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Protocol

Internet-Based HIV Prevention With At-Home Sexually Transmitted Infection Testing for Young Men Having Sex With Men: Study Protocol of a Randomized Controlled Trial of Keep It Up! 2.0

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Abstract

Background: Human immunodeficiency virus (HIV) infections are increasing among young men who have sex with men (YMSM), yet few HIV prevention programs have studied this population. Keep It Up! (KIU!), an online HIV prevention program tailored to diverse YMSM, was developed to fill this gap. The KIU! 2.0 randomized controlled trial (RCT) was launched to establish intervention efficacy.

Objective: The objective of the KIU! study is to advance scientific knowledge of technology-based behavioral HIV prevention, as well as improve public health by establishing the efficacy of an innovative electronic health (eHealth) prevention program for ethnically and racially diverse YMSM. The intervention is initiated upon receipt of a negative HIV test result, based on the theory that testing negative is a teachable moment for future prevention behaviors.

Methods: This is a two-group, active-control RCT of the online KIU! intervention. The intervention condition includes modules that use videos, animation, games, and interactive exercises to address HIV knowledge, motivation for safer behaviors, self-efficacy, and behavioral skills. The control condition reflects HIV information that is readily available on many websites, with the aim to understand how the KIU! intervention improves upon information that is currently available online. Follow-up assessments are administered at 3, 6, and 12 months for each arm. Testing for urethral and rectal sexually transmitted infections (STIs) is completed at baseline and at 12-month follow-up for all participants, and at 3- and 6-month follow-ups for participants who test positive at baseline. The primary behavioral outcome is unprotected anal sex at all follow-up points, and the primary biomedical outcome is incident STIs at 12-month follow-up.

Results: Consistent with study aims, the KIU! technology has been successfully integrated into a widely-used health technology platform. Baseline enrollment for the RCT was completed on December 30, 2015 (N=901), and assessment of intervention outcomes is ongoing at 3-, 6-, and 12-month time points. Upon collection of all data, and after the efficacy of the intervention has been evaluated, we will explore whether the KIU! intervention has differential efficacy across subgroups of YMSM based on ethnicity/race and relationship status.

Conclusions: Our approach is innovative in linking an eHealth solution to HIV and STI home testing, as well as serving as a model for integrating scalable behavioral prevention into other biomedical prevention strategies.

Trial Registration: Clinicaltrials.gov NCT01836445; https://clinicaltrials.gov/ct2/show/NCT01836445 (Archived by WebCite at http://www.webcitation.org/6myMFlxnC)

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KEYWORDS

eHealth; HIV prevention; Internet; risk reduction behavior; sexual behavior; sexually transmitted infections; young MSM

Introduction

Scientific Background

In the United States, young men who have sex with men (YMSM) are the group most affected by the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) [1]. Over 70% of new HIV infections among youth and young adults occur in YMSM between the ages of 13 and 29 [2]. YMSM of color are disproportionately affected by HIV/AIDS, with African Americans and Latinos representing 45% and 28% of new HIV diagnoses, respectively, compared to whites who represent 16% of new HIV diagnoses [3]. The rate of new HIV infections also continues to increase among YMSM [2], making HIV prevention among this population a high priority research area [4,5].

Despite the burden of HIV among YMSM, few proven individual-level HIV prevention programs have been created specifically for this population [4]. Most of the evidence-based interventions (EBIs) recommended by the Centers for Disease Control and Prevention (CDC) focus on reducing HIV infections among heterosexual adults and other high risk youth [6,7]. Most EBIs designed for high risk youth do not specify a particular sexual orientation as an eligibility requirement or special topic of focus within the prevention program. Of the EBIs that are designed for men who have sex with men (MSM), few are designed specifically for younger men or ethnically and racially diverse MSM. One notable exception is the Young Men's Health Project, which was evaluated with a diverse sample of YMSM (37% white, 29% Hispanic/Latino, 21% African American, and 13% other/multiple races) [8]. Participants completed four 1-hour motivational interviewing sessions delivered by therapists over a 12-week period.

To address the limited availability of EBIs for diverse YMSM, Keep It Up! (KIU!), an online HIV prevention intervention, was developed [9]. The intervention consists of interactive multimedia modules tailored to the real-life experiences of diverse YMSM. KIU! 1.0 was piloted in a randomized controlled trial (RCT) to test feasibility, acceptability, and preliminary efficacy [9]. In the pilot RCT, the intervention was delivered to YMSM upon receipt of a negative HIV test result from partner community-based organizations (CBOs). Participants in the intervention arm rated the program as valuable and acceptable, and reported statistically significant lower rates of condomless anal sex (CAS) at 3-month follow-up, compared to participants in the control arm [9]. Following the completion of the pilot RCT, the current multisite RCT (KIU! 2.0) was designed to test the efficacy of the intervention among a larger multisite sample of YMSM, with an extended follow-up assessment of behavioral and biomedical endpoints through 12 months. The multisite study design, online format, and yearlong follow-up period distinguish KIU! 2.0 from the Young Men's Health Project that is currently available as an individual-level EBI for YMSM.

Objectives

The overarching goal of the KIU! 2.0 project is to advance knowledge of technology-based behavioral HIV prevention, as well as improve public health by establishing the efficacy of an innovative electronic health (eHealth) prevention program for YMSM. We will accomplish these goals with three specific aims. First, we will integrate the KIU! intervention into a widely-used health technology platform to increase its scalability, adaptability, and potential for broad implementation. Second, we will test the efficacy of the KIU! intervention in a multisite RCT by (1) enrolling ethnically diverse HIV-negative YMSM (N=900; >65% ethnic/racial minorities) primarily in Atlanta, Chicago, and New York; (2) randomizing participants to either the KIU! intervention or an HIV knowledge control condition; and (3) measuring intervention outcomes at baseline and follow-up assessments at 3, 6, and 12 months.

The primary behavioral outcome will be the count of CAS acts, and the primary biomedical outcome will be incidences of sexually transmitted infections (STIs). Secondary behavioral outcomes include alcohol and drug use prior to sex, risky sex after substance use, condom errors, factors from the Information-Motivation-Behavioral Skills (IMB) theoretical model of HIV risk reduction [10], and receipt of an HIV test. We will test for dose effects based on metrics of intervention engagement and decay in intervention effects over time. Our third aim is to explore whether the KIU! intervention has differential efficacy based on the types of substances used prior to sex, as well as across important subgroups of YMSM based on race/ethnicity, gay/bisexual identity, and relationship status. In this context, *serious relationships* are defined as participants having a boyfriend/girlfriend or dating someone for an extended period of time and feeling very close to them, and *casual relationships* are defined as casual dating, sleeping with someone (eg, friends with benefits), having one night stands, or sex with strangers.

Methods

Trial Design

This is a two-group, active-control, double-blinded RCT of the online KIU! 2.0 intervention. Participants are randomized into two groups in equal proportions, and are blinded to which group

is the intervention of interest. Consent materials indicate that we are evaluating two versions of an online HIV prevention program. Study investigators and staff who have contact with participants for enrollment and retention activities are also blinded to the arm in which participants are enrolled. The KIU! intervention includes seven modules that are completed across three sessions, at least 24 hours apart, totaling approximately 2 hours of content. Across these modules, the KIU! intervention uses diverse delivery methods (eg, videos, animation, and games) to address HIV knowledge, motivate safer behaviors, teach behavioral skills, and instill self-efficacy for preventive behaviors. The intervention is available on desktop, laptop, and tablet computers. Due to the Adobe Flash components of the intervention, KIU! 2.0 is not available on mobile devices. An earlier version of the intervention (KIU! 1.0) that did not contain the enhanced booster content at 3- and 6-month follow-ups, has been reported [9]. The control condition contains the same number of modules as the KIU! condition, with the same requirement to participate across three sessions. The control arm reflects HIV information that is currently available on many websites, with the aim to understand how the KIU! intervention improves upon information that is currently available online. Booster sessions are delivered at 3 and 6 months for each arm, and follow-up assessments are administered at 3, 6, and 12 months for each arm. Testing for urethral and rectal STIs is completed at baseline and 12-month follow-up for all participants, and at 3- and 6-month follow-up for participants who test positive for an STI at baseline. Participants are compensated in the following amounts: US $30 for baseline assessment and STI testing, US $20 for immediate posttest, US $20 for each 3- and 6-month follow-up assessment, and US $30 for 12-month follow-up assessment and STI testing. Some participants receive additional compensation. Participants who complete baseline assessment and STI testing at a university site or health department clinic receive an additional US $20, participants who complete STI testing at 3- and 6-month follow-up receive an additional US $10, and participants who are past due to complete their 12-month follow-up assessment and STI testing are incentivized with an additional US $20.

All procedures performed in this study are approved by the Emory University, Hunter College, and Northwestern University Institutional Review Boards. Informed consent is obtained from all individual participants included in this study.

Participants

Eligibility Criteria

All interested participants are assessed for eligibility by completing a brief screener. Study inclusion criteria include (1) being between the ages of 18 and 29, (2) assigned male at birth and having current male gender identity, (3) receiving an HIV-negative test result from a study site or remote HIV testing, (4) reporting at least one act of CAS with a male partner in the prior 6 months, (5) not being in a behaviorally monogamous relationship lasting longer than 6 months, (6) having the ability to read English at an 8thgrade level, and (7) having an email address that can be used for research contact for retention purposes.

Recruitment

Participants are recruited from a variety of sources including (1) HIV testing clinics and mobile testing units of our partner CBOs in Atlanta, Chicago, and New York; (2) university-based HIV testing at research sites in Atlanta and New York; (3) local health department clinics in Chicago; (4) street outreach by university staff in Atlanta, Chicago, and New York; (5) local and national print, online, and telephone-recorded ads; (6) referrals from completed observational studies and research participant registries at the university sites; (7) referrals from CBOs not affiliated with the study who provide HIV testing; and (8) nationwide online ads on social media apps linked with remote, at-home HIV testing (see Figure 1). Eligible participants across all study sites are offered the opportunity to visit Emory University, Hunter College, or Northwestern University to complete the baseline assessment and first set of self-administered STI test kits. Northwestern University and Emory University also offer Food and Drug Administration (FDA)-approved kits for at-home self-testing for HIV for participants recruited through these online and community-based recruitment methods.

Study Setting

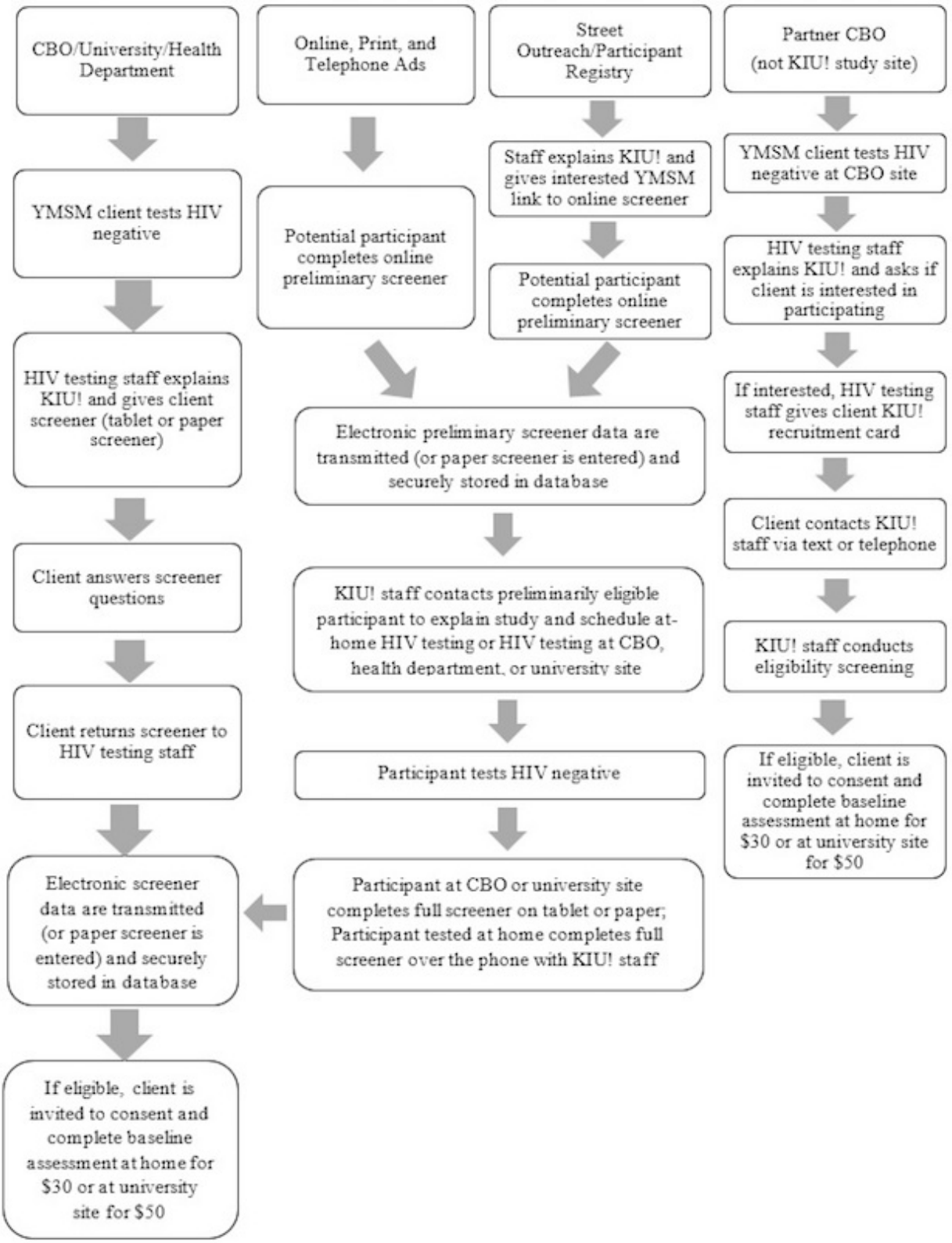
Participants complete self-report assessments at baseline, immediately postintervention, and 3, 6, and 12-months postintervention. Assessments are completed via the Internet using a Computer-Assisted Self Interview. Participants are also mailed kits to collect urine and rectal swabs for STI testing at baseline and 12-month follow-up. Participants who test positive for an STI at baseline also provide samples for STI testing at the 3- and 6-month follow-ups, in addition to the 12-month follow-up.

Intervention Arms

Keep It Up! Intervention Condition

In the context of a National Institutes of Health R34 grant, we collaborated with local CBOs to develop and pilot test KIU!, an interactive online HIV prevention project tailored to ethnically and racially diverse YMSM [9]. The intervention is informed by principles of e-learning [11] and based on the IMB model of HIV risk behavior change [10,12]. Our mixed-methods research, including qualitative interviews with ethnically-diverse YMSM, also directly informed the intervention design and content (eg, identification of myths about HIV transmission), particularly the refinement of messaging that was appealing across ethnic/racial groups [13].

Figure 1. Recruitment strategies workflow, Keep It Up! 2.0.



The KIU! intervention includes seven modules completed across three sessions, completed at least 24 hours apart (ie, across at least 3 days), which total approximately 2 hours to complete. An innovative aspect of KIU! is that each module is based on a particular setting or situation that is relevant to the lives of YMSM, with developmentally appropriate health behavior change content embedded within each of these settings (see Table 1). For example, one intervention module follows a diverse cast of YMSM and highlights (1) the risks in making assumptions about a partner's HIV status, (2) the risks of

assumed monogamy in relationships, (3) the importance of regular HIV testing, (4) the skills for negotiating condom use within relationships, and (5) the limits of serosorting among HIV-negative YMSM. Across the KIU! modules, the intervention uses diverse delivery methods (eg, videos, animation, and games) to address gaps in HIV knowledge, motivate safer behaviors, teach behavioral skills, and instill self-efficacy for preventive behaviors. Additional information about the intervention content can be found in a previously published manuscript [9]. KIU! was piloted in an RCT to test feasibility, acceptability, and preliminary efficacy [9]. An ethnically and racially diverse sample of YMSM from the Chicagoland area was enrolled, excellent retention was achieved through 3-month follow-up (89%), and there was a significant 44% decrease in CAS relative to an active control group [9]. The intervention was then delivered as KIU! 1.5, a service project at a Chicago CBO from 2012 to 2014 [14].

Table 1. Intervention modules, Keep It Up! 2.0.

	Module	Style	Content
Session 1	Healthy and Whole Person	Diverse peer videos	The first module welcomes and engages participants in the KIU! intervention. Diverse YMSM are interviewed on the streets of Atlanta, Chicago, and New York and discuss connections to family, community, and romantic partners for setting positive norms for condom use and obtaining support from family of origin and choice [15,16].
	Hooking up Online	Stylized animation with three scenarios	This animated module follows three diverse YMSM chatting online with a focus on identifying triggers for CAS. Embedded content focuses on the effects of mood on risk [17,18], negotiating correct condom use, consequences of drug and alcohol on decision making [4], and facts about STI symptoms and prevention.
Session 2	The Club Game	Virtual reality game	In this interactive game, participants address pros/cons of condom use, steps to correct condom use, consequences of excessive alcohol consumption or drug use, issues with presuming HIV status in others, and effects of sexual arousal on decision making [4].
	Dating (an Older Partner)	Illustrated story in Flash animation	The power dynamics between an older and younger man in a dating relationship are explored as well as how YMSM can assert healthy behaviors [19]. Embedded in the module is a continuum of safer sex behaviors and strategies for implementing them.
Session 3	A Serious Relationship	Illustrated story in Flash animation and scripted scenarios on video	An illustrated story about dating considers ways to get sexual, emotional, and health needs met in relationships and how ongoing condom use can be an important aspect of that. The module also includes a video of a YMSM who receives an HIV-positive diagnosis while in a relationship. It wraps up with a video with actors portraying examples of good and bad communication about condom use.
	Setting Risk Reduction Goals	Health educator video and HIV prevention goals worksheet	Participants develop three realistic and practical goals based on topics covered in the intervention such as consistent condom use, regular HIV testing, and improving communication with partners. The purpose is to plan to engage in behaviors that preserve emotional, sexual, and physical health, and to troubleshoot obstacles to successful implementation of the goals.
	Sex in the City	Scripted soap opera - style video	A diverse cast of YMSM highlights the risks in making assumptions about a partner's HIV status or monogamy, the limits of serosorting in HIV negative YMSM, the importance of regular testing, and skills for negotiating condom use within relationships. The soap opera is divided into four short videos that are shown across multiple sessions of the intervention. Part 1 is shown in the first session, part 2 in the second session, and parts 3 and 4 in the third session.
3 month follow-up	3 month booster	Scripted videos	A series of videos follow a young man named Antoine as he learns the importance of regular HIV testing and condom use after a condom failure due to incorrect use by his partner. Also included is video follow-up of a character from the "Sex in the City" soap opera who received an HIV negative test result and is working to maintain his risk reduction strategies. Participants are also given information about pre-exposure prophylaxis and other biomedical prevention strategies in various formats (video, fact sheet, and embedded Twitter feed). At the end of the booster, participants have a chance to revisit intervention modules and goals, troubleshoot obstacles to meeting goals, and set new goals or re-affirm existing ones.
6 month follow-up	6 month booster	Scripted videos	A series of videos follow Antoine as he navigates the dating scene before entering a serious relationship in which stopping condom use is discussed. In addition, participants have a chance to revisit 3 month booster content and goals, troubleshoot obstacles to meeting goals, and set new goals or re-affirm existing ones.

Control Condition

The control condition contains the same number of modules as the KIU! intervention condition, with the same requirement to participate across three sessions. Participants in the control condition also complete follow-up assessments and STI testing at the same time points as those in the KIU! condition. The control content reflects HIV information that is currently available on many websites, with the aim to understand how the KIU! intervention improves upon what is currently available online. Information on transmission, treatment, and prevention is provided through static slides with text and images. The control condition is didactic, not tailored to YMSM, noninteractive, and focuses on HIV/STI knowledge. Modifications were made to the control arm prior to the launch of KIU! 2.0 to include facts about biomedical prevention strategies. The use of this approach as a control condition ensures that both groups have equivalent access to the Internet for HIV-related content.

Booster Sessions

In the current study, there are two booster sessions paired with follow-up assessments for both the intervention and control arms. These sessions occur at 3- and 6-month time points. At all follow-up time points, data collection occurs prior to booster session content, to prevent any effect on participant responses. The content provided at each follow-up varies by study arm.

Intervention Condition

The 3- and 6-month booster sessions reinforce learning from the intervention and provide additional HIV prevention information. The 3-month booster for the KIU! intervention focuses on the importance of repeat HIV testing, following the CDC's recommendation of twice annual HIV testing among high-risk MSM [20]. The 6-month booster focuses on healthy romantic relationships, and is based on the findings that building and maintaining healthy relationships were two of the most popular topics in previous needs-assessments of online sexual health content for YMSM [21,22]. During each booster session, participants are provided the opportunity to review and update goals that they set during the postintervention assessment. At the end of each booster session, participants can review previous content. The 12-month follow-up assessment has no booster content and participants are administered the same measures that were previously completed at baseline and follow-up.

