adapted for multiple disease types including breast cancer.

**Methods:** A single-arm unblinded clinical trial will be conducted to determine the feasibility of conducting a 24-week comprehensive lifestyle modification intervention that targets weight loss and increased physical activity modeled on the Diabetes Prevention Program in 30 men on ADT for prostate cancer. Secondary aims are to determine the effect of the intervention on cardiometabolic markers and quality of life. The tertiary aim is to determine the effect of the intervention on markers of inflammation and angiogenesis, important mechanisms for prostate cancer progression. Participants will be recruited from the University of Arizona Cancer Center and the surrounding community. The intervention will be delivered weekly in person and over the phone for 16 weeks. For Weeks 16-24, participants receive weekly phone calls from the study health coach to motivate them to continue their lifestyle modification. Questionnaire and biological data are collected at baseline, 12 weeks, and 24 weeks. Body composition using dual-energy x-ray absorptiometry scans will be performed at baseline and end of study.

**Results:** Based on a sample size of 30, the two-sided 95% confidence interval will not be wider than 0.373 standard deviations for the adherence rate and will not be wider than 0.374 for the retention rate. In addition, the study will have a power of 80% to detect a change of 0.47 standard deviations from baseline for each of the markers investigated in the secondary and tertiary aims assuming a within-subject correlation of 0.20 at a significance level of 5%. The recruitment period is from October 2018 to April 2019.

**Conclusions:** The aim of CLIPP is to determine the feasibility of conducting a Diabetes Prevention Program–style comprehensive lifestyle modification intervention in men with ADT for prostate cancer and its effects on cardiometabolic adverse effects, quality of life, as well as markers of inflammation and angiogenesis. Results will inform the development of future clinical trials in this population.

## Introduction

Androgen deprivation therapy (ADT) has been demonstrated to improve disease-free survival and overall survival in men with prostate cancer (PCa) [1,2]. Androgen deprivation can be accomplished through surgical castration (bilateral orchiectomy) or medical castration through gonadotropin-releasing hormone (GnRH) agonist and antagonist as well as antiandrogen medication [3,4]. Changed hormonal milieu due to ADT is associated with a number of adverse effects such as metabolic syndrome, weight gain, decreased libido, insulin resistance, obesity, sarcopenia, as well as diabetes, myocardial infarction, and cerebrovascular events. These adverse effects not only lower the individual's quality of life (QoL) but also contribute to increased mortality [3,5,6]. Reports by Cheung and Alibhai demonstrate that ADT is associated with clinically significant decreased QoL especially in the physical and sexual domains [5,6]. In a meta-analysis by Bosco et al, relative risk (RR) for any type of nonfatal cardiovascular disease was 1.38 (95% CI 1.29-1.48) for men with PCa on GnRH agonists, compared with men not treated with ADT [3]. The associations between GnRH agonists and myocardial infarction or stroke were even stronger: RR 1.57 (95% CI 1.26-1.94) and RR 1.51 (95% CI 1.24-1.84), respectively [3].

Comprehensive multicomponent lifestyle modification interventions have demonstrated improvement in metabolic profile and cardiovascular risk factors [7]. The Diabetes Prevention Program (DPP) was a randomized clinical trial (N=3234) comparing the effect of intensive multicomponent lifestyle modification, metformin, or placebo on development of diabetes in persons with impaired glucose tolerance [7]. In this trial, the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years for placebo, metformin, and lifestyle modification, respectively. Compared to placebo, incidence of diabetes was reduced by 58% in the lifestyle arm and 31% in the metformin arm. Although there was slight attenuation of the effect, the incidence of diabetes was still lower in the lifestyle arm as compared to the metformin arm (34% and 18%, respectively) after 10 years of follow-up [8]. The 10-year follow-up demonstrated major reductions for blood pressure (systolic, 2-3 mmHg and diastolic, 5-6 mmHg), low-density lipoprotein cholesterol (0.47-0.54 mmol/l), and triglycerides (0.18-0.32 mmol/l) as well as increases in high-density lipoprotein (0.13-0.16 mmol/l) for all the three groups, whereas hyperlipidemia ($P<.012$), hypertension ($P<.09$) [9], and medication use was lower for the lifestyle group. Lack of differentiation between the three groups could potentially be due to all three groups' receiving the lifestyle intervention when the primary clinical trial ended. The DPP has been successfully adapted for breast cancer patients [10]. In the Lifestyle Exercise And Nutrition (LEAN) study, 100 women with breast cancer were randomized to in-person or phone-based lifestyle modification or usual care. There was a statistically significant decrease in weight ($P=.004$ and $P=.009$ for in-person or phone-based intervention) compared to usual care. Additionally, women who lost >5% weight demonstrated significant improvements in metabolic (insulin and leptin, $P=.05$ and .002, respectively) and inflammatory (C-reactive protein and interleukin-6, $P=.02$ for both) markers [10]. These data served as the premise for the ongoing Breast Cancer Weight Loss trial of a DPP-modified intervention for weight loss in breast cancer survivors [11].

Interventions addressing either exercise or nutrition have demonstrated benefit in men on ADT for PCa [12]. However, there is a lack of data with respect to comprehensive multicomponent standardized lifestyle improvement programs. Recently published results from the Individualized Diet and Exercise Adherence-Pilot (IDEA-P) trial demonstrated that a multicomponent lifestyle modification program is effective in improving mobility performance ($P<.02$), muscular strength ($P<.01$), body fat percentage ($P<.05$), and fat mass ($P<.03$) [13]. However, cardiometabolic risk factors or QoL were not outcome variables in this paper nor was a standardized intervention like the DPP used in the study.

Obesity is an important risk factor for not only cardiometabolic diseases but also for PCa progression. As many as 77% men diagnosed with PCa can be classified as overweight or obese, which is higher than the national average [14]. Obesity has been associated with PCa aggressiveness, progression, and cancer-specific mortality [15]. The Continuous Update Project report on PCa identifies overweight and obesity to be strong risk factors for PCa progression [16]. Hence, an intervention like the DPP with proven efficacy towards reducing weight and improving cardiometabolic risk factors could be hypothesized to have the same effect in men on ADT for PCa.

The current trial addresses the above-mentioned deficiencies by conducting a feasibility and early efficacy study to determine the utility of a DPP-style lifestyle modification intervention on cardiometabolic risk factors and QoL in men on ADT for PCa. Additionally, the effect of the intervention on markers of inflammation and angiogenesis will be determined to understand its impact on PCa progression, as inflammation and angiogenesis are important mechanisms for PCa progression [17-21].

## Methods

### Study Design

The aims of the Comprehensive Lifestyle Improvement Program for Prostate Cancer (CLIPP), a single-arm unblinded clinical trial, are to determine (1) the feasibility of conducting a 24-week comprehensive lifestyle modification intervention in men on ADT for PCa, (2) the effect of a comprehensive lifestyle

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modification on cardiometabolic risk factors and QoL in men on ADT for PCa, and (3) the effect of a comprehensive lifestyle modification on markers of inflammation and angiogenesis. Regulatory approval for this project has been obtained from the University of Arizona Institutional Review Board and its affiliated hospital system, Banner University Medical Center. Thirty subjects will be recruited from the University of Arizona Cancer Center (UACC), a National Cancer Institute–designated Comprehensive Cancer Center located in Tucson, Arizona, and its surrounding community. The UACC Cancer Survivorship Clinic, Genitourinary Oncology Clinic, and Radiation Oncology Clinic will be involved in recruitment. Flyers will be distributed at various locations around the cancer center informing potential participants about the study. Principal investigators and study staff will reach out to various prostate cancer support groups around the city to recruit participants. Principal investigators and collaborators will introduce the study to potential participants. If the potential participant is willing to participate, their information will be shared with the clinical research associate who will determine eligibility via telephone. Participants recruited through other methods will be instructed to call the clinical research associate directly for timely screening. After eligibility screening, the associate will explain the study purpose, answer questions, and ascertain interest in participation. If the participant agrees, informed consent will be obtained.

## Eligibility

To be eligible for this study, participants are required to meet the following inclusion and exclusion criteria. Since this is a feasibility trial, criteria are purposefully broad. Participants must (1) be men diagnosed with prostate cancer (Stage I-III) within the past 10 years, who are on ADT for their disease, (2) be age 40 or older with at least a 5-year life expectancy, (3) be willing to participate in a lifestyle modification intervention, including all assessments and measurements, (4) speak English, and (5) if participating in any other clinical trial participants, have a 30-day washout period before they can become eligible for this trial. The exclusion criteria for the study consist of the following: (1) PCa survivors currently participating in any other clinical trials, (2) PCa survivors on hospice or with a life expectancy less than 5 years, (3) survivors with Stage IV PCa, (4) having digestive diseases (eg, inflammatory bowel disease, diverticulitis) that make for intolerance of significant increases in plant food intake, and (5) individuals unable to fully comprehend the informed consent or other procedural requirements. Individuals with high adherence to lifestyle guidelines (eg, consuming a vegan diet or participating in moderate to vigorous physical activity for >45 minutes/day, 7 days/week) will be excluded.

## Informed Consent

The investigational nature and objectives of the trial, the procedures, and interventions involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to subjects and a signed informed consent

obtained. The informed consent form approved by the University of Arizona Institutional Review Board will be used for this. Documentation of informed consent for screening will be maintained in the subject's research file.

## Study Procedure

Participants will be scheduled for a baseline visit after informed consent has been obtained. This visit will consist of obtaining anthropometric measures, questionnaire data, biological samples, and body composition data using dual-energy absorptiometry (DXA) scan. The intervention will be initiated at this visit. Participants will be provided with a fitness tracking device (FitBit Charge2) that will support the tracking of fitness goals and provides the study team with physical activity data. Participants will keep the fitness tracker after completion of study. Participants will be followed weekly for a duration of 24 weeks. Baseline and every fourth visit will be in-person, whereas the remainder of the intervention support will be provided over the phone. This delivery strategy was adopted based on results of focus group discussions conducted with PCa survivors at the UACC regarding their interests in participating in a lifestyle modification intervention [22]. Anthropometric measurements will be collected at each in-person visit. Questionnaire data and biological samples will be collected at baseline, 12 weeks, and 24 weeks. DXA scans will be obtained at baseline and end of study (24 weeks) to assess body composition changes over time. An exit survey will be carried out at the end of the study to assess acceptance and feasibility including an understanding of their experience and suggestions for improvement. A similar survey will be carried out if the participant decides to terminate their participation earlier than study completion. See Multimedia Appendix 1 for the study timeline.

## Intervention

The intervention has been modeled on the DPP and adapted for men with PCa. The goals of the intervention are to help participants (1) achieve and maintain 7% weight loss from their starting weight (if participant body mass index [BMI] is >25) and (2) achieve and maintain 150 minutes of moderate intensity physical activity weekly. If participant BMI is <25 or if they are already engaging in 150 minutes of moderate intensity physical activity weekly, the goal will be to maintain that for the duration of the trial. The 16-week curriculum covering nutrition, physical activity, as well as supportive strategies to promote and maintain behavior modification was designed to help the participants achieve these goals [7]. Topics covered during the weekly sessions are listed in Figure 1. The curriculum will be taught by an experienced health coach trained by a DPP principal investigator and master trainer. After completion of the curriculum-based intervention, participants will be followed for 8 weeks. During this time, participants will receive weekly calls from the health coach aimed at maintaining motivation and problem solving as well as behavioral goal maintenance. The fundamental components of the intervention are based on social cognitive theory, the theory of planned behavior, and the transtheoretical model [23].

**Figure 1.** Intervention details.

| Session Date | Session Title |
| --- | --- |
| Week 1 _____ | Welcome to CLIPP ! |
| Week 2 _____ | Be a Fat and Calorie Detective |
| Week 3 _____ | Reducing Fat and Calories |
| Week 4 _____ | Healthy Eating |
| Week 5 _____ | Move Those Muscles |
| Week 6 _____ | Being Active: A Way of Life |
| Week 7 _____ | Tip the Calorie Balance |
| Week 8 _____ | Take Charge of What's Around You |
| Week 9 _____ | Problem Solving |
| Week 10 _____ | Four Keys to Healthy Eating Out |
| Week 11 _____ | Talk Back to Negative Thoughts |
| Week 12 _____ | The Slippery Slope of Lifestyle Change |
| Week 13 _____ | Jump Start Your Activity Plan |
| Week 14 _____ | Make Social Cues Work *for* You |
| Week 15 _____ | You Can Manage Stress |
| Week 16 _____ | Ways to Stay Motivated |

## Outcome Measures

### Feasibility Measures

Aim 1 of this study is to determine feasibility and hence the outcome measures for this aim will be recruitment, retention, and maintaining protocol adherence by the participants. The recruitment goal is set at 30 participants recruited over a 6-month period. The retention goal is set at 80%, and the adherence goal is set at 75% participation. If 80% (24/30) of participants complete the trial, the retention goal for this trial will be achieved. If participants attend 75% of the intervention delivery visits (in-person and phone combined), they will be considered adherent to the protocol.

### Efficacy Measures

For Aim 2, anthropometric measures (ie, height in inches, weight in pounds, waist and hip circumference in inches) and blood pressure (ie, systolic and diastolic mm of hg) will be carried out by the same, trained study personnel for all participants at all visits, using established protocols. This will ensure consistency between measurements and reduction in error. Serum samples for metabolic markers (ie, fasting glucose, hemoglobin A1C, lipid panel) will be collected and sent to a certified clinical laboratory. We will determine QoL using standardized and validated questionnaires. The Patient Reported Outcomes Measurement Information System (PROMIS) global physical and mental health scale will be used to determine the overall quality of life, whereas the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) will be used to assess disease-specific QoL. Preliminary efficacy will be established if the intervention results in a significant decrease in body weight, body fat, and metabolic indices as well as improvement in general and disease-specific QoL over the course of the trial (24 weeks). For Aim 3, serum collected at baseline, 12 weeks, and 24 weeks will be processed for markers of inflammation (ie, Interleukin-6, Interleukin 1-beta, Interleukin-8, stromal cell derived factor 1-alpha, and basic fibroblast growth factor) and angiogenesis (ie, vascular endothelial growth factor and plasma placental growth factor) using enzyme linked immunosorbent assay (ELISA). Kits will be purchased from Meso Scale Discovery (Rockville, MD) and R&D Systems (Minneapolis, MN). Prior literature demonstrates changes in these markers due to ADT [4], hence, the reason for choosing these markers.

### Ancillary Measures

In addition to the outcome measures mentioned above, ancillary measures will also be collected that will be used for correlative analyses in the future. Other ancillary measures will consist of Pittsburgh Sleep Quality Index to assess sleep quality, Arizona Food Frequency Questionnaire to assess food patterns, DXA scans for body composition assessment, and urine samples. Questionnaires and urine samples will be collected at baseline, 12 weeks, and 24 weeks and stored for future analyses. DXA scans will be conducted at baseline and end of study. Extra serum samples will also be stored in -80°Celsius freezers for future use. The samples will be housed in the central freezer

facility of the University of Arizona Cancer Center, which is monitored through a 24-hour alarm system.

## Statistical Considerations

### Statistical Analysis

The primary aim of this study is to determine feasibility of conducting a lifestyle modification intervention in a population of men with prostate cancer on ADT. This will be determined by calculating the study initiation rate, retention rate, and adherence rate. The study initiation rate will be calculated by dividing the total number of subjects that passed screening by the number started in the study after appropriate informed consent procedures. Retention rate will be calculated by dividing the total number of participants initiated by total number of participants in the study at 12 and 24 weeks. Retention goal for this trial is 80%, and hence participation 24 subjects in the trial at 12 and 24 weeks will satisfy this goal. The adherence rate hypothesized for this study is 75%. Participants will be determined to be adherent if they attend 75% intervention sessions (in-person and telephone intervention sessions combined). The overall adherence and retention rates and the associated 95% confidence intervals will be reported at 12 and 24 weeks. The secondary aim of this project to detect the effect of lifestyle modification on cardiometabolic risk factors and QoL. The tertiary aim of this project is to determine the effect of lifestyle modification on markers of inflammation and angiogenesis. Baseline characteristics will be described using mean and standard deviation for continuous variables and frequency and the associated proportions for categorical variables. Each outcome, for the secondary and tertiary aims, will be measured at 3 time points (ie, baseline, 12 weeks, and 24 weeks). For each outcome, two-sided 95% confidence intervals will be constructed for changes from baseline at both 12 and 24 weeks. In addition, a linear mixed-effects models will be fitted to explore the trajectory of changes overtime. If necessary, baseline value of the marker of interest (eg, cardiometabolic markers and QoL for secondary aim and inflammatory and angiogenic markers for the tertiary aim), age, race, serum prostate-specific antigen (PSA), and Gleason score will be adjusted for in the mixed-effects models. The changes in each of the outcomes over time will allow us to evaluate whether lifestyle modification can improve cardiometabolic risk and QoL (secondary aim) as well as inflammation and angiogenesis (tertiary aim). Analysis will be carried out using intent-to-treat (all participants) and modified intent-to-treat (restricting the analyses to participants who were adherent) approaches in order to determine if study adherence plays a role in mediating the relationship between lifestyle modification and outcome variables. Exit surveys will be carried out at the end of the study or if the participant decides to drop out of the study early. These qualitative and quantitate surveys will help understand participant satisfaction with the intervention and its delivery modalities, which will be helpful in planning the next phases of this project.

### Sample Size and Power

Based on a sample size of 30, the two-sided 95% confidence interval will not be wider than 0.373 standard deviations for the adherence rate and will not be wider than 0.374 for the retention rate at each follow-up visit. In addition, it will have a power of 80% to detect a change of 0.47 standard deviations from baseline over two follow-up visits for each of the markers investigated in the secondary and tertiary aims, assuming a within-subject correlation of 0.20 at a significance level of 5%.

## Results

Results from this arm open label clinical trial will allow us to determine the feasibility of conducting a DPP based intervention in men on ADT for PCa. Results are expected to be available by October 2019 and will inform the development of future trials in this population.

## Discussion

### Principal Considerations

The Comprehensive Lifestyle Improvement Project for Prostate Cancer (CLIPP) is designed to investigate the feasibility and early efficacy of a comprehensive multimodality intervention modeled after the DPP on cardiometabolic risk factors and QoL, as well as markers associated with inflammation and angiogenesis in men treated with androgen deprivation therapy for prostate cancer. This will be the first study in literature to investigate the utility of a DPP-based intervention on cardiometabolic risk factors and pathways associated with tumor progression in men with PCa on ADT. Although ADT improves disease-free survival and overall survival in men with PCa [1,2], its adverse effects lower the individual's QoL and contribute to higher mortality. If an effective intervention is identified to mitigate the adverse effects associated with ADT, it could potentially improve the individual's QoL as well as reduce their risk of treatment-related mortality. Results from the CLIPP study have the potential to provide data on the effect of the lifestyle modification intervention on QoL, cardiometabolic risk factors, as well as markers of inflammation and angiogenesis. Results for the primary aim are expected to be available by October 2019.

### Strengths and Limitations

The strengths of this study lie in its application of an evidence-based and effective multicomponent lifestyle modification intervention. This intervention has been successfully adapted for other disease types including breast cancer with favorable results. The standardized intervention with proven success in multiple disease settings, including cancer, sets this study apart from other comparable studies in current literature. The limitations of this study include its non-randomized treatment assignment and lack of a control group. Since this is a feasibility study, this is an accepted study design and a randomized study with an appropriate control arm would be the next step based on the study results.

### Conclusion

Findings from this study will address a critical gap in current literature by providing data regarding the feasibility of conducting a multimodality lifestyle modification intervention in men on ADT for prostate cancer and its impact on cardiometabolic risk factors, quality of life, as well as markers

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associated with inflammation and angiogenesis. These data are critical in developing future clinical trials in this group of patients. Additionally, the findings hold potential to open new avenues of research such as the impact of lifestyle modification on prostate cancer progression.

## Acknowledgments

## Authors' Contributions

All authors contributed to project design and development and manuscript preparation. AA is responsible for the project concept, and AA and CHH for statistical design and analysis.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Study timeline.

[DOCX File, 14KB - resprot_v8i2e12579_app1.docx ]

## Multimedia Appendix 2

Peer-review report.

[PDF File (Adobe PDF File), 42KB - resprot_v8i2e12579_app2.pdf ]

## Multimedia Appendix 3

Peer-review report.

[PDF File (Adobe PDF File), 37KB - resprot_v8i2e12579_app3.pdf ]

## References

1. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997 Jul 31;337(5):295-300. [doi: 10.1056/NEJM199707313370502] [Medline: 9233866]
2. D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004 Aug 18;292(7):821-827. [doi: 10.1001/jama.292.7.821] [Medline: 15315996]
3. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 2015 Sep;68(3):386-396 [FREE Full text] [doi: 10.1016/j.eururo.2014.11.039] [Medline: 25484142]
4. Saylor PJ, Kozak KR, Smith MR, Ancukiewicz MA, Efstathiou JA, Zietman AL, et al. Changes in biomarkers of inflammation and angiogenesis during androgen deprivation therapy for prostate cancer. Oncologist 2012;17(2):212-219 [FREE Full text] [doi: 10.1634/theoncologist.2011-0321] [Medline: 22302227]
5. Alibhai SMH, Breunis H, Timilshina N, Johnston C, Tomlinson G, Tannock I, et al. Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. J Clin Oncol 2010 Dec 01;28(34):5038-5045. [doi: 10.1200/JCO.2010.29.8091] [Medline: 21041715]
6. Cheung AS, de Rooy C, Hoermann R, Lim Joon D, Zajac JD, Grossmann M. Quality of life decrements in men with prostate cancer undergoing androgen deprivation therapy. Clin Endocrinol (Oxf) 2017 Mar;86(3):388-394. [doi: 10.1111/cen.13249] [Medline: 27696495]
7. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 07;346(6):393-403 [FREE Full text] [doi: 10.1056/NEJMoa012512] [Medline: 11832527]

8. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009 Nov 14;374(9702):1677-1686 [FREE Full text] [doi: 10.1016/S0140-6736(09)61457-4] [Medline: 19878986]

9. Diabetes Prevention Program Outcomes Study Research Group, Orchard TJ, Temprosa M, Barrett-Connor E, Fowler SE, Goldberg RB, et al. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. Diabet Med 2013 Jan;30(1):46-55 [FREE Full text] [doi: 10.1111/j.1464-5491.2012.03750.x] [Medline: 22812594]

10. Harrigan M, Cartmel B, Loftfield E, Sanft T, Chagpar AB, Zhou Y, et al. Randomized Trial Comparing Telephone Versus In-Person Weight Loss Counseling on Body Composition and Circulating Biomarkers in Women Treated for Breast Cancer: The Lifestyle, Exercise, and Nutrition (LEAN) Study. J Clin Oncol 2016 Mar 01;34(7):669-676 [FREE Full text] [doi: 10.1200/JCO.2015.61.6375] [Medline: 26598750]

11. Ligibel JA, Barry WT, Alfano C, Hershman DL, Irwin M, Neuhouser M, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. NPJ Breast Cancer 2017;3:37 [FREE Full text] [doi: 10.1038/s41523-017-0040-8] [Medline: 28948213]

12. Ying M, Zhao R, Jiang D, Gu S, Li M. Lifestyle interventions to alleviate side effects on prostate cancer patients receiving androgen deprivation therapy: a meta-analysis. Jpn J Clin Oncol 2018 Sep 01;48(9):827-834. [doi: 10.1093/jjco/hyy101] [Medline: 30053039]

13. Focht BC, Lucas AR, Grainger E, Simpson C, Fairman CM, Thomas-Ahner JM, et al. Effects of a Group-Mediated Exercise and Dietary Intervention in the Treatment of Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: Results From the IDEA-P Trial. Ann Behav Med 2018 Apr 19;52(5):412-428. [doi: 10.1093/abm/kax002] [Medline: 29684136]

14. Keto CJ, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, et al. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. BJU Int 2012 Aug;110(4):492-498 [FREE Full text] [doi: 10.1111/j.1464-410X.2011.10754.x] [Medline: 22094083]

15. Yang L, Drake BF, Colditz GA. Obesity and Other Cancers. J Clin Oncol 2016 Dec 10;34(35):4231-4237. [doi: 10.1200/JCO.2016.68.4837] [Medline: 27903157]

16. American Institute of Cancer Research. Diet, Nutrition, Physical Activity, and Prostate Cancer: Continuous Update Project. In: Diet, Nutrition, Physical Activity and Cancer: A Global Perspective Expert Report 2018. Washington, DC: American Institute of Cancer Research; 2018.

17. Burke AJ, Garrido P, Johnson C, Sullivan FJ, Glynn SA. Inflammation and Nitrosative Stress Effects in Ovarian and Prostate Pathology and Carcinogenesis. Antioxid Redox Signal 2017 Dec 20;26(18):1078-1090. [doi: 10.1089/ars.2017.7004] [Medline: 28326819]

18. Eisermann K, Fraizer G. The Androgen Receptor and VEGF: Mechanisms of Androgen-Regulated Angiogenesis in Prostate Cancer. Cancers (Basel) 2017 Apr 10;9(4) [FREE Full text] [doi: 10.3390/cancers9040032] [Medline: 28394264]

19. Miyata Y, Sakai H. Reconsideration of the clinical and histopathological significance of angiogenesis in prostate cancer: Usefulness and limitations of microvessel density measurement. Int J Urol 2015 Sep;22(9):806-815 [FREE Full text] [doi: 10.1111/iju.12840] [Medline: 26153072]

20. Stark T, Livas L, Kyprianou N. Inflammation in prostate cancer progression and therapeutic targeting. Transl Androl Urol 2015 Aug;4(4):455-463 [FREE Full text] [doi: 10.3978/j.issn.2223-4683.2015.04.12] [Medline: 26816843]

21. Tourinho-Barbosa RR, de la Rosette J, Sanchez-Salas R. Prostate cancer multifocality, the index lesion, and the microenvironment. Curr Opin Urol 2018 Nov;28(6):499-505. [doi: 10.1097/MOU.0000000000000537] [Medline: 30138121]

22. Aldama JA, Armin J, Algotar AM. Engaging key stakeholders to understand prostate cancer survivor preferences forperceived barriers to a lifestyle modification intervention. 2018 Presented at: American Society for Preventive Oncology; March 11-13, 2018; New York, NY.

23. Sepah SC, Jiang L, Ellis RJ, McDermott K, Peters AL. Engagement and outcomes in a digital Diabetes Prevention Program: 3-year update. BMJ Open Diabetes Res Care 2017;5(1):e000422 [FREE Full text] [doi: 10.1136/bmjdrc-2017-000422] [Medline: 28948027]

## Abbreviations

**ADT:** androgen deprivation therapy
**CLIPP:** Comprehensive Lifestyle Improvement Program for Prostate Cancer
**DPP:** Diabetes Prevention Program
**ELISA:** enzyme linked immunosorbent assay
**EPIC-26:** Expanded Prostate Cancer Index Composite-Short Form
**GnRH:** gonadotropin-releasing hormone
**IDEA-P:** Individualized Diet and Exercise Adherence-Pilot
**LEAN:** Lifestyle Exercise And Nutrition study
**PCa:** prostate cancer

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**PROMIS:** Patient Reported Outcomes Measurement Information System
**QoL:** quality of life
**RR:** relative risk
**UACC:** University of Arizona Cancer Center

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Protocol

# Pilot Testing the Feasibility of a Game Intervention Aimed at Improving Help Seeking and Coping Among Sexual and Gender Minority Youth: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Sexual and gender minority youth (SGMY; eg, lesbian, gay, bisexual, and transgender youth) experience myriad substance use and mental health disparities compared with their cisgender (nontransgender) heterosexual peers. Despite much research showing these disparities are driven by experiences of bullying and cyberbullying victimization, few interventions have aimed to improve the health of bullied SGMY. One possible way to improve the health of bullied SGMY is via a Web-accessible game intervention. Nevertheless, little research has examined the feasibility of using a Web-accessible game intervention with SGMY.

**Objective:** This study aimed to describe the protocol for a randomized controlled trial (RCT) pilot, testing the feasibility and limited efficacy of a game-based intervention for increasing help-seeking–related knowledge, intentions, self-efficacy, behaviors, productive coping skills use, and coping flexibility and reducing health risk factors and behaviors among SGMY.

**Methods:** We enrolled 240 SGMY aged 14 to 18 years residing in the United States into a 2-arm prospective RCT. The intervention is a theory-based, community-informed, computer-based, role playing game with 3 primary components: encouraging help-seeking behaviors, encouraging use of productive coping, and raising awareness of Web-based resources. SGMY randomized to both the intervention and control conditions will receive a list of SGMY-inclusive resources, covering a variety of health-related topics. Control condition participants received only the list of resources. Notably, all study procedures are conducted via the internet. We conveniently sampled SGMY using Web-based advertisements. Study assessments occur at enrollment, 1 month after enrollment, and 2 months after enrollment. The primary outcomes of this feasibility study include implementation procedures, game demand, and game acceptability. Secondary outcomes include help-seeking intentions, self-efficacy, and behaviors; productive coping strategies and coping flexibility; and knowledge and use of Web-based resources. Tertiary outcomes include bullying and cyberbullying victimization, loneliness, mental health issues, substance use, and internalized sexual and gender minority stigma.

**Results:** From April to July 2018, 240 participants were enrolled and randomized. Half of the enrolled participants (n=120) were randomized into the intervention condition and half (n=120) into the control condition. At baseline, 52.1% (125/240) of the participants identified as gay or lesbian, 26.7% (64/240) as bisexual, 24.2% (58/240) as queer, and 11.7% (28/240) as another nonheterosexual identity. Nearly half (113/240) of participants were a gender minority: 36.7% (88/240) were cisgender boys,

and 16.3% (39/240) were cisgender girls. There were no differences in demographic characteristics between intervention and control condition participants.

**Conclusions:** Web-accessible game interventions overcome common impediments of face-to-face interventions and present a unique opportunity to reach SGMY and improve their health. This trial will provide data on feasibility and limited efficacy that can inform future Web-based studies and a larger RCT aimed at improving health equity for SGMY.

**Trial Registration:** ClinicalTrials.gov NCT03501264; https://clinicaltrials.gov/ct2/show/NCT03501264 (Archived by WebCite at http://www.webcitation.org/72HpafarW)

**International Registered Report Identifier (IRRID):** DERR1-10.2196/12164

## Introduction

### Background

Sexual minority youth (eg, lesbian, gay, bisexual, or queer youth) and gender minority youth (ie, youth who identify as a gender different from their sex assigned at birth) experience myriad substance use and mental health disparities [1-27]. In particular, sexual orientation–related disparities have been known for over 20 years [1]: sexual minority youth, compared with heterosexual youth, have approximately 176% higher odds of cigarette use, 155% higher alcohol use, 34% higher heavy alcohol use (eg, binge drinking), and 56% higher marijuana use [2]. Currently, many of these sexual orientation–related disparities appear to be growing larger [3,4]. Similarly, compared with cisgender (ie, nontransgender) youth, gender minority youth have significantly higher use of cigarettes, alcohol, and marijuana [5,27]. These sexual and gender minority youth (SGMY) disparities are also present for novel substances, such as electronic cigarette use [5]. Regarding mental health disparities, SGMY have significantly higher anxiety, depression, and suicidality [20-27]. Meta-analyses show that sexual minority youth, compared with heterosexual youth, have 96% higher odds of having suicidal thoughts, 120% higher odds of making suicide plans, and 218% higher odds of making suicide attempts [20]. Altogether, these substantial and persistent health disparities make SGMY a priority population for interventions that attempt to reduce health inequities.

SGMY also experience disparities in bullying and cyberbullying victimization compared with their cisgender heterosexual peers [5,27-33]. For example, according to the 2015 Youth Risk Behavior Survey (YRBS), gay, lesbian, and bisexual adolescents (compared with heterosexuals) had nearly doubled the prevalence of bullying and cyberbullying victimization [33]. Importantly, research shows that these bullying disparities also contribute to SGMY disparities in substance use and mental health issues [5,13,27,34,35]. Therefore, interventions that help bullied SGMY and reduce bullying victimization may, in turn, reduce substance use and mental health disparities.

In addition to this greater prevalence of bullying, SGMY have unique factors that also contribute to health disparities. When SGMY are bullied, in addition to the typical fears of disclosing their bullying victimization experiences to others, they often fear having to disclose their sexual and gender minority (SGM) status to adults, thereby putting them at risk for further discrimination and harassment [36,37], likely preventing them from reaching out for help. Even when SGMY consider suicide, large proportions of them do not seek help [38], and sexual minority youth have more trouble than heterosexuals with identifying people to talk to about their emotional worries [39]. Moreover, compared with heterosexuals, sexual minority youth are more likely to use nonproductive coping strategies (eg, self-blaming, giving up, ignoring problems, and worrying) to manage the stressors in their lives [40,41], which likely exacerbates their health. Thus, interventions that aim to improve help-seeking behaviors and productive coping strategies (eg, solving problems, seeking relaxing diversions, and being physically active) among bullied SGMY may substantially reduce substance use and mental health disparities.

Notably, few interventions have been rigorously tested to examine whether they are efficacious in reducing substance use and mental health disparities among SGMY [42]. Moreover, 1 possible way to improve the health of bullied SGMY is via a Web-accessible (ie, downloadable via the internet) game intervention. Game interventions can be easily accessible through the internet, thereby providing an effective way to reach large numbers of SGMY, including SGMY living in rural areas and high structural stigma locations (ie, areas with less SGM-inclusive policies, institutions, and attitudes). Furthermore, Web-based game interventions are advantageous because some SGMY may be *out* to only a few people offline, making recruitment and attendance in face-to-face interventions for SGMY quite challenging [43,44]. Web-accessible interventions may be accessed by those who are insufficiently supported in offline programs [45-47]. In addition, Web-accessible gaming programs about sex [48,49], mental health [50], alcohol use [51-55], smoking [56-58], and asthma [59-62] are effective for youth in general. The Web-based environment is also relatively safe for LGB youth to gain coping skills [63,64]. Other advantages of Web-accessible interventions are increased fidelity and cost-effectiveness [65-71]. Overall, Web-accessible game interventions overcome common impediments of face-to-face interventions and present a unique opportunity to reach SGMY to improve their health. Little research, with few exceptions [72,73], has examined the feasibility of using a Web-accessible game intervention with SGMY populations.

Therefore, pilot testing the feasibility of such a study is critical for successfully conducting a large-scale intervention. Feasibility comprises a wide range of topics [74], such as the testing of implementation procedures—how well the study was implemented as planned; intervention demand—the actual use of intervention among participants; intervention acceptability—how the participants react to the intervention; intervention integration—how well the game fits into the participants' lives; intervention adaptation and expansion—the changes necessary for future iterations of the intervention and translation into new environments; and finally, limited efficacy testing—can be used to get estimates for variability and precision to power a larger randomized controlled trial (RCT). To adequately address the multiple dimensions of feasibility related to a game-based intervention tailored to SGMY, a carefully planned pilot trial is needed.

## Study Aims

This paper describes the protocol for a pilot RCT assessing the feasibility and limited efficacy of the game-based intervention to increase help-seeking–related knowledge, intentions, self-efficacy and behaviors, productive coping skills use, and coping flexibility and reduce health risk factors and behaviors among SGMY. The primary, secondary, tertiary, and exploratory aims of the study are described below.

### Primary Aim

Our primary aim is to evaluate implementation procedures for the RCT of the game-based intervention as well as to determine the level of game demand and game acceptability. We hypothesize having high implementation fidelity, game demand, and game acceptability (see Table 1 in the Methods section for specific targets).

### Secondary Aim

Our secondary aim is to test the limited efficacy for the game in increasing the following short-term outcomes: help-seeking intentions, self-efficacy, and behaviors; productive coping strategies and coping flexibility; and knowledge and use of Web-based resources. We hypothesize that compared with the control participants, the intervention participants would have greater improvements in all short-term outcomes.

### Tertiary Aim

Our tertiary aim is to test the limited efficacy for the game in reducing long-term outcomes: bullying and cyberbullying victimization; loneliness; mental health issues (ie, stress, anxiety, depression, and suicidality); substance use; and internalized SGM stigma. We hypothesize that intervention participants, compared with control participants, will have greater decreases in all long-term outcomes.

### Exploratory Aim

We have built in an exploratory aim meant to better our understanding of participants' responses to the game and research procedures and how to improve both. This exploratory aim concerns implementation procedures, integration, and the adaptation and expansion of the game. Given the exploratory nature of this aim, we have no a priori hypotheses.

## Methods

### Study Design

The purpose of this research study is to pilot a 2-arm RCT of a game-based intervention to improve help-seeking behaviors and productive coping strategies to reduce substance use, victimization, and mental health issues among SGMY. The study is led by a team with expertise in SGMY research at the Center for LGBT Health Research in the University of Pittsburgh's Graduate School for Public Health, University of Pittsburgh (Principal Investigators: Friedman and Egan). We engage in team science by partnering with an expert in bullying research, help-seeking research, an interventionist, a biostatistician, a health and game researcher, and a professional game development company. The study is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health (R21HD083561) and is registered as a clinical trial (NCT03501264) [75].

### Study Population and Study Flow

All study procedures related to screening, consenting, surveying, and reminding are completed using REDCap, a free and secure Health Insurance Portability and Accountability Act-compliant website for managing Web-based surveys and databases. Study participant flow is depicted in Figure 1.

First, to determine eligibility, respondents completed a brief Web-based self-reported screening questionnaire before entering in this study. Respondents were eligible if they were English literate, lived in the United States of America, were aged between 14 to 18 years, had experienced bullying or cyberbullying victimization in the past year, had a sexual minority identity (ie, gay, lesbian, bisexual, or queer) or a gender minority identity (ie, considered themselves to be transgender or nonbinary), had a personal computer or Mac laptop or desktop computer where they could download games, and had an email address. Eligible respondents were then directed to a Web-based informed consent form. Participants voluntarily consented using a *click-to-consent* procedure. To protect participants from having to reveal their sexual or gender minority identities to their caregivers, thereby potentially putting them in harm's way, we received a waiver of parental consent [76]. This allowed participants to self-consent. Ineligible respondents were thanked for their time and no additional contact was made.

Once eligible respondents agreed to voluntarily participate in the study, they were emailed a link to the baseline (T1) survey to complete. The T1 survey contained 24 pages with a median of 8.5 items per page (mean 10.3; range 3-26). After completion of the T1 survey, the study team randomized participants to intervention or control conditions (full descriptions of conditions are provided in later sections). Immediately after randomization, participants in the intervention condition automatically received an email with a REDCap survey link containing information that guided participants through the procedures for downloading and installing the game intervention onto their desktop or laptop computers with Microsoft Windows or Apple Mac operating systems. Every 3 days thereafter, participants were automatically sent up to 5 email reminders to download the game. Moreover,

1 day after randomization, participants in both the intervention and control conditions were automatically sent a list of resources related to study outcomes.

The first follow-up (T2) survey was activated 4 weeks after T1 survey completion and remained open for 4 weeks. The T2 survey was similar to the T1 survey; however, participants in the intervention condition who self-reported having played the game also completed questions about their gaming experience. The T2 survey contained 26 pages with a median of 8.5 items per page (mean 11.4; range 3-47).

The final follow-up survey (T3) is activated 8 weeks after T1 survey completion and remains open for 8 weeks. The T3 survey is similar to the T1 survey; however, intervention condition participants who do not complete the gaming experience questions at T2 but self-report having played the game in the T3 survey will be asked questions about their gaming experience at T3. The T3 survey contained 26 pages with a median of 8.5 items per page (mean 11.4; range 3-47).

For each survey, up to 5 email reminders to complete surveys are automatically emailed to participants every 4 days. While completing each survey, participants were able to change their answers by clicking a *back* button. The following incentives are given after the completion of each survey: US $10 for T1; US $25 for T2; and US $50 for T3. At the end of each survey, participants select if they wanted a gift card to Apple iTunes or Google Play.

## Recruitment

Participants were conveniently sampled and recruited throughout the United States using website advertisements posted on social media platforms. This passive approach allowed SGMY from multiple geographic locations (eg, rural and urban, and East and West) to enroll in the study without overextending our limited resources. Facebook was our primary recruitment site. Facebook is an appropriate recruitment platform because it is highly utilized by adolescents; approximately 71% of teens use Facebook [77]. We created a formal side-bar Facebook ad (in-line ads were not used). We also recruited participants from Instagram using the same advertisements. We also recruited participants from SGM-related Web-based gaming groups, such as Geeks OUT, Gay Geeks (Facebook group), GaymerX (Facebook group), Transmission Gaming, and Reddit Gaymer forums. We advertised via Pitt+Me, a community hosted by the University of Pittsburgh comprising patients, volunteers, and researchers working together as partners in research and clinical trials to advance health care. Finally, we advertised on a dedicated Facebook page for the study. Only study team members were able to post comments on this page. An individual who was interested in participating clicked on the advertisement and was directed to the Web-based screening questionnaire. To ensure representation of both sexual and gender minorities, enrollment was monitored weekly. Specific ads were created and used to target underrepresented groups. Depending on the prior week's enrollment numbers, we tailored which ads were used for the upcoming week.

## Randomization

We used permuted block allocation (using blocks of several sizes) to randomize individual participants to the intervention or control conditions. The permuted blocks were created using the ralloc package for Stata. Randomization was performed in REDCap using the Randomization Module.
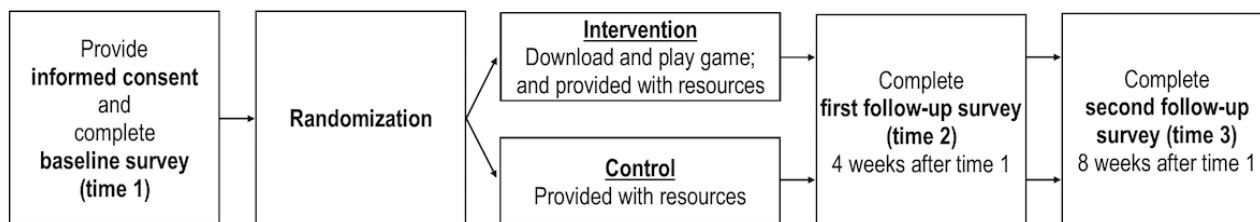
## Control Materials

All participants randomized into the control condition received a list of national SGM-inclusive resources. This list included general lesbian, gay, bisexual, transgender, and queer (LGBTQ) resources (eg, GLAAD resource list), LGBTQ bullying resources (eg, The Trevor Project), general bullying victimization resources (eg, StopBullying.gov), child abuse resources (eg, Child Abuse Resource Center), dating violence resources (eg, National Domestic Violence Hotline), suicide and mental health resources (National Suicide Prevention Lifeline), substance use resources (eg, National Institute of Drug Abuse for Teens), LGBTQ homelessness (eg, True Colors Fund), and LGBTQ emergency hotlines (eg, Gay, Lesbian, Bisexual, and Transgender National Help Center Hotline). These materials were delivered via email the day after participants were randomized to the control condition. In addition, after completion of the final T3 survey, control participants were offered a free download of the intervention game. No additional follow-up was initiated to assess their game use, game satisfaction, or changes in outcomes.

## Intervention Materials

Participants assigned to the intervention condition received a list of SGM-inclusive resources (the same as the control condition materials) and the game intervention. After randomization, intervention condition participants received an email with a link and instructions on how to download the game. Participants were asked to download the game to their computer to play it. The game intervention was based on empirical interviews with SGMY about their gaming preferences, undergirded by etiologic and behavioral change theories and built in collaboration with expert educational game developers.

### Gaming Preferences of Sexual and Gender Minority Youth

Before developing the game, we conducted one-on-one, in-depth interviews with 20 SGMY about their gaming preferences (publication of these results is currently underway). Most SGMY enjoyed playing action-oriented games, and when asked what they liked about their favorite games, the most common response concerned the ability to personalize characters. Therefore, in the game, we incorporated selection of pronouns (Figure 2) and character customization, including skin color, hair, body type, and clothing (Figure 3). SGMY liked engaging, unique storylines, as well as challenging (but not too challenging) mini objectives and missions. Having a multiplayer aspect of the game that requires teamwork and interaction with others was also mentioned. We also incorporated these elements into the game.

**Figure 1.** 2-Arm randomized controlled trial design and data collection schedule.



**Figure 2.** Game intervention name and pronoun selection.



**Figure 3.** Game intervention character customization.

## Theoretical Underpinnings

The conceptual model of the game intervention (Figure 4) is based on 3 theories that inform the etiology and behavioral change strategies of our short-term and long-term outcomes. First, social cognitive theory [78,79] suggests that behavior change (eg, help-seeking behaviors) is facilitated by developing self-efficacy and skills. Self-efficacy and social skills can be achieved through behavioral rehearsal, witnessing outcomes of their choices, and feedback [80-82]. Second, stress and coping theory [83] suggests that specific types of appraisals predict different coping strategies. With bullying, youth who blame themselves, perceive little control, and view the situation primarily as a threat as opposed to a challenge are likely to engage in nonproductive coping [84-87]. On the other hand, identification of the problem, direct problem solving, and help seeking constitutes productive coping [88]. Third, the social and emotional learning framework [89] identifies 4 main

competencies to promote positive health outcomes: awareness of self and others, responsible decision making, positive attitudes and values, and social interaction skills. We considered each of these theories during the process of developing the core game mechanics of the player experience.

Elements of these theories are embedded in the game in unique ways. First, the game encourages help-seeking behaviors by having players create a team with other nonplayable characters and to pair a lonely nonplayable character with an appropriate mentor (Figure 5). Second, the game encourages use of productive coping strategies through active listening and helping a nonplayable character overcome anger in a healthy way (Figure 6). Third, the game raises awareness of Web-based resources through collecting pages from a virtual notebook that contain information about external resources and bullying information (Figures 7 and 8).

**Figure 4.** Game intervention conceptual model.
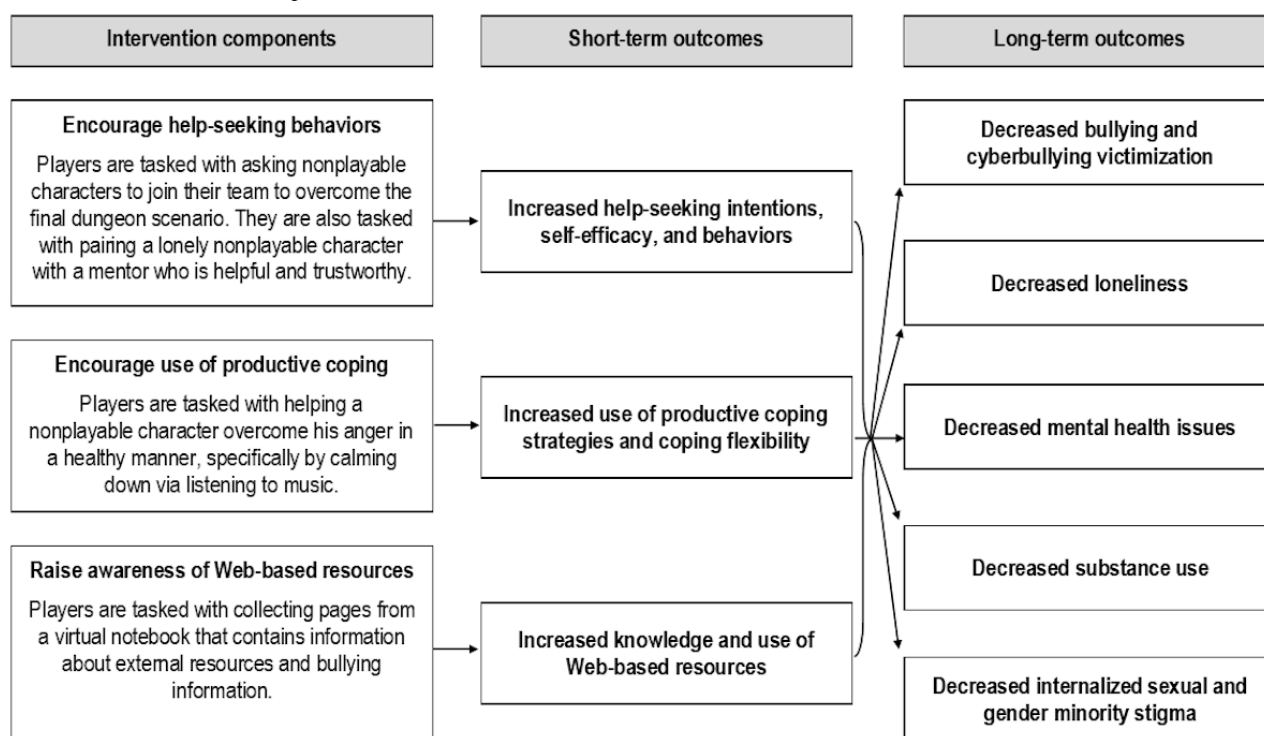
**Figure 5.** Interaction with a nonplayable character who is lonely.



**Figure 6.** Interaction with a nonplayable character who is angry.

**Figure 7.** Virtual notebook page about bullying.
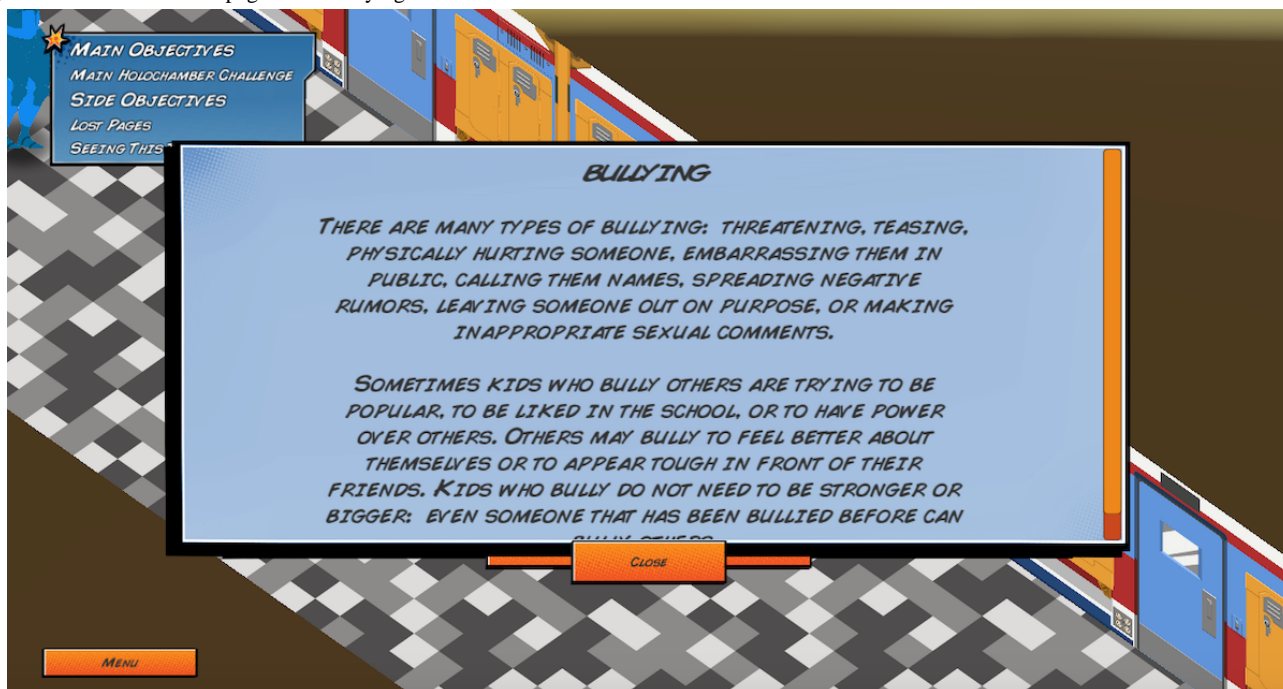


**Figure 8.** Virtual notebook page about the importance of making contact after being bullied.
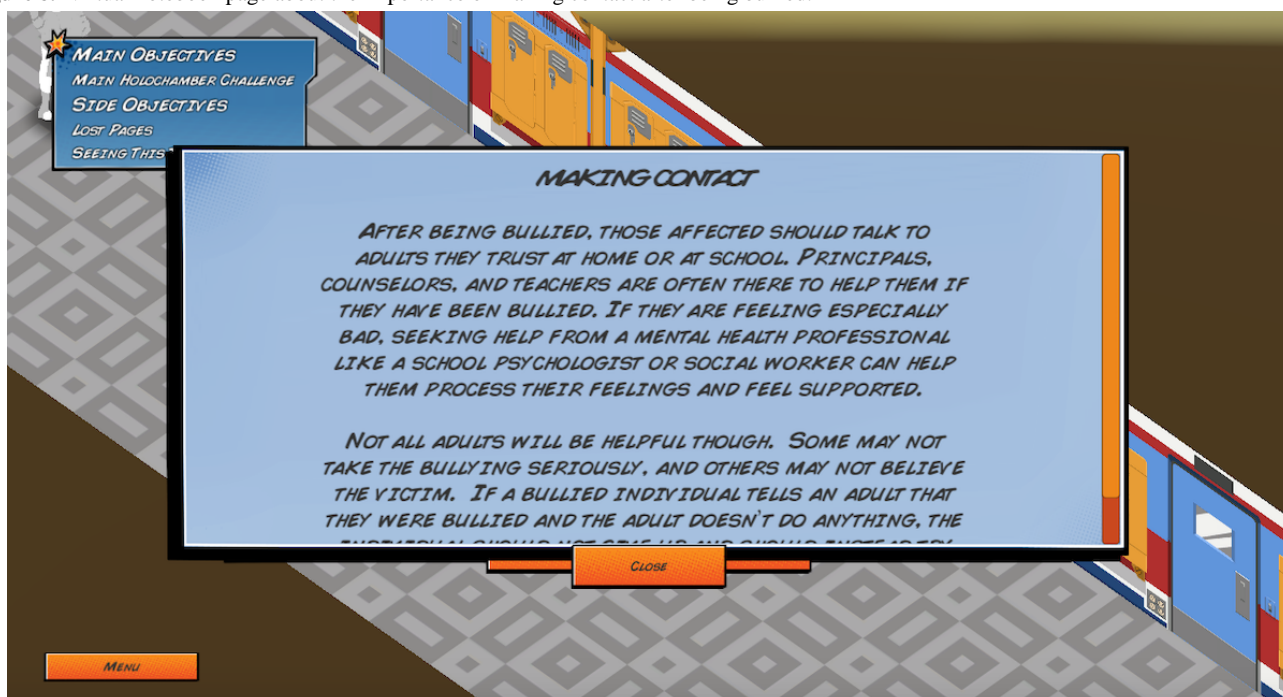


### Game Development

The game was developed in collaboration with Schell Games, an education and entertainment game development company located in Pittsburgh, Pennsylvania, United States. The intervention game is a role-playing game inspired by Japanese role-playing games, which typically involve exploring a space, talking to nonplayable characters, and fighting enemies through turn-based battles. The game runs standalone on desktops and laptops with Windows or Mac operating systems. Before implementation, we user-tested the intervention using think-aloud interviews with 3 SGMY, who found technical bugs

and recommended password protection. Prior research shows that user testing with 3 participants results in finding at least 60% of major usability problems [90]. Schell Games revised the game accordingly before the implementation of the RCT.

### Game Play

In the game, the player takes on the role of a Singular, a superhuman individual with special gifts, who is located in a school. The player is told that because of their uniqueness, Singulars face prejudice, often driven by fear and misunderstanding. After customizing their character, the player is tasked with finding a team to help them complete their final

mission, which is to become a world-class superhero by defeating the robots in the Holochamber Challenge. The player then explores the school, talking to potential peers (ie, nonplayable characters) who can join their team. Some peers deal with problems related to bullying, confidence issues, and anger, which prevent them from performing properly or from wanting to join the player's team. The player's mini objectives are to do the following for each of their peers: (1) best identify the nonplayable characters' problems, (2) find the best individuals or resources to help the nonplayable characters, and (3) help the nonplayable characters properly communicate or utilize their newfound resources. If the player is successful and finds the best way to help the nonplayable characters, then the nonplayable characters will join their team or help them by giving them an item or ability that will help them achieve success in the final Holochamber Challenge (Figure 9). After the player finishes the Holochamber Challenge, the events that took place are evaluated. For every nonplayable character that is successfully helped, the player is given a positive ending; for example, "Thanks to Invisibella's mentoring, Violet Phantom eventually felt comfortable to reveal herself as a Singular. Despite past events, a majority of her other friends and family were supportive. Knowing she was not alone and had support helped her no longer feel afraid." For every nonplayable character that was not successfully helped, the player is given a negative ending; for example, "Gigaton didn't learn to control his anger in this round. One day he snapped and turned on those bullying him. Though no one was seriously injured, the outburst resulted in Gigaton getting in trouble with the Principal." The players are then encouraged to replay the game and given hints to help them receive positive endings. Each player can unlimitedly replay the game.

## Data Collection

We are collecting data in 2 distinct ways. First, we use self-administered surveys via REDCap, where participants completed surveys on their computer, tablet, or phone. Participants complete surveys at T1, T2, and T3 (see the section Study Population and Study Flow for more details). Surveys were created based on the Checklist for Reporting Results of Internet E-Surveys [91]. Second, we collect game play data from participants in the intervention condition. These game play data are transferred via a secure file-transfer-protocol system. Text files containing milestones achieved, time played, and player choices are automatically sent to a secure server housed at the University of Pittsburgh. Participants' game play data are tracked using a unique identification number that does not rely on identifiable information (eg, IP addresses).

## Outcomes

### Primary Outcomes

To answer our primary aim, we will assess the following primary feasibility outcomes: success of the implementation procedures used in our RCT, game demand, and game acceptability. Table 1 details our primary outcomes, assessments, and investigator-generated hypotheses.

Success of our implementation procedures are assessed using a variety of measures. We hypothesize the following: 240 participants will enroll in our trial and complete the first survey, greater than or equal to 80% of eligible participants will consent to participate in the study, 120 participants will be randomized to the intervention condition and 120 to the control condition, greater than or equal to 80% of enrolled participants will complete the T2 survey, greater than or equal to 80% of enrolled participants will complete the T3 survey, and greater than or equal to 75% of participants will complete all surveys. Testing the feasibility of our implementation procedures is essential to inform the design of our future larger-scale RCT.

**Figure 9.** The player's final mission: defeat the Holochamber Challenge with their teammates.

**Table 1.** Primary outcomes, assessments, and hypotheses.

| Primary outcome | Assessment | Hypothesis |
| --- | --- | --- |
| **Implementation procedures** | | |
| Study population | Measured as the total number of participants who were consented and who completed T1[a] | 240 participants |
| Participation rate | Measured as the total number of people who agreed to participate in the study divided by the total number of people who were eligible to participate in the study | ≥80% |
| Number of randomized participants | Measured as the total number of participants randomized | 240 participants |
| Randomization success | Assessed by comparing intervention and control conditions across all demographic and potential confounding variables at baseline | No differences between intervention and control condition at baseline |
| Retention rate for T2[b] | Measured as the total number of participants who completed T2 divided by the total number of participants enrolled in the study | ≥80% |
| Retention rate for T3[c] | Measured as the total number of participants who completed T3 divided by total number of participants enrolled in the study | ≥80% |
| Retention rate in T2 and T3 | Measured as the total number of participants that completed both T2 and T3 surveys divided by the total number of participants enrolled in the study | ≥75% |
| **Game demand** | | |
| Game download | Assessed on T2 and T3 surveys: did you download the game titled "Singularities"?—Yes; No; Unsure | ≥80% selected "Yes" |
| Any game play | Assessed on T2 and T3 surveys: did you play the game titled "Singularities"?—Yes; No; Unsure | ≥80% selected "Yes" |
| Any game play | Total number people who played the game based on game play data from the secure file-transfer-protocol system divided by total number of participants randomized to intervention condition | ≥80% played |
| Total time of game play | Assessed on T2 and T3 surveys: in the past month, about how long did you play the game "Singularities"?—I did not play the game; Less than 1 hour; 1 hour; 2 hours; 3 hours; 4 hours; 5 hours; 6 hours; 7 hours; 8 hours or more | ≥75% selected 1 hour or greater |
| Total time of game play | The number of hours the game was played based on game play data from the secure file-transfer-protocol system | ≥75% played 1 hour or greater |
| **Game acceptability** | | |
| Gaming experience [92] | Assessed on T2 and T3 surveys: response options used a 5-point Likert scale (range: 0-4)—Not at all, Slightly, Moderately, Fairly, Extremely; Question stem was "Please indicate how you felt while playing the game for each of the questions below"; *Competence subscale* —I felt skillful, I felt competent, I was good at it, I felt successful, I was fast at reaching the game's targets; *Sensory and imaginative immersion subscale* —I was interested in the game's story, it was aesthetically pleasing, I felt imaginative, I felt that I could explore things, I found it impressive, It felt like a rich experience; *Flow subscale* —I was fully occupied with the game, I forgot everything around me, I lost track of time, I was deeply concentrated in the game, I lost connection with the outside world; *Tension and annoyance subscale* (reverse coded)—I felt annoyed, I felt irritable, I felt frustrated; *Negative affect subscale* (reverse coded)—It gave me a bad mood, I thought about other things, I found it tiresome, I felt bored; *Positive affect subscale* —I felt content, I thought it was fun, I felt happy, I felt good, I enjoyed it | Mean scores ≥2 for each subscale separately |
| Desire to play game again | Assessed on T2 and T3 surveys: I would like to play this game again—Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree | ≥75% of intervention condition participants selected "Agree" or "Strongly Agree" |
| Likelihood to recommend game to friends | Assessed on T2 and T3 surveys: how likely would you be to recommend that your friends play this game?—Definitely; Very Probably; Probably; Possibly; Probably Not; Definitely Not | ≥75% of intervention condition participants selected "Definitely," "Very Probably," or "Probably" |

[a]T1: baseline.

[b]T2: first follow-up.

Game demand is assessed among the intervention condition participants in 2 ways, via downloading and playing the game. Download of the game is assessed via self-reported surveys (T2 and T3). We hypothesize ≥80% of intervention condition participants will download the game. Game play is assessed via self-reported surveys (T2 and T3) and game play data. We hypothesize ≥80% of intervention condition participants will play the game and ≥75% of intervention participants will play the game for 1 hour or greater.

Game acceptability among the intervention condition participants is assessed via self-reported surveys at T2 and T3. If participants reported playing the game, we ask about their overall impressions of the game using the Gaming Experience Questionnaire. The Gaming Experience Questionnaire is a multidimensional scale that assesses the following domains about the participants' feelings and thoughts during the game: competence, sensory and imaginative immersion, game flow, game tension and annoyance (reverse coded), negative affect (reverse coded), and positive affect. We hypothesize that the mean score for each subscale will be greater than 2, representing a moderately good gaming experience. In addition, we ask participants if they would be interested in playing the game again, and whether they would recommend the game to their friends. We hypothesize ≥75% of participants will "agree" or "strongly agree" that they would like to play the game again, and ≥75% would "definitely," "very probably," or "probably" recommend the game to their friends.

### Secondary Outcomes

To answer our secondary aim, we will measure the following short-term outcomes: help-seeking intentions, self-efficacy, and behaviors; productive coping strategy usage and coping flexibility; and knowledge and use of Web-based resources. All secondary outcomes are assessed via self-reported surveys at all time points. Table 2 details our secondary outcomes, items, response options, and coding procedures.

Help-seeking intentions are assessed using adapted version of the General Help Seeking Questionnaire [93]. In addition, 2 different sets of questions assess how likely participants are to seek help from a variety of sources about (1) emotional problems and (2) suicidal ideation. Help sources include a wide variety of people (eg, doctor and counselor) and places (eg, websites).

We adapted the original items by adding "Phone or text/chat help line (such as the National Suicide Prevention Lifeline or the Trevor Project)" and "teacher." We will create 2 separate overall mean scores for how likely participants are to reach out concerning (1) emotional problems and (2) suicidal ideation.

In addition, we will create a score for each help source individually. Higher mean scores indicate greater likelihood of seeking help from these sources.

Help-seeking self-efficacy is assessed using 2 subscales from Bandura's Multidimensional Scales of Perceived Self Efficacy [94,95]: the enlisting social resources subscale and the enlisting parental and community support subscale. Each subscale has 4 items, which are used to calculate an overall mean score measuring how well participants think they can get support from different sources (eg, "How well can you get a friend to help you when you have social problems" and "How well can you get your parents to take part in school activities").

Help-seeking behaviors are assessed using items adapted from the Help-Seeking Behaviors Scale [96]. We adapted the scale to include the wide variety of help sources used in the aforementioned help-seeking intention scales. Therefore, we created 8 different subscales (1 for each help source) assessed with 3 items each (eg, "In the past month, how often have you asked a teacher for help?"). Each subscale will be analyzed separately.

Coping skill usage is assessed using the Adolescent Coping Scale Second Edition Short Form [88]. This scale uses 18 items measuring 2 different dimensions: productive (problem solving) coping and nonproductive (passive avoidant) coping. We hypothesize that the game-based intervention (vs the control) will increase productive coping and decrease nonproductive coping.

Coping flexibility is assessed using the Coping Flexibility Scale [97], including 2 separate subscales: evaluation coping and adaptive coping. The evaluation coping subscale uses 5 items to assess how well a person monitors and evaluates coping outcomes (eg, "I am aware of how successful or unsuccessful my attempts to cope with stress have been."). The adaptive coping subscale uses 5 items to assess how well a person uses an alternative coping strategy to produce a desirable outcome (eg, "When a stressful situation has not improved, I try to think of other ways to cope with it"). Each subscale will be examined separately.

Knowledge and use of Web-based resources are measured using 2 different scales developed by the investigative team. We created a list of SGM-inclusive resources that match what was provided in the game-based intervention and control materials, such as the Trevor Project. Use of Web-based resources is measured for the past month. We will create 1 summary score for knowledge and 1 for use; each summary score adds together all "yes" response options.

**Table 2.** Secondary outcomes, items, response options, and coding procedures.

| Secondary outcome | Items | Response options | Coding procedure |
|---|---|---|---|
| **Help-seeking intentions, self-efficacy, and behaviors** | | | |
| Help-seeking intentions for personal or emotional problems, adapted from [93] | If you were having a personal or emotional problem, how likely is that you would seek help from the following people?—parent or guardian; other relative or family member; teacher; intimate partner (such as girlfriend or boyfriend); friend (someone not related to you); mental health professional (such as a psychologist, social worker, counselor); phone or text/chat help line (such as the National Suicide Prevention Lifeline or the Trevor Project); website help resources (such as StopBullying.gov); doctor or primary care provider; minister or religious leader (eg, priest, rabbi, chaplain); I would not seek help from anyone; I would seek help from another person/place not listed above | 7-point Likert scale, ranging from "extremely unlikely" (1) to "extremely likely" (7) | Mean score averaged across all items and for each item individually |
| Help-seeking intentions for suicidality, adapted from [93] | If you were experiencing suicidal thoughts, how likely is that you would seek help from the following people?—parent or guardian; other relative or family member; teacher; intimate partner (such as girlfriend or boyfriend); friend (someone not related to you); mental health professional (such as a psychologist, social worker, counselor); phone or text/chat help line (such as the National Suicide Prevention Lifeline or the Trevor Project); website help resources (such as StopBullying.gov); doctor or primary care provider; minister or religious leader (eg, priest, rabbi, and chaplain); I would not seek help from anyone; I would seek help from another person/place not listed above | 7-point Likert scale, ranging from "extremely unlikely" (1) to "extremely likely" (7) | Mean score averaged across all items and for each item individually |
| Help-seeking self-efficacy [94,95] | Please rate how certain you are that you can do each of the things described; *Enlisting social resources subscale* —how well can you get teachers to help you when you get stuck on schoolwork? how well can you get another student to help you when you get stuck on schoolwork? how well can you get adults to help you when you have social problems? how well can you get a friend to help you when you have social problems?; *Enlisting parental and community support subscale* —how much can you get your parent(s) to help you with a problem? how well can you get your brother(s) and sister(s) to help you with a problem? how well can you get your parents to take part in school activities? how well can you get people outside the school to take an interest in your school (community groups, churches)? | 7-point Likert scale, ranging from "not at all well" (1) to "very well" (7) | Mean score for each subscale separately |

| Secondary outcome | Items | Response options | Coding procedure |
|---|---|---|---|
| Help-seeking behaviors, adapted from [96] | In the past month, how often have you: *Parent and guardian help-seeking subscale* —asked your parents/guardians for help? talked to your parents/guardians about personal problems? talked to your parents/guardians about problems at school?; *Relative/family help-seeking subscale* —asked a relative/family member for help? talked to a relative/family member about personal problems? talked to a relative/family member about problems at school?; *Teacher help-seeking subscale* —asked a teacher for help? talked to a teacher about personal problems? talked to a teacher about problems at school?; *Friend help-seeking subscale* —asked a friend for help? talked to a friend about personal problems? talked to a friend about problems at school?; *Mental health provider help-seeking subscale* —asked a mental health professional (such as a psychologist, social worker, counselor) for help? talked to a mental health professional about personal problems? talked to a mental health professional about problems at school?; *Help line help-seeking subscale* —asked a person from a phone or text/chat help line (such as the National Suicide Prevention Lifeline or the Trevor Project) for help? talked to a person from a phone or text/chat help line about personal problems? talked to a person from a phone or text/chat help line about problems at school?; *Doctor help-seeking subscale* —asked a doctor or nurse for help? talked to a doctor or nurse about personal problems? talked to a doctor or nurse about problems at school? | 5-point Likert scale: Never; Rarely; Occasionally; A moderate amount; A great deal | Mean score for each subscale separately |
| **Coping strategies and flexibility** | | | |
| Coping skill usage [88] | Assessed using the Short form of the Adolescent Coping Scale Second Edition Short Form (ACS-2) [88]. For proprietary reasons, we do not list specific items. *Productive (problem-solving) coping subscale* contains 10 items; *Nonproductive (passive avoidant) coping subscale* contains 8 items (reverse coded) | 5-point Likert Scale, ranging from "never" (1) to "very often" (5) | Mean score for each subscale separately |
| Coping flexibility [97] | Please indicate how these situations apply to you by choosing one of the following for each situation: *Evaluation coping subscale* —I only use certain ways to cope with stress (reverse-coded); I am aware of how successful or unsuccessful my attempts to cope with stress have been; I fail to notice when I have been unable to cope with stress (reverse-coded); if I feel that I have failed to cope with stress, I change the way in which I deal with stress; after coping with stress, I think about how well my ways of coping with stress worked or did not work; *Adaptive coping subscale* —when a stressful situation has not improved, I try to think of other ways to cope with it; when stressed, I use several ways to cope and make the situation better; when I haven't coped with a stressful situation well, I use other ways to cope with that situation; if a stressful situation has not improved, I use other ways to cope with that situation; if I have failed to cope with stress, I think of other ways to cope | 4-point Likert Scale: Not applicable; Somewhat applicable; Applicable; Very applicable | Mean score for each subscale separately |
| **Knowledge and use of Web-based resources** | | | |
| Knowledge of Web-based resources | Have you heard of any of these websites?—The Trevor Project; It Gets Better; GLAAD; Accredited Schools online; Teen Line; GSA[a] Network. (Links to each website were provided for reference.) | Yes; No; Unsure | Summary score that adds together all "yes" response options |
| Use of Web-based resources | Have you visited any of these websites in the past month?—The Trevor Project; It Gets Better; GLAAD; Accredited Schools online; Teen Line; GSA[a] Network. (Links to each website were provided for reference.) | Yes; No; Unsure | Summary score that adds together all "yes" response options |

[a]GSA: gay-straight alliance or gender and sexuality alliance.

### Tertiary Outcomes

To answer our tertiary aim, we will measure the following long-term outcomes: bullying and cyberbullying victimization, loneliness, mental health issues, substance use, and internalized SGM stigma. All tertiary outcomes are assessed via self-reported surveys at T1, T2, and T3. Table 3 details our tertiary outcomes, items, response options, and coding procedures.

Bullying victimization is measured using 2 different scales, 1 for traditional face-to-face bullying and 1 for cyberbullying. We assess past-month bullying victimization using an adapted version of the University of Illinois Victimization Scale [98,99], which consists of 6 items assessing the number of times respondents experienced harassment in the past month. In addition, 4 response options range from "never" to "7 or more." These response options are assigned a value from 1 to 4, and a mean score is calculated, with a higher mean score indicating greater bullying victimization. We assess past-month cyberbullying victimization using 4 items adapted from an internally consistent cyberbullying perpetration scale [100]. Response options use a 5-point Likert scale including "not sure," "never," "rarely," "occasionally," and "often," which we will recode to a 4-point scale, where "never" equals 1 and "often" equals 4. We will average scores across all items, with a higher mean score indicating greater cyberbullying victimization.

Loneliness is measured via Robert's Version of the University of California, Los Angeles Loneliness Scale [101], a validated measure of loneliness. Overall, 8 items (eg, "I feel isolated from others") are used to calculate a mean score for how lonely participants felt.

Mental health issues include stress, anxiety, depression, and suicidality. Past-month stress is assessed using the Perceived Stress Scale [102,103], which contains 10 items used to calculate a mean score. Past-week anxiety symptoms are assessed using the Severity Measure for Generalized Anxiety Disorder—Child Age 11-17 [104,105], which contains 10 items used to calculate a mean score. Past-week depressive symptoms are assessed

using the Patient Health Questionnaire-9 for children aged from 11 to 17 years [106], which contains 9 items used to calculate a mean score. Suicidality is assessed with 3 questions adapted from the 2017 YRBS with items measuring suicidal thoughts, plans, and attempts. Although the YRBS questions measured past year suicidality, we adapted them to assess for suicidality in the past month. Each of these 3 suicidality items will be modeled separately as dichotomous (presence vs absence) variables.

Substance use includes alcohol, cigarette, electronic cigarette, and marijuana use. All items are assessed based on the YRBS and adapted to measure past-month use. Alcohol use is assessed via 2 questions: 1 measuring the frequency of past-month alcohol use and 1 item assessing frequency of binge drinking (having 5 or more drinks in a row). Similar to prior research [7], each item will be modeled as continuous variable representing the number of days used. Cigarette smoking is assessed via 2 items measuring past-month number of days smoked and average quantity smoked per day. Cigarette smoking will be modeled continuously by multiplying smoking frequency by quantity, similar to prior research [10]. Electronic cigarette smoking and marijuana use are both assessed using single items that measure past-month frequency of use. Each will be modeled as a continuous variable representing the number of days used. For all substance use items, we will use midpoints for categories with a range (eg, "1 or 2 days" will be coded as 1.5).

Internalized SGM stigma is measured using 2 different scales. To assess internalized gender minority stigma, we use the Transgender Identity Survey [107,108], which consists of 26 items that are divided into 4 different subscales: pride (reverse coded), passing, alienation, and shame. We adapted this scale by adding the term "nonbinary" to each item. To assess internalized sexual minority stigma, we adapted the Transgender Identity Survey [107,108] items by replacing "transgender or nonbinary" with "lesbian, gay, bisexual, or queer"; otherwise, the subscales, response options, and scoring are identical.

**Table 3.** Tertiary outcomes, items, response options, and coding procedures.

| Tertiary outcome | Items | Response options | Coding procedure |
|---|---|---|---|
| **Bullying and cyberbullying victimization** | | | |
| Bullying victimization [98,99] | How many times did these things happen to you in the last 30 days?—other students picked on me; other students called me names; I got hit and pushed by other students; I was threatened by other students; students spread rumors or told lies about me; I was excluded or kept out of a group of friends on purpose. | Never; 1 or 2 times; 3 or 4 times; 5 or 6 times; 7 or more times | Mean score |
| Cyberbullying victimization, adapted from [100] | How often did the following things happen to you in the last month?—someone made rude comments about me online; someone spread rumors about me online, whether they were true or not; someone made aggressive or threatening comments to me online; someone sent a text message that said rude or mean things about me | Not sure; Never; Rarely; Occasionally; Often | Mean score |
| **Loneliness** | | | |
| Loneliness [101] | Indicate how often each of the statements below is descriptive of you—I feel in tune with the people around me (reverse coded); I lack companionship; I do not feel alone (reverse coded); I feel part of a group of friends (reverse coded); I am no longer close to anyone; I feel left out; I feel isolated from others; I can find companionship when I want it (reverse coded) | 4-point Likert scale: Never; Rarely; Sometimes; Often | Mean score |
| **Mental health issues** | | | |
| Stress [103,109] | For each item, mark the description that best represents how often you have felt or thought that way during the past month—Been upset because of something that happened unexpectedly; Felt that you were unable to control the important things in your life; Felt nervous and — "stressed"; Felt confident about your ability to handle your personal problems; Felt that things were going your way; Found that you could not cope with all the things that you had to do; Been able to control irritations in your life; Felt that you were on top of things; Been angered because of things that were outside of your control; Felt difficulties were piling up so high that you could not overcome them | 5-point Likert scale: Never; Almost never; Sometimes; Fairly often; Very often | Mean score |
| Anxiety [104,105] | During the past 7 days, I have: Felt moments of sudden terror, fear, or fright; Felt anxious, worried, or nervous; Had thoughts of bad things happening such as family tragedy, ill health, loss of a job, or accidents; Felt a racing heart, sweaty, trouble breathing, faint, or shaky; Felt tense muscles, felt on edge or restless, or had trouble relaxing or trouble sleeping; Avoided, or did not approach or enter situations about which I worry; Left situations early or participated only minimally because of worries; Spent lots of time making decisions, putting off making decisions, or preparing situations, because of worries; Sought reassurance from others because of worries; Needed help to cope with anxiety (eg, alcohol or medication, superstitious objects, or other people) | 5-point Likert scale: Never; Occasionally; Half the time; Most of the time; All of the time | Mean score |

| Tertiary outcome | Items | Response options | Coding procedure |
|---|---|---|---|
| Depression [106] | How often have you been bothered by each of the following symptoms during the past 7 days?—Feeling down, depressed, irritable, or hopeless; Little interest or pleasure in doing things; Trouble falling asleep, staying asleep, or sleeping too much; Poor appetite, weight loss, or overeating; Feeling tired, or having little energy; Feeling bad about yourself—or feeling that you are a failure, or that you have let yourself or your family down; Trouble concentrating on things like school work, reading, or watching TV; Moving or speaking so slowly that other people have noticed; Or the opposite—being so fidgety or restless that you were moving around a lot more than usual; Thoughts that you would be better off dead, or of hurting yourself in some way | 4-point Likert scale: Not at all; Several days; More than half the days; Nearly every day | Mean score |
| Suicidal ideation, adapted from [110] | During the past month, did you ever seriously consider attempting suicide? | Yes; No | Dichotomously as yes or no |
| Suicide plan, adapted from [110] | During the past month, did you make a plan about how you would attempt suicide? | Yes; No | Dichotomously as yes or no |
| Suicide attempt, adapted from [110] | During the past month, how many times did you actually attempt suicide? | 0 times; 1 time; 2 or 3 times; 4 or 5 times; 6 or more times | Dichotomously as yes or no, similar to prior research [6] |
| **Substance use** | | | |
| Alcohol use [110] | During the past 30 days, on how many days did you have at least one drink of alcohol? | 0 days; 1 or 2 days; 3 to 5 days; 6 to 9 days; 10 to 19 days; 20 to 29 days; All 30 days | Count variable using midpoints (eg, "1 or 2 days" equals 1.5), similar to prior research [7] |
| Binge alcohol use [111] | During the past 30 days, on how many days did you have 5 or more drinks of alcohol in a row (within a couple of hours)? | 0 days; 1 day; 2 days; 3 to 5 days; 6 to 9 days; 10 to 19 days; 20 or more days | Count variable using midpoints (eg, "1 or 2 days" equals 1.5), similar to prior research [7] |
| Cigarette smoking [110] | During the past 30 days, on how many days did you smoke cigarettes? During the past 30 days, on the days you smoked, how many cigarettes did you smoke per day? | For the question pertaining to number of days: 0 days; 1 or 2 days; 3 to 5 days; 6 to 9 days; 10 to 19 days; 20 to 29 days; All 30 days. For the question pertaining to number of cigarettes: I did not smoke cigarettes during the past 30 days; Less than 1 cigarette per day; 1 cigarette per day; 2 to 5 cigarettes per day; 6 to 10 cigarettes per day; 11 to 20 cigarettes per day; More than 20 cigarettes per day | Continuously by multiplying frequency by quantity, similar to prior research [10] |
| Electronic cigarette use [110] | During the past 30 days, on how many days did you use an electronic vapor product? | 0 days; 1 or 2 days; 3 to 5 days; 6 to 9 days; 10 to 19 days; 20 to 29 days; All 30 days | Count variable using midpoints (eg, "1 or 2 days" equals 1.5) |
| Marijuana use [110] | During the past 30 days, how many times did you use marijuana? (Marijuana is also called grass, pot, or weed.) | 0 times; 1 or 2 times; 3 to 9 times; 10 to 19 times; 20 to 39 times; 40 or more times | Count variable using midpoints (eg, "1 or 2 days" equals 1.5) |
| **Internalized sexual and gender minority stigma** | | | |
| Internalized gender minority stigma, adapted from [107,108] | Pride subscale contains 8 items (reverse coded); Passing subscale contains 7 items; Alienation subscale contains 3 items; Shame subscale contains 8 items; To obtain the specific scale items, please contact Robert WS Coulter and Walter O Bockting | 7-point Likert Scale: Strongly disagree; Disagree; Somewhat disagree; Neither agree nor disagree; Somewhat agree; Agree; Strongly agree | Mean score for each subscale separately |

| Tertiary outcome | Items | Response options | Coding procedure |
|---|---|---|---|
| Internalized Sexual Minority Stigma, adapted from [107,108] | Pride subscale contains 8 items (reverse coded); Passing subscale contains 7 items; Alienation subscale contains 3 items; Shame subscale contains 8 items; To obtain the specific scale items, please contact Robert WS Coulter and Walter O Bockting | 7-point Likert Scale: Strongly Disagree; Disagree; Somewhat Disagree; Neither Agree nor Disagree; Somewhat Agree; Agree; Strongly Agree | Mean score for each subscale separately |

## Exploratory Outcomes

To answer our exploratory aim, we assess several outcomes meant to better our understanding of participants' responses to the game and how to improve the game in the future. Our exploratory aim concerns implementation procedures, intervention integration, and intervention adaptation and expansion outcomes. Table 4 details our exploratory outcomes, research questions, and assessments.