Control Condition

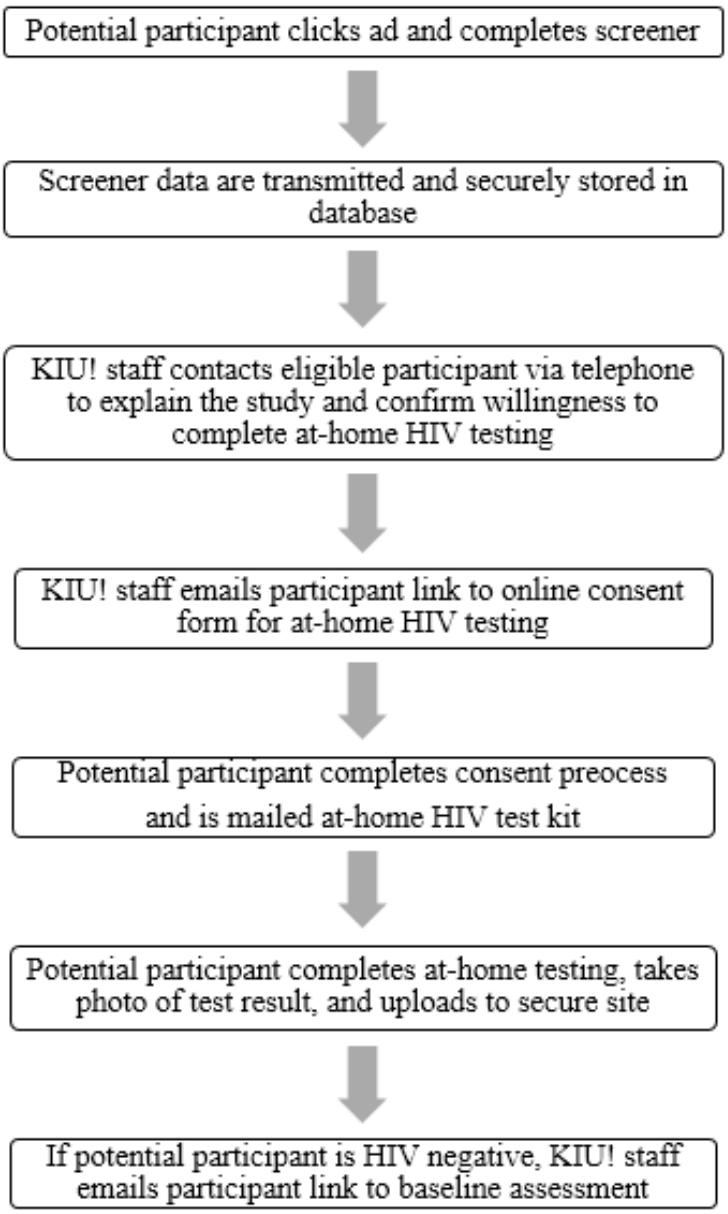
At the 3- and 6-month follow-up sessions, participants review content from the control modules. The slides on HIV information displayed in the initial modules are rearranged and administered at the 3-month follow-up. Slides with information on biomedical prevention strategies such as preexposure prophylaxis (PrEP), microbicides, and male circumcision are also included at the 3-month follow-up. The slides with STI information are rearranged and administered at the 6-month follow-up. Similar to the intervention condition, only the study measures are administered at the 12-month follow-up.

Remote Testing for HIV and Sexually Transmitted Infections

HIV Testing

To assess eligibility for participation in KIU! 2.0, individuals who are recruited online are mailed the FDA-approved, at-home, oral fluid OraQuick HIV test kit (see Figure 2). Following the instructions for self-testing that are included with the kit, participants self-administer the test and interpret their test result by comparing the test stick to the pictures and descriptions on the test kit directions. After determining their test result, participants report their result to study staff by uploading a photograph of the test stick to a secure online database. If the individual tests HIV-negative using the at-home test kit, the research assistant (RA) calls the participant to do a full screening over the telephone, and confirms eligibility. If eligible, an enrollment email with a link to the study is sent to the potential participant's email address. If ineligible, the individual is informed that he is ineligible for KIU! but may be eligible for other studies. If he is interested in other studies, additional contact information is then collected. If the potential participant tests HIV-positive using the at-home test kit, the RA works with the individual to link them to care. The RA uses established organizational linkage-to-care procedures, including referring the individual to a clinic that will conduct a free confirmatory HIV test, and a referral to someone that will work with them to receive treatment if their confirmatory test returns positive. Research staff are responsible for reporting positive HIV test results to the appropriate health department.

Figure 2. At-home HIV testing workflow, Keep It Up! 2.0.



Sexually Transmitted Infection Testing

To enroll in the study, potential participants are mailed at-home urine and rectal swab sample collection kits in a nondescript box to test for urethral and rectal gonorrhea (NG) and chlamydia (CT) at baseline. Easy-to-understand instructions for collecting and returning the samples are provided with the kits. In addition to the written instructions provided with the rectal STI kit, a video with instructions for properly collecting the rectal samples is shared with participants. The protocol for diagnostic testing of STI samples has changed as the study has progressed. Initially, the biotechnology company Identigene tested urine samples, while Emory University tested rectal swabs, for NG and CT. Both laboratories used the Nucleic Acid Amplification Test (NAAT) method, which is the gold standard method of diagnostic testing. As of March 2012, the CDC Division of Sexually Transmitted Diseases (STDs) Prevention laboratory provides diagnostic testing of the test kit samples using the NAAT method. Participants mail the kit to the CDC lab using prepaid boxes provided by the study. After STI test results are received by the KIU! 2.0 study team from the CDC, they are delivered to potential participants using a secure, encrypted email. To open the email and access their results, individuals must enter the unique study identification number that is provided to them with their test kit. Participants can print a hard copy of their results, and may speak to research staff if they wish. If positive STI test results arise, study staff provide local referrals for free or low-cost treatment and make a legally required confidential report to the appropriate health department. Across all stages of the study, the RAs prompt participants to access their results if they have not been viewed within 14 days of being made available. If a participant does not access his results after this reminder, the RA calls or sends additional reminders every 7 days. A minimum of three attempts at contact

are made for both the reminders to return kits, and to access test results. If a participant does not respond to these attempts, the RA makes additional attempts for the duration of the study (as feasible) unless the participant explicitly asks to no longer be contacted. STI testing at follow-up follows the same protocol.

Integration with Patient-Facing Health Technology Platform

The online KIU! intervention was integrated into the online Web-based patient reported outcome (PRO) platform, Assessment Center (AC) [23,24]. The platform is a research management software application that serves as a library for PRO instruments, allows a mechanism for administering surveys, instruments, and forms to participants, and is a central facility for the storage, retrieval, organization, and sharing of study research items and data. The intervention integration consisted of adding a screening module that determined eligibility, and randomized participants into study arms. A tracking module was also developed and integrated with AC to assist in scheduling and managing the timely delivery of STI testing kits to study participants.

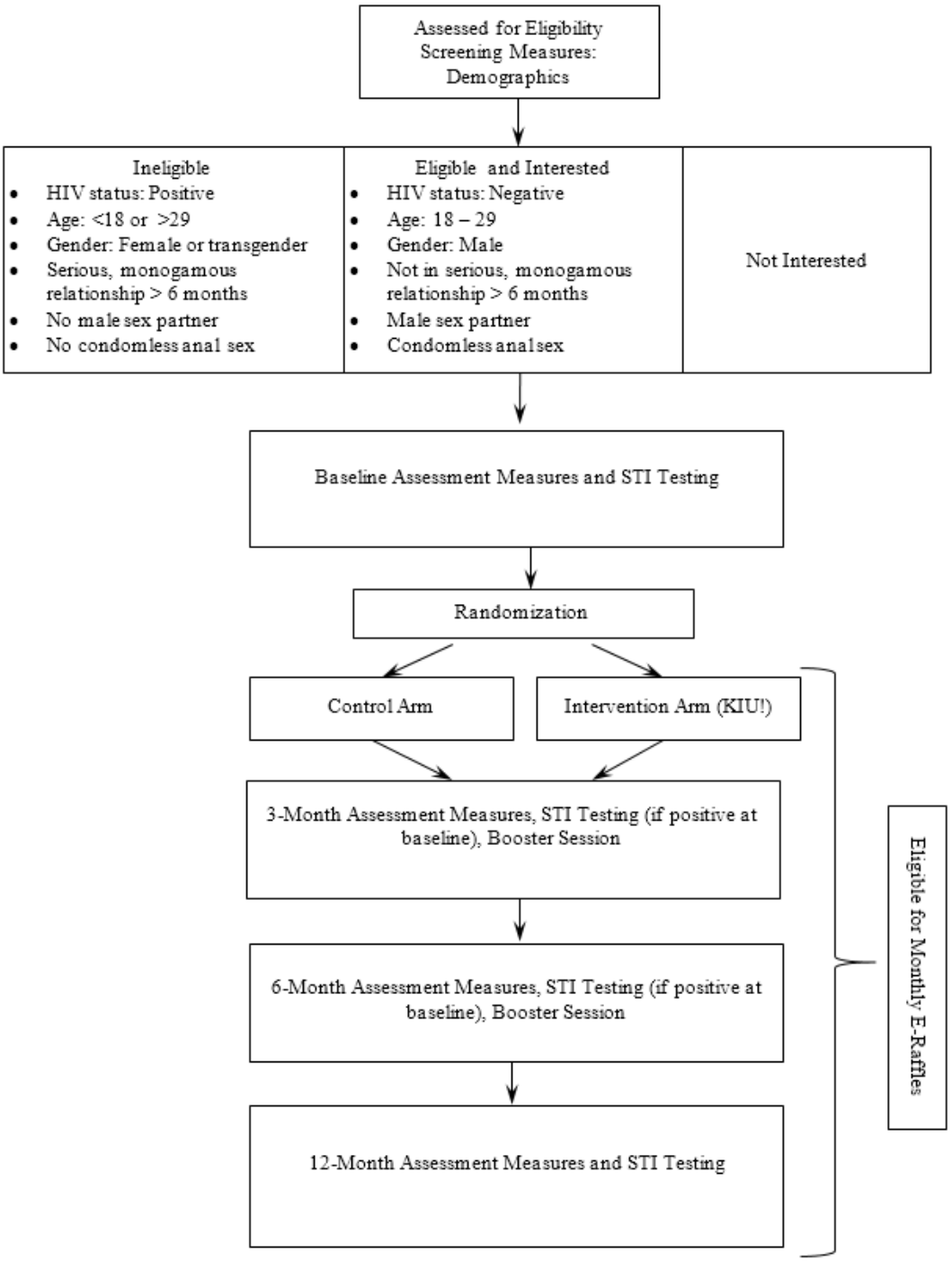
Participant Tracking and Retention

All participant tracking and retention activities are centrally managed at the lead site, Northwestern University, where the tracking technology is based. A supplemental database housed on REDCap, an online application, is used to log staff contact with participants and participant progress in the study. In consideration of difficult-to-reach participants across study sites, the Atlanta- and New York-based research staff members also assist with tracking and retention activities. The belief is that participants will be more responsive to contacts made from local sites, especially if they were recruited from these sites.

Randomization and Allocation

Upon enrollment, participants are randomly assigned by the online program (AC) to receive the KIU! intervention or HIV knowledge control arm. Participants do not know which group is the intervention under evaluation. Study investigators are blinded to the arm in which participants are enrolled. Randomization was performed using 6 permuted blocks of size 4, and stratified by race and HIV testing site at baseline [25]. Stratifying by race assures sufficient representations on each treatment arm to address the aim of exploring potential ethnic/racial differences in outcome effects. Stratification by HIV testing site prevents imbalance in latent geographical factors that may influence intervention responsiveness across cities and clinics. After the pretest assessment and remote STI testing, participants receive the intervention content across three sessions, over a minimum of 3 days and a maximum of 3 weeks, based on principles of effective HIV interventions and high acceptability in the pilot phase (KIU! 1.0). Participants maintain consistent online contact throughout the course of the study (a total of 12 months *after* intervention completion) and booster sessions and follow-up assessments are delivered at 3 and 6 months. The final follow-up assessment is administered at 12 months. All enrolled participants are also emailed a link to enter a monthly e-raffle for a US $50 gift card for the duration of their participation in the study. All participants who click the link and verify or update their contact information in an online survey are entered into the e-raffle. The monthly raffles are modeled on a previous study that used interim e-raffles to maintain participant engagement and up-to-date contact information [26]. The *Participant Flow Diagram* is presented in Figure 3.

Figure 3. Participant workflow, Keep It Up! 2.0.



Results

A total of 2984 potential participants have been screened across all recruitment sources. Of those screened, approximately half were eligible, and 901 participants were enrolled to make up the final study sample (see Table 2). The sample is diverse with 36.6% (330/901) of participants identifying as non-Latino white. The mean age of the sample is approximately 24 years and most participants identify as gay, single, having at least some college education, and being employed at least part time. Close to half (408/901, 45.3%) of all participants identified as having no religious affiliation. Over 60% (560/901) of participants reported substance use in the past 3 months. Most participants (477/901, 52.9%) reported using marijuana, with poppers and cocaine being the second and third most commonly reported drugs (179/901, 19.9%; and 119/900, 13.2%, respectively). Approximately one third (252/841, 30.0%) of participants reported using substances in the four hours before having sex with their partners in the past 3 months.

Table 2. Demographic characteristics of enrolled Keep It Up! 2.0 participants.

Characteristics	n (%)
Total	901
Race/Ethnicity	
White	330 (36.6)
Latino	260 (28.9)
Black	219 (24.3)
Other	92 (10.2)
Sexual identity	
Gay	777 (86.2)
Bisexual	104 (11.5)
Other	20 (2.2)
Relationship status	
Serious relationship	175 (19.5)
Casual dating	223 (24.8)
Not in a relationship	501 (55.7)
Religious affiliation	
Catholic	154 (17.1)
Protestant	102 (11.3)
No religious affiliation	408 (45.3)
Other (eg, Jewish, Muslim)	237 (26.3)
Education	
High school or less	113 (12.5)
Some college	252 (28.0)
College degree	418 (46.4)
Graduate degree	118 (13.1)
Current student	
Yes	328 (36.4)
No	573 (63.6)
Employment status	
Full time	451 (50.1)
Part time	250 (27.8)
Unemployed	199 (22.1)
Substance use (past 3 months)	
Yes	560 (62.2)
No	341 (37.8)
Substance use before sex	
Yes	252 (30.0)
No	589 (70.0)
Age, mean (SD)	24.3 (2.9)
Length (months) of serious relationship, mean (SD)	25.40 (28.6)

Intervention Outcomes

Knowledge, motivation, skills (ie, partner sexual communication, correct condom use), and behavioral outcomes (ie, number of insertive and receptive CAS acts, condom errors) are measured at baseline and the 3-, 6-, and 12-month follow-up assessment time points. We measure intervention acceptability and tolerability immediately postintervention. Whenever possible, we selected measures designed for YMSM that were previously tested with diverse populations, to minimize cultural bias and maximize sensitivity and comparability to other studies. We follow participants for 12 months to assess behavioral outcomes far enough postintervention to allow for the potential occurrence of risk behaviors and HIV testing. This assessment plan also allows us to model possible degradation of treatment effects over time, and to assess outcomes 6 months after the final booster session, which meets CDC criteria for being classified as a tier I best-evidence HIV prevention program [6].

Primary Outcome Measures

The *HIV-Risk Assessment for Sexual Partnerships* (H-RASP) has been used with YMSM [27-29], and assesses sexual behaviors and associated situational and contextual variables on a partner-by-partner level, starting with recent partners, as well as in the aggregate. Partners are classified as serious or casual, and relationship duration is measured [19]. Questions differentiate between insertive and receptive anal sex. A sample question is, “How many times did you have sex without using a condom during anal sex (where you were the top) with this partner?”

The H-RASP measure includes a subset of questions specific to alcohol and drug use prior to sex, and is used to assess substance use as a risk factor for CAS. Substance use is being assessed as a risk factor because YMSM, in comparison to their heterosexual counterparts, are more likely to use a variety of different substances (including alcohol and illicit drugs), to initiate drug use at an earlier age, and to experience more rapid increases in substance use over time [30-33]. Substance use is also a primary risk factor for HIV in this population [4]. A sample question is, “How frequently did you use drugs in the 4 hours before having vaginal or anal sex with this partner?” Respondents indicate drug use via a 5-point frequency scale (1=never, 5=always) on a partner-by-partner level, as well as in the aggregate. For participants reporting drug use, a follow-up question assesses the particular drug(s) used.

To assess biomedical outcomes, urine and rectal samples are tested for NG and CT with the FDA-cleared Gen-Probe APTIMA Combo 2 Assay. All participants are tested at baseline and at the 12-month follow-up. Participants who test positive for an STI at baseline are also tested at the 3- and 6-month follow-ups. We test for both urethral and rectal NG and CT, as recent research shows rectal infections to be just as common, if not more so, than urethral infections, particularly among MSM of color [34]. In this study, the incidence of NG and CT serves as a biomedical endpoint for establishing intervention efficacy, and as a means for determining the feasibility of incorporating an innovative approach to STI testing into an online HIV prevention solution.

Secondary Outcome Measures

The *Brief HIV/AIDS Knowledge Questionnaire* is a true/false survey assessing knowledge of HIV transmission and prevention [35]. This questionnaire has strong internal consistency, test-retest stability [35], and has been used successfully with young adults [36]. Items are modified from the original measure to make them relevant for MSM. A sample question is, “Only the receptive/bottom partner is at risk of being infected with HIV during anal sex.” Correct answers are coded as 1 and incorrect or uncertain responses are coded as 0. Composite scores are calculated to reflect the percentage of correct responses.

The *HIV/AIDS Motivation and Behavioral Skills Questionnaire* [37] assesses motivation (eg, motivation to become safer), social norms (eg, partners’, friends’, or family members’ opinions about condom use), and behavioral skills (eg, negotiating condom use). Internal reliability Cronbach alphas range from .73 to .94 and the measure has been used and developed for MSM. A sample question is, “Based on your sexual behavior over the past 3 months, how much do you think you have been at risk for being infected with HIV or other STDs?”

The *Condom Errors Questionnaire* is an abbreviated version of the *Condom Use Errors and Problems Questionnaire* [38], which has been used with YMSM [39]. Using a 5-point Likert scale (1=never, 5=always) participants indicate the degree to which they had experienced a condom error (ie, using an oil-based lubricant), failure (ie, breakage during sex), or erection loss (ie, occurring prior to or during sex). A sample question is, “As a top during anal sex in the last 3 months, how often did you start having sex without a condom and then put it on later?”

The *Health Protective Communication Scale* [40] measures how respondents discuss health protection with their sex partners. This scale has been used with diverse adolescent and young adult samples (Cronbach alpha=.84 in a national sample) [40]. A sample item is, ‘‘How often in the past 6 weeks have you told a new sex partner that you would not have sex unless a condom is used?’’ Respondents rate items on a 4-point frequency scale (1=always, 4=never).

Additional Measures

We use standard measures of age, ethnicity, education, and socioeconomic status. For YMSM, we use tailored items for gender identity, sexual orientation identity, and anatomic sex at birth.

The *PREP Intentions and Impact on Condom Use Measure* assesses participants’ intention to use PrEP, and is adapted from a measure used with high risk MSM [41,42]. A gateway question is used so that participants who have not used PrEP are asked about their intention to use it in the future, and participants who have used PrEP are asked about their use of, and attitudes towards, PrEP. Descriptive information on this measure in the KIU! 2.0 sample has been published [43].

The study team modified this measure at follow-up to better reflect PrEP use after it became FDA approved. For example, the baseline PrEP measure that was programmed before FDA approval of PrEP asks, “How many times have you taken

anti-HIV medications?" under the assumption that participants might have been receiving PrEP inconsistently, as it was not readily available to most of the population. This question was removed in the follow-up assessments. New questions such as, "On a typical week, how many days did you miss taking your medication?" were added to the follow-up measure to reflect that participants who now take PrEP likely have a prescription for the medication, and to reflect the importance of assessing adherence.

The *Intervention Acceptability and Tolerability Measure* [44] includes a combination of open-ended questions (eg, "What aspect of the program did you like the least?") and closed-ended Likert-style questions that form a scale of intervention acceptability (Cronbach alpha=.87). The questions were adapted from the original measure of 8 items to be specific to an online HIV intervention for adults. These adaptations were based on the investigators' experience in the field, as were newly created items such as, "How interactive did you find the program?"

Statistical Methods

Univariate summary statistics will be computed for all potential covariates. These summary statistics will be stratified by treatment arm, and then compared statistically through tests of two independent binomial proportions for binary variables, and two-sample t-tests for continuous variables to assess a failure of randomization. A Cochran-Mantel-Hanzel test of two independent binomial proportions will be used for the primary outcome measure of incident STIs at the 12-month endpoint, stratified by race and site, and an analogous stratified test for the count of CAS acts. These tests will set Cronbach alpha at .05, two-sided, and unadjusted for risk factors, except for the strata variables (race, site) used in the experimental design of the study. Ordinary generalized linear models and quasi-likelihood will be used to model the primary 12-month efficacy endpoints while adjusting for potential risk factors. Generalized linear mixed models and generalized estimating equations for multiple correlated, longitudinal CAS measures will be used to estimate the time-averaged treatment effect and time trends using all follow-up outcome measures, while adjusting for other potential time-dependent risk factors. The same regression modeling procedures will be used for secondary outcomes, such as condom errors, IMB factors, and receipt of an HIV test. All statistical analyses will be performed under an intent-to-treat principle [45].

To address potential adverse effects of participants' use of PrEP during the study, we will use methods of causal inference under Rubin's causal model [46,47] to adjust for postrandomization variables that allow for consistent estimates of treatment effects under the original study design, while adjusting for potential confounders. Principal stratification [48] will be used to conduct an analysis of the primary KIU! 12-month STI efficacy endpoint as well as CAS endpoint. Here, *any PrEP use* during the study is the principal strata, and this analysis is a comparison of two potential outcomes, had participants remained PrEP-free during the 12-month study. A complementary causal analysis is a regression model stratified by the propensity of PrEP use, where treatment arm is the primary covariate and the propensity score is constructed from a logistic regression model of PrEP use on potential confounders.

Discussion

This evaluation of KIU!, a promising eHealth HIV prevention intervention for YMSM, is an important contribution to the field of HIV prevention for several reasons. To begin, while numerous funded studies regarding the Internet and HIV risk have been undertaken, there have been relatively few funded efficacy RCTs of HIV prevention eHealth projects, particularly among YMSM. Rates of HIV are on the rise among MSM in the period of *emerging adulthood*, but very little intervention research has been conducted with this high-risk group [4,28,49], therefore necessitating an efficacy trial among YMSM.

The KIU! intervention content and recruitment approaches also represent innovations in the field. Intervention content is based on the IMB theory of HIV risk behavior change [10,12,37,50], principals of e-learning [11], and qualitative research with ethnically and racially diverse YMSM, to ensure cultural relevance [13]. Content is delivered through videos, games, and animations to increase engagement and motivate behavior change by addressing peer norms, personal vulnerability, behavioral intentions, and examining safer sex practices (eg, the pros/cons of condom use). Significantly, KIU! uses a novel approach of focusing on situations (eg, dating an older partner) and settings (eg, Internet) commonly experienced by YMSM. Intervention content embedded within these *virtual* settings contrasts with traditional HIV prevention projects, which often have sessions focused on the standard topics of HIV knowledge, transmission, or prevention.

Regarding participant recruitment, KIU! is unique in linking a behavioral HIV prevention project to a clinical encounter (ie, HIV testing) as one of its recruitment strategies. Currently, most testing clinics have limited time and resources to provide prevention resources. This approach produces innovative research on how to catalyze prevention by capitalizing on a key clinical encounter that could then be generalized to other biomedical strategies that require embedded behavioral prevention (eg, PrEP). Such an intervention could play an important role in providing accessible prevention for YMSM, particularly YMSM seeking HIV testing. This approach represents an opportunity to develop a cost-effective and easy-to-use intervention that will engage and motivate participants, while teaching risk reduction behaviors. Additionally, recruitment may be extended beyond the clinic setting to include more traditional recruitment efforts, such as community and street outreach and organization referrals, as well as increasingly common online advertising. As demonstrated in this study, recruitment of diverse YMSM from a variety of sources is feasible for online HIV prevention research. Documenting these efforts will produce research on differences in retention and risk profiles of YMSM recruited from a variety of sources.

Another important contribution to the field of HIV prevention is our approach to incorporate STI testing into an online HIV prevention project, primarily through remote self-testing. This approach is in response to calls to incorporate STI testing and

treatment into HIV prevention efforts [51-53], given that STIs are important risk factors in HIV transmission and acquisition due to increased biological susceptibility [54,55]. Additionally, in efficacy trials of sexual risk reduction interventions, STI infections can serve as sensitive biomarkers, particularly when HIV infection rates are too low to allow sufficient power with attainable sample sizes [56-60]. In KIU! 2.0, a portion of individuals were recruited from nationwide online ads; however, to assess eligibility, these potential participants were required to complete remote, at-home HIV testing. Upon successful enrollment into the study, all participants also completed STI testing as a means of generating a biological study endpoint for establishing intervention efficacy. Together, these strategies represent a public health solution for incorporating HIV and STI testing into an eHealth HIV intervention. To our knowledge, KIU! 2.0 is the first intervention to link remote STI testing into an eHealth HIV prevention intervention.

Limitations

There are important limitations in considering the promise of KIU! 2.0 in its current form. The first limitation concerns access to the Internet for the delivery of online interventions. The Internet has become an important delivery approach for eHealth tools. Online interventions can be convenient for users as they are accessible from anywhere that there is a connection to the Internet. Additionally, online interventions can be used in private settings, which also improves accessibility and engagement without the fear of stigma, particularly for YMSM and other high-risk populations. Although the digital divide is narrowing, the promise of eHealth interventions may be limited for those without consistent and reliable Internet access. Second, issues related to the technology required to deliver and maintain eHealth interventions may serve as a study limitation. Currently, KIU! can only be accessed on laptops or computer tablets because content is not formatted for access on mobile phones. This factor may limit intervention access, particularly among subpopulations who primarily access the Internet via smartphones. Additionally, as with all Web-based applications, regular maintenance is required to ensure that the intervention is compatible with new and updated Web browsers, and to fix emerging bugs that impede participants' ability to complete intervention sessions. Technical support and ongoing maintenance will present a financial challenge to future implementation after this trial is completed. Third, there is the challenge of deciding when and if to update eHealth intervention content during an ongoing RCT as new advances emerge (eg, PrEP) [61]. For example, PrEP became FDA-approved after the trial began, and therefore information on PrEP was added to booster sessions to assure all participants had access to this new information. Despite these considerations, computer- and Internet-based HIV prevention efforts show promise [62]. These resources have the advantages of standardization and ease of replication, as well as the added benefit of reach and increased use (particularly among youth), and are important venues for health interventions [63].

Conclusions

The overarching goal of KIU! 2.0 is to advance scientific knowledge of Internet-based behavioral HIV prevention, and improve public health by establishing the efficacy of an innovative eHealth prevention program for YMSM. This research is making significant progress towards achieving the specified aims. First, the KIU! technology has been successfully integrated into a widely-used health technology platform to increase its scalability, adaptability, and potential for broad implementation. Second, baseline enrollment for the RCT is complete (N=901) and we are currently assessing intervention outcomes (ie, count of CAS acts and STI incidence) via follow-up assessments at 3, 6, and 12 months. Finally, upon collection of all data, and after the efficacy of the intervention has been evaluated, we will explore whether the KIU! intervention has differential efficacy across subgroups of YMSM based on ethnicity/race, relationship status, and other variables. Our approach is innovative in linking an eHealth solution to HIV and STI testing, and serves as a model for integrating scalable behavioral prevention into other biomedical prevention strategies.

Trial Status

Participant recruitment for KIU! 2.0 is complete. Follow-up data is currently being collected and will be completed in early 2017.

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Conflicts of Interest

None declared.

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Abbreviations

AC: Assessment Center
AIDS: acquired immune deficiency syndrome
CAS: condomless anal sex
CBO: community-based organization
CDC: Centers for Disease Control and Prevention
CT: chlamydia
EBI: evidence-based intervention
eHealth: electronic health
FDA: Food and Drug Administration
HIV: human immunodeficiency virus
H-RASP: HIV-Risk Assessment for Sexual Partnerships
IMB: Information-Motivation-Behavioral Skills
KIU!: Keep It Up!
MSM: men who have sex with men

NAAT: Nucleic Acid Amplification Test
NG: gonorrhea
PrEP: preexposure prophylaxis
PRO: patient reported outcome
RA: research assistant
RCT: randomized controlled trial
STD: sexually transmitted disease
STI: sexually transmitted infection
YMSM: young men who have sex with men

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Protocol

Effects of Video Game Training on Behavioral and Electrophysiological Measures of Attention and Memory: Protocol for a Randomized Controlled Trial

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Abstract

Background: Neuroplasticity-based approaches seem to offer promising ways of maintaining cognitive health in older adults and postponing the onset of cognitive decline symptoms. Although previous research suggests that training can produce transfer effects, this study was designed to overcome some limitations of previous studies by incorporating an active control group and the assessment of training expectations.

Objective: The main objectives of this study are (1) to evaluate the effects of a randomized computer-based intervention consisting of training older adults with nonaction video games on brain and cognitive functions that decline with age, including attention and spatial working memory, using behavioral measures and electrophysiological recordings (event-related potentials [ERPs]) just after training and after a 6-month no-contact period; (2) to explore whether motivation, engagement, or expectations might account for possible training-related improvements; and (3) to examine whether inflammatory mechanisms assessed with noninvasive measurement of C-reactive protein in saliva impair cognitive training-induced effects. A better understanding of these mechanisms could elucidate pathways that could be targeted in the future by either behavioral or neuropsychological interventions.

Methods: A single-blinded randomized controlled trial with an experimental group and an active control group, pretest, posttest, and 6-month follow-up repeated measures design is used in this study. A total of 75 cognitively healthy older adults were randomly distributed into experimental and active control groups. Participants in the experimental group received 16 1-hour training sessions with cognitive nonaction video games selected from Lumosity, a commercial brain training package. The active control group received the same number of training sessions with The Sims and SimCity, a simulation strategy game.

Results: We have recruited participants, have conducted the training protocol and pretest assessments, and are currently conducting posttest evaluations. The study will conclude in the first semester of 2017. Data analysis will take place during 2017. The primary outcome is transfer of benefit from training to attention and working memory functions and the neural mechanisms underlying possible cognitive improvements.

Conclusions: We expect that mental stimulation with video games will improve attention and memory both at the behavioral level and in ERP components promoting brain and mental health and extending independence among elderly people by avoiding the negative personal and economic consequences of long-term care.

Trial Registration: Clinicaltrials.gov NCT02796508; https://clinicaltrials.gov/ct2/show/NCT02796508 (archived by WebCite at http://www.webcitation.org/6nFeKeFNB)

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KEYWORDS

attention; C-reactive protein; cognitive training; healthy aging; inflammation; electrophysiology; video games; working memory

Introduction

Background

Neurocognitive frailty is the biggest threat to successful aging [1]. There is overwhelming evidence that the number of inflammatory mediators increases vastly in pathological aging [2] and in healthy aging as well [3]. This inflammation has a negative impact on cognition [4]. C-reactive protein (CRP), an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells, has been identified as a hallmark of systemic inflammation, and it can be assessed by noninvasive methods in saliva [5]. A key challenge that faces the aging society is to find new approaches to understand the aging mind and brain that could enhance successful, optimal aging [6]. Another major challenge is to understand the factors that could reduce or delay the negative consequences of age-related cognitive decline [7]. The idea behind this randomized controlled trial (RCT) is that cognitive abilities could be strengthened by interventions that promote positive brain plasticity [8].

Normal aging is associated with gray and white matter shrinkage. The lateral prefrontal cortex, cerebellum, and medial temporal lobe system including hippocampus are affected. Minimal reduction occurs in the entorhinal and occipital cortices [1,9,10]. These brain changes are associated with declines in several important cognitive functions, including processing speed, executive functions, working memory, and episodic memory [11-14]. However, other crystallized abilities such as general knowledge, verbal abilities [15-17], and implicit memory [18,19] are mostly preserved. Older adults with mild cognitive impairment [20] and Alzheimer disease patients have shown preserved implicit memory despite huge deteriorations in episodic memory [21,22]. Although behavioral priming for repeated pictures is spared in older adults, reduced neural activation, which is a signature of implicit memory, is affected. The relationship between brain function and behavior found in young adults is altered in older adults, although these age-related changes do not affect behavioral facilitation. These findings have implications for the notion that automatic processes, previously considered preserved with age, are susceptible to the effects of aging at the neural level. The age-invariant behavioral facilitation with stimulus repetition is observed as a result of more sustained neural processing of visual stimuli in older adults as a form of compensatory neural activity [23].

Electrophysiological studies have also found significant age-related event-related potential (ERP) changes in brain activity associated with memory retrieval in spite of similar performance in young and older adults [24]. Elders compensate for their lower level of parieto-occipital functioning as shown by smaller P300 amplitude at posterior sites by recruiting frontal sites as a mode of brain adaptation [25]. In touch, despite similar behavioral performance in a recognition memory task involving familiar 3D objects, young and older adults recruited different neural resources to perform the task. Age-related differences were found in brain oscillations, as measured by event-related spectral perturbations (ERSPs), suggesting the recruitment of additional neural resources as shown by greater alpha and beta power reductions in older adults [26]. Despite similar behavior performance, normal aging was found to affect ERPs and oscillatory brain activity during an incidental speeded haptic symmetry detection priming task. However, the young adults showed more positive amplitude than the older adults in the alpha and beta bands from stimulus onset [27]. All these neural results suggest that the older brain adapts in order to maintain the same level of performance as the younger brain both in explicit and implicit memory tasks.

Neural plasticity exists at several levels of the neural substrate [28,10], although not to the same degree in older as in younger adults [15,29,30]. These findings suggest that the aging brain retains some neuroplasticity, which can be influenced by the individual's behavior. The prolonged mismatch between functional organismic supplies and environmental demands produces cognitive plasticity and underlines the capacity of the brain to implement behavioral flexibility [31]. Although there are personal factors, human behavior can change with appropriate training as the brain reorganizes in response to the environment [32]. Based on the idea of neuroplasticity, different types of interventions have been developed to ameliorate cognitive and functional declines by strengthening social networking using new information and communication technology (ICT) [33-35] and cognitive skills training [36,37] and promoting an active lifestyle [38,39] and physical activity training [40,41].

As people age, they experience declines in attentional control, mediated by the dorsolateral prefrontal cortex, and in long-term memory functions, mediated by the medial temporal lobe and the hippocampus. These areas suffer the highest degree of age-related atrophy [9]. Moreover, the prefrontal cortex facilitates the organization and contextualization of incoming information and interacts with the hippocampus during working memory implementation [42,43]. This relationship is strengthened with age [44]. These findings are especially relevant due to the existing links between these basic cognitive

abilities and everyday functioning. The malfunction of these basic abilities is a significant predictor of older adult difficulties with the instrumental activities of daily living, leading to loss of independence [45,46]. Therefore, it is of vital importance to pursue the question of whether cognitive decline can be reversed or delayed through cognitive training interventions [47].

Video games and other computerized programs are receiving increasing interest from cognitive and neuroscientists to investigate the possibility of transfer to untrained tasks [48-50]. Researchers are increasingly using new technology, including cognitive training platforms and video games, to investigate their impact on cognition [48-52]. Computer-based interventions have the advantage that they can be easily used by elderly people living either at home or in nursing homes and could be a good alternative to traditional training programs [53]. This RCT aims to assess the effectiveness of training older adults with digital nonaction video games.

Two challenges must be overcome in order to develop an effective cognitive aging intervention [54-55]: (1) transferring training gains to untrained tasks and (2) designing interventions that encourage compliance. Older adults prefer games that involve mental challenge [56-57], while studies with young adults have shown that fast-paced action games result in broader transfer effects. A “first-person shooter” video game is not an appropriate choice for older adults [58]. Nonaction video games have potential advantages as they are enjoyable, low-cost, and can be self-administered. Recent results from a systematic review [53] and meta-analyses [59-61] suggest that training elders with video games improves information processing, with unexpected larger effects in old-older adults than in young-older adults. Moreover, the results of a recent meta-analysis of action video game training showed that healthy adults benefit from training in overall and specific cognitive domains, but young adults benefit more than older adults [62]. These findings underscore the potential of video game training as an effective intervention tool for cognitive improvement. Results of studies on executive function and working memory are less consistent. It is possible that nonaction video games are not an effective means of improving or maintaining these functions in older adults. Games provide an enjoyable way of passing the time and of giving meaning to the day [56]. In short, video games can offer important benefits to older adults, bearing in mind that intervention compliance is a key factor in longitudinal training studies [54].

A previous RCT conducted in our laboratory investigated the effects of nonaction video game training on a series of cognitive functions that decline with age and subjective well-being. Two groups of older adults participated in the study: an experimental group that received the training and a noncontact control group. Groups were similar at baseline on demographics, vocabulary, global cognition, and depression status. The results showed improvements in the video game–trained group and no change in the passive control group in processing speed, attention, and immediate and delayed visual recognition memory and a trend to improve in 2 dimensions of the Well-being Scale (affection and assertivity) [63]. However, visuospatial working memory and executive control (shifting strategy) functions did not improve [49,64,65].

A recent longitudinal intervention study conducted to investigate the effects of video game training in healthy older adults showed that 15 1-hour training sessions with 6 nonaction video games produced significant improvements on 2 visuospatial working memory tasks and on episodic and short-term memory tasks. Some of these gains were maintained over a 3-month follow-up period [52]. In both previous studies, experimental groups were compared with passive control groups. To better attribute training-related improvement to the intervention and to avoid placebo effects [66], the current RCT compares performance on a series of attentional and visuospatial working memory tasks of an experimental group trained with selected nonaction video games from the commercial Lumosity computerized training program (www.lumosity.com) with that of an active control group carrying out the same number of training sessions with The Sims, a simulation strategy game in which the player takes control of the life of a character in everyday activities, and SimCity, a life simulation game in which the player is the mayor of a city that he or she must develop. Both groups used a mobile tablet device during the training sessions. These video games were chosen to train the active control group because this group should also play with engaging and challenging video games the same training hours, potentially equating the social contact experienced during training by experimental and active-control groups.

Training expectation is an important issue in cognitive training studies [51,67]. To address this issue, participants report their expectations (increase or decrease) regarding their task performance for any assessment task on a 5-point Likert-type scale. After training sessions 1, 8, and 16 (final), participants respond to training feedback questions about engagement and motivation for each training game. The objective was to find out whether both groups were similarly engaged and motivated during training.

In sum, the growth of ICT-based tools, along with their progressive implementation in all social groups, offers a great opportunity to develop low-cost preventive intervention programs able to reach the entire population. This can contribute to improving the quality of life of elderly people, with a substantial reduction in health care costs related to the loss of autonomy and independence in this population group [68]. In this RCT we investigate not only possible cognitive improvement in healthy older adults in selected cognitive domains that decline with aging but also possible neural changes of training using electrophysiological methods at pre- and posttraining and 6-month follow-up. The study also explores neuroinflammatory mechanisms underlying possible cognitive training-induced effects using noninvasive saliva-testing methods.

Objectives and Hypotheses

The study has 3 main complementary objectives:

1. To examine the behavioral and electrophysiological effects of training older adults with nonaction video games on a series of cognitive tasks designed to assess attentional functions (mainly response inhibition, distraction, and alertness) and to maintain and update verbal and visuospatial working memory.

We are also interested in investigating the sustainability of the transfer effects after a 6-month no-contact period.

2. To explore whether motivation, engagement, or expectations account for possible training-related improvements.

3. To examine whether inflammatory mechanisms assessed with noninvasive measurement of CRP in saliva impair cognitive training-induced effects. Inflammatory parameters in the participants obtained by noninvasive saliva-testing methods will be analyzed in biochemical assays to study their possible correlations with cognitive abilities.

We hypothesize that participants in the Lumosity group will improve selective attention assessed with oddball and Stroop tasks and working memory assessed with Corsi blocks and *n*-back tasks in comparison with participants in the active control group. From an electrophysiological perspective, we also hypothetize that in the oddball task the cognitive video game–trained group will improve both the ability to return attention to the relevant task after having been distracted by the novel stimulus (reorientation negativity [RON]) and the ability of the brain to pay attention to the novel stimulus (P300).

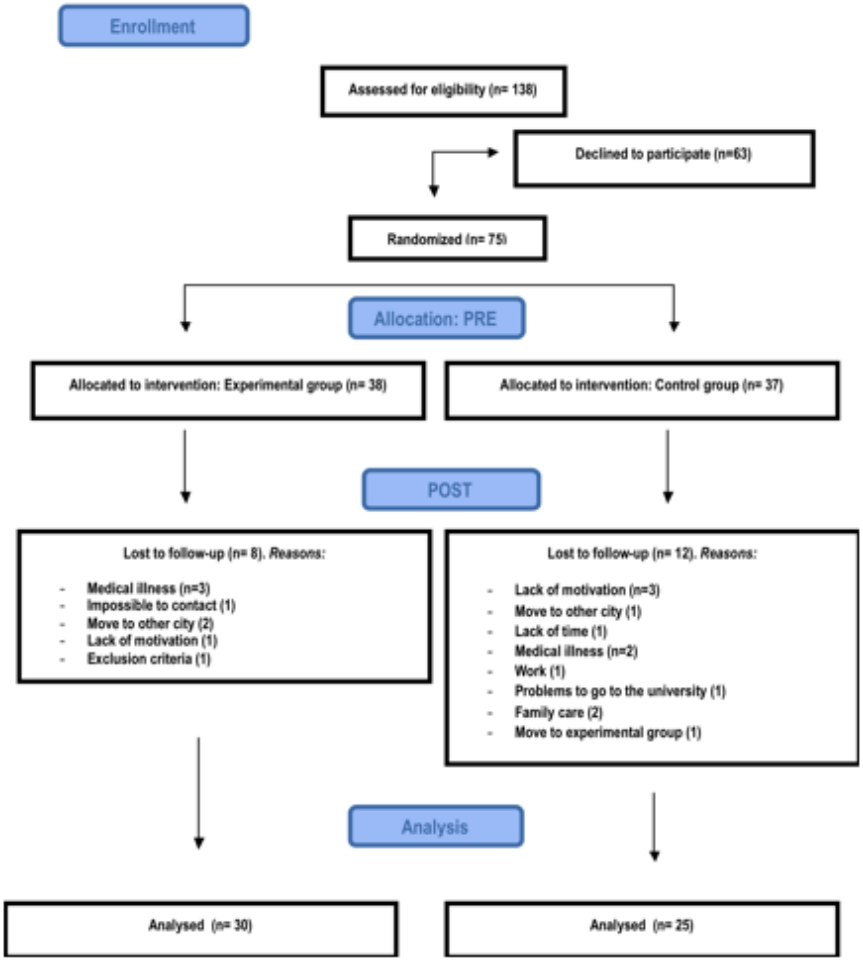
Intervention studies conducted with older adults have focused mostly on training a given cognitive function and then measuring the improvement in that function [69,29] and less often on possible changes in neural activity after training [70,71]. Based on the idea that the older human brain still has some plasticity (the ability to change in response to external stimulation), our main hypothesis is that training older adults with appropriate, adapted, and motivating nonaction video games will transfer to cognitive functions that decline with age, such as attention and working memory, by improving these pillars of cognition, which are crucial to maintaining independent living and cognitive health in old age.

Methods

Overview of the Study Design

A 2-arm, parallel-design RCT [72] was designed to evaluate the effectiveness of video game training to promote cognitive and brain health in older adults. Figure 1 shows the Consolidated Standards of Reporting Trials flow diagram of the study. This RCT is being conducted in Madrid, Spain, with an allocation ratio of 1:1 to evaluate the influence of training with nonaction video games on attention and memory functions. The design was a single-blind design. Eligible participants were randomized using a computer algorithm into intervention (cognitive nonaction video game training) or active control (life-simulation games) groups. Researchers were not blind to treatment allocation. The Universidad Nacional de Educación a Distancia (UNED) Institutional Review Board approved the study protocol. All participants provided written informed consent.

Figure 1. The Consolidated Standards of Reporting Trials flow diagram.



Eligibility and Exclusion Criteria

All participants live independently with normal or corrected-to-normal hearing and vision and are free of neurological or psychiatric disorders or traumatic brain injury. To determine their eligibility, each participant completed a screening battery consisting of the Mini-Mental State Examination (cut-off score 26) [73] to rule out possible cognitive impairment, the Yesavage Depression Scale (cut-off score less than 5) [74], and the Information subscale of the WAIS-III scale (normal score) [75]. Exclusion criteria were a diagnosis of dementia, cognitive impairment (score of <26 on the Mini-Mental State Examination), depression, less than 20/60 vision with or without correction, inability to complete the study activities, communication problems, or current plans to move to another city. All participants were healthy volunteers.

Sample Size

The sample size is based on the number of observations needed to compare the 2 groups of gamers, those trained with Lumosity and those trained with The Sims. As we do not have standard deviations of the scores in our main dependent variables, we used G*Power 3.1 (Department of Psychology) to compute the number of participants, using analysis of variance as a statistical test. For this, using a power of .80, effect size of 0.50, an alpha level of .05, and 2 groups within the *F* test family, we obtained a required total sample size of 57. With a dropout rate of 10%, a total of 63 participants would be required. Rounding up the numbers, we would need more than 64 participants (32×2). As the flow diagram shows, the final number of participants matches these a priori computations closely: 38 participants were assigned to the experimental group (8 lost at posttest) and 37 to the control group (12 lost at posttest).

Participants

Participants were randomly assigned to 1 of the 2 parallel groups, either the intervention video game training group or the active control group (see Figure 1). The pretest, posttest, and 6-month follow-up assessments are conducted at the UNED Department of Basic Psychology II by one of the authors with the assistence of other members of the group. The training sessions were carried out at the UNED Associate Center, Escuelas Pías, Madrid, and lasted 8 to 10 weeks. A total of 138 participants were recruited from flyers, advertisements, by word of mouth, and from UNED's special program for the elderly screened for eligibility. Finally, 75 older adults (age range 55 to 84 years) met the requirements for participation in the study and signed the consent form and were randomly assigned to the experimental or the active control groups before carrying out the laboratory tasks. The 2 groups do not differ significantly in age, years of education, global cognition, depression, memory, or verbal abilities.