Multiple implementation procedures will be explored to inform our future research. These include the following: how long it takes to enroll participants on the internet, which venues participants were recruited from, how long it takes participants to complete the surveys, how many participants complete the game, and which game milestones are achieved by participants. These data are obtained from multiple sources, including the self-reported surveys in REDCap and the game play data.

Implementation integration—or how well the game fits into the participants' lives—will be assessed in a variety of ways. We will examine how many participants were excluded from our study based on not having access to a computer or not having an email address. We will examine if the participants had any problems downloading or playing game and how easy it was for them to participate in the RCT. We will also explore if participants had issues with game security, privacy, or interference. These outcomes are tracked using participants' responses to the screening questionnaire, T2 survey, and T3 surveys, as well as from participants' correspondences with the project email address.

Adaptation and expansion of the game intervention will be assessed via the T2 and T3 surveys. We will ask participants if they prefer to play the game on a different format (eg, on their phones), their favorite and least favorite parts of the game, how they would change and improve the game, and whether they think other SGMY would be interested in the game. Finally, we will explore whether the responses to the Gaming Experience Questionnaire [92] subscale scores differed by participants' gender, sexual orientation, race, ethnicity, and age.

**Table 4.** Exploratory outcomes, research questions, and assessments.

| Exploratory outcome | Exploratory question | Assessment |
| --- | --- | --- |
| **Implementation procedures** | | |
| Enrollment period | How long does it take to get 240 people to enroll in the study? | Measured as number of months between enrollment of first and last participant. |
| Recruitment venues | How many people were recruited from which venue? | Assessed using unique links that track the number of clicks on each advertisement. |
| Survey completion time | How many days before participants completed each survey? | Measured as the number of days between the first survey invitation was sent to the participant and the day they completed the survey. |
| Game completion | How many intervention condition participants completed the game? | Assessed via game play data from the secure file-transfer-protocol (FTP) system as well as T2[a] and T3[b] surveys: Did you complete the game? Yes; No; Unsure |
| Game milestones | What milestones did the participants achieve in the game? | Assessed via game play data from the secure file-transfer-protocol (FTP) system. |
| **Integration** | | |
| Computer access | How many youths were excluded because they were without a personal computer or Mac? | Assessed via the screening questionnaire: Do you have a laptop or desktop computer (either personal computer or Mac) where you can download games? Yes; No; Unsure |
| Email address access | How many youths were excluded because they were without an email address? | Assessed via the screening questionnaire: do you have an email address? Yes; No |
| Ease of download | How easily was the game downloaded without contacting our research coordinator? | Assessed via the number of emails to our project email address. |
| Personal computer versus Mac use | What participants used personal computer and Mac computers to download the game? | Assessed as percentages via the game download materials in REDCap. |
| Ease of participation | How many times was the research staff contacted by participants with questions about surveys or intervention materials? | Assessed via the number and types of emails to our project email address. |
| Game problems | How many problems and what types of problems did participants encounter with the game? | Assessed via T2 and T3 surveys: Did you have any problems in the game?—Yes; No; If yes, please describe; Open-ended text box |
| Game security | How important was the use of password protection in the game? | Assessed via T2 and T3 surveys: How important was it to have the game be protected by a password?—Very Important; Important; Moderately Important; Slightly Important; Not Important |
| Game privacy | How safe did our participants feel playing the game? | Assessed via T2 and T3 surveys: How often were you concerned about other people seeing you play the game?—Always; Very Often; Sometimes; Rarely; Never |
| Game interference | Did the gaming intervention interfere with participants' regular activities? | Assessed via T2 and T3 surveys: During the past 30 days, how many times did playing the game interfere with school, work, or other responsibilities (like being late, missing school, or making it hard to concentrate)—Never; 1 time; 2 times; 3 times; 4 times; 5 or more times |
| **Adaptation and expansion** | | |
| Future gaming platforms | Would our participants like to play the game on other platforms, such as phone? | Assessed via T2 and T3 surveys: In the future where would you like to play this game? My computer only; My phone only; Both my computer and phone |
| Gaming experience [92] by demographics | Were there certain groups that had better or worse experiences with the game? | We will examine whether the Gaming Experience Questionnaire [92] subscale scores (assessed via T2 and T3 surveys) differed by participants' gender, sexual orientation, race, ethnicity, and age. |
| Future appeal to sexual and gender minority youth | Will other sexual and gender minority youth enjoy the game? | Assessed via T2 and T3 surveys: Do you think other LGBTQ people your age would like to play this game? Definitely; Very Probably; Probably; Possibly; Probably Not; Definitely Not |

| Exploratory outcome | Exploratory question | Assessment |
|---|---|---|
| Recommended game changes | What would participants change about the game? | Assessed via T2 and T3 surveys: What would you change about the game? Open-ended text box |
| Favorite parts of game | What did participants like best about the game? | Assessed via T2 and T3 surveys: What were your favorite parts of the game? Open-ended text box |
| Least favorite arts of game | What did participants like least about the game? | Assessed via T2 and T3 surveys: What were your least favorite parts of the game? Open-ended text box |
| Recommended game improvements | How would participants improve the game? | Assessed via T2 and T3 surveys: How would you improve the game? Open-ended text box |

[a]T2: first follow-up.

[b]T3: final follow-up.

## Demographics and Potential Confounders

Demographic variables include age, grade in school, race, ethnicity, parent's highest education level, and eligibility for free or reduced-price lunch at school. We also measure gender using the 2-step process assessing current gender identity and sex assigned at birth [112]. Moreover, 2 items assess gender expression. We measure sexual orientation using 3 questions assessing sexual attraction, behavior, and identity.

In addition to demographic variables, we assess variables that may confound the relationship between the intervention and our outcomes. Structural stigma is assessed by collecting participant's residential zip code. Each zip code will then be given a state-level structural stigma score using Hatzenbuehler scale [113], based on density of same-sex couples, inclusive policies (eg, employee nondiscrimination policies), public opinion, and percentage of high schools with gay-straight alliance (also known as a gender and sexuality alliance; GSA). We have participants self-report whether or not their school had a GSA. We assess the participants' overall school environment with 5 questions from the California School Climate Survey. We assess participants' level of perceived social support using the Multidimensional Scale of Perceived Social Support, measuring support from family and friends [114]. Finally, we measure level of "outness" regarding participant's sexual orientation and gender identity.

## Statistical Analysis

For the measures of implementation procedures, demand, acceptability, integration, and adaptation and expansion (ie, primary and exploratory outcomes), we will report results using descriptive statistics (ie, percentages and frequencies for categorical variables or means and SDs for continuous variables) along with 95% CIs. We will compare our results against our a priori benchmarks (see Table 1). For the limited-efficacy outcomes (ie, secondary and tertiary outcomes), we will use repeated measures (ie, multilevel) statistical models using linear or logistic regression, depending on the distribution of the outcomes. To examine whether there are greater improvements over time in the intervention versus control conditions, we will test the interaction term of time by condition, wherein we will focus on the point estimates and 95% CIs. We will conduct our primary analyses as an intent-to-treat analysis, wherein everyone in the intervention condition is treated equally. As an additional exploratory exercise, we will conduct an analysis wherein we

assess whether intervention effects were stronger with more intensive uptake of the game intervention. For these analyses, instead of a binary intervention indicator variable (1.0 for intervention vs 0.0 for control), we will use an intensity-adjusted intervention variable. The intensity-adjusted intervention variable will be coded as 1.0 for those who complete the game, 0.5 for those who play the game, and 0.0 for those who never played the game or were in the control condition. All analyses will be completed in Stata 15.0 (StataCorp LLC, College Station, Texas), and significance will be set as at $P<.05$.

## Qualitative Analysis

For the open-ended questions, we will conduct qualitative data analysis. First, a group of investigators will read all of the participants' responses and inductively identify the main themes for each item. Second, using these themes, we will develop a codebook with code names and definitions. Finally, 2 independent coders will code the qualitative data using Dedoose. If the 2 coders cannot reach consensus, a third coder will resolve any disagreements.

## Sample Size and Power Calculation

This is a feasibility study, which is primarily being conducted to inform a larger RCT. As such, we powered this study based on our primary outcomes [74,115]. For our primary outcomes regarding the success of implementation procedures (eg, retention rate at T2), assuming 240 participants and 5% type 1 error rate, we will be able to estimate 95% CI width of no more than 0.13. For game demand among 120 intervention condition participants, we will be able to estimate 95% CI width of no more than 0.18. For our secondary and tertiary outcomes, we are primarily interested in effect size and CI estimation; we are not necessarily interested in finding statistically significant effects [74,115]. Estimations of the effect size and CI width will help us power a future, larger RCT.

## Ethics Statement

All study procedures were approved by the Human Research Protection Office at the University of Pittsburgh. To protect participants from having to reveal their sexual or gender minority identities to their caregivers, thereby potentially putting them in harm's way, we received a waiver of parental consent [76]. This allowed participants to self-consent. We did not collect personally identifying information other than email, phone, and zip code. Incentives, in the form of either Apple or Google electronic gift cards, are sent via email. This study was

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covered by a Certificate of Confidentiality from the National Institutes of Health.

## Results

### Enrollment and Randomization

Overall, 2153 individuals clicked the link to the screening questionnaire (Figure 10). In total, 988 individuals completed the screening questionnaire, of which 407 individuals met all eligibility criteria. Overall, 304 individuals consented to participate, and 240 participants completed the T1 survey and were randomized. Of those who were eligible, 59.0% (240/407) were enrolled into the study. Half of the enrolled participants (n=120) were randomized into the intervention condition and half (n=120) into the control condition. All 240 participants were enrolled into the RCT between April 2018 and July 2018. The final surveys (T3) will be completed in November 2018.

### Sample Demographics

At baseline, there were no significant differences in demographic characteristics between intervention and control condition participants (Table 5). Overall, 52.1% (125/240) of participants

identified as gay or lesbian, 26.7% (64/240) as bisexual, 24.2% (58/240) as queer, 11.7% (28/240) as another nonheterosexual identity, 4.6% (11/240) as unsure, and 2.1% (5/240) as heterosexual (all of whom were gender minorities). Nearly half (47.1%; 113/240) of participants were a gender minority, 36.7% (88/240) were cisgender boys, and 16.3% (39/240) were cisgender girls. Among the 113 gender minority participants, 54.9% (62/113) identified as a transgender boy, 33.6% (38/113) as nonbinary, 18.6% (21/113) as a boy, 17.7% (20/113) as genderqueer, 6.2% (7/113) as a transgender girl, 5.3% (6/113) as a girl, and 5.3% (6/113) as another identity (data not shown; participants could select multiple options). Overall, 81.3% (195/240) of participants identified as white, 20.4% (49/240) as Hispanic/Latinx, 10.8% (26/240) as black or African American, 7.5% (18/240) as American Indian or Alaska Native, and 5.8% (14/240) as Asian. Moreover, 36.7% (88/240) of participants were eligible for free or reduced-price lunch, and 52.9% (127/240) had a parent/guardian with a college degree. Figure 11 shows the geographic distribution of participants across the United States of America. In total, participants lived in 30 states.

**Figure 10.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram.
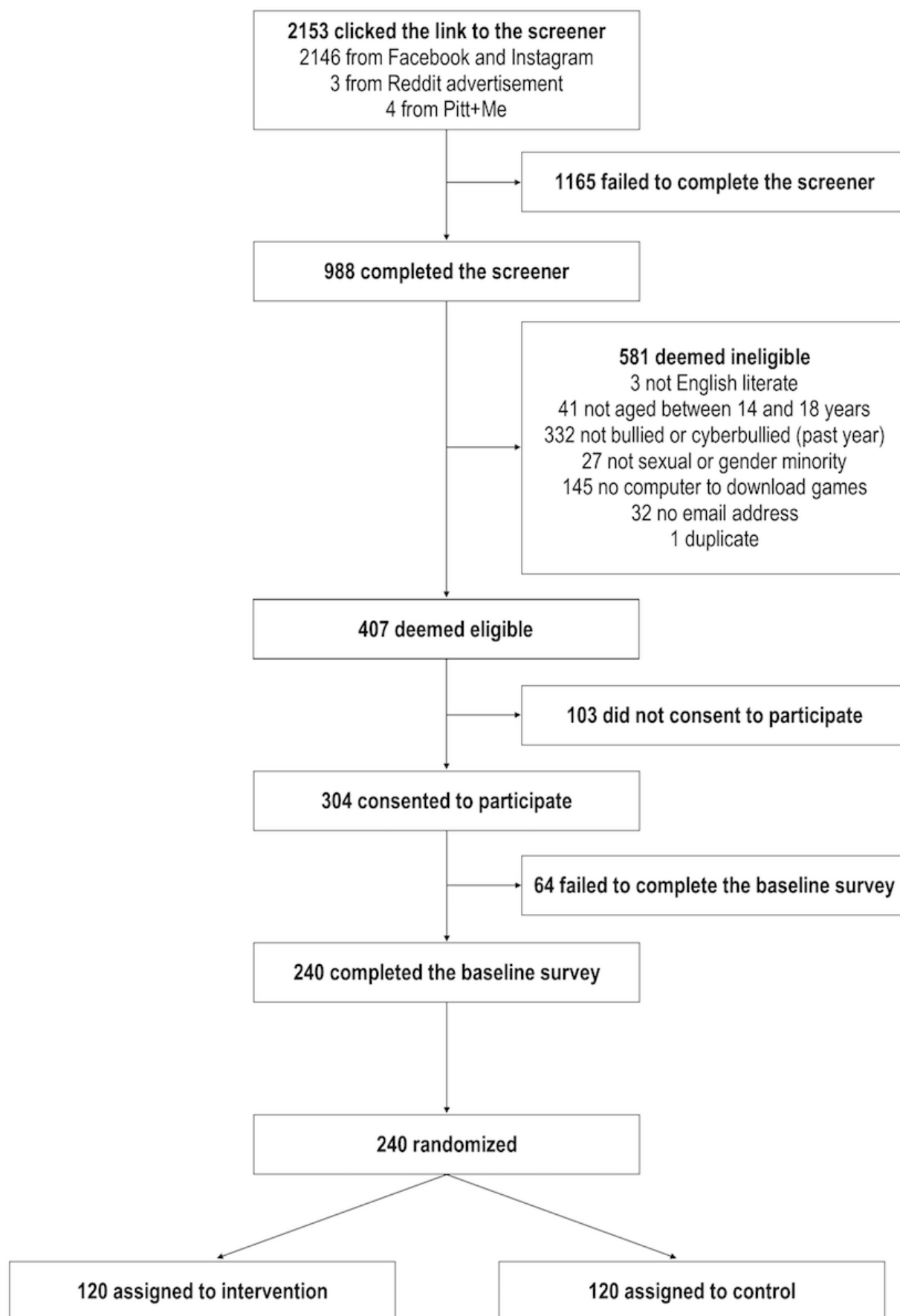
**Table 5.** Baseline demographic characteristics for the total sample and by intervention condition (N=240).

| Demographic characteristics | Total (N=240), n (%) | Condition | | P value[a] |
|---|---|---|---|---|
| | | Intervention (n=120), n (%) | Control (n=120), n (%) | |
| **Sexual identity[b]** | | | | |
| Gay or lesbian | 125 (52) | 62 (52) | 63 (53) | .89 |
| Bisexual | 64 (27) | 32 (27) | 32 (27) | >.99 |
| Queer | 58 (24) | 33 (28) | 25 (21) | .23 |
| Unsure | 11 (5) | 8 (7) | 3 (3) | .12 |
| Another nonheterosexual identity | 28 (12) | 11 (9) | 17 (14) | .23 |
| Heterosexual | 5 (2) | 3 (3) | 2 (2) | >.99 |
| **Gender** | | | | .24 |
| Cisgender girls | 39 (16) | 18 (15) | 21 (18) | |
| Cisgender boys | 88 (37) | 39 (33) | 49 (41) | |
| Gender minority[c] | 113 (47) | 63 (53) | 50 (42) | |
| **Age in years** | | | | .98 |
| 14 | 35 (15) | 16 (13) | 19 (16) | |
| 15 | 66 (28) | 33 (28) | 33 (28) | |
| 16 | 71 (30) | 37 (31) | 34 (28) | |
| 17 | 56 (23) | 28 (23) | 28 (23) | |
| 18 | 12 (5) | 6 (5) | 6 (5) | |
| **Race/ethnicity[b]** | | | | |
| White | 195 (81) | 96 (80) | 99 (83) | .62 |
| Asian | 14 (6) | 5 (4) | 9 (8) | .27 |
| American Indian or Alaska Native | 18 (8) | 6 (5) | 12 (10) | .14 |
| Black or African American | 26 (11) | 15 (13) | 11 (9) | .41 |
| Native Hawaiian or other Pacific Islander | 5 (2) | 3 (3) | 2 (2) | >.99 |
| Hispanic or Latinx | 49 (20) | 28 (23) | 21 (18) | .26 |
| Another race | 21 (9) | 9 (8) | 12 (10) | .49 |
| **Free or reduced-price lunch eligibility** | | | | .98 |
| Yes | 88 (37) | 44 (37) | 44 (37) | |
| No | 109 (45) | 54 (45) | 55 (46) | |
| Unsure | 43 (18) | 22 (18) | 21 (18) | |
| **Highest education level of parent(s) or guardian(s)** | | | | .75 |
| Less than high school degree | 22 (9) | 10 (8) | 12 (10) | |
| High school degree | 38 (16) | 22 (18) | 16 (13) | |
| Some college | 43 (18) | 23 (19) | 20 (17) | |
| College degree | 127 (53) | 61 (51) | 66 (55) | |
| Unsure | 10 (4) | 4 (3) | 6 (5) | |

[a]Generally, P values were derived using chi-square test statistics; however, when expected cell sizes were less than 5, P values were derived using Fisher exact tests.

[b]Participants could select more than one option; therefore, the percentages may not add to 100% (N=240). P values were derived for each response option separately.

[c]Gender minority includes all participants whose gender identity did not match their assigned sex at birth.

**Figure 11.** Geographic distribution of participants in the United States of America.
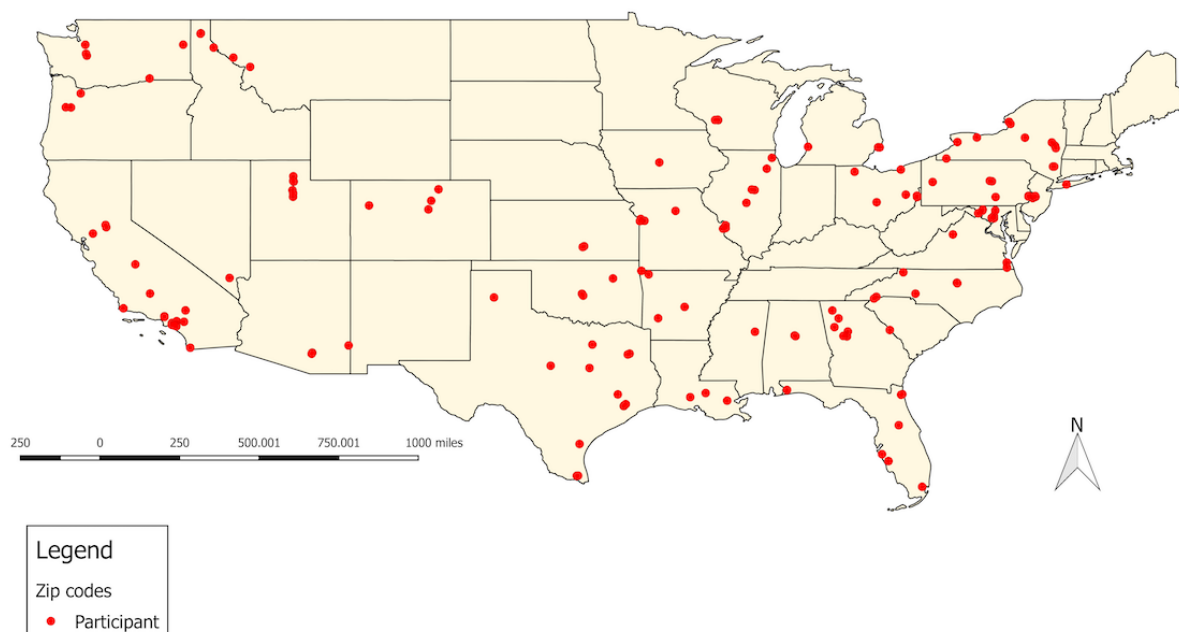


## Discussion

### Principal Findings

In this pilot RCT, a game-based intervention, we successfully enrolled and randomized 240 SGMY participants over a 4-month period. Recruitment was most successful through Facebook and Instagram. Over half of the enrolled sample identified as gay or lesbian and nearly half were gender minority youth. There were no demographic differences between intervention and control conditions.

This study protocol offers several strengths and novel methods that can inform future intervention studies with SGMY. Our game intervention is one of the first Web-accessible programs targeting SGMY who are victims of bullying or cyberbullying. Furthermore, this study engages a younger cohort of individuals focusing on youth aged 14 to 18 years, as opposed to the typical focus of SGMY-relevant intervention research, which concentrates on those aged 18 years and older. This is also one of the first bullying prevention programs to address social and emotional learning (eg, coping strategies) with respect to bullying among SGMY utilizing a gaming format to attract participation and build retention. Finally, the internet-based distribution of the game intervention has the potential to reach far greater numbers of SGMY than traditional face-to-face interventions.

### Limitations

Despite the many strengths of this study protocol, it is not without limitations. Of particular concern is selection bias. Participants in our study were conveniently sampled via the internet. Participants were also required to have a computer with internet access and an email address. Therefore, our study results may not be generalizable to all SGMY (eg, those who are homelessness or have a low socioeconomic status). In addition, participants can only access the game intervention on desktop or laptop computers with Windows or Mac operating systems. In future iterations, we plan to make the game intervention compatible with smartphones, thereby increasing the accessibility and potential usability of the game. Although we used and adapted measures with strong psychometric properties, most of the scales were not validated specifically among SGMY. Finally, an 8-week follow-up period may be too brief to affect our identified long-term outcomes; however, we chose to measure these outcomes as they are important health outcomes to inform a longer-term intervention study.

### Conclusions

SGMY experience great disparities in bullying victimization, substance use, and mental health; however, there are few scientifically tested interventions currently available to reduce these disparities. This paper describes our protocol for the study of a Web-accessible game intervention aimed at improving the health of SGMY. Specifically, the outcomes of this pilot study are to assess the feasibility of implementing a game intervention to SGMY and limited efficacy of this intervention: increasing help-seeking–related knowledge, intentions, self-efficacy, and behaviors; increasing productive coping skills use and coping flexibility; and reducing health risk factors and behaviors among SGMY. Our study protocol directly informs the scientific development of a future, larger RCT testing the limited efficacy of our game intervention.

## Conflicts of Interest

None declared.

## References

1. Garofalo R, Wolf RC, Kessel S, Palfrey SJ, DuRant RH. The association between health risk behaviors and sexual orientation among a school-based sample of adolescents. Pediatrics 1998 May;101(5):895-902. [Medline: 9565422]

2. Marshal MP, Friedman MS, Stall R, King KM, Miles J, Gold MA, et al. Sexual orientation and adolescent substance use: a meta-analysis and methodological review. Addiction 2008 Apr;103(4):546-556 [FREE Full text] [doi: 10.1111/j.1360-0443.2008.02149.x] [Medline: 18339100]

3. Watson RJ, Lewis NM, Fish JN, Goodenow C. Sexual minority youth continue to smoke cigarettes earlier and more often than heterosexuals: findings from population-based data. Drug Alcohol Depend 2018 Mar 1;184:64-70. [doi: 10.1016/j.drugalcdep.2017.11.025] [Medline: 29402681]

4. Watson RJ, Goodenow C, Porta C, Adjei J, Saewyc E. Substance use among sexual minorities: has it actually gotten better? Subst Use Misuse 2018 Jun 7;53(7):1221-1228. [doi: 10.1080/10826084.2017.1400563] [Medline: 29236561]

5. Coulter RW, Bersamin M, Russell ST, Mair C. The effects of gender- and sexuality-based harassment on lesbian, gay, bisexual, and transgender substance use disparities. J Adolesc Health 2018 Jun;62(6):688-700. [doi: 10.1016/j.jadohealth.2017.10.004] [Medline: 29241986]

6. Coulter RW, Kessel Schneider S, Beadnell B, O'Donnell L. Associations of outside- and within-school adult support on suicidality: moderating effects of sexual orientation. Am J Orthopsychiatry 2017;87(6):671-679 [FREE Full text] [doi: 10.1037/ort0000209] [Medline: 27598866]

7. Coulter RW, Birkett M, Corliss HL, Hatzenbuehler ML, Mustanski B, Stall RD. Associations between LGBTQ-affirmative school climate and adolescent drinking behaviors. Drug Alcohol Depend 2016 Apr 1;161:340-347 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.02.022] [Medline: 26946989]

8. Russell ST, Driscoll AK, Truong N. Adolescent same-sex romantic attractions and relationships: implications for substance use and abuse. Am J Public Health 2002 Feb;92(2):198-202. [Medline: 11818291]

9. Corliss HL, Rosario M, Wypij D, Wylie SA, Frazier AL, Austin SB. Sexual orientation and drug use in a longitudinal cohort study of U.S. adolescents. Addict Behav 2010 May;35(5):517-521 [FREE Full text] [doi: 10.1016/j.addbeh.2009.12.019] [Medline: 20061091]

10. Corliss HL, Rosario M, Birkett MA, Newcomb ME, Buchting FO, Matthews AK. Sexual orientation disparities in adolescent cigarette smoking: intersections with race/ethnicity, gender, and age. Am J Public Health 2014 Jun;104(6):1137-1147. [doi: 10.2105/AJPH.2013.301819] [Medline: 24825218]

11. Newcomb ME, Birkett M, Corliss HL, Mustanski B. Sexual orientation, gender, and racial differences in illicit drug use in a sample of US high school students. Am J Public Health 2014 Feb;104(2):304-310. [doi: 10.2105/AJPH.2013.301702] [Medline: 24328653]

12. Rosario M, Corliss HL, Everett BG, Reisner SL, Austin SB, Buchting FO, et al. Sexual orientation disparities in cancer-related risk behaviors of tobacco, alcohol, sexual behaviors, and diet and physical activity: pooled Youth Risk Behavior Surveys. Am J Public Health 2014 Feb;104(2):245-254. [doi: 10.2105/AJPH.2013.301506] [Medline: 24328632]

13. Rosario M, Corliss HL, Everett BG, Russell ST, Buchting FO, Birkett MA. Mediation by peer violence victimization of sexual orientation disparities in cancer-related tobacco, alcohol, and sexual risk behaviors: pooled youth risk behavior surveys. Am J Public Health 2014 Jun;104(6):1113-1123. [doi: 10.2105/AJPH.2013.301764] [Medline: 24825215]

14. Corliss HL, Rosario M, Wypij D, Fisher LB, Austin SB. Sexual orientation disparities in longitudinal alcohol use patterns among adolescents: findings from the Growing Up Today Study. Arch Pediatr Adolesc Med 2008 Nov;162(11):1071-1078 [FREE Full text] [doi: 10.1001/archpedi.162.11.1071] [Medline: 18981356]

15. Corliss HL, Wadler BM, Jun HJ, Rosario M, Wypij D, Frazier AL, et al. Sexual-orientation disparities in cigarette smoking in a longitudinal cohort study of adolescents. Nicotine Tob Res 2013 Jan;15(1):213-222 [FREE Full text] [doi: 10.1093/ntr/nts114] [Medline: 22581940]

16. Talley AE, Hughes TL, Aranda F, Birkett M, Marshal MP. Exploring alcohol-use behaviors among heterosexual and sexual minority adolescents: intersections with sex, age, and race/ethnicity. Am J Public Health 2014 Feb;104(2):295-303 [FREE Full text] [doi: 10.2105/AJPH.2013.301627] [Medline: 24328614]

17. Fish JN, Watson RJ, Porta CM, Russell ST, Saewyc EM. Are alcohol-related disparities between sexual minority and heterosexual youth decreasing? Addiction 2017 Nov;112(11):1931-1941. [doi: 10.1111/add.13896] [Medline: 28678415]

XSL•FO
RenderX

18. White Hughto JM, Biello KB, Reisner SL, Perez-Brumer A, Heflin KJ, Mimiaga MJ. Health risk behaviors in a representative sample of bisexual and heterosexual female high school students in Massachusetts. J Sch Health 2016 Jan;86(1):61-71 [FREE Full text] [doi: 10.1111/josh.12353] [Medline: 26645422]

19. Matthews DD, Blosnich JR, Farmer GW, Adams BJ. Operational definitions of sexual orientation and estimates of adolescent health risk behaviors. LGBT Health 2014 Mar;1(1):42-49 [FREE Full text] [Medline: 25110718]

20. Marshal MP, Dietz LJ, Friedman MS, Stall R, Smith HA, McGinley J, et al. Suicidality and depression disparities between sexual minority and heterosexual youth: a meta-analytic review. J Adolesc Health 2011 Aug;49(2):115-123 [FREE Full text] [doi: 10.1016/j.jadohealth.2011.02.005] [Medline: 21783042]

21. Seil KS, Desai MM, Smith MV. Sexual orientation, adult connectedness, substance use, and mental health outcomes among adolescents: findings from the 2009 New York City Youth Risk Behavior Survey. Am J Public Health 2014 Oct;104(10):1950-1956 [FREE Full text] [doi: 10.2105/AJPH.2014.302050] [Medline: 25121812]

22. Hatzenbuehler ML, Birkett M, Van Wagenen A, Meyer IH. Protective school climates and reduced risk for suicide ideation in sexual minority youths. Am J Public Health 2014 Feb;104(2):279-286. [doi: 10.2105/AJPH.2013.301508] [Medline: 24328634]

23. Russell ST, Joyner K. Adolescent sexual orientation and suicide risk: evidence from a national study. Am J Public Health 2001 Aug;91(8):1276-1281. [Medline: 11499118]

24. Stone DM, Luo F, Ouyang L, Lippy C, Hertz MF, Crosby AE. Sexual orientation and suicide ideation, plans, attempts, and medically serious attempts: evidence from local Youth Risk Behavior Surveys, 2001-2009. Am J Public Health 2014 Feb;104(2):262-271. [doi: 10.2105/AJPH.2013.301383] [Medline: 24328658]

25. Stone DM, Luo F, Lippy C, McIntosh WL. The role of social connectedness and sexual orientation in the prevention of youth suicide ideation and attempts among sexually active adolescents. Suicide Life Threat Behav 2015 Aug;45(4):415-430. [doi: 10.1111/sltb.12139] [Medline: 25388375]

26. Eisenberg ME, Resnick MD. Suicidality among gay, lesbian and bisexual youth: the role of protective factors. J Adolesc Health 2006 Nov;39(5):662-668 [FREE Full text] [doi: 10.1016/j.jadohealth.2006.04.024] [Medline: 17046502]

27. Reisner SL, Greytak EA, Parsons JT, Ybarra ML. Gender minority social stress in adolescence: disparities in adolescent bullying and substance use by gender identity. J Sex Res 2015;52(3):243-256 [FREE Full text] [doi: 10.1080/00224499.2014.886321] [Medline: 24742006]

28. Friedman MS, Marshal MP, Guadamuz TE, Wei C, Wong CF, Saewyc E, et al. A meta-analysis of disparities in childhood sexual abuse, parental physical abuse, and peer victimization among sexual minority and sexual nonminority individuals. Am J Public Health 2011 Aug;101(8):1481-1494 [FREE Full text] [doi: 10.2105/AJPH.2009.190009] [Medline: 21680921]

29. Russell ST, Everett BG, Rosario M, Birkett M. Indicators of victimization and sexual orientation among adolescents: analyses from Youth Risk Behavior Surveys. Am J Public Health 2014 Feb;104(2):255-261. [doi: 10.2105/AJPH.2013.301493] [Medline: 24328633]

30. Coulter RW, Herrick AL, Friedman MR, Stall RD. Sexual-orientation differences in positive youth development: the mediational role of bullying victimization. Am J Public Health 2016 Apr;106(4):691-697. [doi: 10.2105/AJPH.2015.303005] [Medline: 26794177]

31. Kessel Schneider K, O'Donnell L, Stueve A, Coulter RW. Cyberbullying, school bullying, and psychological distress: a regional census of high school students. Am J Public Health 2012 Jan;102(1):171-177. [doi: 10.2105/AJPH.2011.300308] [Medline: 22095343]

32. Goodenow C, Watson RJ, Adjei J, Homma Y, Saewyc E. Sexual orientation trends and disparities in school bullying and violence-related experiences, 1999-2013. Psychol Sex Orientat Gend Divers 2016 Dec;3(4):386-396 [FREE Full text] [doi: 10.1037/sgd0000188] [Medline: 29322064]

33. Kann L, Olsen EO, McManus T, Harris WA, Shanklin SL, Flint KH, et al. Sexual identity, sex of sexual contacts, and health-related behaviors among students in grades 9-12 - United States and selected sites, 2015. MMWR Surveill Summ 2016 Aug 12;65(9):1-202. [doi: 10.15585/mmwr.ss6509a1] [Medline: 27513843]

34. Meyer IH. Minority stress and mental health in gay men. J Health Soc Behav 1995 Mar;36(1):38-56. [Medline: 7738327]

35. 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]

36. Lasser J, Tharinger D. Visibility management in school and beyond: a qualitative study of gay, lesbian, bisexual youth. J Adolesc 2003 Apr;26(2):233-244. [Medline: 12581729]

37. Plöderl M, Faistauer G, Fartacek R. The contribution of school to the feeling of acceptance and the risk of suicide attempts among Austrian gay and bisexual males. J Homosex 2010;57(7):819-841. [doi: 10.1080/00918369.2010.493401] [Medline: 20665326]

38. Lytle MC, Silenzio VM, Homan CM, Schneider P, Caine ED. Suicidal and help-seeking behaviors among youth in an online lesbian, gay, bisexual, transgender, queer, and questioning social network. J Homosex 2017 Oct 11:1916-1933. [doi: 10.1080/00918369.2017.1391552] [Medline: 29020574]

39. Lucassen MF, Merry SN, Robinson EM, Denny S, Clark T, Ameratunga S, et al. Sexual attraction, depression, self-harm, suicidality and help-seeking behaviour in New Zealand secondary school students. Aust N Z J Psychiatry 2011 May;45(5):376-383. [doi: 10.3109/00048674.2011.559635] [Medline: 21361850]

40. Lock J, Steiner H. Relationships between sexual orientation and coping styles of gay, lesbian, and bisexual adolescents from a community high school. J Gay Lesbian Med Assoc 1999 Sep;3(3):77-82. [doi: 10.1023/A:1022235910749]

41. Sornberger MJ, Smith NG, Toste JR, Heath NL. Nonsuicidal self-injury, coping strategies, and sexual orientation. J Clin Psychol 2013 Jun;69(6):571-583. [doi: 10.1002/jclp.21947] [Medline: 23382055]

42. Institute of Medicine (US) Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. The Health of Lesbian, Gay, Bisexual, and Transgender People Building a Foundation for Better Understanding. Washington, DC: National Academies Press; 2011.

43. Mustanski B, Lyons T, Garcia SC. Internet use and sexual health of young men who have sex with men: a mixed-methods study. Arch Sex Behav 2011 Apr;40(2):289-300 [FREE Full text] [doi: 10.1007/s10508-009-9596-1] [Medline: 20182787]

44. Egan J. The New York Times. 2000 Dec 31. Lonely Gay Teen Seeking Same URL: https://www.nytimes.com/2000/12/31/magazine/l-lonely-gay-teen-seeking-same-172898.html [accessed 2019-01-14] [WebCite Cache ID 75QhCoHgr]

45. Stueve A, O'Donnell LN, Duran R, San Doval A, Blome J. Time-space sampling in minority communities: results with young Latino men who have sex with men. Am J Public Health 2001 Jun;91(6):922-926. [Medline: 11392935]

46. Valleroy LA, MacKellar DA, Karon JM, Rosen DH, McFarland W, Shehan DA, et al. HIV prevalence and associated risks in young men who have sex with men. Young Men's Survey Study Group. JAMA 2000 Jul 12;284(2):198-204. [Medline: 10889593]

47. Muhib FB, Lin LS, Stueve A, Miller RL, Ford WL, Johnson WD, Community Intervention Trial for Youth Study Team. A venue-based method for sampling hard-to-reach populations. Public Health Rep 2001;116(Suppl 1):216-222 [FREE Full text] [doi: 10.1093/phr/116.S1.216] [Medline: 11889287]

48. Gilbert LK, Temby JR, Rogers SE. Evaluating a teen STD prevention Web site. J Adolesc Health 2005 Sep;37(3):236-242. [doi: 10.1016/j.jadohealth.2004.09.018] [Medline: 16109344]

49. Lou CH, Zhao Q, Gao ES, Shah IH. Can the internet be used effectively to provide sex education to young people in China? J Adolesc Health 2006 Nov;39(5):720-728. [doi: 10.1016/j.jadohealth.2006.04.003] [Medline: 17046509]

50. Woolderink M, Smit F, van der Zanden R, Beecham J, Knapp M, Paulus A, et al. Design of an internet-based health economic evaluation of a preventive group-intervention for children of parents with mental illness or substance use disorders. BMC Public Health 2010 Aug 10;10:470 [FREE Full text] [doi: 10.1186/1471-2458-10-470] [Medline: 20698962]

51. Elliott JC, Carey KB, Bolles JR. Computer-based interventions for college drinking: a qualitative review. Addict Behav 2008 Aug;33(8):994-1005 [FREE Full text] [doi: 10.1016/j.addbeh.2008.03.006] [Medline: 18538484]

52. Walters ST, Miller E, Chiauzzi E. Wired for wellness: e-interventions for addressing college drinking. J Subst Abuse Treat 2005 Sep;29(2):139-145. [doi: 10.1016/j.jsat.2005.05.006] [Medline: 16135342]

53. Schinke SP, Schwinn TM, Di Noia J, Cole KC. Reducing the risks of alcohol use among urban youth: three-year effects of a computer-based intervention with and without parent involvement. J Stud Alcohol 2004 Jul;65(4):443-449 [FREE Full text] [Medline: 15376818]

54. Hallett J, Maycock B, Kypri K, Howat P, McManus A. Development of a web-based alcohol intervention for university students: processes and challenges. Drug Alcohol Rev 2009 Jan;28(1):31-39. [doi: 10.1111/j.1465-3362.2008.00008.x] [Medline: 19320673]

55. Carey KB, Scott-Sheldon LA, Elliott JC, Bolles JR, Carey MP. Computer-delivered interventions to reduce college student drinking: a meta-analysis. Addiction 2009 Nov;104(11):1807-1819 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02691.x] [Medline: 19744139]

56. Walters ST, Wright JA, Shegog R. A review of computer and internet-based interventions for smoking behavior. Addict Behav 2006 Feb;31(2):264-277. [doi: 10.1016/j.addbeh.2005.05.002] [Medline: 15950392]

57. Buller DB, Borland R, Woodall WG, Hall JR, Hines JM, Burris-Woodall P, et al. Randomized trials on consider this, a tailored, internet-delivered smoking prevention program for adolescents. Health Educ Behav 2008 Apr;35(2):260-281 [FREE Full text] [doi: 10.1177/1090198106288982] [Medline: 17114331]

58. Patten CA, Croghan IT, Meis TM, Decker PA, Pingree S, Colligan RC, et al. Randomized clinical trial of an internet-based versus brief office intervention for adolescent smoking cessation. Patient Educ Couns 2006 Dec;64(1-3):249-258. [doi: 10.1016/j.pec.2006.03.001] [Medline: 16616449]

59. Jan RL, Wang JY, Huang MC, Tseng SM, Su HJ, Liu LF. An internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. Telemed J E Health 2007 Jun;13(3):257-268. [doi: 10.1089/tmj.2006.0053] [Medline: 17603828]

60. Runge C, Lecheler J, Horn M, Tews JT, Schaefer M. Outcomes of a web-based patient education program for asthmatic children and adolescents. Chest 2006 Mar;129(3):581-593. [doi: 10.1378/chest.129.3.581] [Medline: 16537855]

61. Joseph CL, Peterson E, Havstad S, Johnson CC, Hoerauf S, Stringer S, Asthma in Adolescents Research Team. A web-based, tailored asthma management program for urban African-American high school students. Am J Respir Crit Care Med 2007 May 1;175(9):888-895 [FREE Full text] [doi: 10.1164/rccm.200608-1244OC] [Medline: 17290041]

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62. Chan DS, Callahan CW, Hatch-Pigott VB, Lawless A, Proffitt HL, Manning NE, et al. Internet-based home monitoring and education of children with asthma is comparable to ideal office-based care: results of a 1-year asthma in-home monitoring trial. Pediatrics 2007 Mar;119(3):569-578. [doi: 10.1542/peds.2006-1884] [Medline: 17332210]

63. Maczewski M. Exploring identities through the internet: youth experiences online. Child Youth Care Forum 2002 Apr;31(2):111-129. [doi: 10.1023/A:1015322602597]

64. Hillier L, Harrison L. Building realities less limited than their own: young people practising same-sex attraction on the internet. Sexualities 2007 Feb 1;10(1):82-100. [doi: 10.1177/1363460707072956]

65. Schneider F, Schulz DN, Pouwels LH, de Vries H, van Osch LA. Using a proactive dissemination strategy to optimize reach of an internet-delivered lifestyle intervention. Eur Health Psychol 2014 Dec 1;16:603 [FREE Full text]

66. Martinez O, Wu E, Shultz AZ, Capote J, López Rios J, Sandfort T, et al. Still a hard-to-reach population? Using social media to recruit Latino gay couples for an HIV intervention adaptation study. J Med Internet Res 2014 Apr 24;16(4):e113 [FREE Full text] [doi: 10.2196/jmir.3311] [Medline: 24763130]

67. Kurti AN, Logan H, Manini T, Dallery J. Physical activity behavior, barriers to activity, and opinions about a smartphone-based physical activity intervention among rural residents. Telemed J E Health 2015 Jan;21(1):16-23 [FREE Full text] [doi: 10.1089/tmj.2014.0034] [Medline: 25379976]

68. Moessner M, Bauer S, Ozer F, Wolf M, Zimmer B, Kordy H. Cost-effectiveness of an internet-based aftercare intervention after inpatient treatment in a psychosomatic hospital. Psychother Res 2014;24(4):496-503. [doi: 10.1080/10503307.2013.845919] [Medline: 24188127]

69. Arnberg FK, Linton SJ, Hultcrantz M, Heintz E, Jonsson U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. PLoS One 2014 May 20;9(5):e98118 [FREE Full text] [doi: 10.1371/journal.pone.0098118] [Medline: 24844847]

70. Elbert NJ, van Os-Medendorp H, van Renselaar W, Ekeland AG, Hakkaart-van Roijen L, Raat H, et al. Effectiveness and cost-effectiveness of ehealth interventions in somatic diseases: a systematic review of systematic reviews and meta-analyses. J Med Internet Res 2014 Apr 16;16(4):e110 [FREE Full text] [doi: 10.2196/jmir.2790] [Medline: 24739471]

71. Christensen H, Batterham P, Calear A. Online interventions for anxiety disorders. Curr Opin Psychiatry 2014 Jan;27(1):7-13. [doi: 10.1097/YCO.0000000000000019] [Medline: 24257123]

72. Lucassen MF, Merry SN, Hatcher S, Frampton CM. Rainbow SPARX: a novel approach to addressing depression in sexual minority youth. Cogn Behav Pract 2015 May;22(2):203-216. [doi: 10.1016/j.cbpra.2013.12.008]

73. Schwinn TM, Thom B, Schinke SP, Hopkins J. Preventing drug use among sexual-minority youths: findings from a tailored, web-based intervention. J Adolesc Health 2015 May;56(5):571-573. [doi: 10.1016/j.jadohealth.2014.12.015] [Medline: 25744209]

74. 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]

75. U.S. National Library of Medicine, Clinical Trials. 2018. Evaluation of an Online Intervention to Help LGBTQ Youth Cope With Bullying URL: https://clinicaltrials.gov/ct2/show/NCT03501264 [accessed 2018-09-08] [WebCite Cache ID 72HpafarW]

76. Mustanski B. Ethical and regulatory issues with conducting sexuality research with LGBT adolescents: a call to action for a scientifically informed approach. Arch Sex Behav 2011 Aug;40(4):673-686. [doi: 10.1007/s10508-011-9745-1] [Medline: 21528402]

77. Lenhart A, Duggan M, Perrin A, Stepler R, Rainie L, Parker K. Pew Research Center. 2015 Apr 9. Teen, Social Media and Technology Overview 2015 URL: http://www.pewinternet.org/2015/04/09/teens-social-media-technology-2015/ [WebCite Cache ID 720uqQBSS]

78. Bandura A. Human agency in social cognitive theory. Am Psychol 1989 Sep;44(9):1175-1184. [Medline: 2782727]

79. Bandura A. Social cognitive theory: an agentic perspective. Annu Rev Psychol 2001;52:1-26. [doi: 10.1146/annurev.psych.52.1.1] [Medline: 11148297]

80. Bandura A. Social Foundations Of Thought And Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice Hall; Oct 11, 1985:640.

81. Bandura A. Social cognitive theory of self-regulation. Organ Behav Hum Decis Process 1991 Dec;50(2):248-287. [doi: 10.1016/0749-5978(91)90022-L]

82. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]

83. Lazarus RS. Psychological Stress and the Coping Process. New York, New York: McGraw-Hill; 1966:466.

84. Folkman S. Stress, coping, and hope. Psychooncology 2010 Sep;19(9):901-908. [doi: 10.1002/pon.1836] [Medline: 20799373]

85. Folkman S. Personal control and stress and coping processes: a theoretical analysis. J Pers Soc Psychol 1984 Apr;46(4):839-852. [Medline: 6737195]

86. Folkman S, Lazarus RS, Dunkel-Schetter C, DeLongis A, Gruen RJ. Dynamics of a stressful encounter: cognitive appraisal, coping, and encounter outcomes. J Pers Soc Psychol 1986 May;50(5):992-1003. [Medline: 3712234]

87.  Lazarus RS, Folkman S. Transactional theory and research on emotions and coping. Eur J Pers 1987 Sep;1(3):141-169. [doi: 10.1002/per.2410010304]

88.  Frydenberg E, Lewis R. Adolescent Coping Scale-Second Edition (ACS-2): User Manual. Melbourne, VIC: Australian Council for Educational Research (ACER Press); 2011.

89.  Payton JW, Wardlaw DM, Graczyk PA, Bloodworth MR, Tompsett CJ, Weissberg RP. Social and emotional learning: a framework for promoting mental health and reducing risk behavior in children and youth. J Sch Health 2000 May;70(5):179-185. [Medline: 10900594]

90.  Nielsen J, Landauer TK. A mathematical model of the finding of usability problems. 1993 Presented at: Proceedings of the INTERACT'93 and CHI'93 conference on Human Factors in Computing Systems; April 24-29, 1993; Amsterdam, The Netherlands p. 206-213. [doi: 10.1145/169059.169166]

91.  Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004 Sep 29;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]

92.  Johnson D, Gardner MJ, Perry R. Validation of two game experience scales: The Player Experience of Need Satisfaction (PENS) and Game Experience Questionnaire (GEQ). Int J Hum Comput Stud 2018 Oct;118:38-46. [doi: 10.1016/j.ijhcs.2018.05.003]

93.  Wilson CJ, Deane FP, Ciarrochi J, Rickwood D. Measuring help-seeking intentions: properties of the general help seeking questionnaire. Can J Couns Psychother 2005;39(1):15-28 [FREE Full text]

94.  Choi N, Fuqua DR, Griffin BW. Exploratory analysis of the structure of scores from the multidimensional scales of perceived self-efficacy. Educ Psychol Meas 2001 Jun 1;61(3):475-489. [doi: 10.1177/00131640121971338]

95.  Bandura A. Multidimensional Scales of Perceived Self-Efficacy. Stanford, CA: Stanford University; 1989.

96.  Pham YK, McWhirter EH, Murray C. Measuring help-seeking behaviors: factor structure, reliability, and validity among youth with disabilities. J Adolesc 2014 Apr;37(3):237-246. [doi: 10.1016/j.adolescence.2014.01.002] [Medline: 24636684]

97.  Kato T. Development of the Coping Flexibility Scale: evidence for the coping flexibility hypothesis. J Couns Psychol 2012 Apr;59(2):262-273. [doi: 10.1037/a0027770] [Medline: 22506909]

98.  Espelage DL, Holt MK. Bullying and victimization during early adolescence: Peer influences and psychosocial correlates. J Emot Abus 2001 Mar;2(2-3):123-142. [doi: 10.1300/J135v02n02_08]

99.  Second Step: Skills for Social and Academic Success. 2013. Illinois Bully Scale: Student Version URL: http://www.secondstep.org/Portals/0/G3/BPU/Evaluation_Tools/IllinoisBullyScaleStudent.pdf [WebCite Cache ID 720vGuTSr]

100. Low S, Espelage D. Differentiating cyber bullying perpetration from non-physical bullying: commonalities across race, individual, and family predictors. Psychol Violence 2013;3(1):39-52. [doi: 10.1037/a0030308]

101. Roberts RE, Lewinsohn PM, Seeley JR. A brief measure of loneliness suitable for use with adolescents. Psychol Rep 1993 Jun;72(3 Pt 2):1379-1391. [doi: 10.2466/pr0.1993.72.3c.1379] [Medline: 8337350]

102. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]

103. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, editors. The Social Psychology of Health: The Claremont Symposium on Applied Social Psychology. Newbury Park, CA: Sage Publications; 1988:31-67.

104. Lebeau RT, Glenn DE, Hanover LN, Beesdo-Baum K, Wittchen HU, Craske MG. A dimensional approach to measuring anxiety for DSM-5. Int J Methods Psychiatr Res 2012 Dec;21(4):258-272. [doi: 10.1002/mpr.1369] [Medline: 23148016]

105. American Psychiatric Association. 2013. Severity Measure for Generalized Anxiety Disorder-Child Age 11-17 URL: https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM5_Severity-Measure-For-Generalized-Anxiety-Disorder-Child-Age-11-to-17.pdf [accessed 2018-08-28] [WebCite Cache ID 720v6xbvI]

106. Johnson JG, Harris ES, Spitzer RL, Williams JB. 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]

107. Gonzalez C, Miner MH, Bockting WO. An examination of demographic characteristics, components of sexuality, and minority stress as predictors of cannabis, excessive alcohol, and illicit/nonprescription drug use among transgender people in the United States. Journal of Primary Prevention 2017;38(4):419-445 (forthcoming). [Medline: 28405831]

108. Bockting WO. Transgender identity, sexuality, and coming out: Implications for HIV risk and prevention. In: Proceedings of the NIDA-sponsored satellite sessions in association with the XIV International AIDS Conference, Barcelona, Spain, July 7-11, 2002. U.S. Bethesda, MD: National Institute on Drug Abuse, U.S. Department of Health and Human Services, National Institutes of Health; 2003:163-172.

109. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]

110. Centers for Disease Control and Prevention. 2017. Youth risk behavior surveillance system: High school survey URL: https://www.cdc.gov/healthyyouth/data/yrbs/index.htm [WebCite Cache ID 720v2FhYO]

111. Centers for Disease Control and Prevention. 2015. Youth risk behavior surveillance system: High school survey URL: https://www.cdc.gov/healthyyouth/data/yrbs/index.htm [WebCite Cache ID 720v5FvwH]

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RenderX

112.    The GenIUSS Group. 2014. Best practices for asking questions to identify transgender and other gender minority respondents on population-based surveys Los Angeles, CA: The Williams Institute URL: https://williamsinstitute.law.ucla.edu/wp-content/uploads/geniuss-report-sep-2014.pdf [accessed 2018-08-28] [WebCite Cache ID 720vlzdLZ]

113.    Hatzenbuehler ML, Jun HJ, Corliss HL, Austin SB. Structural stigma and cigarette smoking in a prospective cohort study of sexual minority and heterosexual youth. Ann Behav Med 2014 Feb;47(1):48-56 [FREE Full text] [doi: 10.1007/s12160-013-9548-9] [Medline: 24136092]

114.    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]

115.    Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. Clin Transl Sci 2011 Oct;4(5):332-337 [FREE Full text] [doi: 10.1111/j.1752-8062.2011.00347.x] [Medline: 22029804]

## Abbreviations

**GSA:** gay-straight alliance or gender and sexuality alliance
**LGBTQ:** lesbian, gay, bisexual, transgender, and queer
**RCT:** randomized controlled trial
**SGM:** sexual and gender minority
**SGMY:** sexual and gender minority youth
**T1:** baseline
**T2:** first follow-up
**T3:** final follow-up
**YRBS:** Youth Risk Behavior Survey

Protocol

# Blockchain Implementation in Health Care: Protocol for a Systematic Review

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## *Abstract*

**Background:** A blockchain is a digitized, decentralized, distributed public ledger that acts as a shared and synchronized database that records cryptocurrency transactions. Despite the shift toward digital platforms enabled by electronic medical records, demonstrating a will to reform the health care sector, health systems face issues including security, interoperability, data fragmentation, timely access to patient data, and silos. The application of health care blockchains could enable data interoperability, enhancement of precision medicine, and reduction in prescription frauds through implementing novel methods in access and patient consent.

**Objective:** To summarize the evidence on the strategies and frameworks utilized to implement blockchains for patient data in health care to ensure privacy and improve interoperability and scalability. It is anticipated this review will assist in the development of recommendations that will assist key stakeholders in health care blockchain implementation, and we predict that the evidence generated will challenge the health care status quo, moving away from more traditional approaches and facilitating decision making of patients, health care providers, and researchers.

**Methods:** A systematic search of MEDLINE/PubMed, Embase, Scopus, ProQuest Technology Collection and Engineering Index will be conducted. Two experienced independent reviewers will conduct titles and abstract screening followed by full-text reading to determine study eligibility. Data will then be extracted onto data extraction forms before using the Cochrane Collaboration Risk of Bias Tool to appraise the quality of included randomized studies and the Risk of Bias in nonrandomized studies of Interventions to assess the quality of nonrandomized studies. Data will then be analyzed and synthesized.

**Results:** Database searches will be initiated in September 2018. We expect to complete the review in January 2019.

**Conclusions:** This review will summarize the strategies and frameworks used to implement blockchains in health care to increase data privacy, interoperability, and scalability. This review will also help clarify if the strategies and frameworks required for the operationalization of blockchains in health care ensure the privacy of patient data while enabling efficiency, interoperability, and scalability.

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## Introduction

A blockchain is a digitized, decentralized, distributed public ledger that acts as a shared and synchronized database that records cryptocurrency transactions. While blockchains are essentially decentralized databases, there is no primary ownership of the data [1,2]. Through collaboration, users decide which data are added to the blockchain while ensuring that identical copies of the data are received and automatically updated [2]. Health care, in any setting, generates abundant complex and rich data, ranging from sensitive patient-identifiable data to operational analytics. The dissemination and essential actions of exchanging these health-related data mean that they remain at risk of privacy breaches [3]. Blockchain technologies have been proposed to respond to this challenge [3,4]. Once granted permission, verified users gain access to blockchain systems. This allows them to share relevant data with other verified users, guaranteeing accountability, scalability, and efficiency [3]. While this innovation has shown promise in various sectors, to ensure successful implementation in health care, various challenges need to be addressed first [1,5]. Because health-related data are numerous and sourced from many areas, the integration and linkage of data have the potential to generate valuable population-level insight [6]. A key consideration with the greater integration of health data sources is the need for strategies that safeguard access control to sensitive patient data. Additionally, as there is an expansion of health- and lifestyle-related data resulting from, for example, mobile apps and wearable devices, blockchain technologies may be exploited by patients, providers, and researchers through the enablement of novel mechanisms for consent and access [7].

As blockchains utilize cryptographic techniques to authenticate and verify users, their application may be used to control access to sensitive data [3]. While the adoption of electronic medical records in health care has become the de facto standard, most data within electronic medical records cannot be shared and exchanged between users appropriately [7]. Blockchain technologies, therefore, have the potential to increase interoperability between patients, carers, health care professionals, and researchers through the enablement of novel methods for data linkage of disparate sources [7]. As data can be sourced from one location, blockchains have the potential to tackle storage issues. By recording patient consent, blockchains could be a patient-empowering platform [8,9]. Information flow and exchange between users may only take place once the patient has consented [8]. Consent also allows health care providers to trust the data they access, thereby enabling them to treat their patients accordingly [8].

In addition to ensuring access security, scalability, and data privacy [7], blockchains also have the potential to enhance medical research through various use cases. Via implementation of health record blockchains, data sourced from medical records, health apps, and wearable devices could be stored and made accessible to users throughout their lives [7], thereby facilitating the conduct of longitudinal studies and pharmacovigilance applications. Each time a patient obtains a new prescription or test results, a patient could be notified that new data have been encrypted, sent for storage, and added to an automated system [7]. Moreover, patients would be able to add data sourced from wearable devices and health apps into this system [7]. Once the data are encrypted and stored, researchers can trust the data will not be altered [6]. Patients and participants may consent and revoke access, remaining in control of their information [10]. In addition to facilitating the collection of longitudinal data such as heart rate, diet, and exercise frequency, blockchains may store genomic data [10]. Blockchain technology may also be used to counter prescription drug fraud [10]. For example, Nuco, a blockchain company, addresses prescription duplication and "doctor shopping," whereby individuals visit numerous physicians to obtain as many prescriptions as they can [10]. According to Nuco, the problem lies in the inadequate communication between physicians and pharmacists, and blockchains have the capacity to tackle this issue through the verification of prescription authenticity [10]. These implementation scenarios show the strengths of implementation of a secure distributed data technology and the benefits they could make for individual and population data analysis.

Before adopting blockchains to empower patients, advance personalized medicine, accelerate research and development, and engage with populations that are considered "hard-to-reach" [7], challenges restricting their implementation need to be addressed. While broader access to health records may be achieved through blockchains, there is limited information on the costs required to establish and operationalize this decentralized framework [11]. Health systems spend large monetary sums on designing and maintaining traditional information system frameworks [11]. Additionally, various resources are required to troubleshoot issues, update parameters, and extract data [11]. Since blockchains do not require frequent troubleshooting, updates, or third-party involvement in financing, it is predicted that implementing blockchain technologies in health care may reduce costs. [11] To ensure adequate performance, organizations and institutions adopting blockchain technologies need to select specific frameworks to establish the size and format of the data that may be added to the system [11]. It may also prove to be a challenge to incentivize those in the health care sector to adopt novel blockchain technologies [11], thus expanding networks and scalability, owing to the unfamiliarity of the distribution authentication technology and concerns regarding ethics and privacy. A potential benefit, however, is that in addition to allowing clinicians access to real-time data, thereby enabling nationwide interoperability and the delivery of more coordinated patient care, researchers will be able to access and monitor nationwide data that could potentially aid in national surveillance and public health. Because using national programs to encourage digital data adoption have been successful [12], it is envisaged that if similar approaches are applied, the uptake of blockchains may also be achieved.

To the best of our knowledge, there are currently no systematic reviews on the strategies utilized to implement blockchains in health care. Nevertheless, a few reviews have been published focusing on specific aspects of blockchains in health care, such as its applications in health care [1], its potential to finance universal health coverage [13], and its potential to tackle counterfeit medicines [14]. The nature of a public distributed ledger also means that while blockchains could be used for a form of authentication and data access, the health care data would not be suitable for storage on a public ledger due to privacy implications. These considerations surround the application and trade-offs in implementation and require further research and potential standards for their use. Despite its potential to improve health care financing, the right systems must be put in place and "appropriate regulatory guidelines" must be followed before blockchains can be used in health care [13]. This is also true for the use of blockchains for tracking medication trade, which was described to be in its "infancy" and in need of further research [14].

Blockchains have the potential to address various challenges pertaining to data in health care. By requiring patient consent and user verification, privacy and security measures are enforced. Interoperability is facilitated, as data are securely shared among those with permission. Storage issues are also addressed through blockchains, as all the data are found in one location. By engaging various users and allowing for the sharing of multiple data sources at once, implementation of this novel approach may allow for more detailed analyses to be conducted, enhancing research and leading to potential disease prevention and health promotion. This aim of this review is to summarize the evidence on the strategies and frameworks utilized to implement blockchains for patient data in health care to ensure privacy and improve interoperability and scalability, with an aim to serve as an evidence base for development of new design innovations.

## Methods

### Systematic Review Execution

The Cochrane protocol guide will be used to guide the development of the systematic review protocol [15]. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Protocols (PRISMA-P) 2015 Checklist [16] will be used to report this systematic review (Multimedia Appendix 1). We will define a research question and establish a Population, Intervention, Comparator, and Outcome framework to develop and combine Medical Subject Headings, subject headings, and keywords. The review will undergo the following six stages: literature search, selection of articles, extraction of data, appraisal of quality, analysis of data, and synthesis of data.

### Identification of a Research Question

How do implementation strategies, design, and frameworks required for the operationalization of blockchains in health care

enable privacy of patient data while enabling efficiency, interoperability, and scalability?

### Criteria for Considering Studies for the Review

#### Types of Studies

As blockchains applied to the health care sector remain a novel approach, we will not place restrictions on the study type. This review will include all types of studies as long as other eligibility criteria are met, for example, we will consider randomized controlled trials and observational studies. We will only include studies published in English.

#### Types of Participants

The population will consist of patients who have their data incorporated within ecosystems utilizing blockchains in health care data management.

#### Intervention and Comparator

The included studies will assess blockchain technologies in health care systems to improve issues revolving around access, interoperability, and scalability. Dates of publication and study location will not be restricted. Comparators may consist of other traditional frameworks or technological advances adopted in health systems to improve access, interoperability, and scalability, thereby providing more coordinated health care. For example, learning health systems, which utilize data to provide evidence, thereby allowing continuous learning and improvement of health care, may represent a comparator. We will include studies that have not identified a comparator if they meet the remaining criteria required for study inclusion.

#### Types of Outcomes

Textbox 1 outlines the review outcomes. The primary outcomes will include the extent of access, interoperability, scalability of health care blockchains following the implementation of various strategies and frameworks required for their operationalization, impact on computational performance, and costs and benefits for the use of blockchain systems. Health outcomes will be considered as a secondary outcome and will be assessed to determine whether blockchains can improve the health of individuals and populations when compared with more traditional platforms or other technological advances.

We will use Levels of Information Systems Interoperability, a reference model [17], to measure the level of interoperability. The Data Analysis and Synthesis section (below) will discuss details of how to implement this model. We will assess the scalability of the blockchain by measuring blockchain adoption across the study or survey implementation contexts. To assess privacy, we will identify whether the blockchains abide by legal and regulatory frameworks. As regulatory frameworks may vary according to study setting, we will identify relevant frameworks and legislation once studies are selected and the settings identified. As we complete initial scoping of the literature to identify key outcomes relevant for classification in the review, we shall refine the primary and secondary outcomes.

**Textbox 1.** Review outcomes.

Primary outcomes:

- Extent of interoperability

- Extent of scalability

- Privacy, security, and access

- Implications and trade-offs of computational performance

- Costs and benefits to be derived from the use of blockchains in existing systems

Secondary outcomes:

- Health outcomes

## Search Methods

We will systematically search the following electronic databases: MEDLINE and PubMed, Embase, Scopus, ProQuest Technology Collection, and Engineering Index (Compendex). Following exploratory research around the review research question, we will develop Medical Subject Headings, subject headings, and keywords. There will be no restrictions placed on dates of publication, study types, and geographic locations. However, we will only include studies published in English. We intend to search MEDLINE and PubMed first by implementing a search strategy for preliminary research (Multimedia Appendix 2). Based on the findings of this search, we will develop our search strategy and will adapt the strategy for the Embase and Scopus databases. We will not restrict the search by date. EndNote X8.2 (Clarivate Analytics, Philadelphia, PA, USA) will be used to import the results of our searches and remove duplicates. The bibliographic citations of included studies will also be manually searched to identify other studies that fill the review's inclusion criteria. We will also use similar search terms when utilizing search engines such as Google to systematically search the gray literature; we will consider conference proceedings and reports meeting the review criteria.

## Selection of Studies

The titles and abstracts of studies identified following database searches will be screened by two independent reviewers. Upon completion of title and abstract screening, we will assess the remaining studies through full-text reading. Discussion will be used to resolve disagreements. A third reviewer will be consulted if consensus cannnot be reached. The review's selection process will be demonstrated using a PRISMA flow diagram.

## Data Extraction and Management

Data will be extracted and collated by two independent reviewers onto predetermined data extraction forms. Where reviewers cannot agree following discussion, a third reviewer will be asked to assist in the decision-making process. Data extraction forms will be validated by the review team prior to utilization to ensure acceptability. We will extract the following data:

1. Date of publication and author
2. Characteristics of the study: location, duration, sample size, and control

3. Characteristics of the intervention: departments or facilities adopting the blockchain, blockchain enablers, challenges, costs, and implementation strategies or frameworks
4. Characteristics of the comparator: departments or facilities adopting the comparator, comparator enablers, challenges, costs, and implementation strategies or frameworks
5. Outcomes: extent of access (primary outcome), interoperability (primary outcome), scalability (primary outcome), and health outcomes (secondary outcome).

## Assessment of Risk of Bias of Included Studies

The risk of bias of the included studies will be assessed by two independent reviewers. A third reviewer will assist in the decision making if the two reviewers disagree on their assessments regarding the methodological quality of included studies.

For randomized controlled trials, the Cochrane Collaboration Risk of Bias tool will be used to assess the following [12]: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

Subsequent to the determination of the selection, we will categorize performance, detection, attrition, reporting, and other bias assessments of the included studies as high risk, low risk, or unclear risk. A risk of bias graph and a risk of bias summary will then be developed to illustrate the methodological quality of included studies.

Other nonrandomized studies will be assessed using the Risk of Bias in Non-randomized Studies-of Interventions [18]. This tool will be used to assess the following seven domains [19,20]:

1. Bias due to confounding (preintervention)
2. Bias in the selection of participants to the study (preintervention)
3. Bias in the classification of interventions (at intervention)
4. Bias due to deviations from intended interventions (postintervention)
5. Bias due to missing data (postintervention)
6. Bias in the measurement of outcomes (postintervention)
7. Bias in the selection of the reported result (postintervention)

A qualitative bias framework will be identified during the execution of the review to examine the paper quality of any studies that do not fall under the Cochrane Collaboration Risk

of Bias tool or Risk of Bias in Non-Randomized Studies-of Interventions.

## Data Analysis and Synthesis

We intend to summarize our data numerically (by describing the number and type of studies incorporated within the review) and narratively (by synthesizing data from included studies). From the results of our review, we will aim to map the strategies and frameworks enabling operationalization of blockchains within health systems in a clear format. We intend to measure the extent of interoperability using the Levels of Information Systems Interoperability model [17]. Therefore, we will classify the level of interoperability as the following:

1. Enterprise (universal): data are fully shared and distributed across the health system
2. Domain (integrated): data exchange through shared domain-based models
3. Functional (distributed): sharing of logical data models (eg, relational tables) across a health system
4. Connected (peer-to-peer): exchange of data through electronic means
5. Isolated (manual): integration of data from various systems conducted manually.

To assess scalability, we will determine whether studies measured adoption or uptake across the health care sector, thereby enabling us to assess whether nationwide uptake of the automated system is feasible.

In order to assess whether the blockchain addresses privacy and security issues adequately, we will evaluate whether legislation, including the Health Insurance Portability and Accountability Act of 1996 regulations, have been considered [21]. Legislation considered by the review will depend on study settings, and we will identify this upon study selection. If a study uses Health Insurance Portability and Accountability Act of 1996, this will include:

1. Data encryption: whether the system has encrypted information, allowing only those with a "key" to access
2. Audit trail: whether the system stores information on who accessed the information, the application of modifications, and when the system granted access and applied modifications
3. Access control: whether passwords and personal identification numbers are used in the system, limiting access only to those authorized.

## Results

Database searches will be initiated in September 2018. We expect to complete the review in January 2019.

## Discussion

### Principal Findings

By means of the proposed systematic review, we intend to provide evidence of the strategies and frameworks utilized in the implementation of health care blockchains. Through the development of recommendations that will assist key stakeholders in health care blockchain implementation, we predict that the evidence generated will challenge the health care status quo, moving away from more traditional approaches and facilitating decision making of patients, health care providers, and researchers. As the current traditional system applied in health systems does not fully support interoperability, it is predicted that health care blockchains will enable the delivery of team-based health care by means of nationwide interoperability while optimizing precision medicine research and ensuring prescription authenticity. However, prior to large-scale implementation of these automated systems, it is crucial that research and trials ensure that they are cost-effective and secure systems that maintain the privacy and security of patients and comply with regulatory frameworks.

### Strengths and Limitations

A strength of this proposed systematic review is that it will provide evidence on the strategies and frameworks required for the operationalization of efficient health care blockchains. Furthermore, the potential of health care blockchains in enhancing user access, interoperability, scalability, and health outcomes will be assessed. We predict that the unmet needs of patients, health care providers, and researchers regarding data sharing will be identified through conduction of this systematic review. Finally, we predict that areas around the architecture of health care blockchains that require further research will be identified upon completion of the systematic review. A limitation of our review is that studies published in languages other than English will be excluded.

### Conclusions

As systematic reviews provide the highest form of evidence, we anticipate that review findings will provide patients, researchers, and health care providers with information on health care blockchains. Transparent and rigorous methods will be applied, thereby demonstrating replicability of the review. In addition to consulting blockchain experts and professionals, we anticipate that the review will guide the team in developing recommendations pertaining to blockchains that will enable decision making of developers, patients, health care providers, and researchers.

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## Authors' Contributions

EM conceived the study aims and objectives, contributed to drafts, led the methodological review, revised all drafts, responded to peer review feedback, and provided oversight. TO wrote the initial draft report and incorporated feedback from authors on the first draft. MVV provided feedback on methodology. DB, GW, and MVV reviewed the first draft. AA, JC, AM, and KAF reviewed the second draft. TO and AA reviewed BioMed Central guidelines. EM responded to peer review and submitted subsequent drafts. The final report was agreed by all authors. EM is the guarantor.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

The PRISMA-P 2015 Checklist.

[DOCX File, 31KB - resprot_v8i2e10994_app1.docx ]

## Multimedia Appendix 2

MEDLINE/PubMed search strategy.

[DOCX File, 21KB - resprot_v8i2e10994_app2.docx ]

## References

1. Kuo T, Kim H, Ohno-Machado L. Blockchain distributed ledger technologies for biomedical and health care applications. J Am Med Inform Assoc 2017 Nov 01;24(6):1211-1220. [doi: 10.1093/jamia/ocx068] [Medline: 29016974]
2. Nugent T, Upton D, Cimpoesu M. Improving data transparency in clinical trials using blockchain smart contracts. F1000Res 2016;5:2541 [FREE Full text] [doi: 10.12688/f1000research.9756.1] [Medline: 28357041]
3. Xia Q, Sifah E, Smahi A, Amofa S, Zhang X. BBDS: Blockchain-Based Data Sharing for Electronic Medical Records in Cloud Environments. Information 2017:44. [doi: 10.3390/info8020044]
4. Ichikawa D, Kashiyama M, Ueno T. Tamper-Resistant Mobile Health Using Blockchain Technology. JMIR Mhealth Uhealth 2017 Jul 26;5(7):e111 [FREE Full text] [doi: 10.2196/mhealth.7938] [Medline: 28747296]
5. Peterson K, Deeduvanu R, Kanjamala P, Boles K. HealthIT. A Blockchain-Based Approach to Health Information Exchange Networks URL: https://www.healthit.gov/sites/default/files/12-55-blockchain-based-approach-final.pdf [accessed 2018-12-02] [WebCite Cache ID 74MafCang]
6. Asokan GV, Asokan V. Leveraging "big data" to enhance the effectiveness of "one health" in an era of health informatics. J Epidemiol Glob Health 2015 Dec;5(4):311-314 [FREE Full text] [doi: 10.1016/j.jegh.2015.02.001] [Medline: 25747185]
7. Linn LA, Koo MB. Blockchain For Health Data and Its Potential Use in Health IT and Health Care Accessed 24 Nov 2017 URL: https://www.healthit.gov/sites/default/files/11-74-ablockchainforhealthcare.pdf [accessed 2018-08-09] [WebCite Cache ID 71XaF2S1f]
8. Brodersen C, Kalis B, Leong C, Mitchell E, Pupo E, Truscott A. Accenture LLP. 2016. Blockchain: Securing a New Health Interoperability Experience URL: https://pdfs.semanticscholar.org/8b24/dc9cffeca8cc276d3102f8ae17467c7343b0.pdf [accessed 2018-08-09] [WebCite Cache ID 71XcZjO4m]
9. Xhafa F, Li J, Zhao G, Li J, Chen X, Wong DS. Designing cloud-based electronic health record system with attribute-based encryption. Multimed Tools Appl 2014 Feb 11;74(10):3441-3458. [doi: 10.1007/s11042-013-1829-6]
10. Engelhardt M. Technology Innovation Management Review. 2017. Hitching Healthcare to the Chain: An Introduction to Blockchain Technology in the Healthcare Sector URL: https://timreview.ca/article/1111 [accessed 2018-12-02] [WebCite Cache ID 74Mav0ldR]
11. Krawiec R, Housman D, White M, Filipova M, Quarre F, Barr D. Blockchain: Opportunities for Health Care. London: Deloitte; 2016. URL: https://www2.deloitte.com/content/dam/Deloitte/us/Documents/public-sector/us-blockchain-opportunities-for-health-care.pdf [WebCite Cache ID 71XbpfmFz]
12. Meaningful Use. 2017. Centers for Disease Control and Prevention URL: https://www.cdc.gov/ehrmeaningfuluse/introduction.html [accessed 2017-11-24] [WebCite Cache ID 71Xc3VUVh]
13. Till BM, Peters AW, Afshar S, Meara J. From blockchain technology to global health equity: can cryptocurrencies finance universal health coverage? BMJ Glob Health 2017;2(4):e000570 [FREE Full text] [doi: 10.1136/bmjgh-2017-000570] [Medline: 29177101]
14. Mackey TK, Nayyar G. A review of existing and emerging digital technologies to combat the global trade in fake medicines. Expert Opin Drug Saf 2017 May;16(5):587-602. [doi: 10.1080/14740338.2017.1313227] [Medline: 28349715]
15. Cochrane Handbook for Systematic Reviews of Interventions Internet. 2011 URL: http://handbook-5-1.cochrane.org/ [accessed 2018-08-09] [WebCite Cache ID 71Xdyuonj]

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16.   Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for
      systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text]
      [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
17.   Meersman R, Tari Z, Herrero P. On the Move to Meaningful Internet Systems. In: OTM 2008 Workshops. Mexico:
      Monterrey, Mexico. 2008 ed. Springer; 2008.
18.   Cochrane Methods Bias. 2017. Assessing Risk of Bias in Included Studies URL: https://methods.cochrane.org/bias/
      assessing-risk-bias-included-studies [accessed 2018-08-09] [WebCite Cache ID 71XeBov4Y]
19.   Sterne J, Hernán MA, Reeves B, Savović J, Berkman N, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias
      in non-randomised studies of interventions. BMJ 2016 Oct 12;355:i4919 [FREE Full text] [doi: 10.1136/bmj.i4919] [Medline:
      27733354]
20.   Sterne J, Higgins J, Elbers R. Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I): detailed guidance.
      Reeves BC and the development group for ROBINS-I URL: https://www.bristol.ac.uk/media-library/sites/
      social-community-medicine/images/centres/cresyda/ROBINS-I_detailed_guidance.pdf [accessed 2018-08-09] [WebCite
      Cache ID 71XeSGMgT]
21.   Privacy, Security, and Electronic Health records. Washington, DC: US Department of Health & Human Services Office
      for Civil Rights; 2018. URL: https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/consumers/
      privacy-security-electronic-records.pdf [accessed 2018-11-25] [WebCite Cache ID 71XeXbMcL]

## Abbreviations

**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis
**PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

Protocol

# Rationale and Design of a Remote Web-Based Daily Diary Study Examining Sexual Minority Stress, Relationship Factors, and Alcohol Use in Same-Sex Female Couples Across the United States: Study Protocol of Project Relate

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## Abstract

**Background:** The Healthy People 2020 initiative aims to reduce health disparities, including alcohol use, among sexual minority women (SMW; eg, lesbian, bisexual, queer, and pansexual). Compared with heterosexual women, SMW engage in more hazardous drinking and report more alcohol-related problems. Sexual minority stress (ie, the unique experiences associated with stigmatization and marginalization) has been associated with alcohol use among SMW. Among heterosexuals, relationship factors (eg, partner violence and drinking apart vs together) have also been associated with alcohol use. Negative affect has also been identified as a contributor to alcohol use. To date, most studies examining alcohol use among SMW have used cross-sectional or longitudinal designs.

**Objective:** Project Relate was designed to increase our understanding of alcohol use among young SMW who are at risk for alcohol problems. The primary objectives of this study are to identify daily factors, as well as potential person-level risk and protective factors, which may contribute to alcohol use in SMW. Secondary objectives include examining other physical and mental concerns in this sample (eg, other substance use, eating, physical activity, and stress).

**Methods:** Both partners of a female same-sex couple (aged 18-35 years; n=150 couples) are being enrolled in the study following preliminary screening by a market research firm that specializes in recruiting sexual minority individuals. Web-based surveys are being used to collect information about the primary constructs of interest (daily experiences of alcohol use, sexual minority stress, relationship interactions, and mood) as well as secondary measures of other physical and mental health constructs. Data are collected entirely remotely from women across the United States. Each member of eligible couples completes a baseline survey and then 14 days of daily surveys each morning. Data will be analyzed using multilevel structural equation modeling.

**Results:** To date, 208 women (ie, 104 couples) were successfully screened and enrolled into the study. In total, 164 women have completed the 14-day daily protocol. Compliance with completing the daily diaries has been excellent, with participants on average completing 92% of the daily diaries. Data collection will be completed in fall 2018, with results published as early as 2019 or 2020.

**Conclusions:** Project Relate is designed to increase our understanding of between- and within-person processes underlying hazardous drinking in understudied, at-risk SMW. The study includes a remote daily diary methodology to provide insight into variables that may be associated with daily hazardous alcohol use. Before the development of programs that address hazardous alcohol use among young SMW, there is a need for better understanding of individual and dyadic variables that contribute to risk in this population. The unique challenges of recruiting and enrolling SMW from across the United States in a daily diary study are discussed.