Electroencephalograph Acquisition

While performing the experimental tasks, continuous electroencephalograph (EEG) activity is recorded using a NuAmps amplifier (Neuroscan Inc) located inside a soundproof, electrically shielded room. A 34-channel elasticized Quik-Cap with Ag/AgCl sintered electrodes (Neuroscan Inc) is used to record EEG data from scalp electrodes positioned according to the extended international 10-20 system (American Medical EEG Association, 1991). To control for the influence of ocular artifacts, vertical and horizontal electrooculograms are recorded in 2 bipolar channels. Eye blinks and vertical eye movements are monitored via electrodes located below and on the supraorbital ridge of the left eye. Horizontal artifacts are monitored via electrodes on the outer canthus of each eye. Linked mastoids (A1, A2) are used as reference, and participants are grounded to the AFz electrode. All data will be digitized using a NuAmps amplifier in continuous recording mode. Sampling rate will be 250 Hz, and all channels will be online band-pass filtered (0.1-70 Hz) and notch filtered (50 Hz) to eliminate power line artifacts. Analysis of the EEG recordings will be performed using the EEGLAB toolbox [76] and ERPLAB plugin for EEGLAB [77] both running under MATLAB environment (The MathWorks Inc). Continuous data will be filtered offline using a digital Butterworth filter (0.1-40 Hz; 12 dB per octave roll-off), an infinite impulse response filter that achieves a given filtering characteristic using less memory and fewer calculations than a similar finite impulse response filter. After filtering, data will be separated into baseline corrected and nonoverlapping epochs time-locked to the target onset (in both Stroop and oddball tasks) ranging from 200 ms before to 1000 ms after the onset of the target with the prestimulus interval (200 ms) as baseline period. Epochs containing high amplitude/frequency and muscle or other irregular artifacts will be removed by visual inspection. Only artifact-free epochs from correct trials will be selected for averaging. The existence of blinks and other ocular movements will not be a criterion for epoch rejection. This kind of artifact will be eliminated using Infomax Independent Component Analysis (ICA) decomposition [78-82]. We will use the default extended-mode *runica* training parameters [83], an extension of the original algorithm [78]. This extended mode allows a wider range of source signals (both super- and sub-Gaussian) while maintaining simplicity. Stopping weight change will be set to 1e–7. This rather conservative criterion for stopping learning lengthens ICA training, enabling cleaner and more reliable decompositions, particularly with more than 33 channels and limited number of epochs. After submitting epochs to ICA decomposition, artifactual components will be removed by inspection of their scalp topography and spectral power [84,27].

General Procedure

Participants in the study were randomly assigned to the cognitive nonaction video game training group or the noncognitive game training active control group. The introduction of an active control group is necessary to avoid placebo effects [54]. Based on the results of our meta-analytic study [61], we use training regimes that are not too long to avoid loss of motivation, and simple, nonaction games that appeal more to elders. According to the temporal discount hypothesis [85], future rewards are less valuable than inmediate rewards. In each session, the trainees play 10 nonaction video games from Lumosity, described below.

The main question examined in our study is whether group (experimental group, active control group) interacts with testing session (pretest, posttest, and follow-up) with regard to performance on a series of cognitive tasks. At least 2 measures

for each cognitive domain are acquired to examine transfer of training to untrained tasks demanding attention and working memory. We selected these cognitive domains because these functions deteriorate with aging and tax functions that are critical for independent living. To explore the underlying neural mechanisms of successful transfer of training gains to attentional mechanisms (alert, distraction, and inhibitory effects) and executive control (spatial working memory), electrophysiological data (ERPs) are recorded at pretraining (T1), posttraining (T2), and 6-month follow-up (T3).

All the methodological designs of the primary outcome measures have been constructed using the rules of counterbalancing and stimulus rotation. Response keys are counterbalanced across conditions. The computerized tasks have been programmed using E-Prime 2.0 (Psychology Software Tools Inc). All the statistical analyses of the behavioral results will be performed using SPSS (IBM Corp) and results will be considered significant at $P<.05$, with Bonferroni-corrected post hoc tests performed as appropriate. Continuous EEG activity are recorded in our laboratory with thin electrodes from 34 scalp sites using a NuAmps amplifier as mentioned before.

After randomization and initial assessment (baseline), participants were invited to attend the University Center of Escuelas Pias in Madrid to perform the training sessions in small groups. Trained and active control groups followed 16 training sessions carried out on different hours and days that lasted approximately 10 to 12 weeks.

Table 1 presents a short summary of the video games played by the experimental (trained) group. During the training sessions, participants in the experimental group play 10 nonaction video games selected from Lumosity.

The active control group carried out 16 training sessions with The Sims and SimCity BuildIt. Table 2 presents a short summary of these video games.

Table 1. Short description of the 10 video games played by the experimental group.

Game name	Trained function	Description
Tidal Treasures	Working memory	Player chooses objects and memorizes their choice.
Pinball Recall	Working memory	Player predicts a ball's path.
Playing Koi	Divided attention	Player feeds fish and remembers which have already been fed.
Star Search	Selective attention	Player chooses the odd one out in a group of objects.
Lost in Migration	Selective attention	Player swipes in the direction the middle bird is facing in a flock of birds that appears on the screen.
Color Match	Response inhibition	Player compares one word's meaning to another word's color.
Disillusion	Task switching	Player matches tiles with different shapes, colors, or symbols.
Ebb and Flow	Task switching	Player swipes in the direction leaves are moving or pointing.
Highway Hazards	Information processing	Player races a car across the desert avoiding colliding with obstacles.
Speed Match	Information processing	Player determines whether a card appearing on the screen is the same as or different than the previous one.

Table 2. Life simulation games from Electronic Arts Inc played by the active control group.

Game name	Trained function	Description
SimCity BuildIt	None	Life simulation game in which the player is the mayor of a city that he or she must expand.
The Sims	None	Life simulation game in which the player creates characters (The Sims) that live in a virtual world that is similar to the real one. The Sims work, build their own homes, develop relationships, etc.

Ethical Issues

This clinical trial is registered on the ClinicalTrials.gov database [NCT02796508] [72]. The UNED Ethical Review Board approved the trial. All the participants gave their written informed consent before the study started and were informed of their right to terminate participation at any time. The work described has not been published previously.

Measurement of C-Reactive Protein in Saliva by Enzyme-Linked Immunosorbent Assay

Several parameters influencing inflammation (eg, infections, diabetes) are obtained from the participants: height and weight are recorded to obtain the body mass index (gross obesity could increase inflammation), drugs ingested (anti-inflammatories, antibiotics, antioxidants), possible infections and when they happened (last month, last week, or today), smoking habit (which may increase CRP levels in saliva), and defective oral health (eg, bleeding gums). Participants are asked not to eat or smoke at least 30 minutes before saliva collection. Following a mouth rinse with water, 1 mL of saliva is collected with a

straw into a tube containing 2% ethylenediaminetetraacetic acid as preservative. Samples are stored at −80ºC until assayed. Assessment of CRP levels is performed with an enzyme-linked immunosorbent assay (ELISA) obtained from Salimetrics according to the manufacturer instructions. A saliva sample collected from participants at pretest, posttest, and follow-up assessments will be analyzed with ELISA in order to correlate the quantity of CRP with task performance.

Primary Outcomes

Effects of Video Game Training on Attentional Networks: Behavioral and Electrophysiological Results

Oddball Task

The capacity to suppress irrelevant information and to concentrate on the relevant task [86] is negatively affected by aging. The question is whether the effects of training with cognitive video games are transferable to untrained tasks (transfer effect). Despite the great appeal of video games as a way to improve perceptual and cognitive abilities, evidence of their efficacy is mixed [49,50,52,64,87-88]. However, the results of several recent meta-analytic studies [59-62] suggest that video game training can be moderately effective in healthy older adults but that its positive effects are moderated by several variables including the complexity of the games, the age of the participants, the duration of the training program, and the cognitive processes assessed.

Previous studies indicate that deviance distraction occurs because deviant sounds violate the cognitive system's expectations [89]. Attention capture has been studied from an electrophysiological perspective; the distractor is characterized by a pattern of 3 brain responses [90,91]: (1) mismatch negativity (MMN) and enhanced N1 when the distractor deviates considerably from the repetitive background, (2) P3a (novelty P3), and (3) RON. The MMN response reflects the preattentive detection of an unexpected change in the auditory context and results from the comparison between a memory trace for past acoustic stimuli and the current auditory signal [92]. The P3a response represents the involuntary orientation of attention toward the novel sound [93] and results from an attentional interruption involving frontal areas [94]. RON is also observed when participants are performing a primary task and must redirect their attention toward that task [95]. In this RCT, we undertake electrophysiological recordings to explore the underlying neural mechanisms of successful transfer of training to attentional performance in the oddball task. We expect that the cognitive video game–trained group will improve both the ability to return attention to the relevant task after having been distracted by the novel stimulus (RON) and the ability of the brain to pay attention to the novel stimulus (P300). In our lab, we previously investigated the effect of novelty in young adults using a haptic oddball paradigm consisting of processing textured surfaces [96]. We do not expect this pattern of results in the active control group and thus predict a group × session interaction.

Stroop and Negative Priming Task

Cognitive processes that involve top-down control mechanisms decline with aging but more automatic processes do not [20,22]. The Stroop interference effect reflects the extra time needed to resolve the conflict generated by the irrelevant word meaning in the incongruent condition. One view is that suppression processes relying on executive control are engaged in preventing the irrelevant dimension from taking control of the response [97]. In this study, we investigate the effect of training older adults with nonaction video games on inhibition processing using both behavioral and electrophysiological responses. The task has been designed to assess training-related behavioral and neural changes in Stroop interference and in negative priming (NP). NP (a measure of distractor inhibition) and the standard Stroop effect are assessed in the same task. In the standard NP procedure, participants are presented with pairs of prime and probe displays containing 2 stimuli, the to-be-responded target and the to-be-ignored distractor. In the critical trials, participants must respond to a target that served as a distractor in the previous prime display (the ignored repetition condition). The common finding is that reaction times to targets in the ignored repetition condition are slower than in the control condition, in which the distractor in the prime display is not repeated as the target in the probe display [98-101]. The aim is to investigate whether training older adults improves control, effortful inhibition (Stoop interference), to a greater extent than automatic passive inhibition (NP). The experimental task uses ERPs in combination with the Stroop and NP before and after training to examine the neural correlates of inhibition [102]. Responses for the Stroop analysis will be coded as a function of the congruency between the color and the meaning of the stimulus. Congruent trials are those in which the color of the word coincides with the color in which it is presented. Incongruent trials are those in which the color word does not coincide with the color in which it is displayed. We will also code trials according to the congruency of the previous trial (N−1) in order to compute the NP effect for each trial. The design for the NP effect consists of Group (younger, older adults), Session (pretraining, posttraining, follow-up), and Type of intervention (experimental, active control) as between-participants factors and Repetition (ignored repetition and control) as within-participants factors. Responses for NP analyses will be coded as a function of the relationship between the color of the current target word and the color denoted by the word in the previous trial (distractor). Thus, the ignored repetition trials are those in which the word in the preceding trial denoted the color of the word of the current stimulus. Control trials are those in which both the target (color) and the distractor (word) in the current trial are different from the target and distractor in the previous trial. The ignored repetition condition is always an incongruent trial preceded by an incongruent trial. The aim is to investigate whether the Stroop interference effect in older adults decreases after training while NP does not change. An important addition to the behavioral measures will be the ERP recording while performing the task before and after training to investigate brain activity changes after training.

Effects of Training on Spatial Working Memory

Overview

To investigate whether training transfers to improvements in spatial working memory, the participants perform a computerized Corsi blocks task. Recent meta-analytic studies

conducted with trainees from childhood to older adults [60] and with older adults [61] found negligible effects of video game training on executive functions. The absence of improvement after training may depend on the specific kind of video games used. Studies that used first-person shooter action games reported benefits after training [103,104]. This type of game requires great perceptual abilities, preparedness for unpredictability, and strong emphasis on peripheral visual processing [105]. However, older adults do not like this type of game [55]. Previous findings from our lab yielded mixed results. One study [49] showed no transfer to working memory tasks, while a second study [52] showed that the trainees' performance improved significantly after training in 2 visuospatial working memory tasks, the Corsi blocks and the jigsaw puzzle. Our results contrast with those of Nouchi et al [88] who found improvements in executive functions after training for 5 weeks. The ineffectiveness of training in spite of the fact that several of the nonaction video games mimic working memory tasks is in line with the findings of Boot and colleagues [54]. Due to these mixed results, the aim of this RCT is to find out whether training effects transfer to the spatial working memory of older adults.

Corsi Blocks

The original task [106] consists of a set of 9 identical blocks (3 x 3 x 3 cm) irregularly positioned on a wooden board (23 x 28 cm). The participant is required to point to the blocks in their presentation order. The length of the block sequences increases until recall is no longer correct. Numerous variations have been employed. Here, we use a computerized version with 4 difficulty levels (2, 3, 4, and 5 cubes) with 10 trials per level. The task consists of reproducing the pattern of cubes just presented on the computer screen by writing down the order in which the cubes appeared on a response sheet. The score is derived from the number of sequences reproduced correctly divided by the total number of sequences in the corresponding level (correct/total sequences).

Assessing Working Memory Updating

Transfer to working memory after training is assessed with the *n*-back task [107]. We use a computerized version of the task to assess memory updating. In this task, participants indicate whether each visual stimulus in a list matches a stimulus that occurred 1, 2, or 3 stimuli back by pressing a response key with their right hand (counterbalancing index and middle fingers to respond "yes" and "no").

In sum, the primary outcome measures of this RCT are better performance at posttest than at pretest on a series of tasks: (1) Stroop-negative priming task, (b) oddball task, (3) *n*-back task, and (4) Corsi blocks.

Secondary Outcomes

Improved game performance by the experimental group and the active control group between training session number 1 and 16 (final) is a secondary outcome measure. Efficacy of training will be shown by better performance in the trained video games across the training sessions. Another secondary outcome measure, maintained level of motivation and engagement, will be assessed with a questionnaire administered at training sessions 1, 8, and 16.

Results

All analyses will be performed with the SPSS (IBM Corp) program. Statistical significance is considered as a P value of <.05. Analyses of variance will be conducted with 2 groups (experimental and active control) at 3 time points (pretest [baseline], posttest [postintervention], and follow-up [after 6 months without contact]). Electrophysiological data will be analyzed using EEGLAB/ERPLAB.

The preparatory phase for using the games has been completed. License to use the games has been granted by Lumosity. Participants have been recruited, pretested, and trained. The final results from this RCT are expected by the end of 2017.

Discussion

The benefits of this RCT will be at several levels including in-depth knowledge derived from a series of carefully planned behavioral and brain imaging studies conducted to test a series of hypotheses on cognitive and brain aging. This cognitive and brain intervention study conducted in an increasingly active area of research could lead to exciting prospects in the medium and long term by exploring ways to keep older adults (mind and brain) healthy and active longer.

The findings could help prevent the negative impact of mild cognitive impairment and could have an important impact on society due to the increasing number of older adults and the associated number of neurodegenerative diseases. Cognitive decline reduces the capacity to live an independent life with associated personal, family, and social costs. Preventing the negative impact of cognitive decline could have an important effect on limited social and health care resources.

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Authors' Contributions

SB is the principal investigator and conceptualized the design of the proposal (with some help from JM) and wrote the article. SB and JM prepared the protocol registration of the clinical trial. ER enrolled the participants, conducted the training sessions, and collected the data with some help from AP, PT, and JM. AP and JM prepared the experimental tasks. JMR provided statistical support and contributed to sample size calculation. MC will analyze the saliva samples for CRP assessment. All authors reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CRP: C-reactive protein
EEG: electroencephalograph
ELISA: enzyme-linked immunosorbent assay
ERP: event-related potential
ERSP: event-related spectral perturbation
ICA: Independent Component Analysis
ICT: information and communication technology
MMN: mismatch negativity
NP: negative priming
RCT: randomized controlled trial
RON: reorientation negativity
UNED: Universidad Nacional de Educacion a Distancia

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Protocol

A Medical Student–Delivered Smoking Prevention Program, Education Against Tobacco, for Secondary Schools in Brazil: Study Protocol for a Randomized Trial

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Abstract

Background: Smoking is the largest preventable cause of morbidity and mortality in Brazil. Education Against Tobacco (EAT) is a large network of medical students in 13 countries who volunteer for school-based prevention in the classroom setting. A recent quasi-experimental EAT study conducted in Germany showed significant short-term smoking cessation effects on 11- to 15-year-old adolescents.

Objective: The aim of this study is both to describe and to provide the first randomized long-term evaluation of the EAT intervention involving a photoaging app for its effectiveness to reduce the smoking prevalence among 12- to 17-year-old pupils in Brazilian public schools.

Methods: A randomized controlled trial will be conducted among approximately 1500 adolescents aged 12 to 17 years in grades 7-11 of public secondary schools in Brazil. The prospective experimental study design includes measurements at baseline and at 6 and 12 months postintervention. The study groups will consist of randomized classes receiving the standardized EAT intervention (90 minutes of mentoring in a classroom setting) and control classes within the same schools (no intervention). The questionnaire measures smoking status, gender, social, and cultural aspects as well as predictors of smoking. Biochemical validation of smoking status is conducted via random carbon monoxide measurements. The primary end point is the difference of the change in smoking prevalence in the intervention group versus the difference in the control group at 12 months of follow-up. The differences in smoking behavior (smoking onset, quitting) between the 2 groups as well as effects on the different genders will be studied as secondary outcomes.

Results: The recruitment of schools, participating adolescents, and medical students was conducted from August 2016 until January 2017. The planned period of data collection is February 2017 until June 2018. Data analysis will follow in July 2018 and data presentation/publication will follow shortly thereafter.

Conclusions: This is the first evaluative study of a medical student–delivered tobacco prevention program in Brazil and the first randomized trial on the long-term effectiveness of a school-based medical student–delivered tobacco prevention program in general.

ClinicalTrial: ClinicalTrials.gov NCT02725021; https://clinicaltrials.gov/ct2/show/NCT02725021 (archived by WebCite at http://www.webcitation.org/6njy3nNml)

International Registered Report Identifier (IRRID): DERR1-10.2196/resprot.7134

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KEYWORDS

photoaging; schools; tobacco prevention; adolescents; medical students

Introduction

Smoking is one of the main risk factors both for mortality and disability-adjusted life years (DALYs) for noncommunicable chronic diseases in Brazil and globally [1-3]. A study published in 2011 estimated the tobacco-related burden in Brazil and found that smoking was accountable in that year for 147,072 deaths and 2.69 million DALYs, representing a direct cost for the health system of $23.37 billion Brazilian real (US $7.37 billion) [4].

According to a large national study that was conducted in 2012 with 61,037 9th graders in Brazil, over 30.0% of 13- to 15-year-olds try smoking before the age of 12 (National School Health Survey—PeNSE) [5]. The newest data from the 2016 ERICA study with 74,589 Brazilian 12- to 17-year-old participants revealed a current smoking prevalence of 5.7% in this young age group with more smokers in public than in private schools (5.9% vs 4.4%) [6]. Although smoking rates among adolescents and emerging adults have substantially declined since the early 2000s, prevalence is still high and strong socioeconomic and educational inequalities in smoking exist in Brazil [6].

Founded in 2012 in Germany, Education Against Tobacco (EAT) has now enrolled participants in over 80 medical schools in 13 countries worldwide. The network has its roots in the school-based interventions delivered by medical students that cost about US $20 per participating class and reach up to 40,000 students per year worldwide. However, the network is also involved in medical education research on smoking cessation counseling, science-based multilanguage apps, and public awareness and advocacy for tobacco control [7-9].

The school-based intervention has only been evaluated for short-term effects with a quasi-experimental design with multiple potential sources of bias [10,11]. However, its preliminary evaluation involving 1474 students showed a significant reduction in the smoking prevalence of secondary school students in Germany at 6 months of follow-up after interventions motivating them to quit [10,11]. After this first evaluation, the curriculum was optimized for students with a lower educational level because the intervention was less effective in this subgroup [11]. This was done by making the program more interactive and by developing and involving a photoaging app (Smokerface) into our classroom intervention because published research suggests that there is effectiveness of photoaging strategies for our age group [7].

The European Smoking Prevention Framework Approach (ESFA) program developed and tested a smoking prevention program for adolescents aged between 12 and 15 years (students enrolled in the 7th-9th school grades) in 6 European countries [12]. Studies on the ESFA project have shown mixed outcomes: only Portugal, Spain, and Finland achieved positive results [13]. We suspect there will be differences between the outcomes in Brazil and the ones we found in Germany.

Smoking is largely conceptualized to medical students as an adult health problem, although most long-term smokers started as adolescents. Recent studies indicate that tobacco addiction is substantially undertreated by physicians in comparison with other chronic conditions such as diabetes or hypertension [14-16]. The authors conclude that this is mainly due to lack of motivation, skills, and knowledge from the medical community [14-16]. There is evidence that medical student training addressing adolescent health promotion to prevent smoking can increase the frequency of obtaining smoking status of and providing advice to patients [17]. The importance of primary and secondary prevention of smoking uptake has led to calls for a greater engagement and training of future physicians in tobacco control [14]. In this context, the EAT network not only provides school-based prevention but also sensitizes future physicians to the importance of tobacco prevention and cessation [10,11,18].

The aim of this publication is both to describe the optimized EAT intervention and to present the study protocol of a trial designed to determine the long-term effectiveness of the school-based EAT intervention in reducing the smoking prevalence among secondary school students in Brazil.

Methods

Ethics Approval and Consent to Participate

In accordance with Good Epidemiologic Practice guidelines [19], the study protocol was submitted for approval by the responsible ethics committee (Federal University of Ouro Preto, Brazil), and consent was obtained. All legal and data protection issues were discussed with the responsible authorities, and all participants are required to provide active informed consent.

The Education Against Tobacco Intervention

Overview

The school-based intervention under evaluation consists of a 90-minute module in the classroom setting. It is presented by

2 medical students per classroom to about 25 pupils at a time discussing features of smoking that students can relate to in their everyday life in a gain-framed and interactive manner. The goal is to initiate and guide the student evaluation process of smoking with age-appropriate information that helps them to reframe a positive nonsmoking image by asking for their opinions and views in small group settings. The students form 4 groups (mostly with their friends) and rotate to 4 different stations in the classroom.

Station 1

This station, built up near a window or outside, discusses different tobacco products and extraction of substances of tobacco smoke. In the first part, different products (including e-cigarettes, a water pipe, and cigarettes) are displayed and their functionality and harmfulness are discussed in a gain-framed manner.