# Introduction

## Background

One of the goals of Healthy People 2020 [1], a science-based report issued by the US Office of Disease Prevention and Health Promotion that identifies national objectives for improving the health of Americans, is to specifically improve the health and well-being of lesbian, gay, bisexual, and transgender (LGBT) individuals. Compared with heterosexual women, sexual minority women (SMW; eg, lesbian, bisexual, queer, and pansexual) engage in more heavy drinking and have lower rates of abstention from drinking [2-4]. SMW also experience more negative alcohol-related consequences than heterosexual women, such as driving under the influence of alcohol, having unplanned sex, having suicidal thoughts during or after drinking, fighting or arguing with someone, and engaging in sexual harassment during/after drinking [5,6]. Despite evidence for health disparities between heterosexual women and SMW in alcohol use, much remains to be learned regarding why some SMW in particular are at risk. The goal of this study, Project Relate, was to increase the understanding of hazardous drinking among SMW who are in same-sex relationships using an entirely remote Web-based data collection procedure, including a daily diary component. This approach permits examination of research questions at multiple levels, allowing us to consider between-couple characteristics (ie, couple-level; answering the question: *which couples* drink more), between-person characteristics (ie, person-level; answering the question: *who* drinks more), and within-person processes (ie, daily level; answering the question: *when* does one drink more). The primary objective of this study is to examine the daily associations between hazardous alcohol use and sexual minority stress, affect, and relationship factors among young same-sex female couples. The theoretical framework and existing empirical evidence that contributed to the development of this study are described below.

## Sexual Minority Stress and Alcohol Use

Members of minority groups experience unique stressors related to their stigmatized and marginalized social status in society. Stigmatization and marginalization based on sexual identity or orientation is known as sexual minority stress [7-9]. Specifically, Meyer's [9] model of sexual minority stress involves experiences of harassment or discrimination related to sexual identity/sexual orientation (ie, heterosexism), the expectation of and vigilance toward these events, concealment of sexual identity, and the internalization of negative societal attitudes toward one's sexual identity (eg, internalized heterosexism). Together, these experiences create additional stressors beyond those experienced by majority of individuals. There is ample evidence that sexual minority stress is associated with negative health behaviors, such as alcohol use, through emotion regulation and coping strategies [8,10-14] as well as through less perceived social support [12] and more social constraints and social isolation [13]. Although these studies provide important information regarding how minority stress is associated with negative affect and alcohol use at the between-person level, it is important to note that these studies used primarily cross sectional (ie, single assessment points) and traditional longitudinal designs (ie, using repeated assessments over weeks, months, or years). These types of designs limit our understanding of within-person processes by either studying processes as a between-person variable (ie, using cross-sectional designs) or by studying long-term within-person differences (ie, using traditional longitudinal designs). A handful of studies have used daily or momentary assessment of stress and alcohol use among sexual minorities. For example, in research of young men who have sex with men, alcohol use was greater on days when men indicated they were drinking to cope with stress [15] and on days when general stress was reported [16]. Furthermore, in a 9-day daily diary study, the interaction of structural stigma (eg, state policies that promote discrimination) and rejection sensitivity was associated with alcohol use among young men who have sex with men. Most relevant to this study was the finding that discrimination was associated with contemporaneous and prospective substance use in a group of sexual and gender minority individuals [17]. However, the question of how *daily* experiences of sexual minority stress and negative affect contribute to SMW's hazardous drinking remains. In this study, we will test whether greater daily sexual minority stress is directly associated with more alcohol use and associated problems as well as examine indirect associations through negative affect.

## Relationship Factors and Alcohol Use

In addition to the link between sexual minority stressors, negative affect, and alcohol use, it is important to consider the associations between relationship factors and alcohol use. A review of studies on heterosexual couples concluded that unpartnered individuals drank more compared with those in serious romantic relationships and that drinking is associated with poorer relationship quality as well as conflict and violence [18]. Among SMW, several studies have demonstrated associations between partner violence and alcohol use and related problems in samples of SMW. For example, in a study of lesbian couples who experienced intimate partner violence, approximately 64% of both batterers and victims report using alcohol or drugs before the violent incidents [19]. Alcohol use was also associated with SMW's nonphysical domestic violence (eg, verbal threats and damage to property) [20]. Research also suggests that intimate partner violence among SMW is associated with hazardous alcohol use [21], which may stem from emotional distress [22] or sexual minority stressors [23].

Another important characteristic when studying relationships and hazardous alcohol use is the degree to which partners drink together versus separately. Among heterosexuals, drinking together has been associated with more intimacy and fewer negative partner behaviors than drinking apart [24]. Conversely, drinking apart is associated with more negative relationship events [24] as well as less satisfaction, more conflict, and marital dissolution [18,25]. Among lesbian women, when controlling for physical and psychological aggression, discrepant drinking (ie, differences in partners' drinking quantity) is associated with poorer relationship adjustment [26]. Furthermore, in a longitudinal examination of discrepant drinking and intimate partner violence among lesbian partners, a cyclical pattern of alcohol use and violence occurred such that discrepant drinking predicted psychological aggression 6 months later, which in turn predicted later discrepant drinking. Physical violence also predicted subsequent discrepant drinking 6 months later [27]. Considering the small body of work connecting alcohol use to relationship variables in SMW, in this study, we will examine how instances of partners drinking together versus apart and discrepant drinking are associated with relationship functioning on the same day and subsequent days and in turn, how relationship functioning may then be associated with drinking on subsequent days.

## Protective Factors

The impact of minority stress and negative relationship factors may be modifiable at the couple- or individual-level [9,28], but more information is needed to understand what factors may protect SMW from problematic alcohol use [29]. Therefore, the final aim of this research is to investigate societal-, couple-, and person-level characteristics that could be associated with daily experiences of sexual minority stress, relationship quality, and drinking or that may strengthen or weaken the associations among them. For example, connection to the sexual minority community, a stronger sexual minority identity, and social support may all protect against the deleterious effects of sexual minority stress and related negative mental and behavioral outcomes [30-32]. Similarly, being in a legally recognized relationship may also be a protective factor against sexual minority stress and negative health outcomes [33-35]. Although marriage between same-sex individuals is now legal in all states in the United States, other protections (eg, housing, employment, and health care benefits) are not federally mandated and, thus, vary by state. The lack of these state protections (ie, structural stigma) has been associated with health outcomes. For example, in a study published in 2014, sexual minority individuals who lived in states without protections for sexual minorities (eg, in housing and employment benefits) and that banned same sex marriage had a higher prevalence of psychiatric disorders than those who lived in states with such protections [36]. In this study, we will assess a variety of potential factors that may protect against hazardous drinking, including both factors specific to the person or couple (eg, connection to sexual minority community and being in a committed relationship), as well as structural factors (eg, living in a state with protections for people in same-sex relationships). Identification of potentially modifiable individual risk and protective factors can facilitate development of culturally tailored inventions to reduce

hazardous drinking. Furthermore, identification of structural (societal) risk and protective factors may suggest important directions for advocacy efforts.

## Study Objectives

The primary objective of Project Relate is to increase our understanding of hazardous drinking among SMW. Using a daily diary methodology, this project investigates the associations among sexual minority stress, affect, relationship factors, and alcohol use. The development of this study was guided by minority stress theories [7-9] that offer a way to understand the unique stressors that SMW experience related to their marginalized societal status. In addition, because relationship factors are important correlates of alcohol use among heterosexual couples [18], we consider how relationship characteristics are associated with alcohol use among young adult same-sex female couples. In addition, we also look at potential protective factors. Collecting information on sexual minority stressors, emotional functioning, relationship experiences, and alcohol use from both partners will allow us to assess the interactions among these variables as they enhance or reduce the quality of life of SMW. Extensive background information, including personality characteristics, social support, history of discrimination, and community context, will provide information on personal and contextual factors that moderate these associations. A secondary objective of Project Relate is to examine other physical and mental health concerns, including other substance use, eating, physical activity, and general mental health and well-being among SMW. The opportunity to examine daily-, individual-, and couple-level effects is a particular strength of the study methodology.

# Methods

## Project Overview

Project Relate is an ongoing daily diary study of same-sex female couples. Young adult SMW (aged 18-35 years) are the target sample for this study because in community samples they frequently endorse indicators of hazardous drinking [3]. Both partners of the romantic relationship are enrolled to capture information about the relationship from both members' perspectives. Participants are recruited from across the United States, and data collection is occurring remotely via Web-based surveys. Both women in each couple complete a comprehensive baseline survey and then a brief daily survey each morning for the following 14 days. Each member of the couple begins the daily survey on the same day to ensure we have corresponding daily data for each couple. The Old Dominion University Institutional Review Board approved all study procedures (Project #839097).

## Power Analysis

A power analysis to determine the sample size needed for planned analyses was conducted in 2 steps. First, a power analysis was conducted for traditional structural equation modeling using Monte Carlo simulation methods [37], focusing on powering the hardest effects to detect (the small indirect effects, beta=.10). Similar models were conducted incorporating a small-to-medium effect–moderating variable (beta=.20). Monte

Carlo simulation methods indicated that for the effect size expected, a sample size of 200 *cases* yields sufficient power (0.808) to detect the relevant effects. This, however, assumes no correlation among residuals, which we know is not true in nested designs. To determine how to appropriately account for the correlated observations and identify the minimum number of participants needed for power of .8 in the multilevel design, a formula taking into account the expected intraclass correlation coefficients (ICCs), or degree of relatedness within couples, for key variables was used [38]. Assuming an average of 11 days of assessments (80% response rate to account for attrition) and 150 couples, an ICC up to approximately .70 would yield the necessary number of *cases* to maintain a power of .80. Previous daily diary alcohol research suggests we can expect to see lower ICCs, likely ranging from .4 to .7 [39], yielding more power. Therefore, recruiting 150 couples (N=300 people) is more than adequate to provide sufficient power.

## Participant Selection

Recruiting large samples of sexual minorities is difficult to do in many localities, and therefore, we are recruiting participants from across the United States. We partnered with Community Marketing and Insights (CMI), a leading market research firm specializing in Web-based research with the LGBT community. CMI maintains a proprietary research-only panel of over 90,000 individuals who identify as sexual minorities and regularly take part in market research and health research (although psychological research studies are less common). CMI recruits participants to take part in this study from their existing panel and potential new panel members who may be interested in participating in research studies. CMI is consistently recruiting new research panel members through LGBT print, digital, and event outreach activities as well as LGBT-specific outreach on social media sites (eg, Facebook, Craigslist, and sexual minority-specific social media).

To be eligible for the study, both partners have to meet the following eligibility criteria: (1) aged 18 to 35 years, (2) self-identify as a cisgender woman (meaning self-identify as a woman and was assigned female at birth, ie, she is not transgender), (3) currently in a romantic relationship with a woman for at least 3 months, (4) see partner in person at least once per week, and (5) able to respond to daily surveys between 6 am and 12 pm for 2 weeks. In addition to these 5 criteria that must be met by all participants, at least one person in the couple must also meet the following 3 criteria: (6) only or mostly attracted to women, (7) drank alcohol at least 3 days in the previous 2 weeks, (8) drank 4 or more standard alcoholic drinks in 1 sitting at least once in the previous 2 weeks (ie, met criteria for a binge drinking episode).

These inclusion criteria were developed for several reasons. First, although we recognize that people with other gender identities (eg, transgender and nonbinary gender) and sexual identities (eg, bisexual women not in a relationship with a woman) are also at risk for experiencing both sexual minority stress and hazardous alcohol use, individuals with different gender and sexual identities likely experience stressors that differ from one another [29]. In other words, a transgender and cisgender woman's or a lesbian and bisexual woman's daily experiences might differ from each other. Thus, this study focuses solely on individuals who identify as cisgender female and are in a relationship with a woman. Second, we require the couples to see each other in-person at least once a week to avoid potential confounds related to being in a long-distance relationship. Third, although 1 participant has to report only or mostly attracted to women, her partner can describe her attraction in other ways (eg, attracted to men and women equally); this criterion was used both to obtain a sample size large enough to test study aims and to have some variability in attraction (eg, attracted to men and women) and identity (eg, lesbian, bisexual, and queer) that can be explored statistically. Finally, the alcohol inclusion criteria for 1 participant is used to identify participants belonging to the desired at-risk alcohol use population of interest and to increase the likelihood of enrolling couples in which at least 1 partner drinks with some frequency, resulting in occurrence of drinking during the 14-day daily diary reporting period.

## Study Procedures

### Recruitment

CMI initiates the recruitment process by contacting potential participants via email and providing them with a link to a Web-based screening survey. The potential participant is also asked if she thinks her partner would be interested in participating, and if so, to provide her email address. CMI then screens her partner for interest and eligibility, and once potentially eligible couples are identified, CMI provides the researchers with the email addresses of potential participants and their partners. Upon receiving contact information for potentially eligible couples, the researchers conduct a second set of screening assessments (using the criteria described above) to ensure eligibility of the couple.

### Study Description and Informed Consent

Once eligibility and interest are verified for both people in the couple, they are emailed separately with introductory information about the study. Given that data collection is occurring entirely remotely, and daily assessment procedures are likely new to these participants, we developed detailed written and video materials describing the study purpose, procedures, risks, and benefits. The professionally developed videos consist of 5 brief (1-3 min) videos of the study investigators and research assistants describing the study. Corresponding written materials were also developed. Given that developing these videos took additional time and resources above what was required to develop the written materials, we built in a design feature to assess the video utility. Specifically, couples were randomized in blocks of 6 to 1 of 2 introductory information groups: (1) videos plus written materials (video+written) or (2) written materials only (written-only). Couples are randomized (instead of individual participants) to limit contamination between partners. Those in the video+written group receive a Qualtrics survey Web link that guides participants through the series of 5 videos explaining the purpose and procedures of the study; the written material is also available below the video. Couples assigned to the written-only group receive a similar Qualtrics survey link where they review the same information presented in the videos, but

in text form only. The written materials provided for participants can be found in Multimedia Appendix 1. The length of time participants spend reviewing the materials (including time spent on each individual video and corresponding written text) is automatically tracked. Immediately after reviewing the study information, participants are presented with the informed consent document. If participants do not consent within 2 to 3 days of the initial email, they are sent 2 additional email reminders (approximately 2-3 days apart) regarding the study and consent procedures. Both women in the couple must provide consent before either can begin the study.

### Baseline Survey

After both members of the couple provide consent, the couple is enrolled in the study. At that time, each participant receives an email via Qualtrics with an individual link to her baseline survey. The survey takes approximately 30 min to complete. In the email, participants are asked to complete the baseline survey within 3 days. Similar to the consent procedures, if participants do not complete the baseline survey within 2 to 3 days, 2 email reminders are sent approximately 2 to 3 days apart. Both members of the couple must complete the baseline survey to move on to the daily survey. If only 1 partner completes the baseline survey and her partner does not, she is thanked, compensated for completing the baseline survey, and informed that her participation is complete (without being told her partner did not complete the baseline survey).

### Daily Surveys

Once both members of the couple complete the baseline survey, they are notified separately via email of the starting date of the daily survey (which ideally occurs the day after they complete the baseline survey). Each person in the couple is sent separate automated emails through the Qualtrics survey system, with an individual link to their brief daily survey each morning at 6:00 am for the following 14 days. We selected a 14-day assessment period based on research demonstrating daily sexual minority stressors [40,41] and alcohol use [17,42] occur over this length of time as well as our screening criteria requiring binge drinking (in at least 1 partner) during the previous 2 weeks. Thus, using a 14-day daily assessment period should appropriately balance both participants' burdens while ensuring the study is of sufficient duration to capture the experiences and behaviors of interest in daily life. Each daily survey takes approximately 5 min to complete. Participants are instructed to complete the survey independently from their partner using their own personal computer, tablet, or mobile device by 12:00 pm each day. The participants receive a reminder email after 2 consecutive days of missing or incomplete surveys.

Consistent with other daily diary studies of alcohol use [43,44], we elected to have participants complete surveys each morning (about the previous day) instead of at the end of the day (about that day) because our primary research questions of interest were regarding alcohol use, and end of day surveys could present 3 concerns. First, we were concerned we could *miss* reports of drinking if participants elected to complete the survey in the evening before drinking (or before they finished drinking).

Second, some of our questions were regarding alcohol use consequences, and some consequences (eg, being hungover) may not emerge until many hours after drinking stops. Third, on days when participants were drinking, if we asked them to complete a survey in the evening, we were concerned they could be intoxicated while completing the daily survey. We realize that by asking participants to report on their previous day each morning (vs current day each evening) requires some additional retrospection; however, given the focus on alcohol use in this study, any concerns regarding additional retrospective bias were outweighed by the alcohol-related concerns noted above.

### End of Study Survey

On the day after the final daily survey, participants receive an email with a link to take a survey specifically designed for this study about their reactions as a study participant. Additional details regarding this measure can be found in the Measures section.

### Compensation

Participants and their partners each receive US $25 for completing the baseline survey and US $3 each for each daily survey, with a US $10 bonus for completing at least 80% of the daily surveys (ie, more than 11 days). Thus, each participant can earn a maximum of US $77 via their choice of check or gift card.

## Measures

All measures included in the baseline survey are described in Table 1. The measures are organized by those designed to test the primary study aims described above and secondary measures that will supplement testing of the primary aims. For each measure, we provide a brief description of the construct assessed. In addition, several modifications to measures were made and are worth noting. First, most measures in the baseline survey referencing a specific time frame were adapted to 3 months to be consistent throughout the survey and ensure we could examine these constructs during similar time periods. The time frames of the following measures were *not* adapted: the Conflict Tactics Scale [45], the Psychological Maltreatment of Women Inventory [46], the physical health questions Short Form-20 [47], the Daily Heterosexist Experience Questionnaire [48], and the Modified Eating Disorder Examination Questionnaire [49,50]. These measures were not changed to a 3-month time frame because their original time frames (eg, last year and last month) were more appropriate for addressing the study aims. Second, changes were made to several of the measures to be appropriate for same-sex female couples. These adaptions included changing male or gender-neutral pronouns to female pronouns and modifying sexual behavior items that require male partners. Finally, because of the length of the baseline survey, attention check items were added to ensure that participants are paying attention and selecting their answers carefully. Attention check items are included as items in some of the longer measures as well as stand-alone questions. Rationale for inclusion of these items is discussed in more detail in the Discussion section below.

**Table 1.** Baseline measures.

| Construct and description | | Measure name |
|---|---|---|
| **Demographic information** | | |
| Person | Age, ethnicity, race, sexual orientation (identity, attraction, and behavior), gender, height, and weight | Developed for this study |
| Relationship | Status, length, and living situation | Developed for this study |
| Context | Employment status, education, income, and residence | Developed for this study |
| **Primary measures** | | |
| Relationship functioning | Psychological and physical violence toward or from a partner | Conflict Tactics Scale (CTS2)—physical assault and sexual coercion subscales (modified to be appropriate for same-sex relationships) [45] |
| | Maltreatment in an intimate relationship (emotional/verbal and domination/isolation) | Psychological Maltreatment of Women Inventory-short version [46] |
| | Satisfaction with the relationship and perceptions about partners' satisfaction, commitment, and security with the relationship | No scale name [51] |
| | Report of partners' behavior (hostile, jealous, and emotionally supportive) | Reports of partners' behavior [51] |
| | Commitment to romantic relationship | Commitment subscale from the Investment Model [52] |
| | Feelings of jealousy toward romantic partner | Multidimensional Jealousy Scale- cognitive subscale [53] |
| | Anxious expectations of potential rejection from others, generally | Adult Rejection Sensitivity Questionnaire [54] |
| Alcohol use | Identification of at-risk drinkers (hazardous alcohol use, dependence symptoms, and harmful alcohol use) | Alcohol Use Disorders Identification Test [55] |
| | Typical weekly alcohol consumption | Daily Drinking Questionnaire [56] |
| | Importance of certain reasons in someone's decision not to drink | Reasons for Not Drinking [57] |
| | Alcohol consequences experienced by young adult drinkers | Brief Young Adult Alcohol Consequences Questionnaire [58] |
| | Drinking behavior related to partner interaction | Partner drinking questions [59] |
| | Drinking motives (social, coping, enhancement, and conformity) | Drinking Motives Questionnaire [60] |
| Sexual minority stress | Sexual minority identity and psychosocial functioning | Lesbian, Gay, Bisexual Identity Scale [61] |
| | Openness about sexual identity and orientation | Single item openness question [62] |
| | Anxious expectations of potential rejection from others as a result of sexual minority identity | Sexual Minority Women Rejection Sensitivity [63] |
| | Experiences of sexual stigma | Daily Heterosexist Experiences Questionnaire—all subscales except parenting and HIV/AIDS [48] |
| Social support and resilience | Support from family, friends, and significant others | Multidimensional Scale of Perceived Social Support [64] |
| | Ability to recover from stress or "bounce back" | Brief Resilience Scale [65] |
| **Secondary measures** | | |
| Physical health | General health, bodily pain, and activity limitations | 20-Item Short Form Survey Instrument [47] |
| Mental health | Aggression (physical aggression, verbal aggression, anger, and hostility) | Buss-Perry Aggression Questionnaire Short Form [66] |
| | Psychological distress and well-being (anxiety, depression, behavioral control, and positive affect) | Mental Health Inventory [67] |
| | Suicidal behaviors and thoughts | Inventory of Depression and Anxiety Symptoms- Suicidality Subscale [68] |
| Family | Exposure to interparental violence | Items adapted from CTS2 [45] |

| Construct and description | | Measure name |
|---|---|---|
| Drug use | History of marijuana use and form of ingestion | Marijuana use [69] |
| Disordered eating | Eating pathology (body dissatisfaction, binge eating, cognitive restraint, purging, restricting, and excessive exercise) | Eating Pathology Symptoms Inventory [70,71] |
| | Diagnostic criteria for eating disorder behaviors | Modified Eating Disorder Examination Questionnaire [49,50] |

The daily survey measures are described in Table 2 and are similarly organized by primary and secondary constructs of interest. Most of the primary and secondary measures included in the daily survey were adapted from existing daily diary or ecological momentary assessment (EMA) studies or were developed for this study to assess daily behaviors, particularly drinking behaviors and sexual minority stressors. Of note, when adapting items from existing scales, for example, to assess daily sexual minority stressors, we selected and edited items to be appropriate for a daily time frame (ie, would vary day-to-day). To balance the survey length on days when a participant did not drink or interact with her partner, filler items regarding media use, time management, and general social interactions were developed and are administered on nondrinking and noninteraction days. Finally, the format of the survey was optimized for mobile delivery. For example, visual analog slider scales are used instead of matrix tables in some cases so that all response options are visible to the participant when using a smaller screen (eg, on a smartphone). Additional details regarding the daily survey measures can be found in Table 2, and all daily survey items can be found in Multimedia Appendix 2.

The end-of-study survey contains questions concerning whether the participant believed her experiences were captured by the questions asked (eg, "While answering questions related to your gender and/or sexual identity, did you think that the questions you answered were inclusive of the way you describe yourself?") as well as what was her preferred method of accessing the survey materials (ie, computer, tablet, or smartphone). Participants are also asked about their motivation to improve their health and whether they would be comfortable using mobile technology to monitor their physical and mental health. Survey items are included in Multimedia Appendix 3. The feedback gathered from the end-of-study survey will be used to gauge the participant experience in this study as well as provide an opportunity to improve future studies and survey materials.

## Data Analysis Plan

The data being collected in this study are inherently multilevel in nature, with days (level 1) nested within individuals (level 2) nested within couples (level 3). In addition, our research questions incorporate aspects of mediation and moderated mediation. As such, we will utilize an approach that combines multilevel modeling (MLM) [86,87] with mediation pathways available through structural equation modeling. This combined approach, multilevel structural equation modeling (MSEM) [88], allows for bootstrapping of the models, which can accommodate non-normal underlying distributions, particularly relevant for alcohol use outcomes and indirect effects [89,90] such as those incorporated in our proposed models. Regarding missing data, like MLM, MSEM is robust to missing data (eg, skipped observations). In addition, analyses will be conducted in Mplus [91] using maximum likelihood estimation, which allows for the estimation of parameters using all available cases (ie, no listwise deletion for missing variables within a time point). Participants with complete data will be compared with participants with missing data to identify potential attrition biases, and significant predictors will be included as covariates in all subsequent analyses. The MSEM approach allows for the simultaneous examination of level 1 (daily variation), level 2 (person-specific levels), and level 3 (couple factor) associations among variables, including moderating effects that strengthen or weaken those associations.

**Table 2.** Daily measures.

| Construct | Description | Measure name and/or reference |
|---|---|---|
| **Primary measures** | | |
| Daily relationship functioning | Relationship quality and satisfaction | Items adapted from the Daily Positive Relationship Quality Composite [72,73] |
| | Intimacy and conflict | Items adapted [74] |
| | Positive and negative partner behaviors | Items adapted from the Interpersonal Qualities Scale [75] |
| | Partner aggression | Items adapted [76] |
| Daily alcohol use | Quantity, duration, interactions, and location | Items developed for the study to assess daily drinking behaviors |
| | Daily alcohol consequences | Items adapted from the Brief Young Adult Consequences Questionnaire for daily administration [77] |
| | Drinking motives (social, coping, enhancement, and conformity) | Items adapted from the Drinking Motives Questionnaire—social, enhancement, and conformity were combined to a single item per factor [60] |
| | Nondrinking questions | Items developed for the study to balance drinking questions |
| | Daily-level reasons for not drinking | Items adapted for the daily level from the Reasons for Not Drinking [78] |
| | Drinking intentions | Item developed for the study to assess drinking likelihood in the next 24 hours |
| | Partner drinking | Items developed for the study to assess partner drinking |
| Daily sexual minority stressors | Daily sexual minority stressors | Lesbian Women's Daily Sexual Minority Stressors Scale [41] |
| | Sexual minority discrimination | Items adapted from the Heterosexist Harassment, Rejection, and Discrimination Scale [79] |
| | Sexual identity concealment | Items adapted from the Nebraska Outness Scale [80] |
| Affect | Positive and negative affect | Items adapted from different versions of the Positive and Negative Affect Schedule |
| **Secondary measures** | | |
| Drug use | Smoking and marijuana use | Items adapted [69] |
| Eating and body image | Disordered eating | Items adapted from the Eating Attitudes Test [81] and the Eating Disorder Examination Questionnaire [49,50] |
| | Body dissatisfaction | Items developed to assess current satisfaction with body |
| General stress and coping | Stressful or unpleasant experiences | Items adapted from the Daily Inventory of Stressful Events [82] |
| Physical activity | Sitting, walking, moderate activities, and vigorous activities | Items adapted from the International Physical Activity Questionnaire [83] |
| About the survey | Location of survey completion, type of device used, and perceived privacy | Items developed for the study to improve future research |
| **Filler items** | | |
| General social interactions | Importance and pleasantness of social interactions | Items developed for the study to balance questions about partner interactions |
| | Positive social exchanges | Items adapted from the Daily Social Exchanges Checklist [84] |
| Media use | Television, internet, and social media use | Items developed for the study to balance drinking questions |
| Time management | Short-range planning and time attitudes | Items adapted from the Time-Management Questionnaire [85] |

## Results

To date, 228 women (114 couples) have been successfully screened and been identified as eligible to participate in the study. Of these eligible women, 208 women (104 couples) have consented to participate and, thus, have been enrolled in the study. During the consent process, to date we have had to send reminder emails about consenting to 26% of women (59/228); 49 of these 59 women (83%) completed the consent within several days of the email reminder. A total of 6 participants discontinued participation after beginning the study but before the 14-day daily diary surveys. Of the remaining 202 participants, 44 are actively completing the daily surveys, and 164 have completed the study. Of those participants who have completed the study, compliance with the daily diaries has been excellent; on average, participants have completed 92% of the surveys (or 13 of 14 days). In reviewing the distribution of compliance rates by participants, nearly all participants (97.6%, 160/164) have completed at least half of the daily surveys. Data collection and enrollment is ongoing and expected to conclude in fall 2018.

## Discussion

Drawing from the literatures on sexual minority specific processes (eg, sexual minority stress) and general processes (negative affect and relationship factors), the primary objective of Project Relate is to increase our understanding of between- and within-person processes underlying hazardous drinking in the understudied, at-risk population of SMW. A daily diary methodology is being used to gain insight into the affective, behavioral, and relationship experiences of female same-sex couples working toward the goal of reducing health disparities and improving the health of SMW.

### Methodological Challenges and Considerations

Recruitment of couples into research endeavors is always a challenge, and recruiting same-sex couples creates additional challenges. Consequently, we devoted substantial effort to develop and refine processes for participant recruitment and retention. Below, we discuss the challenges faced when designing and implementing Project Relate.

#### Participant Recruitment Decisions and Issues

Several challenges emerged when designing and implementing this study regarding identifying and enrolling participants. First, working with a market research firm to recruit has advantages but also presents challenges. CMI has a large SMW panel who regularly complete Web-based surveys and access to other recruitment resources. The CMI employees are knowledgeable about best practices for Web-based recruitment and survey completion and contribute important ideas to assist with recruitment and retention of participants (eg, length of survey, compensation, and phrasing). At the same time, because CMI does relatively less social science research (compared with traditional market research for products), it was necessary to figure out how to "speak the same language" so that we could be faithful to the best social science practices (eg, measurement fidelity and human subjects' protections). For this study, CMI

is recruiting both through their proprietary panel of individuals who identify as LGBT and through digital and event outreach activities, including on social media sites such as Facebook, Craigslist, and sexual minority-specific sites. By using multiple recruitment sources, it is our goal to recruit a sample of SMW who are diverse in terms of their race/ethnicity and in other ways (eg, education and socioeconomic status). However, it is already a challenge to recruit young sexual minorities for research studies, and therefore, we recognize that to recruit a sufficient sample, it is possible that our sample will be limited in demographic characteristics.

Second, early in the study recruitment process, we observed a trend in the way in which young SMW label their sexual identity, which seemed to suggest that they were not identifying as lesbian as frequently as we had expected. In consultation with CMI, we learned that younger SMW whose attraction and behavior are consistent with the traditional definition of the "lesbian" label (ie, attracted to women or romantically involved with women) are either choosing to identify in other ways (eg, queer or pansexual) or are resisting labels altogether. Our initial planned inclusion criteria required at least 1 partner to identify as lesbian, but as a result of this consultation with CMI as well as internal discussions among our investigators, within the first month of recruitment, we changed this inclusionary criterion to "only or mostly attracted to women" described in the Methods section above. As researchers, our drive toward internal validity encourages us to recruit a homogeneous sample of 1 type of SMW (ie, lesbian women) that we can describe clearly; however, this group may not accurately represent the larger population of SMW, which is quite heterogeneous. This issue of how to appropriately define and describe sexual minority individuals is not new [92-94] and will likely continue to be a challenge for researchers as labels evolve over time and is something we will continue to attend to when designing future studies in this line of work.

Third, given that we are recruiting couples, we were very intentional in our protocol design regarding how and when we contacted participants to ensure privacy, confidentiality, and data fidelity. For example, when communicating with participants, we always contact individuals, never both people in the couple together (eg, in the same email). It is important that no participant feels coerced to participate because of her partner's interest in the project. However, given this is a study of couples, both partners have to consent and complete the baseline survey before continuing in the study and must begin the daily diaries on the same day. In the rare instances when 1 partner does not wish to continue, we thank the other partner for her participation and compensate her for the portions of the study she completed but do not mention her partner's noncompliance. In addition, to try to ensure we are getting independent responses from each participant, in all of our enrollment materials, we instructed participants not to complete the surveys together; we send them individualized survey links daily, and at the end of the daily survey, we enquire about the level of privacy each individual had when completing the survey. These privacy and data fidelity challenges are not unique to studies with sexual minorities but are experienced by researchers studying couples, and the concerns about collecting

independent reports are likely more apparent in daily diary or EMA studies because of the frequent, repeated assessments in daily life.

## Informational and Training Videos

To our knowledge, this study is one of the first to recruit same-sex couples for a completely remote Web-based daily diary collections, and thus, we decided to develop a series of videos to explain the research. To evaluate the efficacy of these videos, couples were randomized to either a written-only or a video+written group to examine whether the videos improve recruitment, attrition, and/or compliance. The videos are considered part of the informed consent process and, thus, are presented before the consent form, allowing us to examine whether consent rates, study attrition, and compliance with the study protocol differ by group. Evaluating the added utility (or lack thereof) of the video instructions for participants in this way can help to inform the design of future daily diary or EMA studies that use remote data collection methods with young adult participants.

## Inclusion of Attention Check Items

As this project relies completely on remote Web-based data collection, we were concerned that for the longer baseline survey, participants could begin to respond randomly, without fully reading each question. To attempt to identify if this is occurring, in the baseline survey, we included a series of attention check items, sometimes called "instructional manipulation checks" [95]. These are items embedded in the larger survey with instructions to select a particular answer (eg, "Please choose 'Frequently'") or questions that have factual answers (eg, "Which of the following is the largest number?") and are similar in format to other items in the survey. The attention checks are only included in the baseline survey, given its length (approximately 30 min). The daily surveys are much shorter (approximately 5 min), so we are less concerned about maintaining attention, and instead worried that including attention check items every day could be excessively burdensome and irritating for participants.

Research shows that including participants who fail attention checks leads to reduced power to detect study aims [95]. Although some have questioned if the inclusion of attention checks can adversely affect scale validity, recent studies have shown that they do not [96,97], and in fact, the inclusion of attention checks can improve performance on subsequent survey items [98]. For this study, we are not interested in eliminating participants who are inattentive but rather helping them to become attentive. Thus, we introduce to participants in the survey instructions (and videos) that these attention checks are embedded to help maintain their attention. Moreover, after failing an attention check, the survey automatically provides feedback stating that we detected the participant was not fully reading the instructions and asking her to respond again. This feedback is repeated as necessary until she answers correctly. This type of real-time feedback on attention checks has been shown to improve subsequent performance [95].

## Future Research Areas

EMA studies of health behaviors [99], as well as EMA studies conducted in the context of couples or families (eg, in which more than one person in a couple/family reports EMA data) [100], are rapidly increasing in popularity because they can examine more nuanced associations that consider individual, dyadic, and contextual variables that may influence behavior within people and couples over time. Despite growing interest in daily health factors and related stressors such as minority stress and alcohol use, research on daily experiences of sexual minority individuals lags far behind [101]. There are 2 important challenges that researchers are facing when conducting this work. First, as has been discussed at length elsewhere with respect to health behavior theories [102], existing theories may need to be refined or redeveloped to be able to guide our understanding of within-person processes that occur over relatively short time frames (eg, minutes, days, and weeks). Minority stress theories, including those that guided the development of Project Relate [8,9] at times, suggest predictions that involve within-person processes that may occur over short time frames but have largely been tested using cross-sectional designs (testing between-person processes) or traditional longitudinal designs (testing longer-term within-person processes). Project Relate is designed such that it will be able to test aspects of minority stress theories and presents an opportunity to extend and refine these theories to further the understanding of within-person processes in daily life.

A second challenge we encountered when designing Project Relate is the relative lack of well-established, validated measures that are appropriate for daily assessments. In Table 2, we provide a description of where we adapted measures from, based on either previous daily diary research with heterosexual couples or from existing retrospective measures. Importantly for Project Relate, we were unable to identify a measure of sexual minority stress that was appropriate for daily administration and, thus, created a daily sexual minority stressor measure [41] to use in this study. The lack of validated measures that are appropriate for daily or EMA studies highlights the importance for future work in this area to create new measures.

At present, the ability to provide education, mental health counseling, and interventions that are optimally effective for SMW is limited by our lack of understanding of key variables to incorporate in these efforts. Furthermore, the limited data available about relationship factors and alcohol use among SMW are typically derived from 1 respondent who provides information about herself and her partner. To address this limitation, our approach requiring both partners to participate is generating higher quality data on both partners' affective, behavioral, and relationship experiences. In addition, we are including other variables both specific to SMW and heterosexual couples that may impact hazardous alcohol use. We believe it is critical to consider how couple-level dynamics/variables may impact hazardous alcohol use and related issues. In addition, we believe that understanding both daily and between-subjects' mechanisms that may increase risk for hazardous alcohol is critical as is identifying protective factors that may attenuate this risk. By testing an empirically informed model that articulates probable within- and between-person factors and

relationship variables that increase hazardous alcohol use, we believe this work will provide a necessary intermediary step toward informing culturally tailored prevention and intervention studies for SMW and contribute to a goal of the Healthy People 2020 initiative to improve the health and well-being of SMW.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Project Relate study introduction information for participants.

[PDF File (Adobe PDF File), 185KB - resprot_v8i2e11718_app1.pdf ]

## Multimedia Appendix 2

Daily diary survey items.

[PDF File (Adobe PDF File), 174KB - resprot_v8i2e11718_app2.pdf ]

## Multimedia Appendix 3

End of study survey items.

[PDF File (Adobe PDF File), 32KB - resprot_v8i2e11718_app3.pdf ]

## References

1.  Office of Disease Prevention and Health Promotion. Lesbian, Gay, Bisexual and Transgender Health URL: https://www.healthypeople.gov/2020/topics-objectives/topic/lesbian-gay-bisexual-and-transgender-health?topicid=25 [accessed 2018-10-18] [WebCite Cache ID 73GWdDSG4]
2.  Green KE, Feinstein BA. Substance use in lesbian, gay, and bisexual populations: an update on empirical research and implications for treatment. Psychol Addict Behav 2012 Jun;26(2):265-278 [FREE Full text] [doi: 10.1037/a0025424] [Medline: 22061339]
3.  Hughes TL, Wilsnack SC, Szalacha LA, Johnson T, Bostwick WB, Seymour R, et al. Age and racial/ethnic differences in drinking and drinking-related problems in a community sample of lesbians. J Stud Alcohol 2006 Jul;67(4):579-590. [doi: 10.15288/jsa.2006.67.579] [Medline: 16736078]
4.  McCabe SE, Hughes TL, Bostwick WB, West BT, Boyd CJ. Sexual orientation, substance use behaviors and substance dependence in the United States. Addiction 2009 Aug;104(8):1333-1345 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02596.x] [Medline: 19438839]
5.  Drabble L, Midanik LT, Trocki K. Reports of alcohol consumption and alcohol-related problems among homosexual, bisexual and heterosexual respondents: results from the 2000 National Alcohol Survey. J Stud Alcohol 2005 Jan;66(1):111-120. [doi: 10.15288/jsa.2005.66.111] [Medline: 15830911]
6.  McCabe SE, Boyd C, Hughes T, d'Arcy H. Sexual identity and substance use among undergraduate students. Subst Abus 2003 Jun;24(2):77-91. [doi: 10.1023/A:1023768215020] [Medline: 12766375]
7.  Brooks V. Minority Stress and Lesbian Women. Lexington, MA: Lexington Books; 1981.
8.  Hatzenbuehler ML. How does sexual minority stigma "get under the skin"? A psychological mediation framework. Psychol Bull 2009 Sep;135(5):707-730 [FREE Full text] [doi: 10.1037/a0016441] [Medline: 19702379]
9.  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]
10. Calhoun D, Mason T, Lewis R. Sexual minority stress and alcohol use: Drinking to cope as a response to stress. 2014 Presented at: 122nd American Psychological Association Annual Convention; August 7-10, 2014; Washington, DC.

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RenderX

11.  Hatzenbuehler ML, Corbin WR, Fromme K. Discrimination and alcohol-related problems among college students: a prospective examination of mediating effects. Drug Alcohol Depend 2011 Jun 01;115(3):213-220 [FREE Full text] [doi: 10.1016/j.drugalcdep.2010.11.002] [Medline: 21145669]

12.  Lehavot K, Simoni JM. The impact of minority stress on mental health and substance use among sexual minority women. J Consult Clin Psychol 2011 Apr;79(2):159-170 [FREE Full text] [doi: 10.1037/a0022839] [Medline: 21341888]

13.  Lewis RJ, Winstead BA, Mason TB, Lau-Barraco C. Social factors linking stigma-related stress with alcohol use among lesbians. J Soc Issues 2017 Sep;73(3):545-562. [doi: 10.1111/josi.12231] [Medline: 29269960]

14.  Pascoe EA, Smart Richman L. Perceived discrimination and health: a meta-analytic review. Psychol Bull 2009 Jul;135(4):531-554 [FREE Full text] [doi: 10.1037/a0016059] [Medline: 19586161]

15.  Feinstein BA, Newcomb ME. Event-level associations among drinking motives, alcohol consumption, and condomless anal sex in a sample of young men who have sex with men. AIDS Behav 2017 Jul;21(7):1904-1913 [FREE Full text] [doi: 10.1007/s10461-017-1734-5] [Medline: 28251377]

16.  Mereish EH, Kuerbis A, Morgenstern J. A daily diary study of stressful and positive events, alcohol use, and addiction severity among heavy drinking sexual minority men. Drug Alcohol Depend 2018 Dec 01;187:149-154. [doi: 10.1016/j.drugalcdep.2018.03.003] [Medline: 29665493]

17.  Livingston NA, Flentje A, Heck NC, Szalda-Petree A, Cochran BN. Ecological momentary assessment of daily discrimination experiences and nicotine, alcohol, and drug use among sexual and gender minority individuals. J Consult Clin Psychol 2017 Dec;85(12):1131-1143 [FREE Full text] [doi: 10.1037/ccp0000252] [Medline: 29189029]

18.  Fischer JL, Wiersma JD. Romantic relationships and alcohol use. Curr Drug Abuse Rev 2012 Jun;5(2):98-116. [doi: 10.2174/1874473711205020098] [Medline: 22455505]

19.  Schilit R, Lie GY, Montagne M. Substance use as a correlate of violence in intimate lesbian relationships. J Homosex 1990 Aug 23;19(3):51-66. [doi: 10.1300/j082v19n03_03]

20.  Bimbi DS, Palmadessa NA, Parsons JT. Substance use and domestic violence among urban gays, lesbians and bisexuals. J LGBT Health Res 2007 Oct;3(2):1-7. [doi: 10.1300/J463v03n02_01] [Medline: 19835036]

21.  Lewis RJ, Milletich RJ, Kelley ML, Woody A. Minority stress, substance use, and intimate partner violence among sexual minority women. Aggress Violent Behav 2012 May;17(3):247-256. [doi: 10.1016/j.avb.2012.02.004]

22.  Lewis RJ, Padilla MA, Milletich RJ, Kelley ML, Winstead BA, Lau-Barraco C, et al. Emotional distress, alcohol use, and bidirectional partner violence among lesbian women. Violence Against Women 2015 Aug;21(8):917-938 [FREE Full text] [doi: 10.1177/1077801215589375] [Medline: 26062874]

23.  Lewis RJ, Mason TB, Winstead BA, Kelley ML. Empirical investigation of a model of sexual minority specific and general risk factors for intimate partner violence among lesbian women. Psychol Violence 2017 Jan;7(1):110-119 [FREE Full text] [doi: 10.1037/vio0000036] [Medline: 28239508]

24.  Levitt A, Cooper ML. Daily alcohol use and romantic relationship functioning: evidence of bidirectional, gender-, and context-specific effects. Pers Soc Psychol Bull 2010 Dec;36(12):1706-1722. [doi: 10.1177/0146167210388420] [Medline: 21098471]

25.  Homish GG, Leonard KE. The drinking partnership and marital satisfaction: the longitudinal influence of discrepant drinking. J Consult Clin Psychol 2007 Feb;75(1):43-51 [FREE Full text] [doi: 10.1037/0022-006X.75.1.43] [Medline: 17295562]

26.  Kelley ML, Lewis RJ, Mason TB. Discrepant alcohol use, intimate partner violence, and relationship adjustment among lesbian women and their relationship partners. J Fam Violence 2015 Nov 01;30(8):977-986 [FREE Full text] [doi: 10.1007/s10896-015-9743-5] [Medline: 26478657]

27.  Lewis RJ, Winstead BA, Braitman AL, Hitson P. Discrepant drinking and partner violence perpetration over time in lesbians' relationships. Violence Against Women 2018 Dec;24(10):1149-1165. [doi: 10.1177/1077801218781925] [Medline: 30037320]

28.  Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychol Bull 1985;98(2):310-357. [doi: 10.1037/0033-2909.98.2.310]

29.  Institute of Medicine, Board on the Health of Select Populations, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities Committee on Lesbian. The Health of Lesbian, Gay, Bisexual, and Transgender People. Washington, DC: National Academies Press; 2011.

30.  Doty ND, Willoughby BL, Lindahl KM, Malik NM. Sexuality related social support among lesbian, gay, and bisexual youth. J Youth Adolesc 2010 Oct;39(10):1134-1147. [doi: 10.1007/s10964-010-9566-x] [Medline: 20593304]

31.  Fingerhut AW, Peplau LA, Gable SL. Identity, minority stress and psychological well-being among gay men and lesbians. Psychol Sex 2010 Jun 03;1(2):101-114. [doi: 10.1080/19419899.2010.484592]

32.  Herek GM, Garnets LD. Sexual orientation and mental health. Annu Rev Clin Psychol 2007 Apr;3:353-375. [doi: 10.1146/annurev.clinpsy.3.022806.091510] [Medline: 17716060]

33.  Riggle ED, Rostosky SS, Horne SG. Psychological distress, well-being, and legal recognition in same-sex couple relationships. J Fam Psychol 2010 Feb;24(1):82-86. [doi: 10.1037/a0017942] [Medline: 20175612]

34.  Rostosky SS, Riggle ED. Same-sex couple relationship strengths: a review and synthesis of the empirical literature (2000–2016). Psychol Sex Orientat Gend Divers 2017;4(1):1-13. [doi: 10.1037/sgd0000216]

35. Wight RG, Leblanc AJ, Lee Badgett MV. Same-sex legal marriage and psychological well-being: findings from the California Health Interview survey. Am J Public Health 2013 Feb;103(2):339-346. [doi: 10.2105/AJPH.2012.301113] [Medline: 23237155]

36. Hatzenbuehler ML, Link BG. Introduction to the special issue on structural stigma and health. Soc Sci Med 2014 Feb;103:1-6. [doi: 10.1016/j.socscimed.2013.12.017] [Medline: 24445152]

37. Muthén LK, Muthén BO. How to use a Monte Carlo study to decide on sample size and determine power. Struct Equ Modeling 2002 Oct;9(4):599-620. [doi: 10.1207/S15328007SEM0904_8]

38. West SG, Ryu E, Kwok O, Cham H. Multilevel modeling: current and future applications in personality research. J Pers 2011 Feb;79(1):2-50. [doi: 10.1111/j.1467-6494.2010.00681.x] [Medline: 21223263]

39. Boynton MH, Richman LS. An online daily diary study of alcohol use using Amazon's Mechanical Turk. Drug Alcohol Rev 2014 Jul;33(4):456-461 [FREE Full text] [doi: 10.1111/dar.12163] [Medline: 24893885]

40. Hatzenbuehler ML, Dovidio JF, Nolen-Hoeksema S, Phills CE. An implicit measure of anti-gay attitudes: prospective associations with emotion regulation strategies and psychological distress. J Exp Soc Psychol 2009 Nov 01;45(6):1316-1320 [FREE Full text] [doi: 10.1016/j.jesp.2009.08.005] [Medline: 20161465]

41. Heron KE, Braitman AL, Lewis RJ, Shappie AT, Hitson PT. Measuring sexual minority stressors in lesbian women's daily lives: initial scale development. Psychol Sex Orientat Gend Divers 2018 Jun 25;5(3):387-395. [doi: 10.1037/sgd0000287]

42. Dworkin ER, Cadigan J, Hughes T, Lee C, Kaysen D. Sexual identity of drinking companions, drinking motives, and drinking behaviors among young sexual minority women: an analysis of daily data. Psychol Addict Behav 2018 Dec;32(5):540-551. [doi: 10.1037/adb0000384] [Medline: 30047754]

43. Littlefield AK, Talley AE, Jackson KM. Coping motives, negative moods, and time-to-drink: exploring alternative analytic models of coping motives as a moderator of daily mood-drinking covariation. Addict Behav 2012 Dec;37(12):1371-1376 [FREE Full text] [doi: 10.1016/j.addbeh.2012.05.020] [Medline: 22867813]

44. Lau-Barraco C, Linden-Carmichael AN. A daily diary study of drinking and nondrinking days in nonstudent alcohol users. Subst Use Misuse 2018 Jul 02:1-8 Epub ahead of print(forthcoming). [doi: 10.1080/10826084.2018.1485700] [Medline: 29963933]

45. Straus MA, Hamby SL, Boney-McCoy S, Sugarman DB. The revised conflict tactics scales (CTS2) development and preliminary psychometric data. J Fam Issues 1996;17(3):283-316. [doi: 10.1177/019251396017003001]

46. Tolman RM. The validation of the Psychological Maltreatment of Women Inventory. Violence Vict 1999;14(1):25-37. [Medline: 10397624]

47. Ware JE, Sherboure CD, Davies AR. Developing and testing the MOS 20-item Short-Form Health survey: a general population application. In: Stewart AL, Ware, Jr JE, editors. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992:277-290.

48. Balsam KF, Beadnell B, Molina Y. The daily heterosexist experiences questionnaire: measuring minority stress among lesbian, gay, bisexual, and transgender adults. Meas Eval Couns Dev 2013 Jan;46(1):3-25 [FREE Full text] [doi: 10.1177/0748175612449743] [Medline: 24058262]

49. Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? Int J Eat Disord 1994 Dec;16(4):363-370. [Medline: 7866415]

50. Fairburn CG, Beglin SJ. Eating disorder examination questionnaire. In: Fairburn C, editor. Cognitive Behavior Therapy and Eating Disorders. New York: Guilford Press; 2008.

51. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. J Pers Soc Psychol 1996;70(6):1327-1343. [doi: 10.1037/0022-3514.70.6.1327]

52. Rusbult CE, Martz JM, Agnew CR. The Investment Model Scale: measuring commitment level, satisfaction level, quality of alternatives, and investment size. Pers Relatsh 1998 Dec;5(4):357-387. [doi: 10.1111/j.1475-6811.1998.tb00177.x]

53. Pfeiffer SM, Wong PT. Multidimensional jealousy. J Soc Pers Relat 1989;6(2):181-196. [doi: 10.1177/026540758900600203]

54. Berenson KR, Gyurak A, Ayduk O, Downey G, Garner MJ, Mogg K, et al. Rejection sensitivity and disruption of attention by social threat cues. J Res Pers 2009;43(6):1064-1072 [FREE Full text] [doi: 10.1016/j.jrp.2009.07.007] [Medline: 20160869]

55. Babor TF, Higgins-Biddle J, Saunders JB, Monteiro MG, World Health Organization. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. Geneva, Switzerland: World Health Organization; 2001.

56. Collins RL, Parks GA, Marlatt GA. Social determinants of alcohol consumption: the effects of social interaction and model status on the self-administration of alcohol. J Consult Clin Psychol 1985;53(2):189-200. [doi: 10.1037/0022-006X.53.2.189] [Medline: 3998247]

57. Johnson TJ, Cohen EA. College students' reasons for not drinking and not playing drinking games. Subst Use Misuse 2004 Dec 07;39(7):1137-1160. [doi: 10.1081/JA-120038033]

58. Kahler CW, Strong DR, Read JP. Toward efficient and comprehensive measurement of the alcohol problems continuum in college students: the Brief Young Adult Alcohol Consequences Questionnaire. Alcohol Clin Exp Res 2005;29(7):1180-1189. [doi: 10.1097/01.ALC.0000171940.95813.A5]

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59. Levitt A, Leonard KE. Relationship-specific alcohol expectancies and relationship-drinking contexts: reciprocal influence and gender-specific effects over the first 9 years of marriage. Psychol Addict Behav 2013 Dec;27(4):986-996 [FREE Full text] [doi: 10.1037/a0030821] [Medline: 23276314]

60. Cooper ML. Motivations for alcohol use among adolescents: development and validation of a four-factor model. Psychol Assess 1994;6(2):117-128. [doi: 10.1037/1040-3590.6.2.117]

61. Mohr JJ, Kendra MS. Revision and extension of a multidimensional measure of sexual minority identity: the Lesbian, Gay, and Bisexual Identity Scale. J Couns Psychol 2011 Apr;58(2):234-245. [doi: 10.1037/a0022858] [Medline: 21319899]

62. Franke R, Leary MR. Disclosure of sexual orientation by lesbians and gay men: a comparison of private and public processes. J Soc Clin Psychol 1991 Sep;10(3):262-269. [doi: 10.1521/jscp.1991.10.3.262]

63. Dyar C, Feinstein BA, Eaton NR, London B. Development and initial validation of the sexual minority women rejection sensitivity scale. Psychol Women Q 2015 Sep 24;40(1):120-137. [doi: 10.1177/0361684315608843]

64. 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]

65. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008 Sep;15(3):194-200. [doi: 10.1080/10705500802222972] [Medline: 18696313]

66. Bryant FB, Smith BD. Refining the architecture of aggression: a measurement model for the Buss-Perry aggression questionnaire. J Res Pers 2001 Jun;35(2):138-167. [doi: 10.1006/jrpe.2000.2302]

67. Veit CT, Ware JE. The structure of psychological distress and well-being in general populations. J Consult Clin Psychol 1983;51(5):730-742. [doi: 10.1037/0022-006X.51.5.730]

68. Watson D, O'Hara MW, Simms LJ, Kotov R, Chmielewski M, McDade-Montez EA, et al. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). Psychol Assess 2007 Sep;19(3):253-268. [doi: 10.1037/1040-3590.19.3.253] [Medline: 17845118]

69. White HR, Mun EY, Morgan TJ. Do brief personalized feedback interventions work for mandated students or is it just getting caught that works? Psychol Addict Behav 2008 Mar;22(1):107-116 [FREE Full text] [doi: 10.1037/0893-164X.22.1.107] [Medline: 18298236]

70. Forbush KT, Wildes JE, Pollack LO, Dunbar D, Luo J, Patterson K, et al. Development and validation of the Eating Pathology Symptoms Inventory (EPSI). Psychol Assess 2013 Sep;25(3):859-878. [doi: 10.1037/a0032639] [Medline: 23815116]

71. Forbush KT, Wildes JE, Hunt TK. Gender norms, psychometric properties, and validity for the Eating Pathology Symptoms Inventory. Int J Eat Disord 2014 Jan;47(1):85-91. [doi: 10.1002/eat.22180] [Medline: 23996154]

72. Young V, Curran M, Totenhagen C. A daily diary study: working to change the relationship and relational uncertainty in understanding positive relationship quality. J Soc Pers Relat 2012 Jul 31;30(1):132-148. [doi: 10.1177/0265407512453826]

73. Totenhagen CJ, Butler EA, Ridley CA. Daily stress, closeness, and satisfaction in gay and lesbian couples. Pers Relatsh 2012;19:219-233. [doi: 10.1111/j.1475-6811.2011.01349.x]

74. Laurenceau JP, Troy AB, Carver CS. Two distinct emotional experiences in romantic relationships: effects of perceptions regarding approach of intimacy and avoidance of conflict. Pers Soc Psychol Bull 2005 Aug;31(8):1123-1133. [doi: 10.1177/0146167205274447] [Medline: 16000272]

75. Oishi S, Sullivan HW. The predictive value of daily vs retrospective well-being judgments in relationship stability. J Exp Soc Psychol 2006 Jul;42(4):460-470. [doi: 10.1016/j.jesp.2005.07.001]

76. Testa M, Derrick JL. A daily process examination of the temporal association between alcohol use and verbal and physical aggression in community couples. Psychol Addict Behav 2014 Mar;28(1):127-138 [FREE Full text] [doi: 10.1037/a0032988] [Medline: 24341618]

77. Braitman A, Kelley M, Heron K, Lewis R, Pearson M. Developing a Daily assessment of alcohol-related consequences: Examining intra-individual variability. 2016 Presented at: Annual meeting of the Association for Psychological Sciences; May 2016; Chicago, IL.

78. O'Hara RE, Armeli S, Tennen H. College students' daily-level reasons for not drinking. Drug Alcohol Rev 2014 Jul;33(4):412-419 [FREE Full text] [doi: 10.1111/dar.12162] [Medline: 24976084]

79. Szymanski DM. Does internalized heterosexism moderate the link between heterosexist events and lesbians' psychological distress? Sex Roles 2006 Feb;54(3-4):227-234. [doi: 10.1007/s11199-006-9340-4]

80. Meidlinger PC, Hope DA. Differentiating disclosure and concealment in measurement of outness for sexual minorities: the Nebraska Outness Scale. Psychol Sex Orientat Gend Divers 2014;1(4):489-497. [doi: 10.1037/sgd0000080]

81. Garner DM, Olmsted MP, Bohr Y, Garfinkel PE. The eating attitudes test: psychometric features and clinical correlates. Psychol Med 2009 Jul 9;12(4):871-878. [doi: 10.1017/S0033291700049163] [Medline: 6961471]

82. Almeida DM, Wethington E, Kessler RC. The daily inventory of stressful events: an interview-based approach for measuring daily stressors. Assessment 2002 Mar;9(1):41-55. [doi: 10.1177/1073191102091006] [Medline: 11911234]

83. 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]

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84.  Rook KS. Emotional health and positive versus negative social exchanges: a daily diary analysis. Appl Dev Sci 2001 Apr;5(2):86-97. [doi: 10.1207/S1532480XADS0502_4]

85.  Britton BK, Tesser A. Effects of time-management practices on college grades. J Educ Psychol 1991;83(3):405-410. [doi: 10.1037/0022-0663.83.3.405]

86.  Raudenbush SW, Bryk AS. Hierarchical Linear Models: Applications and Data Analysis Methods. Newbury Park, CA: SAGE Publications; 2002.

87.  Snijders TA, Bosker RJ. Multilevel Analysis: An Introduction To Basic And Advanced Multilevel Modeling. Thousand Oaks, CA: SAGE Publications; 1999.

88.  Preacher KJ, Zyphur MJ, Zhang Z. A general multilevel SEM framework for assessing multilevel mediation. Psychol Methods 2010 Sep;15(3):209-233. [doi: 10.1037/a0020141] [Medline: 20822249]

89.  Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 2004 Nov;36(4):717-731. [doi: 10.3758/BF03206553]

90.  Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008 Aug;40(3):879-891. [doi: 10.3758/BRM.40.3.879] [Medline: 18697684]

91.  Muthén LK, Muthén BO. Mplus: Statistical Analysis With Latent Variables: User's Guide. Los Angeles, CA: Muthén & Muthén; 1998.

92.  Savin-Williams RC, Joyner K, Rieger G. Prevalence and stability of self-reported sexual orientation identity during young adulthood. Arch Sex Behav 2012 Feb;41(1):103-110. [doi: 10.1007/s10508-012-9913-y] [Medline: 22302504]

93.  Talley AE, Stevens JE. Sexual orientation self-concept ambiguity: scale adaptation and validation. Assessment 2017 Jul;24(5):632-645 [FREE Full text] [doi: 10.1177/1073191115617016] [Medline: 26643117]

94.  Young RM, Meyer IH. The trouble with "MSM" and "WSW": erasure of the sexual-minority person in public health discourse. Am J Public Health 2005 Jul;95(7):1144-1149. [doi: 10.2105/AJPH.2004.046714] [Medline: 15961753]

95.  Oppenheimer DM, Meyvis T, Davidenko N. Instructional manipulation checks: detecting satisficing to increase statistical power. J Exp Soc Psychol 2009 Jul;45(4):867-872. [doi: 10.1016/j.jesp.2009.03.009]

96.  Hauser DJ, Sunderrajan A, Natarajan M, Schwarz N. Prior exposure to instructional manipulation checks does not attenuate survey context effects driven by satisficing or gricean norms. Methods, Data, Analyses 2016;10:195-220 [FREE Full text] [doi: 10.12758/mda.2016.008]

97.  Kung FY, Kwok N, Brown DJ. Are attention check questions a threat to scale validity? Appl Psycho 2017 Aug 24;67(2):264-283. [doi: 10.1111/apps.12108]

98.  Hauser DJ, Schwarz N. It's a trap! Instructional manipulation checks prompt systematic thinking on "tricky" tasks. SAGE Open 2015 May 22;5(2):215824401558461. [doi: 10.1177/2158244015584617]

99.  Smyth J, Heron K. Health Psychology. In: Mehl MR, Connor TS, editors. Handbook of Research Methods for Studying Daily Life. New York: Guilford Press; 2012:569-584.

100. Heron KE, Miadich SA, Everhart RS, Smyth JM. Ecological momentary assessment and related intensive longitudinal designs in family and couples research. In: Fiese B, Deater-Deckard K, Celano M, Joyriles E, Whisman M, editors. APA handbook of contemporary family psychology. Washington DC: American Psychological Association; 2018.

101. Livingston NA. Avenues for future minority stress and substance use research among sexual and gender minority populations. J LGBT Issues Couns 2017 Feb;11(1):52-62. [doi: 10.1080/15538605.2017.1273164]

102. 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]

## Abbreviations

**CMI:** Community Marketing and Insights
**EMA:** ecological momentary assessment
**ICCs:** intraclass correlation coefficients
**LGBT:** lesbian, gay, bisexual, and transgender
**MLM:** multilevel modeling
**MSEM:** multilevel structural equation modeling
**SMW:** sexual minority women

Protocol

# Artificial Intelligence for the Detection of Diabetic Retinopathy in Primary Care: Protocol for Algorithm Development

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## Abstract

**Background:**   Diabetic retinopathy (DR) is one of the most important causes of blindness worldwide, especially in developed countries. In diabetic patients, periodic examination of the back of the eye using a nonmydriatic camera has been widely demonstrated to be an effective system to control and prevent the onset of DR. Convolutional neural networks have been used to detect DR, achieving very high sensitivities and specificities.

**Objective:**   The objective of this is paper was to develop an artificial intelligence (AI) algorithm for the detection of signs of DR in diabetic patients and to scientifically validate the algorithm to be used as a screening tool in primary care.

**Methods:**   Under this project, 2 studies will be conducted in a concomitant way: (1) Development of an algorithm with AI to detect signs of DR in patients with diabetes and (2) A prospective study comparing the diagnostic capacity of the AI algorithm with respect to the actual system of family physicians evaluating the images. The standard reference to compare with will be a blinded double reading conducted by retina specialists. For the development of the AI algorithm, different iterations and workouts will be performed on the same set of data. Before starting each new workout, the strategy of dividing the set date into 2 groups will be used randomly. A group with 80% of the images will be used during the training (training dataset), and the remaining 20% images will be used to validate the results (validation dataset) of each cycle (epoch). During the prospective study, true-positive, true-negative, false-positive, and false-negative values will be calculated again. From here, we will obtain the resulting confusion matrix and other indicators to measure the performance of the algorithm.

**Results:**   Cession of the images began at the end of 2018. The development of the AI algorithm is calculated to last about 3 to 4 months. Inclusion of patients in the cohort will start in early 2019 and is expected to last 3 to 4 months. Preliminary results are expected to be published by the end of 2019.

**Conclusions:**   The study will allow the development of an algorithm based on AI that can demonstrate an equal or superior performance, and that constitutes a complement or an alternative, to the current screening of DR in diabetic patients.

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**KEYWORDS**

diabetes mellitus; diabetic retinopathy; fundus oculi; artificial intelligence; computer assisted diagnosis; neural network computer

## Introduction

Diabetic retinopathy (DR) is one of the most important causes of blindness worldwide, especially in the most developed countries [1,2]. Up to 20% of type 2 diabetics have DR lesions at the time of diagnosis, and after 20 years of evolution of the illness, >60% of the patients have developed DR. The percentage of diabetic patients who have never undergone an ophthalmoscopic exploration exceeds 30% according to different studies [3].

DR appears and evolves asymptomatically for years, and it is in the early stages (asymptomatic) when the treatments to avoid vision loss are really effective. With early detection, DR can be treated with techniques that have been shown to reduce the risk of severe vision loss by >90% [3].

Regularly examining the fundus of the eye of known diabetic patients using a nonmydriatic camera has been widely shown to be an effective system to control and prevent the onset of DR [3-6]. Nonmydriatic retinal photography is a good alternative to direct ophthalmoscopy for the screening of DR; it offers high sensitivity and specificity (87% and 97%, respectively), simplicity of the technique, greater accessibility, ease in the registration of information (the computerized file that allows the evolutionary monitoring of the lesions), and better cost-effectiveness ratio compared with the ophthalmoscopy method with pupillary dilatation [7,8].

On the other hand, in recent years, there has been a substantial improvement in the field of artificial intelligence (AI) applied to the classification of medical images through deep learning techniques using convolutional neural networks (CNNs) [9]. In some cases, performances comparable to those obtained using specialist physicians have been reported [10-12]. These CNNs have also been used for the detection of DR, obtaining high sensitivities and specificities [13,14] with accuracies of up to 97.71% [15,16]. A recent study has reported a sensitivity and specificity of 92.5% and 98.5%, respectively. In this study, 85.6% of false-positive cases were due to a misclassification of mild or moderate DR and 77.3% of all false-negative cases occurred for undetected intraretinal microvascular abnormalities [17]. However, none of these algorithms have been developed with a population from southern Europe.

The current state-of-the-art screening for AI systems for medical images like the fundus images is a combination of AI technology (deep learning system) connected to a reading center with a board of retinal experts to confirm the positive cases diagnosed by the deep learning system and optimized to achieve high sensitivities. An AI system incorporated into routine clinical practice to detect DR is currently being beta-tested by the Singapore National Diabetic Retinopathy Screening Program [18,19].

The aim of this study is to develop an AI algorithm for the detection of signs of DR in diabetic patients and to scientifically validate the algorithm to be used as a screening tool in primary care.

## Methods

### Study Design

This project will follow a methodology similar to that used by Li et al [17] and will consist of 2 concomitant studies: In the first study, we will develop an AI algorithm to detect the signs of DR in patients with diabetes. The phases of the study are described in Textbox 1.

The second part of the project will consist of the elaboration of a prospective study that will allow comparing the diagnostic capacity of the algorithm with that of the family medicine physicians and with retina specialists. The reference will be a blinded double reading conducted by the retina specialists (with a blinded third reading in case of disagreement in the previous 2 readings). In this way, the results obtained, both by the AI algorithm and by family medicine specialists, will be compared using the gold standard (accuracy, sensitivity, specificity, area under the curve, etc). The inclusion of nurses who received training in fundus readings will be considered to compare their diagnostic capacity.

### Study Population, Site Participation, and Recruitment

Images for the development of the algorithm will be ceded by the CHS and will include images from the whole Catalan population. The prospective study will take place in the primary care centers managed by the Catalan Health Institute in Central Catalonia, which includes the counties of Bages, Osona, Berguedà, and Anoia. The reference population will be the population assigned to these primary care centers. This population included about 512,000 people in 2017 [20], with an estimated prevalence of diabetes of 7.1% [21].

The study period will include 2010-2017 for the development of the algorithm with AI. The prospective study will begin once the algorithm is developed and will run until the number of readings needed is obtained (about 3-4 months).

### Conduct of the Study

For the development of the AI algorithm, all fundus images labeled as DR of patients from primary care centers in Catalonia between 2010 and 2017 will be included. For the prospective study, all the images of patients who underwent an eye fundus examination will be included from the study start period until the adequate number of patients is reached.

A high percentage of fundus images must have sufficient quality; that is, a 40-degree vision of the central retina where at least a three-fourth part of the optic nerve, a well-focused macula, and well-defined veins and arteries of the upper and lower arcs can be seen. Eye fundus images that do not have adequate technical quality (dark) or that cannot be evaluated due to the opacity of the media (eg, for cataracts) will be excluded. Development of the AI algorithm is explained in Textbox 2.

**Textbox 1.** Phases of the first study.

1. Transfer of anonymized retinal images labeled as DR by the Department of Health though the Catalan Health Service (CHS).

2. Evaluation of the quality of the images to discard images of very low quality and evaluation of data distribution.

3. Machine learning. Iterative process with 2 phases (training and adjustments) until satisfactory results are obtained:

   - Training of the machine with the dataset and obtention of results.

   - Making the necessary adjustments:

     - A specialized engineer from OPTretina will evaluate the possibility of improving the algorithm and will determine the following:

       - The adjustments that should be made in the design of the neural network (preprocessing, number of layers, optimizer, learning rate, dropout, batch size, epoch number, etc) that can help improve the algorithm.

       - The most interesting batch of images that must be revised in order to significantly improve the learning of the algorithm in the next training. These images are images with predictions contrary to labeling (possible mislabeling) and predictions of low confidence (border cases).

     - Retina specialists (collaborators of OPTretina) will review the labeling of all the images selected in the previous step. In the final phases, up to 3 readings from different retina ophthalmologists may be necessary to reach a consensus in the labeling of border cases.

   - Development or installation of the algorithm in the CHS Electronic Medical Records system to be used by family medicine physicians in their workplace in real time. This integration is not essential for the realization of the project, but it will start during the development of the project.

**Textbox 2.** Development of the artificial intelligence algorithm.

Independent variables:

- (number of) true positives (TPs)

- (number of) true negatives (TNs)

- (number of) false positives (FPs)

- (number of) false negatives (FNs)

Dependent variables:

- Sensitivity or true positive rate=TP/(TP+FN)

- Specificity or true negative rate=TN/(TN+FP)

- Accuracy=(TP+TN)/(TP+FP+FN+TN)

- Area under the receiver operating characteristic curve: graphic representation that shows the diagnostic capacity of a binary classifier based on the variation in the discrimination threshold. It is obtained by plotting the sensitivity against (1−specificity) under different discrimination thresholds.

## Data Collection

For the development of the AI algorithm, it is necessary to have the anonymized images with the corresponding label that classifies each image (in one of the classes with which the algorithm is to be trained). The personnel responsible for information technology (IT) of the CHS will evaluate the best strategy for the anonymization and extraction of the images from the computer systems of the CHS, as well as the identification of each image with a unique identifier. On the other hand, a tabulated file type CSV or TXT will be required to relate each image identifier with the corresponding classification. The person responsible for IT of the CHS, together with the technical manager of OPTretina, will agree on the best way to transfer these 2 sources of information, in a secure way, from the CHS servers to the OPTretina servers (SSH File Transfer Protocol, external hard disk) depending on the volume of data to be transferred and the internal policy of the CHS. OPTretina is experienced in developing AI models for automatic fundus image classification and is a Spanish Agency of Medicines and Health Products-certified medical device manufacturer.

For the prospective study, anonymized weekly fundus data readings collected by family medicine physician readers of fundus images in Central Catalonia will be collected. The images will be transferred to the OPTretina servers to be first analyzed by the diagnostic algorithm and then by the retina specialists who will make the definitive diagnosis. The person responsible for IT of the CHS, together with the technical manager of OPTretina, will agree on the best way to transfer these data in a secure manner.

## Ethical Considerations

We will follow the ethical principles of the Declaration of Helsinki of 1964 reviewed by the World Health Organization

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in the year 2000 in Edinburgh as well as the Spanish Organic Law 15/1999 Protection of Personal Data of Character adapted to the General Regulation of Data Protection. All information collected will be treated confidentially in strict compliance with legislation in observational studies.

For the development of the AI algorithm, only anonymized data will be used to guarantee at all times the confidentiality of the data shared with the computer systems of OPTretina. Image property rights will always remain with the CHS. OPTretina will return the images once the algorithm has been developed.

Our study does not foresee any contact with patients during the development of the AI algorithm. During the prospective study, family medicine physicians, who are the regular readers of fundus images, will not know the determination made by the algorithm. In this way, the medical criteria of the family doctor will be the usual, without any possibility of interference or bias. During the study, all readings will be blind and independent. At the end of the study, the results of the evaluations of the images of the prospective study will be compared with the readings made by the retina specialists (considered the gold standard) and analyzed. If any discrepancy is detected that is potentially dangerous for the patient, the family doctors who have made the assessment will be informed so that they can take the measures they consider appropriate according to their clinical criteria. This study protocol has been already approved by the Catalan Institute in Primary Care Research (IDIAP Jordi Gol) Health Care Ethics Committee on 29/06/2018 (code P18/109).

## Statistical Analysis

### Sample Size Calculation

For the development of the AI algorithm, it is convenient to have at least 80,000 fundus images with a distribution of classes (classification groups) that have enough examples of each class. It is recommended that the classes are as balanced as possible and that the minority group has at least 5000 examples. These calculations have been made taking into account the available literature [19] and the conclusions and consensus of specialized discussion groups such as Kaggle [22], among others.

For the prospective study, we calculated that 1000 consecutive patients (who meet the inclusion criteria) would be needed. This number has been calculated taking into account the recent precedent of scientific evidence accepted by the Food and Drug Administration in the validation of a similar algorithm [14,23].

### Planned Analysis

When developing the AI algorithm, as explained in the methodology and design section, different iterations and trainings will be conducted on the same dataset. Before starting every new training, we will use a widely known strategy in CNN, whereby the dataset is started in 2 groups in a random way. A group with 80% of the images will be used during training (training dataset), and the other, the remaining 20% of the images (validation dataset), will be used to validate the results of each cycle (epoch). Provided we have a large dataset, 80% of instances will be enough to avoid variance in parameter estimation. Using the other 20% for cross-validation will be

enough to avoid variance in the performance metric. Depending on the results of the first experiments (training and validation), we will adjust the 80:20 split ratio. At the end of each epoch, we will record the values of accuracy and loss, both for the training dataset and the validation dataset, and will paint a graphic showing the evolution. Analyzing these graphs, the engineer will be able to extract very valuable information to know how many epochs will be necessary, whether the learning rate is adequate, whether the phenomenon known as overfitting is appearing, etc.

With the validation dataset, we will calculate true positives (TPs), true negatives (TNs), false positives (FPs), and false negatives (FNs); from there, we will obtain the confusion matrix as well as the rest of the indicators that measure the performance of the algorithm. With a more detailed image-by-image analysis, the candidate images to be revised in order to improve the quality of the labeling will be obtained.

During the prospective study, family medicine physician readers will evaluate the fundus images as usual and report their findings in the electronic medical notes. After this, they will upload the images, together with a unique patient ID, in a Web application provided by OPTretina. The uploaded images will then be available for the AI algorithm and for the board of retina specialists to perform the corresponding diagnostic and classification analysis. A blinded double reading will be done by the retina specialists with a third reading in case of disagreement.

Once all the patients included have been evaluated, all data will be exported and linked based on the patient unique ID to analyze the results and calculate the performance metrics for the comparisons. Furthermore, we will measure the performance of the AI algorithm using the public Messidor-2 dataset (collection of DR examinations). We will again calculate the values of TP, TN, FP, and FN; from there, we will obtain the confusion matrix and the rest of the indicators to measure the performance of the algorithm. Both the algorithm and the readings made by the team of family medicine physician readers will be compared with the reference blinded double readings made by the retina specialists, and the final indicators will be obtained.

- Sensitivity or true positive rate=$TP/(TP+FN)$
- Specificity or true negative rate=$TN/(TN+FP)$
- Accuracy=$(TP+TN)/(TP+FP+FN+TN)$
- Area under the receiver operating characteristic curve (AUC)

In cases where the AUC of the algorithm is superior to that of the specialists in family medicine readers and superior to 0.75, we will be able to say that we have obtained a good algorithm. The following intervals have been established for different values of AUC [24]:

- [0.5, 0.6]: Bad test
- [0.6, 0.75]: Regular test
- [0.75, 0.9]: Good test
- [0.9, 0.97]: Very good test
- [0.97, 1]: Excellent test

# Results

Cession of the images began at the end of 2018. Once the quality of the images has been evaluated, we will start with the development of the algorithm, which is calculated to last about 2 months. The inclusion of patients in the cohort will begin in early 2019 and is expected to last 3 to 4 months. We expect the preliminary results to be published by the end of 2019 and complete analysis to be published by 2020.

# Discussion

## Summary

This project offers several benefits. First, it facilitates the use of information and knowledge accumulated in the existing database available to the CHS and presentation of a success case of great relevance for similar future projects. Second, other signs of pathology are also detectable in retinal images, which opens the door for the development of new algorithms, such as those for the detection of macular degeneration associated with age, for suspicion of glaucoma, for presence of nevus and epiretinal membrane. This may allow, with certain indications for use, establishment of protocols for screening of general population or of certain risk groups. Third, so far, no similar algorithm has been developed with a population from southern Europe. It would be the first time that images taken from local population from this area are used, giving greater sensitivities and specificities to our environment.

If the results are found to be satisfactory, they can be used as a tool to support family medicine physicians' decisions and, therefore, can save them valuable time. In addition, if the results of the scientific validation are found to be satisfactory, it will be possible to obtain the CE mark as a sanitary product, which opens the door for its use as an automatic system that does not require the intervention of a doctor.

## Strengths and Limitations of the Study

The difficulties and limitations that we can expect for this project are those related to projects of these characteristics:

- Data volume: It is always difficult to transfer and store gigabytes of images. We will solve these difficulties by hiring Amazon Web Services to obtain the bandwidth and storage capacity necessary to host the data in a secure and encrypted manner.
- Necessary graphic processing capacity: The iterative training of deep neural networks imposes a very important cost in time and money, requiring special servers with a graphic calculator capacity of last generation. To mitigate this limitation, in the preprocessing of the images, the resolution of the images is reduced (eg, from 2400×2400 pixels to 512×512 pixels), which can cause information loss. For example, small microaneurysms (characteristic of incipient DR) cannot be detected in low resolution. With the available bibliography and with the publications of the winners of the Kaggle [22] contest, we know that with 512×512 pixels, we can obtain the best results while at the same time overcoming or adequately mitigating the limitation of the processing capacity necessary during the iterations in learning.
- Presence of noise (problematic images or incorrect labels) that makes learning difficult: A certain level of noise has been shown to be positive in order to obtain a more tolerant and robust algorithm, in view of the real day-to-day data, but it is necessary that the noise ratio is low so that this does not to interfere with the learning of the machine. The noise comes mainly from the following:
  - mislabeled images
  - low-quality images (darkness, brightness, contrast, too much flash, etc)
  - presence of artifacts (dirt on the camera lens)
- Class distribution: Usually, there are many normal images and very few of a certain class or group of pathology. This is one of the main problems presented in the Kaggle contest [22]. In our study, we will not have this problem because we have access to many images labeled with different grades of DR.

## Conclusions

It is possible to develop an algorithm based on AI that can demonstrate an equal or superior performance (measurable and comparable) and that constitutes a complement or an alternative to the current system based on screening of DR performed by family medicine physicians.

## Authors' Contributions

JV-A, DRF, and MAZ were the major contributors in writing the manuscript. All coauthors were involved in the conceptualization of the project and design of the study. FXM-G and OSF critically appraised and edited the manuscript. All authors read and approved the final manuscript.

## Conflicts of Interest

DRF and MAZ are cofounders of and employed by the company OPTretina. They have personal financial interests in this study as their company may be able to commercialize the algorithm. To minimize potential conflict of interest, both authors will be

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involved in the development of the AI algorithm, providing scientific and technical support, but they will not be involved in the scientific validation of the algorithm.