Second, the students are instructed to conduct an experiment using a hand-vacuumizer, a napkin, a plastic bottle and a cigarette. The napkin is put between cigarette and bottle and burned down to demonstrate the ingredients of the smoke by the discoloration of the napkin. The process is repeated with e-cigarettes that show little discoloration and are regarded as less harmful but still contain cancerogenic substances [20].

Station 2

The attractiveness and photoaging consequences of nonsmoking and mechanisms related to the face are discussed. In the first part, pictures of monozygotic non-/smoking twins are displayed that were extracted from the publication of Okada et al [21]. The students are asked which twin is the smoker and what differences they note.

In the second part, Galaxy Tab E tablets (Samsung Electronics Inc, Seoul, Korea) are used to show each student the effects of non-/smoking on their own faces by the help of the photoaging app Smokerface that we described and piloted in great detail elsewhere [7,9]. By this means, the students' faces are captured via a selfie and photoaged into 1- and 15-years-older versions of themselves (normal aging vs normal aging plus smoking) (Figures 1 and 2 and Multimedia Appendix 1 demonstrate the effects of the app). The app's underlying aging algorithms are based on publications showing an increased risk for acne, pale skin, wrinkles, and other capillary and connective tissue changes in smokers. The use of the app influences numerous predictors of smoking in students of this age group in accordance with the theory of planned behavior and as demonstrated in our recent paper [9].

Figure 1. Photoaged image of a 17-year-old woman showing the consequences of smoking 1 pack a day for 1 year (vs nonsmoking).

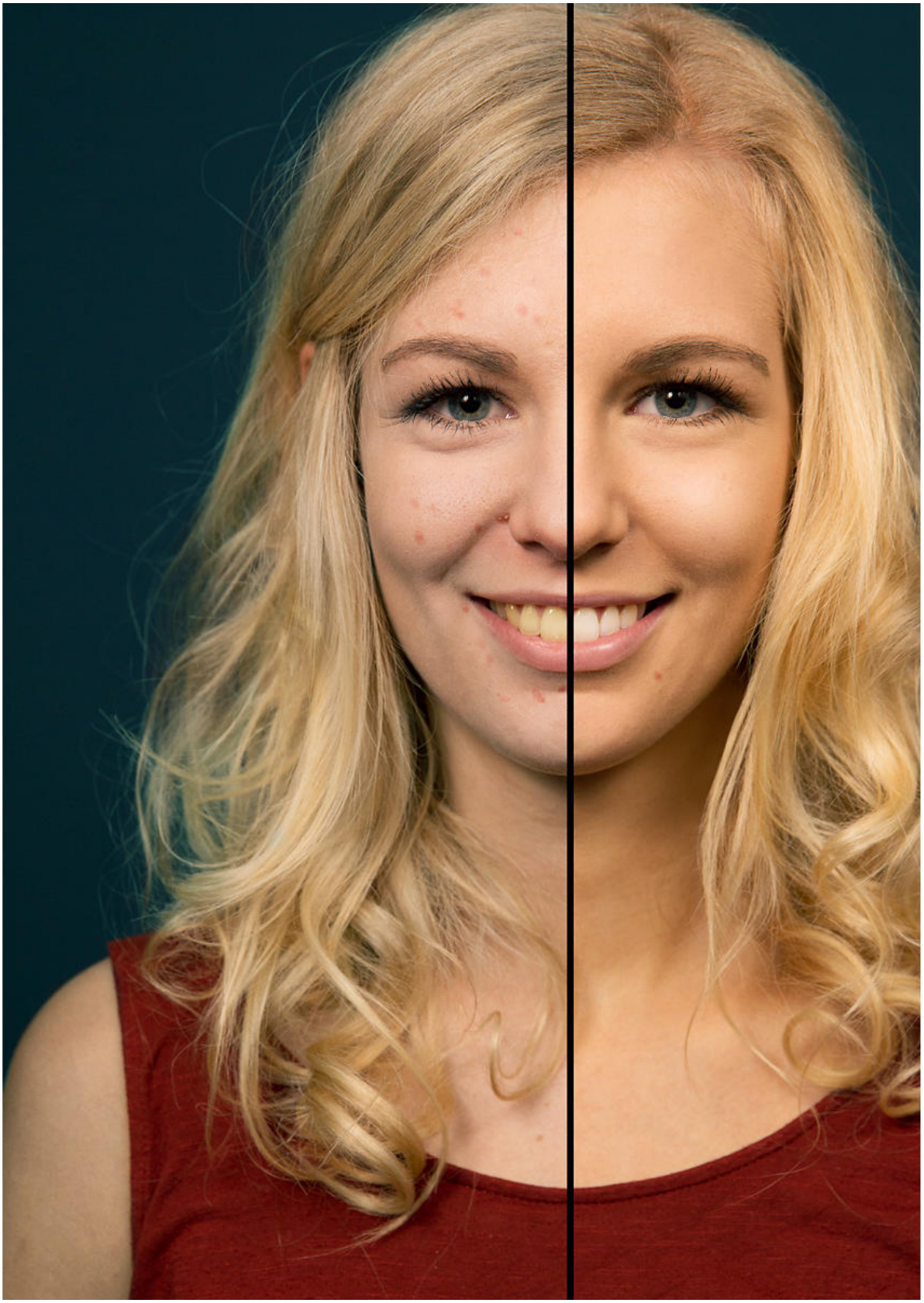
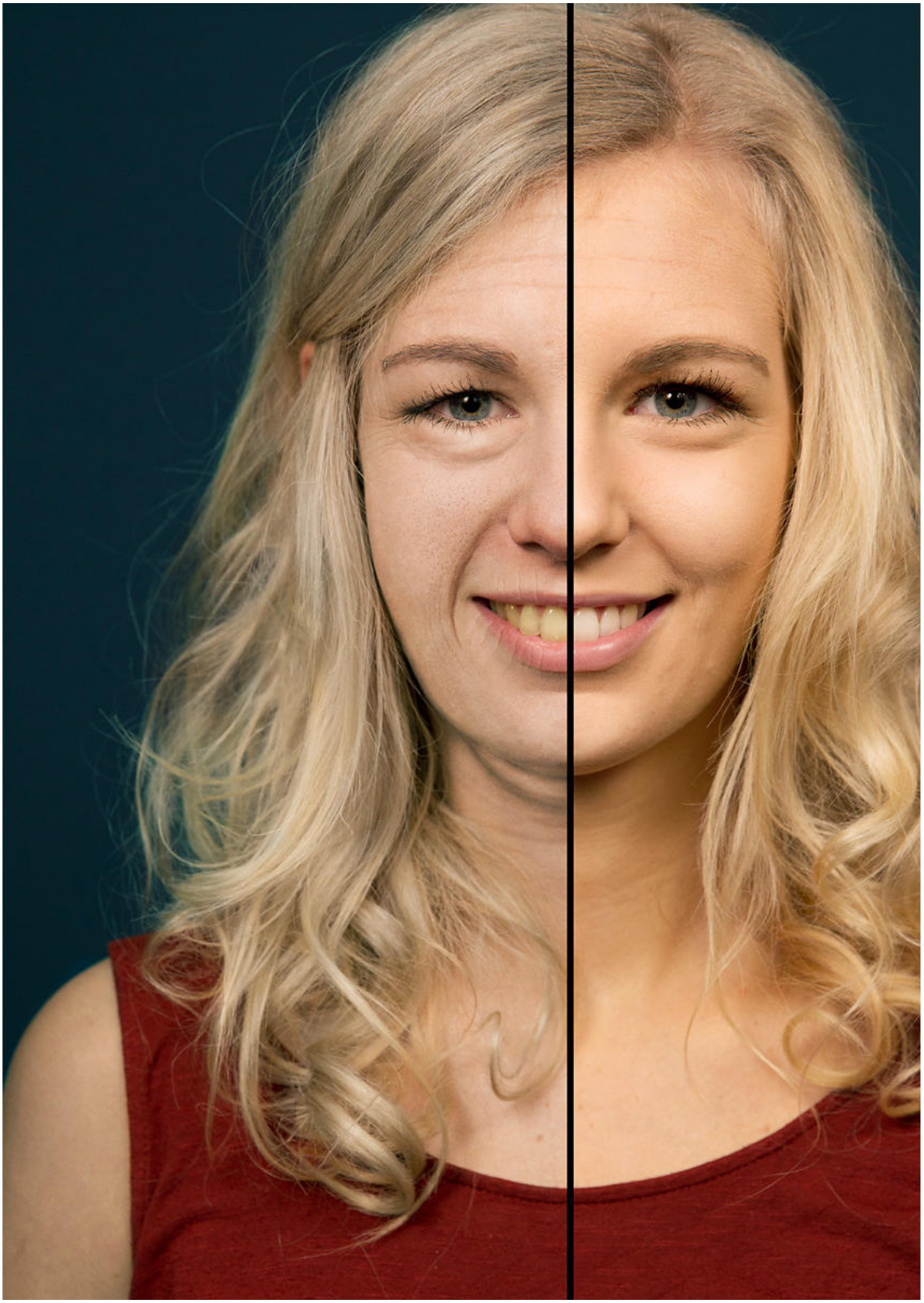


Figure 2. Photoaged image of a 17-year-old woman showing the consequences of smoking 1 pack a day for 15 years (vs nonsmoking).



Station 3

Performance benefits of nonsmoking (physical performance, stress, common colds) and understanding the mechanisms of how tobacco smoking affects the body with age-appropriate examples (eg, occluded vessels lead to loss of connective tissue in women's breasts which equals less volume and tightness and impotence in both men and women [22], pale skin, mechanisms of acne); this is explained via pencil-and-paper drafts and interactive questions. In addition, obesity [23,24], lung growth

[25], and body growth impairment in adolescent smokers are discussed on a body model with pencil-and-paper sketches and by the use of growth curves [24].

Station 4

The aim of this station is to discuss the student's own experiences with tobacco and how they reacted in the past to peer pressure and to the strategies of the tobacco industry to influence their decision. The groups' knowledge and experience is shared and discussed in a team setting where the medical students take the role of older friends by complementing the students' experiences with their own experiences to increase the perceived self-efficacy of the students, which is the most important predictor of future smoking in accordance to the theory of planned behavior [26]. It has been shown to predict both the intention to smoke and actual smoking behavior in a meta-analysis [27].

At the end of the classroom seminar we ask for the students' final judgments on smoking to create positive peer pressure and influence the students' subjective norm in accordance with the theory of planned behavior [26]. As a final exercise, all students breathe through a straw after having physically exercised in the classroom together to learn how lung impairment due to smoking feels with exercising.

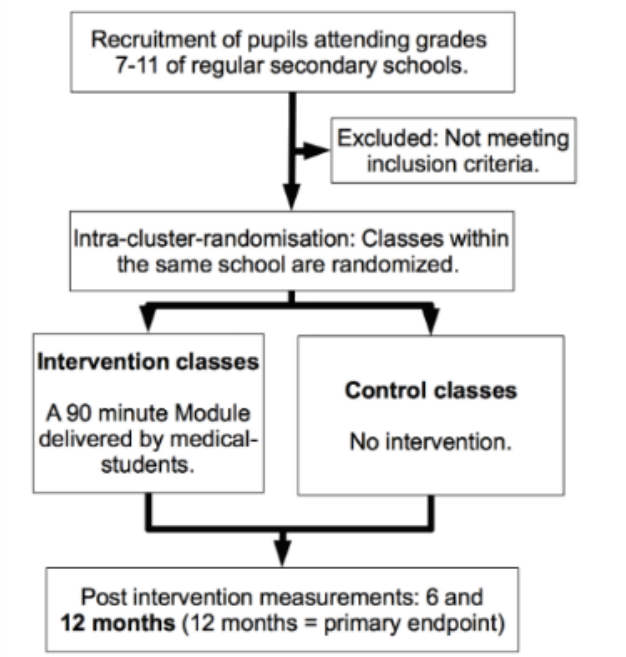
Overall, long-term health consequences are not discussed in great detail as fear approaches were proven to be ineffective and information on the diseases can be found on every cigarette pack [28]; besides that, these long-term harms (such as lung cancer, vascular disease, and chronic pulmonary disease) are too far in the future to fathom. Instead, the program focuses on information relevant for teenagers, particularly related to attractiveness and physical performance, as both of these aspects have been shown in several publications to strongly influence the behavior, self-confidence, and quality of life of adolescents [29-31].

Design

A randomized controlled trial will be conducted among approximately 1500 adolescents in grades 7-11 of secondary schools in Brazil (Figure 3). The planned study period is February 2017 until June 2018. The prospective experimental study design includes measurements at baseline (t1) and 6 months (t2) and 12 months (t3) postintervention. The study groups will consist of randomized classes receiving the standardized EAT intervention (90 minutes of mentoring in a classroom setting) and control classes within the same schools (no intervention). The study questionnaire that measures smoking status and gender, social, and cultural aspects uses items from previously tested and published questionnaires. By the use of the conceptual method for translation described by the World Health Organization/United Nations Economic and Social Commission for Asia and the Pacific Project on Health and Disability Statistics, the items were translated to Portuguese [32] and afterwards pretested with students from Brazil [32]. Smoking status is validated by a random carbon monoxide (CO) breathing test at baseline and endline.

Baseline collection will be completed by mid-February 2017. The intervention will be conducted from end of February 2017 until May 2017. The first follow-up survey will be 6 months thereafter. At 1-year follow-up (May/June 2018), the data collection is complete.

Figure 3. Study design.



Randomization

In accordance with the guidelines of Good Epidemiologic Practice, randomization is externally and centrally performed via computer by a statistician from the University of Gießen, Germany, on the class level within each school (group allocation is 1:1), which is the strongest method according to the recent Cochrane Analysis [19,33]. Different educational levels within 1 school grade are used for stratification.

Participants and Sample Size

In accordance with the first evaluation of our program in Germany, a total of 1500 eligible secondary school students will be recruited [7]. Inclusion criteria are the attendance of grades 7-11 at public secondary schools in Brazil with age ranging from 12 to 17 years. Exclusion criteria are defined as inability to fulfill the inclusion criteria (ie, private schools, different grades). The age range for inclusion in the study is higher than in our German study [10] as the median age of smoking onset is higher in Brazil than in Germany [6,11]. As we expect the same loss-to-follow-up effect as in our quasi-experimental trial in Germany (18.6%), a test power of 70% and a 2-sided alpha of .05 are considered appropriate for our primary end point.

Data Collection

A pencil-and-paper questionnaire is used for the collection of the data and the smoking status is biochemically validated by randomized CO measurements in the exhaled air of the students. In addition to sociodemographic data (age, gender, and school type), the questionnaire will capture the smoking status of the school students concerning cigarettes and multiple other tobacco products (such as e-cigarettes and water pipes). These items are based on 3 established studies [34-36] and were either used in the original form or adapted to the specific circumstances of this study.

The class teachers supervise their classes during the completion of the questionnaire and seal them right after completion for confidentiality reasons. The envelopes are then shipped to the Federal University of Ouro Preto in Brazil where they are opened and the data entry is performed.

Biochemical Validation

Using a portable CO analyzer (Smokerlyzer piCO+, Bedfont Scientific Ltd), CO testing will be randomly performed at baseline and endline in at least 10% of students [37]. CO measurements will be supervised by medical students with recordings made in the afternoon. The cutoff point is defined as 6 parts per million or less for nonsmoking and more than 6 parts per million for smoking [38-40].

Outcomes

The primary end point is the difference of the change in smoking prevalence in the intervention group versus the difference in the control group at 12 months of follow-up. The same longitudinal prevalence effects are studied on our females exclusively as a secondary outcome because our photoaging intervention is suspected to be more successful in females [41]. As our sample size is quite small, the secondary outcome criteria is met if 20% fewer females start smoking in the intervention group during the study period of 1 year. The differences in smoking behavior (smoking onset, quitting) between the 2 groups will be studied as additional secondary outcomes with a positive 20% difference in change of behavior set as met outcome criteria. A smoker is defined as a pupil who claims to smoke at least once in the past 30 days within the survey.

Data Entry

The data entry is performed manually at the Federal University of Ouro Preto in Brazil by the help of the newest version of Excel (Microsoft Corp) spreadsheet.

Analysis

To examine baseline differences we will use chi-square tests (categorical variables) and *t* tests (continuous variables). The effects of predictors (gender, culture, and social characteristics) on smoking behavior after 12 months (t3) will be calculated by robust panel logistic regression analysis. The significance level is 5% for *t* tests (double-sided) and 95% for confidence intervals (double-sided). Statistical analysis (intention-to-treat) will be performed using SPSS Statistics version 23 (IBM Corp) and STATA 14 (StataCorp LLC). In our sample, the group allocation is not on the individual level but on the class level. In order to take into account this clustering statistically we will use robust panel logistic regression (xtlogit procedure with vce [cluster] option). This procedure is also used to calculate the difference from t1 to t3 of the smoking prevalence in the control group versus the difference from t1 to t3 in the intervention group (our primary end point) by the help of STATA 14.

Results

TJB raised a grant from the German Heart Foundation that provided funding for the Smokerface App and a grant from the German Center for Lung Research that funded the CO measurement device and the Samsung tablets. The Federal University of Ouro Preto will contribute to the project providing logistic support and copies of the questionnaire to be distributed to every participating student.

The recruitment of schools, participating adolescents, and medical students began in August 2016 and was ongoing until the end of January 2017. The planned period of data collection is February 2017 until June 2018. Data analysis will follow in July 2018 and data presentation/publication will follow shortly thereafter.

Discussion

Summary

Tobacco prevention programs for secondary schools conducted by physicians have shown short-term and long-term effectiveness [42-44]. EAT is a novel, fast-growing network of volunteering medical students supported and implemented by medical schools worldwide which has never been evaluated for long-term effects in form of a randomized trial. At the same time, it is valuable to sensitize future physicians while they are still in medical school to tobacco control and to develop their skills, highlighting the associated responsibilities within communities, as they are not only in charge of educating and assisting their future patients effectively about cessation measures but also to develop advocacy skills [45,46]. For instance, at 9 medical schools in Germany, novel smoking cessation counseling teaching courses for medical students have been established by medical students involved in the EAT network. However, the school-based aspect of this network

appears to be the most attractive one for medical students not sensitized for the topic as a whole yet.

An important gap in the literature that is addressed by EAT is the fact that there are no guidelines regarding what school-based tobacco prevention programs must specifically cover [47]. The field of school-based tobacco prevention awaits age-appropriate and culturally innovative interventions that can be deemed as effective and then serve as a model to be reproduced. Our study has the potential to directly contribute to tobacco control programs worldwide as our detailed intervention and specific mentoring and training on how to do so are made freely available through the EAT network. The key point in the novelty of the EAT intervention is the use of communication and strategies that are interactive and in line with information relevant for adolescents, especially the smoking-related effects on appearance and physical performance.

Limitations

Limitations and advantages of the CO testing in exhaled air have been described in great detail elsewhere [37]. Conclusively, our method used for biochemical validation is a widely accepted cost-effective procedure even if it does not have the sensitivity of cotinine saliva testing, which is far more costly [33].

As our research is not conducted multinationally, we can not generalize its results to all cultural backgrounds. However, our intervention involves a photoaging intervention and outward appearance has been described to be the most relevant component of the self-concept in adolescents from multiple cultural backgrounds [48], which increases the international validity of our research.

Conclusions

This is the first evaluative study of a medical student–delivered tobacco prevention program in Brazil and the first randomized trial on the effectiveness of school-based medical student–delivered tobacco prevention in general. Our research has the potential to foster the way for EAT in Brazil by measuring its effects on different gender, social, and cultural backgrounds. Health systems worldwide could benefit from the development of such novel and low-cost school-based tobacco prevention programs.

Acknowledgments

The authors would like to thank all participating medical students, schools, and pupils in Brazil. A special thanks goes out to medical student Marco Haertlé, an EAT group leader from Hannover, Germany, who introduced the investigators to one another.

Authors' Contributions

TJB invented, designed, and organized the intervention, provided the original classroom materials translated in Portuguese, wrote the manuscript, provided all figures, concepted the study design, provided the questionnaire, raised the grants for the study and supports the conduction of the study, data entry, and the statistical analysis. DAG and WS contributed to the design of the study and proofread the manuscript. PCRPC contributed to the design of the study, assisted with the translation of classroom materials, wrote parts of the manuscript, and reviewed the final version of the manuscript. LEFX, BBS, and OCL conduct data entry and coordinate/conduct the intervention in Brazil, supported the translation of the classroom materials, and proofread the manuscript. FNF and TT contributed to the study design and the development of the new EAT curriculum and proofread the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

3-Dimensional animation of a selfie via the Smokerface app illustrating one of the touch effects (cough) the students can trigger on their own selfies.

[MP4 File (MP4 Video), 556KB - resprot_v6i1e16_app1.mp4]

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Abbreviations

CO: carbon monoxide
DALY: disability-adjusted life year
EAT: Education Against Tobacco
ESFA: European Smoking Prevention Framework

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Protocol

Neurofeedback as a Treatment for Impulsivity in a Forensic Psychiatric Population With Substance Use Disorder: Study Protocol of a Randomized Controlled Trial Combined With an N-of-1 Clinical Trial

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Abstract

Background: Impulsivity and substance use disorder (SUD) are strongly interconnected, with persons scoring high on impulsivity being more vulnerable to develop substance abuse, facing more challenges for successful treatment, and being more prone to engage in criminal behavior. Studies have shown that impulsivity and craving for substances are strongly correlated. Neurofeedback is an effective treatment to reduce impulsive behavior. This study intends to determine to what extent a neurofeedback-intervention that is aimed at reducing impulsivity can also reduce levels of craving in forensic patients with SUD and comorbid Axis I and/or II diagnoses.

Objective: The main objective of this study is to investigate to what extent a reduction in impulsivity by a sensorimotor rhythm (SMR)-neurofeedback intervention will lead to a reduction in craving in a population of forensic psychiatric patients with a diagnosis of SUD.

Methods: Participants will be male SUD patients with various comorbidities residing in an inpatient forensic treatment facility approached through treatment supervisors for participation. Participants have tested positive for drug use in the past 24 months. The study consists of 2 parts: a randomized controlled trial (RCT) and a n-of-1 clinical series. In the RCT, 50 patients will be randomly assigned to an intervention (n=25) or a control (n=25) condition. Patients in the intervention group will receive 20 SMR neurofeedback sessions aimed at reducing impulsivity; participants in the control group receive treatment-as-usual (TAU). Additionally, 4 in depth n-of-1 clinical trials will be conducted where effects of an SMR neurofeedback intervention will be compared to effects of sham neurofeedback.

Results: Results of this study are expected by the end of 2017.

Conclusions: This protocol describes the design of a study testing the effects of an impulsivity-based neurofeedback protocol among forensic patients with SUD and various comorbidities. We expect a significant reduction in impulsive behavior, level of craving, and actual drug-use for participants receiving the SMR neurofeedback protocol. The n-of-1 approach might help to explain effects possibly found in the RCT study since it allows for a more direct focus on treatment effects by following participants more closely and thereby being able to directly attribute behavioral and neurophysiological change to the SMR neurofeedback protocol employed.

ClinicalTrial: Dutch National Trial Register NTR5386; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5386 (Archived by WebCite at http://www.webcitation.org/6nXLQuoLl)

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KEYWORDS

impulsive behavior; substance use disorders; neurofeedback; craving; offenders

Introduction

Background

Impulsivity has been defined as a dysfunctional trait, leading to a tendency for an individual to display behavior that is performed with little or inadequate forethought [1] and might be criminal and possibly harmful to oneself or to others [2]. Impulsivity has been operationalized in different ways with inadequate behavioral inhibition being conceived as one of the key factors [3]. Impulsive behavior is hypothesized to involve a disinhibition of cognitive control that occurs without conscious deliberation [4].

Several studies have demonstrated that substance use disorder (SUD) is strongly associated with elevated impulsivity scores on various measures [3]. In SUD, the use of a substance is continued even though a person is aware of the negative consequences of prolonged drug use. This can be explained by deficient inhibitory control over drug-taking which provides immediate (positive) reinforcement [2]. Higher levels of impulsivity were found in individuals scoring high on alcohol, stimulant, and opiate use [3] as measured by self-report instruments, such as the Barratt Impulsivity Scale (BIS-11) [4]. Individuals with combined cocaine and alcohol abuse show impaired response inhibition as compared to controls on continuous performance tasks measuring impulse control such as the cued go/no-go task [5]. Furthermore, a strong relation between elevated impulsivity scores during childhood/early adulthood and substance abuse problems later in life has been observed, indicating that heightened levels of impulsivity might precede the development of substance abuse problems (in Hawkins et al [6], for example). In alcoholism, for example, behavioral disinhibition as assessed with a novelty-seeking scale has been shown to predict early onset alcoholism [7]. Individuals scoring high on impulsivity are therefore more prone to develop SUD than healthy controls and more often exhibit antisocial behavior [7].

The concept of impulsivity has been of particular interest in studies involving criminal offenders, as these individuals often suffer from major mental disorders and are therefore more likely to be involved in criminal acts than persons without major mental disorders [8]. In criminal offenders, cluster B personality disorders and schizophrenia are frequently diagnosed [9]. Comorbidity rates between these disorders and SUD are as high as 70% [9]. Generally, treatment of SUD has proven to be difficult, with relapse rates as high as 60% after treatment in opiate abusers [10]. For patients with a criminal history and a combination of SUD and comorbid disorders characterized by high levels of impulsivity, long-term treatment outcomes are worse [9]. High impulsivity levels both predict early relapse and increase chances of premature termination of treatment [11]. This, in turn, increases the risk of recidivism in criminal behavior [12]. Adequate treatment for this vulnerable patient population is therefore extremely important, as impulsivity can be understood as an important risk factor in both the onset of SUD as well as post-treatment relapse [13].

Neurofeedback Treatment for Impulsivity and Substance Use Disorder

Electroencephalographic (EEG) spectral analysis is a frequently used method to compare healthy controls with prolonged drug users by focusing on differences in the (relative) strength of naturally occurring rhythms in the EEG (in Alper et al [14], for example). EEG alterations most commonly found in individuals with SUD are characterized mainly by alterations in the strength of theta (4-8 Hz), alpha (8-12 Hz), and beta (12-20 Hz) frequency bands [15] and are hypothesized to be related to symptoms of drug use disorder, such as over attention to drug cues, feelings of restlessness, and loss of impulse control. Although alterations in several EEG spectral measures have been observed that vary by type of addiction, they persist even after drug abuse is in remission [14].

Neurofeedback is an intervention that uses real-time EEG measurements and displays information about these EEG measurements back to the participant, allowing them to not only see but also change their brain electrical activity over time [16]. By principles of operant conditioning, participants learn to reinforce or inhibit specific frequencies of the EEG activity [17] and thereby normalize abnormal EEG states, which in turn aims at changing abnormal psychological states [18]. Sensors are placed on the scalp and moment-to-moment information about brain activity is fed back to the participant [19].

Several studies have shown neurofeedback to be a promising intervention for various disorders, ranging from SUD to attention deficit hyperactivity disorder (ADHD) [16]. In SUD, a widely used neurofeedback protocol is the Scott-Kaiser modification of the Peniston Protocol, consisting of a combination of sensorimotor rhythm feedback (SMR, 12-15 Hz) followed by alpha-theta based feedback [17]. With this type of protocol, patients first receive neurofeedback that focuses on reinforcing SMR (12-15 Hz) while inhibiting slower frequencies such as delta (2-5 Hz) and theta (5-8 Hz) and also inhibiting high beta (ranging from 18-30 Hz) [15,17]. This type of feedback is first employed for 10 to 20 sessions before the neurofeedback protocol is switched to an alpha-theta based protocol, where alpha (ranging from 8-12 Hz) is decreased while theta (5-8 Hz) is augmented until the amplitude of alpha drops below the level of theta [15,17]. The Scott-Kaiser modification of the Peniston Protocol has shown to be effective in opiate-dependent patients as well as in patients with a mixed substance dependency, as it led to the reduction of feelings of craving [15], a powerful predictor of relapse in drug-taking [20-21] and therefore promoted treatment attendance and abstinence rates of participants [17]. As most criminal offenders with SUD also suffer from comorbid psychiatric conditions however, treatment with neurofeedback may become more complicated [16]. For patients having a combination of impulsivity issues due to

comorbidity with other psychiatric disorders, as well as substance abuse problems, it is suggested that an SMR-enhancing neurofeedback protocol should be applied to address the issue of impulsivity first [22]. Studies performing a neurofeedback protocol consisting of suppressing slow waves such as theta (4-7 Hz) and enhancing faster waves such as SMR (12-15 Hz) have demonstrated an improvement of impulse control in a population of students (in Egner and Gruzelier [23], for example) and have shown to positively affect motor control and cortical inhibitory function (in Sokhadze et al [16], for example). This type of neurofeedback protocol is also commonly applied with patients suffering from the hyperactive-impulsive ADHD subtype, and there are many studies reporting reduction in impulsivity after treatment (in Fuchs et al [24], for example). Several studies have shown that impulsivity and craving for substances are strongly correlated no matter the administered drug of choice. For example, in a study by Tziortzis et al [25] with methamphetamine users, individuals with higher levels of impulsivity reported significantly more craving than individuals scoring lower on impulsivity. In alcohol-dependent patients, higher scores of craving were correlated with higher self-reported impulsivity on the BIS-11 [26]. Moeller et al [27] found a significant correlation between the motor impulsivity subscale of the BIS-11 and craving in a population of cocaine-dependent subjects. Also for cocaine-dependent patients, higher impulsivity was associated with greater severity of addiction symptoms such as craving [28,29]. Also, contemporary neuropsychological models stress impulsivity and SUD to be the result of the same imbalance between bottom-up and top-down neural systems [30,31]. Bottom-up systems concern subcortical brain circuitry promoting impulsive reward behavior (regardless of long-term outcomes), whereas top-down processes concern reflective and self-control functions driven by prefrontal brain circuitry [32]. Within SUD, chronic substance abuse may produce neural changes leading to a structural state of disinhibition and impulsivity [33,34], causing immediate reaction to substance-related cues that elicit craving [35]. Not only acute but also prolonged effects of substance abuse have proven to be of great influence in disrupting these neuropsychological mechanisms, therefore maintaining problems with inhibitory control even after drug use is terminated [36]. Although impulsivity and craving are both independently identified as key elements in SUD, to date, there has been no study investigating whether a reduction in one will also lead to a reduction of the other.

This Study

Although the relationship between impulsivity and symptoms of SUD such as craving and actual drug use has been established, to date there is no evidence about the effects of an impulsivity-based neurofeedback protocol and its effectiveness on impulsivity and on symptoms of SUD. This study aims to examine the treatability of impulsivity with an SMR-neurofeedback intervention in a population of forensic psychiatric patients with SUD and comorbid Axis I and/or II disorders. It also aims to investigate whether a reduction of impulsivity through an SMR-based neurofeedback protocol will also result in a reduction of SUD symptoms such as craving and actual drug use.

The study will combine a randomized controlled trial (RCT) design with an n-of-1 clinical trial. The RCT allows for investigating to what extent an SMR-neurofeedback protocol can reduce craving and actual drug use by augmenting levels of impulsivity for forensic psychiatric patients at a group level. However, RCTs have several disadvantages. First, they focus on between-group differences, making it difficult to determine the exact working mechanisms of neurofeedback at the single patient level. Despite the fact that the number of studies employing neurofeedback has increased over the past 2 decades, to date the underlying working mechanisms of neurofeedback remain unclear. Success of treatment is usually determined by a reduction in subjective complaints or based on other behavioral measures, independent of patients' responses to neurofeedback on a neurophysiological level (eg, change in mean amplitude of brain frequencies). Second, most RCTs focus on participants with single, well-defined disorders or diagnoses, making it difficult to apply previous findings to patients who have a more complex psychopathology as is usually the case in forensic patients. Third, finding a reduction in subjective complaints could partially be explained by the interaction with the person giving the treatment, as this occurs with almost all frequently given types of therapy in the psychological field [37]. To rule this out, large RCTs with a treatment and a sham arm are necessary. Unfortunately, these studies are very difficult to conduct in a forensic psychiatric setting due to the fact that forensic patients generally have low levels of treatment compliance [38]. As the current study concerns a single-site study with only a limited number of patients who fit the inclusion criteria to begin with (but on forehand sufficient according to power analysis), adding a sham arm to the RCT would most likely further reduce the motivation of patients to participate and hence increase nonresponse. However, insight into possible sham effects is needed to differentiate between specific and nonspecific treatment effects which are independent of the neurofeedback trainer. Finally, RCT studies showing treatment effects of neurofeedback often vary in the applied protocols, number of sessions, and treatment intensity. To date, there have been no guidelines developed that specify these neurofeedback parameters. Especially for forensic patients, developing a treatment that is well applicable and helps to reduce symptoms of SUD is of great importance, as forensic treatment is aimed at protecting society and reducing the risk of reoffending. By adding several n-of-1 clinical trials we attempt to cope with these disadvantages. A well-conducted n-of-1 trial allows testing of the specific working mechanisms of neurofeedback in a single patient and is therefore able to detect detailed behavioral and neurophysiological changes that can then be attributed more definitely to neurofeedback treatment.

Objectives

Primary outcome variables are the degree of impulsivity as measured with the Dutch version of the BIS-11 [39]; inhibitory control as measured with a cued go/no-go reaction time task [40]; degree of drug craving as measured with an altered version of the Desire for Alcohol Questionnaire (DAQ) [41]; actual drug use as measured with urine, saliva, or breathalyzer analysis; and changes in resting state EEG pattern.

Primary objective: To what extent does a reduction in impulsivity by using SMR-neurofeedback result in a reduction of core symptoms of SUD such as craving and actual drug use in a population of forensic psychiatric patients with a diagnosis of SUD?

Secondary objectives:

1. To what extent can an SMR-based neurofeedback intervention reduce levels of impulsivity as measured by BIS-11 and a cued go/no-go task in a population of forensic psychiatric patients with a diagnosis of SUD?

2. To what extent can an SMR-based neurofeedback intervention reduce levels of craving as measured by self-report questionnaire DAQ-SF (short form) in a population of forensic psychiatric patients with a diagnosis of SUD?

3. To what extent can an SMR-based neurofeedback intervention reduce actual drug use as measured with urine, saliva, or breathalyzer analysis in a population of forensic psychiatric patients diagnosed with SUD?

Methods

Overview

This study will be conducted according to the principles of the Declaration of Helsinki (version 59, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act. It has been approved by the medical ethical council of Brabant, the Netherlands (study number NL46390.008.13).

This study takes place in Forensic Psychiatric Centre (FPC) Dr S van Mesdag, a maximum security inpatient forensic treatment facility in Groningen, the Netherlands. Patients in this treatment facility are male criminal offenders with at least one Axis I or II diagnosis and considered to be at risk for criminal recidivism if not treated properly. About 70% of all patients treated in this facility have a comorbid diagnosis of SUD [9].

Randomized Controlled Trial

A randomized controlled trial with N=50, where 25 participants are randomly assigned to treatment as usual (TAU) combined with 20 SMR-based neurofeedback sessions and 25 participants are randomly assigned to TAU only, without neurofeedback intervention. The 2 groups are compared pretreatment (T0) and posttreatment (T1) on variables linked to the research questions. Both groups will receive pre- and posttreatment measurements with an interval between T0 and T1 of approximately 10 weeks in which participants in the intervention group will receive 20 neurofeedback treatment sessions and participants in the control condition will follow TAU.

The design of this part of the study is a 2×2 design with the condition (neurofeedback vs TAU) as a between-subjects factor and time as a within-subjects factor (pre- and postintervention).

N-of-1 Clinical Trial

To zoom in on specific treatment effects, 4 single case studies with an $A^1B^1A^2B^2$design (single time series) will be conducted, of which 2 single case studies will apply an actual SMR-neurofeedback protocol and 2 single case studies will apply a sham neurofeedback training. The clinical trial will be single-blinded, indicating that participants do not know which part of the training they will receive. Participants are selected from the control group of the previously described RCT protocol who have already completed pre- (T0) and posttreatment (T1) measurements. Inclusion in the n-of-1 trial will be selective: participants with the highest scores on outcome measures on T1 of the RCT will be approached first as it is believed that these patients have the highest need for treatment. However, allocation to treatment (sham or real) will be random.

For a detailed description of this design of n-of-1 studies, see Rizvi and Nock [42]. Basically, in this design, a baseline period (A^1: no treatment, lasting 3 weeks) is followed by a treatment period (B^1: neurofeedback, sham or real, lasting 4 weeks and resulting in 8 neurofeedback sessions), which is followed by a period where treatment is withdrawn (A^2: lasting 3 weeks). During all periods, outcome measures DAQ-SF and BIS-11 will be assessed 2 times per week. At the end of the A^2period, statistical analyses are applied to test for significant improvements in study end points. In cases of significant improvement during treatment, a second period of neurofeedback, B^2(sham or real), will be applied. This way, if neurofeedback does not prove to be effective within B^1, participants will not be burdened with the requirement of completing more sessions. It is expected that patients who have not shown any significant improvement during neurofeedback sessions in B^1will not show any further improvements when undergoing more sessions. After completion of the study, patients and treatment supervisors will be debriefed about whether the neurofeedback intervention was real or sham.

To test for transient effects of the neurofeedback intervention, a follow-up measurement of resting state EEG, BIS-11, DAQ-SF, and cued go/no-go task will be performed 12 months after completing the posttreatment measures for both participants in the intervention group of the RCT and for participants in the n-of-1 clinical trial.

Participants

A power analysis calculation for the RCT using G*Power 3 (Department of Psychology) based on a 1-tailed alpha value of .05, a power value of 0.80, and an effect size (*f*) of 0.80 yielded a recommended sample size of 21 participants each in the control and intervention conditions. Given the special research population we aim to select 25 participants for each condition.

Participants are male patients diagnosed with SUD (substance dependency or substance abuse) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Review (DSM-IV-TR [43]) and currently staying at the treatment facility. Participants have tested positive for drug use in the past 24 months at time of inclusion. Drug use is operationalized as urine, saliva, or breathalyzer analysis testing positive for either marijuana and/or psychostimulant/opioid drugs and/or alcohol. Corresponding with treatment facility policy, nonprescribed medication that is used for recreational drug consumption such as inhaled methylphenidate will also

be scored as positive drug testing, as will refusal to undergo drug testing.

Participants are allowed to continue using prescription medication (as prescribed by a psychiatrist or general physician of the treatment facility) but are required to inform researchers of any medication they are currently using or any change in medication during treatment with neurofeedback.

Recruitment

Recruitment will start with the selection of patients for the RCT part of the study. Participants are approached through treatment supervisors for participation. Treatment supervisors are informed about the general inclusion criteria for this study. Out of all participants that meet the requirements, a random sample of 50 will be drawn and randomly assigned to 1 of the 2 conditions (intervention and control). Prior to participation in the trial all participants are asked to provide written consent. If at this point a participant chooses not to participate in the trial, this will be coded as a nonresponse. Missing numbers of participants will be complemented by randomized allocation of other suitable participants who are willing to participate in order to guarantee the sample size. Once all patients for the RCT have been recruited, recruitment for the n-of-1 clinical trial will begin. All participants will receive a financial reward after completing pre- and posttreatment measurements.

Measures

Electroencephalography

Participants will undergo a 21-channel EEG measurement with Nexus-32 hardware and Biotrace+ software (Mind Media BV). The EEG will be collected from 19 standard 10/20 positions [44] and the right and left mastoid with a sampling rate of 512 samples per second. The left mastoid will serve as the online reference. Flat type electrodes will be placed above and below the left eye and at the outer canthi of each eye to correct for vertical and horizontal eye movements. Participants will be seated comfortably while 5 minutes of eyes closed resting state EEG data is collected. EEG measures will be conducted at T0 and T1 as well as at 12 months follow-up for participants in the intervention group (T2).

For participants in the neurofeedback group, a 1-minute baseline recording over 3 conditions will be conducted before start of the first neurofeedback session and after the last session. EEG signal will be recorded from electrode position Cz against a right ear mastoid reference across the conditions (1) eyes open, (2) eyes closed, and (3) cognitive task (where participants are instructed to solve simple mathematical calculations). These measurements will be used to determine neurofeedback threshold values and to assess change in mean magnitude of frequency bands before and after neurofeedback training.

Barratt Impulsivity Scale–11

The Dutch version of the BIS-11 (eleventh edition) [45] is a self-report questionnaire designed to measure the behavioral and personality construct of impulsivity across 3 second-order factors: attentional, motor, and nonplanning. It consists of 30 items scored on a 4-point scale ranging from rarely/never to almost always/always. The BIS-11 has been proven to be an internally consistent measure of impulsivity among inmate populations [45].

Cued Go/No-Go Task

The cued go/no-go task is a continuous performance test measuring impulse control by the ability to inhibit prepotent responses [40]. Participants are instructed to respond to a green square by pressing a button as quickly as possible while not responding to a blue square. A go or no-go cue is given before the actual target appears, providing information about the likelihood of an actual go or no-go target [40]. The likelihood of a correct target after a cue is manipulated with a 80/20 ratio, with 80% being a correct cue and 20% being an incorrect cue. Cues are presented with 4 fixed stimulus onset asynchronies (100, 200, 300, and 400 ms), giving participants time to prepare for responding. The cued go/no-go task has been proven to be a useful measurement of impulse control in substance abusing populations [40]. It consists of 250 trials spread over 5 rounds with a 30-second break between each round, taking approximately 20 minutes to complete. Outcome measurements are omission (the participant does not respond when he should respond) and commission errors (the participant responds when he should not respond) and reaction time.

Modified Desire for Alcohol Questionnaire

The DAQ-SF [46] is a self-report questionnaire assessing the desire to use drugs at the moment of assessment. It is derived from the original desire for alcohol questionnaire (DAQ) with 36 items. The short-form version of the DAQ consists of 14 item that can be scored on a scale from 1 to 7 ranging from strongly disagree to strongly agree. It consists of 3 factors: (1) strong desires/intention to drink, (2) negative reinforcement, and (3) ability to control drinking. The abbreviated version has been shown to be reliable in measuring alcohol craving [46].

All questions of the original questionnaire are designed to measure craving purely for alcohol; however, within the treatment facility alcohol use is less common than other drug use (such as marijuana and/or cocaine). Therefore, questions from the questionnaire have been altered so they can fit any type of drug dependency. An example of this is “My desire to drink seems overpowering” which has been altered to “My desire to use drugs seems overpowering.”

Instrument for Forensic Treatment Evaluation

The Instrument for Forensic Treatment Evaluation (IFTE) is an observational treatment evaluation instrument consisting of 22 items measuring 3 factors: Problematic behavior, protective behavior, and resocialization skills. It is scored on a 17-point Likert scale with 5 anchor points: none, rarely, sometimes, often, and always [47]. The IFTE assesses forensic risk behaviors such as impulsivity, hostility, and violating treatment conditions. These risk behaviors might be manifestations of impulsive behavior and could help assess engagement in impulsive behavior that is not assessed by the BIS-11 and the cued go/no-go task. Furthermore, the IFTE also assesses cooperation with treatment, which measures the amount of effort a patient puts in to make progress in his treatment, giving an indication of the degree of commitment (and thereby, motivation) of a patient to forensic treatment. The IFTE is scored twice a year

by clinicians involved in patients' treatment as part of routine outcome measurement within the treatment facility. Patients also score the IFTE on a self-report version of the original IFTE (IFTE-SR), where they can give an indication of treatment progress during the past 6 months. Scores of the IFTE and IFTE-SR are assessed from the moment a patient arrives at the treatment facility up until release. Therefore, scores on the IFTE are available throughout the research. Relevant scores included in this study will be assessments 6 months prior to inclusion up until 12 months after the last measurement.

Actual Drug Use

Drug testing is performed on a regular basis, usually once every 2 weeks. Whenever staff suspects illegal use of substances within 2 moments of drug testing, spontaneous and unexpected drug testing can be performed. Number of drug tests will be counted, as will be positive (meaning drug use in the period of time since last drug test) and negative (meaning no drug use since last testing) outcome scores. Drug testing is done in the form of urine, saliva, or breathalyzer (for alcohol use only) analysis.

Covariates

Covariates are sociodemographic characteristics; specific psychopathology; duration of forensic treatment; actual drug use during the past 24 months (or as long as patients reside in the treatment facility); medication use; clinical risk assessment score (Historical/Clinical/Future-Revised, HKT-R) [48]; actual drug use; and mean score of delta, theta, alpha, beta, and gamma resting state EEG frequency band power. Covariates will be collected through case file information. Medication and medication change will be categorized according to class of medication (eg, benzodiazepines, antipsychotic medication).

Intervention

All participants already receive TAU at the moment of inclusion. They will continue to do so during the course of this trial. Type of TAU is dependent on disorder and behavior but can range from cognitive behavioral therapy, psychotherapy, and psychomotor therapy to relapse prevention treatment and can be either individual treatment or in-group treatment. Treatment can also be supplemented by medication for psychotic symptoms or depressive symptoms, for example. In some rare cases, aversion or craving reducing medication is prescribed.