## References

1.  Bourne RRA, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, et al. Causes of vision loss worldwide, 1990–2010: a systematic analysis. The Lancet Global Health 2013 Dec;1(6):e339-e349. [doi: 10.1016/S2214-109X(13)70113-X]
2.  Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004 Nov;82(11):844-851 [FREE Full text] [Medline: 15640920]
3.  Garg S, Davis RM. Diabetic Retinopathy Screening Update. Clinical Diabetes 2009 Oct 15;27(4):140-145. [doi: 10.2337/diaclin.27.4.140]
4.  Sánchez González S, Calvo Lozano J, Sánchez González J, Pedregal González M, Cornejo Castillo M, Molina Fernández E, et al. Assessment of the use of retinography as a screening method for the early diagnosis of chronic glaucoma in Primary Care: Validation for screening in populations with open-angle glaucoma risk factors [In Spanish]. Aten Primaria 2017;49(7):399-406 [FREE Full text] [doi: 10.1016/j.aprim.2016.10.008] [Medline: 28126193]
5.  Chan CKW, Gangwani RA, McGhee SM, Lian J, Wong DSH. Cost-Effectiveness of Screening for Intermediate Age-Related Macular Degeneration during Diabetic Retinopathy Screening. Ophthalmology 2015 Nov;122(11):2278-2285. [doi: 10.1016/j.ophtha.2015.06.050] [Medline: 26315045]
6.  Surendran TS, Raman R. Teleophthalmology in Diabetic Retinopathy. J Diabetes Sci Technol 2014 Mar;8(2):262-266 [FREE Full text] [doi: 10.1177/1932296814522806] [Medline: 24876576]
7.  Gomez-Ulla F, Fernandez MI, Gonzalez F, Rey P, Rodriguez M, Rodriguez-Cid MJ, et al. Digital Retinal Images and Teleophthalmology for Detecting and Grading Diabetic Retinopathy. Diabetes Care 2002 Aug 01;25(8):1384-1389. [doi: 10.2337/diacare.25.8.1384]
8.  Sender Palacios MJ, Monserrat Bagur S, Badia Llach X, Maseras Bover M, la Puente Martorell MLD, Foz Sala M. Cámara de retina no midriática: estudio de coste-efectividad en la detección temprana de la retinopatía diabética. Med Clin (Barc) 2003;121(12):446-452. [doi: 10.1157/13052791]
9.  Dankwa-Mullan I, Rivo M, Sepulveda M, Park Y, Snowdon J, Rhee K. Transforming Diabetes Care Through Artificial Intelligence: The Future Is Here. Popul Health Manag 2018 Oct 02. [doi: 10.1089/pop.2018.0129] [Medline: 30256722]
10. Quellec G, Charrière K, Boudi Y, Cochener B, Lamard M. Deep image mining for diabetic retinopathy screening. Med Image Anal 2017 Jul;39:178-193. [doi: 10.1016/j.media.2017.04.012] [Medline: 28511066]
11. Usher D, Dumskyj M, Himaga M, Williamson T, Nussey S, Boyce J. Automated detection of diabetic retinopathy in digital retinal images: a tool for diabetic retinopathy screening. Diabet Med 2004 Jan;21(1):84-90. [Medline: 14706060]
12. Somfai GM, Tátrai E, Laurik L, Varga B, Ölvedy V, Jiang H, et al. Automated classifiers for early detection and diagnosis of retinopathy in diabetic eyes. BMC Bioinformatics 2014 Apr 12;15:106 [FREE Full text] [doi: 10.1186/1471-2105-15-106] [Medline: 24725911]
13. Abràmoff MD, Lou Y, Erginay A, Clarida W, Amelon R, Folk JC, et al. Improved Automated Detection of Diabetic Retinopathy on a Publicly Available Dataset Through Integration of Deep Learning. Invest Ophthalmol Vis Sci 2016 Oct 01;57(13):5200-5206. [doi: 10.1167/iovs.16-19964] [Medline: 27701631]
14. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. npj Digital Med 2018 Aug 28;1(1). [doi: 10.1038/s41746-018-0040-6]
15. Kar SS, Maity SP. Automatic Detection of Retinal Lesions for Screening of Diabetic Retinopathy. IEEE Trans Biomed Eng 2018 Dec;65(3):608-618. [doi: 10.1109/TBME.2017.2707578] [Medline: 28541892]
16. Takahashi H, Tampo H, Arai Y, Inoue Y, Kawashima H. Applying artificial intelligence to disease staging: Deep learning for improved staging of diabetic retinopathy. PLoS One 2017;12(6):e0179790 [FREE Full text] [doi: 10.1371/journal.pone.0179790] [Medline: 28640840]
17. Li Z, Keel S, Liu C, He Y, Meng W, Scheetz J, et al. An Automated Grading System for Detection of Vision-Threatening Referable Diabetic Retinopathy on the Basis of Color Fundus Photographs. Diabetes Care 2018 Dec;41(12):2509-2516. [doi: 10.2337/dc18-0147] [Medline: 30275284]
18. Channel NewAsia. 2017 Dec 14. In a world first, Singapore-developed artificial intelligence system detects 3 major eye conditions URL: https://www.channelnewsasia.com/news/health/in-a-world-first-singapore-developed-artificial-intelligence-9498742 [accessed 2018-11-04]
19. Ting DSW, Cheung CY, Lim G, Tan GSW, Quang ND, Gan A, et al. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. JAMA 2017 Dec 12;318(22):2211-2223 [FREE Full text] [doi: 10.1001/jama.2017.18152] [Medline: 29234807]
20. Institut Català de la Salut. Memòria de l'Institut Català de la Salut a la Catalunya Central. 2017. URL: http://ics.gencat.cat/ca/lics/memories-dactivitat/memories-territorials/catalunya-central/ [accessed 2018-11-30] [WebCite Cache ID 74JXWnagv]
21. Technical Area. Gerència Territorial de la Catalunya Central. Prevalence of Diabetes in the Catalan Central Region. Sant Fruitós de Bages: Institut Català de la Salut; 2018.
22. Kaggle. Diabetic Retinopathy Detection: Identify signs of diabetic retinopathy in eye image URL: https://www.kaggle.com/c/diabetic-retinopathy-detection [accessed 2018-12-04]

23.  US Food and Drug Administration. 2018 Apr 11. FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems URL: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604357.htm [accessed 2019-01-28] [WebCite Cache ID 75lq9VTLK]

24.  Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010 Sep;5(9):1315-1316 [FREE Full text] [doi: 10.1097/JTO.0b013e3181ec173d] [Medline: 20736804]

## Abbreviations

**AI:** artificial intelligence
**AUC:** area under the receiver operating characteristic curve
**CHS:** Catalan Health Service
**CNN:** convolutional neural network
**DR:** diabetic retinopathy
**FP:** false positive
**FN:** false negative
**IT:** information technology
**TP:** true positive
**TN:** true negative

Protocol

# A Tablet App– and Sensor-Based Assistive Technology Intervention for Informal Caregivers to Manage the Challenging Behavior of People With Dementia (the insideDEM Study): Protocol for a Feasibility Study

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## *Abstract*

**Background:** Despite the enormous number of assistive technologies (ATs) in dementia care, the management of challenging behavior (CB) of persons with dementia (PwD) by informal caregivers in home care is widely disregarded. The first-line strategy to manage CB is to support the understanding of the underlying causes of CB to formulate individualized nonpharmacological interventions. App- and sensor-based approaches combining multimodal sensors (actimetry and other modalities) and caregiver information are innovative ways to support the understanding of CB for family caregivers.

**Objective:** The main aim of this study is to describe the design of a feasibility study consisting of an outcome and a process evaluation of a newly developed app- and sensor-based intervention to manage CB of PwD for family caregivers at home.

**Methods:** In this feasibility study, we perform an outcome and a process evaluation with a pre-post descriptive design over an 8-week intervention period. The Medical Research Council framework guides the design of this feasibility study. The data on 20 dyads (primary caregiver and PwD) are gathered through standardized questionnaires, protocols, and log files as well as semistructured qualitative interviews. The outcome measures (neuropsychiatric inventory and Cohen-Mansfield agitation inventory) are analyzed by using descriptive statistics and statistical tests relevant to the individual assessments (eg, chi-square test and Wilcoxon signed-rank test). For the analysis of the process data, the Unified Theory of Acceptance and Use of Technology is used. Log files are analyzed by using descriptive statistics, protocols are analyzed by using documentary analysis, and semistructured interviews are analyzed deductively using content analysis.

**Results:** The newly developed app- and sensor-based AT has been developed and was evaluated until July in 2018. The recruitment of dyads started in September 2017 and was concluded in March 2018. The data collection was completed at the end of July 2018.

**Conclusions:** This study presents the protocol of the first feasibility study to encompass an outcome and process evaluation to assess a complex app- and sensor-based AT combining multimodal actimetry sensors for informal caregivers to manage CB. The feasibility study will provide in-depth information about the study procedure and on how to optimize the design of the intervention and its delivery.

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## Introduction

### Background

The management of dementia is complicated by the presence of behavioral and psychological symptoms, also referred to as challenging behavior (CB) [1,2]. CB includes a wide range of behaviors such as screaming, restlessness, wandering, pilfering, or hoarding [3]. CB represents a complex construct that results from the interaction of biological, psychological, and social factors that are idiosyncratic to the person with dementia (PwD) [4]. This behavior causes considerable stress for family caregivers [5] and is one of the most common reasons why family members transfer care responsibilities to residential care, for example, nursing homes [6,7]. Due to the limited positive effects of psychotropic medications and their tremendous adverse effects [8,9], individualized nonpharmacological approaches combining caregiver education and support with direct intervention for the PwD are the first-line strategies to manage CB [10,11]. Consequently, the current guidelines on CB emphasize the importance of describing the behavior and the context in which behavioral symptoms occur as well as identifying potential modifiable triggers for CB from which to derive a treatment plan to address the underlying contributors [12-14]. Therefore, approaches are needed that include an assessment of the topography (nature, duration, and frequency), consequences (safety and stress), and multitude of the possible bio-psycho-social causes of CB. Afterwards, the results of the assessment must be linked to individual interventions in a meaningful way [15]. To date, systematic approaches incorporating both the description of the behavior and its underlying causes and linking the assessment to individualized interventions in a meaningful way, especially for the homecare environment, are rare [15].

Several widely used instruments are available to assess CB such as the neuropsychiatric inventory (NPI) [16], the Cohen-Mansfield agitation inventory (CMAI) [17], and in homecare, the revised memory and behavior problems checklist [18]. However, the primary focus of these instruments is the description of the behavior rather than the understanding of the underlying causes of CB [19]. In the German context, the *Innovative dementia-oriented Assessment system (IdA)* is available, which was originally developed to systematically guide nursing staff in the description and analysis of the underlying causes of CB of nursing home residents [19]. The theoretical framework of the IdA instrument is the need-driven dementia-compromised behavior model [20]. There is evidence that the IdA instrument in combination with dementia-specific case conferences stimulates self-reflection and external reflection about the CB by members of nursing staff [21]. Furthermore, this approach supports the nursing staff to describe the CB and its circumstances more accurately [21]. Although

the IdA instrument was originally developed for use in the nursing home setting, it might also be a useful instrument for family caregivers in the home care setting. To support family caregivers in the caring of PwD and the management of CB, many different approaches have been developed [1]. In this regard, many studies have highlighted the potential of assistive technologies (ATs) to support family caregivers [22]. AT is an umbrella term that describes "a product, equipment or device, usually electronic or mechanical in nature, which helps people with disabilities to maintain their independence or improve their quality of life" [23,24]. Despite the enormous number and diversity of ATs in dementia care [24], the technology-based management of CB is highly underrepresented [25,26]. ATs combined with multimodal actimetry sensor technology might provide a promising and innovative addition to the existing face-to-face approaches for family caregivers [27,28]. Actimetry sensors can capture wide facets of CB by measuring acceleration, movement, rotation, and the location of an individual. In-depth information about the context in which the CB occurs can be assessed particularly well by measuring air pressure, loudness, and light level with actimetry sensors [29]. Although using standardized assessments, these reports are related to the point of view of the caregiver, which is influenced by many different factors. These factors can include the subjective view of the caregiver, the period that the caregiver and PwD spend together, or even the memory of the caregiver [30]. In addition, accelerometric measures show associations between the accelerometric motion score (AMS) and the physical nonaggressive behavior domain of CMAI [28]. To the best of our knowledge, there is only 1 Web-based technology, the WeCareAdvisor, that supports caregivers in analyzing the underlying causes and management of CB [31]; however, it does not include the potential to employ actimetry sensor technologies. The insideDEM study aims to develop and test the feasibility of an assistive technology–based intervention that includes a multimodal actimetry sensor technology for family caregivers of PwD to understand CB and to manage CB in the home care environment. The purpose of this paper is to describe the design of a feasibility study as the Medical Research Council (MRC) framework recommends in the development of complex interventions. The feasibility study includes outcome and process evaluations.

### Objectives

The primary aim of the outcome evaluation is to test the study procedure and the practicability of the intervention itself and to select the appropriate outcomes. The main aim of the process evaluation is to gain information about the processes of delivery, the acceptance of the intervention, and the requirements to optimize the design of the intervention. Both evaluations contribute to the development of a pilot study and even a trial on a larger scale [32].

**Table 1.** Domains according to the Medical Research Council framework for process evaluation and research questions.

| Domain | Subdomain | Research questions |
|---|---|---|
| A: Implementation of the intervention | Recruitment and reach of households | How were the households recruited for the intervention, and which individuals received the intervention? |
| | Delivery of the intervention to households | Was the intervention delivered as intended for each of the households? |
| | Adaptations of the implementation | What adaptations of the delivery of the intervention are made during the intervention phase? |
| B: Mechanism of impact of the intervention | Response or acceptance | How is the acceptance of the caregivers with respect to the intervention? |
| | Response or acceptance | How is the acceptance of persons with dementia with respect to the intervention? |
| | Unexpected consequences and pathways | Does the intervention lead to unexpected consequences and pathways? |
| | Adaptation of the intervention | What adaptations of the intervention had to be made during the intervention? |
| C: Context of the intervention | Ethical evaluation | What are the ethical implications of the assistive technology, and how are they influencing the design of the ATI[a]? |
| | Social and legal implications | What are the legal and social implications of the ATI in the German context regarding reimbursement by the statutory health insurance and the regulations of the German Act on Medical Devices (Medizinproduktegesetz)? |
| | Economic evaluation | What are the economic implications of the actual effort of the development, delivery and standard operating costs, and further costs for realizing a sufficient ATI? |

[a]ATI: assistive technology intervention.

## Research Questions

The outcome evaluation is guided by the following research questions:

1. What effect does the assistive technology intervention (ATI) have on CB and agitation of the PwD?
2. What effect does the new ATI have on the (1) primary caregivers' skills to manage the CB of the PwD, (2) quality of the current caregiving relationship to the PwD, (3) behavior-related distress, (4) self-perceived health, and (5) goals of caregiving?

The process evaluation is guided by the following research questions, which are subdivided into 3 domains (Table 1).

## Methods

### Study Design and Setting

This prospective exploratory feasibility study is a phase 2 study according to the MRC framework for the development and evaluation of complex health care interventions [32,33]. This study uses a pre-post design with an 8-week intervention period, without a control group. The setting of the study is the home environment of family caregivers and PwD in the region of Krefeld, North Rhine-Westfalia (Germany).

## Eligibility Criteria

### Person With Dementia

A PwD is included in the study if he or she (1) has either a documented diagnosis of dementia or a Mini-Mental State Examination [34] score of 24 or less and (2) shows at least one CB according to NPI [35]. The exclusion criteria are a documented restless legs syndrome (International Statistical Classification of Diseases and Related Health Problems, ICD 10, G25.81), a Korsakoff syndrome (ICD 10, F10.6 and F11-F 19), or a disorder of adult personality and behavior (ICD 10, F60.0-F60.9).

### Family Caregiver

A caregiver is included if he or she (1) is the primary caregiver; (2) lives in the same household as the PwD; (3) provides at least 4 hours/day of care; (4) understands, reads, and writes in the German language; (5) has no visual impairment; and (6) is willing to use the technology over the course of the intervention period. Specific competences in the use of any technology are not required.

## Intervention

The new complex ATI for caregivers to manage the CB of PwD was developed by a multidisciplinary team using a user-centered design process with different methods: user workshops, usability tests, cognitive debriefing, and consecutive expert panels. The user of the ATI is a primary caregiver of a PwD. The ATI will be placed in the homes of caregivers of PwD, and it aims to support the caregiver in understanding the behavior of his or

her family member with dementia, in monitoring their behavior, and in choosing individualized interventions. Moreover, the ATI should help the caregiver to collect and communicate information regarding behavior to relevant health care workers. The ATI consists of different hardware and software components (Figure 1).

### App User Interface

The key component of the ATI is an app user interface (AppUI) with the IdA [19], which was transformed into a digital app-based version. The AppUI consists of 4 major components (I-IV), shown in yellow in Figure 2.

**Figure 1.** Software and hardware components of the insideDEM intervention. GP: general practitioner.
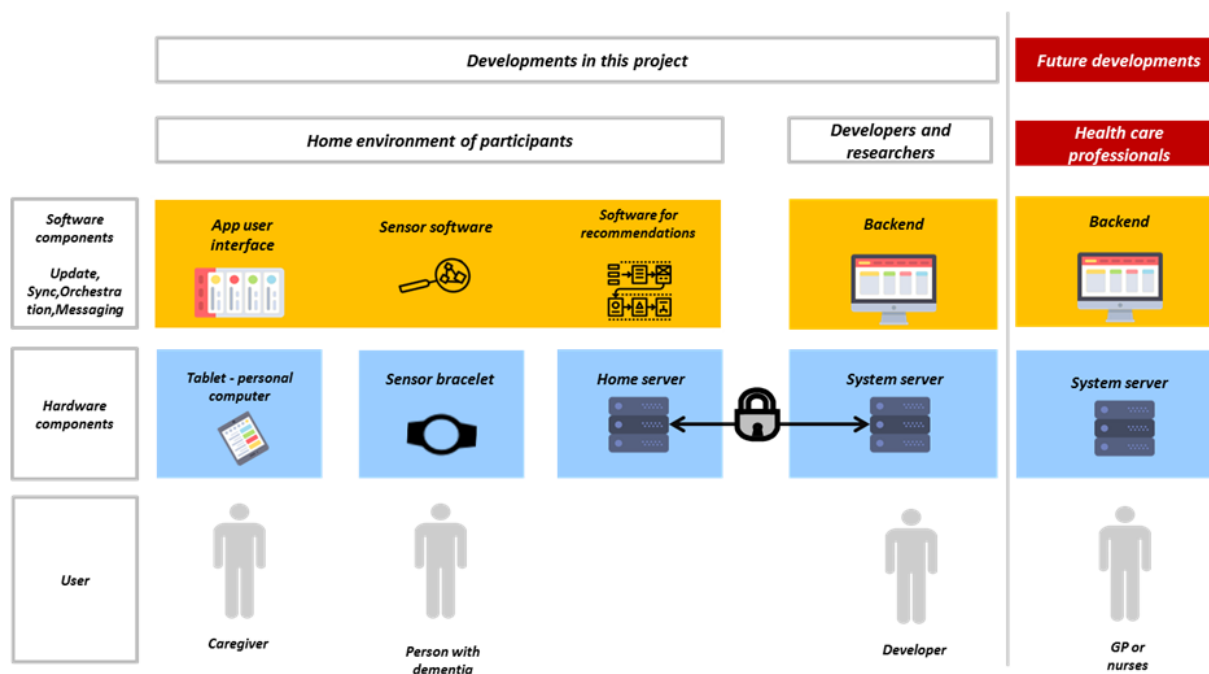


**Figure 2.** Components of the app user interface. GP: general practitioner; PwD: persons with dementia.
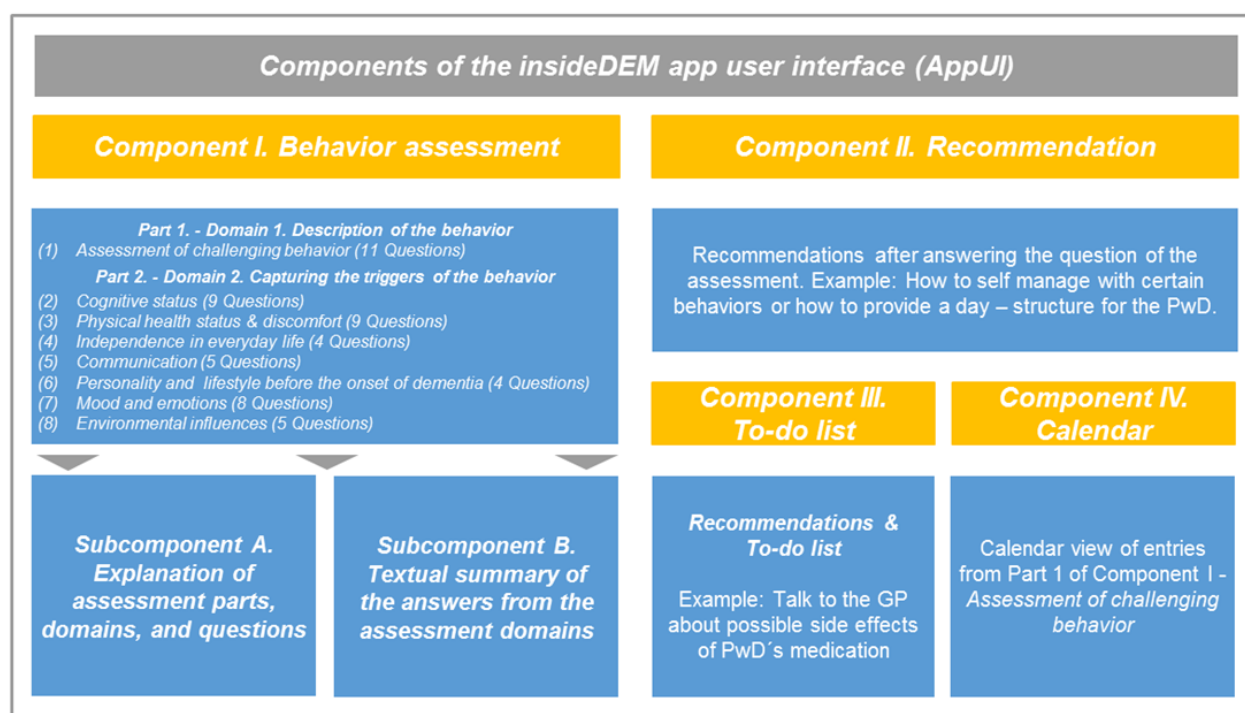
## Component I: Behavior Assessment

This component contains a home care–adapted digital version of the IdA that is divided into 2 parts with 8 domains encompassing 55 questions. Part 1: domain 1: description of the behavior includes 11 questions concerning general information on the behavior (description of the behavior, situation, frequency, occurrence, severity, and context) and the level of perceived burden [19]. Part 2: domains 2 to 8: capturing the triggers of the behavior: domain 2 cognitive status (9 questions), domain 3 physical health status and discomfort (9 questions), domain 4 independence in everyday life (4 questions), domain 5 communication (5 questions), domain 6 personality and lifestyle before the onset of dementia (4 questions), domain 7 mood and emotions (8 questions), and domain 8 environmental influences (5 questions).

In addition, component I includes 2 subcomponents: subcomponent A, explanation of assessment parts, domains, and questions and subcomponent B, textual summary of the collected information.

Subcomponent A is a guiding and educational element of AppUI intended to lead the caregiver through the assessment process (introduction to every assessment domain). Every question of the assessment is accompanied by an on-demand information button. This button will provide more detailed information about the specific topic of a question displayed on a pop-up screen. This information contains a textual explanation of why the specific question is important to answer in the context of CB, and there are examples of how caregivers obtain information to answer the question. In Subcomponent B, a textual summary of the information collected is shown after the user has completed an assessment domain. The collected data are slightly rephrased, and the summary has to be acknowledged by the user to ensure its validity.

## Component II: Recommendation

On the basis of the collected information in domains 1 to 8 of component I, the user will obtain individualized recommendations for possible nonpharmacological interventions. For example, the assessment contains the question "Did you talk to the general practitioner (GP) about possible side effects of the medication?" Here, for example, the user obtains suggestions about important questions for the GP for the next visit.

## Component III: To-Do List

The to-do list includes the important questions for the GP from the recommendations in component II. The list can be accessed by the user from the home screen.

## Component IV: Calendar

The calendar shows all entries from the behavior assessment according to the date of the documentation from the user (component I).

## Hardware Components and Technical Infrastructure

### Home Server Operating Case

The delivery of the technical infrastructure is based on a modular and flexible distributed system architecture to provide a basis for future enhancements (eg, a more complex integration of sensor data). The hardware consists of a tablet personal computer and a sensor bracelet for gathering vital data from the PwD. The data processing (storage, distribution, and signal processing, which should be emphasized in future projects) is performed by a dedicated embedded system in the domicile of the study participants. A central home server is responsible for gathering data from all clients for observation and subsequent analysis and to enable further system extensions, for example, giving access to external entities such as caregivers and medical services. Moreover, this server is responsible for maintenance tasks and the automatic configuration and updating of the client systems (Figure 1). All involved systems use a message broker for communications in a secured environment (dedicated wireless local area network [WLAN] and virtual private network tunnels) and are accessible to external systems through standard interfaces. For the delivery of the technical infrastructure, we developed a home server operating case that includes the home server, an independent WLAN router and the capability for all devices to be charged by the user.

### Sensor Bracelet

A sensor bracelet tailored to the specific needs of the insideDEM study has been developed [29,36]. As shown in Figure 3, this instrument is a watch-like device to be worn on the wrist or ankle. The bracelet contains numerous sensors to record data from the PwD and the environment. The sensors, including their specifications, are listed in Table 2. The bracelet is fully programmable and is currently setup in such a way that it records the data in a manner that is as detailed as possible. For example, accelerometers and gyroscopes record with a sampling rate of up to 100 Hz. On the basis of Bluetooth low-energy and dedicated beacons (Texas Instruments CC2650STK, shown in Figure 4), location information is recorded.

During the study, the bracelet has to be charged through a Universal Serial Bus connection to the home server. In this system, the *offload manager* is used to (1) load the recorded data from the bracelet, (2) scan the data with respect to symptoms indicating malfunctioning or an incorrect use of the sensor, and (3) prepare the bracelet for the next recording session (cleaning and synchronizing times). As soon as the sensor is ready for recording (indicated on the display) and detached from the home server, it starts recording the data, that is, no manual intervention is needed to prevent loss of data. The recorded data are transformed into an activity plot highlighting very active and very passive episodes. Due to the cognitive decline of the PwD, the primary caregiver of the PwD must be responsible for equipping the PwD with the nonintrusive sensor bracelet and for monitoring its proper functioning on a daily basis.

**Figure 3.** Sensor bracelet developed for insideDEM.



**Table 2.** Sensor modalities and corresponding sampling frequencies recorded by the sensor bracelet.

| Sensor modality | Frequency of data |
| --- | --- |
| 3-axis accelerometer | 100 Hz |
| 3-axis gyroscope | 100 Hz |
| Skin temperature sensing | 50 Hz |
| Reference temperature sensing | 50 Hz |
| Photoplethysmography | 50 Hz |
| Bluetooth beacon recording | On every Bluetooth event |

The intervention assistants who deliver the ATI to the participants are trained nurses (later called intervention assistants) from a day care center of a communal residential care institution in Krefeld, Germany, with longstanding working experience in the care of PwDs. The intervention assistants are trained in using the ATI and in counseling alongside a self-developed delivery protocol (Multimedia Appendix 1). The caregivers obtain several in-house trainings (Table 3) and information sheets with important information about the ATI and the general study procedure. To manage participant attrition [37] and to encourage the use of the ATI, family dyads are visited twice after the first initial in-home visit. A second in-home visit is conducted in the second week and a third, in the fourth week with an intervention period at the end. In addition, intervention assistants provide the opportunity for individualized in-home visits, which can be requested by the participants through a telephone support hotline. The intervention assistants provide first-level troubleshooting for all technical problems. To provide a standardized process for all participants in the use of the ATI, in this early development phase, the participants are asked to complete the whole assessment in component I with all questions at least once in 1 week. In addition, the participants are encouraged to use the ATI as often as they feel comfortable doing so. From our previous study, we have found that most PwDs will have good compliance regarding the bracelet [29]. We are aware that wearing a device can be a burden for the PwD and it might not be tolerated. Especially during the first in-house face-to-face training for caregivers (1-1.5 hours), the intervention assistants will focus on how the bracelet will be tolerated by the PwD. If there is any sign of burden or extra CB by the PwD before or during the intervention, we will instruct the caregiver to take off the bracelet immediately. The ATI can be used without the bracelet.

## Delivery of Intervention

The process of delivery of the ATI is facilitated by different actions (Table 3).

**Figure 4.** Bluetooth low energy beacon (red) and the sensor bracelet.



**Table 3.** Components of the delivery of the intervention.

| Timeline | Elements | Performance of the delivery |
| --- | --- | --- |
| Preintervention | Training of the main intervention assistants in the use of the assistive technology (2 days and 10 hours) | Project team |
| Preintervention | Counseling training of the assistive technology intervention (2 days and 16 hours) | External provider |
| First week of intervention | In-house face-to-face training for caregivers (1-1.5 hours) | Intervention assistants |
| Second week of intervention | In-house visit and supervision of the caregivers | Intervention assistants |
| Fourth week of intervention | In-house visit and supervision of the caregivers | Intervention assistants |
| Fifth to eighth weeks of intervention | Additional in-house visits on demand | Intervention assistants |
| First to eighth weeks of intervention | Telephone hotline for prompt help, leaflet with written instructions | Intervention assistants |

## Data Collection

### Sociodemographic Data

The sociodemographic data of the PwD encompass gender, age, education, and year of diagnosis of dementia. The severity of the cognitive impairment is assessed according to the Global Deterioration Scale [38] at the baseline assessment before the intervention starts (T0) and after 8 weeks of the intervention (T1). The use of health care services is assessed with the questionnaire for Health-Related Resource Use in an Elderly Population (FIMA) [39]. This questionnaire includes 29 items focusing on aspects such as medication, GP visits, and other health care resources in the last 4 to 12 weeks.

For the primary caregiver, the sociodemographic characteristics include gender, age, education, living arrangement, hours of care per week, relationship to the PwD, and self-perceived stability of the care arrangement [40].

In addition to the sociodemographic data, the affinity for using technology of the family caregiver is assessed with the technology affinity questionnaire (TA-EG) at T0. In this questionnaire, affinity for using technology is defined as a personality characteristic that consists of trust in and a positive attitude and excitement toward the use of technologies (such as mobile phones and computers) [41]. The TA-EG involves 19 items rated with a 5-point Likert scale covering 4 domains: excitement related to technology use, self-perceived competence, perceived positive impact, and perceived negative impact of the use of technology [41]. A higher mean indicates a higher affinity for using technology [41].

### Outcome Measures

Data on outcome measures are gathered face-to-face by trained interviewers (researchers of the German center for neurodegenerative diseases) with the family caregivers at T0 and T1 (Table 4). To provide maximum flexibility according to the individual needs of caregivers and PwDs, the interviews are conducted either at home or at the day care center that recruited the participants.

**Table 4.** Data collection for the outcome study.

| Outcome or variable | Measurement | Number of items | Type of variable | Measurement |
|---|---|---|---|---|
| **Outcome for the person with dementia** | | | | |
| Challenging behavior | Neuropsychiatric inventory [35] | 12 | Outcome | T0-T1 |
| Agitation | Cohen-Mansfield agitation inventory [17] | 29 | Outcome | T0-T1 |
| Challenging behavior and agitation | Sensor data | Modalities according to Table 2 | Outcome | Ongoing |
| **Outcome for caregivers of the person with dementia** | | | | |
| Skills to manage challenging behavior | Caregiver Assessment of Behavioral Skill Self-Report [47] | 29 | Outcome | T0-T1 |
| Quality of the current relationship | The Scale for the Quality of the Current Relationship in Caregiving [43] | 14 | Outcome | T0-T1 |
| Behavior related distress | Caregiver distress score from the Neuropsychiatric Inventory [35] | 12 | Outcome | T0-T1 |
| Self-perceived health | General Health Survey Questionnaire Short Form 12 [44] | 12 | Outcome | T0-T1 |
| Goals of caregiving | Goal Attainment Scale [46] | 1 | Outcome | T0-T1 |

## Person With Dementia

### Challenging Behavior

The CB of the PwD is assessed with the NPI, proxy version [35]. The NPI assesses the presence, frequency, and severity of dementia-related behaviors in 12 different domains: delusions, hallucinations, depression, anxiety, euphoria, aggression, apathy, disinhibition, irritability, aberrant motor behavior, problems with sleeping, and appetite and eating disorders in the last 14 days. Frequency is rated on a 4-point scale (occasionally, often, frequently, and very frequently), and severity is rated on a 3-point scale (mild, moderate, and severe) [41]. The total NPI score will be calculated by adding the first 12 behavioral domains together. Therefore, we will calculate frequency×severity. A higher score indicates a higher level of the relevant domain of the NPI.

### Agitation

For measurement of agitation, the CMAI [17] is used. The CMAI covers 29 items, each rated on a 7-point scale, to assess the occurrence and frequency of agitation (never, less than once a week but still occurring, once or twice a week, several times a week, once or twice a day, to several times a day, and several times an hour [17]). A higher cumulative score indicates a higher level of agitation.

## Family Caregiver

### Skills to Manage Challenging Behavior

Self-reported management skills regarding CB from the perspective of the caregiver are measured with the German version of the Caregiver Assessment of Behavioral Skill Self-Report (CABS-SR). The CABS-SR includes 3 subscales: general approaches to caregiving (11 items), behavioral management of skill (17 items), and a single skill item scored between 1 and 4 as follows: 1=I do not do this very well; 2=I have some difficulty doing this; 3=I usually do this well; and 4=I do this very well. The cumulative score ranges between 11

and 44, with higher scores indicating higher levels of self-perceived skills [42].

### The Quality of Current Relationship

The self-rated quality of the current relationship between the caregiver and the PwD is assessed with the scale for the Quality of the Current Relationship in Caregiving (QCPR), which includes 14 items scored on a 5-point scale (1: totally disagree; 2: disagree; 3: not sure; 4: agree; and 5: totally agree) [43]. The total score ranges from 14 to 70, with a median score more than 42 indicating a *better* relationship and less than 42 indicating a *poorer* relationship between the caregiver and the PwD [43].

### Behavior-Related Distress

The behavior-related distress is assessed with the distress scale of the NPI. The distress is rated on a 5-point scale (no distress to minimal, mild, moderate, moderately severe, very severe, and extreme distress) [41]. The total distress score is generated by adding the scores of the 12 items from the questions related to distress [33].

### Self-Perceived Health

Self-rated health is assessed with the General Health Survey Questionnaire Short Form 12 (SF-12) [44]. This instrument measures 8 different concepts such as physical functioning and role limitations because of general or physical health problems.

### Goals of Caregiving

As standardized assessments often fail to depict the individual situation of complex care situations and the related problems [45], we measure the individual goal of caregivers on what should change in the care situation with the Goal Attainment Scale (GAS) [46], which has previously been used in dementia-specific technology studies [25]. At T0, the caregiver defines the specific goals that he or she would like to achieve using the AT. To indicate a subjective decrease or increase in the expected outcomes, numerical weights are assigned to evaluate goal attainment at T1: more than expected=1, much

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more than expected=2, less than expected=−1, and much less than expected=−2. Considering that behavioral or health-related aspects can change rapidly in a PwD, we ask the caregivers at T1 whether the goals are still relevant.

## Recruitment

A convenience sample of 20 dyads (primary caregiver-PwD) will be recruited face-to-face over a 5-month period. For pragmatic reasons, we determined the number of participants based on a realistic estimation of the intervention assistants in the day care centers. The intervention assistants from the day care center who are delivering the ATI to the home environment of the dyads are in charge of the recruitment process as well. In addition, the process of recruitment will be guided by the research team. The intervention assistants have longstanding working experience in the care of PwDs and a close relationship with the dyads to ensure the success of the recruitment. Different recruitment strategies used are (1) day care center with intervention assistants as gatekeepers, (2) a second local day care center as gatekeepers, (3) 2 neurologists as gatekeepers, and (4) an announcement in the local newspaper, followed by an open 2-hour information event at one of the day care centers. As the study will only take place in the home environment of the caregivers and the PwD, it is not important whether a PwD is a guest at the day care or not. In case of interest in the study, the intervention assistants conduct a face-to-face introduction

with individuals and describe the aims, scope, study procedure, and participation requirements. Simultaneously, the potential participants receive written information about the study procedure and the document to give informed consent. After a minimum period of 7 days, the intervention assistants conduct a second detailed face-to-face introduction to receive the actual consent. Afterwards, the eligibility criteria are determined either in the care center or at the home of the families. No incentives are provided to participate in the study.

## Process Evaluation

The domains of the process evaluation are guided by the MRC framework for the process evaluation of complex interventions [48]. The process evaluation addresses the following domains: (A) implementation of the intervention, (B) mechanism of impact of the intervention, and (C) context of the intervention. Each domain comprises different subdomains (Figure 5), for which different means of data collections are used.

### Domain A: Implementation of the Intervention

This domain describes the process of recruitment and reach of households, the process of delivery of the intervention, and whether any adaptations were necessary according to what was initially planned in regard to how to implement the intervention. This aspect allows us to evaluate whether the implementation of the intervention was successful and how it possibly impacts the success of the intervention.

**Figure 5.** Framework of the insideDEM process evaluation. CABS-SR: Caregiver Assessment of Behavioral Skill Self-Report; CMAI: Cohen-Mansfield agitation inventory; GAS: Goal Attainment Scale; NPI: neuropsychiatric inventory; NPI-CB: neuropsychiatric inventory-challenging behavior; QCPR: Quality of the Current Relationship in Caregiving; SF-12: Short Form 12.
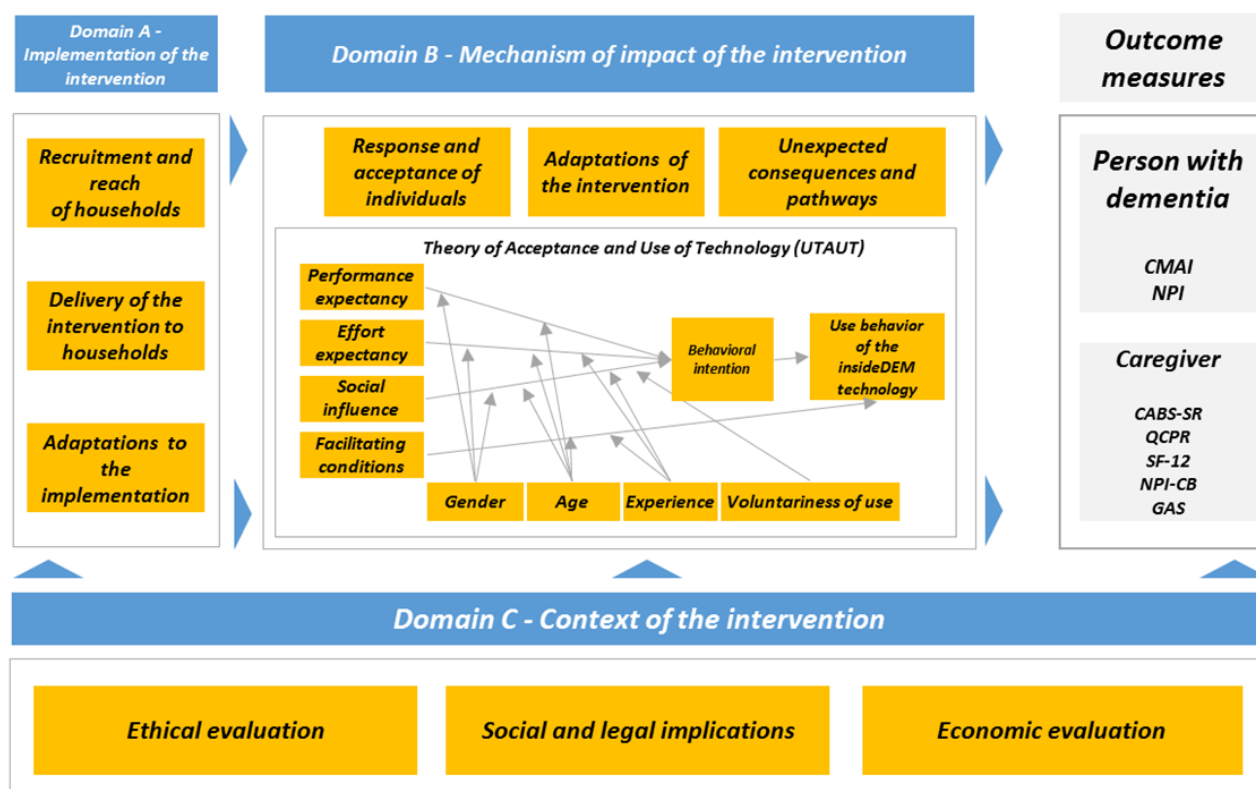
## Subdomain: Recruitment and Reach of Households

The process of recruitment and reach is documented in a standardized handwritten recruitment protocol (Multimedia Appendix 1). As the intervention assistants are essentially in charge of the recruitment process, we additionally conduct semistructured qualitative interviews with them (Multimedia Appendix 1).

## Subdomain: Delivery of the Intervention to Households

The intervention assistants document in a standardized handwritten delivery and intervention protocol whether all of the components of the intervention will actually be delivered to the participants (Multimedia Appendix 1). The protocol is applied during and after the initial in-house face-to-face training and is continued throughout the entire 8-week intervention period. Similarly, in this document, we record the feasibility of the application of the delivery curriculum. All nonconformities to the curriculum are documented by the intervention assistants. In addition, semistructured qualitative interviews are conducted with the intervention assistants to review the process of delivery (Multimedia Appendix 1).

## Subdomain: Adaptations of the Implementation

Adaptations of the implementation of the intervention during the study phase are documented by the intervention assistants in a handwritten standardized delivery and intervention protocol (Multimedia Appendix 1). Furthermore, the intervention assistants will review the process of delivery after the initial delivery meeting on an audio recorder to obtain more qualitative data on the process of delivery (Multimedia Appendix 1). To monitor the quality of the delivery and to integrate potential adjustments immediately, a daily meeting among the researchers, intervention assistants, and developers of the software takes place in each week of the intervention phase. In addition, after the intervention, we will conduct semistructured qualitative interviews with the intervention assistants (Multimedia Appendix 1) and caregivers (Multimedia Appendix 1) to evaluate this domain.

## Domain B: Mechanism of Impact of the Intervention

This domain describes the response and the user acceptance of the intervention, the unexpected consequences and pathways of the intervention, and the adaptations of the intervention.

## Subdomain: Response and Acceptance

For the evaluation of the user acceptance, Venkatesh's Unified Theory of Acceptance and Use of Technology (UTAUT) is used [49]. The UTAUT is a helpful model for analyzing technology acceptance in the field of dementia [50]. The UTAUT consists of 6 main variables: performance expectancy (PE), effort expectancy (EE), social influence (SI), facilitating conditions (FC), intention to use (ITU) and usage behavior (UB). PE is defined as the degree to which an individual believes that using the system will help or improve a certain task. EE is defined as the degree of ease that an individual associates with the use of the technology. SI is defined as the degree to which the user perceives that other important persons believe that the user should use the technology. FC is defined as the degree to which an organizational or technical infrastructure is available to support the use of the technology. In addition to acceptance,

any unexpected consequences of using the AT are assessed. ITU is defined as "the degree to which a person has formulated conscious plans to perform or not perform some specified future behavior" [51], and UB describes the characteristics of use of the AT. The first 4 variables are moderated, in turn, by gender, age, experience, and voluntariness of use [49]. Information on the acceptance of the intervention from different perspectives is collected using quantitative and qualitative approaches. The Technology Usage Inventory (Multimedia Appendix 1) is a standardized questionnaire based on, for example, the UTAUT to evaluate the acceptance of new technology. It contains 30 items covering dimensions such as ITU, accessibility, user-friendliness, and usefulness. Higher scores in each domain indicate a higher level of acceptance. To assess system usability and the overall user experience and to adjust the user scenarios, we use the User Experience Questionnaire (UEQ) (Multimedia Appendix 1). The UEQ includes 26 pairs of opposite adjectives describing the attributes: attractiveness (6 pairs), perspicuity (4 pairs), efficiency (4 pairs), dependability (4 pairs), stimulation (4 pairs), and novelty (4 pairs); each pair is rated on a 7-point scale (from −3 to +3). A product with a highly rated usability is effective, efficient, and satisfying for the user and his or her needs. We administer the UEQ after the first use of the ATI and after the intervention period at T1. In addition, we assess the log files of the users' app navigation and the overall UB characteristics via log files (Multimedia Appendix 1). The variables of interest are the time spent on a page, the time needed for the major tasks, the number of reverse navigations, the number of completed assessments (intervention component I), the number of documented behaviors per intervention period and per week (intervention component I), the number of displayed texts clicked per assessment question and the time spent on a specific text page (subcomponent A), and the number of user comments. Finally, we conduct qualitative semistructured interviews with the caregivers and intervention assistants based on the UTAUT (Multimedia Appendix 1), which will provide in-depth information on the reasons for using the ATI and further factors influencing its acceptance. To assess the acceptance of the ATI by the PwD, we use the caregiver as a proxy informant and the qualitative semistructured interviews with the intervention assistants (Multimedia Appendix 1). The duration of time the bracelet was actively worn is collected via log files (Multimedia Appendix 1).

## Subdomain: Unexpected Consequences and Pathways

The semistructured interviews with the caregivers and the intervention assistants are analyzed regarding any unexpected consequences (Multimedia Appendix 1). Moreover, data from the delivery and intervention protocol as well as from the review the process of delivery are used (Multimedia Appendix 1).

## Subdomain: Adaptations of the Intervention

With respect to the intervention's adaptions, we distinguish between technology-external and technology-internal factors. Technology-internal aspects include bug fixes, periods of down time, and content changes during the intervention phase. Technology-external aspects include the counseling activities of the intervention assistants and the number of visits. The information source is the delivery and intervention protocol (Multimedia Appendix 1) and the semistructured qualitative

interviews with the intervention assistants (Multimedia Appendix 1).

### Domain C: Context of the Intervention

This domain describes any contextual factor that is external to the intervention and that potentially influences the impact of the intervention. In this study, we focus on ethical, social and legal, and economic implications (ELSIs).

#### Subdomain: Ethical Evaluation

The ethical evaluation is conducted in a workshop based on the model for the ethical evaluation for social-technical arrangements (MEESTAR) [52], including significant stakeholders, project partners, and members of the advisory board (Multimedia Appendix 1).

#### Subdomain: Social and Legal Implications

Expert interviews will be conducted to evaluate the social and legal implications and the perceived acceptance of the intervention in the field of home care (Multimedia Appendix 1). The experts represent different areas of the health care system such as medical device regulation (Medizinproduktegesetz), statutory health insurance companies, GPs, and home health care providers. As they play a major role in dementia care as gatekeepers for new technologies, we will conduct semistructured qualitative interviews with GPs and nurse managers of home health care providers in the home care setting (Multimedia Appendix 1). The aim is to assess their perspectives and attitudes regarding the use of the new ATI.

#### Subdomain: Economic Evaluation

The individual costs of the deployment, delivery, and standard operation of the ATI are calculated and described separately in an economic evaluation. Subsequently, a comparison of all originating costs is performed (Multimedia Appendix 1).

#### Ethical Approval

The Ethics Committee of the German Society of Nursing Science approved the design and the study protocol in March 2017 (application number 17-004).

#### Data Analysis

In this section, we describe the data analysis for the outcome evaluation and the process evaluation separately.

### Outcome Evaluation

The outcome data are analyzed by applying descriptive statistics (means, SDs, and counts) relevant to the individual assessment. The Kolmogorov-Smirnov test is used to determine whether a sample is normally distributed [53]. After determining whether the related outcome samples of each assessment are normally distributed, we compare the 2 samples from T0 and T1 and analyze the differences between the 2 datasets. For non-normally distributed samples, we apply a Wilcoxon signed-rank test, and for normally distributed samples, a dependent-sample $t$ test. Nominal data are compared with a chi-square test. For all quantitative data analyses, we use IBM SPSS Version 21. The significance level is set to 5%.

On the basis of the recorded data from the sensor bracelet, AMS [28] is computed; this score can be used to capture the overall activities of the PwD.

### Process Evaluation

Descriptive statistics are applied to all quantitative data (Multimedia Appendix 1) and for all relevant log files (Multimedia Appendix 1). We compare the baseline characteristics of the quantitative data with the characteristics at T1.

All semistructured qualitative interviews (Multimedia Appendix 1) are transcribed into digital versions and subsequently analyzed by applying content analysis [54]. The handwritten recruitment protocol and the handwritten delivery and intervention protocol (Multimedia Appendix 1) are analyzed by using documentary analysis [55]. The results of the workshop based on the MEESTAR model are summarized in a workshop report (Multimedia Appendix 1).

## Results

The newly developed app- and sensor-based AT has been developed and was evaluated until July in 2018. The recruitment of dyads started in September 2017 and was concluded in March 2018. The data collection was completed at the end of July 2018.

## Discussion

The management of CB is a highly individual and complex task, and it poses a significant psychological and physical burden to the PwD and his or her caregivers [5]. To the best of our knowledge, the insideDEM technology is one of the very few examples to support the process of understanding the CB of the PwD via an ATI. In fact, to the best of our knowledge, there is no comparable technology that encompasses the functionalities of a caregiver assessment and a sensor assessment of the CB, questions that reflect possible factors influencing the CB, and the provision of recommendations to support caregivers to manage the CB of the PwD. In our view, it is important to evaluate the factors that shape the acceptance of the ATI from different perspectives as early as possible in the development of an ATI. This perspective is based on the assumption that acceptance is a necessary but not sufficient factor for evaluating the effectiveness of complex interventions [56]. The feasibility study will provide useful information on how to shape the intervention and the overall study procedure for trials at a larger scale. In the context of this study, understanding the delivery and use of the ATI in the real-life context of PwDs and their caregivers is indispensable.

A possible weakness of this study is that it is more likely that healthier and more motivated participants will take part in the study, which could possibly limit the results and transferability of the results for larger trials. A main concern is that the results could lead to an overestimation of the factors shaping the acceptance of the technology because of the participation of motivated and healthier participants. In addition, study attrition is a main concern, despite our strategy to mitigate this issue. Nevertheless, we think that the close and flexible support of the

intervention assistants and their years-long experience in dementia care will lower this effect.

Before it is even possible to design a high-quality randomized controlled trial for this intervention, the process evaluation will provide valuable information for further steps of development by including the results of the intervention phase and the ELSIs. An important part of the ELSI criteria is the ethical aspects entailed in an ATI. Assistive systems may affect values such as independence or privacy and create tensions with other values such as safety or health. Moreover, different stakeholders hold different values, which further complicate the matter. Specifically designed for ATs, the model for the ethical evaluation of sociotechnical arrangements, MEESTAR [52], provides a suitable framework, allowing a normative ethical orientation in the design of an ATI.

## Acknowledgments

## Authors' Contributions

SK, MH, and DH developed the design of the feasibility study. SK wrote the paper. PP wrote the "Hardware Components and Technical Infrastructure" section and SB wrote the "Sensor Bracelet" section. DH and MH reviewed the paper and gave major comments.

## Conflicts of Interest

There is no distinction between the developers and evaluators of the intervention. MH developed the original IdA instrument. The authors have no competing interests. The sensor bracelet has been developed in cooperation with Grey Innovation Pty Ltd.

Multimedia Appendix 1
Data sources of the process evaluation domains.
[PDF File (Adobe PDF File), 28 KB - resprot_v8i2e11630_app1.pdf ]

## References

1. Moniz Cook ED, Swift K, James I, Malouf R, De Vugt M, Verhey F. Functional analysis-based interventions for challenging behaviour in dementia. Cochrane Database Syst Rev 2012 Feb 15(2):CD006929. [doi: 10.1002/14651858.CD006929.pub2] [Medline: 22336826]

2. James IA. Understanding Behaviour in Dementia That Challenges: A Guide to Assessment and Treatment. London: Jessica Kingsley Pub; 2018:176.

3. Moniz-Cook E, Woods R, Gardiner E, Silver M, Agar S. The Challenging Behaviour Scale (CBS): development of a scale for staff caring for older people in residential and nursing homes. Br J Clin Psychol 2001 Sep;40(Pt 3):309-322. [Medline: 11593958]

4. Moniz-Cook E, Hart C, Woods B, Whitaker C, James I, Russel I, et al. Challenge Demcare: management of challenging behaviour in dementia at home and in care homes – development, evaluation and implementation of an online individualised intervention for care homes; and a cohort study of specialist community mental health care for families. Southampton, UK: National Institute for Health Research; Feb 2017.

5. Feast A, Moniz-Cook E, Stoner C, Charlesworth G, Orrell M. A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being. Int Psychogeriatr 2016 Dec;28(11):1761-1774. [doi: 10.1017/S1041610216000922] [Medline: 27345942]

6. de Vugt ME, Stevens F, Aalten P, Lousberg R, Jaspers N, Verhey FR. A prospective study of the effects of behavioral symptoms on the institutionalization of patients with dementia. Int Psychogeriatr 2005 Dec;17(4):577-589. [doi: 10.1017/S1041610205002292] [Medline: 16185379]

7. Sansoni J, Anderson KH, Varona LM, Varela G. Caregivers of Alzheimer's patients and factors influencing institutionalization of loved ones: some considerations on existing literature. Ann Ig 2013;25(3):235-246 [FREE Full text] [doi: 10.7416/ai.2013.1926] [Medline: 23598807]

8. Wang J, Yu JT, Wang HF, Meng XF, Wang C, Tan CC, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2015 Jan;86(1):101-109. [doi: 10.1136/jnnp-2014-308112] [Medline: 24876182]

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9.    Ma H, Huang Y, Cong Z, Wang Y, Jiang W, Gao S, et al. The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials. J Alzheimers Dis 2014;42(3):915-937. [doi: 10.3233/JAD-140579] [Medline: 25024323]

10.   Barton C, Ketelle R, Merrilees J, Miller B. Non-pharmacological management of behavioral symptoms in frontotemporal and other dementias. Curr Neurol Neurosci Rep 2016 Feb;16(2):14 [FREE Full text] [doi: 10.1007/s11910-015-0618-1] [Medline: 26750129]

11.   Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry 2012 Sep;169(9):946-953. [doi: 10.1176/appi.ajp.2012.11101529] [Medline: 22952073]

12.   International Psychogeriatric Association. 2002. Behavioral and Psychological Symptoms of Dementia (BPSD) Educational Pack URL: http://myalzheimersstory.com/wp-content/uploads/2017/05/IPA_BPSD_Educational_Pack-1998.pdf [accessed 2018-12-07] [WebCite Cache ID 74UBsRoyt]

13.   Dementia: The NICE-SCIE Guideline on Supporting People with Dementia and Their Carers in Health and Social Care (National Clinical Practice Guideline). Leicester: British Psychological Society and RCPsych Publications; 2007.

14.   Bartholomeyczik S, Halek M, Sowinski C, Besselmann K, Dürrmann P, Haupt M, et al. Gesamtpublikation Rahmenempfehlungen.: Bundesministerium für Gesundheit; 2006. Rahmenempfehlungen zum Umgang mit herausforderndem Verhalten bei Menschen mit Demenz in der stationären Altenhilfe URL: https://tinyurl.com/ybx3qfph [accessed 2018-06-20]

15.   Holle D, Halek M, Holle B, Pinkert C. Individualized formulation-led interventions for analyzing and managing challenging behavior of people with dementia - an integrative review. Aging Ment Health 2017 Dec;21(12):1229-1247. [doi: 10.1080/13607863.2016.1247429] [Medline: 27809556]

16.   Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 1997 May;48(5 Suppl 6):S10-S16. [Medline: 9153155]

17.   Cohen-Mansfield J. Assessment of agitation. Int Psychogeriatr 1996;8(2):233-245. [Medline: 8994894]

18.   Teri L, Truax P, Logsdon R, Uomoto J, Zarit S, Vitaliano PP. Assessment of behavioral problems in dementia: the revised memory and behavior problems checklist. Psychol Aging 1992 Dec;7(4):622-631. [Medline: 1466831]

19.   Halek M, Holle D, Bartholomeyczik S. Development and evaluation of the content validity, practicability and feasibility of the innovative dementia-oriented assessment system for challenging behaviour in residents with dementia. BMC Health Serv Res 2017 Dec 14;17(1):554 [FREE Full text] [doi: 10.1186/s12913-017-2469-8] [Medline: 28806934]

20.   Kolanowski AM, Whall AL. Toward holistic theory-based intervention for dementia behavior. Holist Nurs Pract 2000 Jan;14(2):67-76. [Medline: 12119972]

21.   Holle D, Krüger C, Halek M, Sirsch E, Bartholomeyczik S. Experiences of nursing staff using dementia-specific case conferences in nursing homes. Am J Alzheimers Dis Other Demen 2015 May;30(3):228-237. [doi: 10.1177/1533317514552320] [Medline: 25260597]

22.   Parra-Vidales E, Soto-Pérez F, Perea-Bartolomé MV, Franco-Martín MA, Muñoz-Sánchez JL. Online interventions for caregivers of people with dementia: a systematic review. Actas Esp Psiquiatr 2017 May;45(3):116-126 [FREE Full text] [Medline: 28594057]

23.   Marshall M, editor. State Of The Art In Dementia Care. London: Centre For Policy On Ageing; Feb 23, 1999:224.

24.   Khosravi P, Ghapanchi AH. Investigating the effectiveness of technologies applied to assist seniors: a systematic literature review. Int J Med Inform 2016 Jan;85(1):17-26. [doi: 10.1016/j.ijmedinf.2015.05.014] [Medline: 26216463]

25.   Kerssens C, Kumar R, Adams AE, Knott CC, Matalenas L, Sanford JA, et al. Personalized technology to support older adults with and without cognitive impairment living at home. Am J Alzheimers Dis Other Demen 2015 Feb;30(1):85-97 [FREE Full text] [doi: 10.1177/1533317514568338] [Medline: 25614507]

26.   Lauriks S, Reinersmann A, Van der Roest HG, Meiland FJ, Davies RJ, Moelaert F, et al. Review of ICT-based services for identified unmet needs in people with dementia. Ageing Res Rev 2007 Oct;6(3):223-246. [doi: 10.1016/j.arr.2007.07.002] [Medline: 17869590]

27.   Meiland F, Innes A, Mountain G, Robinson L, van der Roest H, García-Casal JA, et al. Technologies to support community-dwelling persons with dementia: a position paper on issues regarding development, usability, effectiveness and cost-effectiveness, deployment, and ethics. J Med Internet Res Rehabil Assist Technol 2017 Jan 16;4(1):e1 [FREE Full text] [doi: 10.2196/rehab.6376] [Medline: 28582262]

28.   Kirste T, Hoffmeyer A, Koldrack P, Bauer A, Schubert S, Schröder S, et al. Detecting the effect of Alzheimer's disease on everyday motion behavior. J Alzheimers Dis 2014;38(1):121-132. [doi: 10.3233/JAD-130272] [Medline: 24077435]

29.   Teipel S, Heine C, Hein A, Krüger F, Kutschke A, Kernebeck S, et al. Multidimensional assessment of challenging behaviors in advanced stages of dementia in nursing homes-The insideDEM framework. Alzheimers Dement (Amst) 2017 Apr 4;8:36-44 [FREE Full text] [doi: 10.1016/j.dadm.2017.03.006] [Medline: 28462388]

30.   Valembois L, Oasi C, Pariel S, Jarzebowski W, Lafuente-Lafuente C, Belmin J. Wrist actigraphy: a simple way to record motor activity in elderly patients with dementia and apathy or aberrant motor behavior. J Nutr Health Aging 2015 Aug;19(7):759-764. [doi: 10.1007/s12603-015-0530-z] [Medline: 26193860]

31.   Kales HC, Gitlin LN, Stanislawski B, Marx K, Turnwald M, Watkins DC, et al. WeCareAdvisor™: the development of a caregiver-focused, web-based program to assess and manage behavioral and psychological symptoms of dementia. Alzheimer Dis Assoc Disord 2017;31(3):263-270 [FREE Full text] [doi: 10.1097/WAD.0000000000000177] [Medline: 27849639]

32.  Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. Br Med J 2008 Sep 29;337:a1655 [FREE Full text] [doi: 10.1136/bmj.a1655] [Medline: 18824488]

33.  Campbell NC, Murray E, Darbyshire J, Emery J, Farmer A, Griffiths F, et al. Designing and evaluating complex interventions to improve health care. Br Med J 2007 Mar 3;334(7591):455-459 [FREE Full text] [doi: 10.1136/bmj.39108.379965.BE] [Medline: 17332585]

34.  Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975 Nov;12(3):189-198. [Medline: 1202204]

35.  Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 1997 May;48(5 Suppl 6):S10-S16. [Medline: 9153155]

36.  Krüger F, Heine C, Bader S, Hein A, Teipel S, Kirste T. On the applicability of clinical observation tools for human activity annotation. 2017 Presented at: 2017 IEEE International Conference on Pervasive Computing and Communications Workshops (PerCom Workshops); March 13-17, 2017; Kona, HI, USA p. 129-134 URL: https://ieeexplore.ieee.org/document/7917545 [doi: 10.1109/PERCOMW.2017.7917545]

37.  Eysenbach G. The law of attrition. J Med Internet Res 2005 Mar 31;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]

38.  Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982 Sep;139(9):1136-1139. [doi: 10.1176/ajp.139.9.1136] [Medline: 7114305]

39.  Seidl H, Bowles D, Bock JO, Brettschneider C, Greiner W, König HH, et al. FIMA–Fragebogen zur erhebung von gesundheitsleistungen im alter: entwicklung und pilotstudie [FIMA--questionnaire for health-related resource use in an elderly population: development and pilot study]. Gesundheitswesen 2015 Jan;77(1):46-52. [doi: 10.1055/s-0034-1372618] [Medline: 24806594]

40.  von Kutzleben M, Köhler K, Dreyer J, Holle B, Roes M. Stabilität von häuslichen Versorgungsarrangements für Menschen mit Demenz [in German]. Z Gerontol Geriatr 2017 Apr;50(3):210-218. [doi: 10.1007/s00391-015-0990-0]

41.  Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. J Am Geriatr Soc 1998 Feb;46(2):210-215. [Medline: 9475452]

42.  Farran CJ, McCann JJ, Fogg LG, Etkin CD. Developing a measurement strategy for assessing family caregiver skills: conceptual issues. Alzheimers care today 2009;10(3):129-139 [FREE Full text] [doi: 10.1097/ACQ.0b013e3181b15d82] [Medline: 20179779]

43.  Spruytte N, Van Audenhove C, Lammertyn F, Storms G. The quality of the caregiving relationship in informal care for older adults with dementia and chronic psychiatric patients. Psychol Psychother 2002 Sep;75(Pt 3):295-311. [Medline: 12396755]

44.  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]

45.  Hurn J, Kneebone I, Cropley M. Goal setting as an outcome measure: a systematic review. Clin Rehabil 2006 Sep;20(9):756-772. [doi: 10.1177/0269215506070793] [Medline: 17005500]

46.  Schaefer I. Universität Bielefeld - Fakultät für Gesundheitswissenschaften. 2015 Apr. Leitfaden: Goal Attainment Scaling (Zielerreichungsskalen) URL: https://www.uni-bielefeld.de/gesundhw/ag4/GAS_Leitfaden.pdf [accessed 2018-12-07] [WebCite Cache ID 74U9EprjP]

47.  Farran CJ, Fogg LG, McCann JJ, Etkin C, Dong X, Barnes LL. Assessing family caregiver skill in managing behavioral symptoms of Alzheimer's disease. Aging Ment Health 2011 May;15(4):510-521 [FREE Full text] [doi: 10.1080/13607863.2010.536140] [Medline: 21500018]

48.  Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. Br Med J 2015 Mar 19;350:h1258 [FREE Full text] [doi: 10.1136/bmj.h1258] [Medline: 25791983]

49.  Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: toward a unified view. MIS Q 2003 Sep;27(3):425-478. [doi: 10.2307/30036540]

50.  Liu L, Miguel Cruz A, Rios Rincon A, Buttar V, Ranson Q, Goertzen D. What factors determine therapists' acceptance of new technologies for rehabilitation – a study using the Unified Theory of Acceptance and Use of Technology (UTAUT). Disabil Rehabil 2015;37(5):447-455. [doi: 10.3109/09638288.2014.923529] [Medline: 24901351]

51.  de Veer AJ, Peeters JM, Brabers AE, Schellevis FG, Rademakers JJ, Francke AL. Determinants of the intention to use e-Health by community dwelling older people. BMC Health Serv Res 2015 Mar 15;15:103 [FREE Full text] [doi: 10.1186/s12913-015-0765-8] [Medline: 25889884]

52.  Manzeschke A, Weber K, Rother H, Fangerau H. Bundesministerium für Bildung und Forschung [Federal Ministry of Education and Research]. 2013. Ethische Fragen im Bereich Altersgerechter Assistenzsysteme URL: https://www.technik-zum-menschen-bringen.de/service/publikationen/ethische-fragen-im-bereich-altersgerechter-assistenzsysteme [accessed 2018-12-07] [WebCite Cache ID 74U8f4XgX]

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53. Birnbaum ZW. Numerical tabulation of the distribution of Kolmogorovs statistic for finite sample size. J Am Stat Assoc 1952 Sep;47(259):425-441. [doi: 10.2307/2281313]

54. Mayring P. Qualitative Inhaltsanalyse: Grundlagen und Techniken. Basel, Beltz: Weinheim; 2015.

55. Coffey A. Analyzing Documents. In: Flick U, editor. The SAGE Handbook of Qualitative Data Analysis. London: Sage; 2018:664.

56. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017 Dec 26;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]

## Abbreviations

**AMS:** accelerometric motion score
**AppUI:** app user interface
**AT:** assistive technology
**ATI:** assistive technology intervention
**CABS-SR:** Caregiver Assessment of Behavioral Skill Self-Report
**CB:** challenging behavior
**CMAI:** Cohen-Mansfield agitation inventory
**QCPR:** Quality of the Current Relationship in Caregiving
**EE:** effort expectancy
**ELSI:** ethical, legal, and social implication
**FC:** facilitating conditions
**GP:** general practitioner
**ICD:** International Statistical Classification of Diseases and Related Health Problems
**IdA:** Innovative dementia-oriented Assessment system
**ITU:** intention to use
**MEESTAR:** model for the ethical evaluation for social-technical arrangements
**MRC:** Medical Research Council
**NPI:** neuropsychiatric inventory
**PE:** performance expectancy
**PwD:** persons with dementia
**SF-12:** Short Form 12
**SI:** social influence
**TA-EG:** technology affinity questionnaire
**UB:** usage behavior
**UEQ:** User Experience Questionnaire
**UTAUT:** Unified Theory of Acceptance and Use of Technology
**WLAN:** wireless local area network

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Protocol

# Identifying Positive Adaptive Pathways in Low-Income Families in Singapore: Protocol for Sequential, Longitudinal Mixed-Methods Design

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## Abstract

**Background:** This study aims to examine the adaptive process of children and mothers from multistressed low-income families in Singapore. It aims to bridge the knowledge gap left by existing poverty studies, which are predominately risk focused. Through a sequential longitudinal mixed-methods design, we will differentiate children and mothers who demonstrate varied social, developmental, and mental health trajectories of outcomes. Through utilizing the Latent Growth Curve Model (LGCM), we aim to detect the development and changes of the positive *Family Agency* and adaptive capacities of these families over time. The construct of *Family Agency* is underpinned by the theoretical guidance from the Social Relational Theory, which examines child agency, parent agency, relational agency, and the interactions among these members. It is hypothesized that positive *Family Agency* within low-income families may lead to better outcomes. The key research questions include whether the extent of positive *Family Agency* mediates the relationship among financial stress, resource utilization, home environment, and parental stress.

**Objective:** The study elucidates the *Family Agency* construct through interviews with mother-child dyads. It also aims to understand how financial stress and resources are differentially related to home environment, parent stress, and parent and child outcomes.

**Methods:** In phase 1, 60 mother-child dyads from families receiving government financial assistance and with children aged between 7 and 12 years will be recruited. In-depth interviews will be conducted separately with mothers and children. On the basis of 120 interviews, a measurement for the construct of *Family Agency* will be developed and will be pilot tested. In phase 2a, a longitudinal survey will be conducted over 3 time points from 800 mother-child dyads. The 3 waves of survey results will be analyzed by LGCM to identify the trajectories of adaptation pathways of these low-income families. In addition, 10 focus groups with up to 15 participants in each will be conducted to validate the LGCM results.

**Results:** This project is funded by the Social Science Research Thematic Grant (Singapore). The recruitment of 60 mother-child dyads has been achieved. Data collection will commence once the amendment to the protocol has been approved by the Institutional

Review Board. Analysis of phase 1 data will be completed by the end of the first quarter of 2019, and the first set of results is expected to be submitted for publication by the second quarter of 2019. Phase 2 implementation will commence in the second quarter of 2019, and the project end date is in May 2021.

**Conclusions:**   Findings from this study can potentially inform social policy and programs as it refines the understanding of low-income families by distinguishing trajectories of adaptive capacities so that policies and interventions can be targeted in enhancing the adaptive pathways of low-income families with children.

**International Registered Report Identifier (IRRID):**   PRR1-10.2196/11629

## *Introduction*

### Background

The Singapore government has, in recent years, shifted its policies aiming to rectify the trend of income divide and make Singapore a more inclusive society. This is reflected in the national budget in the past decade [1], introducing an increased number of redistributive measures of wealth to families from the lowest stratum. These include Workfare, which was implemented in 2007, ComCare—a government-funded short-term financial assistance scheme introduced in 2005— as well as progressive tax rebates and utility subsidies [2]. Together with civic charity efforts through nonprofit organizations [3], there are initial signs of narrowing of the rapid income divide as reflected in slightly declined Gini coefficient rates in recent years from a peak in 2007 [4]. Such interventions may avert the potential formation of an underclass as warned by some economists [5]. This shift in the government's fundamental approach to poverty and welfare should be acknowledged as crucial steps toward social inclusion, preventing a weakening of social cohesion and the consequent wide range of social ills if inequality grows unchecked [6].

Little is known, however, as to whether the new redistributive schemes have strengthened the organic adaptive capacities of the lowest quintile (bottom 20%) of households. In an attempt to bridge this gap, this proposed study seeks to examine adaptive microprocesses and approaches that low-income families used in their daily interactions and transactions to navigate the challenges and new redistributive opportunities in coping with financial constraints. This proposed study aims to advance the construct of family adaptation using an innovative perspective posited by the Social Relational Theory (SRT) [7]. SRT is a dynamic systems framework used in studying family dynamics as it pertains to children's socialization and development. SRT's core constructs, which emphasize that family members, both children and parents, are active agents. The construct of *Family Agency* is conceptualized as the agency of family members acting individually on behalf of the family or collaboratively to manage their financial challenges. It is hypothesized that positive *Family Agency* mediates the financial difficulties and outcomes. In other words, families with positive *Family Agency* are better able to manage the financial challenges they face that result in better social, emotional health, and mental health outcomes for children and mothers of these low-income families [8-11].

Some of the dynamic constructs of *Family Agency* can be tested using existing instruments: *children as agent* in poor families by Children's Family Influence Behavior [12], *relational agency* between family members in dealing with poverty by Influence in Families Questionnaire [13], and Network of Relationships Inventory [14]. The dimensions of *Family Agency* that lack existing instruments as proxy include children's contributions to their families and the bidirectional influences between mothers and children that enhance Family Agency. These dimensions will be distilled from in-depth observations of low-income families in Singapore in phase 1 of this proposed study. We will then formulate measurement items that will be the best proxy for these constructs.

### Impact of Poverty on Children and Families

Economic deprivation is 1 pervasive environmental factor that cuts deeply to affect families and children in diverse ways. An overview of the literature suggests that families with low socioeconomic status do not only face significant physical and mental risks but also expose their children to various developmental vulnerabilities that have come to predict their developmental trajectories in major domains of functioning: physical and mental health, educational performance and achievement, emotional and behavioral well-being, as well as executive function and social competence [15-18]. These effects are cumulative, pervasive, and can impact one's life course in the long run and possibly transmitted intergenerationally [15,19].

Chronic economic strain influences children's future life experiences and outcomes [17,20]. Research has shown that families with fewer economic, educational, and psychological resources are less able to provide a home environment that supports their children's cognitive growth and development and prepare them for school [21,22]. The income effect is a potential mediating or moderating pathway through the materials and services parents provide for their children [19].

Economically deprived families are often compounded by attendant life stressors such as poor housing, chronic unemployment or unstable employment, single parenthood, teenage pregnancy, family violence, parental incarceration, and family members' physical or mental health issues [15,19,23,24]. Parenting stress arising from these compounded stressors then mediates the effects of poverty on child adjustment [25,26]. A recent Singapore study [27] concurs with major studies that show poorer mental health conditions by primary caregivers compared with those of the typical population. Between 14%

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and 31% reported *severe* to *extremely severe* scores measured with the Depression, Anxiety and Stress Scale (DASS) [28], above the reported national statistics of 10% for depressive and anxiety disorders in Singapore.

A body of research has built up to reveal the long reach of poverty on the psychological well-being of parents, particularly with mothers and in relation to maternal depression, and on specific coping styles [29]. However, the challenge remains for researchers to isolate the respective contribution of the families' impoverished experiences to their state of well-being when these poverty-related forces impinging on their lives are dynamic and interactive in nature. Socioeconomic disadvantage in childhood is evidently related to both immediate and persisting impairments in mental health and well-being [23,30]. Family processes and family stress models have shown children and adolescents who grow up in families in poverty to have both more internalizing and externalizing symptoms compared with their peers raised in more affluent families [31]. The level and stability of family income have distinct effects on family functioning and children's well-being [32,33].

## Aims of This Study

The study aims to examine the following research questions:

1.  To elucidate the *Family Agency* construct through interviews with mother-child dyads (qualitative data).
2.  How are financial factors, including financial stress and resources, differentially related to home environment, parent stress, and parent and child outcomes?
3.  Does *Family Agency* mediate the relationship between financial stress, internal and external resources, and home environment, which result in better parents' and children's outcomes?
4.  Are there subgroups of children with distinct trajectories in terms of the levels of positive *Family Agency* perceived by the participants? How do they differ in terms of home environment and parent stress factors? Are there significantly different outcomes experienced by the children in each subgroup over 3 time points? Do the family outcomes differ significantly?
5.  What is the strength of the relationships among financial stress, internal and external resources, home environment, parental stress, and outcomes according to gender and ethnicity?
6.  What are the characteristics of the microagentic processes and the dynamics of intersections between families and the external ecological environment among families with positive children, parents, and family outcomes based on 2 SD above mean versus with outcomes 2 SD below mean scores?

## Methods

### Overview

This study will employ a sequential longitudinal mixed-methods design, which consists of 2 phases of data collection. In phase 1, in-depth interviews will be conducted with 60 mother-child dyads. To examine the adaptive processes of different families

facing financial stress, maximum variant sampling criteria will be utilized to include (1) ethnicity (the 3 major ethnic groups of Chinese, Malays, and Indian families); (2) genders of children; and (3) family types: intact, single parent, and stepfamily. The mothers and children will be asked to describe their relationship with one another and share with the interviewers' things that worry them the most and how they formulate solutions to these challenges. On the basis of the results from the 120 interviews, the team will operationalize and develop measures for the construct of *Family Agency* guided by the SRT.

In phase 2 of the study, we collect repeated measures longitudinal survey data over 3 time points. A total of 800 pairs of mother-child dyads with children aged between 7 and 12 years whose families are receiving ComCare financial assistance will be invited to participate in this longitudinal study. Phase 2 tests the conceptual framework of this proposed study, built on known risk factors of children growing up in families facing financial stress, together with the measurements of *Family Agency* developed in phase 1. On the basis of the findings of the longitudinal data, 10 focus groups discussions with up to 15 participants in each group will be held after each preliminary data analysis is completed to validate the findings. These 150 participants will be drawn from the participants of phase 2a of this study.

Figure 1 gives an overview of the data collection methods that will be used in this study.

### Ethics

This study has been approved by the Institutional Review Board at the National University of Singapore (S-18-003).
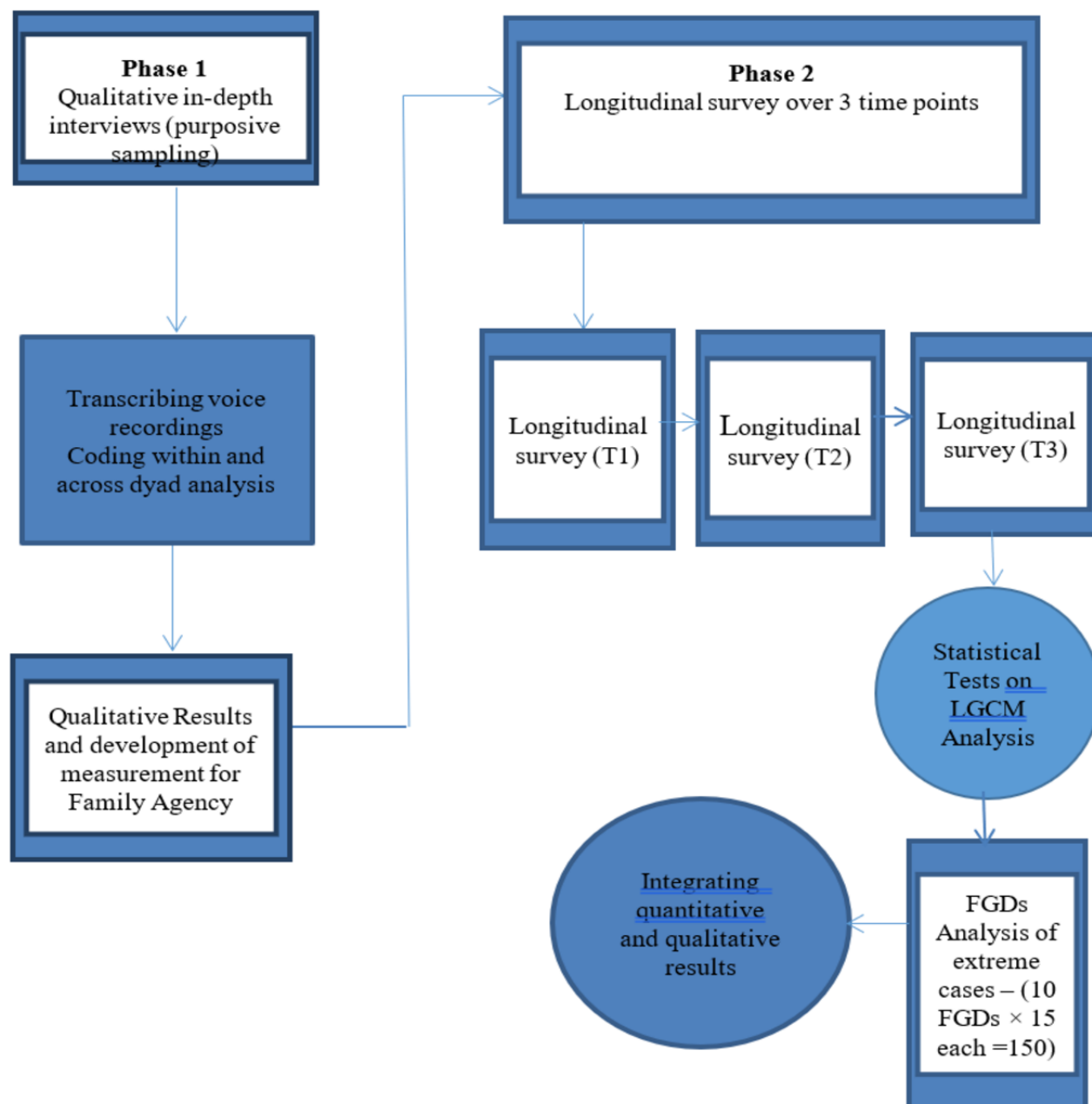
### Participants

Singaporean families with 1 or more children aged between 7 and 12 years and currently receiving government financial assistance are eligible to participate in this study. The mother and 1 child within the mentioned age range will be recruited from each participating family. To examine the adaptive processes of different families facing financial stress, maximum variant sampling criteria will be utilized to include (1) 4 major ethnic groups: Chinese, Malay, Indian, and others; (2) both genders of children aged between 7 and 12 years; and (3) different family types: intact, single parent, and stepfamily.

### Recruitment Process

#### Phase 1

The officers from the Ministry of Social and Family Development will identify recipients of ComCare financial assistance that fit into the recruitment criteria. A letter of invitation to participate in this study has been sent out to all these families. To expedite the recruitment process, 2 part-time research assistants (RAs) have been hired to telephone potential participants from the sampling list to attain the desired sample size. In addition to phone calls, the RAs will make home visits to potential participants by knocking on doors during the recruitment.

**Figure 1.** Schematic design.



Verbal consent will first be obtained when the families indicate interest to participate. Written consent will be obtained from both mother and child when the researchers visit the families. The RAs will also spend time to break the ice and build trust with the participants. The child and mother dyad will be interviewed separately. Children and mothers will be assured that the information provided by one party will not be disclosed to the other to maintain confidentiality.

### Phase 2a

Approximately 800 mother-child dyads from the same source will be sampled, based on the expected correlation of the variable ($\rho$), type 1 error, power, extent of measurement errors ($\sigma^2$), within-subject variance ($s_x^2$), and the smallest meaningful differences are set at 0.6, 0.05, 0.8, 0.8, 0.6, and 0.05, respectively. This sample size is based on longitudinal sample size consideration [34]. Survey interviews will be conducted

with the same sample at 3 different points in time with a 6-month interval between waves of data collections. The feedback from review panel has been provided as Multimedia Appendix 1. The researchers will visit the mothers and children of the families to obtain consent. They will be informed that it is a 3-wave data collection with intervals of 6 months, and the same interviewer will be conducting the 3 waves of survey with the same families to facilitate building trust and rapport. To minimize attrition rates, tokens of appreciation will be presented to the mother and children after each wave of survey completion. The RAs will also send festive greeting cards to keep in touch with the participants. The mothers and children will also be informed that at the end of the 3 waves of survey, they may be invited to focus group discussions (FGDs) to provide inputs to the analysis of the findings. They are considered the experts of their own lives and are in the best position to validate the findings.

## Phase 2b

After the initial data analysis of phase 2a, the major trajectories of adaptive behaviors will be identified among the samples. According to the trajectories identified, focus groups will be formed. From the original sampled families, the research team will invite participants from similar trajectories (outcome measures) for the specific focus groups to collect their input for the analysis. It is estimated that up to 150 participants will take part in the focus groups.

## Measures

For covariates including gender, ethnicity, citizenship, and educational levels of mothers and children, a demographic form will be filled in to capture the basic information. The *antecedents* include the financial stress and resources of the family, which will be measured by the *Economic Hardship Questionnaire* [35] consisting of 12 items focusing on financial conditions experienced by the family in the past 6 months and family resilience, which will be measured by the 10-item *Family Hardiness Scale* [36]. The construct refers to the internal strengths and durability of the family unit and is characterized by a sense of control over the outcomes of life events and hardships, a view of change as beneficial and growth producing, and an active rather than passive orientation in adjusting to and managing stressful situations. Intermediary constructs include *Family Agency*, which will be measured by the scale we would develop in phase 1; *Parents' Efficacy* measured by the *Adult Hope Scale*-12 items [37]; *Children's Efficacy* measured by the *Children Hope Scale* consisting of 6 items tapping agency and pathways of agency [38]; and *Home Environment* construct measures how families tap on resources within the home, which serves as sources of strength and support to its family members. This is measured by the *Family Environment Scale* [39], which has 45 items measuring 2 dimensions of family relationships and systems maintenance. *Outcome variables* include *Children's outcomes*, which is measured by the *Behavior Assessment System for Children* [40] and self-assessment of health condition using EQ-5D-Y [41]. *Parents' Outcomes* will be measured by the DASS [42], which examines parent health by assessing the extent to which parents experience life stresses, particularly under economic stress, and *Brief COPE Scale* [43], consisting of 28 items assessing specific adaptive and maladaptive coping strategies and EQ-5D [41].

These scales are selected as they have been used by researchers examining low-income families. This will facilitate the comparison of results. We will conduct separate Confirmatory Factor Analyses to validate the *a priori* factor structures of all measures. All the scales will be translated into Mandarin, Malay, and Tamil as we expect a good proportion of the families from different ethnic groups to be more conversant in these languages. The constructs will be measured with self-reporting questionnaires to be completed by parent and child. The questionnaires used in this study have been provided as Multimedia Appendix 2.

## Data Analysis

### Data Analysis Plans for Phase 1

The data analysis at this phase aims to stay close to the data, which are a low-level interpretation with the goal to understand the latent variables closely related to the construct of Family Agency. Thematic coding will be performed on all the transcripts of the semistructured interviews with the aid of qualitative software QSR Nvivo 11. Quasi-statistical analysis methods will be used to summarize data with descriptive statistics for concept clarification on the construct *Family Agency* and instrument development.

### Data Analysis Plans for Phase 2a

Sequential Equation Model (SEM) will be used to analyze the data collected at the 3 time points. The estimated coefficients of SEM will provide the magnitudes of the level of influences on the various constructs on child and family outcomes. Descriptive statistics such as Pearson correlational analyses will be carried out to examine the degree of association of financial stress, internal and external resources, home environment, parental stress, and the 2 outcomes, breakdown by gender and ethnicity by chi-square. As gender and ethnicity are discrete variables and the number of groups is relatively small, multiple-group longitudinal SEM will be carried out to test whether the regression coefficients differ for gender and ethnicity. Factorial invariance across groups will be examined before proceeding with multiple-group longitudinal SEM. The existence of different trajectories in these low-income families will be examined using the Latent Growth Curve Model (LGCM) to find out whether heterogeneity exists for the families. Factor scores will be generated for the dimensions of the *Family Agency* construct over the 3 waves. The mediating role of *Family Agency* will be investigated in 2 ways. First, path analysis approach using SEM will be used to examine the fit between *Family Agency* as an intermediate between financial stress "and" or "or" resources. Model fit will be examined by the Root Means Squared Error of Approximation, Comparative Fit Index, Akaike's information criterion, and Bayes information criterion. Evidence of a mediating role of *Family Agency* will be defined by statistically significant ($P<.05$) coefficients for paths between independent variables (financial stress and resources) and *Family Agency* and between *Family Agency* and the dependent variables (child outcome and parent outcome). Second, if statistically significant paths are identified, the potential causal role of *Family Agency* will be investigated via a doubly robust propensity score approach, inverse probability-weighted regression adjustment [44,45]. Briefly, the approach proceeds as follows: the proportion of the total effects of the independent variables because of controlled direct effects and natural indirect effects (as mediated through Family Agency) will be estimated using a system of 2 multivariable logistic regressions (1 for the mediator and 1 for the outcome) weighted by the joint inverse probability of the independent variable and mediator (Family Agency). These equations will be used to predict outcomes under different levels of treatment, with the difference between predicted outcomes providing estimates of the direct and indirect effects using regression adjustment. These methods are shown to be doubly robust to

misspecification of either the exposure or outcome models and thus less vulnerable to residual confounding [46]. As *Family Agency* may also modify the relationship between independent variables on outcomes, we will also investigate the presence of interaction in estimated mediation models [44].

### *Phase 2b: Focus Group Discussions*

On the basis of these identified trajectories, qualitative data through FGDs (n=10) will be used to conduct contrasting case analysis. Moreover, 2 FGDs for each trajectory will be conducted separately with children and mothers (2 FGDs × 5 trajectories=10 FGDs with up to 15 members each) and will be used to closely examine the contrasting family processes between highest and lowest score cases. Group comparisons across ethnicities, family types, and family size among the positive deviance sample will be examined.

## Sample Size and Power Calculations

### *Sample Size Justification for Longitudinal Survey Data*

A total of 800 children aged between 7 and 12 years and their mothers matching the sampling criteria stated in phase 1 will be invited to participate. The sample size of 800 is based on the degree of accuracy of 0.034 [47]. Survey interviews will be conducted with the same sample at 3 different points in time with 6-month intervals between waves of data collections. This sample size of 800 is based on longitudinal sample size consideration [43]. The expected correlation of the variable ($\rho$), type 1 error, power, extent of measurement errors ($\sigma^2$), within-subject variance ($s_x^2$), and smallest meaningful difference (d) are set at 0.6, 0.05, 0.8, 0.8, 0.6, and 0.05 respectively. Package R longpower, liu.liang.linear.power function, is used to calculate the sample.

### *Phase 1: Sample Size n=60 (Mother-Child Dyads)*

This phase aims to obtain an intimate understanding of the microprocesses of low-income families. A total of 60 mothers and children will be interviewed separately with a semistructured guide. Children should be aged between 7 and 12 years and their families should be current recipients of financial aid from ComCare.

### *Phase 2a: Sample Size n=800 for 3 Waves of Surveys*

Children (n=800) together with their mothers (n=800) who fulfill the sampling criteria stated in phase 1 will be invited to participate. Survey interviews will be conducted with the same sample at 3 different points, with a 6-month interval before the next wave of data collection. The sample size determination has been provided in Table 1.

Calculation for sample size has been illustrated in Figure 2, where s is the required sample size; $X^2$ is chi square for $df$=1 (3.841); $N$ is population size; $p$ is population proportion (assumed 0.5); and $d$ is degree of accuracy expressed as a proporation.

## Strategies to Minimize Attrition Rates

One of the biggest challenges in collecting longitudinal data is the loss of contact over several time points, which will compromise the validity and integrity of the study [48]. A 2-pronged protocol will be employed in this proposed study to minimize dropout.

### *Prong 1: Researcher-Oriented Strategies*

The 800 child-mother dyads will be interviewed by 40 trained interviewers who will follow the same families over the 3 waves of interviews. Each interviewer will follow up with 20 child-mother dyads. All interviewers have to undergo intensive training in engaging low-income families, rapport building, interview skills, interview ethics, role playing, handling confidentiality, and cultural sensitivity, conducted over 3 weekends (15 hours in total). Systematic training manual documenting the protocols will be utilized to guide the interviewers.

### *Prong 2: Participant-Oriented Strategies*

In the 6-month gap between the waves of the interviews, the interviewers will make 1 call to each family per month and send festive greeting cards to keep in touch. The token of appreciation per dyad is incremental across progress time points to incentivize the participants to stay in the study. Nevertheless, the overall dropout rate is estimated to be 10 ± 5% [49]. The statistical difference between lost-to-follow-up dyad and those remaining in the study will be assessed using appropriate methods (eg, chi-square), regarding input/outcome variables pertinent to the objectives/hypothesis of this study.

**Table 1.** Sample size determination based on degree of accuracy and population size.

| Particular | Population (n=10,000) | Population (n=20,000) |
| --- | --- | --- |
| Degree of accuracy | 0.033 | 0.034 |
| Sample size | 810 | 798 |

**Figure 2.** Calculation of sample size.

$$s = \frac{\chi^2 N p(1-p)}{d^2(N-1) + \chi^2 p(1-p)}$$

# Results

Phase 1 recruitment has achieved the planned 60 dyads as on October 1, 2018. Interviews will start in November 2018 and continue until February 2019. The development of the measurement scale for the *Family Agency* construct will be developed and piloted between March and May 2019. Moreover, 3 waves of survey will be implemented between May 2019 and July 2020. Data analysis will be performed for every wave. The statistical analysis to identify the trajectories of adaption will take place concurrently. FGDs will be held in August 2020. The final analysis and integration of results will be carried out by the research team between September 2020 and January 2021. These results will be written for publications between February and May of 2021 before the project concludes.

# Discussion

## Principal Findings

This proposed study aims to contribute to family research scholarship on 2 fronts: *conceptual advancement* and *longitudinal empirical evidence*. These advancements in concept and datasets will inform and facilitate the *shift in policy and practice* with low-income families. In this proposed study, the team plans to conduct a short-term 3-wave longitudinal survey over 18 months. The major benefit of using a 3-wave longitudinal study for this project is the advantage of detecting developments and changes of *Family Agency* and adaptive capacities over time. Conducting 3 waves is the minimum period that allows the application of LGCM to examine whether these lower-income families grow, decline, or remain stable in their Family Agency. LGCM focuses on within-individual changes, resulting in more accurate and nuanced conclusions concerning the adult and child outcomes [50]. More importantly, predictor variables and their consequences are built into the model [51]. Thus, it allows us to investigate different growth parameters

and the incorporation of both time-varying predictors (eg, child and parent hope) and time-invariant predictors (eg, gender and race). Establishing the best possible causal effect is made possible through LGCM, whereas a cross-sectional design does not allow this. For instance, how the effect of financial stress of parents at first wave might affect parenting in the second wave. Without 3 waves of data collection design, the taxonomy on the *Family Agent* would be a static concept. While examining the changes over the 3 waves using a latent-class growth model, the dynamics of *Family Agency* are incorporated into the taxonomy.

## Contributions to Policy and Practice

Existing local, economic, and social policy researchers [52-55] have underscored the risk of a rich-poor divided Singapore and the pileup risks confronted by poor families [2,56] and have advocated for decisive corrective measures. Results of these studies by economists are valuable in providing a clearer problem definition to policy makers, which may have contributed, at least in part, to the move from the traditionally welfare-aversive government stance to one that actively puts in place measures to promote inclusive growth and strengthen its redistributive role [57].

This meticulous examination of social problems to achieve a clear problem definition as the base of policy construction has to be balanced with similar attention in assessing the strengths of the low-income families and the environment that the policies target. Indeed, emerging behavioral economics research has shown that resource availability may be insufficient to *move* families out of poverty and that attention should instead be given to default adaptive processes that some families use to help them rise above their economic and social situations [58,59]. In other words, locating change factors at the individual family level helps to identify the impetus for sustainable practices within lived contexts and helps us to understand what low-income families draw on to foster their hope and optimism amidst multiple impositions and constraints.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Peer-reviewer report from Social Science Research Council Singapore.

[PDF File (Adobe PDF File), 172KB - resprot_v8i2e11629_app1.pdf ]

## Multimedia Appendix 2

Questionnaires used in this study.

[PDF File (Adobe PDF File), 407KB - resprot_v8i2e11629_app2.pdf ]

## References

1. Ministry of Finance Singapore. 2012 Feb 17. Budget Speech 2012: An Inclusive Society, A Stronger Singapore URL: https://www.mof.gov.sg/Newsroom/Press-Releases/An-Inclusive-Society-A-Stronger-Singapore [accessed 2018-10-05] [WebCite Cache ID 72wVPg5l2]

2. Ng IYH. Being poor in a rich "Nanny State": developments in Singapore social welfare. Singapore Econ Rev 2015 Aug;60(3):1550038. [doi: 10.1142/S0217590815500381]

3. Smith P, Lynn P, Elliot D. Sample design for longitudinal surveys. In: Lynn P, editor. Methodology of Longitudinal Surveys. Hoboken, New Jersey: John Wiley & Sons, Ltd; Feb 20, 2009:21-33.

4. Ministry of Finance Singapore. 2015. Building our Future, Strengthening Social Security URL: https://www.singaporebudget.gov.sg/budget_2015/pb [accessed 2018-10-05] [WebCite Cache ID 72wW5WDnC]

5. Bhaskaran K, Forbes HJ, Douglas I, Leon DA, Smeeth L. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). Br Med J Open 2013 Sep 13;3(9):e003389 [FREE Full text] [doi: 10.1136/bmjopen-2013-003389] [Medline: 24038008]

6. Wilkinson R, Pickett K. The Spirit Level: Why Equality is Better for Everyone. London: Penguin; Nov 4, 2010:372.

7. Kuczynski L, De Mol J. Dialectical models of socialization. In: Lerner RM, Overton WF, Molenaar PC, editors. Handbook of Child Psychology and Developmental Science 7th ed. Hoboken, NJ: John Wiley & Sons, Inc; Mar 2015:323-368.

8. Goh EC. Theoretical Constructs According Mothers and Children as Equally Agent- A Relational Perspective. In: Proceedings of 6th Conference of the International Society for Child Indicators. 2017 Jun 30 Presented at: 6th Conference of the International Society for Child Indicators; June 28-30, 2017; Montreal, Canada URL: http://www.isci2017.org/wp-content/uploads/2017/07/ISCI-2017.-Abstracts-Book.pdf

9. Tok KL, Goh EC. An Exploratory Study on the Characteristics of Parent-Child Relationship Among Low-income Families that Promote Children's Academic Success. 2017 Jun 30 Presented at: 6th Conference of the International Society for Child Indicators; June 28-30, 2017; Montreal p. 179 URL: http://www.isci2017.org/wp-content/uploads/2017/07/ISCI-2017.-Abstracts-Book.pdf

10. Tan LX, Goh EC. Dynamics of Low-income Mothers Supporting their Children Succeed Academically:Insights from Diary Methods. In: Proceedings of 6th Conference of the International Society for Child Indicators. 2017 Jun 30 Presented at: 6th Conference of the International Society for Child Indicators; June 28-30, 2017; Montreal URL: http://www.isci2017.org/wp-content/uploads/2017/07/ISCI-2017.-Abstracts-Book.pdf

11. Cheang CJ, Goh EC. Accessing Poor Children's Success Stories through Diary Methods. 2017 Jun 30 Presented at: 6th Conference of the International Society for Child Indicators; June 28-30, 2017; Montreal URL: http://www.isci2017.org/wp-content/uploads/2017/07/ISCI-2017.-Abstracts-Book.pdf

12. Sun Q, Lou VW, Law BM. Validating the effectiveness scale of children's familial influencing behavior within three-generational relationships. Res Soc Work Pract 2018;28(4):482-492. [doi: 10.1177/1049731516656463]

13. Maes SD, De Mol J, Buysse A. Children's experiences and meaning construction on parental divorce: a focus group study. Childhood 2012;19(2):266-279. [doi: 10.1177/0907568211421220]

14. Furman W, Buhrmester D. The network of relationships inventory: behavioral systems version. Int J Behav Dev 2009 Sep 1;33(5):470-478 [FREE Full text] [doi: 10.1177/0165025409342634] [Medline: 20186262]

15. Anderson S, Leventhal T, Dupéré V. Exposure to neighbourhood affluence and poverty in childhood and adolescence and academic achievement and behaviour. Appl Dev Sci 2014 Jul 17;18(3):123-138. [doi: 10.1080/10888691.2014.924355]

16. Arnold DH, Doctoroff GL. The early education of socioeconomically disadvantaged children. Annu Rev Psychol 2003;54(1):517-545. [doi: 10.1146/annurev.psych.54.111301.145442] [Medline: 12209026]

17. Barr AB. Family socioeconomic status, family health, and changes in students' math achievement across high school: a mediational model. Soc Sci Med 2015 Sep;140:27-34. [doi: 10.1016/j.socscimed.2015.06.028] [Medline: 26189011]

18. Bradley RH, Corwyn RF. Socioeconomic status and child development. Annu Rev Psychol 2002 Feb;53:371-399. [doi: 10.1146/annurev.psych.53.100901.135233] [Medline: 11752490]

19. Ziol-Guest KM, McKenna CC. Early childhood housing instability and school readiness. Child Dev 2014;85(1):103-113. [doi: 10.1111/cdev.12105] [Medline: 23534607]

20. Shonkoff JP, Bales SN. Science does not speak for itself: translating child development research for the public and its policymakers. Child Dev 2011;82(1):17-32. [doi: 10.1111/j.1467-8624.2010.01538.x] [Medline: 21291426]

21. Chazan-Cohen R, Raikes H, Brooks-Gunn J, Ayoub C, Pan BA, Kisker EE, et al. Low-income children's school readiness: parent contributions over the first five years. Early Educ Dev 2009 Dec 11;20(6):958-977. [doi: 10.1080/10409280903362402]

22. Maggi S, Irwin LJ, Siddiqi A, Hertzman C. The social determinants of early child development: an overview. J Paediatr Child Health 2010 Nov;46(11):627-635. [doi: 10.1111/j.1440-1754.2010.01817.x] [Medline: 20796183]

23. Conger RD, Conger KJ, Martin MJ. Martin MJ. Socioeconomic status, family processes, and individual development. J Marriage Fam 2010 Jun;72(3):685-704 [FREE Full text] [doi: 10.1111/j.1741-3737.2010.00725.x] [Medline: 20676350]

24. Edin K, Kissane RJ. Poverty and the American family: a decade in review. J Marriage Fam 2010 Jun;72(3):460-479. [doi: 10.1111/j.l741-3737.2010.00713]

25. Cadima J, McWilliam RA, Leal T. Environmental risk factors and children's literacy skills during the transition to elementary school. Int J Behav Dev 2009 Sep 10;34(1):24-33. [doi: 10.1177/0165025409345045]

26. Hindman AH, Skibbe LE, Miller A, Zimmerman M. Ecological contexts and early learning: contributions of child, family, and classroom factors during Head Start, to literacy and mathematics growth through first grade. Early Child Res Q 2010;25(2):235-250. [doi: 10.1016/j.ecresq.2009.11.003]

27. Chong WH, Choo H, Goh EC, Wee PY, Goh WH, Chay OM. Preventive child healthcare in Singapore: a parents' well-being perspective. Ann Acad Med Singapore 2015 Dec;44(12):550-553 [FREE Full text] [Medline: 27090071]

28. 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]

29. Aranda MP, Lincoln KD. Financial strain, negative interaction, coping styles and mental health among low-income Latinos. Race Soc Probl 2011 Dec 3;3(4):280-297. [doi: 10.1007/s12552-011-9060-4]

30. Komro KA, Flay BR, Biglan A, Promise Neighborhoods Research Consortium. Creating nurturing environments: a science-based framework for promoting child health and development within high-poverty neighborhoods. Clin Child Fam Psychol Rev 2011 Jun;14(2):111-134 [FREE Full text] [doi: 10.1007/s10567-011-0095-2] [Medline: 21468644]

31. Ponnet K. Financial stress, parent functioning and adolescent problem behavior: an actor-partner interdependence approach to family stress processes in low-, middle-, and high-income families. J Youth Adolesc 2014 Oct;43(10):1752-1769. [doi: 10.1007/s10964-014-0159-y] [Medline: 25053382]

32. Wagmiller RL, Lennon MC, Kuang L, Alberti PM, Aber JL. The dynamics of economic disadvantage and children's life chances. Am Sociol Rev 2016 Oct 1;71(5):847-866. [doi: 10.1177/000312240607100507]

33. Yeung WJ, Linver MR, Brooks-Gunn J. How money matters for young children's development: parental investment and family processes. Child Dev 2002;73(6):1861-1879. [Medline: 12487499]

34. Diggle P, Heagerty P, Liang KY, Zeger SL. Analysis of Longitudinal Data. Second Edition. UK: Oxford University Press; May 8, 2013:400.

35. Lempers JD, Clark-Lempers D, Simons RL. Economic hardship, parenting, and distress in adolescence. Child Dev 1989 Feb;60(1):25-39. [Medline: 2702872]

36. Dunst CJ, Trivette CM, Hamby DW. In: McCubbin MA, McCubbin HI, Thompson A, editors. Technical Manual for Measuring and Evaluating Family Support Program Quality and Benefits. Asheville, North Carolina: Winterberry Press Monograph Series; 1999:144.

37. Lopez SJ, Ciarlelli R, Coffman L, Stone M, Wyatt L. Diagnosing for strengths: on measuring hope building blocks. In: Synder CR, editor. Handbook of Hope: Theory, Measurement and Applications. San Diego: Academic Press; 2000:57-85.

38. Snyder CR, Hoza B, Pelham WE, Rapoff M, Ware L, Danovsky M, et al. The development and validation of the Children's Hope Scale. J Pediatr Psychol 1997 Jun;22(3):399-421 [FREE Full text] [Medline: 9212556]

39. Moos RH, Moos BS. Family Environment Scale Manual. A Social Climate Scale. Palo Alto, CA: Consulting Psychologists Press; 1994:96.

40. van Reenen M, Janssen B, Oppe M, Kreimeir S, Greiner W. The EuroQol Research Foundation. 2018 Aug. EQ-5D-Y User Guide. Basic information on how to use the EQ-5D-Y instrument URL: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-Y_User_Guide_v1.0_2014.pdf [accessed 2018-10-05] [WebCite Cache ID 72wYYEp8x]

41. Reynolds CR, Kamphaus RW. Pearson Education. Circle Pines, MN: American Guidance Service; 2004. BASC: Behavior assessment system for children URL: https://www.pearsonclinical.com/education/products/100000658/behavior-assessment-system-for-children-second-edition-basc-2.html#tab-details

42. Crawford JR, Henry JD. The Depression Anxiety Stress Scales (DASS): normative data and latent structure in a large non-clinical sample. Br J Clin Psychol 2003 Jun;42(Pt 2):111-131. [doi: 10.1348/014466503321903544] [Medline: 12828802]

43. 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]

44. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. Epidemiology 2014 Sep;25(5):749-761 [FREE Full text] [doi: 10.1097/EDE.0000000000000121] [Medline: 25000145]

45. Valente MJ, Pelham WE, Smyth H, MacKinnon DP. Confounding in statistical mediation analysis: what it is and how to address it. J Couns Psychol 2017 Nov;64(6):659-671. [doi: 10.1037/cou0000242] [Medline: 29154577]

46. Drukker DM. UK Stata Users Group. 2016 Sep. Estimating average treatment effects from observational data using teffects, stteffects and eteffects URL: http://fmwww.bc.edu/repec/usug2016/drukker_uksug16.pdf [accessed 2018-10-05] [WebCite Cache ID 72wXDrsjL]

47. Krejcie RV, Morgan DW. Determining sample size for research activities. Educ Psychol Meas 1970 Sep 1;30(3):607-610. [doi: 10.1177/001316447003000308]

48. Boys A, Marsden J, Stillwell G, Hatchings K, Griffiths P, Farrell M. Minimizing respondent attrition in longitudinal research: practical implications from a cohort study of adolescent drinking. J Adolesc 2003 Jun;26(3):363-373. [Medline: 12770532]

49. Gao XL, Hsu CY, Xu Y, Hwarng HB, Loh T, Koh D. Building caries risk assessment models for children. J Dent Res 2010 Jun;89(6):637-643. [doi: 10.1177/0022034510364489] [Medline: 20400721]

50. Wickrama KA, Lee TK, O'Neal CW, Lorenz FO. Higher-Order Growth Curves and Mixture Modeling With Mplus: A Practical Guide. New York: Routledge; Apr 9, 2016:346.

51. Karney BR, Bradbury TN. Assessing longitudinal change in marriage: an introduction to the analysis of growth curves. J Marriage Fam 1995 Nov;57(4):1091-1108. [doi: 10.2307/353425]

52.  Asher MG, Nandy A. Singapore's policy responses to ageing, inequality and poverty: an assessment. Int Soc Secur Rev 2008 Jan;61(1):41-60. [doi: 10.1111/j.1468-246X.2007.00302.x]

53.  Tan KY. Managing Singapore's globalization and its discontents: a long term perspective. In: Hoe SF, Soon C, editors. Singapore Perspectives 2015: Choices. Singapore: World Scientific and Institute of Policy Studies; Feb 2016:37-50.

54.  Hui WT. Economic growth and inequality in Singapore: the case for a minimum wage. Int Labour Rev 2013 Mar;152(1):107-123. [doi: 10.1111/j.1564-913X.2013.00171.x]

55.  Low L, Aw TC. Social Insecurity in the New Millennium: The Central Provident Fund in Singapore. Singapore: Marshall Cavendish Intl; Dec 1, 2004:466.

56.  Ng IY. Multi-stressed low-earning families in contemporary policy context: lessons from work support recipients in Singapore. J Poverty 2013;17(1):86-109 [FREE Full text]

57.  Ministry of Finance Singapore. 2015. Budget Debate Round-Up Speech. Transcript Of Budget 2015 Debate Round-up Speech By Deputy Prime Minister And Minister For Finance, Mr Tharman Shanmugaratnam On 5 March 2015 URL: https://www.singaporebudget.gov.sg/data/budget_2015/download/FY2015_Budget_Statement.pdf [accessed 2018-10-05] [WebCite Cache ID 72wVWT6o9]

58.  Banarjee AV, Duflo E. Poor Economics: Barefoot Hedge-Fund Managers, DIY Doctors and the Surprising Truth About Life on Less Than 1 Dollar a Day. London: Penguin Books; Mar 29, 2012:320.

59.  Mullainathan S, Shafir E. Scarcity: The True Cost of Not Having Enough. London: Penguin Books; Sep 4, 2014:304.

## Abbreviations

**DASS:** Depression, Anxiety and Stress Scale
**FGD:** focus group discussion
**LGCM:** Latent Growth Curve Model
**RA:** research assistant
**SEM:** Sequential Equation Model
**SRT:** Social Relational Theory

Protocol

# Determining Best Practices for Management of Bacteriuria in Spinal Cord Injury: Protocol for a Mixed-Methods Study

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## *Abstract*

**Background:** Bacteriuria, either asymptomatic (ASB) or symptomatic, urinary tract infection (UTI), is common in persons with spinal cord injury (SCI). Current Veterans Health Administration (VHA) guidelines recommend a screening urinalysis and urine culture for every veteran with SCI during annual evaluation, even when asymptomatic, which is contrary to other national guidelines. Our preliminary data suggest that a positive urine culture (even without signs or symptoms of infection) drives antibiotic use.

**Objective:** Through a series of innovative studies utilizing mixed methods, administrative databases, and focus groups, we will gain further knowledge about the attitudes driving current urine testing practices during the annual exam, as well as quantitative data on the clinical outcomes of these practices.

**Methods:** Aim 1 will identify patient, provider, and facility factors driving bacteriuria testing and subsequent antibiotic use after the SCI annual evaluation through qualitative interviews and quantitative surveys. Aim 2 will use national VHA databases to identify the predictors of urine testing and subsequent antibiotic use during the annual examination and compare the clinical outcomes of those who received antibiotics with those who did not. Aim 3 will use the information gathered from the previous 2 aims to develop the *Test Smart, Treat Smart* intervention, a combination of patient and provider education and resources that will help stakeholders have informed conversations about urine testing and antibiotic use; feasibility will be tested at a single site.

**Results:** This protocol received institutional review board and VHA Research and Development approval in July 2017, and Veterans Affairs Health Services Research and Development funding started on November 2017. As of submission of this manuscript, 10/15 (67%) of the target goal of provider interviews were complete, and 77/100 (77%) of the goal of surveys. With regard to patients, 5/15 (33%) of the target goal of interviews were complete, and 20/100 (20%) of the target goal of surveys had been completed. Preliminary analyses are ongoing; the study team plans to present these results in April 2019. Database analyses for aim 2 will begin in January 2019.

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**Conclusions:** The negative consequences of antibiotic overuse and antibiotic resistance are well-documented and have national and even global implications. This study will develop an intervention aimed to educate stakeholders on evidence-based management of ASB and UTI and guide antibiotic stewardship in this high-risk population. The next step will be to refine the intervention and test its feasibility and effectiveness at multiple sites as well as reform policy for management of this common but burdensome condition.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/12272

## Introduction

### Background

Antibiotic stewardship (promoting appropriate use of antibiotics) is a high-level policy and public health initiative, as shown by recent mandates from the Center for Disease Control and the United Nations [1,2]. Persons with spinal cord injury (SCI) are vulnerable to inappropriate antibiotic use because of their medical complexity and frequent health care contact [3]. Specifically, bacteriuria is a common consequence of neurogenic bladder after SCI; asymptomatic bacteriuria (ASB) has a prevalence of 30% to 90% depending on the bladder management strategy used [4]. For comparison, the prevalence rate in healthy premenopausal women is 5%. ASB, defined as the presence of bacteria in the urine of a person not otherwise having signs or symptoms of a urinary tract infection (UTI), does not require treatment except in pregnancy and before urologic procedures [4]. In fact, evidence-based guidelines published by the Infectious Diseases Society of America recommend against collecting screening urine cultures or treating ASB in persons with SCI [4,5]. The Veterans Health Administration (VHA) guidelines outlining care for persons with SCI, however, recommend a yearly urinalysis and urine culture as part of an annual physical checkup, regardless of whether signs or symptoms of infection are present [6]. Obtaining these tests in asymptomatic patients is essentially a screening for ASB. Although the VHA guideline does not explicitly recommend treatment of ASB, review of 2 years of annual examination visits uncovered that 35% of cases of ASB were subsequently treated with antibiotics [7].

Our goal is to develop an effective antibiotic stewardship program for bacteriuria tailored to the SCI population and SCI providers. To address gaps in knowledge relevant to antibiotic stewardship in SCI, we will utilize a mixed methods approach. First, we will answer the following question: do providers and persons with SCI believe that testing the urine and treating asymptomatic colonization will lead to better outcomes? We will explore this by conducting qualitative interviews with patients with SCI and SCI providers to understand their perceptions and expectations related to having their urine tested annually, and being prescribed and adhering to prescribed antibiotics, and correlating this information with quantitative knowledge surveys. Next, we hypothesize that urine testing during the annual examination leads to antibiotic use, and the antibiotics, in turn, have downstream consequences. This will be examined through analysis of VHA data sources. Finally, we will develop an intervention to more effectively deliver evidence-based bacteriuria management to persons with SCI. We hypothesized that the intervention will be feasible to use and increase patient satisfaction with bacteriuria management during the annual evaluation.

### Conceptual Framework

Cabana et al and others have explored the barriers to successful implementation of clinical practice guidelines into actual practice [8]. Clinical practice guidelines for bacteriuria management are often long and complex, requiring users to keep a sequential mental record of the statements to arrive at the diagnosis of UTI or ASB. Clinical practice guidelines may conflict with the users' pre-existing biases of the standard of care, also limiting their use [9,10]. For example, many providers that take care of persons with SCI believe that treating ASB from urease-producing organisms such as *Proteus* species is beneficial, but the evidence is not convincing toward this [11,12]. Our project will utilize the Cabana framework to lessen the diagnostic challenge of distinguishing UTI from ASB.

## Methods

### Project Design Overview

Figure 1 provides an overview of the project aims. We will identify *contextual factors* influencing provider and patient knowledge and beliefs about urine testing and treatment at the annual examination, using quantitative and qualitative methods (aim 1). We will then identify the *evidence* regarding patient, provider, and facility predictors of urine testing and subsequent antibiotic use, as well as compare the clinical outcomes of those who received antibiotics with the outcomes of those who did not (aim 2). We will then use information gained from the above aims and previously successful antibiotic stewardship initiatives [5] to *intervene*, by providing evidence-based bacteriuria management through education and resources for patients and providers (aim 3).

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**Figure 1.** Optimizing bacteriuria management in the veteran spinal cord injury population. An overview of the planned project.
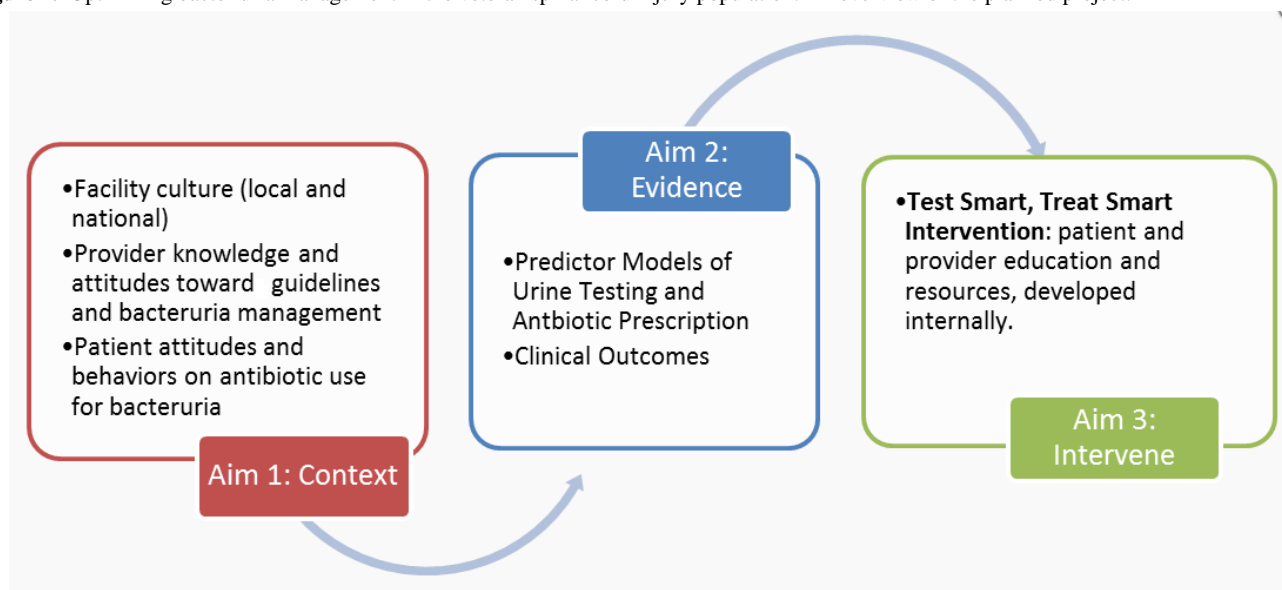


To develop an effective intervention to lessen the burden of utilizing clinical practice guidelines, we need a complete understanding of the key factors that drive provider testing and treatment behaviors (eg, knowledge and attitudes) and patient engagement. We will utilize the Cabana model, as described above, to understand provider barriers to using clinical practice guidelines in clinical practice [8]. During the development of the intervention (aim 3), we will use the concept of intervention mapping described by Kok et al [13], as well as audit and feedback, as a main component of the intervention. Intervention mapping is a process to develop theory- and evidence-based interventions and involves the following 6 steps: (1) needs assessment; (2) identification of change objectives; (3) selection of theory-based intervention methods and practical applications to enact change; (4) development of intervention components; (5) intervention adoption, implementation, and maintenance plan; and (6) plan for evaluation of intervention effectiveness. Audit and feedback or providing health care professionals with up-to-date data about their performance, has previously been shown to improve quality of care and was a successful component of the *Kicking catheter-associated urinary tract infection (CAUTI)* intervention [14,15]. We have also included a medical anthropologist in our team to explore how organizational culture intersects with and shapes medical practices in SCI clinics.

## Aim 1

This aim focuses on identifying patient, provider, and facility factors driving bacteriuria management in persons with SCI. We will employ qualitative and quantitative phases to identify patient, provider, and facility factors driving urine testing and antibiotic use during the annual evaluation.

### Participants and Approach: Qualitative Phase

Semistructured, open-ended interviews will be conducted with health care providers (n=15) at 5 national VHA SCI outpatient centers (ie, hub sites) and 2 to 3 of their corresponding satellite primary care clinics (ie, spoke sites) and SCI patients (n=15). Maximum variation sampling, a purposeful sampling strategy,

will guide our approach [16]. We are deliberately including physicians and nonphysician (ie, physician assistants and nurse practitioners) providers to capture a broad variety of experiences, and identify overarching themes, across geographically diverse sites; this sample size will allow for maximum variation in our data [17]. Our patient sample will be inclusive of factors such as age, ethnicity or race, and bladder management strategy (ie, indwelling catheter, intermittent catheter, etc) to capture a wide range of perspectives.

The interview guides are based on the major domains of our conceptual model. Provider interviews will begin by collecting demographic information that will include age, level of training, and information on board certification (physical medicine and rehabilitation, SCI medicine board-certified, and/or other specialties). Additional provider questions will focus on the utility of obtaining an annual urinalysis or urine culture and attitudes toward antibiotic stewardship. Patient interviews will begin by collecting demographic information that includes age, level of injury, numbers of years since injury, and method of bladder management. Patient interviews will focus on related topics discussed during the provider interviews, as well as previous experiences with UTI treatment and medication adherence.

### Participants and Approach: Quantitative Phase

Following the interviews, all SCI patients and providers will be invited to participate in phone surveys. Patients who received a prescription for antibiotics for UTI will be invited to complete the Morisky Medication Adherence Scale-8 (MMAS-8). This is an 8-item validated questionnaire to evaluate intentional and unintentional medication nonadherence [18-20]. Providers will receive a closed-ended survey to assess knowledge in 6 domains about bacteriuria management. This is a validated survey used previously to explore this topic [21].

### Analysis for Aim 1

Analysis of the qualitative and quantitative data will be concurrent. For the qualitative analysis, a combined inductive and deductive coding approach will be used to code the data.

Moreover, 2 members of the research team (FS and LM) will read through the transcripts and develop a list of codes, based on participants' experiences (inductive) and the subelements of our conceptual model (deductive). The full research team will hold regular meetings to discuss results and resolve any discrepancies in the coding process. Once coding is complete, individual codes will be sorted (ie, grouped together into like categories) by the research team to identify larger themes [22]. Qualitative analysis software, Atlas.ti, (Scientific Software Development GmbH) will be utilized to facilitate the coding process.

For the quantitative analysis, the patient scores on the MMAS-8 will be reported using descriptive statistics (mean, median, interquartile range, etc). The provider surveys provide data in the form of self-report ASB/UTI guidelines familiarity score, a knowledge score (series of hypothetical clinical scenarios testing the application of ASB/UTI guidelines), and a cognitive-behavioral domain score. We have previously used this survey to assess knowledge and behavior concerning ASB in acute and long-term care [21]. The knowledge score is the percentage of correct answers to the hypothetical clinical scenarios, with each correct response receiving 1 point. Descriptive statistics will be used to report the mean knowledge scores for various groups of respondents, and analysis of variance will be used to compare knowledge scores by provider type (ie, attending physician, physician assistant, and nurse practitioner, etc) and level of training. The relationship between the guideline familiarity score and knowledge score will be assessed using a Pearson correlation coefficient. The cognitive behavioral responses in each domain will be averaged to generate a numerical score for that domain. Correlations between the cognitive behavioral constructs and knowledge score will be calculated using the Pearson correlation coefficient.

The quantitative and qualitative data for patient and providers will then be integrated. For patients, we will integrate the mean scores on the MMAS-8 to interview responses on adherence to antibiotics. For providers, we will integrate the knowledge and guideline familiarity scores from the survey with their interview responses on familiarity with the guidelines. Congruence and incongruence between the quantitative and qualitative findings will be explored; for example, if providers answered in the affirmative about knowledge of guidelines, we will correlate the qualitative data with their scores on the knowledge survey.

## Aim 2

This objective will determine (1) which patient, provider, and facility factors are predictors of urine testing and subsequent antibiotic use during the annual evaluation and (2) compare the clinical outcomes of those who received antibiotics with the outcomes of those who did not, utilizing national VHA data sources. These databases (especially for use in SCI) have been described previously [23,24]. The corporate data warehouse (CDW) is a national repository including clinical and administrative data from the VHA. Data are stored in a relational database and are updated on a continual basis. We will use data from several domains within CDW to obtain demographics on the patient population (age, gender, race or ethnicity, and marital status); diagnoses, individual patient utilization (number of visits and admissions), provider type, and facility characteristics (SCI center vs non-SCI center and number of visits and admissions for the facility); temperature and heart rate; and laboratory data including albumin, creatinine, total white blood cell count, urea, glucose, hematocrit, electrolyte panels, and microbiology data (ie, date and time of culture, specimen type, organisms, and antibiotic susceptibilities). Outpatient medications to assess antibiotics filled and history of exposure to antibiotics will be obtained from all available outpatient pharmacy domains.

### Participants

All adult patients with SCI treated at VHA facilities for an outpatient annual examination during the years 2015 and 2016 will be included. The study sample will be drawn from a cumulative list of veterans with SCI maintained by the Veterans Affairs Allocation Resource Center since 1988, which includes approximately 33,000 patients. Veterans are added to the list when an administrative record indicates an SCI in the inpatient diagnostic field with certain International Classification of Disease (ICD)-10 code.

The inclusion criteria for this aim are veterans who were seen for their annual examination in the outpatient setting in the VHA SCI system of care during the years 2015 and 2016 (approximately 6300 veterans are seen each year across the nation). Exclusion criteria are veterans who were seen for their SCI annual evaluation in the inpatient setting because visits may be complicated by other acute medical issues occurring at the time. The study will also exclude veterans with a history of genitourinary tract tumors per ICD-10 codes (and, therefore, more likely to have altered anatomy and/or immunosuppression), as well as those that died less than a year from the annual evaluation encounter. Only the first eligible encounter for each participant will be included. On the basis of our study looking at bacteriuria management in a single VHA center [7], we anticipate approximately 6000 participants after applying the exclusion criteria.

### Approach

Aim 2a is to determine which patient, provider, and facility factors are predictors of urine testing and subsequent antibiotic use. To identify the annual examination encounter, we will use outpatient visits in the clinic stop code for SCI (210) that also has a current procedural terminology code for a renal ultrasound (usually ordered only during the annual evaluation).

The general schema for this objective is shown in Figure 2. This is derived from the Cabana model for adherence to clinical guidelines.

Themes from aim 1 will guide an administrative database search of clinical outcomes of the current VHA urine testing and treatment practices.

**Figure 2.** Bacteriuria management decision making in the veteran spinal cord injury population.
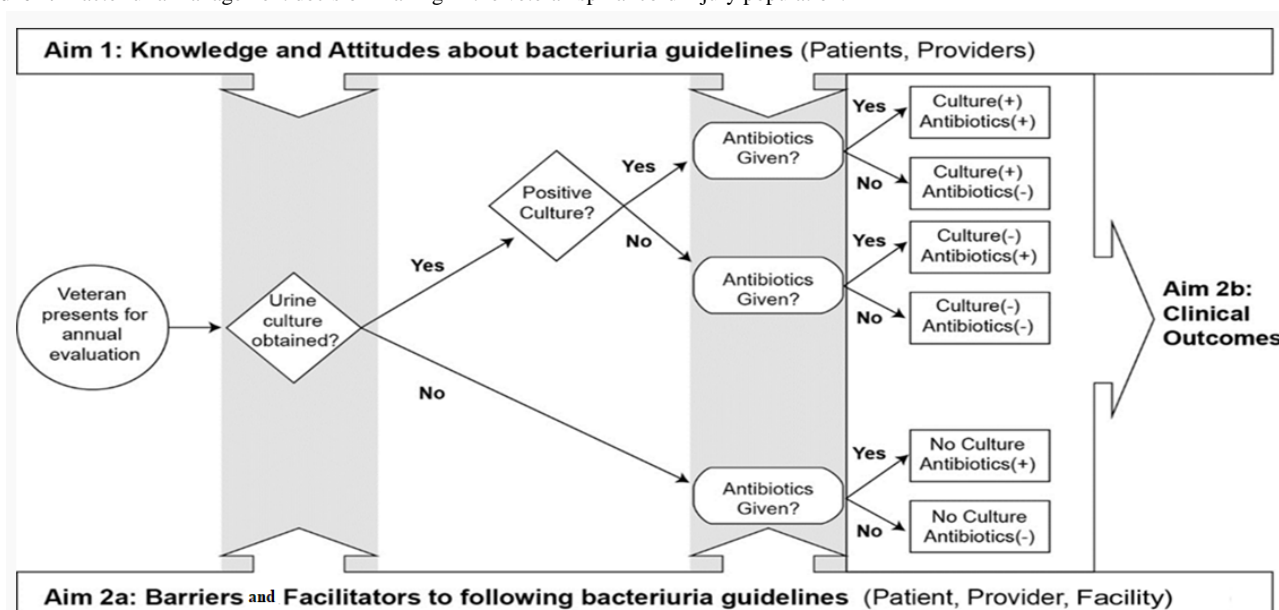


The variables to be collected are described in Table 1. These were generated by the preliminary study results [7] and will be amended, based on other themes identified from objective 1. Zip codes of addresses will be obtained and given a GeoScore, a type of neighborhood socioeconomic index that is emerging as health services and health disparity research and is moving toward large administrative datasets, and was used by Hamilton et al exploring socioeconomic impact on health care utilization after SCI [25]. Deyo comorbidity index will also be calculated using VHA data sources.

Aim 2b will compare the clinical outcomes of those who received antibiotics with the outcomes of those who did not. We will use the same cohort as defined above. Table 2 defines the exposure and outcome variables, as well as covariates that will be considered for the second part of this aim.

### Analysis for Aim 2

It would be clinically meaningful to show no difference in the outcomes between the 2 groups as we hypothesized that one driver of treating ASB at the annual exam is to prevent some of these negative downstream effects.

We will construct separate logistic regression models to determine the predictors of the following: (1) urine testing and (2) the initiation of antibiotics in the 7 days following the annual examination, with day 1 being the day of the examination. First, univariate analyses will be performed between each exposure variable (Table 1) and the outcome variables. Variables that satisfy a previously established $P$ value criterion (.25) on univariate analysis will be considered for entry into a multivariate logistic regression model. We will use a lower $P$

value threshold for the univariate analysis to ensure a robust model. Odds ratios will be used to determine the impact of each variable on antibiotic use. The alpha of .05 will be used to determine statistical significance. Multivariable logistic regression will be used to test all variables for independent associations. For aim 2b, rates of the above outcomes between those who received antibiotics versus those who did not will be compared using chi-square tests for nominal variables and $t$ tests for continuous variables. The Mann-Whitney nonparametric U test will be used if the distribution of any continuous variable is not normal. We will construct a logistic regression model to determine the effect of antibiotics in the 7 days following the annual examination on the outcomes defined in Table 2. Univariate and multivariate analyses will be the same as aim 2a.

### Aim 3

The provider components of the *Test Smart, Treat Smart* intervention (aim 3a) will be an adaptation of the successful *Kicking CAUTI* intervention, consisting of audit and feedback, visual aids, and order sets, refined for SCI providers using iterative design. The patient components will be developed more de novo but be driven by previous work on how patients with SCI prefer to receive information (combination of internet and provider-driven sources) as well as the concept of intervention mapping described above [13,26,27].

Aims 3a and 3b will complete steps 1 to 4 of the intervention mapping process and lay the foundation for step 5 by pilot testing the intervention to assess feasibility (aim 3c). Specifically, we will assess time to complete the intervention, perceived burden to providers, and patient satisfaction.

**Table 1.** Definition of variables for aim 2a.

| Variable type and name | Definition |
| --- | --- |
| **Exposure variables** | |
| **Patient factors** | |
| Age at encounter | Calculated using date of birth CDW[a] patient domain |
| Gender | Male or female |
| Ethnicity or race | As per VHA[b] convention |
| Socioeconomic status | GeoScore to zip code to median income |
| Neurologic level of injury | ICD-10[c] codes for complete and incomplete quadriplegia and paraplegia |
| Bladder management strategy | Catheter prescriptions in pharmacy data |
| Urease-producing organism on culture | Determine positive culture from CDW Micro |
| Level of pyuria on urinalysis | Use as continuous variable from CDW Micro |
| Number of clinic visits per year | Use clinic stop code 210 for SCI[d] clinic |
| Others (as determined by aim 1) | __[e] |
| **Provider factors** | |
| Provider type | Physician, physician assistant |
| Provider load of SCI patients | Number of SCI patients seen by provider in 2015 and 2016 |
| Others (as determined by Aim 1) | — |
| **Facility factors** | |
| Seen at SCI center (hub) or SCI satellite clinic (spoke) | Identify by unique facility codes from majority of visits |
| Geographical region | Using VA[f] Citrix Access Groupings for north, south, east, and west |
| Facility complexity | General knowledge code that is applied to each facility |
| Presence of antimicrobial stewardship program | Provide results from Healthcare Analysis and Information Group (HAIG) 2012 survey |
| Others (as determined by aim 1) | — |
| **Outcome variables** | |
| Urine culture obtained | Identified in CDW microdomain |
| Antibiotics given for urine within 7 days | Antibiotic prescription noted in CDW outpatient pharmacy domain |

[a]CDW: corporate data warehouse.

[b]VHA: Veterans Health Administration.

[c]ICD-10: International Classification of Disease-10.

[d]SCI: spinal cord injury.

[e]Not applicable.

[f]VA: Veterans Affairs.

**Table 2.** Definition of variables for aim 2b.

| Variable type and name | Definition |
| --- | --- |
| **Exposure variable** | |
| Antibiotic use | Antibiotics within 7 days of urine culture |
| **Outcome variables (within 60 days of annual evaluation encounter)** | |
| Emergency visits | As recorded in CDW[a] emergency domain |
| GU[b] complication | ICD-10[c] codes for hematuria, urethral stricture, urethral injury, acute kidney injury, UTI[d] |
| Admission for GU complication | Presence of an admission with above ICD-10 codes in CDW inpatient domain |
| *Clostridium difficile* infection | Positive culture or toxin result, per CDW micro |
| Repeat urine culture | Presence of urine culture in CDW microdomain |
| Diagnosis of GU stone | ICD-10 codes for bladder, ureter, renal calculus |
| **Covariates** | |
| Age | Calculated using date of birth CDW patient domain |
| Gender | Male or female |
| Race or ethnicity | As per VHA[e] convention |
| Neurologic level of injury | ICD-10 codes for complete and incomplete quadriplegia and paraplegia |
| Bladder management strategy | Catheter prescriptions in pharmacy data |

[a]CDW: corporate data warehouse.

[b]GU: genitourinary.

[c]ICD-10: International Classification of Disease-10.

[d]UTI: urinary tract infection.

[e]VHA: Veterans Health Administration.

## *Development of Provider and Nursing Intervention*

For the provider intervention, the study team will conduct a series of focus groups with the SCI clinic team (providers and nurses) to receive feedback on the proposed intervention. The intervention design will be based on antibiotic stewardship principles of right drug, right dose, and right duration. The duration and number of meetings will be determined by the group and adjusted in response to the pace of progress. The components of the provider intervention will be refined through iterative design to address the potential barriers and facilitators to adoption of their use. Lab order sets will be refined to help providers not send urinalysis and urine cultures on asymptomatic patients during the annual evaluation and, if they are inadvertently sent, to prevent providers from ordering antibiotics. The current annual evaluation laboratory order set in the Houston Veterans Affairs electronic medical record includes a urinalysis and urine culture; this will be removed. The decision aid will be a pocket card that makes the ASB and UTI guidelines actionable and, thus, applicable to individual patients at the point of care. If providers state during focus groups that having a communication tool would be helpful, *talking points* will be developed on how to discuss bladder management, urine testing, and bacteriuria treatment with patients during the annual evaluation. Nursing interventions will include developing a script and symptom checklist for nurses to use when interacting with patients requesting urine testing and bacteriuria management during the annual evaluation. Although the focus of the intervention is on helping providers decide whether to use antibiotics or not, we will also provide education and material on how to choose the right drug given latest information about antibiotic resistance in organisms causing UTI in SCI.

Attending, resident, and physician extender education sessions will be incorporated into the weekly SCI lecture series. The first such meeting will introduce the intervention and underlying rationale, review the relevant ASB and UTI guidelines, and explain how and when core components such as order sets will be introduced. After this initial introductory meeting, the decision aids and other intervention materials will be given to all participants. During follow-up sessions, a case example from the annual evaluation clinic from the prior month will be discussed using the decision aid to clarify whether management was or was not compliant with ASB/UTI guidelines. This type of small-group, case-based audit and feedback was highly effective in the *Kicking CAUTI* campaign, as it retains key characteristics of effective audit and feedback, in that it is personalized (to the clinic), timely, nonpunitive, and provides the correct answer [14]. Group discussion will enable providers to ask questions about other cases they managed recently. Nursing education and audit and feedback will be done monthly during nursing in service by the study team.

### Development of Patient Intervention

Aim 3b focuses on developing patient intervention materials. As an analogous intervention to *Kicking CAUTI* for patients does not exist, the second part of this aim will focus on ways to intervene on the patient aspect of urine testing and bacteriuria management. The intervention components will focus on patient education on objectives such as understanding neurogenic bladder and bladder management strategies after SCI and how the consequences of neurogenic bladder and/or catheterization place persons at higher risk for bacteriuria. Intervention components will include a webpage linked to the Texas Paralyzed Veterans of America (PVA) homepage with information targeting the above objectives, a paper flyer summarizing information such as that presented on the website, as well as *talking points* on how to ask a provider for more information on neurogenic bladder and bacteriuria management. We will create a video that will be housed on the PVA website, which can be readily accessed on the computers in the clinic room.

Aim 3c is to conduct a quasi-experimental pilot study of the *Test Smart, Treat Smart* intervention at the Houston VHA. For providers, the main objectives of this pilot study are to assess the following: (1) time to use or complete components of the intervention and (2) perceived burden of using intervention components. For patients, the main objectives of the pilot study are to test the following: (1) their quality of life regarding bladder management before the annual evaluation and (2) satisfaction with neurogenic bladder management and bacteriuria testing education received during the annual evaluation. A *Test Smart, Treat Smart* kick-off meeting with clinic staff will occur before the start of the intervention trial. It will also be discussed at the local PVA meeting the month before the start of the trial. The trial of the intervention will total 4 months. At the 2- and 4-month marks, providers and patients will participate in separate focus groups to provide feedback about the intervention. Patients will receive the SCI-Quality of Life-Bladder Complication assessment before the annual evaluation encounter. This is a validated instrument exploring how bladder management affects patients emotionally, and it has 6 items specifically for UTI [28]. To assess the fidelity of the intervention and prudent safety monitoring, we will compare rates of clinic visits and hospitalizations for UTI/CAUTI before the intervention, at the midpoint of the intervention, at the end of the intervention, and 2 months after the intervention.

### Analysis for Objective 3

The qualitative responses will be coded and analyzed as described for objective 1. The SCI-Quality of Life scores will give us ideas on baseline satisfaction with bladder management to be used for future effectiveness studies. Descriptive statistics will be used to analyze the rates of the hospitalization and clinic visits for UTI/UTI for safety monitoring, and a *t* test will be used to analyze the difference in the rates of these outcomes at different time points.

## Declarations

### Ethics Approval and Consent to Participate

This protocol has been approved by the Baylor College of Medicine institutional review board (IRB) and VHA Research and Development (H-38357).

### Aim 1

The qualitative interviews and quantitative surveys will be performed after verbal informed consent and approved waiver of written informed consent.

### Aim 2

The database analysis will be completed under approved waiver of informed consent.

### Aim 3

The focus groups will be completed after verbal consent is obtained with approved waiver of written informed consent. The quasi-experimental study will be completed after verbal consent is obtained and with approved waiver of written informed consent.

## Results

This protocol received IRB and VHA Research and Development approval in July 2017, and the funding start date for the project was November 2017. The initial plan of having patients complete a Web-based survey had to be abandoned to achieve IRB approval; phone surveys are being completed instead, which has proven to be challenging. We have recently made the addition of a scripted phone message identifying who we are and why we are calling, informing potential participants that we are not solicitors. Recruitment for aim 1 is progressing; as of submission of this manuscript, 10 (67%) of the target goal of 15 provider interviews were complete, and 77 (77%) of the target goal of 100 surveys. With regard to patients, 5 (33%) of the target goal of 15 interviews were complete, and 20 (20%) of the target goal of 100 surveys had been completed. The study team plans to present the results for providers in April 2019. Database analyses for aim 2 will begin in January 2019.

## Discussion

Our previous work shows that the resources for effective antibiotic stewardship programs are more likely to be in place in VHA facilities with SCI units versus hospitals that do not [29]. Specifically, VHA facilities with SCI centers are more likely to have at least 1 full-time infectious diseases physician, an infectious diseases fellowship program, and a clinical pharmacist with formal infectious diseases training—all characteristics that have been shown to decrease antibiotic use in previous studies [30]. However, deploying these resources effectively requires a more complete understanding of the barriers and facilitators of their use, which is the purpose of this protocol.

We anticipate several challenges in carrying out the work as described in this protocol. Difficulty in scheduling time for the provider interviews and surveys due to busy clinic schedules is

anticipated. The team will work individually with providers to find a convenient time for their interviews. The study team has strong contacts with national VHA SCI leadership and will enlist their help in contacting local SCI leadership in the various sites to explain our project and encourage participation. We are aware that a database study cannot provide an explanation for why a test was done or what factors went into the provider's decision to place the order for a test or antibiotics. For this reason, the findings from our database studies of the clinical outcomes downstream from the annual urine testing will be triangulated with our qualitative results. The association we expect to find between urine tests and higher use of antibiotics, even potentially *Clostridium difficile*, will provide evidence to make our intervention acceptable to end users. In other words,

if we find that potential harms result from routine urine testing in SCI, this finding will encourage people to adopt new practices. The literature supports the concept that interventions are more likely to be adopted if the evidence base is considered trustworthy and source of evidence is relevant [31].

Bacteriuria management in persons with SCI is a routine task that involves complex decision making to be handled in a guidelines-compliant manner, particularly the given conflicting guidelines on this topic. Our future work will focus on the implementation and sustainability of antibiotic stewardship interventions for bacteriuria in this high-risk population. We have developed regional and national partners on this work to increase the likelihood of widespread adoption.

## Authors' Contributions

FS is the primary author of the manuscript. LAM, CTE, LG, JK, PR, MEK, SAH, IOP, and BWT all contributed significantly to the design of the study and the writing and editing of select portions of the manuscript pertaining to their expertise; in addition, BT is the direct mentor to FS and significantly edited the manuscript.

## Conflicts of Interest

LG receives support from Zambon Pharmaceuticals. All other authors have nothing to disclose.

## Multimedia Appendix 1

Grant summary statement.

[[PDF File (Adobe PDF File), 151KB](#) - [resprot_v8i2e12272_app1.pdf](#) ]

## Multimedia Appendix 2

Funding announcement letter.

[[PDF File (Adobe PDF File), 147KB](#) - [resprot_v8i2e12272_app2.pdf](#) ]

## References

1.  Centers for Disease Control and Prevention. Making Health Care Safer: Stop Spread of Antibiotic Resistance URL: https://www.cdc.gov/vitalsigns/stop-spread/index.html [accessed 2019-01-21] [WebCite Cache ID 75b21GzV0]
2.  United Nations. High-level Meeting on Antimicrobial Resistance URL: https://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/ [accessed 2019-01-23] [WebCite Cache ID 75dND2HjL]
3.  Fitzpatrick MA, Suda KJ, Safdar N, Goldstein B, Jones MM, Poggensee L, et al. Unique risks and clinical outcomes associated with extended-spectrum β-lactamase enterobacteriaceae in veterans with spinal cord injury or disorder: a case-case-control study. Infect Control Hosp Epidemiol 2016 Dec;37(7):768-776. [doi: 10.1017/ice.2016.60] [Medline: 27025908]
4.  Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM, Infectious Diseases Society of America, American Society of Nephrology, American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005 Mar 1;40(5):643-654. [doi: 10.1086/427507] [Medline: 15714408]
5.  Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, Infectious Diseases Society of America. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice

Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010 Mar 1;50(5):625-663. [doi: 10.1086/650482] [Medline: 20175247]

6. US Department of Veterans Affairs. 2018. Spinal Cord Injury and Disorders System of Care URL: https://www.sci.va.gov/ [accessed 2019-01-21] [WebCite Cache ID 75b2NxJlh]

7. Skelton F, Grigoryan L, Holmes SA, Poon IO, Trautner B. Routine urine testing at the spinal cord injury annual evaluation leads to unnecessary antibiotic use: a pilot study and future directions. Arch Phys Med Rehabil 2018 Feb;99(2):219-225. [doi: 10.1016/j.apmr.2017.10.005] [Medline: 29107038]

8. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. J Am Med Assoc 1999 Oct 20;282(15):1458-1465. [doi: 10.1001/jama.282.15.1458] [Medline: 10535437]

9. Reyna VF, Lloyd FJ. Physician decision making and cardiac risk: effects of knowledge, risk perception, risk tolerance, and fuzzy processing. J Exp Psychol Appl 2006 Sep;12(3):179-195. [doi: 10.1037/1076-898X.12.3.179] [Medline: 16953744]

10. Reyna VF, Weldon RB, McCormick M. Educating intuition: reducing risky decisions using fuzzy-trace theory. Curr Dir Psychol Sci 2015 Oct;24(5):392-398 [FREE Full text] [doi: 10.1177/0963721415588081] [Medline: 26594099]

11. Hung EW, Darouiche RO, Trautner BW. Proteus bacteriuria is associated with significant morbidity in spinal cord injury. Spinal Cord 2007 Sep;45(9):616-620. [doi: 10.1038/sj.sc.3102004] [Medline: 17179975]

12. Lewis RI, Carrion HM, Lockhart JL, Politano VA. Significance of asymptomatic bacteriuria in neurogenic bladder disease. Urology 1984 Apr;23(4):343-347. [doi: 10.1016/0090-4295(84)90136-5] [Medline: 6369712]

13. Kok G, Gottlieb NH, Peters GJ, Mullen PD, Parcel GS, Ruiter RA, et al. A taxonomy of behaviour change methods: an intervention mapping approach. Health Psychol Rev 2016 Sep;10(3):297-312 [FREE Full text] [doi: 10.1080/17437199.2015.1077155] [Medline: 26262912]

14. Hysong SJ, Kell HJ, Petersen LA, Campbell BA, Trautner BW. Theory-based and evidence-based design of audit and feedback programmes: examples from two clinical intervention studies. BMJ Qual Saf 2017 Dec;26(4):323-334. [doi: 10.1136/bmjqs-2015-004796] [Medline: 27288054]

15. Trautner BW, Bhimani RD, Amspoker AB, Hysong SJ, Garza A, Kelly PA, et al. Development and validation of an algorithm to recalibrate mental models and reduce diagnostic errors associated with catheter-associated bacteriuria. BMC Med Inform Decis Mak 2013 Apr 15;13:48 [FREE Full text] [doi: 10.1186/1472-6947-13-48] [Medline: 23587259]

16. Patton MQ. Qualitative Research & Evaluation Methods: Integrating Theory and Practice Fourth Edition. Thousand Oaks, California: Sage Publications; 2015.

17. Guest G, Bruce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field methods 2006;18:59-82 [FREE Full text] [doi: 10.1177/1525822X05279903]

18. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009 Jan;15(1):59-66 [FREE Full text] [Medline: 19146365]

19. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008 May;10(5):348-354 [FREE Full text] [doi: 10.1111/j.1751-7176.2008.07572.x] [Medline: 18453793]

20. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. J Clin Epidemiol 2011 Mar;64(3):255-257 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.09.002] [Medline: 21144706]

21. Trautner BW, Petersen NJ, Hysong SJ, Horwitz D, Kelly PA, Naik AD. Overtreatment of asymptomatic bacteriuria: identifying provider barriers to evidence-based care. Am J Infect Control 2014 Jun;42(6):653-658. [doi: 10.1016/j.ajic.2014.02.003] [Medline: 24713596]

22. Bernard HR, Ryan GW. Analyzing Qualitative Data: Systematic Approaches. Thousand Oaks, California: Sage Publications; 2010.

23. Smith BM, Evans CT, Ullrich P, Burns S, Guihan M, Miskevics S, et al. Using VA data for research in persons with spinal cord injuries and disorders: lessons from SCI QUERI. J Rehabil Res Dev 2010;47(8):679-688 [FREE Full text] [doi: 10.1682/JRRD.2009.08.0117] [Medline: 21110243]

24. Evans CT, Rogers TJ, Chin A, Johnson S, Smith B, Weaver FM, et al. Antibiotic prescribing trends in the emergency department for veterans with spinal cord injury and disorder 2002-2007. J Spinal Cord Med 2013 Sep;36(5):492-498 [FREE Full text] [doi: 10.1179/2045772312Y.0000000076] [Medline: 23941797]

25. Hamilton R, Driver S, Noorani S, Callender L, Bennett M, Monden K. Utilization and access to healthcare services among community-dwelling people living with spinal cord injury. J Spinal Cord Med 2017 Dec;40(3):321-328 [FREE Full text] [doi: 10.1080/10790268.2016.1184828] [Medline: 27221396]

26. Edwards L, Krassioukov A, Fehlings MG. Importance of access to research information among individuals with spinal cord injury: results of an evidenced-based questionnaire. Spinal Cord 2002;40(10):529-535. [doi: 10.1038/sj.sc.3101364] [Medline: 12235536]

27. Burkell JA, Wolfe DL, Potter PJ, Jutai JW. Information needs and information sources of individuals living with spinal cord injury. Health Info Libr J 2006 Dec;23(4):257-265 [FREE Full text] [doi: 10.1111/j.1471-1842.2006.00686.x] [Medline: 17177946]

28.    Tulsky DS, Kisala PA, Tate DG, Spungen AM, Kirshblum SC. Development and psychometric characteristics of the
       SCI-QOL Bladder Management Difficulties and Bowel Management Difficulties item banks and short forms and the
       SCI-QOL Bladder Complications scale. J Spinal Cord Med 2015 May;38(3):288-302 [FREE Full text] [doi:
       10.1179/2045772315Y.0000000030] [Medline: 26010964]
29.    Skelton F, Suda K, Evans C, Trautner B. Effective antibiotic stewardship in spinal cord injury: challenges and a way forward.
       J Spinal Cord Med 2018 Jan 11:1-4. [doi: 10.1080/10790268.2017.1396183] [Medline: 29324181]
30.    Chou AF, Graber CJ, Jones M, Zhang Y, Goetz MB, Madaras-Kelly K, et al. Characteristics of antimicrobial stewardship
       programs at Veterans Affairs hospitals: results of a nationwide survey. Infect Control Hosp Epidemiol 2016
       Dec;37(6):647-654. [doi: 10.1017/ice.2016.26] [Medline: 26905338]
31.    Rushforth B, Stokes T, Andrews E, Willis TA, McEachan R, Faulkner S, et al. Developing 'high impact' guideline-based
       quality indicators for UK primary care: a multi-stage consensus process. BMC Fam Pract 2015 Oct 28;16:156 [FREE Full
       text] [doi: 10.1186/s12875-015-0350-6] [Medline: 26507739]

## Abbreviations

**ASB:** asymptomatic bacteriuria
**CAUTI:** catheter-associated urinary tract infection
**CDW:** corporate data warehouse
**ICD:** International Classification of Disease
**IRB:** institutional review board
**MMAS-8:** Morisky Medication Adherence Scale-8
**PVA:** Paralyzed Veterans of America
**SCI:** spinal cord injury
**UTI:** urinary tract infection
**VHA:** Veterans Health Administration

Protocol

# Student Activity and Sport Study Ireland: Protocol for a Web-Based Survey and Environmental Audit Tool for Assessing the Impact of Multiple Factors on University Students' Physical Activity

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## Abstract

**Background:** Increasing proportions of the global population transition through a university setting, a setting associated with engagement in behaviors that diminish health such as high levels of physical inactivity. Increasing physical activity (PA) is a key element of health promotion strategies in many countries, but a better understanding of students' PA and how it is associated with personal, behavioral, and environmental factors is needed. Studies provide protocols to collect information regarding these factors separately; however, none have developed a validated systematic approach to gather information pertaining to all across a whole country.

**Objective:** The purpose of this project is to examine students' physical activity and how it is associated with personal, behavioral, and environmental factors.

**Methods:** Student Activity and Sport Study Ireland (SASSI) is a university-based cross-sectional study that was carried out across the island of Ireland in 2014. A novel and comprehensive Web-based environmental audit tool (EAT) gathered information pertaining to the environment provided by universities for physical activity. A Web-based student survey (SS) collected information about physical activity beliefs, attitudes, motivations, and behaviors of students. The audit tool and SS were developed through rigorous consultation processes involving international experts. An institutional champion volunteered at each university to recruit, administer, and ensure the completion of both assessments.

**Results:** Data collection was undertaken between May and December 2014. A total of 80% (33/41) of universities completed the EAT, whereas 88.31% (8122/9197) of students (49.10% [3966/8122] male; mean 23.17 [SD 6.75], years) completed the SS sufficiently. Studies are currently underway with the data collected using this protocol.

**Conclusions:** SASSI provides a novel and comprehensive protocol for systematically assessing the PA of students and the related personal, behavioral, and *actual* environmental factors. The strengths of the SASSI study are presented and include high response rates and a unique dataset that can provide information to relevant stakeholders and policy makers, along with aiding the development of university environments and interventions that promote PA involvement. The weaknesses of the protocol are recognized with suggestions given to overcome them in future research. This protocol is applicable for other countries and has great potential to create harmonization of data, which would allow for direct comparisons across nations.

**International Registered Report Identifier (IRRID):** RR1-10.2196/10823

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## Introduction

### Background

Early adulthood (ie, ages 18-24 years) is regarded as an exploratory phase, which anchors health-related behaviors that often persist into later life and determine long-term health outcomes [1]. It is becoming increasingly popular for individuals to attend a university during early adulthood. The global student population exceeded 178 million in 2010 and is expected to reach 263 million by 2025 [2]. Research indicates a high proportion of university students engage in behaviors that diminish their health, such as high levels of physical inactivity (23%-44%) [3], and exceeding the daily recommended alcohol and tobacco smoking limits [4]. With students exposed to multiple health-related behaviors of both a positive and negative nature, it seems prudent to focus on a behavior known to benefit the physical, cognitive, and social health of individuals, such as physical activity (PA) [5]. The recommendation to increase PA is a key element of health promotion strategies in many countries [3], where PA includes sport, structured exercise, and active transport [6]. In the general population, PA is an important factor for the prevention of noncommunicable diseases such as obesity, cardiovascular heart diseases, and type 2 diabetes mellitus [7,8]. Although PA levels of children and adults across the globe are well documented [9], university students' behaviors, beliefs, and attitudes, and how these are formed and reinforced, require further research, particularly in representative or random samples [10].

Understanding the factors that relate to PA is a key step for developing effective evidence-based programs [11]. Social cognitive models have performed well for understanding the factors that relate to individuals' PA, with Bandura's social cognitive theory [12] seen as a popular choice for this purpose [13,14]. Social cognitive theory proposes an agentic perspective, suggesting that not only is the environment dictating behavior but also that individuals are being self-regulating and self-developing [12]. Social cognitive theory is founded on a causal model of triadic reciprocal causation in which personal factors, behavioral patterns, and environmental characteristics all interact and influence one another in a bidirectional fashion [12]. However, this theory has been said to focus mainly on the social environment and rarely address the multidimensional role of the physical environment [15].

For this reason, it seems appropriate to also use an ecological approach that summarizes the multiple levels of influence on a behavior, breaking them down into intrapersonal, interpersonal, physical environment, and policy [16]. Furthermore, research has noted the benefits of using social cognitive theory and ecological approaches in combination to investigate the factors relating to PA [17]. Research suggests that personal (eg, age, sex, attitudes, and knowledge of benefits), behavioral (eg, past PA and smoking), and environmental (eg, peer support and recreational PA opportunities) factors are associated with adults

and students' PA [10,18]. Personal and behavioral factors relating to PA are much better understood in university students when compared with research examining associations between PA and the physical environment [10,19,20]. Research is needed to determine and better understand how the environment within which individuals spend time might act to enhance or constrain PA [20]. Our understanding of the impact of the university setting on students' PA is limited [21], but the physical environment has been shown to influence students' decision-making process regarding engagement in PA [17]. Nonetheless, evidence is lacking regarding the impact of institution size, support staff, extent and nature of facilities, financial investment, opportunities for participation, and institutional ethos and policy on students' PA participation.

### Objectives

To date, studies provide protocols to collect both individual [22-24] and environmental information [25,26]; however, none have developed a validated systematic approach to gather information pertaining to the individual (ie, personal and behavioral) and environment across a whole country. Student Activity and Sport Study Ireland (SASSI), the first of its kind, addresses the important topic of the interaction between these factors and participation in PA on the island of Ireland. First, this study aimed to develop and create a comprehensive and usable audit tool for examining the environment, provision, and support offered by universities for students' PA participation. Second, it aimed to develop a survey to collect information regarding the level, type, and nature of PA participation by students, including the associated determinants, health-related behaviors, and outcomes. Finally, this study aimed to create a protocol, guided by social cognitive theory and an ecological approach that would allow for the audit tool and survey to be used together and provide a holistic view of the factors relating to university students' PA.

## Methods

### General Information

Guided by social cognitive theory and an ecological approach, SASSI is a university-based environmental audit tool (EAT) and student survey (SS), which was conducted in 2014. All universities (n=41) on the island of Ireland were invited to partake in SASSI, with universities classified into the following categories, based on their size: (1) large=≥11,000 students; (2) medium=4000 to 10,999 students; and (3) small=≤3999 students. The university size was based on the distribution of the 2013 to 2014 full-time undergraduate and postgraduate enrollment figures across all universities [27,28]. The active partners in the study included the research team, the Student Sport Ireland (SSI) Research Management Group, and the institutional champions (ICs; Figure 1). SSI is the governing body of university sport in Ireland. Owing to the all-island approach, ethical clearance from relevant ethical committees in the

Republic of Ireland (Waterford Institute of Technology School of Health Science Research Ethics Committee) and Northern Ireland (Ulster University Research Governance) was obtained and extended through recognition by all universities involved. Detailed information sheets about the study were provided before the start of the EAT and SS. Signed informed institutional consent was received for the EAT, and students were informed that they were providing consent when they chose to proceed with the SS. The data collection process used for the EAT and SS are presented in the coming sections and in Figure 2.

## Institutional Champions

Given the extent of the study and the geographical spread of the universities, the research team relied heavily upon the voluntary contribution of ICs (n=52). In the majority of cases,

the IC was the designated contact person for SSI in each of the universities. The ICs were an integral part of the study; their key roles were to promote the research within their university, lead the completion of the EAT through engagement with other institutional stakeholders, and recruit for and administer the SS according to predetermined quotas. To maintain consistency across all universities and ensure the collection of valid data, each IC completed a half-day training program that was used to empower the IC to assist with sufficient data collection. Not only did this process ensure standardization in the implementation across each university, it also created an opportunity to build grassroots commitment and ownership in the study. A research manager was employed as part of the research team and was responsible for overall quality control and ensuring that the ICs were supported in their roles.

**Figure 1.** Active partners in Student Activity and Sport Study Ireland. SSI: Student Sport Ireland.



**Figure 2.** Data collection process for Student Activity and Sport Study Ireland.
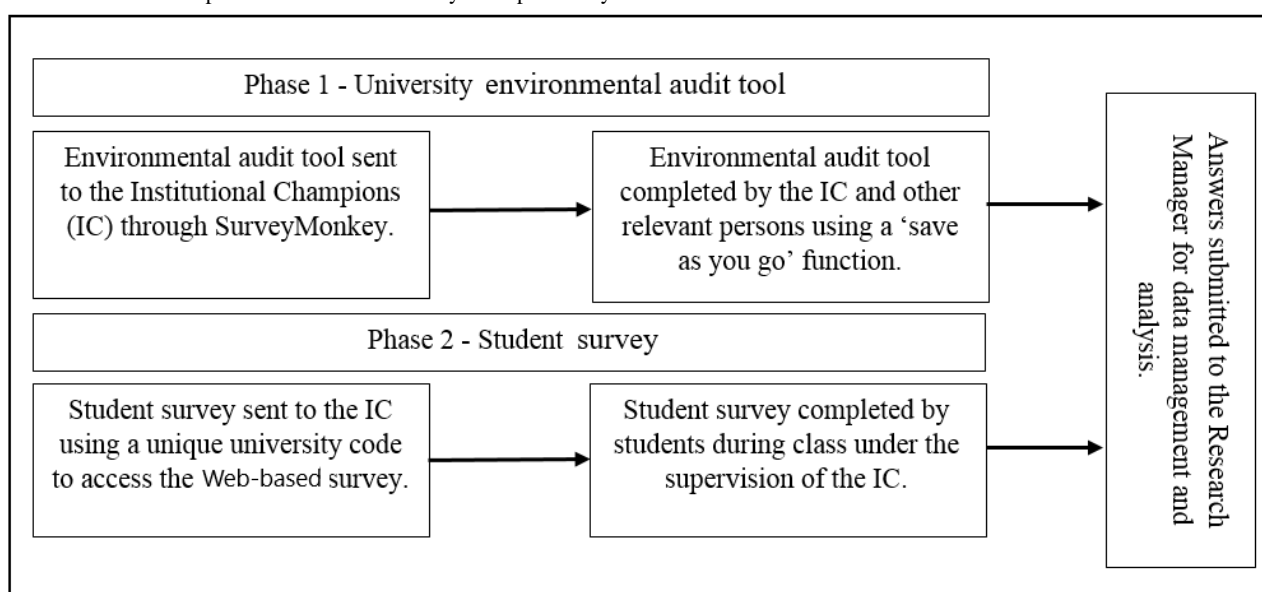
## Environmental Audit Tool

The purpose of the EAT was to provide an analysis of the environment and provision made by universities to support student participation in PA. The EAT consisted of eight sections, with 39 questions addressing the following constructs potentially relevant to university support for PA participation: (1) organizational structures; (2) personnel; (3) facilities; (4) funding or investment; (5) opportunities for participation; (6) high-performance athletic support; and (7) institutional ethos, prioritization, and quality of provision. An initial section gathered information on the respondents (eg, title, contact details, and section responsible for completing).

### Environmental Audit Tool Administration and Completion Procedure

To aid with the distribution and data collection, the EAT was translated into a Web-based instrument using SurveyMonkey (SurveyMonkey Inc, San Mateo, California, USA). The research manager then uploaded the university-specific audit tools, generating a Web-based link for each. This link was sent to the ICs of each participating university via email, who were requested to identify the appropriate personnel in their universities to complete or inform each section. Owing to the time and information required, a *save as you* go function was applied to the EAT, allowing the participants to save answers and return later. This function also allowed the respondents to edit answers before submitting to the research manager.

### Environmental Audit Tool Development

To guide the development of the EAT, SSI identified the following aspects that should be investigated: (1) local context (eg, location and enrollments); (2) policies and provision; (3) culture (eg, perceived level of support for PA participation); (4) facilities; and (5) needs and resources assessment (eg, current needs and resources to further promote PA). In addition to the above guidance, additional insight into possible content was gained by examining existing literature and other published audits on environments provided by universities in England and Scotland [25,26]. Subsequent to the production of the final EAT, an extensive 6-month consultation process took place to further develop, refine, and confirm it. This included consultation with (1) members of the research team and the SSI research management group (n=10); (2) key stakeholders in the PA provision in universities (n=15, SSI designated contact person); and (3) international experts (n=3, personnel involved in the Sports Provision in Scottish Universities and Irish Higher Education Surveys, and a statistician). These consultations were used to review draft versions of the EAT and maximize face validity of the tools used in the EAT. Face validity is seen as the extent to which a measure appears to provide the desired information and is usually assessed by expert consensus [29]. The whole process resulted in the development of a comprehensive EAT, designed to investigate the environment provided by universities to support and promote PA engagement. An overview of the sections included in the EAT is provided below, with the full version available in Multimedia Appendix 1.

## Organizational Structure of Physical Activity

To understand the organizational structures of PA within universities, two questions were asked. First, the number of organizational structures (eg, Department of Sport, sport clubs, and student union) which provide direct support to PA participation, the individual (eg, Director of Sport and student services) within the institution that the organizational structure reports to, and a brief description of the role of the structure were asked about. Second, the nature and number of other partnerships within the institution that support sport and PA participation (eg, health service and disability service) were assessed. Responses were open, allowing the respondents to answer from their universities' perspective.