Participants in the intervention condition of the RCT will receive 20 neurofeedback sessions, each lasting approximately 40 minutes. EEG magnitude is measured across delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12 Hz), beta (12-20 Hz), SMR (12-15 Hz), high beta (20-32 Hz), and gamma (32-49 Hz) frequency bands. To reduce inattention and impulsivity, a conventional neurofeedback protocol will be used that consists of suppressing theta magnitude and enhancing SMR magnitude [49,50]. The aims of the neurofeedback sessions are therefore to reduce slow waves (specifically theta, 3.5-7.5 Hz, and if necessary delta, 0.5-3.5 Hz) and increase faster waves (SMR, 12-15 Hz). A maximum of 3 different frequency bands will be trained during each session. Neurofeedback training will be performed on the EEG signal recorded from electrode position Cz against a right ear mastoid reference.

For the n-of-1 design of the trial, 2 participants will receive the SMR-neurofeedback intervention and 2 participants will receive sham neurofeedback.

Real and sham neurofeedback procedures will be similar (eg, electrode position, preparation, instructions given to participants) except that for the sham neurofeedback training group, participants are instructed to enhance an irrelevant frequency band that is randomly chosen from higher beta bands (20-23 Hz, 23-26 Hz, 26-29 Hz, and 29-32 Hz). Therefore, no specific frequency band is systematically modulated and thus should not result in desired treatment outcomes. Participants will still be given positive feedback and be able to influence the video games in order to minimize possible irritation of participants.

Neurofeedback will be applied as implemented within the BrainMarker software engine (BrainMarker Device, Brainmarker BV Gulpen).

Participants will be shown simple video games implemented in the software that will provide feedback about their brain activity. During the video games, they are instructed to be attentive to the feedback (no movement/movement of objects) in the video game and to find the most successful strategy to reach the goal of the game. Example of such video games are a car moving on a road, where participants are instructed to keep the car in the right lane of the road, or a basketball court where participants are instructed to try to throw the ball in the basket. The video game–based neurofeedback rounds will last 1 minute at a time, with a short break between rounds. Also, movie-based neurofeedback will be applied. During movie-based neurofeedback participants will watch a digital video disk of their own choice and be instructed to keep the monitor as free as possible from black curtains appearing on both sides of the monitor and keep the volume of the movie at an audible level. Movie-based training will last 90 seconds at a time with a short break when necessary. Participants will receive both game- and movie-based neurofeedback in each session.

Thresholds will be set manually in a way that if a participant maintains the reinforced frequency band above a threshold for 80% of time, positive feedback will be received. To determine threshold values, mean magnitude of the baseline measurement across the 3 conditions described above will be used to roughly assess threshold values for the neurofeedback training. For each training session, mean magnitude values will be calculated for all frequencies.

Statistical Analysis

All statistical analysis will be conducted using SPSS version 19 (IBM Corp). Summarizing descriptive statistics and frequency tables will be provided.

Randomized Controlled Trial

Resting state EEG data will be analyzed using custom-made Matlab R2012b scripts [51]. A repeated measures multivariate analysis of variance with factors condition (neurofeedback vs control) and frequency band (delta, theta, alpha, beta, or gamma) will be conducted. If main or interaction effects are observed, post hoc tests will be used to determine which levels of the factors are explaining the observed effects.

Repeated measurement with time (pre- [T0] and postintervention [T1]) as the within-subject factor and group (control vs intervention) as the between-subject factor will be conducted for the DAQ-SF, BIS-11, IFTE, and IFTE-SR. If main or interaction effects are observed, post hoc test will be used to determine which levels of the factors are explaining the observed effects. A repeated measures analysis of covariance will be conducted to examine differences in actual drug use as dependent variables to test for a moderating effect of impulsivity on craving and actual drug use.

N-of-1 Trial

First, a time-plot will be inspected using the autocorrelation coefficient (ie, correlogram) [52]. After inspection, time-series analysis will be applied to test for significant slope and level changes as well as a trend analysis. Analysis techniques will be based on the study by Solanas et al [53].

Results

Results of all measurements will be expected by the end of 2017 and will be published in corresponding articles.

Discussion

This study aims to evaluate the efficacy of an SMR-based neurofeedback treatment on reducing impulsivity in a population of inpatient forensic patients. Possible effects of a reduction in impulsivity on substance abuse will be assessed as well. We expect a significant reduction in impulsive behavior, level of craving, and actual drug use for participants receiving the SMR-neurofeedback protocol. The n-of-1 approach might help to explain effects possibly found in the RCT study since it allows for a more direct focus on treatment effects by following participants closely and thereby being able to directly attribute behavioral and neurophysiological change to the SMR-neurofeedback protocol employed. The study aims to extend previous findings on the efficacy of neurofeedback treatment in reducing impulsivity, not only by linking possible findings regarding a reduction of impulsivity to substance abuse symptoms but also by examining effects in a forensic psychiatric population with various comorbid disorders.

Studies about the efficacy of neurofeedback in a psychiatric forensic setting, in which the population is characterized by various comorbidities and various kinds of medication, are lacking. In our study, exclusion criteria are kept to a minimum to include as many participants with SUD as possible and to be able to generalize effects of an SMR-neurofeedback treatment over different types of comorbidities.

Although RCTs with a treatment and a sham treatment arm are considered the gold standard in research, conducting large trials is often times difficult in forensic settings; treatment motivation might be low for the type of patients in the treatment facility because they are placed under compulsory inpatient custody and are not seeking treatment due to inner motivation for change. In RCTs, number of participants usually has to be quite high to reach the desired effect size [54]. Participating patients might be even less inclined to take part in the trial if they know that they might end up in a placebo condition.

By employing an n-of-1 approach combined with an RCT, this study might help shed light on the underlying mechanisms of neurofeedback because an n-of-1 approach allows closer monitoring of treatment effects and provides valuable insight into an individual's treatment progress that might otherwise be lost in a between-group design [42].

If effective, neurofeedback could be a noninvasive treatment option for the reduction of impulsivity, which may lead to a reduction in feelings of drug craving and in actual drug use. Both impulsivity and drug-seeking behavior are known to hamper treatment progress and are strongly linked to criminal behavior [32]. By reducing impulsivity, chances of successful treatment for SUD may increase, thereby decreasing the risk for relapse in drug use and reducing criminal behavior.

There are several important issues to consider that might influence the results. First of all, participants are not selected based on their level of impulsivity. Even though the most commonly observed disorders in the treatment facility are schizophrenia and personality disorder and both types of disorders are associated with increased impulsive behavior, not all suitable participants might show elevated levels of impulsivity. Studies have shown that although there is evidence that heightened impulsivity can be found across different types of substance use disorders, there is still substantial heterogeneity on impulsivity levels within these groups [2]. A recent study by Albein-Urios et al [55] found several subgroups of addicted individuals that exhibited different clinical presentation and most interesting, different severity levels of craving. In the study, a latent class analysis showed that greater impulsivity levels were associated with worse clinical outcomes, whereas conventional diagnostic groups showed no significant differences on outcome variables. Also, there have been studies that show that antisociality is actually associated with better impulse control, independent of extent of drug use [56]. To ensure a sufficient number of participants, inclusion criteria in this study are quite lenient, which may provide heterogeneity within this sample. Ideally, participants would have to present with the same diagnoses, same type of medication, etc, however, this would limit the number of available participants to such an extent that it will be hard to find any effects. The heterogeneity of the population makes it possible that an impulsivity-based neurofeedback protocol might not result in a reduction of craving and actual drug use.

Also, participants will be included who have tested positive for drug use in the past 24 months. This implies that there will also be participants whose substance use disorder is in early remission. Although substance abuse–related symptoms such as craving are known to persist even after drug use is terminated, this period of time might be too long for these participants to report any craving at the moment of the administered questionnaire.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-EHEALTH checklist V1.6.1 [57].

[PDF File (Adobe PDF File), 362KB - resprot_v6i1e13_app1.pdf]

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Abbreviations

ADHD: attention deficit hyperactivty disorder
BIS-11: Barratt Impulsiveness Scale
DAQ: Desire for Alcohol Questionnaire
DAQ-SF: Desire for Alcohol Questionnaire–Short Form
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Review
EEG: electroencephalograph
FPC: Forensic Psychiatric Centre
HKT-R: Historical/Clinical/Future–Revised
IFTE: Instrument for Forensic Treatment Evaluation
IFTE-SR: Instrument for Forensic Treatment Evaluation–Self-Report
NFB: neurofeedback
RCT: randomized controlled trial
SMR: sensorimotor rhythm
SUD: substance use disorder
TAU: treatment as usual

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Protocol

Acupuncture for Children with Cerebral Palsy: A Systematic Review Protocol

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Abstract

Background: Cerebral palsy (CP), a childhood disease of high morbidity and serious harmfulness, has no effective therapies to completely relieve the associated pain. Acupuncture has been used widely in China to alleviate several CP symptoms, such as pain and motion disorders, despite the deficiency of high-quality evidence related to this practice.

Objective: The aim of this systematic review protocol is to assess the efficacy and safety of acupuncture for the treatment of children with CP.

Methods: The following electronic databases will be searched: Cochrane Library, Web of Science, EBASE, Springer, World Health Organization International Clinical Trials Registry Platform, China National Knowledge Infrastructure, Wan-fang database, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, and other sources. All published randomized controlled trials from inception to December 2016 will be included. RevMan V.5.3 software will be implemented for the assessment of bias risk, data synthesis, subgroup analysis, and meta-analyses if inclusion conditions are met. Individuals recruited into the trials will include children with all types of CP, and these individuals will be involved as coresearchers to develop and evaluate the efficacy and safety of acupuncture for the treatment of children with CP. Due to language barriers, only English and Chinese articles will be retrieved.

Results: The systematic review will synthesize the available knowledge surrounding acupuncture for children with CP. The findings will be synthesized to determine the efficacy and safety of acupuncture for children with CP.

Conclusions: The review has not been completed. This protocol presents a proper method to implement the systematic review, and ensures transparency for the completed review. Findings from the systematic review will be disseminated in a peer-reviewed journal and results will be presented at relevant conferences. The data of individual patients will not be included, so ethical approval is not required.

Trial Registration: PROSPERO registration number: CRD42016038275, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016038275 (Archived by WebCite at http://www.webcitation/6nGxoJrqm

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KEYWORDS

cerebral palsy; CP; children; acupuncture therapy; efficacy; safety

Introduction

Cerebral palsy (CP), the most common chronic disability of childhood, encompasses a heterogeneous group of movement and posture disorders that originate in the developing fetal or infant brain [1,2]. Epidemiological studies have found that the global prevalence of CP is 1.5-4 per 1000 live births, and the prevalence is higher in poor areas [3,4]. For example, with a prevalence of 3.6 per 1000 newborns in the United States, more than one hundred thousand children are affected in this country alone [5]. Considering the parents and caretakers of these children, the number of people who are negatively impacted by CP is far more considerable than that the patients themselves.

As an incurable illness, CP not only brings significant economic burdens to families (an average lifetime cost of one million dollars per person in the United States), but the disease if also associated with additional psychological problems [6,7]. Compared to healthy individuals, CP is associated with a higher frequency of autism spectrum disorders, sclerotic deformity, and the incidence of fractures [8,9].

Considering the complex manifestations of CP, treatments are targeted at improving function and reducing disability. Current treatments include pharmacological interventions, surgical interventions, physical and behavioral therapy, mechanical aids, and management of associated medical conditions. Although these commonly used clinical treatments of CP are multitudinous, none have accomplished a satisfying curative effect [3].

Acupuncture has increasingly been integrated into pediatric health care [10], and although numerous studies have been published, the safety and efficacy of this CP treatment is still ambiguous. Previous systematic reviews regarding acupuncture showed pain relief descriptively, and none included quantitative analyses for specific outcomes, leading to controversial results [11,12]. As more studies examining acupuncture for CP are performed, systematic reviews updated in 2008 or 2009 have become obsolete [13].

In traditional Chinese medicine (TCM), acupuncture therapy has been used for thousands of years, and has incorporated clinical treatment experiences to fine tune the procedures [14]. The theory of TCM suggests that health is achieved by maintaining an uninterrupted flow of Qi. Qi flows through a network of 14 channels, called *meridians*, which run along the surface of the human body. The acupuncture needles insert into the specific pathways or meridians at specific angles to correct the imbalance of energy in the body and restore natural internal homeostasis [15].

The theory of TCM deems that acupuncture is thought to correct the imbalance of energy in the body and restore natural internal homeostasis by stimulating various meridian points. At specific points, the needle inserts into the skin for dredging stasis in the meridian to adjust Yin and Yang. Studies have demonstrated that scalp acupuncture therapy may have the potential to treat epilepsy by increasing the blood flow speed of microchannel architecture, and upregulate anticardiolipin levels [16]. Decreased expression levels of cystathionine beta-synthase, and increased expression levels heme oxygenase-1 and hypoxia-inducible factor-1α, have been observed in perinatal rat cortex cells after electrical acupuncture treatment, implicating a novel protective mechanism for CP [17]. Furthermore, some studies indicate a high rate of symptom improvement in patients with CP after acupuncture treatment [18-21]. However, the safety and effect of acupuncture is not clear. The goal of this systematic review is to estimate the effectiveness and safety of acupuncture on CP, and to formulate treatment recommendations.

Methods

The Systematic Review

All Chinese and English randomized controlled trials (RCTs) published in electronic databases from inception to October 2016 will be included in this review. If inclusion criteria are met, we will use RevMan V.5.3 software to assess the risk of bias, examine data synthesis, undertake subgroup analysis, and conduct meta-analyses.

Electronic Search Strategy

Relevant databases include: Cochrane Library, Web of Science, EBASE, Springer, World Health Organization International Clinical Trials Registry Platform, China National Knowledge Infrastructure, Wan-fang database, Chinese Biomedical Literature Database, and Chinese Scientific Journal Database. The search strategy will be formulated in accordance with the guidance provided by the Cochrane Handbook [22]. The Medline search strategy is listed in Table 1, which includes all search terms, and other searches will be conducted based on these results.

Screening and Selection Criteria

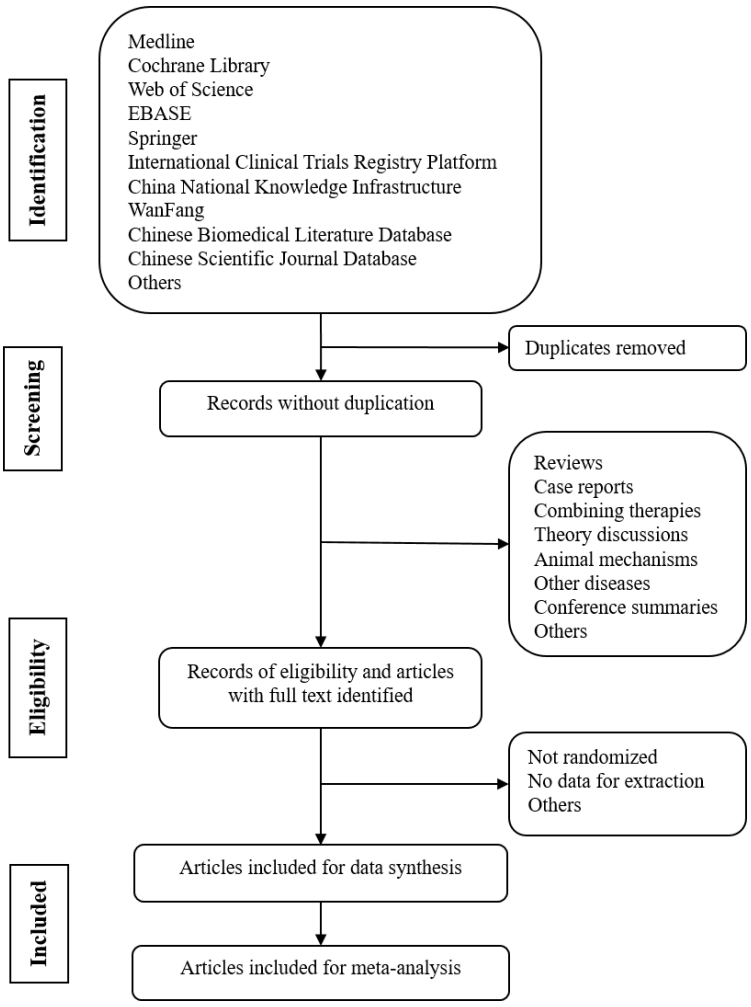
Overview

Two authors (ZBW and ZQ) will individually screen the title and abstract of each publication. Articles that clearly do not meet the inclusion criteria, and those that are not relevant to the study, will be excluded. Disagreements or discrepancies related to the inclusion criteria will be resolved through discussion. The screening process is summarized in Figure 1.

Table 1. Medline search strategy.

Number	Search terms
1	Randomized controlled trial
2	Controlled clinical trial
3	Randomly
4	Randomised
5	Randomized
6	Trial
7	or/1-6 (“or” is a representative of connecting two coordinating relation words)
8	Cerebral palsy
9	CP
10	Brain paralysis
11	Feilian
12	Encephala paralysis
13	or/8-12
14	Acupuncture
15	Acupoint
16	Meridian
17	Electro-acupuncture
18	Electroacupuncture
19	Transcutaneous electrical nerve stimulation
20	Acupoint catgut embedding
21	Acupressure
22	Cupping jar
23	Moxibustion
24	Auricular points
25	Abdominal acupuncture points
26	Scalp acupuncture points
27	Laser
28	Magnets
29	Bleeding
30	Acupoint injection
31	Fire needle
32	Needle-knife
33	Superficial needling
34	or/14-33
35	7 and 13 and 34

Figure 1. Medline search strategy.



Intervention

Several types of acupuncture will be included in the review: electro-acupuncture, body acupuncture, scalp acupuncture, ear acupuncture, fire needling, laser acupuncture, transcutaneous electrical nerve stimulation, and point injection. Multiple control interventions will also be included: no treatment, placebo/sham acupuncture, and other interventions (eg, surgery, drugs, and physical interventions). We will also include trials that evaluate acupuncture in addition to other therapies, if these combinations are compared to the other therapy alone.

Comparisons

If possible, we will execute the following analyses: (1) comparisons between acupuncture and sham, placebo, or no treatment; (2) comparisons between acupuncture and pharmacological interventions; and (3) comparison between acupuncture and physical interventions.

Review Manager 5.3 will be employed to test for interactions. When considering different types of CP, we will use a graphical display to assess each one separately for the curative effect and safety of acupuncture. Subgroup analyses will be performed between the different types of acupuncture.

Primary and Secondary Outcomes

Primary outcomes will include (1) motor function improvement; (2) intellectual development; (3) improvement of self-care ability and daily living; and (4) side effects of acupuncture. Secondary outcomes will include (1) symptom improvement; (2) quality of life, self-esteem, and self-concept development; and (3) satisfaction with the treatment.

Study Design

Inclusion Criteria

We will examine RCTs that involve at least one test treatment that aimed to improve or eliminate CP symptoms, and one control treatment (or no treatment) with concurrent enrolment. Study participants must conform to diagnosis standards established by bodies such as the American Academy of Neurology or the American Association of Cerebral Palsy. All children <18 years of age will be included in the study, with no limits on the ethnicity, nationality, type of CP, or gender of the subjects.

Exclusion Criteria

Trials comparing different types of acupuncture will be excluded. Participants that did not have a specific diagnosis of pediatric CP will be excluded. Patients with motor development diseases, diseases of bones and muscles, common genetic

diseases, spinal cord diseases, and peripheral neuropathy will be excluded.

Date Extraction

Using a standalone electronic form, two review authors (YYJ and HQ) will extract data independently and examine the publication date of each report, to minimize errors and reduce potential risk of bias. The information of participants, interventions, controls, and outcomes will be extracted. Disagreements will be resolved through discussion.

Quality Assessment

Depending on the sample size of each study, and the influence of pooled effect size and strength of evidence, discussions will be undertaken to determine if the study will be included. Two authors (ZBW and GTP) will assess the risk of bias based on the domains and criteria of the Cochrane Collaboration's tool [22]. Six domains of bias will be examined: (1) selection bias, (2) performance bias, (3) attrition bias, (4) detection bias, (5) reporting bias, and (6) other biases.

Any problems or disagreements will be discussed with a third author (GTP). For dichotomous data, we will present a risk ratio (RR) with 95% CIs. For continuous outcomes, we will present a standard mean difference with 95% CI. Other binary data will be changed into the RR form. If missing data is evident in any of the studies, we will attempt to contact the authors by phone or email. If the missing data are not obtained, the available data will be analyzed with the assumption that it is missing at random. If necessary, missing data will be imputed using replacement values.

A standard $\chi 2$ statistic and I^2statistic will be used to measure heterogeneity among trials. If there is no statistical heterogeneity observed between subgroups (I^2<50%), heterogeneity will be accepted. If substantial heterogeneity exists (I^2>50%), indicating a level of inconsistency, we will examine possible causes of heterogeneity. If a sufficient number of studies are available (a minimum of 10 are required), we will use funnel plots to detect the reporting biases.

Data Synthesis

If two or more eligible RCTs are identified, we will perform meta-analyses with Review Manager 5.3. When I^2<50%, the fixed-effect model will be chosen, and the random-effect model will be selected I^2>50%. We will explore possible causes and analyze the data with a random-effect model. If clinical and methodological heterogeneity is presented, we will perform subgroup analyses; if not, we will not pool the data and a systematic narrative synthesis will be performed to summarize and explain the characteristics and findings of the included studies.

Results

This systematic review aims to evaluate the effectiveness and safety of acupuncture for CP in children, and assist with future research planning. By synthesizing included studies, the systematic review results will provide insights regarding which components of interventions are most effective and safe. The completion date for the review is projected to be early-to-mid 2017.

Discussion

CP is a disease with complex pathogenesis and brings huge burdens to the patients and their families [23]. TCM has long-standing and abundant experiences in treatments for children with CP. As an important therapy of TCM, acupuncture might also play an important role in the treatment of all CP cases. Systematic reviews show that acupuncture is a safe intervention for pediatric patients, and no severe side effects have been reported [12,24].

A systematic review of acupuncture usage in the treatment of CP should provide a reliable basis of evidence, and expand the understanding of acupuncture in CP. Although acupuncture is extensively used in the treatment of children in clinics, adverse events of acupuncture are often ignored or not reported in reviews [13]. In addition to evaluating the efficacy of acupuncture, this systematic review will also examine the safety of acupuncture in pediatric health care by evaluating the safety of acupuncture for children with CP.