## Personnel

The EAT included questions regarding (1) the number of full-time employees, part-time employees, and volunteers supporting PA participation in 2009 and 2014 and (2) the relevant staff titles (eg, *Director of Sport*). This question was answered for each named organizational structure within the university (ie, from previous section). Information regarding training and recognition available to student volunteers was also gathered.

## Facilities Provision

Questions regarding the extent and nature of both indoor and outdoor facilities available to each university at all locations were included in the EAT. Details about the type of facility (eg, courts and pitches), facility dimensions, specifications and number, ownership (owned or hired), and accessibility for individuals with a disability were gathered. A list of named facilities was included (n=19), and respondents had the option to include *other* facilities. The section included closed responses (ie, yes or no and owned or hired) and open responses to allow more details about the facilities to be provided. Respondents were asked to complete this section for each location used by their university to provide PA opportunities.

## Funding or Investment for Physical Activity

Investment in PA provision within universities was investigated by gaining insights into the (1) past (last 20 years) and planned (next 5 years) capital investment in facilities by institutional, private, and public sources; (2) current investment in each of the previous 5 years; (3) provision of direct institutional grants for sports clubs; (4) annual fees or charge to students; and (5) student charge to access facility or PA opportunity. Specific funding ranges (eg, up to 25,000; 25,001-35,000) were provided for capital and current investment questions. Open responses were facilitated in the remaining questions.

## Student Sport and Physical Activity Participation Provision

Questions were asked regarding (1) sports clubs provided by the university; (2) the nature of sports clubs provided (ie, type and provision for individuals with a disability); (3) number of participants; (4) description of link between sports clubs and the universities' organizational structures; and (5) participation rates in exercise and fitness opportunities. Additional detail was gathered regarding the competition levels engaged in, level of training hours, staffing, income, and expenditure of clubs. A response was requested for a list of 54 named sports clubs

([Multimedia Appendix 1](#)), with an option for the respondent to include additional options. The majority of questions were closed in nature, with drop-down menus to facilitate selection of the most appropriate answers.

### High-Performance Programs and Athletes

Questions regarding various aspects of provision for high-performance programs and athletes were included in the EAT. High performance or elite was defined as students currently competing at national or international standards at either senior or junior levels. The following aspects were examined: (1) institutional partnership with national governing bodies of sport and national or international-level sports clubs and (2) provision, nature, source, and value of athletic scholarships and of *in-kind* athletic support (eg, free access to facilities and sport science support). A combination of open and closed questions was used, and the option of adding *other* choices was included as appropriate.

### Institutional Ethos and Prioritization

The EAT concluded with questions regarding perceived institutional ethos and prioritization for PA provision. First, respondents were asked about the perceived importance placed on participation in and the promotion of PA and how this importance has changed over the last three years. This was followed by asking about the impact of specific factors (eg, cost of provision and health of students) on the institutional prioritization of PA. Subsequently, the perceived quality of provision under a range of headings (eg, indoor and outdoor facilities, PA opportunities, and funding) for PA was assessed. Finally, the existence and availability of strategic priorities for PA in each university was asked. Likert scales were used to assess the above, with an exception to the final area, which allowed respondents to include a link to any strategic information regarding PA provision.

### *Data Management of the Environmental Audit Tool*

The responses from SurveyMonkey (SurveyMonkey Inc, San Mateo, California, USA) were directed to an SPSS database version 22 (SPSS Inc). Each university was given a unique identification (ID) number, which allowed the data to be matched across the EAT and SS. To produce a clean and complete dataset, the following steps were followed: (1) successful data transferal from SurveyMonkey (SurveyMonkey Inc, San Mateo, California, USA) to SPSS was confirmed; (2) missing data were identified and appropriately coded; (3) university size was added; and (4) to ensure that the datasets were anonymous, any text that would enable identification of a specific university was edited. The EAT was developed so that provision for each construct by universities could be usefully scored and analyzed. From the EAT, the following key performance indicators (KPIs) were agreed to represent the environment and provision made by universities to support student participation in PA ([Multimedia Appendix 2](#)).

An institutional score for total provision and for provision relative to 100 students was calculated for each KPI listed above. The development of the provision score facilitates analysis of total and relative provision for each KPI across small, medium, and large institutions. In addition, it is also possible to categorize universities as making high, medium, and low provision for each KPI. The different categories of provision were determined by calculating a university rank (1-33) for both the total provision score and the total score relative to 100 students. These two ranking values were then summed and ranked to get a composite rank for each university. On the basis of this composite rank, institutions were assigned equally to either a high, medium, or low provision category for each KPI (ie, ranks 1-11=high; ranks 12-22=medium; and ranks 23-33=low). Details regarding calculation of university total provision score for each KPI are provided in [Multimedia Appendix 2](#).

### Student Survey

The purpose of the SS was to provide information of the students' behaviors, beliefs, and attitudes regarding sport and PA. The SS consisted of 8 sections, with 98 questions addressing the following areas: (1) general PA; (2) determinants of PA; (3) volunteering in sport; (4) coaching acquired; (5) sport and recreational PA participation; (6) elite athlete satisfaction; and (7) related health behaviors. Additional questions gathered demographic information about the respondent (eg, sex, age, and household income).

### *Student Survey Administration and Completion Procedure*

To achieve a nationally representative sample from each university, 3% (7/32) of the student population in large universities, 5% (12/32) of the population in medium-sized universities, and 6% (13/32) of the population in smaller universities were sought. Students were also required from different fields and years of study within each university, depending on the student enrollments [27,28]. Data collection implemented a stratified cluster design for subject selection, stratified by year group and across fields of study, which allowed for a representative sample based on university enrollments. A quota of students needed from each university was developed and given to the IC responsible. The IC then worked alongside the research manager to ensure that the sample was representative of their student body. The IC requested access to the required students and administered the SS during class time, which was completed using the SurveyMonkey software (SurveyMonkey Inc, San Mateo, California, USA). Before the students were given their university-specific survey link, the study was explained, and it was advised that the SS be completed on a laptop, tablet, or mobile phone. The use of a supervised Web-based survey was to maximize response rates, minimize potential for data entry errors, and facilitate the merging of data from over 30 universities. Administering the survey during class time was based on previous research where response rates in excess of 90% have been achieved [3,30]. To ensure that the ICs collected the data as requested, the date stamp of responses was examined by the research manager. Where the majority of responses (>90%) occurred in batches and within normal university hours, it was deemed likely that the protocol was adhered to. The ICs were encouraged to collect as many responses as possible. Where the response rate was greater than the quota needed, the research manager drew a random stratified sample to obtain a representative sample for the overall study. This allowed each university to use their own

full dataset for further local analysis while the quota for the national survey was achieved.

### Student Survey Development

The SS was developed using versions of known tools and measures that have been used in similar studies [23,24,31-33]. The research team consulted with the SSI research management group (n=7), international experts (n=3; health professionals), and statisticians (n=2) to develop and refine the SS through a series of drafts (n=4) over a 5-month period. Again, these consultations were used to review draft versions of the survey, generate consensus among experts, and maximize the face validity of the tools used in the SS. The final SS used open and closed questions to gain the relevant responses, with any sensitive questions related to personal or financial circumstances placed at the end of the survey, as they can be a barrier to further survey completion [34]. Filtering was applied throughout the survey so that the relevant questions were asked based on participants' previous responses. An overview of the SS's main sections can be found below, with more information of how the SS was structured, along with the filtering information available in Multimedia Appendix 3.

### General Physical Activity

Students' views of their PA levels were asked using five single-item questions, including (1) if they think they take enough PA to keep healthy; (2) their PA levels compared with others; (3) their PA levels compared with those of last year; (4) increasing PA over the next year; and (5) how important PA opportunities were when enrolling. Responses were recorded using a range of Likert scales and categories. Knowledge of the PA guidelines was asked using a single question, with responses allowed in minutes per week or day. General PA levels were measured using three valid and reliable measurement tools for assessing attainment of the PA guidelines [35]: the International Physical Activity Questionnaire-Short Form [36], an adapted version of the *Patient-Centered Assessment andCounselingfor Exercise* [37], and a single-item measure [38]. Domains of PA were measured, including PA as a form of transport, cycling, walking, and muscle strengthening exercises. PA as a form of transport was measured using two questions asking about the form of transport used to get to the university and the duration of time it takes [24]. Students who travelled to the university by a motorized form were asked to give three reasons for not actively travelling, with 12 options available. Walking for recreation was measured with a 3-item question asking about the frequency, duration, and intensity [24]. The frequency and duration of cycling PA [31] and muscle strengthening PA were also assessed using 2-item questions [24].

### Determinants of Physical Activity

The psychosocial determinants of PA participation were assessed using the Determinants of PA Questionnaire (DPAQ) [39]. Shortened from its original for practical purposes, 1 item for each of the 11 determinants was selected based on the items with the highest factor loading from a confirmatory factor analysis [39]. The shortened DPAQ presents 11 statements, worded positively and negatively, asking students to respond using a 7-point Likert scale ranging from strongly disagree to strongly agree. The determinant areas included knowledge, environmental resources, motivation, beliefs about capabilities, emotion, skills, social influences, beliefs about consequences, action planning, coping planning, and goal conflict related to PA.

### Volunteering in Sport

A question asked students if they completed any sports voluntary work in the past four weeks, with responses dichotomized into volunteers and nonvolunteers. Those who *volunteered* were asked to indicate the duration (hours per week) and type (range of 7 activities) of volunteering both inside and outside the university.

### Coaching

This section asked students if they had received any formal coaching or instruction to improve PA performance in the past four weeks, with responses dichotomized into yes or no. If "yes," then information about where it was accessed was asked with 6 responses provided.

### Sport and Recreational Physical Activity Participation

Student engagement in recreational PA inside their university was assessed by asking "Did you do any sport or recreational PA in the last four weeks?" with four options that acted as filters, categorizing students as "nonparticipants," participating only "within university," "outside university," or "both in and outside university." Each category directed to a specific set of questions designed to find out more about their behavioral choices.

Those in the "within university" and "both" categories were asked about the frequency, intensity, duration, standard, and the type of PA they participate in, with options given for each [33]. These students were asked to rate the top five reasons for participation within their university, with 17 responses provided [40], and their satisfaction with provision for PA by their university using 10-point Likert scales. Students were then asked to indicate the uptake of any new PA since beginning in the university and the highest level that they have participated at, through closed questions [41].

Those in the "outside university" category were asked about the frequency, intensity, duration, standard, and the type of PA they participate in, along with whom they participate. The top three reasons for not participating through the university were asked with an option to suggest what their university could do to encourage participation [33]. Questions regarding the reasons for PA participation, the uptake of new activities, and the highest standard participated were then asked.

Those in the "nonparticipants" category were asked for the three reasons for nonparticipation in any PA, the length of time since they last participated, if they could be encouraged to participate in PA (yes or no), and what would encourage them to participate (13 options) both inside and outside the university [26].

### Elite Athlete Satisfaction

Students who indicated that the highest level participated as "elite" were asked if they received a scholarship or bursary from their university. If "yes," questions about the sufficiency of scholarship, the type of activities participated in, and their satisfaction with the provision for elite athletes by their university followed.

### Related Health Behaviors

Questions were asked to assess the health-related behavior choices of students. Alcohol intake, smoking, and drug use were all measured using single-item frequency questionnaires [23]. Sedentary behaviors were measured by students to estimate the minutes spent sitting on weekdays and weekends in a range of 8 situations [42]. Dietary habits were measured using two adapted single-item frequency measures, asking about convenience foods (eg, fast food) and fresh foods (eg, fruit and vegetables) [23]. Students' perception of body image, general health in the past 12 months, and happiness were assessed using single-item measures with responses recorded using Likert scales [24,31]. Mental health was measured using the 5-item Mental Health Index, a subscale from the Short Form Health Survey [43,44].

### *Data Management of the Student Survey*

The sample collected was reviewed against the nationally representative figures once the data collection was complete. This enabled a weighting to be matched to the selection process based on the parameters of age and sex, depending on any gaps or underrepresentation in the initial data collection. The decision to weight by gender and age was based on the knowledge from previous research that participation in sport and PA is significantly influenced by both factors. Weighting of the dataset was completed by statisticians (n=2) and allowed the data to be representative of the national statistics regarding university enrollments. Each dataset was given an ID when data collection was complete, which was the only identifier for each respondent. An ID was also generated based on the university the responses came from, which reflected the ID of the universities in the EAT. This meant the environmental data and SS responses could be matched, allowing examination of the relationship between the university environment and students' responses to the SS. Reliability of data would affect any future analysis; thus, data cleaning and reliability checks were paramount to this phase. This involved checking data for consistency, completeness, and accuracy through spot checks.

## Results

### Environmental Audit Tool

Data collection using the EAT was undertaken between May and August 2014. A total of 80% (33/41) of universities responded to the EAT. Overall, 70 people from the participating universities played a part in the completion of the EAT, including the following staff or equivalent in each university: Director of Sport; Sports or Clubs and Societies Officer; and Health or PA Promotion Officer. In 42% (14/33) of institutions, the IC only played a role in the completion of the EAT.

### Student Survey

Data collection using the SS was undertaken between October and December 2014. Students from 78% (32/41) of universities participated in this phase of the study. Of the 9197 students administered the SS, 88.31% (8122/9197) provided sufficient responses (49.12% [3966/8122] male; mean 23.17 [SD 6.75] years). Analyses were conducted on the datasets to examine the PA attitudes, beliefs, and behaviors of students and to investigate the influence of relevant factors (ie, individual, behavioral, and environmental) for student PA engagement. The full findings generated from this protocol are available in the SASSI report [45], with additional studies planned in the near future.

## Discussion

### Potential of the Protocol

The SASSI study is a novel, two-phase cross-sectional study combining a purposefully developed EAT and a supervised Web-based SS. Together, the measurement tools provide comprehensive data, which permits an investigation of how personal, behavioral, and environmental factors relate to students' PA. This enables us to have a holistic view of the factors related to behavior as guided by the social cognitive theory and ecological approach used. In addition, the protocol allows the evaluation of the *actual* environment provided by universities and their association with students' PA. This has the potential to eliminate the gap in the literature regarding the association of the physical environment with PA engagement in students [10,20]. The data collection tools developed can be used to evaluate existing university provision for PA and measure change in that provision; interrogate and inform the future research agenda; and provide a platform for the pooling and harmonization of data collected. Finally, the authors believe that this protocol is generalizable and can be used in other nations and by other stakeholders to quantify and evaluate the factors that are important for student PA engagement. Such evaluations will contribute to the impact of health promotion efforts for this population.

### Strengths

The protocol has several strengths, which encourage the possibility of its use in other nations wishing to investigate PA in this population. Identification of similar survey instruments and the consultation process throughout the development phases were strengths that allowed for the creation of 2 assessment tools that were used in over 30 universities across 2 nations. The consultation process in both phases also allowed for face validity to be maximized for the EAT and SS by the research team, management group, and international experts. Both the EAT and SS are comprehensive in assessing their intended areas but are designed to be used together, which provide a unique dataset. This unique dataset has the potential to increase our understanding of the *actual* environment provided by universities and the effects it has on students' PA, while also assessing personal and behavioral factors. Other major strengths of the SASSI protocol concern the training, buy-in, and input from the ICs throughout both phases and the success of administering the EAT and SS through a Web-based platform. These strengths were key factors for the high response rates in the EAT (80% of universities invited completed the EAT) and SS (88.31%; 8122/9197) of the 9197 students administered the SS sufficiently completed it). For phase 2, the use of a supervised survey delivered during class time replicated the response rates of similar study protocols [3,30].

## Limitations

Although the SASSI protocol possesses strengths, the weaknesses also need to be recognized here and addressed for future research. The EAT and SS required a great deal of information and were time-consuming. This magnifies the importance of the buy-in from the ICs and the features offered through Web-based administration (eg, stop-save and ease of administration), which aided completion. Additional limitations concerning the questions used in the EAT and SS need to be addressed. Despite both tools being comprehensive, certain questions and options offered may have resulted in responses that do not provide all the information needed. For example, in the EAT, capital and current investment were assessed using closed questions with the lowest option being "up to €25,000." This meant that universities that invested €25,000 were grouped with others who invested zero, with no way for the research team to tell the difference. In addition, in the SS, certain health-related behavior questions (eg, alcohol and smoking) assessed frequency but not the intensity of the behavior (eg, units of alcohol or cigarettes). The primary focus of SASSI was PA, which meant less importance was put on other questions, but this is still a limitation of this protocol. Suggestions for future research may be to provide additional options in the closed questions or offer open responses instead. Finally, the validity and reliability of some measures included have not been acquired for this population, with certain measures used in the SS shortened and adapted for practical reasons and to reduce the burden on students. Evidence suggests that lengthy measurement tools lead to greater amounts of missing data on individual questions, decreased variability in answers to grid-based questions, and shorter responses to open-ended questions [46]. Although the methodology allows for face validity of the measures used in the EAT and SS to be maximized through the use of known measures, a consultation phase and training days, there may be a need for future research to test their concurrent validity and reliability. A further weakness of the SASSI protocol was the cross-sectional design that meant the correlates of PA could be measured, but not the true determinants.

## Conclusions

Nevertheless, the authors believe that the SASSI protocol, with its whole country approach, is unique and can be used as a model for other nations hoping to investigate the PA and its related factors in university students. The use of one standardized comprehensive protocol to study such a topic would lead to the harmonization of data, allowing for the comparison of findings across countries. The information collected using the SASSI protocol may have potential uses such as providing information to relevant stakeholders and policy makers, providing strategic guidance for future policy and planning of university settings and university health interventions to enhance the health, well-being, and sustainability of students. The authors also hope that the tools developed in SASSI can be used in future longitudinal research, hoping to investigate the personal, behavioral, and environmental determinants of PA in university students.

## Authors' Contributions

JJM developed a plan for this protocol and acted as an institutional champion for the SS. CM, MHM, NM, and CBW developed the overall protocol for SASSI and acted as coauthors for this paper. NB acted as the research manager for SASSI.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Environmental audit tool.

[PDF File (Adobe PDF File), 810KB - resprot_v8i2e10823_app1.pdf ]

## Multimedia Appendix 2

Computation for each key performance indicator stemming from the environmental audit tool responses.

[PDF File (Adobe PDF File), 143KB - resprot_v8i2e10823_app2.pdf ]

## Multimedia Appendix 3

Student survey including the filtering process.

[PDF File (Adobe PDF File), 437KB - resprot_v8i2e10823_app3.pdf ]

## References

1.  Epton T, Norman P, Sheeran P, Harris PR, Webb TL, Ciravegna F, et al. A theory-based online health behavior intervention for new university students: study protocol. BMC Public Health 2013 Feb 5;13:107 [FREE Full text] [doi: 10.1186/1471-2458-13-107] [Medline: 23384237]

2.  Murray D, Adams T, Banks M, Bundesen C, Burns D, Clayton D, International Education Association of Australia (IEAA). In: Davis D, Mackintosh B, editors. Making a Difference: Australian International Education. Sydney: University of New South Wales Press; Apr 1, 2012:352.

3.  Haase A, Steptoe A, Sallis JF, Wardle J. Leisure-time physical activity in university students from 23 countries: associations with health beliefs, risk awareness, and national economic development. Prev Med 2004 Jul;39(1):182-190. [doi: 10.1016/j.ypmed.2004.01.028] [Medline: 15208001]

4.  Epton T, Norman P, Dadzie AS, Harris PR, Webb TL, Sheeran P, et al. A theory-based online health behaviour intervention for new university students (U@Uni): results from a randomised controlled trial. BMC Public Health 2014 Jun 5;14:563 [FREE Full text] [doi: 10.1186/1471-2458-14-563] [Medline: 24903620]

5.  Department of Health and Children, Health Service Executive. 2009. The National Guidelines on Physical Activity for Ireland URL: http://health.gov.ie/wp-content/uploads/2014/03/active_guidelines.pdf [accessed 2019-01-12] [WebCite Cache ID 75NSCZUOS]

6.  World Health Organization. Physical Activity - Fact Sheet URL: http://www.euro.who.int/en/health-topics/disease-prevention/physical-activity/data-and-statistics/physical-activity-fact-sheets [accessed 2018-04-19] [WebCite Cache ID 6ynXQK6d9]

7.  Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity--a systematic review of longitudinal studies. BMC Public Health 2013 Sep 8;13:813 [FREE Full text] [doi: 10.1186/1471-2458-13-813] [Medline: 24010994]

8.  Lee I, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012 Jul 21;380(9838):219-229 [FREE Full text] [doi: 10.1016/S0140-6736(12)61031-9] [Medline: 22818936]

9.  Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, Lancet Physical Activity Series Working Group. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 2012 Jul 21;380(9838):247-257. [doi: 10.1016/S0140-6736(12)60646-1] [Medline: 22818937]

10. Keating XD, Guan J, Piñero JC, Bridges DM. A meta-analysis of college students' physical activity behaviors. J Am Coll Health 2005;54(2):116-125. [doi: 10.3200/JACH.54.2.116-126] [Medline: 16255324]

11. Clemente FM, Nikolaidis PT, Martins FM, Mendes RS. Physical activity patterns in university students: do they follow the public health guidelines? PLoS One 2016 Mar 29;11(3):e0152516 [FREE Full text] [doi: 10.1371/journal.pone.0152516] [Medline: 27022993]

12. Bandura A. Social Foundations Of Thought And Action: A Social Cognitive Theory. New Jersey: Prentice Hall; Oct 11, 1985:640.

13. Rovniak LS, Anderson ES, Winett RA, Stephens RS. Social cognitive determinants of physical activity in young adults: a prospective structural equation analysis. Ann Behav Med 2002;24(2):149-156. [doi: 10.1207/S15324796ABM2402] [Medline: 12054320]

14. Farren GL, Zhang T, Martin SB, Thomas KT. Factors related to meeting physical activity guidelines in active college students: a social cognitive perspective. J Am Coll Health 2017;65(1):10-21. [doi: 10.1080/07448481.2016.1229320]

15. Sallis JF, Owen N, Fisher E. Ecological models of health behavior. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: Theory, Research, and Practice. California: Jossey-Bass; 2008:465-482.

16. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. Health Educ Q 1988;15(4):351-377. [Medline: 3068205]

17. Deliens T, Deforche B, De Bourdeaudhuij I, Clarys P. Determinants of physical activity and sedentary behaviour in university students: a qualitative study using focus group discussions. BMC Public Health 2015 Feb 28;15:201 [FREE Full text] [doi: 10.1186/s12889-015-1553-4] [Medline: 25881120]

18. Choi J, Lee M, Lee J, Kang D, Choi JY. Correlates associated with participation in physical activity among adults: a systematic review of reviews and update. BMC Public Health 2017 Apr 24;17(1):356 [FREE Full text] [doi: 10.1186/s12889-017-4255-2] [Medline: 28438146]

19. Reed JA, Phillips DA. Relationships between physical activity and the proximity of exercise facilities and home exercise equipment used by undergraduate university students. J Am Coll Health 2005;53(6):285-290. [doi: 10.3200/JACH.53.6.285-290] [Medline: 15900992]

20. Johnson LG. LSU Digital Commons, LSU Doctoral Dissertations. 2006. Physical activity behavior of university students: an ecological approach URL: https://digitalcommons.lsu.edu/gradschool_dissertations/1556/ [accessed 2018-04-19] [WebCite Cache ID 6ynXyGO51]

21. Leslie E, Sparling PB, Owen N. University campus settings and the promotion of physical activity in young adults: lessons from research in Australia and the USA. Health Educ 2001;101(3):116-125. [doi: 10.1108/09654280110387880]

22. Hope A, Dring C, Dring J. Drugs and Alcohol. 2005. College Lifestyle and Attitudinal National (CLAN) Survey URL: https://www.drugsandalcohol.ie/4327/1/2670-2853.pdf [accessed 2018-04-19] [WebCite Cache ID 6ynYKuGdv]

XSL•FO

RenderX

23.  Morgan K, McGee H, Watson D, Perry I, Barry M, Shelley E, et al. Dublin: Department of Health and Children. 2008 Jan 1. SLAN 2007: survey of lifestyle, attitudes & nutrition in Ireland: main report URL: https://epubs.rcsi.ie/cgi/viewcontent.cgi?article=1002&context=psycholrep [accessed 2018-04-19] [WebCite Cache ID 6ynYUzacu]

24.  Woods CB, Moyna N, Quinlan A, Tannehill D, Walsh J. School of Health and Human Performance, Dublin City University and The Irish Sports Council, Dublin, Ireland. 2010. The Children's Sport Participation and Physical Activity Study (CSPPA Study). Research Report No 1 URL: https://www.ucd.ie/t4cms/CCLSP_Study_Report1.pdf [accessed 2018-04-19] [WebCite Cache ID 6ynYgfzsj]

25.  Taylor J. Edinburgh Sport Scotland. 2003 Jan 1. An Audit of Sports Provision in the Higher Education Sector in Scotland URL: https://www.stir.ac.uk/research/hub/publication/709869 [accessed 2019-01-12] [WebCite Cache ID 75Na5HS1y]

26.  Lambley C. Sport England. 2004 Mar 15. Audit of sports provision in the higher education sector URL: https://www.sportengland.org/media/3435/higher-education-exec-summary-1.pdf [accessed 2018-04-19] [WebCite Cache ID 6ynZwDvhV]

27.  Higher Education Authority. 2014. Key facts and figures. Higher Education 2013/14 URL: http://hea.ie/assets/uploads/2017/06/Key-Facts-and-Figures-201314.pdf [accessed 2018-04-19] [WebCite Cache ID 6yna5ktkj]

28.  Department for Employment and Learning. 2014 Feb 13. Enrolments at UK higher education institutions: Northen Ireland analysis 2012/2013 URL: https://www.economy-ni.gov.uk/publications/enrolments-uk-higher-education-institutions-northern-ireland-analysis-2012-2013 [accessed 2019-01-12] [WebCite Cache ID 75NaS6a04]

29.  Kelly P, Fitzsimons C, Baker G. Should we reframe how we think about physical activity and sedentary behaviour measurement? Validity and reliability reconsidered. Int J Behav Nutr Phys Act 2016 Mar 1;13:32 [FREE Full text] [doi: 10.1186/s12966-016-0351-4] [Medline: 26931142]

30.  Patterson E, McGeough D, Cannon E, Hagströmer M, Bergman P, Kearney J, et al. Self-efficacy, stages of change and physical activity in Irish college students. J Public Health 2006 Apr;14(2):81-86. [doi: 10.1007/s10389-006-0028-6]

31.  Sport Northern Ireland. 2010. Adult Sport and Physical Activity Survey 2010. A Baseline Report URL: http://www.sportni.net/sportni/wp-content/uploads/2013/03/SAPASReport.pdf [accessed 2019-01-12] [WebCite Cache ID 75NaurTcx]

32.  Harmon D, Foubert O. Higher Education Authority. 2013. Eurostudent Survey V Report on the Social and Living Conditions of Higher Education Students in Ireland 2013 URL: https://www.ucd.ie/t4cms/Eurostudent%20Survey%20V%20Report.pdf [accessed 2018-04-19] [WebCite Cache ID 6ynaXH8E0]

33.  Sport England. 2012. Higher Education Sport Participation and Satisfaction Survey. National Report Year One URL: https://www.sportengland.org/media/4271/higher-education-sport-participation-and-satisfaction-national-year-one-report.pdf [accessed 2018-04-19] [WebCite Cache ID 6ynahR8Me]

34.  Colton D, Covert RW. Designing and Constructing Instruments for Social Research and Evaluation. San Francisco, CA: John Wiley & Sons; 2007:412.

35.  Murphy JJ, Murphy MH, MacDonncha C, Murphy N, Nevill AM, Woods CB. Validity and reliability of three self-report instruments for assessing attainment of physical activity guidelines in university students. Meas Phys Educ Exerc Sci 2017;21(3):134-141. [doi: 10.1080/1091367X.2017.1297711]

36.  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]

37.  Prochaska JJ, Sallis JF, Long B. A physical activity screening measure for use with adolescents in primary care. Arch Pediatr Adolesc Med 2001 May;155(5):554-559. [Medline: 11343497]

38.  Milton K, Bull FC, Bauman A. Reliability and validity testing of a single-item physical activity measure. Br J Sports Med 2011 Mar;45(3):203-208 [FREE Full text] [doi: 10.1136/bjsm.2009.068395] [Medline: 20484314]

39.  Taylor N, Lawton R, Conner M. Development and initial validation of the determinants of physical activity questionnaire. Int J Behav Nutr Phys Act 2013 Jun 11;10:74 [FREE Full text] [doi: 10.1186/1479-5868-10-74] [Medline: 23758912]

40.  European Commission. 2014 Mar. Special Eurobarometer 412: sport and physical activity; report URL: http://ec.europa.eu/commfrontoffice/publicopinion/archives/ebs/ebs_412_en.pdf [accessed 2019-04-19] [WebCite Cache ID 6ynarsxPD]

41.  Hardie Murphy M. Dublin City University. 2016. CSPPA Plus: a 5-year longitudinal study of children's sport and physical activity participation URL: http://doras.dcu.ie/21386/ [accessed 2018-04-19] [WebCite Cache ID 6ynb0I62l]

42.  Marshall AL, Miller YD, Burton NW, Brown WJ. Measuring total and domain-specific sitting: a study of reliability and validity. Med Sci Sports Exerc 2010 Jun;42(6):1094-1102. [doi: 10.1249/MSS.0b013e3181c5ec18] [Medline: 19997030]

43.  Ware JE, Snow KK, Kosinski M, Gandek B, New England Medical Center hospital. The Health Institute. SF-36 Health Survey: Manual and Interpretation Guide, The Health Institute. Boston: The Health Institute, New England Medical Center, 1993; 1993.

44.  Houghton F, Keane N, Murphy N, Houghton S, Dunne C. Tertiary level students and the Mental Health Index (MHI-5) in Ireland. Irish J Appl Soc Stud 2011 Jan 1;10(1):40-48. [doi: 10.21427/D75Q81]

45.  Murphy MH, Murphy N, MacDonncha C, Woods C, Byrne N, Ferguson K, et al. Student Sport Ireland. 2015. Student Activity and Sports Study Ireland (SASSI) URL: http://www.studentsport.ie/wp-content/uploads/2016/02/SASSI-Full-Report-Without-Appendices..pdf [accessed 2018-04-19] [WebCite Cache ID 6ynbNzr9F]

46.    Galesic M, Bosnjak M. Effects of questionnaire length on participation and indicators of response quality in a web survey. Public Opin Q 2009 Jan;73(2):349-360. [doi: 10.1093/poq/nfp031]

## Abbreviations

**DPAQ:** Determinants of Physical Activity Questionnaire
**EAT:** environmental audit tool
**IC:** institutional champion
**ID:** identification
**KPI:** key performance indicator
**PA:** physical activity
**SASSI:** Student Activity and Sport Study Ireland
**SS:** student survey
**SSI:** Student Sport Ireland

# Accessibility of Primary, Specialist, and Allied Health Services for Aboriginal People Living in Rural and Remote Communities: Protocol for a Mixed-Methods Study

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## Abstract

**Background:** Primary, specialist, and allied health services can assist in providing equitable access in rural and remote areas, where higher proportions of Aboriginal and Torres Strait Islander people (Aboriginal Australians) reside, to overcome the high rates of chronic diseases experienced by this population group. Little is currently known about the location and frequency of services and the extent to which providers believe delivery is occurring in a sustained and coordinated manner.

**Objective:** The objective of this study will be to determine the availability, accessibility, and level of coordination of a range of community-based health care services to Aboriginal people and identify potential barriers in accessing health care services from the perspectives of the health service providers.

**Methods:** This mixed-methods study will take place in 3 deidentified communities in New South Wales selected for their high population of Aboriginal people and geographical representation of location type (coastal, rural, and border). The study is designed and will be conducted in collaboration with the communities, Aboriginal Community Controlled Health Services (ACCHSs), and other local health services. Data collection will involve face-to-face and telephone interviews with participants who are health and community professionals and stakeholders. Participants will be recruited through snowball sampling and will answer structured, quantitative questions about the availability and accessibility of primary health care, specialist medical and allied health services and qualitative questions about accessing services. Quantitative data analysis will determine the frequency and accessibility of specific services across each community. Thematic and content analysis will identify issues relating to availability, accessibility, and coordination arising from the qualitative data. We will then combine the quantitative and qualitative data using a health ecosystems approach.

**Results:** We identified 28 stakeholder participants across the ACCHSs for recruitment through snowball sampling (coastal, n=4; rural, n=12; and border, n=12) for data collection. The project was funded in 2017, and enrolment was completed in 2017. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2019.

**Conclusions:** The study will give an indication of the scope and level of coordination of primary, specialist, and allied health services in rural communities with high Aboriginal populations from the perspectives of service providers from those communities. Identification of factors affecting the availability, accessibility, and coordination of services can assist ways of developing and implementing culturally sensitive service delivery. These findings could inform recommendations for the provision of health services for Aboriginal people in rural and remote settings. The study will also contribute to the broader literature of rural and remote health service provision.

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## Introduction

Access to coordinated and timely specialist care improves health outcomes for people with complex health needs [1]. During 2010-2012, the estimated life expectancy at birth for Aboriginal and Torres Strait Islander Australians (hereafter Aboriginal Australians) was 10 years lower than that for non-Aboriginal Australians [2]. Much of this gap in life expectancy between Aboriginal Australians and non-Aboriginal Australians has been attributed to chronic diseases [3]. The rates of these chronic diseases are considerably higher among Aboriginal people than among the overall Australian population [4]. In 2008, a 25-year political commitment called Closing the Gap was made through the establishment of seven targets across health, education, and employment, yet only modest progress has been achieved over almost a decade [5].

Approximately one-third of the Australian population lives outside the eight major cities, roughly 7.7 million people [6]. However, a significant disparity between the decentralization of the population and health expenditure exists both between urban versus rural and regional and remote areas [7] as well as among rural or regional and remote comparative areas. Nationally, age-standardized services for very remote areas were funded at less than a third of the amount received by major cities [8]. This may lead to inequity in both the funding and provision of health services in these regions. The state of New South Wales (NSW) is home to the largest proportion of Australia's Aboriginal population, 65% of which live outside metropolitan areas compared with only 25% of the non-Aboriginal population [9]. Large tertiary medical centers located in metropolitan areas can be accessed by the entire population, yet time and cost barriers in traveling long distances to facilities can be prohibitive, particularly for socioeconomically disadvantaged groups such as Aboriginal Australians.

Tackling chronic diseases requires a multidisciplinary approach [10], with regular, appropriate consultation, treatment, and support. Various policy initiatives have been developed at the national, state, and local level to respond to this situation. At the national level, the mainstream strategy outlines the need to manage chronic diseases among Aboriginal Australians and indicates that access to appropriate services is vital for reducing the burden of disease [11]. Providing such services will not only reduce the burden of chronic diseases to communities and the country at large but also impact the quality and longevity of life for Aboriginal Australians significantly [5]. The implementation of the most recent, long-term national Aboriginal health plan focuses on improving the health system through more comprehensive, culturally competent, and effective services, including investing in increased capability of Aboriginal Community Controlled Health Services (ACCHSs) to meet identified needs [12]. Ensuring that services are adequately resourced is vital to ensuring this outcome is achieved [13,14].

The unique social and cultural needs of Aboriginal Australians should be carefully considered in the provision of care to ensure culturally competent service delivery [15]. The National Aboriginal Community Controlled Health Organization, the Aboriginal Health and Medical Research Council (AHMRC), and rural ACCHSs have led to significant improvements in the delivery of health care to Aboriginal Australians [16,17]. However, the capacity of ACCHSs are limited, and most health care services are provided to Aboriginal people through mainstream health care services [15]. The coordination of services across multiple agencies and health problems is challenging. An ecosystems approach provides a way to think about health issues as a whole through a system lens, enabling integrated responses across and between health services and health issues. A health ecosystem approach brings key stakeholders together to form partnerships and facilitates engagement between all relevant sectors necessary for connected health care to occur [18,19]. The approach has been used to help conceptualize and understand health in its wider environmental or ecosystem context and provide innovation in health care [19,20]. Determining the location and frequency of current health care services over a geographical jurisdiction allows for the identification of targeted areas for coordinated future service provision to create a fairer spread of care across the population.

The primary aim of this study is to determine the availability and accessibility of primary health care, specialist medical, and allied health services to Aboriginal people living in three rural or remote towns in NSW and their current level of coordination from the perspectives of service providers in those communities.

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## *Methods*

### Study Design

#### *Study Approach*

Our study design will utilize a mixed-methods approach to give a broader, more comprehensive perspective to answer the aims of the study and combine the strengths of quantitative and qualitative approaches. We will use both inductive and deductive approaches, using initial deductive reasoning driven by the examination of the aims of the study in combination with generating findings that emerge from observations from the data. The study will take place in 3 communities (coastal, remote, and border) across NSW with higher than average populations of Aboriginal people [9]. These three communities have been selected based on their locations being representative of centers with varying access to metropolitan health services and each having a strong history of community-driven health service development. The investigators have existing, established relationships with the three communities, built up over several years of collaborative working and co-designed research. The coastal, remote, and border communities have populations of 14,000 (17% Aboriginal), 1400 (65% Aboriginal), and 500 (63% Aboriginal) people, respectively [6,9].

We will conduct the study in collaboration with ACCHSs and other service providers including hospitals, general practice clinics, pharmacies, and community health centers. Stakeholder participants will be staff recruited from local health districts and primary health networks, ACCHSs, pharmacies, early childhood centers, general practices, Aboriginal working parties, schools, local councils, and the private health sector. By interviewing representatives from multiple service providers in each community, we will be able to triangulate the data to ensure that we capture a comprehensive picture of service providers' perspectives.

#### *Phase 1: Community Engagement and Recruitment*

Figure 1 presents a flowchart of the study phases. In Phase 1, the researchers approached ACCHS stakeholders in the three selected locations to participate in the study. We gave these stakeholders the opportunity to join the research team and contribute to the development and implementation of the research design and data collection tools. We have established an independent study advisory group to oversee the study and its governance [21]. The advisory group comprises both Aboriginal and non-Aboriginal professionals and community members who have knowledge and expertise relating to at least one of the three communities. This group can enhance the reflexivity of the research process by guiding the researchers during each of the three phases. Each organization involved in the study was asked to nominate individual participants who meet the study inclusion criteria of having existing relationships within the communities and knowledge of and access to information regarding the provision of services to these communities.

While we selected the three communities for the study based on their demographic characteristics and their established relationships with the researchers, a snowball sampling recruitment process will be used to recruit individual participants. We asked partner ACCHSs to provide information on all relevant service providers in their community for recruitment. Subsequently, the research team contacted each of these organizations to invite them to participate in the study. Where consent was granted by the organization to approach their staff members to participate in the study, the organization subsequently introduced the study to their staff and facilitated recruitment by providing contact details of potential participants. While snowball sampling does not provide a known sampling population size, it gives a more effective means of accessing vulnerable and isolated population groups, such as rural populations and professionals (including those who identify as Aboriginal) working with Aboriginal communities, for mixed-methods research [22].

#### *Phase 2: Data Collection*

We will deidentify each location to ensure confidentiality and privacy for the participants, which may facilitate more honest and candid responses, and to protect the privacy of the communities. All participants will go through an informed consent process and sign consent forms prior to data collection. We will collect the data over a 2-week period in each community using both face-to-face and telephone interviews. Each community supported the undertaking of data collection in this timeframe and considered it to be appropriate for answering the aims of the study and that it would not place an undue burden on the community. We will invite the participants to undertake a structured, quantitative interview about the primary health care, specialist medical and allied health services in their community and give them the opportunity to provide longer, open-ended (qualitative) answers for each question. The quantitative component will allow the participants to indicate the specific services (primary, specialist, and allied health services, eg, podiatry, renal nurse, or sonography) available in these communities, by providing a response of "yes," "no," or "unsure." Participants will be asked to identify where (through giving an open-ended response, eg, ACCHS or local hospital) these services are offered. We will also ask the participants about the frequency of service delivery, measured through a 9-point scale from "always" to "never" (including the responses "weekly," "monthly," and "annually"). The qualitative component will collect information about the participant's experiences, beliefs, and expectations about accessing health services in their community. Participants will also be asked open-ended questions about the barriers and enablers to health care services for Aboriginal people in their respective locations.

One of the authors and a project manager, who are experienced in conducting interviews for qualitative research in Aboriginal communities, will conduct the interviews. All interviews will be audio recorded and transcribed by a transcription service. Quantitative data will be collected using REDCap (REDCap Software), a secure electronic data capture tool hosted at The George Institute for Global Health [23].

**Figure 1.** Flow chart of the study.
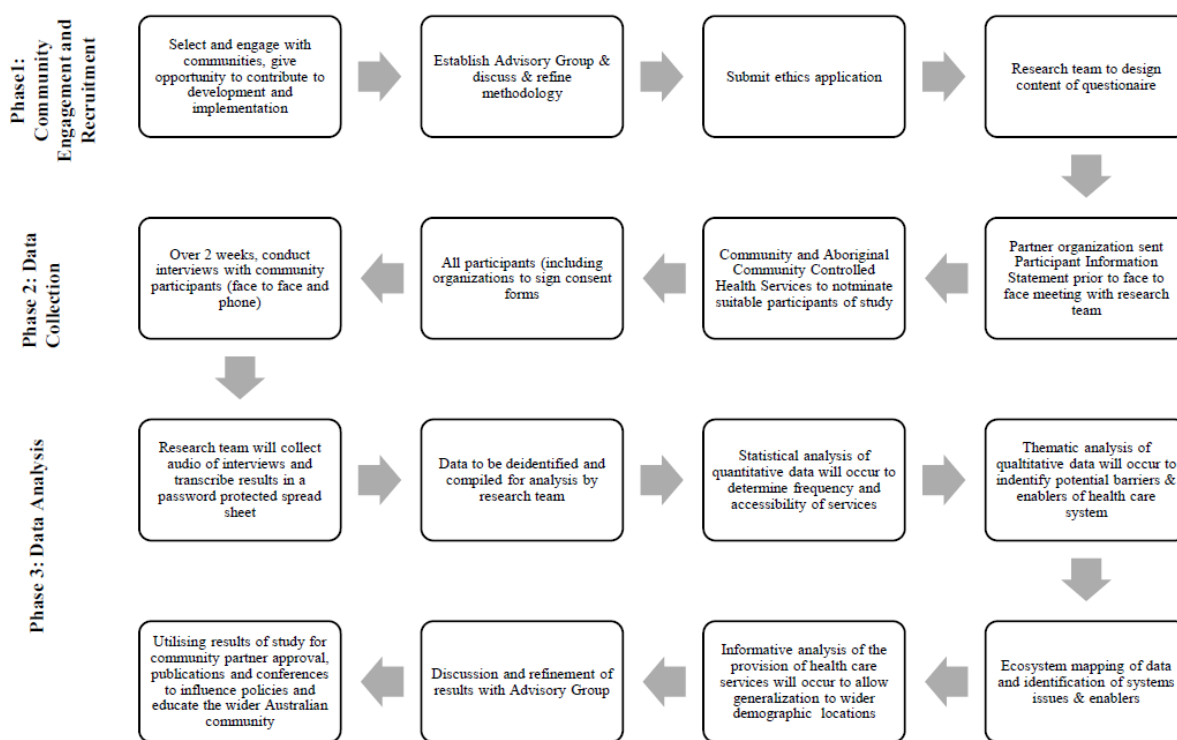


## Phase 3: Data Analysis

We will analyze the data to provide an informative analysis of service providers' perceptions of the provision of health care services to these communities. A research student who was not involved in the data collection will conduct the initial data analyses, with subsequent data interpretation by the study investigators and the advisory group.

Descriptive statistical analysis will be used for all quantitative data to determine the frequency of specific services, across the three communities and combined, to determine their availability. We anticipate that data on services will be defined and categorized by service type (eg, primary, specialist, or allied), service delivery type (eg, nurse, podiatrist, or sonographer), and delivery organization (eg, public or private). In each community, we will compare participant reports of the type and frequency of health services available. We will tabulate services readily identified by all participants as well as those where there is uncertainty or dispute. Similarly, the reported frequency of services will be compared across participants in each community to determine knowledge about services available at a community level.

All qualitative data will undergo thematic and content analysis using both inductive and deductive approaches [24]. This analysis will include the identification of any potential barriers or enablers or broader emerging themes relating to the provision of and access to health services for Aboriginal people. The qualitative and quantitative data will be visually combined and mapped using a health ecosystem approach [18]. This will provide an ecological framework [25] to analyze how the various parts of the health care systems in this study, such as perceptions of coordination, funding, and design, interact. A

member-checking [26] process will subsequently be undertaken through consultation with the advisory group to examine the validity of the findings and ensure reflexivity has occurred across the study.

Quantitative analyses will be performed using SPSS 19.0 (IBM Corp) and qualitative analyses using NVivo 10 (QSR International).

### Ethics and Governance

The AHMRC of NSW gave ethical approval for this study (1173/16). A requirement of ethical approval was the establishment of an advisory group to advise the research team. The advisory committee comprised representatives from ACCHSs and mainstream (including rural-specific) health organizations. This committee met twice at the development and start-up of the study and will meet again once data collection is complete. The study addresses the AHMRC and National Health and Medical Research Council principles and guidelines for Aboriginal and Torres Strait Islander research [21]. We will share the findings of this study with the three Aboriginal communities and their ACCHSs, the advisory group supporting the study, and the AHMRC as well as in peer-reviewed publications and at conferences.

## Results

We identified 28 stakeholder participants across the ACCHSs for recruitment through snowball sampling (n=4 coastal, n=12 rural, and n=12 border) in Phase 1 for data collection in Phase 2. The project was funded in 2017, and enrolment was completed in 2017. Data analysis is currently underway, and

the first results are expected to be submitted for publication in 2019.

## Discussion

This study will use quantitative and qualitative data to provide unique insight into the lived experiences of service providers in 3 rural communities with high Aboriginal populations in NSW. Further, this study provides insights into the availability and frequency of primary, specialist, and allied health services in those communities. Combining the quantitative and qualitative data will provide a comprehensive way to identify issues and enablers from a systems perspective and make explicit how all the parts of the health system might interact, support, and influence outcomes [25]. The results of this study may identify barriers and enablers of health services in rural and remote communities. This information will help inform recommendations about how to improve health care services to Aboriginal people. Subsequently, this will contribute to easing the burden of chronic diseases for people in these communities specifically and to other nonmetropolitan jurisdictions across and beyond Australia.

The provision of health care services to Australians is a multifaceted undertaking that is often influenced by a range of factors, particularly social, cultural, political, and geographical factors. When this provision exists outside major cities, the challenges and expenses faced by health care providers are significantly increased [8]. The provision of coordinated primary, specialist, and allied health services may help overcome some of the barriers relating to access to services and in turn improve health outcomes among Aboriginal people living in rural and remote areas [27]. These barriers include geographic remoteness, socioeconomic factors, cultural competence of services, and specialist availability [28] in addition to the general limitations of public and primary health care systems [29], such as waiting times and hospital service structure.

The strengths of this study are its collaborative development and delivery, with the key stakeholders involved in health service delivery to Aboriginal Australians including community-controlled health services. Another strength is the application of the novel ecosystems approach that enables a broader lens on the interactions between individuals, issues, and system [19,20]. Limitations may include bias relating to the representativeness of the participant sample and the validity of self-report responses as well as the interpretation of qualitative data by the researchers. We will attempt to ameliorate any biases through member-checking of the results and undertaking snowball sampling until data saturation is reached. The study is the first of its kind to comprehensively map the primary, specialist and allied health activities in identified geographical areas of need for a high priority population group from the perspectives of service providers. Ultimately, this study will provide insights into how to better provide health care services for Aboriginal people in rural and remote communities. The findings will also contribute to the broader literature of rural and remote health service provision [30] and provide recommendations for future practice, which if adopted could lead to improvement of population health services.

### Conflicts of Interest

None declared.

### References

1. Gruen RL, Weeramanthri TS, Knight SE, Bailie RS. Specialist outreach clinics in primary care and rural hospital settings. Cochrane Database Syst Rev 2004(1):CD003798. [doi: 10.1002/14651858.CD003798.pub2] [Medline: 14974038]
2. Australian Institute of Health and Welfare. 2014 Sep 05. Mortality and life expectancy of Indigenous Australians 2008 to 2012 URL: https://www.aihw.gov.au/reports/indigenous-australians/mortality-life-expectancy-2008-2012/contents/table-of-contents [accessed 2018-12-11] [WebCite Cache ID 74bMd5lnm]
3. Australian Institute of Health and Welfare. 2015. The health and welfare of Australia's Aboriginal and Torres Strait Islander peoples URL: https://www.aihw.gov.au/reports-data/health-welfare-overview/indigenous-health-welfare/overview [accessed 2018-12-11] [WebCite Cache ID 74bMlNhIv]
4. Australian Bureau of Statistics (ABS). 2012. Australian Aboriginal and Torres Strait Islander Health Survey: First Results, Australia, 2012-13 URL: http://www.abs.gov.au/ausstats/abs@.nsf/mf/4727.0.55.001 [accessed 2018-12-11] [WebCite Cache ID 74bNGLwdr]
5. Department of the Prime Minister and Cabinet. Closing the Gap: Prime Minister's Report 2018. 2018. URL: https://closingthegap.pmc.gov.au/sites/default/files/ctg-report-2018.pdf [accessed 2018-12-11] [WebCite Cache ID 74bNResQc]
6. Australian Bureau of Statistics. Canberra, ACT: Australian Government; 2016. Census of Population and Housing: Understanding the Census and Census Data, Australia, 2016 URL: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2900.02016?OpenDocument [accessed 2018-12-12] [WebCite Cache ID 74bOB9bHZ]

7.      Australian Institute of Health and Welfare. 2004. Rural, regional and remote health: a guide to remoteness classifications URL: https://www.aihw.gov.au/reports/rural-remote-australians/guide-to-remoteness-classifications/contents/table-of-contents [accessed 2018-12-12] [WebCite Cache ID 74bP8lJU7]

8.      Australian Institute of Health and Welfare. 2011. Australian health expenditure by remoteness: a comparison of remote, regional and city health expenditure URL: https://www.aihw.gov.au/reports/health-welfare-expenditure/australian-health-expenditure-by-remoteness-a-com/contents/table-of-contents [accessed 2018-12-12] [WebCite Cache ID 74bP5KNML]

9.      Australian Bureau of Statistics. 2012. Census of Population and Housing: Characteristics of Aboriginal and Torres Strait Islander Australians, 2011 URL: http://www.abs.gov.au/ausstats/abs@.nsf/lookup/2076.0main+features1102011 [accessed 2018-12-12] [WebCite Cache ID 74bP24wZ0]

10.     Bousquet J, Anto JM, Sterk PJ, Adcock IM, Chung KF, Roca J, et al. Systems medicine and integrated care to combat chronic noncommunicable diseases. Genome Med 2011 Jul 06;3(7):43 [FREE Full text] [doi: 10.1186/gm259] [Medline: 21745417]

11.     Australian Health Ministers' Advisory Council. Department of Health. Canberra, ACT: Australian Government; 2017. National Strategic Framework for Chronic Conditions URL: https://www.health.gov.au/internet/main/publishing.nsf/Content/A0F1B6D61796CF3DCA257E4D001AD4C4/$File/National%20Strategic%20Framework%20for%20Chronic%20Conditions.pdf [accessed 2018-12-12] [WebCite Cache ID 74bPO80AY]

12.     The Department of Health. Canberra, ACT: Australian Government; 2018 Jul. National Aboriginal and Torres Strait Islander Health Plan 2013-2023 URL: http://www.health.gov.au/natsihp [accessed 2018-12-12] [WebCite Cache ID 74bPFBCnD]

13.     Panaretto KS, Wenitong M, Button S, Ring IT. Aboriginal community controlled health services: leading the way in primary care. Med J Aust 2014 Jun 16;200(11):649-652. [Medline: 24938346]

14.     Australian Institute of Health and Welfare. 2010. Expenditure on health for Aboriginal and Torres Strait Islander people 2010–11: An analysis by remoteness and disease. Health and welfare expenditure series no. 49. Cat. no. HWE 58 URL: https://www.aihw.gov.au/getmedia/a1d7ec9d-7735-4293-8a32-956c20026aa2/15080.pdf.aspx?inline=true [accessed 2018-12-12] [WebCite Cache ID 74bOtj4GS]

15.     Gwynne K, Jeffries T, Lincoln M. Improving the efficacy of healthcare services for Aboriginal Australians. Aust Health Rev 2018 Jan 16. [doi: 10.1071/AH17142] [Medline: 29335090]

16.     Couzos S. ResearchOnline@JCU. Braddon, ACT: National Aboriginal Community Controlled Health Organisation; 2009. Towards a national primary health care strategy: fulfilling Aboriginal peoples aspirations to close the gap URL: https://researchonline.jcu.edu.au/35080/ [accessed 2018-12-12] [WebCite Cache ID 74bOpKuPT]

17.     Campbell MA, Hunt J, Scrimgeour DJ, Davey M, Jones V. Contribution of Aboriginal Community-Controlled Health Services to improving Aboriginal health: an evidence review. Aust Health Rev 2018 Apr;42(2):218-226. [doi: 10.1071/AH16149] [Medline: 28263705]

18.     Serbanati LD, Ricci FL, Mercurio G, Vasilateanu A. Steps towards a digital health ecosystem. J Biomed Inform 2011 Aug;44(4):621-636 [FREE Full text] [doi: 10.1016/j.jbi.2011.02.011] [Medline: 21362497]

19.     European Connected Health Alliance. ECH Alliance Ecosystems URL: https://echalliance.site-ym.com/?page=EcosystemsOverall [WebCite Cache ID 73gj19mPG]

20.     Asakura T, Mallee H, Tomokawa S, Moji K, Kobayashi J. The ecosystem approach to health is a promising strategy in international development: lessons from Japan and Laos. Global Health 2015 Feb 16;11:3 [FREE Full text] [doi: 10.1186/s12992-015-0093-0] [Medline: 25880569]

21.     National Health and Medical Research Council. Canberra, ACT: NHMRC; 2009. Road map II: A strategic framework for improving the health of Aboriginal and Torres Strait Islander people through research URL: https://nhmrc.gov.au/about-us/publications/road-map-ii-strategic-framework-improving-health-aboriginal-and-torres-strait-islander-people-through-research [accessed 2018-12-12] [WebCite Cache ID 74bOf3cte]

22.     Sadler GR, Lee H, Lim RS, Fullerton J. Recruitment of hard-to-reach population subgroups via adaptations of the snowball sampling strategy. Nurs Health Sci 2010 Sep 01;12(3):369-374 [FREE Full text] [doi: 10.1111/j.1442-2018.2010.00541.x] [Medline: 20727089]

23.     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]

24.     Thomas DR. A General Inductive Approach for Analyzing Qualitative Evaluation Data. American Journal of Evaluation 2006;27(2):237-246.

25.     Nurse J, Edmondson-Jones P. A framework for the delivery of public health: an ecological approach. J Epidemiol Community Health 2007 Jun;61(6):555-558 [FREE Full text] [doi: 10.1136/jech.2005.039073] [Medline: 17496266]

26.     Guba EG, Lincoln Y. Naturalistic Inquiry. Newbery Park: SAGE Publications; 1985.

27.     Schmidt B, Wenitong M, Esterman A, Hoy W, Segal L, Taylor S, et al. Getting better at chronic care in remote communities: study protocol for a pragmatic cluster randomised controlled of community based management. BMC Public Health 2012 Nov 21;12:1017 [FREE Full text] [doi: 10.1186/1471-2458-12-1017] [Medline: 23170964]

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28. Brundisini F, Giacomini M, DeJean D, Vanstone M, Winsor S, Smith A. Chronic disease patients' experiences with accessing health care in rural and remote areas: a systematic review and qualitative meta-synthesis. Ont Health Technol Assess Ser 2013;13(15):1-33 [FREE Full text] [Medline: 24228078]

29. Gravel K, Légaré F, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: a systematic review of health professionals' perceptions. Implement Sci 2006 Aug 09;1:16 [FREE Full text] [doi: 10.1186/1748-5908-1-16] [Medline: 16899124]

30. Tyack Z, Frakes K, Cornwell P, Kuys SS, Barnett AG, McPhail SM. The health outcomes and costs of people attending an interdisciplinary chronic disease service in regional Australia: protocol for a longitudinal cohort investigation. BMC Health Serv Res 2013 Oct 11;13:410 [FREE Full text] [doi: 10.1186/1472-6963-13-410] [Medline: 24119303]

## Abbreviations

**ACCHS:** Aboriginal Community Controlled Health Service
**AHMRC:** Aboriginal Health and Medical Research Council
**NSW:** New South Wales

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Original Paper

# System Setup to Deliver Air Impact Forces to a Sheep Limb: Preparation for Model Development of Blast-Related Heterotopic Ossification

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## Abstract

**Background:** Heterotopic ossification (HO) is a significant complication for wounded warriors with traumatic limb loss. Although this pathologic condition negatively impacts the general population, ectopic bone has been observed with higher frequency for service members injured in Iraq and Afghanistan due to blast injuries. Several factors, including a traumatic insult, bioburden, tourniquet and wound vacuum usage, and bone fractures or fragments have been associated with increased HO for service members. A large combat-relevant animal model is needed to further understand ectopic bone etiology and develop new pragmatic solutions for reducing HO formation and recurrence.

**Objective:** This study outlines the optimization of a blast system that may be used to simulate combat-relevant trauma for HO and replicate percussion blast experienced in theater.

**Methods:** We tested the repeatability and reproducibility of an air impact device (AID) at various pressure settings and compared it with a model of blunt force trauma for HO induction. Furthermore, we assessed the ability of the higher-power air delivery system to injure host tissue, displace metal particulate, and disperse bone chips in cadaveric sheep limbs.

**Results:** Data demonstrated that the air delivery setup generated battlefield-relevant blast forces. When the AID was charged to 40, 80, and 100 psi, the outputs were 229 (SD 13) N, 778 (SD 50) N, and 1085 (SD 114) N, respectively, compared with the blunt force model which proposed only 168 (SD 11) N. For the 100-psi AID setup, the force equaled a 5.8-kg charge weight of trinitrotoluene at a standoff distance of approximately 2.62 m, which would replicate a dismounted improvised explosive device blast in theater. Dispersion data showed that the delivery system would have the ability to cause host tissue trauma and effectively disperse metal particulate and host bone chips in local musculature compared with the standard blunt force model (13 mm vs 2 mm).

**Conclusions:** Our data showed that a high-pressure AID was repeatable or reproducible, had the ability to function as a simulated battlefield blast that can model military HO scenarios, and will allow for factors including blast trauma to translate toward a large animal model.

## Introduction

Heterotopic ossification (HO) refers to ectopic bone formation, typically in residual limbs or periarticular regions following trauma, surgery, or injury [1]. This pathological process manifests outside the skeleton [2] and comprises a hybrid of cortical and cancellous bone [3]. HO is induced by damage to soft tissue and inflammation [4,5] and has been most frequently observed after combat-related trauma to service members with blast injuries [6].

Reviews of orthopedic injuries from Operation Iraqi Freedom and Operation Enduring Freedom have reported that approximately 70% of war wounds involved the musculoskeletal system [7], largely in part from the use of improvised explosive devices (IEDs) and rocket-propelled grenades. Given the intense nature of blast injuries, which require rapid tourniquet use, debridement, and surgical intervention, HO has been reported to occur in approximately 63%-65% of wounded service members with limb loss or major extremity injuries [8-10]. Reports of recent Operation Iraqi Freedom and Operation Enduring Freedom combat-related amputees with known HO have indicated that approximately 20%-40% of affected patients required surgery to excise their bony masses [10-13]. Symptomatic HO may delay rehabilitation regimens, as ectopic bone resection often requires modifications to prosthetic limb componentry and socket size [11,14].

The causative factors of HO development, especially in the case of blast injuries, are not well known. However, it has been hypothesized that contributing factors may include the following: (1) the blast, which generates extensive trauma and potential concomitant brain injury [15]; (2) tourniquet use, which alters local pH and creates a hypoxic environment [16]; (3) the presence of bacteria and biofilms [17]; (4) negative pressure wound therapy that may be used postinjury [9]; and (5) fractured bone, which may be dispersed into the musculature (clinical observations, unpublished data). To identify the various contributing factors for ectopic bone and to provide new evidence-based medicine that may inform clinical guidelines, animal models are currently being developed. However, as noted by Forsberg et al in *Burned to the Bone*, "one of the challenges preventing advances in this field has been the lack of robust animal models for HO" [18].

While rats and rabbits are the most commonly used animals for HO research, their bone growth rates are 600% and 40% higher, respectively, than those of humans [19,20]. This may limit the translatability of this work because HO has been documented to be more metabolically active than nonpathological osseous tissue [1,3,21-24]. Small animal models also cannot accurately reflect combat casualty care because variables such as serial debridement and negative pressure wound therapy must be omitted [25]. The most practical model, and one that is highly understudied, is the ovine model, which has almost identical mineral apposition rates [26] and bone ingrowth into intramedullary implants [27] compared with that of humans. Despite this evidence, only a single study by Walton et al [28] has evaluated HO development in an ovine model; the study results indicated that ectopic bone occurred only 17% of the time. However, Walton et al used blunt force rather than blast trauma, which does not replicate combat conditions, and histological data confirmed that HO formation did not occur. In an effort to address these limitations, preparations are underway to expand HO data collection into a large animal model that includes use of a simulated blast scenario. The first step in this process was to develop a system that could deliver a repeatable and reproducible high-pressure blast. This study outlines the optimization of a simulated blast system that may be translated to a large animal ovine model to assess the development of HO in blast-related scenarios.

## Methods

### Incident Pressures and Air Impact Device Selection

IEDs are often fabricated from 120-mm artillery rounds and contain approximately 5.8 kg trinitrotoluene (TNT) or its equivalent [29,30]. At a standoff distance of 5.5 m (one of the most commonly used measures for blast assessment), this yields an incident pressure of 110.9 kilopascal (kPa) based on the Kingery-Bulmash blast parameter calculator, which was used for calculating estimated incident pressures in this study [31]. Previous military blast injury models in rodents have utilized pressurized gas systems to mimic IED repercussions [29]. It has been shown that these system types result in incident pressures and other blast parameters, including waveform shape and impulse to detonation, that correlate with IED or other blast outputs [29,32].

In order to more closely simulate an IED or rocket-propelled grenade blast that may occur in theater, and to appropriately translate this to a large animal model, we consulted a special effects pyrotechnics expert who was familiar with the creation of controllable blasts using pressurized gas or air. We identified Martin Tornado Air Cannon with a 4-inch valve (Model BB4-12-28, Martin Engineering, Neponset, IL) as a viable option for simulating a blast. Based on technical sheets, the Tornado system provides rapid depressurization of air within 0.1 seconds [33]. Incident pressures were estimated to range between approximately 174 and 588 kPa (ie, 40-100 psi), consistent with what may be experienced in the range of a battlefield blast setting based on parameters from the Kingery-Bulmash blast parameter calculator [29-31]. The Martin Tornado Air Cannon and its setup, which have been termed the air impact device (AID), were assembled based on manufacturer's recommendations and assessed initially for force output.

## Force Plate Testing

Animal limbs and carcasses for this and subsequent analyses were obtained from local butcher shops and from separate Institutional Animal Care and Use Committee-approved studies. To determine force outputs of the AID, NeuLog force plates (Amazon, Seattle, WA, Model Number NUL225) and accompanying sensors were purchased. The AID was secured to a metal cart using industrial strength tie-downs and situated such that the air release opening was directly over a force plate (Figure 1). Tie-down straps were used to secure the device. The NeuLog force plate was adjustable in height and tested at a distance of 2 inches from the AID air release opening to collect force plate data. The force plate was bolted to a custom-made aluminum stand, and tie-downs were used to secure the structure during AID discharge. The force plate was positioned 2 inches from the AID, and data was collected via universal serial bus to a general use Apple MacBook Pro on which NeuLog's publicly available software had been downloaded. The AID was pressurized using a DeWalt fast charge air compressor and tested at pressures of 40, 80, and 100 psi. These settings were assessed experimentally to, in future, determine their ability to cause localized trauma but be within a factor of safety to not cause ovine fractures at this stage of the model. Once pressurized, the AID was discharged. Data were collected with 10 repeat measurements at each psi.

In order to establish baseline force outputs for ovine-induced trauma, we also reproduced the method performed by Walton et al [28], which required a weight of approximately 3.5 kg (head of a sledge hammer) to be dropped from a height of 1 meter. The force of this impact was recorded 10 times for comparison against the AID outcomes. Once force data were collected, testing of the AID system was advanced to *ex vivo* cadaveric sheep limb analysis.

## Cadaveric Limb Testing

The AID blast was evaluated on 8 ovine carcass limbs and 4 whole sheep cadavers to characterize the effect of the air blast, to ensure that the force would not generate a localized fracture, and to optimize the surgical model. To ensure that the limb was in the same position between each blast, a support frame was custom welded and a brace secured in the midregion of the limb to prevent flexion and fracture. This was done for disarticulated limbs (Figure 2), as well as whole carcasses (Figure 3). The AID was placed 2 inches from the cadaveric limb (Figure 2) to be consistent with the force plate testing. Bolts were used to attach the limb to the metal frame. Note the metal brace on the back of the limb provided support to the femur and prevented breakage or severe ligament damage from occurring (Figure 2). Radiographs were taken following AID blasts to verify postprocedure bone integrity.

## Mock Shrapnel Displacement Testing

IED blast injuries often afflict wounded warriors with shrapnel in the distal limbs. To model this scenario and assess the ability of the AID blast procedure to disperse simulated shrapnel particles into the musculature of cadaveric sheep limbs, a whole carcass was obtained. An incision was made in the midshaft region of a femur. Deep tissue was dissected longitudinally until bone was exposed. A 2.5-g mixture of Cobalt-Chromium (CoCr) beads having a diameter of approximately 0.5 mm was suspended in 5 mL saline solution. The slurry was pipetted over the bone surface. A radiograph was obtained to determine the initial distribution of the CoCr beads (Figure 4).

**Figure 1.** Setup of the air impact device for force plate analysis.
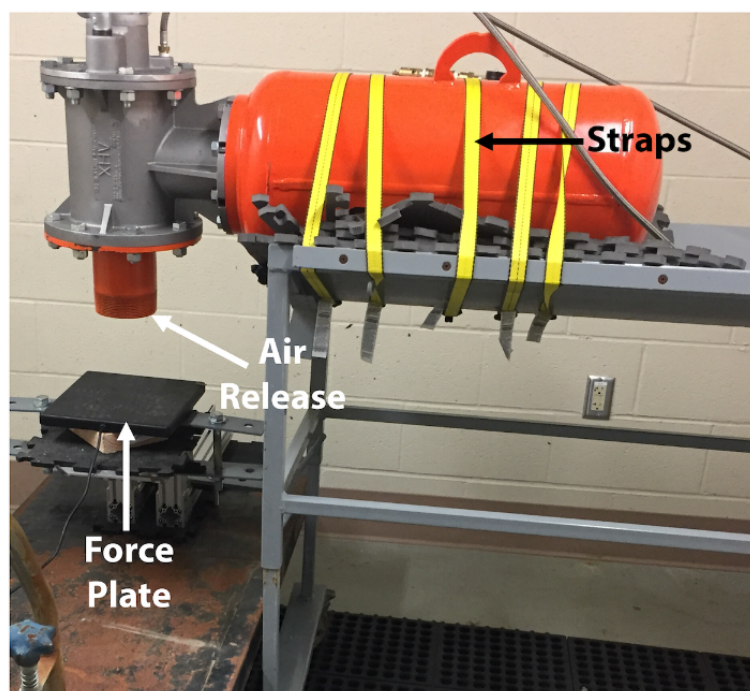
**Figure 2.** Representative image of a cadaveric sheep limb attached to a metal support frame for air impact device (AID) testing.
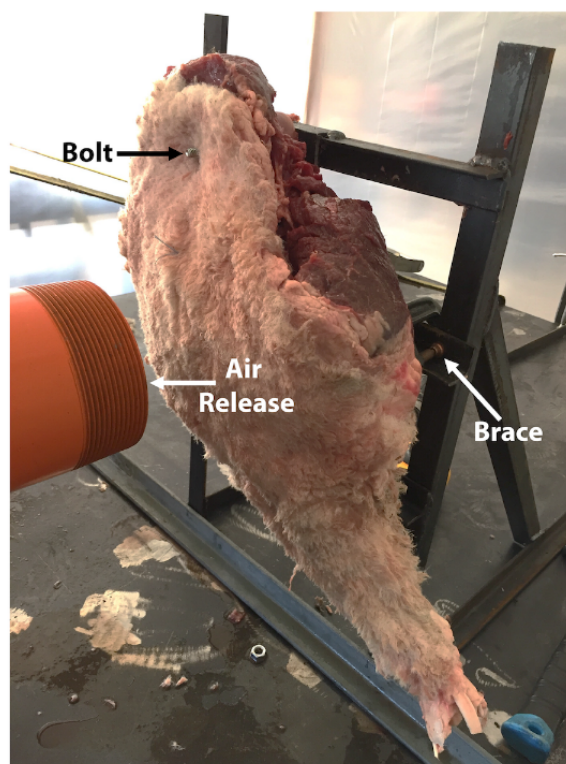


**Figure 3.** Impact of the air impact device (AID) blast on a cadaveric sheep. Left: Representative image showing a surgically prepared limb prior to an AID blast. The air release opening of the AID was positioned directly above the incision; Right: Still shot showing the effect of the impact force of the AID blast.
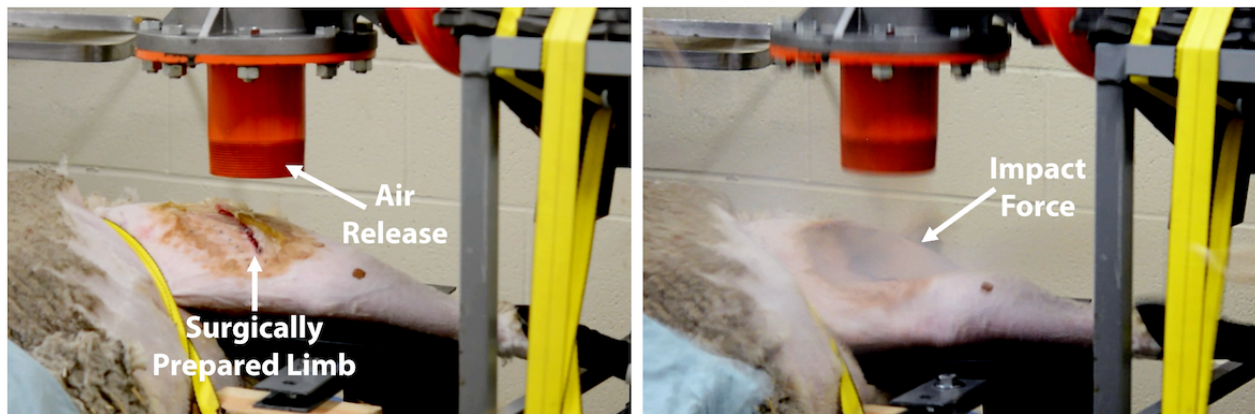


Once placement was determined, the midshaft incision was sutured closed and covered with clear adhesive (ie, Tegaderm), and the AID discharge procedure, as outlined above, was performed. To assess for particulate dispersion, the blasting procedure was repeated 5 times. After each blast, a radiograph was obtained to track the displacement of CoCr beads in the deep tissue. This process was repeated in 2 cadaveric limbs.

For comparison, CoCr displacement testing was also performed using the Walton et al [28] method. More specifically, a sheep cadaver was obtained, an incision made in the midshaft region of the femur as described, and a 3.5-kg weight was dropped from 1-m height. Bead placement was again imaged using

radiography at time zero and after each drop of the weight to track the movement of the CoCr beads.

In addition to assessing the displacement of CoCr beads, testing was also performed to determine whether the AID could cause host bone chips or fragments to disperse in cadaveric sheep tissue. A mock surgery was performed wherein a bone core of approximately 10 mm was taken from the distal femur. Bone chips were created using a rongeur, mixed with saline to create a slurry, and placed in apposition to the bone in the midshaft of the femur (Figure 5). The sheep was covered with a drape to prevent any contamination that may have been forced though the incision site and to protect equipment in the room (Figure 6). Radiography was obtained after AID blasts (Figure 7).

**Figure 4.** Radiograph demonstrating that following air impact device exposure or blunt force trauma, femora were intact and not fractured. In addition, images show dispersion of Cobalt-Chromium beads (white).
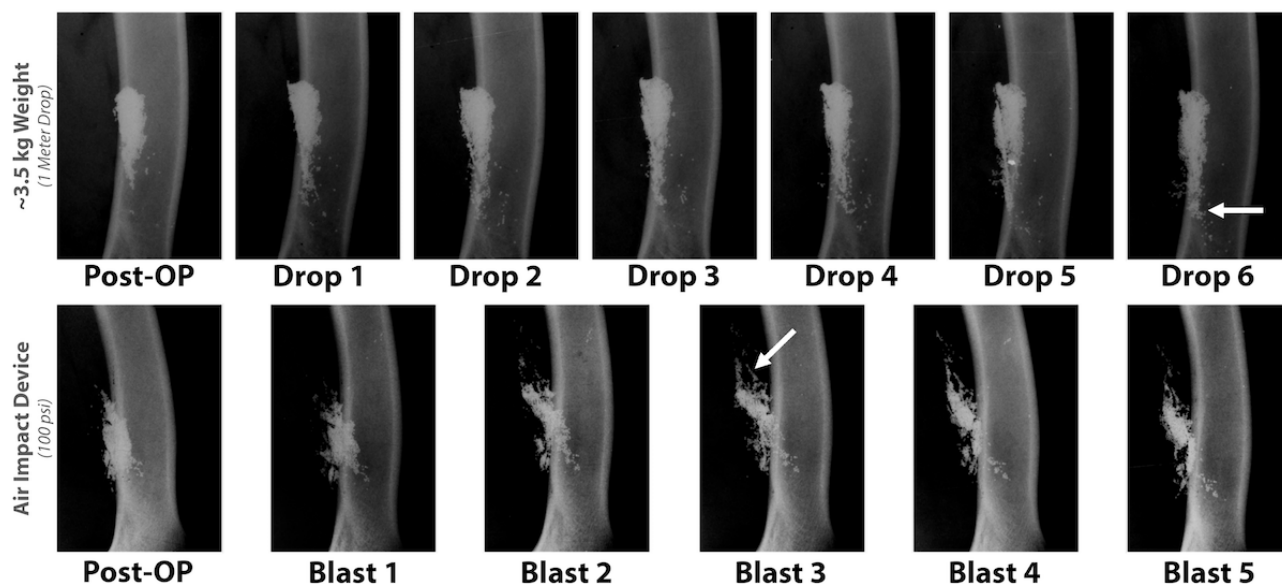


**Figure 5.** Photography demonstrating a mock surgery on a cadaver sheep for bone chip collection and placement. Left to right: Incision being made toward the distal end of the femur. A 10-mm bone core (arrow) was taken from the distal femur. Bone chips (arrow) were placed on the exposed midshaft of the femur. The incision site was sutured closed. Note that the fascia was also closed by suturing to ensure that the air impact device would not result in surgical site dehiscence.
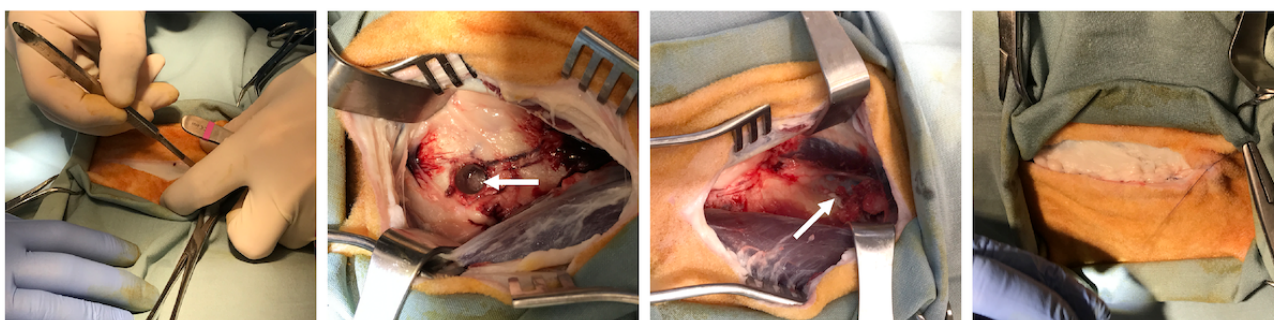


**Figure 6.** Photography demonstrating the AID blast. Left: A custom limb support created from 80/20 aluminum. This ensured the femur was supported during the lateral air impact device (AID) blast. Right: The final setup of the AID blast over a surgically operated leg.
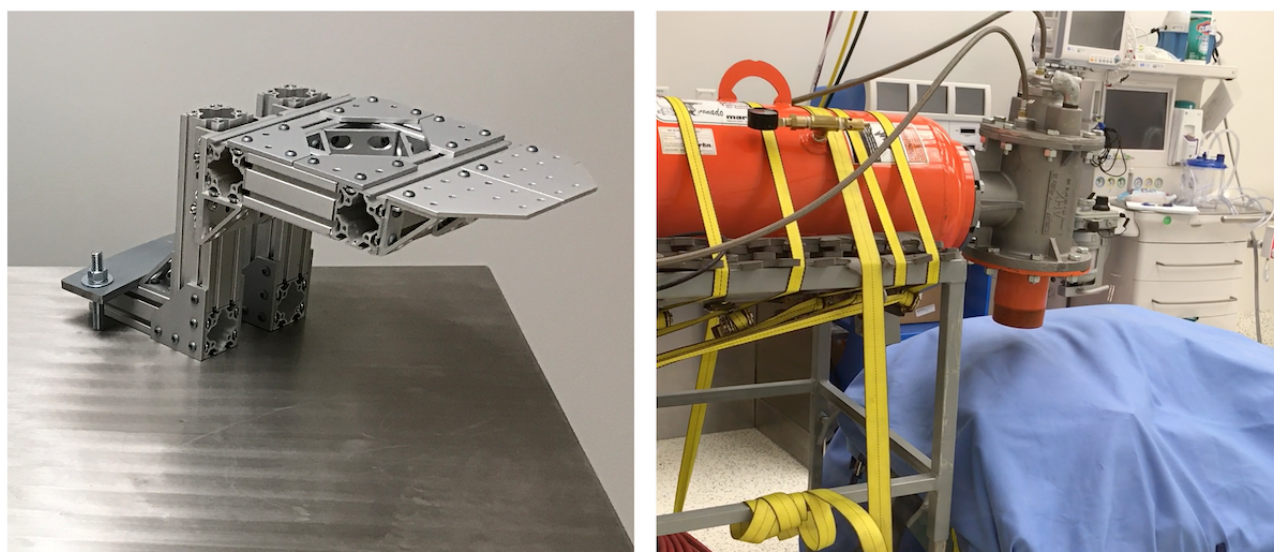
**Figure 7.** Radiograph obtained after 5 AID blasts revealed that the bone chips placed on the lateral side of the femur had migrated posteriorly as well as into the adjacent muscle tissue.
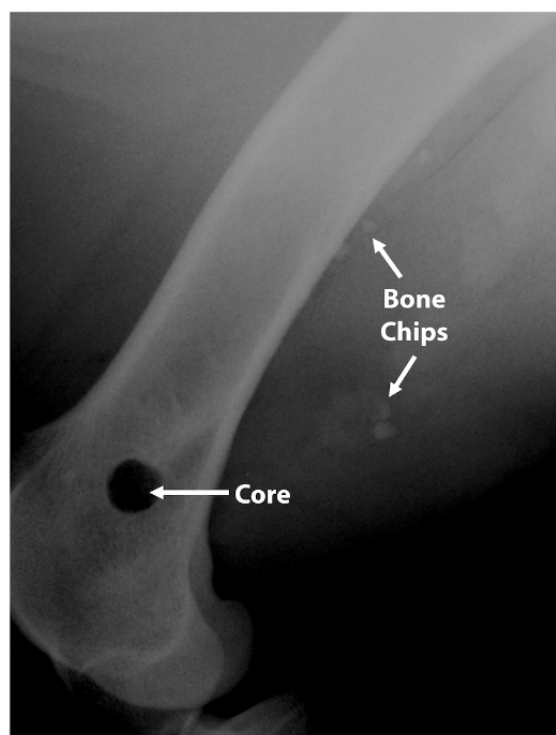


## Results

### Force Plate Testing

Results from the force plate portion of testing showed that the air discharge forces of the AID exceeded the force achieved by Walton et al, which required dropping a 3.5-kg weight from a 1-m height (Figure 3). When the AID was pressurized to 40 psi, the air volume was 6.2 cubic feet [33]. At this psi, the incident pressure was 174 kPa, which would equate to a 5.8-kg charge weight of TNT at a standoff distance of approximately 4.5 m [31]. Incident pressure in this case was defined as a free air burst, meaning a burst that had no contact with the ground before striking an object [34]. The force output was 229 (SD 13) N. At 80 psi, the air volume was 10.7 cubic feet [33]. At this psi, the incident pressure was 450 kPa, which would equate approximately to a 5.8-kg charge weight of TNT at a standoff distance of approximately 2.95 m [31]. The force output was 778 (SD 50) N. At 100 psi, the air volume was 12.9 cubic feet [33]. At this psi, the incident pressure was 588 kPa, which would equate approximately to a 5.8-kg charge weight of TNT at a standoff distance of approximately 2.62 m [31]. The force output was 1085 (SD 114) N. Testing did not go higher than 100 psi given that the AID began to have connection leaks at higher pressures.

The force of dropping the 3.5-kg weight was 168 (SD 11) N. Taken together, the data indicated that the AID resulted in a force output that was approximately 7× greater than the dropped weight (Tables 1 and 2) and provided incident pressures that may more closely model an IED.

### Cadaveric Limb Testing

Tests from the cadaveric limbs indicated that with a support bar in place (Figure 2), limbs did not fracture. However, it was found that when an incision was present in the leg, the rapid discharge of air opened the incision and created a pocket that compromised the subdermal tissues. To mitigate this outcome, the incision site was covered with durable plastic, such as Tegaderm, which prevented the explosive air from entering the incision site and compromising the musculature. Whole carcass testing was performed in a horizontal plane to more closely simulate a sheep that would be lying on a table for a procedure to be performed.

**Table 1.** Force plate data output comparisons.

| Group | Force output (N) | | |
|---|---|---|---|
| | Mean (SD) | 95% CI | Minimum, maximum |
| ~3.5-kg weight | 168 (11) | 159-177 | 148, 179 |
| AID[a] (40 psi) | 229 (13) | 217-241 | 214, 245 |
| AID (80 psi) | 778 (50) | 745-811 | 732, 881 |
| AID (1000 psi) | 1080 (114) | 968-1190 | 1008, 1252 |

[a]AID: air impact device.

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**Table 2.** Force plate data statistical comparisons.

| Group | $P$ value[a] |
| --- | --- |
| ~3.5-kg weight versus AID[b] (40 psi) | <.001 |
| ~3.5-kg weight versus AID (80 psi) | <.001 |
| ~3.5-kg weight versus AID (100 psi) | <.001 |
| AID (40 psi) versus AID (80 psi) | <.001 |
| AID (40 psi) versus AID (100 psi) | <.001 |
| AID (80 psi) versus AID (100 psi) | <.001 |

[a]$P<.05$ is significant.

[b]AID: air impact device.

### Mock Shrapnel and Bone Displacement Testing

Results from the mock shrapnel displacement testing showed that the AID discharge procedure dispersed CoCr beads within the musculature of a cadaveric sheep limb (Figure 4). More specifically, groups of beads were tracked and dispersed to a distance of approximately 2.7 mm with each blast that was performed. By the fifth blast, beads resided approximately 13.3 mm distal to their start point. The data also indicated that the sheep limbs were able to withstand multiple sequential blasts. More specifically, radiographs indicated that the limbs did not fracture following multiple AID discharges (Figure 4).

For comparison, the process of dropping a 3.5-kg weight on the limb resulted in minimal movement of the CoCr beads with each sequential hit (Figure 4). Beads primarily tracked parallel to the bone and may have been an artifact from motion during the capturing of the radiographs or as saline drained through the surgical pocket that was created (Figure 4). By the fifth drop of the weight, beads had dispersed by approximately 2 mm or less into the surrounding tissue regions.

## Discussion

### Principal Findings

The setup of an AID system described herein generated repeatable and reproducible blast of pressurized air that resulted in a force of approximately 1100 N. This may cause significant trauma to local tissue without compromising the underlying skeletal structure of a large animal (which may be critically important for a translatable animal model because lameness and extreme discomfort may necessitate euthanasia). The forces generated in our model were approximately 7× greater than those generated in the blunt force trauma model previously developed to induce ectopic bone [28].

The delivery of a pressurized blast of air was consistent with previous animal studies and incident pressures that may be present in an IED blast [29]. However, the overall goal was not to create massive polytrauma, but rather consistent blasts of air. The AID used in this model also demonstrated that it could effectively disperse metal particulate within the muscle, which would be expected with percussion blasts. Metal beads tracked parallel to the bone following the weight drop, displacing within the soft tissue planes of our intermuscular approach. In contrast, beads that dispersed into the musculature following AID blasts appeared to disperse in a radial pattern created by the pressurized blast of air.

Bone chips or fragments were also found to be affected by the AID. This may be particularly important when the animal model portion of testing begins because in a battlefield-relevant scenario, bone chips or fragments are a common result of blast-related trauma. These data indicate that as this work progresses toward animal modeling, clinically relevant outcomes may be achieved. Current testing has been limited to *ex vivo* analysis. Live animal modeling will be needed to determine whether these data model parameters are safe and effective. *In vivo* data will also reveal whether an approach of highly pressurized air, as opposed to blunt force, will lead to higher rates of HO formation in an ovine model.

### Conclusion

HO negatively affects the quality of life for service members and those in the public sector. For example, the pathology can inhibit the ability of those with limb loss to effectively use prosthetic socket systems due to pain as soft tissues compress against bony HO. This in turn delays rehabilitation and, in some cases, requires surgical excision. Methods to better understand the etiology and ectopic bone mitigation will improve clinical outcomes. This study outlines the setup of a high-pressure air blast system to simulate combat-related trauma that may lead to future HO manifestation.

of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of Defense, or the United States government.

## Conflicts of Interest

None declared.

## References

1. Isaacson BM, Stinstra JG, MacLeod RS, Pasquina PF, Bloebaum RD. Developing a quantitative measurement system for assessing heterotopic ossification and monitoring the bioelectric metrics from electrically induced osseointegration in the residual limb of service members. Ann Biomed Eng 2010 Sep;38(9):2968-2978 [FREE Full text] [doi: 10.1007/s10439-010-0050-2] [Medline: 20458630]

2. Brown KV, Dharm-Datta S, Potter BK, Etherington J, Mistlin A, Hsu JR, et al. Comparison of development of heterotopic ossification in injured US and UK Armed Services personnel with combat-related amputations: preliminary findings and hypotheses regarding causality. J Trauma 2010 Jul;69 Suppl 1:S116-S122. [doi: 10.1097/TA.0b013e3181e44cc7] [Medline: 20622605]

3. Isaacson BM, Brown AA, Brunker LB, Higgins TF, Bloebaum RD. Clarifying the structure and bone mineral content of heterotopic ossification. J Surg Res 2011 May 15;167(2):e163-e170. [doi: 10.1016/j.jss.2010.12.047] [Medline: 21392799]

4. Errico T, Fetto J, Waugh T. Heterotopic ossification. Incidence and relation to trochanteric osteotomy in 100 total hip arthroplasties. Clin Orthop Relat Res 1984 Nov(190):138-141. [Medline: 6435920]

5. Bayley S. Funnybones: A Review of the Problem of Heterotopic Bone Formation. Orthopaedic Review 1979;8:113-120.

6. Melcer T, Belnap B, Walker GJ, Konoske P, Galarneau M. Heterotopic ossification in combat amputees from Afghanistan and Iraq wars: five case histories and results from a small series of patients. J Rehabil Res Dev 2011;48(1):1-12 [FREE Full text] [Medline: 21328158]

7. Covey D. Combat orthopaedics: a view from the trenches. J Am Acad Orthop Surg 2006;14(10 Spec No):S10-S17. [Medline: 17003178]

8. Forsberg J, Pepek J, Wagner S, Wilson K, Flint J, Andersen R, et al. Heterotopic ossification in high-energy wartime extremity injuries: prevalence and risk factors. J Bone Joint Surg Am 2009 May;91(5):1084-1091. [doi: 10.2106/JBJS.H.00792] [Medline: 19411456]

9. Forsberg J, Potter B. Heterotopic ossification in wartime wounds. J Surg Orthop Adv 2010;19(1):54-61. [Medline: 20371008]

10. Potter B, Burns T, Lacap A, Granville R, Gajewski D. Heterotopic ossification following traumatic and combat-related amputations. Prevalence, risk factors, and preliminary results of excision. J Bone Joint Surg Am 2007 Mar;89(3):476-486. [doi: 10.2106/JBJS.F.00412] [Medline: 17332095]

11. Potter B, Granville R, Bagg M, Forsberg J, Hayda R, Keeling J, et al. Special Surgical Considerations for the Combat Casualty with Limb Loss. In: Pasquina P, Cooper R, editors. Rehabilitation of Combat Casualties with Limb Loss. Washington DC: Borden Institute; 2010:153-190.

12. Tintle S, Baechler M, Nanos G, Forsberg J, Potter B. Reoperations following combat-related upper-extremity amputations. J Bone Joint Surg Am 2012 Aug 15;94(16):e1191-e1196. [doi: 10.2106/JBJS.K.00197] [Medline: 22992825]

13. Tintle S, Shawen S, Forsberg J, Gajewski D, Keeling J, Andersen R, et al. Reoperation after combat-related major lower extremity amputations. J Orthop Trauma 2014 Apr;28(4):232-237. [doi: 10.1097/BOT.0b013e3182a53130] [Medline: 24658066]

14. Dudek N, DeHaan M, Marks M. Bone overgrowth in the adult traumatic amputee. Am J Phys Med Rehabil 2003 Nov;82(11):897-900. [doi: 10.1097/01.PHM.0000087459.94599.2D] [Medline: 14566159]

15. Isaacson B, Potter B, Bloebaum R, Epperson R, Kawaguchi B, Swanson T, et al. Link Between Clinical Predictors of Heterotopic Ossification and Histological Analysis in Combat-Injured Service Members. J Bone Joint Surg Am 2016 Apr 20;98(8):647-657. [doi: 10.2106/JBJS.15.00895] [Medline: 27098323]

16. Clarke MT, Longstaff L, Edwards D, Rushton N. Tourniquet-induced wound hypoxia after total knee replacement. J Bone Joint Surg Br 2001 Jan;83(1):40-44. [Medline: 11245536]

17. Pavey G, Qureshi A, Hope D, Pavlicek R, Potter B, Forsberg J, et al. Bioburden Increases Heterotopic Ossification Formation in an Established Rat Model. Clin Orthop Relat Res 2015 Sep;473(9):2840-2847 [FREE Full text] [doi: 10.1007/s11999-015-4272-3] [Medline: 25822455]

18. Forsberg J, Davis T, Elster E, Gimble J. Burned to the bone. Sci Transl Med 2014 Sep 24;6(255):255fs37. [doi: 10.1126/scitranslmed.3010168] [Medline: 25253672]

19. Stenström A, Hansson LI, Thorngren KG. Cortical bone remodeling in normal rat. Calcif Tissue Res 1977 Jun 28;23(2):161-170. [Medline: 890554]

20. Isaacson B, Brunker L, Brown A, Beck J, Burns G, Bloebaum R. An evaluation of electrical stimulation for improving periprosthetic attachment. J Biomed Mater Res B Appl Biomater 2011 Apr;97(1):190-200. [doi: 10.1002/jbm.b.31803] [Medline: 21381193]

21. Isaacson BM, Pasquina PF, Bloebaum RD, Potter K. Defense Technical Information Center. Establishing the Mineral Apposition Rate of Heterotopic Ossification for Prevention of Recurrence URL: https://apps.dtic.mil/dtic/tr/fulltext/u2/1008259.pdf [accessed 2018-12-10] [WebCite Cache ID 74YMKuDYi]

22. Isaacson B, Swanson T, Potter B, Pasquina P. Tourniquet use in combat-injured service members: a link with heterotopic ossification? ORR 2014 Mar:27. [doi: 10.2147/ORR.S56636]

23. Isaacson B, Weeks S, Pasquina P, Webster J, Beck J, Bloebaum R. The road to recovery and rehabilitation for injured service members with limb loss: a focus on Iraq and Afghanistan. US Army Med Dep J 2010:31-36. [Medline: 21181652]

24. Isaacson B, Weeks S, Potter K, Pasquina P, Bloebaum R. Relationship Between Volumetric Measurements of Heterotopic Ossification in Wounded Service Members and Clinically Available Screening Tools. JPO Journal of Prosthetics and Orthotics 2012;24(3):138-143. [doi: 10.1097/JPO.0b013e31825fb080] [Medline: 21181652]

25. Polfer E, Hope D, Elster E, Qureshi A, Davis T, Golden D, et al. The development of a rat model to investigate the formation of blast-related post-traumatic heterotopic ossification. Bone Joint J 2015 Apr;97-B(4):572-576. [doi: 10.1302/0301-620X.97B4.34866] [Medline: 25820900]

26. Bloebaum R, Willie B, Mitchell B, Hofmann A. Relationship between bone ingrowth, mineral apposition rate, and osteoblast activity. J Biomed Mater Res A 2007 May;81(2):505-514. [doi: 10.1002/jbm.a.31087] [Medline: 17236212]

27. Willie B, Bloebaum R, Bireley W, Bachus K, Hofmann A. Determining relevance of a weight-bearing ovine model for bone ingrowth assessment. J Biomed Mater Res A 2004 Jun 01;69(3):567-576. [doi: 10.1002/jbm.a.30038] [Medline: 15127404]

28. Walton M, Rothwell A. Reactions of thigh tissues of sheep to blunt trauma. Clin Orthop Relat Res 1983 Jun(176):273-281. [Medline: 6406125]

29. Goldstein L, Fisher A, Tagge C, Zhang X, Velisek L, Sullivan J, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med 2012 May 16;4(134):134ra60 [FREE Full text] [doi: 10.1126/scitranslmed.3003716] [Medline: 22593173]

30. Nelson T, Clark T, Stedje-Larsen E, Lewis C, Grueskin J, Echols E, et al. Close proximity blast injury patterns from improvised explosive devices in Iraq: a report of 18 cases. J Trauma 2008 Jul;65(1):212-217. [doi: 10.1097/01.ta.0000196010.50246.9a] [Medline: 17514045]

31. UN SaferGuard International Ammunition Technical Guidelines. United Nations. 2017. Kingery-Bulmash Blast Parameter Calculator URL: https://www.un.org/disarmament/un-saferguard/kingery-bulmash/ [accessed 2018-12-10] [WebCite Cache ID 74YN8BmHw]

32. Hyde D. Conventional weapons effects program. Vicksburg, MS: United States Army Corps of Engineers; 2004.

33. Martin Engineering. 2017. Tech Data Sheet: Tornado Air Cannon with 4 URL: https://static.martin-eng.com/www.martin-eng.com/resources/L3705.pdf [accessed 2018-12-10] [WebCite Cache ID 74YNTctRE]

34. Janney S. Blast resistant design of steel structures. Knoxville, TN: University of Tennessee; 2007.

## Abbreviations

**AID:** air impact device
**HO:** heterotopic ossification
**IED:** improvised explosive device
**TNT:** trinitrotoluene

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<u>Protocol</u>

# Digital Technology in Somatic and Gene Therapy Trials of Pediatric Patients With Ocular Diseases: Protocol for a Scoping Review

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## *Abstract*

**Background:** Pharmacogenomics suggests that diseases with similar symptomatic presentations often have varying genetic causes, affecting an individual patient's response to a specific therapeutic strategy. Gene therapies and somatic cell therapies offer unique therapeutic pathways for ocular diseases and often depend on increased understanding of the genotype-phenotype relationship in disease presentation and progression. While demand for personalized medicine is increasing and the required molecular tools are available, its adoption within pediatric ophthalmology remains to be maximized in the postgenomic era.

**Objective:** The objective of our study was to address the individual hurdles encountered in the field of genomic-related clinical trials and facilitate the uptake of personalized medicine, we propose to conduct a review that will examine and identify the digital technologies used to facilitate data analysis in somatic and gene therapy trials in pediatric patients with ocular diseases.

**Methods:** This paper aims to present an outline for Healthcare Information Technology and Information and Communication Technology resources used in somatic and gene therapy clinical trials in children with ocular diseases. This review will enable authors to identify challenges and provide recommendations, facilitating the uptake of genetic and somatic therapies as therapeutic tools in pediatric ophthalmology. The review will also determine whether conducting a systematic review will be beneficial.

**Results:** Database searches will be initiated in September 2018. We expect to complete the review in December 2019.

**Conclusions:** Based on review findings, the authors will summarize methods used for facilitating IT integration in personalized medicine. Additionally, it will identify further research gaps and determine whether conducting further reviews will be beneficial.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/10705

## Introduction

"Personalized medicine" and more specifically, genomics, is transforming health care through the implementation of strategies aiming to individualize prevention and treatment [1]. By matching patients to specific drugs and therapies, thereby providing customized and tailored treatments, patient needs, values, and preferences are considered [2]. While personalized medicine requires quantitative assessment methods including, but not limited to, genotype sequencing, it also relies heavily on the involvement of patients in their management and treatment [2]. Multiple gene therapy trials targeting corneal and retinal disorders are currently underway [3]. Ideally, retinal gene therapies will be administered to patients before significant vision loss. Gene therapy can, currently, only prevent further degeneration of retinal cells by delivering the critical missing gene, not halting disease progression or blindness [4]. Therefore, pediatric patients stand to benefit greatly from the development of gene therapies for retinal diseases. Patient-centered personalized medicine has been facilitated by the integration of informatics within health care (Healthcare Information Technology [HIT]), as well as access to information by means of telecommunications (Information and Communication Technology [ICT]), which have enabled interactions and exchange of information [5,6,7]. Developed by researchers at the Picker Institute in 1988, "patient-centered care" represents a health care delivery methodology driven by patient needs and perspectives, empowering patients to become partners in the management of their own health [8], thereby improving the quality of service delivery. In fact, according to the "Crossing the Quality Chasm" report developed by the Institute of Medicine, patient-centered care represents one of the 6 essential elements of high-quality care [9] and has the potential to shift medical practice away from the more conventional approach of "one size fits all" [10].

HIT and ICT have tremendous potential to contribute to and enhance patient-centered approaches [11]. Electronic health (eHealth), or the use of ICT in health care [12], has facilitated the flow of information and improved health care quality [8]. Although eHealth remains underutilized, its role in personalized medicine and the improvement of communication in clinical settings is significant [13]. While health systems implementing patient-centered approaches facilitate advances in personalized medicine, research suggests that promoting the utilization and integration of big data and ICT solutions in personalized medicine remains a challenge to overcome [14]. HIT, an enabling and fundamental component of health systems, facilitates the improvement of health system quality and efficiency, as well as patient safety by addressing patient needs and preferences in the right setting at the right time, subsequently enforcing active patient engagement and autonomy [15,16]. Through digital methods utilizing personal health records, or digital collection of health-related information recorded and maintained by patients [17], patients and their caregivers have additional control over their illnesses [18,19],

improving patient engagement [20]. The wide adoption of HIT requires addressing issues including data storage, fragmentation of data, and lack of interoperability to be addressed before the full potential of this strategy may be realized in personalized medicine.

Recent advances in scientific technology, including facile genome sequencing, advanced genome editing techniques, and controlled isolation and differentiation of cells *in vitro*, have clear translational value [21]. In addition to understanding why individuals with similar diseases respond differently to different therapeutics, big data in health care can allow researchers to determine why individuals with analogous conditions are attributed different prognoses [14], enabling early intervention through risk stratification [22]. Therapies that utilize these and related strategies are referred to as "gene therapy medicinal product" and "somatic cell therapy medicinal product" by the European Medicines Agency [23]; here we will refer to them as gene therapy and somatic cell therapy, respectively. Somatic cell therapy refers to the administration of processed or manipulated somatic cells to alter biologic characteristics [24]. Gene therapy alters genes in targeted cells, thereby preventing and treating disorders [24]. "Corrected" versions of the gene may be delivered to the patient's cells [25], for example by adeno-associated virus, ameliorating disease prognosis. These therapeutic strategies may be combined by first genetically modifying cells *ex vivo* before delivering them to the patients [22]. As inherited diseases are clearly amenable to a gene therapy strategy, pediatric patients represent a population that may gain tremendously from advances in this field [3].

New technologies in health care are allowing physicians to tailor and customize treatments to individual patients, translating genomic research into medical practice. Acting as a driving force, novel technologies are central to the advancement of gene and somatic therapy trials. As there is no existing synthesis of the electronic processes used in somatic and gene therapy trials in pediatric patients with ocular diseases, this gap will be addressed by the proposed review.

## Methods

### Background

We will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol PRISMA-P 2015 Checklist (Multimedia Appendix 1) and the Cochrane protocol guide to develop the protocol. In order to establish Medical Subject Headings (MeSH), subject heading, and keywords (Multimedia Appendix 2), a clear research question will be developed and a Population, Intervention, Comparator, and Outcome framework will be completed. To provide replicable and transparent methods, we will describe the following 6 stages in detail: (1) Literature search; (2) article selection; (3) data extraction; (4) quality appraisal; (5) data analysis; and (6) data synthesis.

Systematic scoping reviews intend to promptly gather and provide evidence on essential concepts pertaining to broad research subjects [26]. As opposed to systematic reviews that answer narrow and specific questions, scoping reviews may answer broad questions and provide evidence that lie outside of the effectiveness of an intervention [25]. Thus, where systematic reviews may not be conducted due to evidence deficiency, systematic scoping reviews have been proven to be valuable [27].

Although scoping reviews do not require a strict methodological approach, methodological frameworks have been developed by Arksey and O'Malley in 2005 and by Levac, Colquhoun, and O'Brien in 2010 [26,27].

## Identification of a Research Question

Following preliminary and exploratory reading on somatic and gene therapy trials involving pediatric patients with ophthalmic conditions, no synthesis of evidence around the technological advances used in these trials was found, demonstrating a research gap. In light of this evidence paucity, we formulated the following research question: What are the range of health care information and communication technologies applied to achieve patient-centered care in children undergoing somatic and gene therapies for ocular diseases?

## Search Strategy

We will systematically search MEDLINE/PubMed, Embase, and Scopus through the Imperial College London library. Subsequent to the identification of MeSH, subject headings, and keywords, the medical librarian at Imperial College London will be asked to review the search strategy. Search terms will consist of MeSH and keywords linked to (1) pediatric population; (2) digital technologies; (3) traditional care; and (4) outcomes. No restrictions will be applied on publication date, publication status, or study location. Subsequent to the MEDLINE/PubMed search, the search strategy will be converted to Embase and Scopus searches. The search strategy may be requested from the first author once finalized. Following database searches, results will be imported to EndNote, a reference software. Once the included studies are determined, we will thoroughly search their bibliographic citations to identify supplemental relevant studies.

## Inclusion and Exclusion Criteria

The following Population, Intervention, Comparator, and Outcome framework was developed for the purpose of the review's research question.

### Population

Eligible studies will consist of pediatric patients with ocular diseases undergoing somatic and gene therapy trials.

### Intervention

Interventions will consist of advances in health care technologies, including, eHealth, mobile health, big data, and real-world data utilized in genomic and somatic therapies in children with ocular diseases.

### Comparison

No comparisons will be made.

### Outcomes

Treatment and process outcomes will be assessed. Treatment outcomes will consist of clinical effectiveness, clinical efficacy, and patient-relevant outcomes. Process outcomes will evaluate the quality and accessibility of technological advances.

### Study Type

The following studies will be included (1) No restrictions will be placed on study type; (2) English publications; (3) publications obtained from MEDLINE/PubMed, Embase, and Scopus; and (4) publications focusing on digital technologies used in pediatric somatic and gene therapy clinical trials.

### Exclusion Criteria

We excluded non-English publications.

## Study Record Management

EndNote X8.2 (Clarivate Analytics) will be used for the collection of bibliographic references. Following the assemblage of references following database searches, duplicates will be removed using a deduplication tool on the bibliographic software. Where duplicates are not removed automatically by means of the EndNote software, reviewers will examine and compare findings thoroughly. Upon agreement, duplicates will be removed. Authors of included studies will be contacted if required.

## Study Selection

In the first phase of the selection process, 2 reviewers will independently perform screening of titles and abstracts. Following elimination of papers with discernible ineligibility, eligibility of the remaining papers will be assessed in the second phase of the study selection process through full-text reading. Disagreements on study eligibility will be resolved through discussion between reviewers. If no consensus is reached, a third reviewer will assist in the selection process. In the final phase of the selection process, bibliographic references of included studies will be reviewed, thereby identifying additional potentially relevant papers. A PRISMA flow diagram will be used to illustrate the selection process, as well as exclusion reasons, demonstrating the review's transparency and replicability.

## Data Extraction

### Data Extraction Process

We will extract data from included studies and compile onto data extraction forms designed by the research team. Prior to comparison of completed data extraction forms, data will be extracted independently by 2 reviewers. Differences in opinions will be resolved through discussion and, if required, assistance of a third reviewer. A single form consisting of the required data will be generated.

**Table 1.** Details of extracted data.

| Type of extracted data | Details of extracted data |
| --- | --- |
| Paper information | • Author<br>• Date of publication<br>• Country where the clinical trial was conducted |
| Study characteristics | • Clinical trial setting<br>• Type of somatic or gene therapy<br>• Trial duration or length<br>• Sample size<br>• Use of a control<br>• Follow-up duration |
| Participant characteristics | • Number of participants<br>• Age of participants<br>• Gender of participants |
| Intervention details | • Type of technological advances<br>• Information technology use in somatic or gene therapy trials (stage)<br>• Challenges around implementation<br>• Enabling factors |
| Comparator details | • Type of comparator (traditional approach, standard care, none) |
| Outcome measures | • Treatment outcomes<br>• Process outcomes |

### *Data Items*

Data extracted from included studies will consist of the following information: (1) paper specifications; (2) study characteristics; (3) participant characteristics; (4) intervention details; (5) comparator details; and (6) outcome measures. Details pertaining to extracted data may be found in Table 1. Through collection of the extracted data, evidence around the technological advances used in somatic and gene therapy trials will be presented and discussed. To ensure adequate collection of data, the team will review the data extraction forms prior to usage.

### Risk of Bias Assessment of Included Studies

The methodological quality of included studies will be assessed by 2 independent reviewers. If, following discussion, reviewers cannot reach consensus on the risk of bias pertaining to included studies, a third reviewer will be asked to aid in decision making.

To assess the methodological quality of included studies, the Cochrane Collaboration Risk of Bias Tool will be applied. The following 6 criteria will be evaluated in each included study: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding (performance bias and detection bias); (4) incomplete outcome data (attrition bias); (5) selective reporting (reporting bias); and (6) other bias.

Following criteria assessment, risk of bias of included studies will be determined, and studies will be judged as "high risk," "low risk," or "unclear risk." To illustrate the methodological quality of the review's included studies, a Risk of Bias Graph and a Risk of Bias Summary will be presented.

### Data Synthesis

Subsequent to data extraction, results will first be synthesized numerically or by means of a descriptive statistic. Providing an overview of the quantity and type of included papers, the descriptive analysis will consist of the following information: (1) intervention type, control group, sample size; (2) characteristics of the population involved including, age, gender, ocular disease targeted, location; and (3) intervention outcomes including, health treatment and process outcomes

Results will also be synthesized narratively. Using the PRISMA-P 2015 Checklist, data will be presented in a tabular format to supplement the narrative synthesis. This will consist of a synthesis of all included papers that will enable guidance and allow assessment of potential heterogeneity between included studies. To ensure the reliability of our findings, narrative synthesis reporting will be conducted in a transparent manner.

Providing a holistic analysis of the intervention, the quality of the studied intervention will be determined by evaluating through outcome measures, as well as satisfaction of health care professionals and patients and the complexity of the intervention. Recommendations regarding future research, policy, and practice will be developed by the authors. Details of this stage are currently being developed by the research team and may be subjected to iterations or further updates following review commencement. We intend to finalize this stage in December 2017.

## *Results*

Database searches will be initiated in September 2018. We expect to complete the review in December 2019.

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## *Discussion*

### Overview

The review intends to provide evidence on technology applied to genetic and somatic cell therapy trials in children with ocular diseases. In addition to developing recommendations that will enable collaboration between key stakeholders, we aim to provide a comprehensive overview that will facilitate decision making and improve pediatric health care. Thus, we aspire to move evidence into practice, or translate research into medical practice, through the circulation of our review findings. We predict that the review will also provide insight to other researchers as additional research gaps that may need to be addressed will be identified by means of evidence gathered in the proposed review.

### Strengths

Responding to a research gap, the review will provide evidence on technological advances related to somatic and gene therapy trials in children. We will perform rigorous and systematic search of multiple health and medicine databases. No restrictions applied on publication date, status, or location. The review will identify unmet needs of pediatric patients with ophthalmologic disorders, thereby informing policy makers and donors. On completion of the review, additional research gaps will be identified, thereby guiding the conduct of future systematic reviews. Review findings will enhance the management of pediatric patients undergoing somatic and gene therapies by identifying digital technologies that improve patient safety, engagement, and satisfaction. The effectiveness of digital technologies on treatment outcomes will be assessed.

### Limitations

Language restrictions will be imposed (non-English papers will be excluded). As the review will outline the existing electronic processes applied in somatic and gene therapy trials for children, quality appraisal will not be conducted on identified papers.

### Consultation

We believe consulting experts will provide valuable insight regarding the development of recommendations, challenges that need to be addressed, and potential solutions. In addition to consulting pediatric somatic and gene therapy experts and researchers, regulatory authorities and eHealth experts at Imperial College London, the University of Oxford, and Stanford University will be consulted throughout the conduction of the review. This will allow the reviewers to obtain guidance that has not been provided in the searched literature. Their feedback on the protocol and review findings will be requested prior to completion of the final report. Through multiple consultations, we intend to engage subject experts in the development and design of the systematic review in addition to the subsequent action plan. It is intended that by means of various consultations, we will develop strategies facilitating the uptake of novel technological advancements by researchers, health care practitioners, and patients in the field of personalized medicine.

### Knowledge Translation and Dissemination

The review intends to provide evidence on the digital technologies used in data analysis and interpretation in pediatric somatic and gene therapy trials. The review intends to develop and circulate strategies to promote their uptake, enhance patient safety and enhance development of personalized medicine within health care systems. In order to enable informed decision-making skills of consumers and improve health care quality and access, results will be actively communicated to health care providers, patients, and other relevant stakeholders. To ensure transparency, replicability, and applicability of the proposed systematic review, we intend to distribute our work from the initial stage (protocol) to the final product.

### Conclusions

Genomics is reshaping health systems. While advancements in technologies are enabling the personalization and customization of care, there is paucity around the evidence of their utilization and impact in somatic and gene therapy trials in children. As eHealth and mobile health resources have the potential to empower patients through enhancement of decision-making skills and patient engagement, the review intends to exhibit how their utilizations may be maximized in pediatric somatic and gene therapy trials to improve the quality of pediatric ophthalmology.

### Authors' Contributions

EM conceived the study aims and objectives, led the draft, led the methodological review, revised all drafts, responded to peer-review feedback, and provided oversight. TO composed the initial draft report and incorporated feedback from authors on the first draft. DB and GW reviewed the first draft. AA, JC, and AM reviewed the second draft. The final report was agreed on by all authors. EM is the guarantor.

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## Conflicts of Interest

CLHH is a consultant and employee of multiple life sciences companies and biotechnology investment firms, which may develop therapeutics utilizing gene editing technology or invest in such companies. REM is an academic cofounder of NightStar Therapeutics Inc (London, UK), a biotechnology company that develops gene therapeutics for various indications including choroideremia. NightStar had no role in the conception, design, or execution of this protocol or the following study. DB is a stockholder in Translation Ventures Ltd (Charlbury, Oxfordshire, UK) and IP Asset Ventures Ltd (Oxford, Oxfordshire, UK), companies that, among other services, provide cell therapy biomanufacturing and regulatory and financial advice to pharmaceutical clients. DB is also subject to the Chartered Financial Analyst Institute's codes, standards, and guidelines; therefore, he must stress that this piece is provided for academic interest only and not be construed in any way as an investment recommendation. Additionally, at the time of publication, DB and the organizations with which he is affiliated may or may not have agreed or have pending funding commitments from the organizations named here.

## Multimedia Appendix 1

The PRISMA-P 2015 checklist.

[PDF File (Adobe PDF File), 59KB - resprot_v8i2e10705_app1.pdf ]

## Multimedia Appendix 2

MEDLINE/PubMed search strategy.

[PDF File (Adobe PDF File), 28KB - resprot_v8i2e10705_app2.pdf ]

## References

1. Hood L, Auffray C. Participatory medicine: a driving force for revolutionizing healthcare. Genome Medicine 2013;5(12):110 [FREE Full text] [doi: 10.1186/gm514] [Medline: 24360023]
2. Chouchane L, Mamtani R, Dallol A, Sheikh JI. Personalized medicine: a patient-centered paradigm. Journal of Translational Medicine 2011 Dec 01;9:206 [FREE Full text] [doi: 10.1186/1479-5876-9-206] [Medline: 22133076]
3. Buckland KF, Bobby GH. Gene and cell therapy for children--new medicines, new challenges? Advanced Drug Delivery Reviews 2014 Jun;73:162-169 [FREE Full text] [doi: 10.1016/j.addr.2014.02.010] [Medline: 24583376]
4. Sivan PP, Syed S, Mok P, Higuchi A, Murugan K, Alarfaj AA, et al. Stem Cell Therapy for Treatment of Ocular Disorders. Stem Cells International 2016;2016:8304879 [FREE Full text] [doi: 10.1155/2016/8304879] [Medline: 27293447]
5. US Department of Health & Human Services. Advancing Excellence in Health Care. Agency for Healthcare Research and Quality URL: https://www.ahrq.gov/professionals/prevention-chronic-care/improve/health-it/index.html [accessed 2018-12-05] [WebCite Cache ID 74Rp7H5pv]
6. TechTerms. 2010. ICT URL: https://techterms.com/definition/ict [accessed 2018-12-05] [WebCite Cache ID 74RpCgEty]
7. Minvielle E, Waelli M, Sicotte C, Kimberly JR. Managing customization in health care: a framework derived from the services sector literature. Health Policy 2014 Aug;117(2):216-227 [FREE Full text] [doi: 10.1016/j.healthpol.2014.04.005] [Medline: 24837516]
8. Gibbons MC, eHealth Solutions for Healthcare Disparities. Märsche, RV 8-RV 652. Austria: Strauss Edition Wien; 2018:8147.
9. Institute of Medicine (US) Committee on Quality of Health Care in America. Crossing the Quality Chasm : A New Health System for the 21st Century. 2001. [Medline: 25057539]
10. Liu ET, Johnston PG. Personalized medicine: does the molecular suit fit? Oncologist 2013 Jun;18(6):653-654 [FREE Full text] [doi: 10.1634/theoncologist.2013-0191] [Medline: 23814161]
11. Cliff B. Using technology to enhance patient-centered care. Journal of Healthcare Management 2012;57(5):301-303. [Medline: 23087992]
12. World Health Organization. 2017. eHealth URL: http://www.who.int/ehealth/en/ [accessed 2018-12-05] [WebCite Cache ID 74RpTHakJ]
13. Madhavan S, Sanders AE, Chou WS, Shuster A, Boone KW, Dente MA, et al. Pediatric palliative care and eHealth opportunities for patient-centered care. American Journal of Preventive Medicine 2011 May;40(5 Suppl 2):S208-S216 [FREE Full text] [doi: 10.1016/j.amepre.2011.01.013] [Medline: 21521596]
14. PerMed. Strategic Research and Innovation Agenda (SRIA). Shaping Europe's Vision for Personalised Medicine URL: https://www.permed2020.eu/_media/PerMed_SRIA.pdf [accessed 2018-12-05] [WebCite Cache ID 74RpbqElT]
15. Barello S, Triberti S, Graffigna G, Libreri C, Serino S, Hibbard J, et al. eHealth for Patient Engagement: A Systematic Review. Frontiers in Psychology 2015;6:2013 [FREE Full text] [doi: 10.3389/fpsyg.2015.02013] [Medline: 26779108]
16. Cresswell KM, Bates DW, Sheikh A. Ten key considerations for the successful implementation and adoption of large-scale health information technology. Journal of the American Medical Informatics Association 2013 Jun;20(e1):e9-e13 [FREE Full text] [doi: 10.1136/amiajnl-2013-001684] [Medline: 23599226]

17.    Rouse M. TechTarget. Personal Health Record (PHR) URL: https://searchhealthit.techtarget.com/definition/
       personal-health-record-PHR [accessed 2018-12-05] [WebCite Cache ID 74RqFh6KN]

18.    Chan D, Howard M, Dolovich L, Bartlett G, Price D. Revolutionizing patient control of health information. Can Fam
       Physician 2013 Aug;59(8):823-824 [FREE Full text] [Medline: 23946017]

19.    Archer N, Fevrier-Thomas U, Lokker C, McKibbon KA, Straus SE. Personal health records: a scoping review. Journal of
       the American Medical Informatics Association 2011;18(4):515-522 [FREE Full text] [doi: 10.1136/amiajnl-2011-000105]
       [Medline: 21672914]

20.    Wiljer D, Urowitz S, Apatu E, DeLenardo C, Eysenbach G, Harth T, et al. Patient accessible electronic health records:
       exploring recommendations for successful implementation strategies. Journal of Medical Internet Research 2008;10(4):e34
       [FREE Full text] [doi: 10.2196/jmir.1061] [Medline: 18974036]

21.    Liu ET, Johnston PG. Personalized medicine: does the molecular suit fit? Oncologist 2013 Jun;18(6):653-654 [FREE Full
       text] [doi: 10.1634/theoncologist.2013-0191] [Medline: 23814161]

22.    Kessler DA, Siegel JP, Noguchi PD, Zoon KC, Feiden KL, Woodcock J. Regulation of somatic-cell therapy and gene
       therapy by the food and drug administration. New England Journal of Medicine 1993 Oct 14;329(16):1169-1173. [doi:
       10.1056/NEJM199310143291607] [Medline: 8377782]

23.    NHS ICT Strategy. Executive Summary URL: https://www.torbayandsouthdevon.nhs.uk/uploads/ict-strategy.pdf [accessed
       2018-12-05] [WebCite Cache ID 74RqcarwT]

24.    European Medicines Agency. Summaries of scientific recommendations on classification of advanced therapy medicinal
       products. Science Medicines Health URL: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/
       advanced-therapies/advanced-therapy-classification/
       summaries-scientific-recommendations-classification-advanced-therapy-medicinal-products [accessed 2018-12-05] [WebCite
       Cache ID 74RqexiJl]

25.    Kohn DB. Gene therapy for XSCID: the first success of gene therapy. Pediatric Research 2000 Nov;48(5):578. [doi:
       10.1203/00006450-200011000-00002] [Medline: 11044472]

26.    Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research
       Methodology 2005 Feb;8(1):19-32 [FREE Full text] [doi: 10.1080/1364557032000119616]

27.    Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE
       Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]

## Abbreviations

**eHealth:** electronic health
**HIT:** Healthcare Information Technology
**ICT:** Information and Communications Technology
**MeSH:** Medical Subject Headings

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Protocol

# Adolescent Trials Network for HIV-AIDS Scale It Up Program: Protocol for a Rational and Overview

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## Abstract

**Background:**  The past 30 years have witnessed such significant progress in the prevention and treatment of HIV/AIDS that an AIDS-free generation and the end to the global AIDS epidemic are ambitious, but achievable, national and global goals. Despite growing optimism, globally, youth living with HIV are markedly less likely to receive antiretroviral therapy than adults (23% vs 38%). Furthermore, marked health disparities exist regarding HIV infection risk, with young men of color who have sex with men disproportionately affected. A large body of research has identified highly impactful facilitators of and barriers to behavior change. Several efficacious interventions have been created that decrease the rate of new HIV infections among youth and reduce morbidity among youth living with HIV. However, full benefits that should be possible based on the tools and interventions currently available are yet to be realized in youth, in large part, because efficacious interventions have not been implemented in real-world settings. *Scale It Up* (SIU) primarily aims to assemble research teams that will ultimately bring to practice evidence-based interventions that positively impact the youth HIV prevention and care cascades, and in turn, advance the fields of implementation science and self-management science.

**Objective:**  This paper aims to describe the structure of the U19-SIU and the effectiveness-implementation hybrid trials, as well as other center-wide protocols and initiatives, implemented within SIU.

**Methods:**  SIU will achieve its aims through 4 individual primary protocols, 2 center-wide protocols, and 3 cross-project initiatives.

**Results:**  SIU was funded by National Institute for Child Health and Human Development (U19HD089875) and began in October 2016. As of November 2018, 6 SIU protocols have launched at least the first phase of work (ATN 144 SMART: Sequential Multiple Assignment Randomized Trial; ATN 145 YMHP: Young Men's Health Project; ATN 146 TMI: Tailored Motivational Interviewing Intervention; ATN 153 EPIS: Exploration, Preparation, Implementation, Sustainment model; ATN 154 CM: Cascade Monitoring; ATN 156 We Test: Couples' Communication and HIV Testing). Further details can be found in the individual protocol papers.

**Conclusions:**  To date, the youth HIV research portfolio has not adequately advanced the important care area of self-management. SIU protocols and initiatives address this broad issue by focusing on evaluating the effectiveness and implementation of self-management interventions. SIU is highly innovative for 5 primary reasons: (1) our research framework expands the application of "self-management"; (2) the 4 primary protocols utilize innovative hybrid designs; (3) our Analytic Core will conduct cost-effectiveness analyses of each intervention; (4) across all 4 primary protocols, our Implementation Science Core will apply implementation scales designed to assess inner and outer context factors; and (5) we shall advance understanding of the dynamics between provider and patient through analysis of recorded interactions.

## Introduction

The last 30 years have witnessed significant progress in the prevention and treatment of HIV/AIDS. Combination antiretroviral therapy (ART) has transformed HIV infection from a rapidly debilitating, fatal disease into a manageable chronic disease with high potential for a healthy life for multiple decades [1,2]. Combinations of >25 formulations of 6 classes of ART maintain the effectiveness of drug therapy in reducing viral transmission. Combined with widely available, accurate, and rapid HIV testing, pre-exposure prophylaxis (PrEP) for individuals at high risk, and universal viral suppression for those infected, an AIDS-free generation and the end to the global AIDS epidemic are ambitious, but achievable national and global goals [3,4].

However, despite growing optimism about this potentially achievable outcome, the epidemic remains a major and increasing cause of morbidity and mortality among adolescents and young adults (hereafter called "youth") and ethnic and racial minorities. Globally, youth living with HIV (YLH) are markedly less likely to receive ART than adults (23% vs 38%) [3,5-7]. In the United States, while the overall HIV incidence from 2003 to 2014 decreased by 25%, among youth aged 13-24 years, it has increased by 43% [8]. Moreover, among youth, new infections have not been evenly distributed. Several minority groups have been overly represented; almost three-fourths of new infections were among men who have sex with men (MSM), and over half of new infections were among African American youth [9]. Young MSM of color continue to see disproportionate HIV infection rates, and these clear disparities have guided the focus for the National HIV/AIDS Strategy for the United States [10].

For ART to be effective, YLH must develop self-management behaviors at every stage of the HIV treatment cascade—linkage to care, timely initiation of care, persistence, and adherence to ART. Similarly, youth at high-risk for HIV infection must develop self-management behaviors to be fully engaged in the HIV prevention cascade—routine HIV and sexually transmitted infections testing and PrEP knowledge, access, uptake, and adherence when warranted [10-12]. While multiple barriers across range systems affect the HIV prevention and treatment cascades for youth, self-management interventions focus on how to negotiate these barriers in their current state, developing resilience even in the face of such obstacles. A quarter century of behavioral intervention research has focused on improving self-management for primary and secondary HIV prevention. This large body of research has identified highly impactful facilitators of and barriers to behavior change and has created several efficacious interventions that decrease the rate of new HIV infections among youth and reduce morbidity among YLH.

However, full benefits that should be possible based on the tools and interventions currently available have yet to be realized in youth, in large part, because efficacious interventions have not been implemented in real-world settings. As a recent systematic review concluded, "As we move towards an era of universal treatment for HIV, the clinical and public health benefits of widening access to ART for adolescents will not be realized until cost-effective and sustainable service delivery interventions are widely implemented" [13].

Despite the success of the Center for Disease Control's (CDC's) program for disseminating evidence-based HIV-related behavioral interventions, a growing body of literature highlights substantial barriers to the effective implementation of these interventions in real-world settings [14] particularly those addressing self-management. Even less attention has been paid to the study of the implementation of behavioral interventions in HIV care settings [15], particularly in adolescent HIV clinics and community-based organizations. The *Scale It Up* (SIU) U19 was funded as a National Institutes of Health cooperative agreement as part of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). SIU is committed to the development and assessment of the effectiveness of theoretically and developmentally sound interventions to improve HIV prevention and care self-management and to accelerating the pace of implementation. The primary aim of SIU is to assemble research teams that will develop, test, and bring to practice theoretically and developmentally sound self-management interventions that positively impact the youth HIV prevention and care cascades. SIU protocols focus on implementing interventions that have already been shown to be culturally appropriate and efficacious in minority populations most impacted by the epidemic. By utilizing common models and methods across protocols, we hope to advance the fields of implementation science (IS) and self-management science.

## Methods

### Aims

SIU will achieve its aims through 4 primary study protocols (ATN 144 SMART: Sequential Multiple Assignment Randomized Trial; ATN 145 YMHP: Young Men's Health Project; ATN 146 TMI: Tailored Motivational Interviewing Intervention; ATN 156 We Test: Couples' Communication and HIV Testing) [16-18], 2 center-wide protocols (ATN 153 EPIS and ATN 154 Cascade Monitoring; Carcone et al, under review, and Pennar et al, under review), and 3 cross-project initiatives. A substantial amount of literature underscores the importance of shortening the time from conceptualization of a research idea to service delivery. This concern has led to the development of *effectiveness- implementation hybrid designs* to facilitate the transition of promising interventions into practice [19]. *Type 1*

*hybrid* designs maintain a primary focus on a rigorous evaluation of the intervention but also gather data that will inform a subsequent implementation program. *Type 2 hybrids* place a dual focus on assessing the effectiveness of the intervention and evaluating the implementation strategy. *Type 3 hybrid* designs also focus on the implementation strategy and its effect of adaption and fidelity, but, in addition, assess patient-level or subject-level outcomes such as symptoms or disease progression [19,20]. The 4 SIU primary study protocols include 2 Type 1 hybrids, 1 Type 2 hybrid, and 1 Type 3 hybrid. Two additional center-wide protocols measure contextual factors and cascade outcomes across the primary studies, and the 3 cross-project initiatives address cost-effectiveness, self-management constructs, and communication science within each protocol (Figure 1).

## Scale It Up Structure

SIU is organized into 3 cores as follows: Management Core (MC); Analytic Core (AC); and an Implementation Science Core (ISC). The MC includes a Recruitment and Enrollment Center that is responsible for protocol development, project management, clinical site communication, recruitment and retention, and data collection and management. Subject recruitment venues (SRVs) are both Web-based and actual physical sites (12 sites, 10 of which provide HIV care). Our SRVs were selected on the basis of the HIV incidence (as shown in Figure 2) and based on previous successful experience with the enrollment of youth into intervention trials. Virtual recruitment strategies include the following: (1) *Social Media*

*Recruitment* via national ad campaigns on social media sites; (2) *Geosocial Networking Apps Recruitment* —staff will also recruit through ads on geosocial networking dating apps using a pop-up message shown when a user first logs in and through a message sent by the app directly to the user's inbox; and (3) *Text-based Recruitment*— flyers and other recruitment materials will be distributed to HIV-related organizations and those serving youth. Using Trumpia, a popular short message service (SMS) text messaging marketing service, interested youth will text a keyword (eg, "RESEARCH") to a 5-digit number (eg, 99-000) to learn about how to screen for the protocols.

In addition, the MC includes a Community Engagement Center, with a Youth Community Advisory Board (YCAB) consisting of youth representatives from each of the 12 physical sites within SIU. The group meets virtually on a monthly basis and convenes annual in-person meetings. The SIU research team does not take the importance of meaningful community involvement in all aspects of our research lightly [21], with several of us having devoted a substantial portion of our research careers to cultivating such relationships [22-32]. Our YCAB develops their own strategic plan for community engagement, provide commentary on summaries of the protocols before they go to the field, and are included in discussions of progress and problems. The YCAB collaborates with investigators on how to best inform the communities about the planned research, that is, posting descriptions of the research projects at each site and discussions in advance of implementation with local staff and community representatives.

**Figure 1.** The effectiveness-implementation hybrid designs used in *Scale It Up* (SIU).

**Figure 2.** The HIV incidence in the United States and subject recruitment venue locations.
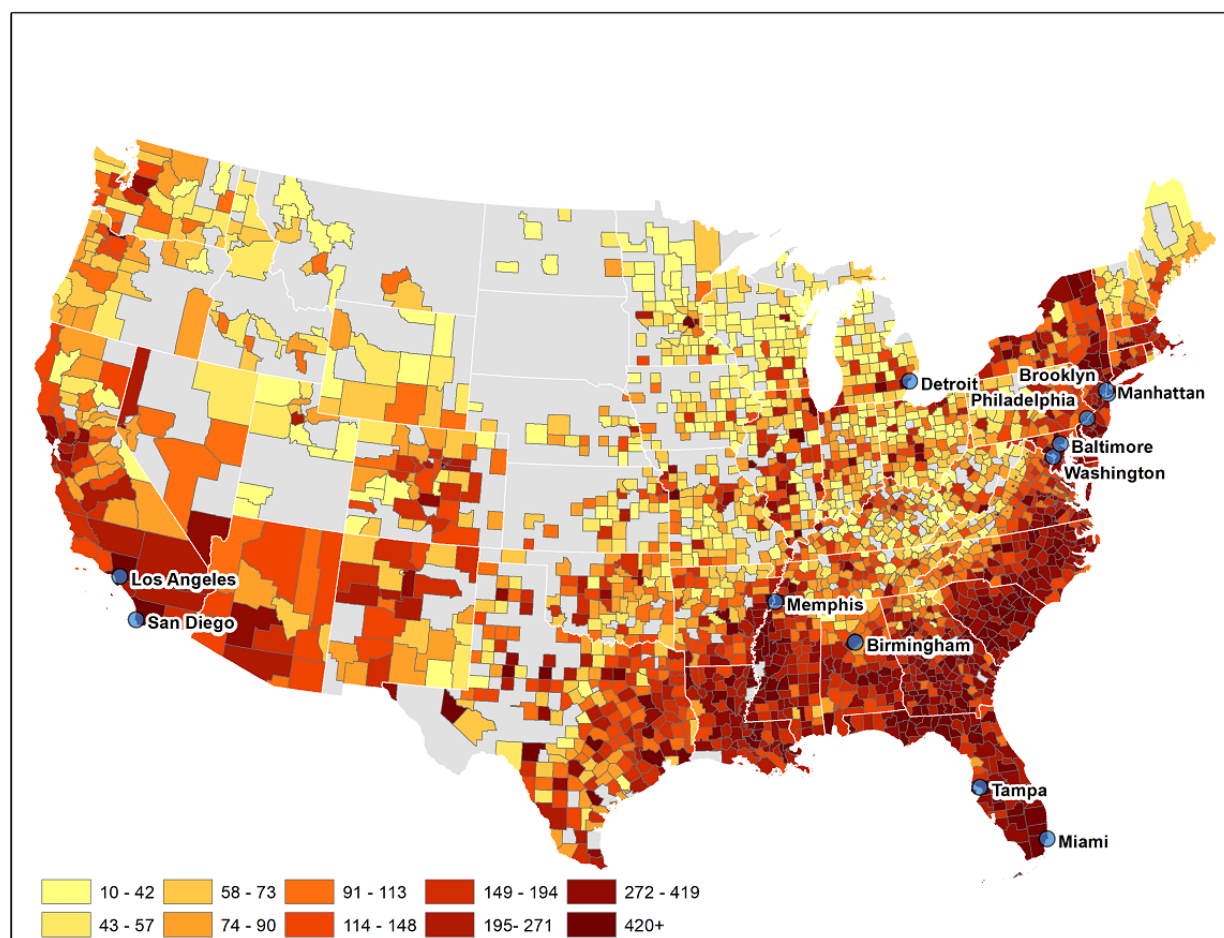


The YCAB will be involved in presenting the findings so that the community can understand them and in a fashion that will reach and be beneficial to community members. Furthermore, community and ATN provider input will be especially important with regard to implementing successful interventions beyond the network.

The AC provides optimal analytic support for the protocol development with the MC, statistical analysis plans for quantitative data, and the development of new methodologies and analytic strategies to accelerate the time from idea generation to program delivery. In addition, the AC facilitates the integration of scientific efforts and resources (including empirical data) across multiple research projects in a cost-effective way by providing a virtual platform for resource coordination and sharing and provide analytic support for center-wide protocols and initiatives. Finally, the AC aims to enhance the research capacity of participating institutes or investigators in areas of adolescent HIV self-management and IS through training and mentoring in advanced and innovative research methodologies, fostering high-quality research, data sharing, and improving the scholarly productivity of the network investigators, especially early career investigators.

The ISC facilitates a unified approach to IS research by applying a unified IS model to strengthen planning and implementation. The ISC provides core measures for understanding contextual

factors and assessing intervention fidelity and maintains a library of categorized research papers. The ISC develops facilitator training and support resources and tools for wide-scale intervention implementation and researchers' strategies or commercialization models for publishing the intervention products or preparing for the next steps with the interventions. Finally, the ISC develops and maintains the SIU website both internal for the center, as well as for the public, and supports early-stage investigators to develop IS studies.

## Regulatory

SIU uses a single Institutional Review Board (IRB) to accelerate the timeline of clinical research. All SRVs and investigator institutions sign reliance agreements with the IRB of record, which is located at Florida State University. While SRVs receive regular updates and notices of continuations or changes in protocol, amendments are only submitted to the IRB of record. A waiver of parental consent or assent is obtained for participants who are 15-17 years old. All clinical trials are registered on ClinicalTrials.gov, and all protocols utilize the ATN Certificate of Confidentiality. SIU utilizes a single monitoring system for all protocols to harmonize review standards across protocols. The review process of the most vulnerable protocol will be applied to all SIU protocols, thereby ensuring adequate oversight. An independent study monitoring committee consists of 3 independent experts who possess the

relevant expertise (eg, HIV-related research and prevention, adolescent medicine, and sexual health) to evaluate each center protocol and who do not have a conflict of interest. The committee will review each protocol and monitor data and safety monitoring every 6 months, with additional ad-hoc reviews as necessary.

## Results

### Scale It Up Protocols and Initiatives

The SIU U19 cores evaluate and prepare for implementation self-management interventions to increase the likelihood that youth will be adherent with each step of the HIV prevention and care cascades with 4 individual effectiveness-implementation hybrid trial protocols and 2 center-wide protocols that assess contextual implementation factors and cascade outcomes. Furthermore, the cross-project initiatives of cost-effectiveness analyses, analysis of a theoretically driven self-management model, and analysis of patient-provider communication are incorporated into multiple protocols.

### Effectiveness-Implementation Hybrid Trials

The individual project protocols are described later in this supplement. The following is a brief synopsis of each (Figure 3).

*ATN 144* is a SMART design that tests the sequencing of SMS text message cell phone support (CPS), and contingency management in youth nonadherent to ART [16]. All study procedures will be conducted over the Web or by phone so that youth need not attend a clinic to participate, and clinics only need to refer participants to the study website instead of staffing for recruitment. As a Type 1 effectiveness-implementation hybrid, while implementation context will be assessed, the focus is on the intervention effectiveness in true real-world settings (in and out of the clinic and across the nation). Youth are first randomized to 12 weeks of CPS versus SMS text messaging. Several critical issues surrounding incentives and intervention tapering are explored through a second randomization—(1) if CPS or SMS text messaging for 12 weeks is successful, does viral load (VL) suppression persist longer if the intervention dose is tapered (ie, less frequent) over the next 12 weeks versus terminating CPS and receiving standard care; (2) if CPS or SMS text messaging is not successful in the first 12 weeks, will VL suppression occur if incentives for intervention adherence are added for 12 more weeks; and (3) if CPS or SMS text messaging is not successful, will VL suppression occur if youth receive the other intervention condition (with the addition of incentives) or if they are allowed 12 more weeks within their initial condition (with the addition of incentives). Details are provided in ATN 144 SMART [16].

**Figure 3.** Scale It Up (SIU) overall. PreP: pre-exposure prophylaxis. STI: sexually transmitted infection.
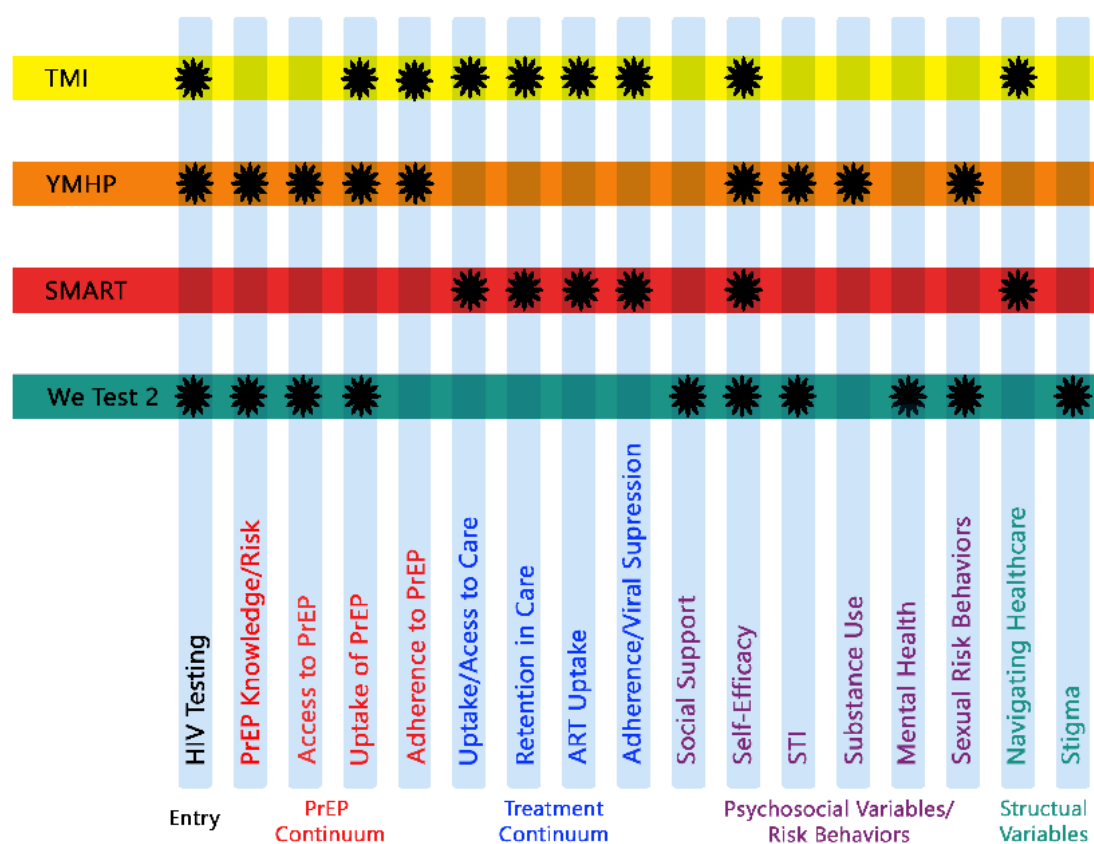
*ATN145,* the YMHP, tests a 4-session intervention integrating motivational interviewing (MI), personalized feedback, and problem-solving skills to reduce condomless anal sex (CAS) and substance use among HIV-negative young MSM (Parsons et al, under review). Previous studies have found that youth receiving YMHP reported markedly greater reductions in CAS and substance use than youth in the comparison condition, and the CDC recently rated YMHP as "Best Evidence" and included it in the compendium of Evidence-Based Interventions for HIV Prevention [33]. YMHP now requires evaluation through an effectiveness-implementation Hybrid Type 2 trial to both provide the best evidence to inform practitioners as to which approach to delivery (clinic-based or phone-based) is most effective and cost-effective prior to dissemination on a wider scale (comparative effectiveness design) while simultaneously testing a model of intervention implementation through training local supervisors and studying contextual barriers and facilitators. The trial will assess HIV prevention-focused outcomes (sexually transmitted infections, PrEP uptake) and self-management behaviors (condom use, reduction in substance use, PrEP adherence if uptake is achieved), as well as intervention fidelity. Participants complete the 4-session intervention and an immediate posttest assessment 3 months after the baseline. They are then assessed every 3 months for 12 months postintervention. Details are provided in ATN 145 YMHP (Parsons et al, under review).

*ATN 146*, TMI [17] addresses the training of health care providers to deliver MI, a method of communication shown to improve multiple points across the youth prevention and care cascades [27,34-45]. Pilot work to develop the TMI included tailoring initial workshop training based on innovative methods in communication science, developing efficient fidelity measurement, and preliminary testing of implementation strategies. The effect of TMI on fidelity to the original evidence-based program, and secondarily on cascade-related outcomes (see ATN 154 below), will be achieved by using a dynamic waitlist-controlled design with 150 providers nested within the 10 clinical care sites of our 12 physical SRVs, yielding 5 clusters to receive TMI. For each randomization, 2 of the clinics receive TMI, and the others remain in the wait-list condition. This will continue until the fifth cluster has been randomized to TMI. After 1 year of TMI's external facilitation based on the dynamic adaptation process, second randomization will compare internal facilitator monitoring and coaching plus the encouragement of communities of practice to communities of practice alone. Fidelity will be assessed using ratings of standard patient interactions on a quarterly basis through the 24 months of intervention and an additional 6 months of follow-up. As a Hybrid Type 3 Implementation-Effectiveness, the primary focus is also on exploring the role of the barriers and facilitators to implementation with repeated qualitative interviews and quantitative surveys of implementation context (see ATN 153 below). Details are provided in ATN 146 TMI [17].

*ATN 156,* Enhancing Sexual Safety: Couples' Communication and HIV Testing Among YMSM (We Test), is a comparative effectiveness trial of couples HIV testing and counseling (CHTC) for adolescent age (15-19 years) same-sex male couples [18]. This design tests the added benefits of adjunct intervention components delivered prior to receipt of CHTC-Assertive Communication Training (CT) videos viewed by the couple together and individually delivered MI-based Communication Skills Training (MI-CST). These target the development of communication skills necessary to participate fully in HIV prevention and sexual safety discussions inherent to CHTC. This protocol will assess a continuum of intervention packages to address the developmental needs of young MSM (CHTC; CT videos + CHTC; MI-CST + CT videos + CHTC) to identify which package optimizes outcomes while minimizing delivery cost. Participants complete the intervention session and an immediate posttest assessment 3 months after the baseline; they are then assessed every 3 months for 9 months postintervention. Details are provided in ATN 156 We Test [18].

## Center-Wide Protocols and Initiatives

The 4 primary protocols, with support from the 3 cores, *defacto* form center-wide protocols and cross-project initiatives, exploiting synergies created by our U19 and creating value-added scientific contributions that would not be possible from individual projects alone or through traditional R01-level funding. First, individually and collectively, the 4 research protocols are guided by the same IS conceptual model. SIU employs the National Institutes of Health's definition of implementation "the use of strategies to introduce or change evidence-based health interventions within specific settings" [46]. While implementation and dissemination models now abound, we selected an adapted version of Aaron's EPIS model to guide our work as it is logical, evidence-based [47,48], supported by a growing number of evidence-based instruments [49], and has broad reach among youth HIV researchers (see Figure 1). Thus, ATN 153 EPIS (Carcone et al, under review), described later in this supplement, is a mixed-methods study that includes qualitative interviews and quantitative surveys with staff at 12 physical SRVs to assess barriers and facilitators of the adoption and use of evidence-based behavioral interventions in general and project-specific interventions. Anticipated factors are assessed at the baseline, factors identified during implementation are assessed at 12-18 months postbaseline, and factors identified during sustainment are assessed at 24-30 months postbaseline.

The 10 clinical care sites in SIU will provide deidentified data from electronic health records regarding demographics and HIV treatment cascade variables annually in ATN 154 Cascade Monitoring (Pennar et al, under review). These data will not only serve as outcomes of implementation but also will provide rough but rapid estimations of demographic indices and measures of response (such as new care entry and percent viral suppression) that can provide useful indicators of the epidemic at large for ATN strategic planning. In addition, we hoped to capture prevention cascade variables, but early interviews with the clinical sites determined that consistency in electronic record documentation of these variables was not sufficient for this protocol. Thus, the ATN is developing a new cross-network protocol to assess the capability of all recruitment venues to provide consistent and valid prevention and treatment cascade records and develop an intervention to achieve this end (ATN 162).

Several initiatives are represented across the protocols. First, the 3 primary protocols gathering data from youth (ATN 144 SMART, ATN 145 YMHP, and ATN 156 We Test) are guided by the same theoretical model for self-management [50]. According to the Five Components Model, self-management includes 5 essential skills—*problem solving*, *decision making*, *resource utilization*, *forming of a patient/heath care provider partnership*, and *taking action* [50,51]. Thus, all 3 protocols will include the following measures: (1) the BRIEF [52] to assess both problem solving and decision making; (2) Patient Activation Measure [53] in which participants rate the relationship with their providers and the degree to which they are involved in their care using a 4-point Likert scale; (3) an adapted version of the 12-item Services and Support measure utilized in ATN 004 (Healthy Choices) [54] to capture participant self-report of health care and related services (eg, emergency department care, hospitalizations, residential substance use treatment facilities, case management, and support group; *resource utilization*); and (4) self-reported medication adherence and condom use and viral suppression (*taking action*). The model will be tested utilizing Structural Equation Modeling with 820 youth.

Second, given the importance of *provider-patient interactions* in encouraging youth self-management, we plan to identify provider communication behaviors that predict self-management and health outcomes using innovative sequential analysis [55,56] of coded audiorecordings across all 4 primary protocols. We will use MI as a framework (eg, emphasizing autonomy and reflections of change talk) using the Minority Youth Sequential Code of Process Exchanges (MY-SCOPE), adapted from existing MI coding schemes [57]. This analysis generates transition probabilities for patient-provider communication sequences, allowing provider communication behaviors to predict subsequent youth communication and, then, later link to youth outcomes (Figure 4).

Finally, we will determine the relative cost-effectiveness of interventions within each primary protocol to assist in the implementation and rapid diffusion of effective and cost-effective interventions in the practice community. Each protocol will collect detailed resource use for the interventions using consistent methods. These data will be assigned standard cost weights developed by the AC for performing incremental cost-effectiveness analyses across studies. The use of resource use measures with standard cost values will assure that the economic analyses associated with the clinical trial meet the International Society for Pharmacoeconomics and Outcomes Research Good Practices for Economic Evaluation Alongside Clinical Trials [58]. We will use a modification of The Drug Abuse Treatment Cost Analysis Program (DATCAP) [59,60], combined with study contract and expenditure records, capturing both contractually allowed expenditures, and relevant expenditures supported from other budgets, to estimate the cost of the CPS and SMS text messaging conditions.

**Figure 4.** Self-management components.
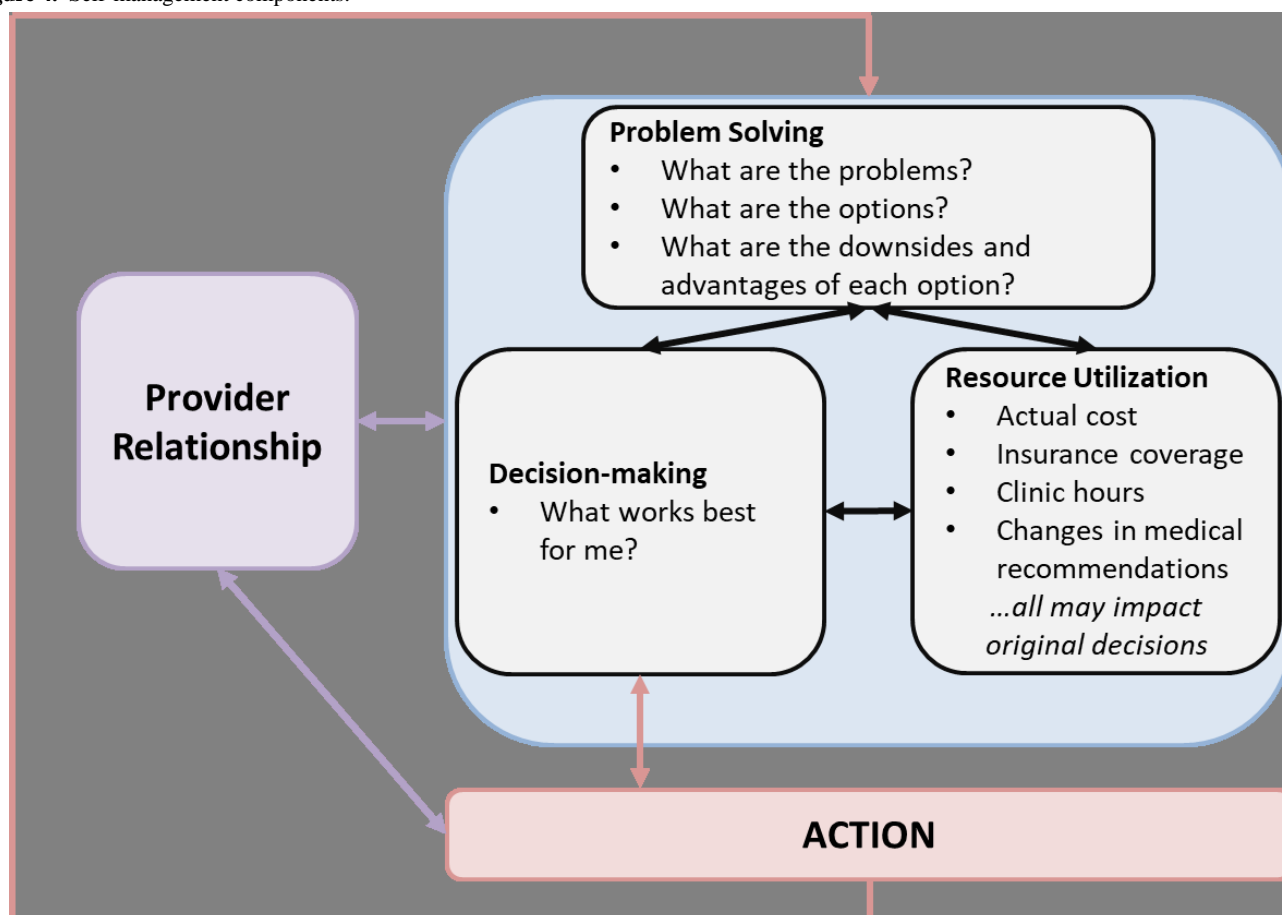
The DATCAP is a standardized instrument that estimates the economic cost of alcohol and other drug treatment programs (eg, personnel, facilities, and supplies). Client case flow data are incorporated to determine the average weekly and annual cost or client for each service type, average cost per intervention episode, and marginal cost per contact.

When available, data on sexual activity will be collected to be used with recent national estimates [61] of cost per HIV infection avoided, and/or on cost per HIV infection delayed, a more conservative measure. This will allow the estimation of potential cost savings in a reduction in new HIV infections. If warranted by study findings, we will use a previously validated Markov decision analysis model [62] to estimate the expected treatment cost savings resulting from the increase in time with suppressed VL. The resource use measures and cost data collected will be used to develop budget impact scenarios to help inform "scale up" and diffusion planning for the most cost-effective intervention combinations.

## Discussion

### Principal Findings

A dramatic decline in HIV transmission is achievable with currently available protocols and interventions (including ART, PrEP, rapid and widespread testing); however, such decline has not yet been realized among youth. Our goal must be complete self-management as mathematical modeling indicates that even achieving 90% compliance at different points on the cascade is insufficient to curb the epidemic [11]. Self-management is critical and complex at any age, but may be especially challenging among adolescents and emerging adults as they transition from a largely dependent to a more independent status ("transition to self-management") [63] during a developmental period marked by identity exploration, development of new social networks, increased opportunities and choices, both positive and risk-laden [64], and increased independence and risk-taking behavior [65,66]. The transition to adult health care can be abrupt and can occur with little preparation because age, rather than developmental maturity, triggers the transition. Given these developmental and systemic challenges, it is not surprising that self-management tends to deteriorate during this transitional period [54,67]. New approaches to HIV education, prevention, and treatment of youth must be integrated with issues in self-management to achieve an AIDS-free generation and/or the end of the AIDS epidemic by 2030 in the United States and globally [3,4]. To date, the youth HIV research portfolio has not adequately advanced this important care area [13]. SIU protocols and initiatives address the broad issue of persistent disproportionately high rates of HIV infection among youth and failure to engage in the HIV prevention and treatment cascades [68] by focusing on evaluating the effectiveness and implementation of self-management interventions.

SIU is highly innovative for 5 primary reasons. First, the 4 primary study protocols utilize innovative hybrid designs to capture critical information to facilitate and expedite the introduction of effective programs into practice by exploring important implementation issues while testing the effectiveness [19,20]. In keeping with the theme of expeditiously and parsimoniously assessing intervention effectiveness and moving it to practice, we shall use innovations in evaluating the intervention effectiveness, a SMART [69], 2 comparative effectiveness trials [70], and a Dynamic Wait List-controlled trial [71]. Second, our research framework expands the application of "self-management" from the *management of chronic disease* [72,73] to the *prevention* [74] *and management of chronic disease*, HIV/AIDS. We will test an innovative theoretical model of self-management over time among all enrolled youth in SIU protocols (N=500) using standardized measures. Third, our AC will conduct cost-effectiveness analyses of each intervention within the 4 primary study protocols, enabling us to compare the effectiveness and cost-effectiveness to further shorten the research to practice gap. Fourth, across all 4 primary protocols, our ISC will apply implementation scales designed to assess *inner* and *outer context* factors based on a strong theoretical model [47-49,75] to determine their relevance to fidelity and sustainability both for evidence-based behavioral practice in general and for interventions grounded in MI as the method of communication. Fifth, we shall advance understanding of the dynamics between the provider and patient by introducing an analytic approach from Communication Science ("sequential analysis") to the provider-youth interaction across all 4 primary protocols through analysis of recorded interactions [76].

### Limitations

Challenges experienced to date include the inexperience of SRVs in single Internal Review Board and reliance agreements, recruitment and retention difficulties when staff are participants in implementation trials, recruitment of high-risk YLH who are nonadherent to ARVs outside of the clinic setting and obtaining VL data for those youth who are not regularly attending clinic, inexperience of clinical sites in electronic health record downloads, and the need for communication systems for complex protocols with multiple moving parts.

### Conclusions

In summary, the 4 SIU primary protocols, 2 center-wide protocols, 3 cross-project initiatives, and 3 supporting cores are highly integrated and carefully constructed to support the overarching themes of improved self-management on the part of YLH and at-risk youth and expeditious, but appropriate, implementation of effective prevention and treatment programs into practice in a cost-effective manner. We aspire to address specific research hypotheses concerning the HIV prevention or care cascades for youth while advancing self-management theory and IS. This agenda is dependent on the synergy of connections between these protocols, initiatives and cores and our clinical and community partners, without which these advances would not be achievable.

Given that SIU implements multiple protocols and initiatives, managing this multifaceted U19 project has proved challenging. The challenges range from recruiting participants from clinics with a smaller than expected pool to select from (both among staff and YLH) to grant transfer delays between institutions, as well as IRB and reliance agreements, which, in turn, creates a substantial bureaucratic burden. Nevertheless, these challenges did inform the cores on how to learn from and adapt to the

always changing landscape of SIU. At the bureaucratic level, the cores found that maintaining close contact with IRB and financial administrators allows SIU to operate efficiently. At the clinic level, the cores learned that sites rely on ATN support for infrastructure and that even the simplest of protocols can prove difficult to implement. For example, the small pool of participants and participation from multiple sites required innovative approaches for recruitment, data collection, and interventions. As mentioned before, SIU specifically focuses on the process of improving self-management among youth (both YLH and at-risk youth). For these evidence-based practices within SIU to be effective, youth must be fully engaged in interventions at every stage of the HIV care (treatment and prevention) cascades. SIU initially seeks to implement within clinics, outside of the research context, and ultimately assess if clinics have the capacity to implement these interventions independently, thus improving health outcomes for the targeted youth populations.

## Acknowledgments

## Conflicts of Interest

None declared.

## References

1.   El-Sadr WM, Holmes CB, Mugyenyi P, Thirumurthy H, Ellerbrock T, Ferris R, et al. Scale-up of HIV treatment through PEPFAR: a historic public health achievement. J Acquir Immune Defic Syndr 2012 Aug 15;60 Suppl 3:S96-104 [FREE Full text] [doi: 10.1097/QAI.0b013e31825eb27b] [Medline: 22797746]

2.   Kanters S, Mills EJ, Thorlund K, Bucher HC, Ioannidis JPA. Antiretroviral therapy for initial human immunodeficiency virus/AIDS treatment: critical appraisal of the evidence from over 100 randomized trials and 400 systematic reviews and meta-analyses. Clin Microbiol Infect 2014 Feb;20(2):114-122 [FREE Full text] [doi: 10.1111/1469-0691.12475] [Medline: 24274661]

3.   Fauci AS, Folkers GK. Toward an AIDS-free generation. JAMA 2012 Jul 25;308(4):343-344. [doi: 10.1001/jama.2012.8142] [Medline: 22820783]

4.   Joint United Nations Programme on HIV/AIDS (UNAIDS). Fast-Track - Ending the AIDS epidemic by 2030. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2014. URL: http://www.unaids.org/en/resources/documents/2014/JC2686_WAD2014report [accessed 2019-01-10] [WebCite Cache ID 75K8JzGpZ]

5.   Porth T, Suzuki C, Gillespie A, Kasedde S, Ideleditors. Disparities and trends in AIDS mortality among adolescents living with HIV in low- and middle-income countries. In: 20th International AIDS Conference. 2014 Presented at: 20th International AIDS Conference; July 21, 2014; Melbourne, Australia.

6.   UNICEF. Children, Adolescents and AIDS. New York, NY: UNICEF; 2014. URL: https://www.unicef.org/publications/files/Children_and_AIDS_Sixth_Stocktaking_Report_EN.pdf [WebCite Cache ID 75qCE7Ruc]

7.   United Nations. The Millennium Development Goals Report 2014. New York: United Nations; 2014 Jul 7. URL: http://www.un.org/millenniumgoals/2014%20MDG%20report/MDG%202014%20English%20web.pdf [accessed 2019-01-10] [WebCite Cache ID 75K8Sifur]

8.   Frieden TR, Foti KE, Mermin J. Applying Public Health Principles to the HIV Epidemic--How Are We Doing? N Engl J Med 2015 Dec 03;373(23):2281-2287. [doi: 10.1056/NEJMms1513641] [Medline: 26624243]

9.   Centers F. Vital signs: HIV infection, testing, and risk behaviors among youths - United States. MMWR Morb Mortal Wkly Rep 2012 Nov 30;61(47):971-976 [FREE Full text] [Medline: 23190571]

10.  The White House Office of National AIDS Policy. National HIV/AIDS Strategy for the United States: Updated to 2020. Washington, DC: The White House Office of National AIDS Policy; 2015. URL: https://files.hiv.gov/s3fs-public/nhas-update.pdf [accessed 2019-01-10] [WebCite Cache ID 75K8YqbBk]

11.  Gardner EM, McLees MP, Steiner JF, Del RC, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis 2011 Mar 15;52(6):793-800 [FREE Full text] [doi: 10.1093/cid/ciq243] [Medline: 21367734]

12.  The White House Office of National AIDS Policy. National HIV/AIDS Strategy for the United States. Washington, DC: The White House Office of National AIDS Policy; 2010. URL: https://obamawhitehouse.archives.gov/sites/default/files/uploads/NHAS.pdf [WebCite Cache ID 75qCHlLpN]

13.  MacPherson P, Munthali C, Ferguson J, Armstrong A, Kranzer K, Ferrand RA, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. Trop Med Int Health 2015 Aug;20(8):1015-1032 [FREE Full text] [doi: 10.1111/tmi.12517] [Medline: 25877007]

14. Norton WE, Amico KR, Cornman DH, Fisher WA, Fisher JD. An agenda for advancing the science of implementation of evidence-based HIV prevention interventions. AIDS Behav 2009 Jun;13(3):424-429 [FREE Full text] [doi: 10.1007/s10461-009-9556-8] [Medline: 19360464]

15. Schackman BR. Implementation science for the prevention and treatment of HIV/AIDS. J Acquir Immune Defic Syndr 2010 Dec;55 Suppl 1:S27-S31 [FREE Full text] [doi: 10.1097/QAI.0b013e3181f9c1da] [Medline: 21045596]

16. Belzer M, MacDonnell K, Ghosh S, Naar S, MacAvoy-Banerjea J, Gurung S, et al. Adaptive Antiretroviral Therapy Adherence Interventions for Youth Living with HIV Through Text Message and Cell Phone Support With and Without Incentives: Sequential Multiple Assignment Randomized Trial (SMART) Design. JMIR Res Protoc. Epub ahead of print DOT:10.2196/11183 2018 (forthcoming). [doi: 10.2196/11183]

17. Naar S, MacDonnell K, Chapman J, Todd L, Gurung S, Cain D, et al. Tailored Motivational Interviewing (TMI) Implementation-Effectiveness Trial in Multidisciplinary Adolescent HIV Care Settings. JMIR Res Protoc. Epub ahead of print DOT:10.2196/11200 2018 (forthcoming). [doi: 10.2196/11200]

18. Starks TJ, Feldstein ES, Lovejoy T, Gurung S, Cain D, Borkowski T, et al. Enhancing Sexual Safety: Couples' Communication and HIV Testing Among YMSM. JMIR Research Protocols. Epub ahead of print DOT:10.2196/11186 2018 (forthcoming). [doi: 10.2196/11186]

19. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]

20. Bernet AC, Willens DE, Bauer MS. Effectiveness-implementation hybrid designs: implications for quality improvement science. Implementation Sci 2013;8(Suppl 1):S2. [doi: 10.1186/1748-5908-8-S1-S2]

21. Wallerstein NB, Duran B. Using community-based participatory research to address health disparities. Health Promot Pract 2006 Jul;7(3):312-323. [doi: 10.1177/1524839906289376] [Medline: 16760238]

22. Galbraith J, Ricardo I, Stanton B, Black M, Feigelman S, Kaljee L. Challenges and Rewards of Involving Community in Research: An Overview of the "Focus on Kids" HIV Risk Reduction Program. Health Education Quarterly 2016 Sep 04;23(3):383-394. [doi: 10.1177/109019819602300308]

23. Hightow-Weidman LB, Jones K, Wohl AR, Futterman D, Outlaw A, Phillips G, YMSM of Color SPNS Initiative Study Group. Early linkage and retention in care: findings from the outreach, linkage, and retention in care initiative among young men of color who have sex with men. AIDS Patient Care STDS 2011 Aug;25 Suppl 1:S31-S38. [doi: 10.1089/apc.2011.9878] [Medline: 21711141]

24. Naar-King S, Outlaw AY, Sarr M, Parsons JT, Belzer M, Macdonell K, Adolescent Medicine Network for HIV/AIDS Interventions. Motivational Enhancement System for Adherence (MESA): pilot randomized trial of a brief computer-delivered prevention intervention for youth initiating antiretroviral treatment. J Pediatr Psychol 2013 Jul;38(6):638-648 [FREE Full text] [doi: 10.1093/jpepsy/jss132] [Medline: 23359664]

25. Nanin JE, Bimbi DS, Grov C, Parsons JT. Community reactions to a syphilis prevention campaign for gay and bisexual men in Los Angeles County. J Sex Res 2009 Nov;46(6):525-534 [FREE Full text] [doi: 10.1080/00224490902829590] [Medline: 19291502]

26. Nanín JE, Parsons JT, Bimbi DS, Grov C, Brown JT. Community reactions to campaigns addressing crystal methamphetamine use among gay and bisexual men in New York City. J Drug Educ 2006 Jul;36(4):297-315 [FREE Full text] [doi: 10.2190/9818-1W43-1876-2062] [Medline: 17533803]

27. Outlaw AY, Naar-King S, Parsons JT, Green-Jones M, Janisse H, Secord E. Using motivational interviewing in HIV field outreach with young African American men who have sex with men: a randomized clinical trial. Am J Public Health 2010 Apr 01;100 Suppl 1:S146-S151. [doi: 10.2105/AJPH.2009.166991] [Medline: 20147689]

28. Outlaw AY, Naar-King S, Tanney M, Belzer ME, Aagenes A, Parsons JT, Adolescent Medicine Trials Network for HIV/AIDS Interventions. The initial feasibility of a computer-based motivational intervention for adherence for youth newly recommended to start antiretroviral treatment. AIDS Care 2014 Jan;26(1):130-135 [FREE Full text] [doi: 10.1080/09540121.2013.813624] [Medline: 23869650]

29. Outlaw AY, Phillips G, Hightow-Weidman LB, Fields SD, Hidalgo J, Halpern-Felsher B, Young MSM of Color SPNS Initiative Study Group. Age of MSM sexual debut and risk factors: results from a multisite study of racial/ethnic minority YMSM living with HIV. AIDS Patient Care STDS 2011 Aug;25 Suppl 1:S23-S29. [doi: 10.1089/apc.2011.9879] [Medline: 21711140]

30. Pachankis JE, Lelutiu-Weinberger C, Golub SA, Parsons JT. Developing an online health intervention for young gay and bisexual men. AIDS Behav 2013 Nov;17(9):2986-2998 [FREE Full text] [doi: 10.1007/s10461-013-0499-8] [Medline: 23673791]

31. Stanton B, Cole M, Li X, Kaljee L, Galbraith J, Cottrell L. Preventionrisk reduction among adolescents: A 16 year community-research partnership. In: Rhodes TC. editor. Focus on Adolescent Behavior Research Frontiers. Hauppauge, NY: Nova Science Publishers; 2007:A-16.

32. Stanton B, Galbraith J, Kaljee L. The Uncharted Path from Clinic-Based to Community-Based Research. Hauppauge, NY: Nova Science Publishers; 2008:978-971.

33.   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]

34.   Miller W, Rollnick S. The atmosphere of change. In: Miller WR, Rollnick S. editors. Motivational interviewing: Preparing people to change addictive behavior. New York, NY: The Guilford Press; 1991:3-13.

35.   Naar-King S. In: Suarez M, editor. Motivational Interviewing with Adolescents and Young Adults. New York: Guilford Publications, Inc; 2011.

36.   Lundahl BW, Kunz C, Brownell C, Tollefson D, Burke BL. A Meta-Analysis of Motivational Interviewing: Twenty-Five Years of Empirical Studies. Research on Social Work Practice 2010 Jan 11;20(2):137-160. [doi: 10.1177/1049731509347850]

37.   Chen X, Murphy DA, Naar-King S, Parsons JT, Adolescent MTNFHI. A clinic-based motivational intervention improves condom use among subgroups of youth living with HIV. J Adolesc Health 2011 Aug;49(2):193-198. [doi: 10.1016/j.jadohealth.2010.11.252] [Medline: 21783053]

38.   Naar-King S, Outlaw A, Green-Jones M, Wright K, Parsons JT. Motivational interviewing by peer outreach workers: a pilot randomized clinical trial to retain adolescents and young adults in HIV care. AIDS Care 2009 Jul;21(7):868-873. [doi: 10.1080/09540120802612824] [Medline: 20024744]

39.   Naar-King S, Parsons JT, Murphy DA, Chen X, Harris DR, Belzer ME. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. Arch Pediatr Adolesc Med 2009 Dec;163(12):1092-1098 [FREE Full text] [doi: 10.1001/archpediatrics.2009.212] [Medline: 19996045]

40.   Mbuagbaw L, Ye C, Thabane L. Motivational interviewing for improving outcomes in youth living with HIV. Cochrane Database Syst Rev 2012 Sep 12(9):CD009748. [doi: 10.1002/14651858.CD009748.pub2] [Medline: 22972147]

41.   Bartlett J, Cheever L, Johnson M, Paauw D. A guide to primary care of people with HIV/AIDS. Rockville, MD: U.S. Department of Health and Human Services; 2004.

42.   Kahn J. Predictors of papanicolaou smear return in a hospital-based adolescent and young adult clinic. Obstetrics & Gynecology 2003 Mar;101(3):490-499. [doi: 10.1016/S0029-7844(02)02592-9]

43.   Magnus M, Jones K, Phillips G, Binson D, Hightow-Weidman LB, Richards-Clarke C, YMSM of color Special Projects of National Significance Initiative Study Group. Characteristics associated with retention among African American and Latino adolescent HIV-positive men: results from the outreach, care, and prevention to engage HIV-seropositive young MSM of color special project of national significance initiative. J Acquir Immune Defic Syndr 2010 Apr 01;53(4):529-536. [doi: 10.1097/QAI.0b013e3181b56404] [Medline: 19755914]

44.   New York State Department of Health. Substance use and dependence among HIV-infected adolescents and young adults. New York, NY: New York State Department of Health; 2009.

45.   Centers for Disease Control Prevention, HIV/AIDS Prevention Research Synthesis Project. Compendium of HIV Prevention Interventions with Evidence of Effectiveness. Atlanta, GA: Centers for Disease Control and Prevention; Nov 1999.

46.   National Institute for Mental Health. Dissemination and Implementation Research in Health (R01). Bethesda, MD: National Institutes of Health; 2005. URL: https://grants.nih.gov/grants/guide/pa-files/PAR-06-039.html [accessed 2018-11-26] [WebCite Cache ID 74E4ELJwA]

47.   Aarons GA, Hurlburt M, Horwitz SM. Advancing a conceptual model of evidence-based practice implementation in public service sectors. Adm Policy Ment Health 2011 Jan;38(1):4-23 [FREE Full text] [doi: 10.1007/s10488-010-0327-7] [Medline: 21197565]

48.   Novins DK, Green AE, Legha RK, Aarons GA. Dissemination and implementation of evidence-based practices for child and adolescent mental health: a systematic review. J Am Acad Child Adolesc Psychiatry 2013 Oct;52(10):1009-1025.e18 [FREE Full text] [doi: 10.1016/j.jaac.2013.07.012] [Medline: 24074468]

49.   California Evidence-Based Clearinghouse for Child Welfare. Implementation Measures. San Diego, CA; 2018. URL: http://www.cebc4cw.org/implementing-programs/tools/measures/ [accessed 2018-11-26] [WebCite Cache ID 74E5GAg29]

50.   Center for the Advancement of Health. Essential elements of self-management interventions. Washington, DC:: Center for the Advancement of Health; 2002.

51.   Grady PA, Gough LL. Self-management: a comprehensive approach to management of chronic conditions. Am J Public Health 2014 Aug;104(8):e25-e31. [doi: 10.2105/AJPH.2014.302041] [Medline: 24922170]

52.   Roth R, Isquith P, Gioia G. PARiConnect. 2005. Behavior rating inventory of executive function-adult version (BRIEF-A) URL: https://www.parinc.com/Products/Pkey/25

53.   King S, King G, Rosenbaum P. Evaluating Health Service Delivery to Children With Chronic Conditions and Their Families: Development of a Refined Measure of Processes of Care (MPOC–20). Children's Health Care 2004 Mar;33(1):35-57. [doi: 10.1207/s15326888chc3301_3]

54.   Macdonell KE, Naar-King S, Murphy DA, Parsons JT, Harper GW. Predictors of medication adherence in high risk youth of color living with HIV. J Pediatr Psychol 2010 Jul;35(6):593-601 [FREE Full text] [doi: 10.1093/jpepsy/jsp080] [Medline: 19755495]

55.   Creswell J, Klassen A, Plano CV, Smith K. Best practices for mixed methods research in the health sciences. Bethesda, MD: National Institutes of Health; 2011.

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56. Ivankova NV. Using Mixed-Methods Sequential Explanatory Design: From Theory to Practice. Field Methods 2006 Feb 01;18(1):3-20. [doi: 10.1177/1525822X05282260]

57. Carcone AI, Naar S, Eggly S, Foster T, Albrecht TL, Brogan KE. Comparing thin slices of verbal communication behavior of varying number and duration. Patient Educ Couns 2015 Feb;98(2):150-155 [FREE Full text] [doi: 10.1016/j.pec.2014.09.008] [Medline: 25441095]

58. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. BMJ 2011 Apr 07;342(apr07 2):d1548-d1548. [doi: 10.1136/bmj.d1548]

59. French M. Drug Abuse Treatment Cost Analysis Program (DATCAP): User's Manual Eighth Edition. Miami, FL: University of Miami; 2003.

60. French MT, Dunlap LJ, Zarkin GA, McGeary KA, Thomas McLellan A. A structured instrument for estimating the economic cost of drug abuse treatment. Journal of Substance Abuse Treatment 1997 Sep;14(5):445-455. [doi: 10.1016/S0740-5472(97)00132-3]

61. Schackman BR, Fleishman JA, Su AE, Berkowitz BK, Moore RD, Walensky RP, et al. The lifetime medical cost savings from preventing HIV in the United States. Med Care 2015 Apr;53(4):293-301 [FREE Full text] [doi: 10.1097/MLR.0000000000000308] [Medline: 25710311]

62. Simpson KN, Pei PP, Möller J, Baran RW, Dietz B, Woodward W, et al. Lopinavir/ritonavir versus darunavir plus ritonavir for HIV infection: a cost-effectiveness analysis for the United States. Pharmacoeconomics 2013 May;31(5):427-444. [doi: 10.1007/s40273-013-0048-3] [Medline: 23620210]

63. Giarelli E, Bernhardt BA, Mack R, Pyeritz RE. Adolescents' transition to self-management of a chronic genetic disorder. Qual Health Res 2008 Apr;18(4):441-457. [doi: 10.1177/1049732308314853] [Medline: 18354044]

64. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry 2003 Jun;160(6):1041-1052 [FREE Full text] [doi: 10.1176/appi.ajp.160.6.1041] [Medline: 12777258]

65. Parsons J, Halkitis P, Bimbi D, Borkowski T. Perceptions of the benefits and costs associated with condom use and unprotected sex among late adolescent college students. Journal of Adolescence 2000 Aug 23(4):377-391 [FREE Full text]

66. Parsons J, Siegel A, Cousins J. Late adolescent risk-taking: effects of perceived benefits and perceived risks on behavioral intentions and behavioral change. J Adolesc 1997 Aug;20(4):381-392 [FREE Full text] [doi: 10.1006/jado.1997.0094] [Medline: 9268413]

67. MacDonell K, Naar-King S, Huszti H, Belzer M. Barriers to medication adherence in behaviorally and perinatally infected youth living with HIV. AIDS Behav 2013 Jan;17(1):86-93 [FREE Full text] [doi: 10.1007/s10461-012-0364-1] [Medline: 23142855]

68. 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]

69. Hartlieb KB, Jacques-Tiura AJ, Naar-King S, Ellis DA, Jen KC, Marshall S. Recruitment strategies and the retention of obese urban racial/ethnic minority adolescents in clinical trials: the FIT families project, Michigan, 2010-2014. Prev Chronic Dis 2015 Feb 19;12:E22 [FREE Full text] [doi: 10.5888/pcd12.140409] [Medline: 25695260]

70. Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI). Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. JAMA 2012 Apr 18;307(15):1636-1640. [doi: 10.1001/jama.2012.466] [Medline: 22511692]

71. Brown CH, Wyman PA, Guo J, Peña J. Dynamic wait-listed designs for randomized trials: new designs for prevention of youth suicide. Clin Trials 2006 Sep;3(3):259-271. [doi: 10.1191/1740774506cn152oa] [Medline: 16895043]

72. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Education and Counseling 2002 Oct;48(2):177-187. [doi: 10.1016/S0738-3991(02)00032-0]

73. National Institute of Nursing Research. Bethesda, MD: National Institute of Nursing Research. Self-Management: Improving Quality of Life for Individuals with Chronic Illness URL: http://www.ninr.nih.gov/newsandinformation/iq/self-management-workshop [accessed 2018-04-20] [WebCite Cache ID 6ypNYd5fN]

74. Lorig KR, Holman HR. Self-management education: history, definition, outcomes, and mechanisms. Ann Behav Med 2003 Aug;26(1):1-7. [doi: 10.1207/S15324796ABM2601_01] [Medline: 12867348]

75. Aarons GA, Cafri G, Lugo L, Sawitzky A. Expanding the domains of attitudes towards evidence-based practice: the evidence based practice attitude scale-50. Adm Policy Ment Health 2012 Sep;39(5):331-340 [FREE Full text] [doi: 10.1007/s10488-010-0302-3] [Medline: 20607597]

76. Montague E, Chen P, Xu J, Chewning B, Barrett B. Nonverbal interpersonal interactions in clinical encounters and patient perceptions of empathy. J Participat Med 2013 Aug 14;5(5):e33.

## Abbreviations

**AC:** Analytic Core
**CT:** Assertive Communication Training

**ART:** antiretroviral therapy
**ATN:** Adolescent Medicine Trials Network for HIV/AIDS Interventions
**CHTC:** couples HIV testing and counseling
**CPS:** cell phone support
**DATCAP:** Drug Abuse Treatment Cost Analysis Program
**EPIS:** Exploration, Preparation, Implementation, Sustainment model
**IS:** implementation science
**ISC:** Implementation Science Core
**MC:** Management Core
**MI:** motivational interviewing
**MSM:** men who have sex with men
**PrEP:** pre-exposure prophylaxis
**SIU:** Scale It Up
**SMART:** Sequential Multiple Assignment Randomized Trial
**SMS:** short message service
**SRV:** subject recruitment venue
**TMI:** Tailored Motivational Interviewing Intervention
**VL:** viral load
**YCAB:** Youth Community Advisory Board
**YLH:** youth living with HIV
**YMHP:** Young Men's Health Project

Protocol

# The Stepped Care Intervention to Suppress Viral Load in Youth Living With HIV: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:**  Among youth living with HIV (YLH) aged 12-24 years who have health care in the United States, only 30% to 40% are virally suppressed. YLH must achieve viral suppression in order to reduce the probability of infecting others as well as increasing the length and quality of their own life.

**Objective:**  This randomized controlled trial aimed to evaluate the efficacy of an Enhanced Standard Care condition (n=110) compared to an Enhanced Stepped Care intervention condition (n=110) to increase viral suppression among YLH aged 12-24 years with established infection (not acutely infected).

**Methods:**  YLH (N=220) who are not virally suppressed will be identified at homeless shelters, health clinics, and gay-identified community-based organizations in Los Angeles, CA, and New Orleans, LA. Informed consent will be obtained from all participants. YLH will be randomly assigned to one of two study conditions: Enhanced Standard Care, which includes standard clinical care plus an automated messaging and monitoring intervention (AMMI), or an Enhanced Stepped Care, which includes three levels of intervention (AMMI, Peer Support via social media plus AMMI, or Coaching plus Peer Support and AMMI). The primary outcome is viral suppression of HIV, and YLH will be assessed at 4-month intervals for 24 months. For the Enhanced Stepped Care intervention group, those who do not achieve viral suppression (via blood draw, viral load<200 copies/mL) at any 4-month assessment will "step up" to the next level of intervention. Secondary outcomes will be retention in care, antiretroviral therapy adherence, alcohol use, substance use, sexual behavior, and mental health symptoms.

**Results:**  Recruitment for this study began in June 2017 and is ongoing. We estimate data collection to be completed by the end of 2020.

**Conclusions:**  This is the first known application of an Enhanced Stepped Care intervention model for YLH. By providing the lowest level of intervention needed to achieve viral suppression, this model has the potential to be a cost-effective method of helping YLH achieve viral suppression and improve their quality of life.

**Trial Registration:**  ClinicalTrials.gov NCT03109431; https://clinicaltrials.gov/ct2/show/NCT03109431

**International Registered Report Identifier (IRRID):**  DERR1-10.2196/10791

**KEYWORDS**

HIV seropositivity; adolescent; young adult; sustained virologic responses

## Introduction

### Background

New diagnoses of HIV among youth aged 12-24 years continue to be a challenging public health problem in the United States [1,2], with one in four new HIV diagnoses and 60,900 youth living with HIV (YLH) [3]. The substantial improvements in scientists' ability to prevent and treat HIV infection [4,5] are underutilized by YLH. Similar to adults, if a YLH has an undetectable viral load, there is a 94% likelihood of not transmitting HIV [6] and the YLH is likely to live longer [7] and have a better quality of life [8]. Furthermore, only 30% to 44% of those diagnosed are virally suppressed [2,9]. This study evaluates a Stepped Care model to support YLH to achieve viral suppression.

YLH are concentrated in areas of the United States where the epidemic has grown, with certain groups disproportionately impacted, particularly in the South [10]. Black and Latino men-who-have-sex-with-men are at the highest risk for new HIV infections [11]. Among youth diagnosed with HIV, 81% are gay, bisexual, and transgender youths (GBTY), with the highest rates reported among black and Hispanic/Latino men [2]. GBTY coming of age today may not perceive the same risk of premature death, which characterized young men earlier in the epidemic when there were fewer treatment options.

It is imperative that YLH achieve viral suppression in order to reduce the probability of infecting others as well as increase the length and quality of their lives [7,8]. Among YLH, viral suppression requires linkage and retention in care as well as antiretroviral therapy (ART) adherence. As part of the HIV Treatment Continuum [12], YLH must overcome all barriers to seeking and receiving medical care and then adhere daily to their ART [1,13]. Historically, achieving an undetectable viral load required 95% ART adherence [14]. However, rates as low as 80% may lead to viral suppression [15]; at present, the pills are combined in regimens and ART is more robust. The duration of "drug holidays" (ie, days without medication) is at least as important as the number of pills taken as prescribed when monitoring adherence that aims to result in an undetectable viral load [16]. However, even with only an 80% adherence rate required for viral suppression and the typical regimen consisting of only one pill daily, YLH are far from meeting this target.

Retention in care and adherence to ART are related. Although 41% of YLH know their serostatus, only 62% receive medical care within 12 months of diagnosis [1]. Retention rates can be low, with only one in four YLH retained in care at 3 years after treatment initiation [17]. Among one sample of YLH (atypically, 72% women), initial ART adherence was 69%, but by 1 year, ART adherence was negligible, partly due to only a 30% retention in HIV care [18]. Young people are also more likely to dropout from care than middle-aged and older adults [13,19]. Existing studies suggest that few YLH remain in medical care more than a year, ensuring that ART treatment adherence will also be low [20-22].

### Barriers to Adherence Among Youth Living With HIV

In addition to connecting YLH to care, it is important to identify and address barriers to adherence. Others have suggested that targeting patient group characteristics to improve adherence may not be the answer, but instead, focusing on individual needs with the flexibility to address specific identified barriers may be helpful [23]. Barriers can be structural issues, and many of the challenges to adherence faced by YLH are interrelated. Drawing upon the work of Maslow [24], Barroso and colleagues assert that people living with HIV must first have their basic biological and physiological needs met to become adherent, including food and transportation, and there must be a focus on reducing stigma and addressing community-level barriers that contribute to disparities [25]. Psychological issues can be part of this complex problem, and even forgetting to take one's medication can be due to the lack of a set routine or a more complex process that involves cognitive or behavioral struggles [26]. Shame as well as mental health problems and substance abuse may also contribute to delayed medication initiation and difficulties with adherence [27]. Thus, it is important that interventions targeting viral suppression have the flexibility to address multiple factors in the lives of YLH.

### Intervention Innovation of the Protocol: Stepped Care

Stepped Care is a strategy used in managing chronic diseases and mental health problems [28-30], but has only recently been applied to YLH in one trial [31]. Using a Stepped Care approach, providers implement the least intensive intervention needed to achieve the treatment goal and intensify the intervention until the treatment goal is achieved. With this Stepped Care framework, this study will implement a low-intensity intervention, followed by sequential introduction of more intense and comprehensive interventions. The interventions at the lowest levels require little individual tailoring and may be sufficient for some youth. However, for YLH who do not achieve viral suppression, a more individualized, tailored intervention will be implemented.

Mobile technologies saturate the lives of youth and young adults and offer an opportunity for a variety of interventions. HIV mobile health interventions are a growing area of interest and have been used as interventions for both self-management and medication adherence [32]. One intervention that may be beneficial for Stepped Care models for YLH is an automated messaging and monitoring intervention (AMMI). AMMI interventions using daily text messaging have been shown to be a useful method for medication reminders for HIV-infected individuals [33] and have demonstrated positive effects on medication adherence [34-40] and viral load [41]. We have demonstrated the efficacy of text messaging interventions with various high-risk groups in prior studies [42-46]. In this study, AMMI is based on promoting ART adherence by enhancing self-management of one's care using the concepts of social cognitive theory [32,47,48]. Self-management or self-monitoring among persons living with HIV can include reflection, reinforcement of behaviors, and support of cues to action such as taking medications [49]. Peer support is another intervention that is well-suited for use in a Stepped Care model. Positive relationships are a major dimension related to retention in care

and adherence to ART medications [50-53]. Relationships provide motivation to increase retention in care for a range of other chronic diseases (eg, diabetes, weight reduction, alcohol treatment, and mental health) [54-56]. Although peer support is a component of many evidence-based interventions, there are mixed findings in the meta-analyses conducted on peer support; some found a significant benefit [57,58] and others found a major benefit [59]. Reviews of peer support studies for persons living with HIV, which aimed at reducing stress [60], have found peer support to be a critical intervention component. In particular, adolescence is a developmental period wherein the influence of peers is crucial and has been consistently recognized as an important period from the 1980s [61] to the most recent Lancet reviews on adolescent health determinants [62].

Coaching interventions adapted for YLH are more intensive, individualized interventions that can be used in a Stepped Care model. The roots of coaching can be traced to sports, where a coach, typically working with a group of youths, is a leader who provides guidance, support, and direction. The earliest mention of coaching in the literature was in the 1970s in relation to assertiveness training [63] and later as a method for improving social skills among children [64] and helping families [65] and other types of groups. Since then, coaching has increased in popularity as an alternative to psychotherapy in the business world [66] and as an intervention for a variety of health professionals. Originally done face-to-face, most recently, this type of intervention, commonly known as "health coaching," is also delivered electronically [67]. Coaching has been used as an intervention for chronic pain [68], weight loss [69], HIV medication adherence [70], and other health conditions. A recent review of coaching interventions found positive effects in most studies but highlighted the need for research to be more specific in describing coaching interventions including the types of behavior-change strategies used [71].

## Methods

### Overview of Methods and Aims

As outlined in Figure 1, we will conduct a randomized control trial (RCT) to evaluate the efficacy of an Enhanced Standard Care Intervention (n=110) as compared to an Enhanced Stepped Care Intervention Model (n=110) in order to significantly increase viral suppression among YLH in two cities, Los Angeles, CA, and New Orleans, LA (Trial Registration: ClinicalTrials.gov NCT03109431). This protocol is part of the U19 Research Program Grant that is funded by the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN 148; 1U19HD089886).

The specific aims of this study are (1) to assess if Enhanced Standard Care or an Enhanced Stepped Care results in the primary outcome of more sustained viral suppression and improvements in secondary outcomes, (2) to test whether

secondary outcomes such as mental health symptoms and drug use mediate the effect of the intervention on viral suppression over time, (3) and to conduct a cost-effectiveness analysis to weigh the benefit of intervention effects on primary and secondary outcomes against intervention implementation costs beyond costs incurred through the standard of care.

All procedures in this study have been approved by the Institutional Review Board of the University of California, Los Angeles, which serves as the single Institutional Review Board of Record for researchers at the collaborating institutions.

### Recruitment

In both New Orleans and Los Angeles, teams of predominantly bachelor's degree–level interviewers aim to screen up to 1500 youths to recruit a cohort of 220 seropositive youths. A description of the study sites in Los Angeles and New Orleans can be found in Rotheram-Borus' and colleagues' article [12].

### Inclusion and Exclusion Criteria

The current inclusion criteria are age of 12-24 years, HIV-positive status, established HIV infection (not acutely infected), and ability to provide informed consent. Exclusion criteria include age under 12 years or above 24 years, HIV-negative status, acute infection with HIV, inability to understand the study procedures due to intoxication or cognitive difficulties (any youth who appears to be under the influence of alcohol or drugs will be unable to enroll in the study but invited to return at a later date), and inability to provide voluntary written informed consent.

### Recruitment Procedures

To identify eligible participants, youth in high-risk settings will be asked to complete a brief screening and rapid HIV test. All screenings are done face-to-face with a study team member from our Recruitment, Engagement, and Retention Center. Older youths (aged 15-24 years) will provide oral consent for the screening, and younger youths (aged 12-14 years) will provide written consent for the screening to ensure that they understand the screening process. Next, all youths aged 12-24 years whose judgment does not appear to be impaired from a disability or substance use will be asked to give written informed consent to complete the screening. Interviewers are trained to assess for problems with cognition, and additional screening questions will be asked if any concerns are identified. To qualify as "eligible" for recruitment, youths must test seropositive on a rapid HIV test and be virally unsuppressed. Based on these screening criteria, eligible youths will be invited to complete the voluntary informed consent (we have a waiver of parental consent for minors). YHL will be randomized to the intervention conditions via the CommCare system (see next section) after viral load results are obtained and entered, which typically takes several days.

**Figure 1.** Design of ATN Protocol 148—randomized controlled trial for youth living with HIV (YLH). AMMI: automated messaging and monitoring intervention.
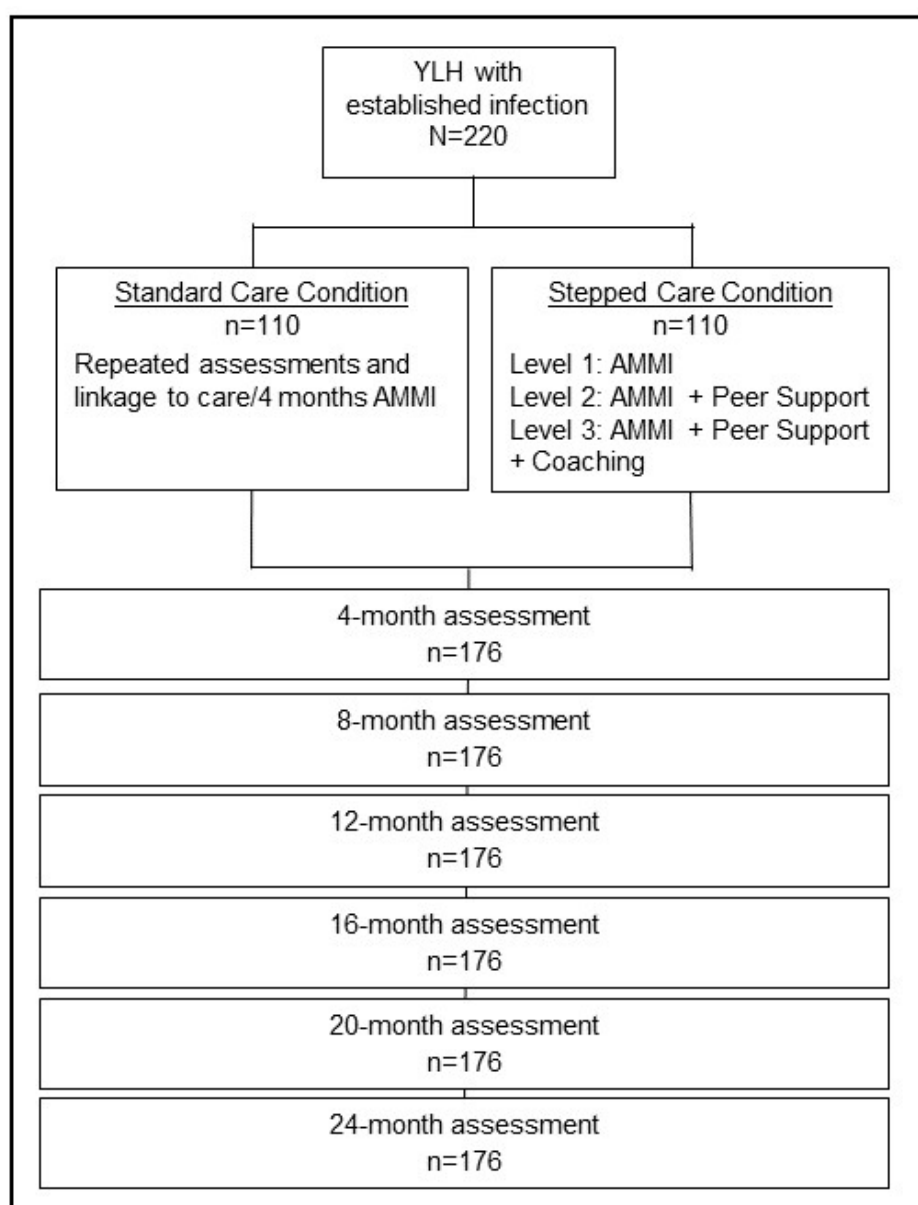


As part of the voluntary informed consent procedures, YHL are asked to provide additional consent to access sensitive information for care coordination and study retention (locating missing participants) for the duration of the study (24 months), which includes their contact information; social media accounts; contact information of their close relatives, friends, and providers including case managers and probation officers; social security number; driver's license or identification card number; and access to their medical records. Providing this additional information is not mandatory, and YLH can refuse to provide these permissions as long as they provide their own contact information; all information will be stored securely in the CommCare system. Only the study team will have access to this information.

## Assessments

Following enrollment, study participants will be asked to complete a baseline assessment, which is administered by the interviewer using Android tablets in approximately 45 minutes.

This assessment covers the following sections: background, risk behaviors, and sociodemographic variables as well as eight cross-cutting domains related to the HIV Treatment Continuum [12]. Interviewers enter the participants' responses in the CommCare system developed by the Dimagi Corporation, Cambridge, MA. CommCare is an open-source, mobile phone-based platform that is cloud based and HIPAA (Health Insurance Portability and Accountability Act) 1996 compliant. This mobile app is used to collect all study data and send out short message service (SMS) messages and weekly surveys as part of AMMI as well as spontaneous broadcast messages for particular groups of participants.

Participants also have a blood draw for viral load monitoring and a series of rapid diagnostic tests (RDTs) which include the following:

- HIV as part of screening: Potential study participants undergo HIV testing using the CLIA-waived Alere

(Waltham, MA) Determine HIV-1/2 Ag/Ab Combo finger stick blood test for both HIV-1/2 antibodies and the HIV-1 p24 antigen with a window period of 12-26 days, which can be read in 20-30 minutes. Once enrolled in the study, participants also receive HIV testing using the Cepheid (Sunnyvale, CA) Xpert HIV-1 Qual Assay, which is highly sensitive, uses whole blood to detect HIV-1 total nucleic acids, and has a 92-minute read time.

- Chlamydia and Gonorrhea are tested using a Food and Drug Administration-approved Cepheid Xpert CT/NG Assay polymerase chain reaction that is read in 90 minutes.
- Syphilis is tested using the CLIA-waived Syphilis Health Check finger stick blood test to detect treponemal antibodies with a 10- to 15-minute read time.
- Hepatitis C is tested using the CLIA-waived OraQuick HCV Rapid Antibody test finger stick blood test with a 20- to 40-minute read time.
- Substance use is tested using a multidrug urine test panel to detect the presence of marijuana, cocaine, opiates, and methamphetamine with a 2- to 5-minute read time.
- Alcohol use is assessed using a breathalyzer test that is sensitive for assessing alcohol use in the last 24 hours.

Following completion of the baseline assessment, participants will receive a US $50 cash incentive. Any study participant who tests positive for HIV or a sexually transmitted infection (STI) will be offered immediate access to treatment.

## Follow-Up Assessments

Study participants will be reassessed every 4 months over a period of 24 months. In total, the study participants will complete six follow-up assessments and receive a US $50 cash incentive for each follow-up assessment. Follow-up assessments will include another 45-minute assessment, a blood draw for viral load monitoring, and a series of RDTs for STIs and substance use, as described above. In addition, if study participants report any potential STI symptoms or exposure, they will immediately be offered testing. In between assessments, YLH who need STI testing can use standard care in the community or contact the study team for assistance. At these assessments, participants who are not virally suppressed (viral load<200 copies/mL) will "step up" to the next level of care while still receiving the prior level(s) of care.

## Outcome Measures

### Primary Outcome: HIV Viral load

The primary outcome measure is a suppressed viral load at each 4-month assessment for 24 months. At both sites, whole blood is collected with the anticoagulant EDTA and sent at ambient temperature to an internal laboratory where plasma is separated. In addition, 1.5-3.0 mL plasma is shipped to an off-site CLIA-certified laboratory to measure viral load by quantitative HIV-1 RNA real time polymerase chain reaction with a level of detection of 20 copies/mL. Samples from New Orleans are measured at room temperature and those from Los Angeles are measured after they are frozen and thawed. The study team will receive the results through the laboratory's online portal.

### Secondary Outcomes

The following secondary outcomes are also measured at each 4-month assessment for 24 months.

#### Retention in Care

YLH are deemed to be retained in care if they attend at least two medical appointments annually. When starting ART, three appointments are scheduled in the first 3 months. Therefore, retention in care also depends on how long YLH have been prescribed ART. We will assess YLH every 4 months; therefore, there are six opportunities over the 24 months of follow-up to obtain self-reports during medical appointments and ensure adherence to ART regimens.

#### Antiretroviral Therapy Adherence

ART adherence is based on a Likert scale that asks YLH to rate their ability to take all their HIV medications as prescribed over the prior 30 days. Response categories range from "Very poor" (1) to "Excellent" (6) [72,73].

#### Alcohol Use Over the Past 4 Months

This parameter will be assessed using the Alcohol Use Disorders Identification Test, consisting of three questions with Likert-scale responses [74].

#### Substance Use

YLH will be asked to indicate if they used any of the following substances over the past 4 months: marijuana, synthetic marijuana, cocaine or crack, heroin, ecstasy, methamphetamines, prescription stimulants or amphetamines, gamma hydroxybutyric acid, ketamine, poppers, inhalants, hallucinogens, prescription painkillers not used as prescribed, and other prescription medications not used as prescribed. YLH will also be asked how many times they injected "drugs such as heroin, opiates, cocaine or amphetamines (crystal)" over the past 4 months. RDTs for alcohol and substance use will be administered to evaluate the degree of underreporting when RDTs indicate use but self-reports do not. Given the fairly short window of detection for RDTs (eg, 24 hours for alcohol), RDTs are not used as outcomes.

#### Sexual Behavior

YLH will be asked to report on the following sexual behaviors over the past 4 months: the number of sexual partners (in total and partners who are HIV positive) and the number of insertive and receptive anal sex acts. YLH will also be asked the frequency of condom use with sexual partners at each sexual encounter. Responses categories range from "None of the time" (0) to "All of the time" (5).

#### Mental Health

Mental health is assessed using three scales. YLH will be administered four questions from the 12-item Short Form Health Survey [75]. Specifically, they will be asked if they "felt calm and peaceful," had "a lot of energy," and "felt sad and blue" during the past 4 weeks. Response categories range from "None of the time" (0) to "All of the time" (5). YLH are administered the Patient Health Questionnaire for adolescents (PHQ-A) [76], which asks YLH to report how often they were bothered by problems from a list of nine items over the past 2 weeks. Lastly,

YLH are administered the Generalized Anxiety Disorder 7-item scale [77]. Similar to the PHQ-A, YLH are asked to report how often they were bothered by problems from a list of seven items over the past 2 weeks, such as "Feeling nervous, anxious or on edge."

SMS weekly surveys consist of six items that inquire about how many days YLH felt "sad or depressed;" if they had "any genital itching/pain/discharge, burning during urination, lower stomach pain, or discomfort during sex;" how many times they had sex without using a condom; how many days they used "alcohol and/or drugs;" how many days they did not have a place to sleep; and how many days they missed taking medications. Surveys mainly serve as a tool for research staff to monitor YLH health; check in with them, if needed; and encourage YLH to self-monitor their health and behavior. Items for medication adherence, alcohol/substance use, and sadness/depression will also be treated as outcomes in analyses similar to secondary-outcome analyses. However, low SMS survey–response rates are anticipated based on prior studies with YLH [78]. Therefore, analyses on SMS survey outcomes will be treated as exploratory; precedence will be given to analysis results for secondary outcomes from the 4-month assessment.

## Costing

Costs are of two types: costs of delivering the intervention and additional costs incurred by participants for their use of health care services and services from other agencies. The cost of delivering the intervention requires an estimation of staff time. Coaching logs and other intervention information will be entered into CommCare, which does not provide information regarding the amount of time spent performing study tasks. Thus, staff activity information that is captured by this system will be supplemented by *Time It*, a mobile app that allows individuals to record the time spent carrying out different staff activities [79]. Each staff member, including program directors, interviewers, and coaches, will record relevant categories of activity over the course of 1 week per quarter. A set of staff activity categories will be prespecified in the mobile app. However, staff are allowed to add more categories as they perform other tasks not previously specified. In addition, personnel time will be estimated from several sources; budgeted time and time recorded on time sheets, for hourly employees, will provide a basis for each staff member's hours devoted to the project.

The costs of additional services are derived from respondent reports of utilization and medical records and will be estimated using publicly available data. Research-specific costs (eg, incentive payments, informed consent, screens, and software adaptation for survey tools) are excluded from the total costs. All cost data will be adjusted for price back to Year 1 of the study by using the medical care component of the consumer price index.

## Description of the Intervention

As shown in Figure 1, the Enhanced Stepped Care condition has three levels of intervention: Level 1, Enhanced Standard Care plus AMMI; Level 2, online peer support via social media plus AMMI plus Enhanced Standard Care; and Level 3, coaching plus online peer support via social media and AMMI plus Enhanced Standard Care. If YLH fail to be virally suppressed (based on analyses of viral load in the blood stream at 4-month intervals), YLH in the Enhanced Stepped Care condition will be provided the next level of intervention in addition to the other levels of care to which they were previously assigned. Note that these interventions overlap with our team's other study of HIV-negative youths and are also described in Swendeman et al [49]. To assess dose of the interventions, we will examine the number of responses to the AMMI surveys (Level 1), the number of peer support posts and logins (Level 2), and the number of coaching sessions (Level 3).

### Level 1

Level 1 of the Enhanced Stepped Care model is Enhanced Care plus AMMI. As this is not a medication treatment study, YLH are treated in the community using best practices that are consistent with available treatment guidelines for providers. However, given that YLH have failed to achieve viral suppression with the existing services available to them, we are enhancing standard care by adding an additional component. Thus, Enhanced Care includes existing services received by YHL from health care providers and other agencies as well as daily text messages. Messages for this study focus on five areas: wellness, health care, medication reminders, drug use, and sexual health. We have tailored and adapted preexisting libraries of theoretically based text messages that have been found to be successful in other RCTs with similar populations [80-83], with messages tailored for two different groups—GBTY and non-GBTY. Messages include a focus on empowering YLH (ie, "Don't rely on other people, take your health seriously," and "When you take your meds regularly, you're in control") as well as providing health-related facts ("Meds keep HIV in check" and "Syphilis can increase your viral load"). The goal of AMMI is to target the areas that can impact adherence to ART that will translate into increased rates of viral suppression.

### Level 2

The second level of our Enhanced Stepped Care intervention is a secure, private online/social media peer-support intervention. Participants are invited to participate in an online discussion board through muut.com, an open-source discussion forum that is mobile and desktop friendly. Project staff review access requests to ensure that only participants are attempting to join the board. YLH can personalize their Muut profiles using avatars and (nonidentifying) photos, but cannot choose usernames that compromise their anonymity. Online discussion boards are tailored to topics relevant to youth. Others' experiences with interpersonal group interventions for high-risk youth indicate that group cohesion based on these factors can be a key factor influencing group participation and retention [84,85]. Discussions can be initiated by youth or study team members, including HIV-specific topics related to linkage and retention in care as well as other challenges experienced by YLH.

On all discussion boards, study team members have administrator privileges, allowing them to monitor all activities, post information for discussion, and credit incentives for participants. They take multiple steps to safeguard

confidentiality and continually review online postings and delete any identifying information posted. Users are removed from the discussion boards if they post inappropriate content three times after receiving feedback for each occurrence, which includes solicitation for sex and drug use; racist, homophobic, or other stigmatizing content; pornographic content; or "trolling" inflammatory remarks or personal insults.

### Level 3

Participants who fail to achieve viral suppression at levels 1 or 2 of the intervention will be assigned to our coaching intervention. Coaching will focus on a variety of risk factors concurrently, as is common in HIV research [86-88], and build on our prior work with this type of intervention. Coaching is based on the strength-based model [89,90] that has demonstrated positive impacts on persons living with HIV [91,92] and HIV prevention [93,94]. Identifying and accomplishing goals are critical components of the model. Sessions can be conducted via phone or in person. At the first session, the coach and youth complete a strength assessment that will addresses six main life domains: daily living (survival needs such as food, housing, finances, and employment), physical health (non-HIV-related health problems), health services and health care related to HIV (insurance, linkage to care, ART adherence, viral suppression, treatment cascade, and adherence), social relationships (social support, disclosure, and stigma), mental health (eg, depression, anxiety, and coping), and risks (substance use and risky sexual behaviors). This assessment is used to guide the development of up to three personalized goals with shared responsibility between the youth and coach, depending on the nature of the goals.

After the assessment, sessions will focus on goal attainment. At each session, the coaches use the skills common to 80% of all child and adolescent evidence-based interventions (EBIs) [95,96]: relaxation, relapse prevention, positive activities/alternatives, referrals, modeling/role playing, positive self-talk, triggers, emotional regulation, monitoring/self-monitoring, support networking/building social support, assertive communication, setting up rewards, problem solving, goal setting, praise, and engagement/rapport building. The use of these skills and their relevance to our coaching intervention are described in further detail in Swendeman et al [49]. The coaching intervention is not manualized but rather relies on the strength assessment, goal setting, and the use of evidence-based skills to develop a personalized plan of intervention for each youth that addresses the unique factors that impact adherence and ultimately, viral suppression. Participation in coaching will continue while the YLH is in the study, but we expect that coaching sessions will decrease in frequency over time as the goals are accomplished.

### Selection and Training Coaches

Our coaching model uses paraprofessionals who have experience and skills in working with the population but do not have advanced degrees [97]. These community members have expertise in addressing the "predictable problems" [98] that these youth experience and will use evidence-based practices to intervene and address specific identified goals [97]. Coaches are also hired based on their interpersonal skills, ability to

connect with YLH, and skills in implementing an evidence-based but nonmanualized intervention. They receive intensive training prior to field work to participate in ongoing weekly supervision and have access to real-time supervision in the field.

## Data Analyses

### Aim 1

Intent-to-treat analyses will be used to compare viral suppression as our primary outcome and secondary outcomes between YLH randomized to the Enhanced Stepped Care or Enhanced Standard Care conditions. Comparisons of the same outcomes will also be made between steps in the Enhanced Stepped Care condition as exploratory analyses; the study is only powered for comparisons between study arms. Multilevel models (MLM [99]) will be used to model correlations between repeated observations on the same YLH in order to properly estimate standard errors. Generalized linear MLM will be fit to discrete outcomes such as the binary outcome for viral suppression. MLM fit to the primary outcome for viral suppression will be parameterized to test for the average of viral suppression differences over the follow-up period between study arms (ie, time-averaged effects). This parameterization will be used because all participants are virally unsuppressed at baseline based on eligibility criteria. Secondary outcome levels can differ across study arms; a more standard parameterization that allows for baseline and slope differences over time will be used. We anticipate that randomization will balance out sociodemographic and other important background characteristics across study arms. If characteristics are found to differ across study arms, they will be included as adjustment covariates in MLM. More sophisticated adjustment methods such as propensity scores will be implemented as needed [100]. Data will also be checked for missing data patterns. Appropriate statistical techniques such as multiple imputation will be applied [98,101].

### Aim 2

We will use bivariate-outcome MLM to examine temporal relationships between primary and secondary outcomes. Model parameterization will be based on a number of factors, including visualizations of outcome trajectories and model fit statistics. One parameterization that may be used in a bivariate-outcome MLM is a bivariate random intercept and slope model that we have used in a prior HIV study to examine the time-varying relationship between HIV-transmission behaviors and mental health symptoms [102]. This model is formulated through two separate MLM equations for each outcome that is linked through random effects to model random intercepts and slopes. A variance-covariance matrix is modeled to estimate correlations between random effects. Correlations capture time-varying associations between outcomes such as the correlation between the first outcome at baseline and the second outcome over time and vice versa. The bivariate-outcome model offers a flexible modeling framework to test different mediational models. For example, if the bivariate-outcome model contains outcomes for viral suppression, a secondary outcome such as mental health symptoms, and an intervention effect covariate, then we can test if mental health symptoms mediate the impact of the intervention on viral suppression. Details on bivariate random

intercept and slope models and other model parameterizations to test for mediational effects in longitudinal data are provided in a previous study [103].

### Aim 3

Cost-effectiveness analyses will be conducted to weigh the benefit of intervention effects on primary and secondary outcomes against intervention implementation costs beyond those incurred through the standard of care. Specifically, analyses will compare the additional cost required, on an average, to obtain an additional unit of outcome in the Enhanced Stepped Care intervention by calculating the cost effectiveness ratio (CER) [104]. The CER is the difference in total costs of providing an Enhanced Stepped Care intervention versus Enhanced Standard Care, divided by the difference in outcomes of Enhanced Stepped and Enhanced Standard Care [104,105]. The primary outcome of viral suppression and secondary outcomes are outcomes of interest. CER is calculated for different combinations of YLH and provider characteristics. We will conduct sensitivity analyses, as recommended by Gold et al [104], to estimate the extent to which the CER calculation is affected by differences in assumptions about the size of the differences in treatment effect. In particular, we will determine how sensitive the CER is to assumptions that the difference in treatment effect is 1 SD below or above the mean estimated effect size. Similarly, we estimate the sensitivity of conclusions to costs that are 1 SD below or above the estimated mean.

### Sample Size Calculations

Sample size calculations are estimated for our primary analysis, which is a comparison of the probability of viral suppression between Enhanced Stepped and Enhanced Standard Care conditions over five time points. The first follow-up is not included in the comparisons because we anticipate that it will take 6 months for improvements in viral suppression to be seen in the Enhanced Stepped Care condition. Based on our proposed sample size of 220 (n=110 in each condition), we anticipate 80% power for a two-sided test with a .05 alpha level to detect time-averaged percentage differences in viral suppression as small as 9%-13% between conditions. Based on consultation with HIV clinicians, we expect viral suppression rates to be fairly low in the Enhanced Standard Care condition, and we will use a range of rates from 6% to 20% in our calculations. Calculations assume a compound symmetry covariance structure. An autocorrelation coefficient is specified to account for correlations between repeated measurements. Calculations are conducted with a range of autocorrelation coefficient values similar to what we have found in prior studies, from .1 to .3. Lastly, we make a conservative assumption of 20% loss to follow-up so that the sample size in each condition is 88. In practice, we anticipate a much lower attrition rate. Sample size calculations were carried out using Power Analysis and Sample Size software, version 08.0.11 (Englewood, NJ) [106].

## Results

Recruitment for this study began in June 2017 and is ongoing. We estimate data collection to be completed by the end of 2020.

## Discussion

This RCT is the first known application of an Enhanced Stepped Care intervention for adolescents and young adults living with HIV. One of the most innovative aspects of this protocol is one that is slightly more difficult to discern: It will provide guidelines on how to implement evidence-based practices, rather than replicating an EBI manual with full fidelity. Although a great deal of progress has been made in secondary prevention with EBI manuals [107], an Enhanced Stepped Care approach requires assessments to uniquely become part of the intervention process when it is time to step up the intervention. There are individual differences in the need for intervention, and there is no need to provide more intervention than is needed. Instead of each YLH receiving the same intervention (as in many EBIs), the dose and type of intervention are linked to outcomes. Training staff in specific skills allows them to apply these skills based on the needs of the youth in a personalized manner that promotes self-management of one's health.

Enhanced Stepped Care is a particularly important model since the funding and resources for HIV care have not increased in recent years. If Enhanced Stepped Care is more successful than the Enhanced Standard Care, this model may be a novel way for others to think about their implementation of a typical EBI. It will be critical to establish cost-effective and diffusible strategies that can be nationally diffused; knowing the cost of the two intervention conditions in this study will be important to inform public policy and the selection of interventions by communities. Without a dramatic reversal, HIV incidence among adolescents is expected to increase, and each additional infection costs US $379,668 (in 2010) [108]. The Enhanced Stepped Care model proposed in this study is expected to result in better outcomes and cost savings for society by preventing HIV secondary transmission and postponing disease progression. The clinical benefits of Enhanced Stepped Care without increased costs are documented for diabetes [109] and depression [110]; however, data evaluating the cost-effectives of the Stepped Care model for HIV care are lacking. This study will perform an economic evaluation within the RCT and provide valuable data to support the cost-effectiveness of the Enhanced Stepped Care approach in order to enhance HIV treatment and care among YLH groups from both clinical and societal perspectives. If the Enhanced Stepped Care program results in lower or comparable total health care costs relative to usual care, this finding will offer a unique venture point for scaling up the Stepped Care program across the country.

This protocol is particularly relevant to YLH nationally, who typically face challenges of homelessness, mental health problems, school or job issues, contact with the criminal justice system, and risks within their sexual partnerships in addition to their seropositive HIV status. Studies of ART adherence and retention in care have consistently found depression and the types of life challenges young people are experiencing to be directly related to engagement, retention, and adherence to care over time [16,111]. If we fail to address these comorbid issues with YLH, we will not succeed in meeting the goal of viral suppression with YLH. Our Enhanced Stepped Care approach aims to address these issues with increasingly intensive

interventions, based on the individual needs of YLH. Although addressing comorbid issues may be costlier initially, it may have substantial savings in terms of reducing the probability of HIV transmission among YLH, which is an important individual-level and public health outcome.

## Conflicts of Interest

None declared.

## References

1. 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]
2. Centers for Disease Control Prevention. HIV among youth. 2017. URL: http://www.cdc.gov/hiv/group/age/youth/ [WebCite Cache ID 6vU9ArZvf]
3. Centers for Disease Control Prevention. CDC vital signs: HIV among youth in the US. 2012. URL: https://www.cdc.gov/vitalsigns/hivamongyouth/index.html [WebCite Cache ID 6vU7YtpQD]
4. Kim SH, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. AIDS 2014 Aug 24;28(13):1945-1956 [FREE Full text] [doi: 10.1097/QAD.0000000000000316] [Medline: 24845154]
5. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. Curr HIV/AIDS Rep 2011 Mar;8(1):62-72 [FREE Full text] [doi: 10.1007/s11904-010-0063-3] [Medline: 20941553]
6. 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]
7. Centers for Disease Control Prevention, Human Resources and Services Administration, National Institutes of Health, American Academy of HIV Medicine, Association of Nurses in AIDS Care, International Association of Providers of AIDS Care, National Minority AIDS Council, Urban Coalition for HIV/AIDS Prevention Services. Recommendations for HIV prevention with adults and adolescents with HIV in the United States. 2014. URL: https://stacks.cdc.gov/view/cdc/44064 [WebCite Cache ID 6vYgtAQtl]
8. Mitchell MM, Nguyen TQ, Isenberg SR, Maragh-Bass AC, Keruly J, Knowlton AR. Psychosocial and service use correlates of health-related quality of life among a vulnerable population living with HIV/AIDS. AIDS Behav 2017 Jun;21(6):1580-1587 [FREE Full text] [doi: 10.1007/s10461-016-1589-1] [Medline: 27787675]
9. Kahana SY, Jenkins RA, Bruce D, Fernandez MI, Hightow-Weidman LB, Bauermeister JA, Adolescent Medicine Trials Network for HIV/AIDS Interventions. Structural determinants of antiretroviral therapy use, HIV care attendance, and viral suppression among adolescents and young adults living with HIV. PLoS One 2016;11(4):e0151106 [FREE Full text] [doi: 10.1371/journal.pone.0151106] [Medline: 27035905]
10. AIDSVu. 2018. Understanding HIV where you live URL: https://aidsvu.org/ [accessed 2018-03-30] [WebCite Cache ID 6yJ8dQddd]
11. Centers for Disease Control Prevention. HIV among gay and bisexual men. 2017. URL: https://www.cdc.gov/hiv/pdf/group/msm/cdc-hiv-msm.pdf [WebCite Cache ID 6vU7oe4kf]
12. Rotheram MJ, Fernandez MI, Lee SJ, Abdalian SE, Kozina L, Koussa M, Adolescent Medicine Trials Network (ATN) CARES Team. Strategies to Treat and Prevent HIV in the United States for Adolescents and Young Adults: Protocol for a Mixed-Methods Study. JMIR Res Protoc 2019 Jan 21;8(1):e10759 [FREE Full text] [doi: 10.2196/10759] [Medline: 30664482]

13.  Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis 2011 Mar;52(6):793-800 [FREE Full text] [doi: 10.1093/cid/ciq243] [Medline: 21367734]

14.  Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000 Jul;133(1):21-30. [Medline: 10877736]

15.  Viswanathan S, Detels R, Mehta SH, Macatangay BJC, Kirk GD, Jacobson LP. Level of adherence and HIV RNA suppression in the current era of highly active antiretroviral therapy (HAART). AIDS Behav 2015 Apr;19(4):601-611 [FREE Full text] [doi: 10.1007/s10461-014-0927-4] [Medline: 25342151]

16.  Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M, Adolescent Medicine HIV/AIDS Research Network. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. AIDS Care 2001 Feb;13(1):27-40. [doi: 10.1080/09540120020018161] [Medline: 11177463]

17.  Farmer C, Yehia BR, Fleishman JA, Rutstein R, Mathews WC, Nijhawan A, et al. Factors associated with retention among non-perinatally HIV-infected youth in the HIV Research Network. J Pediatric Infect Dis Soc 2016 Mar;5(1):39-46 [FREE Full text] [doi: 10.1093/jpids/piu102] [Medline: 26908490]

18.  Murphy DA, Belzer M, Durako SJ, Sarr M, Wilson CM, Muenz LR, Adolescent Medicine HIV/AIDS Research Network. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. Arch Pediatr Adolesc Med 2005 Aug;159(8):764-770. [doi: 10.1001/archpedi.159.8.764] [Medline: 16061785]

19.  Hall HI, Holtgrave DR, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. AIDS 2012 Apr 24;26(7):893-896. [doi: 10.1097/QAD.0b013e328351f73f] [Medline: 22313960]

20.  Belzer ME, Fuchs DN, Luftman GS, Tucker DJ. Antiretroviral adherence issues among HIV-positive adolescents and young adults. J Adolesc Health 1999 Nov;25(5):316-319. [Medline: 10551660]

21.  Ferrand R, Ford N, Kranzer K. Maximising the benefits of home-based HIV testing. Lancet HIV 2015 Jan;2(1):e4-e5. [doi: 10.1016/S2352-3018(14)00039-3] [Medline: 26424234]

22.  Garofalo R, Kuhns LM, Hotton A, Johnson A, Muldoon A, Rice D. A randomized controlled trial of personalized text message reminders to promote medication adherence among HIV-positive adolescents and young adults. AIDS Behav 2016 May;20(5):1049-1059. [doi: 10.1007/s10461-015-1192-x] [Medline: 26362167]

23.  Yard SS, Huh D, King KM, Simoni JM. Patient-level moderators of the efficacy of peer support and pager reminder interventions to promote antiretroviral adherence. AIDS Behav 2011 Nov;15(8):1596-1604 [FREE Full text] [doi: 10.1007/s10461-011-0001-4] [Medline: 21739291]

24.  Maslow AH. Motivation and personality. New York, NY: Harper and Row; 1970.

25.  Barroso J, Leblanc NM, Flores D. It's not just the pills: a qualitative meta-synthesis of HIV antiretroviral adherence research. J Assoc Nurses AIDS Care 2017;28(4):462-478. [doi: 10.1016/j.jana.2017.02.007] [Medline: 28286006]

26.  Chandwani S, Koenig LJ, Sill AM, Abramowitz S, Conner LC, D'Angelo L. Predictors of antiretroviral medication adherence among a diverse cohort of adolescents with HIV. J Adolesc Health 2012 Sep;51(3):242-251. [doi: 10.1016/j.jadohealth.2011.12.013] [Medline: 22921134]

27.  Fields EL, Bogart LM, Thurston IB, Hu CH, Skeer MR, Safren SA, et al. Qualitative comparison of barriers to antiretroviral medication adherence among perinatally and behaviorally HIV-infected youth. Qual Health Res 2017 Jul;27(8):1177-1189 [FREE Full text] [doi: 10.1177/1049732317697674] [Medline: 28682737]

28.  Zatzick D, Jurkovich G, Rivara FP, Russo J, Wagner A, Wang J, et al. A randomized stepped care intervention trial targeting posttraumatic stress disorder for surgically hospitalized injury survivors. Ann Surg 2013 Mar;257(3):390-399 [FREE Full text] [doi: 10.1097/SLA.0b013e31826bc313] [Medline: 23222034]

29.  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]

30.  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]

31.  Mimiaga MJ, Kuhns LM, Biello KB, Olson J, Hoehnle S, Santostefano CM, 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). [doi: 10.1186/s12889-018-5815-9] [Medline: 30001703]

32.  Kanfer FH. Self-monitoring: methodological limitations and clinical applications. J of Consulting and Clin Psych 1970;35(2):148-152. [doi: 10.1037/h0029874]

33.  Sherman E, Clauson KA, Elrod S, Eckardt P, Alkhateeb F, Jacobs R. Patient perceptions of text messaging to improve antiretroviral therapy adherence: a qualitative study of patients in a Ryan White Clinic. J Int Assoc Provid AIDS Care 2018;17:2325958218759209. [doi: 10.1177/2325958218759209] [Medline: 29473483]

34.  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]

35.  Dowshen N, Kuhns LM, Johnson A, Holoyda BJ, Garofalo R. Improving adherence to antiretroviral therapy for youth living with HIV/AIDS: a pilot study using personalized, interactive, daily text message reminders. J Med Internet Res 2012;14(2):e51 [FREE Full text] [doi: 10.2196/jmir.2015] [Medline: 22481246]

36.  Mbuagbaw L, van der Kop ML, Lester RT, Thirumurthy H, Pop-Eleches C, Smieja M, et al. Mobile phone text messages for improving adherence to antiretroviral therapy (ART): a protocol for an individual patient data meta-analysis of randomised trials. BMJ Open 2013;3(5) [FREE Full text] [doi: 10.1136/bmjopen-2013-002954] [Medline: 23793704]

37.  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]

38.  Dunbar PJ, Madigan D, Grohskopf LA, Revere D, Woodward J, Minstrell J, et al. A two-way messaging system to enhance antiretroviral adherence. J Am Med Inform Assoc 2003;10(1):11-15 [FREE Full text] [Medline: 12509353]

39.  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]

40.  Lewis MA, Uhrig JD, Bann CM, Harris JL, Furberg RD, Coomes C, et al. Tailored text messaging intervention for HIV adherence: a proof-of-concept study. Health Psychol 2013 Mar;32(3):248-253. [doi: 10.1037/a0028109] [Medline: 22545972]

41.  King E, Kinvig K, Steif J, Qiu AQ, Maan EJ, Albert AY, et al. Mobile text messaging to improve medication adherence and viral load in a vulnerable Canadian population living with human immunodeficiency virus: a repeated measures study. J Med Internet Res 2017 Jun 01;19(6):e190 [FREE Full text] [doi: 10.2196/jmir.6631] [Medline: 28572079]

42.  Levine D, McCright J, Dobkin L, Woodruff AJ, Klausner JD. SEXINFO: a sexual health text messaging service for San Francisco youth. Am J Public Health 2008 Mar;98(3):393-395. [doi: 10.2105/AJPH.2007.110767] [Medline: 18235068]

43.  Reback CJ, Grant DL, Fletcher JB, Branson CM, Shoptaw S, Bowers JR, et al. Text messaging reduces HIV risk behaviors among methamphetamine-using men who have sex with men. AIDS Behav 2012 Oct;16(7):1993-2002 [FREE Full text] [doi: 10.1007/s10461-012-0200-7] [Medline: 22610370]

44.  Reback CJ, Fletcher JB, Shoptaw S, Mansergh G. Exposure to theory-driven text messages is associated with HIV risk reduction among methamphetamine-using men who have sex with men. AIDS Behav 2015 Jun;19 Suppl 2:130-141. [doi: 10.1007/s10461-014-0985-7] [Medline: 25563501]

45.  Reback CJ, Fletcher JB, Swendeman D. Associations between sociodemographic characteristics and sexual risk behaviors among methamphetamine-using men who have sex with men. Subst Use Misuse 2018 Feb 12:1-8. [doi: 10.1080/10826084.2018.1436566] [Medline: 29432057]

46.  Cornelius JB, Dmochowski J, Boyer C, St Lawrence J, Lightfoot M, Moore M. Text-messaging-enhanced HIV intervention for African American adolescents: a feasibility study. J Assoc Nurses AIDS Care 2013;24(3):256-267 [FREE Full text] [doi: 10.1016/j.jana.2012.06.005] [Medline: 23122907]

47.  Kanfer F, Gaelick-Buys L. Self-management Methods. Elmsford, NY: Pergamon Press; 1991:0080378935.

48.  Bandura A. Social cognitive theory of self-regulation. Organizational Behavior and Human Decision Processes 1991 Dec;50(2):248-287. [doi: 10.1016/0749-5978(91)90022-L]

49.  Swendeman D, Arnold E, Harris D, Rotheram-Borus MJ, Team TASC. What strategies are enough to protect youth from HIV: automated messaging, weekly behavioral monitoring, peer social media networks, or interpersonal coaching? (preprint). JMIR Research Protocols 2019 [FREE Full text] [doi: 10.2196/preprints.11165]

50.  Yehia BR, Stewart L, Momplaisir F, Mody A, Holtzman CW, Jacobs LM, et al. Barriers and facilitators to patient retention in HIV care. BMC Infect Dis 2015 Jun 28;15:246 [FREE Full text] [doi: 10.1186/s12879-015-0990-0] [Medline: 26123158]

51.  Rajabiun S, Mallinson RK, McCoy K, Coleman S, Drainoni M, Rebholz C, et al. "Getting back on track": the role of outreach interventions in engaging and retaining people living with HIV/AIDS in medical care. AIDS patient care STDs 2007;21 Suppl 1:S20-S29. [doi: 10.1089/apc.2007.9990] [Medline: 17563286]

52.  Christopoulos KA, Massey AD, Lopez AM, Geng EH, Johnson MO, Pilcher CD, et al. "Taking a half day at a time": patient perspectives and the HIV engagement in care continuum. AIDS Patient Care STDS 2013 Apr;27(4):223-230 [FREE Full text] [doi: 10.1089/apc.2012.0418] [Medline: 23565926]

53.  Rice E, Milburn NG, Rotheram-Borus MJ. Pro-social and problematic social network influences on HIV/AIDS risk behaviours among newly homeless youth in Los Angeles. AIDS Care 2007 May;19(5):697-704 [FREE Full text] [doi: 10.1080/09540120601087038] [Medline: 17505933]

54.  DiClemente CC, Nidecker M, Bellack AS. Motivation and the stages of change among individuals with severe mental illness and substance abuse disorders. J Subst Abuse Treat 2008 Jan;34(1):25-35. [doi: 10.1016/j.jsat.2006.12.034] [Medline: 17574798]

55.  Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. Prev Chronic Dis 2013;10:E26 [FREE Full text] [doi: 10.5888/pcd10.120180] [Medline: 23428085]

56.  Boothroyd RI, Fisher EB. Peers for progress: promoting peer support for health around the world. Fam Pract 2010 Jun;27 Suppl 1:i62-i68. [doi: 10.1093/fampra/cmq017] [Medline: 20483801]

57.   Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. J Acquir Immune Defic Syndr 2009 Dec 1;52(4):465-473 [FREE Full text] [Medline: 19911481]

58.   Eysenbach G, Powell J, Englesakis M, Rizo C, Stern A. Health related virtual communities and electronic support groups: systematic review of the effects of online peer to peer interactions. BMJ 2004 May 15;328(7449):1166 [FREE Full text] [doi: 10.1136/bmj.328.7449.1166] [Medline: 15142921]

59.   Fisher EB, Boothroyd RI, Coufal MM, Baumann LC, Mbanya JC, Rotheram-Borus MJ, et al. Peer support for self-management of diabetes improved outcomes in international settings. Health Aff (Millwood) 2012 Jan;31(1):130-139 [FREE Full text] [doi: 10.1377/hlthaff.2011.0914] [Medline: 22232103]

60.   Brown JL, Vanable PA. Cognitive-behavioral stress management interventions for persons living with HIV: a review and critique of the literature. Ann Behav Med 2008 Feb;35(1):26-40 [FREE Full text] [doi: 10.1007/s12160-007-9010-y] [Medline: 18347902]

61.   Steinberg L, Morris AS. Adolescent development. Annu Rev Psychol 2001;52:83-110. [doi: 10.1146/annurev.psych.52.1.83] [Medline: 11148300]

62.   Viner RM, Ozer EM, Denny S, Marmot M, Resnick M, Fatusi A, et al. Adolescence and the social determinants of health. Lancet 2012 Apr 28;379(9826):1641-1652. [doi: 10.1016/S0140-6736(12)60149-4] [Medline: 22538179]

63.   McFall RM, Lillesand DB. Behavior rehearsal with modeling and coaching in assertion training. J Abnorm Psychol 1971 Jun;77(3):313-323. [Medline: 5556941]

64.   Gresham FM, Nagle RJ. Social skills training with children: responsiveness to modeling and coaching as a function of peer orientation. J Consult Clin Psychol 1980 Dec;48(6):718-729. [Medline: 7440828]

65.   Eells MA. Interventions with alcoholics and their families. Nurs Clin North Am 1986 Sep;21(3):493-504. [Medline: 3638703]

66.   Feldman DC, Lankau MJ. Executive coaching: a review and agenda for future research. Journal of Management 2016 Jul;31(6):829-848. [doi: 10.1177/0149206305279599] [Medline: 22973420]

67.   Butterworth SW, Linden A, McClay W. Health coaching as an intervention in health management programs. Disease Management & Health Outcomes 2007;15(5):299-307. [doi: 10.2165/00115677-200715050-00004]

68.   Sullivan M, Langford DJ, Davies PS, Tran C, Vilardaga R, Cheung G, et al. A controlled pilot trial of PainTracker Self-Manager, a web-based platform combined with patient coaching, to support patients' self-management of chronic pain. J Pain 2018 Mar 29. [doi: 10.1016/j.jpain.2018.03.009] [Medline: 29605691]

69.   Painter SL, Ahmed R, Kushner RF, Hill JO, Lindquist R, Brunning S, et al. Expert coaching in weight loss: retrospective analysis. J Med Internet Res 2018 Mar 13;20(3):e92 [FREE Full text] [doi: 10.2196/jmir.9738] [Medline: 29535082]

70.   Haug NA, Sorensen JL, Gruber VA, Lollo N, Roth G. HAART adherence strategies for methadone clients who are HIV-positive: a treatment manual for implementing contingency management and medication coaching. Behav Modif 2006 Nov;30(6):752-781. [doi: 10.1177/0145445506288229] [Medline: 17050764]

71.   Hill B, Richardson B, Skouteris H. Do we know how to design effective health coaching interventions: a systematic review of the state of the literature. Am J Health Promot 2015;29(5):e158-e168. [doi: 10.4278/ajhp.130510-LIT-238] [Medline: 24720388]

72.   Wilson IB, Lee Y, Michaud J, Fowler FJ, Rogers WH. Validation of a new three-item self-report measure for medication adherence. AIDS Behav 2016 Nov;20(11):2700-2708 [FREE Full text] [doi: 10.1007/s10461-016-1406-x] [Medline: 27098408]

73.   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]

74.   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]

75.   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]

76.   Spitzer RL, Johnson JG. The Patient Health Questionnaire-Adolescent Version. New York: Biometrics Research Unit, New York State Psychiatric Institute; 1995.

77.   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]

78.   Dowshen N, Kuhns LM, 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]

79.   Google Play. 2018. Time It URL: https://play.google.com/store/apps/details?id=com.cubestudio.timeit&hl=en [accessed 2019-01-27] [WebCite Cache ID 6y8mqT0u2]

80.   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]

81. 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]

82. Swendeman D, Comulada WS, Ramanathan N, Lazar M, Estrin D. Reliability and validity of daily self-monitoring by smartphone application for health-related quality-of-life, antiretroviral adherence, substance use, and sexual behaviors among people living with HIV. AIDS Behav 2015 Feb;19(2):330-340 [FREE Full text] [doi: 10.1007/s10461-014-0923-8] [Medline: 25331266]

83. Swendeman D, Jana S, Ray P, Mindry D, Das M, Bhakta B. Development and pilot testing of daily Interactive Voice Response (IVR) calls to support antiretroviral adherence in India: a mixed-methods pilot study. AIDS Behav 2015 Jun;19 Suppl 2:142-155 [FREE Full text] [doi: 10.1007/s10461-014-0983-9] [Medline: 25638037]

84. Prado G, Pantin H, Schwartz SJ, Lupei NS, Szapocznik J. Predictors of engagement and retention into a parent-centered, ecodevelopmental HIV preventive intervention for Hispanic adolescents and their families. J Pediatr Psychol 2006 Oct;31(9):874-890. [doi: 10.1093/jpepsy/jsj046] [Medline: 16049264]

85. Izumi BT, Schulz AJ, Mentz G, Israel BA, Sand SL, Reyes AG, et al. Leader behaviors, group cohesion, and participation in a walking group program. Am J Prev Med 2015 Jul;49(1):41-49 [FREE Full text] [doi: 10.1016/j.amepre.2015.01.019] [Medline: 26094226]

86. Merson MH, O'Malley J, Serwadda D, Apisuk C. The history and challenge of HIV prevention. Lancet 2008 Aug 09;372(9637):475-488. [doi: 10.1016/S0140-6736(08)60884-3] [Medline: 18687461]

87. Rotheram-Borus MJ, Swendeman D, Flannery D, Rice E, Adamson DM, Ingram B. Common factors in effective HIV prevention programs. AIDS Behav 2009 Jun;13(3):399-408 [FREE Full text] [doi: 10.1007/s10461-008-9464-3] [Medline: 18830813]

88. Rotheram-Borus MJ, Swendeman D, Lee SJ, 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]

89. Rapp CA, Goscha RJ. The strengths model: A recovery-oriented approach to mental health services. New York: Oxford University Press; 2012.

90. Arnold EM, Walsh AK, Oldham MS, Rapp CA. Strengths-based case management: implementation with high-risk youth. Families in Society 2018 May 03;88(1):86-94. [doi: 10.1606/1044-3894.3595]

91. Craw JA, Gardner LI, Marks G, Rapp RC, Bosshart J, Duffus WA, et al. Brief strengths-based case management promotes entry into HIV medical care: results of the antiretroviral treatment access study-II. J Acquir Immune Defic Syndr 2008 Apr 15;47(5):597-606. [doi: 10.1097/QAI.0b013e3181684c51] [Medline: 18285714]

92. Kral AH, Lambdin BH, Comfort M, Powers C, Cheng H, Lopez AM, et al. A strengths-based case management intervention to reduce HIV viral load among people who use drugs. AIDS Behav 2018 Jan;22(1):146-153. [doi: 10.1007/s10461-017-1903-6] [Medline: 28916898]

93. Surratt HL, O'Grady C, Kurtz SP, Levi-Minzi MA, Chen M. Outcomes of a behavioral intervention to reduce HIV risk among drug-involved female sex workers. AIDS Behav 2014 Apr;18(4):726-739 [FREE Full text] [doi: 10.1007/s10461-014-0723-1] [Medline: 24558098]

94. Corsi KF, Lehman WE, Min SJ, Lance SP, Speer N, Booth RE, et al. The Feasibility of interventions to reduce HIV risk and drug use among heterosexual methamphetamine users. J AIDS Clin Res 2012 Jun 04;S1(10) [FREE Full text] [doi: 10.4172/2155-6113.S1-010] [Medline: 23493796]

95. Rotheram-Borus MJ, Swendeman D, Becker KD. Adapting evidence-based interventions using a common theory, practices, and principles. J Clin Child Adolesc Psychol 2014;43(2):229-243 [FREE Full text] [doi: 10.1080/15374416.2013.836453] [Medline: 24079747]

96. Chorpita BF, Daleiden EL. Mapping evidence-based treatments for children and adolescents: application of the distillation and matching model to 615 treatments from 322 randomized trials. J Consult Clin Psychol 2009 Jun;77(3):566-579. [doi: 10.1037/a0014565] [Medline: 19485596]

97. Rotheram-Borus MJ, Swendeman D, Rotheram-Fuller E, Youssef MK. Family coaching as a delivery modality for evidence-based prevention programs. Clin Child Psychol Psychiatry 2018 Jan;23(1):96-109. [doi: 10.1177/1359104517721958] [Medline: 28849666]

98. Morin SF, Steward WT, Charlebois ED, Remien RH, Pinkerton SD, Johnson MO, et al. Predicting HIV transmission risk among HIV-infected men who have sex with men: findings from the healthy living project. J Acquir Immune Defic Syndr 2005 Oct 01;40(2):226-235. [Medline: 16186742]

99. Weiss R. Modeling longitudinal data. In: Modeling Longitudinal Data (Springer Texts In Statistics). Berlin, Germany: Springer; 2019.

100. Lightfoot M, Rotheram-Borus MJ, Comulada WS, Reddy VS, Duan N. Efficacy of brief interventions in clinical care settings for persons living with HIV. J Acquir Immune Defic Syndr 2010 Mar;53(3):348-356. [doi: 10.1097/QAI.0b013e3181c429b3] [Medline: 19996978]

101.  Comulada WS. Model specification and bootstrapping for multiply imputed data: an application to count models for the frequency of alcohol use. Stata J 2015 Jun;15(3):833-844 [FREE Full text] [Medline: 26973439]

102.  Comulada WS, Rotheram-Borus MJ, Pequegnat W, Weiss RE, Desmond KA, Arnold EM, et al. Relationships over time between mental health symptoms and transmission risk among persons living with HIV. Psychol Addict Behav 2010 Mar;24(1):109-118 [FREE Full text] [doi: 10.1037/a0018190] [Medline: 20307117]

103.  Selig J, Preacher KJ. Mediation models for longitudinal data in developmental research. Research in Human Development. (2-3) 2009;6:144-164. [doi: 10.1080/15427600902911247]

104.  Gold M. Panel on cost-effectiveness in health and medicine. Med Care 1996 Dec;34(12 Suppl):DS197-DS199. [Medline: 8969326]

105.  Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996 Oct 09;276(14):1172-1177. [Medline: 8827972]

106.  Hintze J. NCSS Statistical Software - PASS Sample Size. 2008. Sample Size & Power URL: https://www.ncss.com/software/pass/ [accessed 2018-04-10] [WebCite Cache ID 6yZzpwASq]

107.  Complete listing of LRC best practices. Centers for Disease Control Prevention URL: https://www.cdc.gov/hiv/research/interventionresearch/compendium/lrc/completelist.html [accessed 2019-01-27] [WebCite Cache ID 737VSWW0z]

108.  HIV cost-effectiveness. Centers for Disease Control Prevention URL: https://www.cdc.gov/hiv/programresources/guidance/costeffectiveness/index.html [accessed 2019-01-27] [WebCite Cache ID 6y8mUxvKk]

109.  Katon W, Unützer J, Fan MY, Williams Jr JW, Schoenbaum M, Lin EHB, et al. Cost-effectiveness and net benefit of enhanced treatment of depression for older adults with diabetes and depression. Diabetes Care 2006 Feb;29(2):265-270. [Medline: 16443871]

110.  Meeuwissen JAC, Feenstra TL, Smit F, Blankers M, Spijker J, Bockting CLH, et al. The cost-utility of stepped-care algorithms according to depression guideline recommendations - results of a state-transition model analysis. J Affect Disord 2019 Jan 01;242:244-254. [doi: 10.1016/j.jad.2018.08.024] [Medline: 30216769]

111.  Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J Acquir Immune Defic Syndr 2011 Oct 01;58(2):181-187 [FREE Full text] [doi: 10.1097/QAI.0b013e31822d490a] [Medline: 21857529]

## Abbreviations

**AMMI:** automated messaging and monitoring intervention
**ART:** antiretroviral therapy
**CER:** cost-effectiveness ratio
**EBI:** evidence-based intervention
**GBTY:** gay, bisexual, and transgender youth
**HIPAA:** Health Insurance Portability and Accountability Act
**MLM:** multilevel models
**PHQ-A:** Patient Health Questionnaire for adolescents
**RCT:** randomized control trial
**RDT:** rapid diagnostic tests
**SMS:** short message service
**STI:** sexually transmitted infection
**YLH:** youth living with HIV

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