Due to language barriers, we will only retrieve English and Chinese articles, which may affect the strength of results. Two researchers will independently examine the articles to eliminate personal biases related to study selection, data extraction, and quality assessment. To evaluate the safety and efficacy of pediatric CP, the protocol will be carried out to explore any sources of heterogeneity in different acupuncture therapies.

This study will evaluate the efficacy and safety of acupuncture for the treatment of children with CP. This protocol presents a proper method to implement the systematic review, and ensures the transparency of the completed review.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CP: cerebral palsy
RCT: randomized controlled trial
RR: risk ratio

TCM: traditional Chinese medicine

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Protocol

Assessing the Quality, Feasibility, and Efficacy of Electronic Patient Platforms Designed to Support Adolescents and Young Adults With Cancer: A Systematic Review Protocol

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Abstract

Background: A range of innovative websites, mobile technologies, eHealth and mHealth platforms have emerged to support adolescents and young adults (AYAs) with cancer. Previous reviews have identified these various applications and solutions, but no review has summarized the quality, feasibility, and efficacy of existing patient platforms (inclusive of websites, mobile technologies, mHealth and eHealth platforms) developed specifically for young people with cancer.

Objective: This paper describes the design of a protocol to conduct a review of published studies or reports which describe or report on an existing platform designed specifically for AYAs who have had a cancer diagnosis.

Methods: A search string was developed using a variety of key words and Medical Subject Heading and applied to bibliographic databases. General data (sample characteristics, patient platform development, design and, if applicable, pilot testing outcomes) will be extracted from reports and studies. Drawing on a previously developed coding schematic, the identified patient platforms will be coded for mode of delivery into (1) automated functions, (2) communicative functions, and (3) use of supplementary modes. An adapted version of the Mobile App Rating Scale (MARS) will be used to assess the of quality of each identified patient platform. The methodological quality of included studies will be assessed using the Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields (QualSyst). Both authors will independently screen eligible studies for final inclusion and will both be responsible for data extraction and appraisal. Data will be synthesized narratively to provide an overview of identified patient platforms.

Results: The review began in October 2016 and is currently in progress. The review paper will be submitted for peer-review and publication in the summer of 2017.

Conclusions: This review will be unique in its focus on assessing, where possible, the quality and efficacy of patient platforms for adolescents and young adults diagnosed with cancer. Results generated from this review will provide an invaluable insight into the utility of modern technology in supporting young people with cancer.

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KEYWORDS

adolescent; neoplasms; telemedicine; review

Introduction

Specifically as a cancer diagnosis and its subsequent treatment may be the first time a young person independently encounters the health care system and is required to learn self-management skills relating to their health and well-being. Each year approximately 14,000 adolescents and young adults (AYAs) are diagnosed with cancer within Europe [1]. Although this number accounts for only a small proportion of the total cancer diagnoses that occur annually, young people with cancer have unique care needs and require tailored support from the point of diagnosis, during treatment, and throughout their lifetime as survivors of cancer [2-4]. AYAs who have had a cancer diagnosis are at increased risk of cancer recurrence, chronic disease, and often face physical, emotional, and social difficulties [5,6]. Specifically, time spent in hospital can disrupt normal social and educational milestones and common treatment-related side-effects such as hair loss, weight gain, scarring, infertility, and amputation can often impact a young person's body image, trust in health, and self-esteem [6,7]. Following successful cancer treatment more than 60% of AYA survivors of cancer will experience at least 1 long-term chronic health problem as a result of their original diagnosis and treatment [8]. Addressing the specific care needs of young people with cancer has been at the heart of the AYA cancer profession since its inception in the early 1990s [9]. Internationally, efforts and advancements in research, policy, and care are continually being made to ensure young people with cancer receive the specific medical, emotional, and practical support they require during cancer treatment and beyond [1,5,10]. A cancer diagnosis and its subsequent treatment may be the first time a young person independently encounters the health care system and is required to learn self-management skills relating to their health and wellbeing.

Within this context, websites, mobile technologies, and eHealth platforms have emerged as promising and innovative strategies for assisting young people with cancer in accessing information-rich environments and accessing support suitable to their needs [11]. Such technologies offer potential opportunities for AYA survivors of cancer to self-monitor or self-assess their health needs and access peer-to-peer support in a safe environment. Moreover, remote-based health interventions overcome geographical and time-constraint barriers typically faced by health care professionals and researchers attempting to engage this population [12]. A previous review of mobile and tablet-based apps available to young people with cancer identified 7 apps in total [13]. Of these 7 apps, the majority were piloted in proof-of-concept investigations among only a small sample of young people. Despite noted limitations like this coupled with a lack of empirical testing of the identified apps, Wesley and Fizur (2015) concluded that apps were a favorable means of health intervention for young people with cancer due to the positive perceptions of the usability of the apps and their functionalities [13]. This is reflective of previous studies which report high levels of desire for technology-based information resources and self-management tools among AYAs living with or beyond a diagnosis of cancer [11,12].

However, to date there has been no focused effort to fully synthesize and review existing patient platforms (inclusive of websites, mobile technologies, and mHealth and eHealth platforms) developed specifically for young people with cancer. Understanding component features of existing technology platforms is an important step in characterizing the potential utility of technology-based interventions for young people with cancer. Thus, the aim of this review protocol is to outline the staged approach that will be adopted to address this knowledge gap. The objective of the review is to identify, characterize, and fully assess the quality, feasibility, and efficacy of existing patient platforms developed specifically for adolescents and young adults who have had a cancer diagnosis. Such a comprehensive review will provide further important insight into the utility of technology in the health care and support of AYAs with cancer.

Methods

The methods to be adopted in this literature review are outlined below and follow the standard Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidance [14].

Inclusion Criteria

Types of Studies and Reports

Any study or report which describes or reports an existing electronic platform designed specifically for young people aged between 13 and 39 years of age living with or beyond a cancer diagnosis will be included for review.

Types of Participants

The age range of 13 to 39 years has been used to reflect United Kingdom and United States of America accepted definitions of young people with cancer [15,16]. Participants of interest are those who fall within this age bracket and are defined as teenagers, adolescents, or young adults living with or beyond cancer. This includes young people who are AYA-aged survivors of a childhood cancer diagnosis. No studies will be excluded based upon participants' treatment status or position on the cancer care continuum. This aligns with the National Cancer Institute, World Cancer Research Fund, and American Institute of Cancer Research definitions of cancer survivor as anyone who has had cancer from the point of diagnosis onwards [17,18].

Types of Interventions

Patient platforms for the purposes of this review will encompass any eHealth, mHealth, or health informatics efforts which apply modern computing and communication methods such as digital technologies for the provision of health care.

Types of Outcome Measures

The efficacy of patient platforms piloted as health interventions within randomized controlled trials or quasi-experimental trials will be assessed by extracting data on health outcomes, specifically the magnitude of change in health outcome.

Exclusion Criteria

Studies or reports will be excluded from the review if they report on platforms developed for young people with comorbid conditions other than cancer or if AYAs with cancer are not the primary focus of the paper (ie, where AYAs with cancer are included as a subsample of AYAs more generally or AYAs with other illness conditions). In addition, studies or reports with insufficient detail on the target population, intervention, and mode of delivery (even after author contact to clarify) will be excluded from the review. Studies investigating patient platforms designed for adult cancer survivors aged 40 years and older and studies where the mean age of the sample is older than 39 years will also be excluded. Likewise, electronic platforms designed for use exclusively by parents or caregivers and health care professionals who work directly with AYA cancer patients will be not be included in the final review.

Identification and Screening

A literature search for patient platforms developed specifically for or piloted among AYAs who have had a cancer diagnosis will be conducted. The search string outlined below will be applied to bibliographic databases. Where possible, authors of studies selected for review will be contacted to inquire as to whether they know of any additional patient platforms designed specifically for AYAs living with or beyond a diagnosis of cancer, either published or unpublished.

The search strategy includes a range of Medical Subject Headings terms and a range of relevant keywords for the interventions of interest in this review. Grey literature and the reference lists of all included papers and reports will also be reviewed to identify any additional relevant studies or reports.

Search String: Teen* OR Adolesc* OR Young Adult OR Child AND Cancer OR Cancer Survivor AND app OR apps OR application or mobile OR Android OR droid OR iphone OR ios OR blackberry or web OR internet OR portal OR portlet OR microsite OR website OR “web site” OR url OR mhealth OR ehealth OR internet OR online OR digital OR email OR social network OR electronic communication OR e-health OR e-learning OR elearning OR social network OR facebook OR myspace OR virtual world OR short messaging service OR virtual clinic OR computer assisted therapy OR information technology OR electronic communication OR digital divide OR e-mail OR email OR telehealth.

Evaluation Criteria

Data will be extracted, appraised, and evaluated to allow a comprehensive synthesis of included studies and reports.

Data Extraction

General data and information regarding sample characteristics, patient platform development, design, and (if applicable) pilot testing outcomes will be extracted from reports and studies.

Coding of Platform Characteristics

Mode of delivery will be coded based upon the coding scheme developed by Webb and colleagues [19]. Automated functions will be classed as either (1) enriched information environment (eg, supplementary materials, testimonials videos, or games), (2) automated tailored feedback based upon individual progress monitoring (eg, comparison to norms, goals, reinforcing messages, or coping messages), or (3) automated follow up messages (eg, reminders, tips, newsletters, and encouragement). Communicative functions will be categorized into (1) access to an advisor to request advice (eg, ask the expert/expert-led discussions or chat functions), (2) scheduled contact with an advisor (eg, emails), and (3) peer-to-peer support access. Supplementary modes of communication will be classified into email, telephone, short messaging service, CD-ROM, and videoconferencing.

Assessment of Quality

An adapted version of the Mobile App Rating Scale (MARS) will be used to evaluate each patient platform. The MARS scale will be used to classify and evaluate each platform in 5 areas: engagement, functionality, aesthetics, information quality, and subjective quality [20].

The methodological quality of included studies will be assessed using the Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields (QualSyst). This tool incorporates scoring systems previously used for assessing qualitative and quantitative research. There are 14 items to assess quantitative studies and 10 items to assess qualitative studies.

Assessment of Feasibility and Efficacy

Data and information regarding reported acceptability, compliance, delivery of the intervention, recruitment, and participant retention will be extracted from each of the studies and reports and synthesized in order to gather an overview of the feasibility of each individual patient platform.

Data Synthesis

Extracted and appraised data will be collated in relevant Excel tables (Microsoft Corp). Synthesis data will be presented narratively in text and summary tables in the review publication.

Results

The review began in October 2016 and is currently in progress. The review paper will be submitted for peer-review and publication in the summer of 2017.

Discussion

The application of technology in the supportive care of AYAs is an emerging field of interest [11]. To date, however, there has been no collective effort to fully synthesize the literature within this area or identify key features and functionalities of existing patient platforms for AYAs with cancer. This methodological review of eHealth, mHealth, or health informatics efforts that apply modern computing and communication methods for the provision of health care and information to AYA cancer patients and survivors will allow an invaluable insight into the range of existing patient platforms for young people with cancer. Furthermore, the use of multiple coding frameworks to classify and assess intervention features will allow rigorous assessment of patient platform quality,

feasibility, and efficacy. This approach will provide a novel and comprehensive overview of this topical area. The participant inclusion criteria of this review has purposefully been kept broad in order to reflect international variations in AYA cancer age brackets [15,21] and variations in the terminology used to describe AYA cancer patients and cancer survivors [22]. Equally, the intervention inclusion criteria is broad in order to fully capture the wide range of existing patient platforms for this unique population group. This approach to searching existing literature for studies concerning AYA cancer populations has been previously applied within other systematic reviews [23,24]. It is hoped this review will provide an invaluable insight into existing patient platforms and underscore future developments within this field of cancer research.

Acknowledgments

LM is a current member of the National Cancer Research Institute Clinical Studies Group for Teenagers and Young Adults with Cancer in the United Kingdom; GP is a former trainee member of the same group. This work is being conducted on behalf of and with support of this group.

GP and LM conceptualized and designed this review protocol and will be responsible for all stages of the literature review. Both GP and LM were involved in drafting, reviewing, editing, and finalizing this manuscript. Order of authorship was also approved by both authors.

Conflicts of Interest

None declared.

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Abbreviations

AYA: adolescents and young adults
MARS: Mobile App Rating Scale
QualSyst: Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields

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Protocol

Epidemiology of Patient Harms in New Zealand: Protocol of a General Practice Records Review Study

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Abstract

Background: Knowing where and why harm occurs in general practice will assist patients, doctors, and others in making informed decisions about the risks and benefits of treatment options. Research to date has been unable to verify the safety of primary health care and epidemiological research about patient harms in general practice is now a top priority for advancing health systems safety.

Objective: We aim to study the incidence, distribution, severity, and preventability of the harms patients experience due to their health care, from the whole-of-health-system lens afforded by electronic general practice patient records.

Methods: "Harm" is defined as disease, injury, disability, suffering, and death, arising from the health system. The study design is a stratified, 2-level cluster, retrospective records review study. Both general practices and patients will be randomly selected so that the study's results will apply nationally, after weighting. Stratification by practice size and rurality will allow comparisons between 6 study groups (large, medium-sized, small; urban and rural practices). Records of equal numbers of patients from each study group will be included in the study because there may be systematic differences in patient harms in different types of practices. Eight general practitioner investigators will review 3 years of electronic general practice health records (consultation notes, prescriptions, investigations, referrals, and summaries of hospital care) from 9000 patients registered in 60 general practices. Double-blinded reviews will check the concordance of reviewers' assessments. Study data will comprise demographic data of all 9000 patients and reviewers' assessments of whether patients experienced harm arising from health care. Where patient harm is identified, their types, preventability, severity, and outcomes will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 18.0.

Results: We have recruited practices and collected electronic records from 9078 patients. Reviews of these records are under way. The study is expected to be completed in August 2017.

Conclusions: The design of this complex study is presented with discussion on data collection methods, sampling weights, power analysis, and statistical approach. This study will show the epidemiology of patient harms recorded in general practice records for all of New Zealand and will show whether this epidemiology differs by rural location and clinic size.

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KEYWORDS

general practice; patient harm; safety; retrospective studies; electronic health records; New Zealand

Introduction

Prior Related Research

Harming people who seek help from health services causes distress in both harmed patients and in the health care workers involved [1]. It is also morally wrong and costly, posing an often avoidable burden on already stretched health systems. Knowing where and why most harm occurs will enable patients to make informed decisions regarding the risks and benefits of treatment options and enable health care providers to improve systems and processes to deliver safer care.

Reviewing patient records as a methodology for understanding patient safety started in US hospitals more than 20 years ago and has been repeated in many countries, including New Zealand, but has extended beyond hospital care in only one country to date (the Netherlands [2]) [3-6]. Epidemiological research in general practice is important for advancing health systems safety [7] because the overwhelming majority of health care is delivered in primary care [8]. Health care delivered in general practice is known to harm patients, and many safety incidents identified in hospitals originate in primary care [9-12]. Conversely, many harms originating in hospitals may not become apparent until after discharge. The burden of patient harms on health systems is mainly from frequent repetitions of minor incidents rather than from rare extreme events [13].

The development of initiatives to protect patients from harm in general practice has been constrained by a lack of knowledge about the epidemiology of harm: the types of patient harms that occur, their likelihood of occurrence, severity, and degree of preventability. The only available general practice epidemiological patient safety study that has been conducted using the records review method found 211 incidents in 1 year of reviewed records of 1000 patients from 37 general practices [2]. No incidents resulted in severe harm or death, leading the authors to conclude that general practice is relatively safe. Although this is a critical early study, other research gives a different perspective.

In New Zealand, primary care medicine is typically provided by vocationally trained general practitioner (GP) doctors who care for patients of all ages and with all conditions. Although other medical specialists (including pediatricians and general physicians) occasionally work in general practice, they are most often employed in other settings. Our analyses of primary care treatment injury claims to the Accident Compensation Corporation in New Zealand [14] and of malpractice claims in the United States [15] show that health care delivered outside hospital settings can result in severe harm and death. Not all injured patients initiate malpractice suits or lodge claims for compensation for treatment injuries [16], so claims data underestimate both prevalence and incidence of these events. We therefore aim in this study to define the epidemiology of patient harms detectable in general practice records using retrospective record review methodology.

We recently completed a feasibility study to prepare for this proposed study. In the feasibility study, we derived information for calculating sample sizes for the full study and developed a workable rule-based definition of “harm.” We also discovered that the reviews needed to be completed by GPs as nonmedical reviewers were unable to adequately interpret general practice records and identify patient harm. We developed forms and processes to collect the study data.

Hypotheses

As well as the need for descriptive epidemiology research, we aim to address unresolved questions relating to the influence of practice size and location on patient safety. In the last decade, reports of better quality care by higher-volume hospitals have fueled a shift of services from smaller to larger hospitals internationally [17] and mergers of small general practices into larger centers are now occurring in New Zealand [18]. If larger general practices were shown to be safer (or less safe) than smaller ones, this would have important implications for the future organization of general practice. Different types of harm might occur in different kinds of practices. For example, patients attending smaller practices may experience harm related to clinician availability, while patients of larger practices may be harmed by more complex communications processes. This study will therefore test the hypothesis that there is no difference between small, medium-sized, and large general practices in the epidemiology of patient harm detectable from general practice records.

The research will also test the hypothesis that there is no difference between rural and urban general practices in the epidemiology of patient harm detectable from general practice records. Patients of rural practices face the obvious disadvantage of greater distance from medical services than patients of urban general practices and distance from services is a recognized (but not measured) safety risk [19]. Rural patients may experience more harm than patients of urban practices related to limited access to hospital and specialty care, but no research has yet shown that rural patients experience more or different health care harms than urban patients [20]. In New Zealand, rural patients have reported concerns about primary health care costs, lack of access to doctors in emergencies, and inappropriate early discharge from hospitals [21].

We therefore aim in this study to provide the epidemiology of harms detectable from general practice records and to test

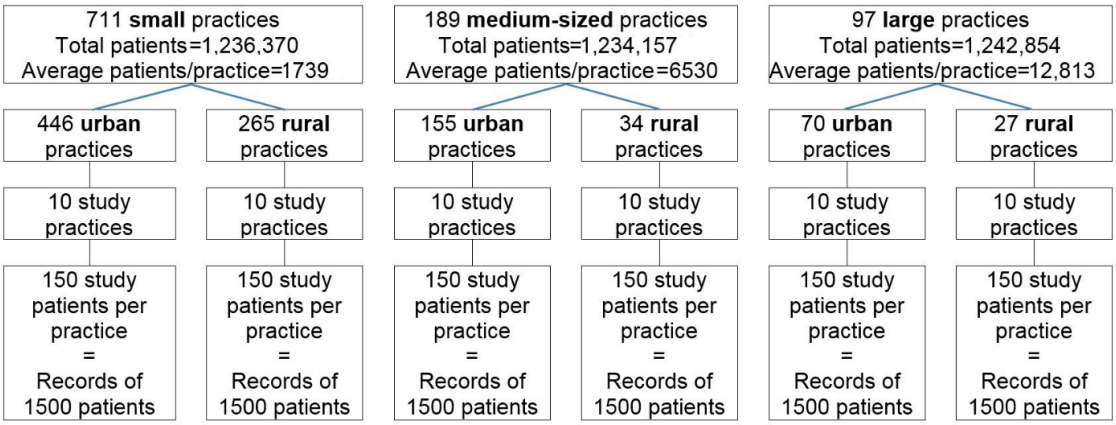
whether there are epidemiological differences in recorded harms by practice size and location.

Methods

Study Design

The study design is a stratified, 2-level cluster, retrospective records review study (shown in Figure 1). New Zealand has a robust national database of enrolled general practice patients. Patients are incentivized to enroll with one general practice as unenrolled patients pay considerably more to receive general practice care. Patients are identified by their National Health Index (NHI) code, a unique alphanumeric identifier assigned to everyone using health services in New Zealand. General practices are required to advise their local Primary Health Organization quarterly of their enrolled patients using patients' NHI codes. Practices receive a capitation payment based on this information and are penalized for providing incorrect information, so accuracy is paramount for both practices and primary health organizations.

Figure 1. Study design using Primary Health Organization data from the third quarter, 2013.



Study Population

We developed the study design using the enrollment database from the third quarter of 2013 because this was the most recent data available when the study was planned. Each quarter, earlier versions of the database are overwritten, so study general practices have now been randomly selected from practices in the fourth quarter 2014 Primary Health Organization database because this was the latest available data before the study started. The sample frame includes all New Zealand general practices, except the 2.85% of all general practices (29/1018) based solely in aged care residential facilities, universities or polytechnics, or specialty practices such as sports medicine, men's health, or appearance medicine clinics. We excluded these clinics because they provide targeted primary care to specific populations and their inclusion could misrepresent typical general practice. We also excluded general practices that our data extraction software was unable to access.

From randomly selected general practices consenting to participate in the study, we will draw a random selection of patients enrolled at the midpoint of the study period, July 1, 2012. The number of patients whose records will be reviewed from each participating practice will vary according to the number of enrolled patients in the practice but will total 1500 for each of the 6 location and size study groups (for a total of 9000 randomly selected general practice patients to be studied). This will oversample minority groups compared with proportional selection, ensuring all group-specific estimates have reliable levels of precision.

Study Period

The study period is the calendar years 2011, 2012, and 2013. Patients' anonymized medical records for the 3 calendar years will be extracted. All randomly selected patients will be included for analysis even if they were not enrolled for the entire study period, to capture people who were born, changed practices, or died during the study period. The analysis will adjust for patient-years enrolled in study practices during the 3 study years.

Power Calculation

From our feasibility study, we calculated that a randomly selected sample of 1345 patients in each study group will allow 5% differences in the proportion of patients harmed by their health care to be defined between urban and rural, and small, medium-sized, and large practices, with alpha=.05 and power=.80. Neither harm severity nor intraclass correlation was among the assumptions in our power calculations. We will include the records of all randomly selected patients, even if they had no recorded health care encounters during the study years.

Recruitment

Although the power calculation is based on patient numbers, we wish to ensure that a nationally representative geographic distribution is achieved by the sampling process. We have therefore invited participation in the study of 12 randomly selected practices from each of the 6 study groups shown in Figure 1. We expect that 10 practices from each group will agree to participate, for a total study group of 60 general practices. This expectation is based on the assumption that most New Zealand general practices exclusively use electronic health records, with approximately 80% using the Medtech system [22]. Randomly selected practices will be excluded from the study if they do not use this records management system as we do not have funding to design data abstraction tools for the

many different software packages used by the other 20% of general practices.

To encourage participation, the study has been endorsed by the Royal New Zealand College of General Practitioners as an audit activity, and participation counts toward the audit requirement for the maintenance of professional standards recertification program for participating GPs. No other incentives will be offered to participants.

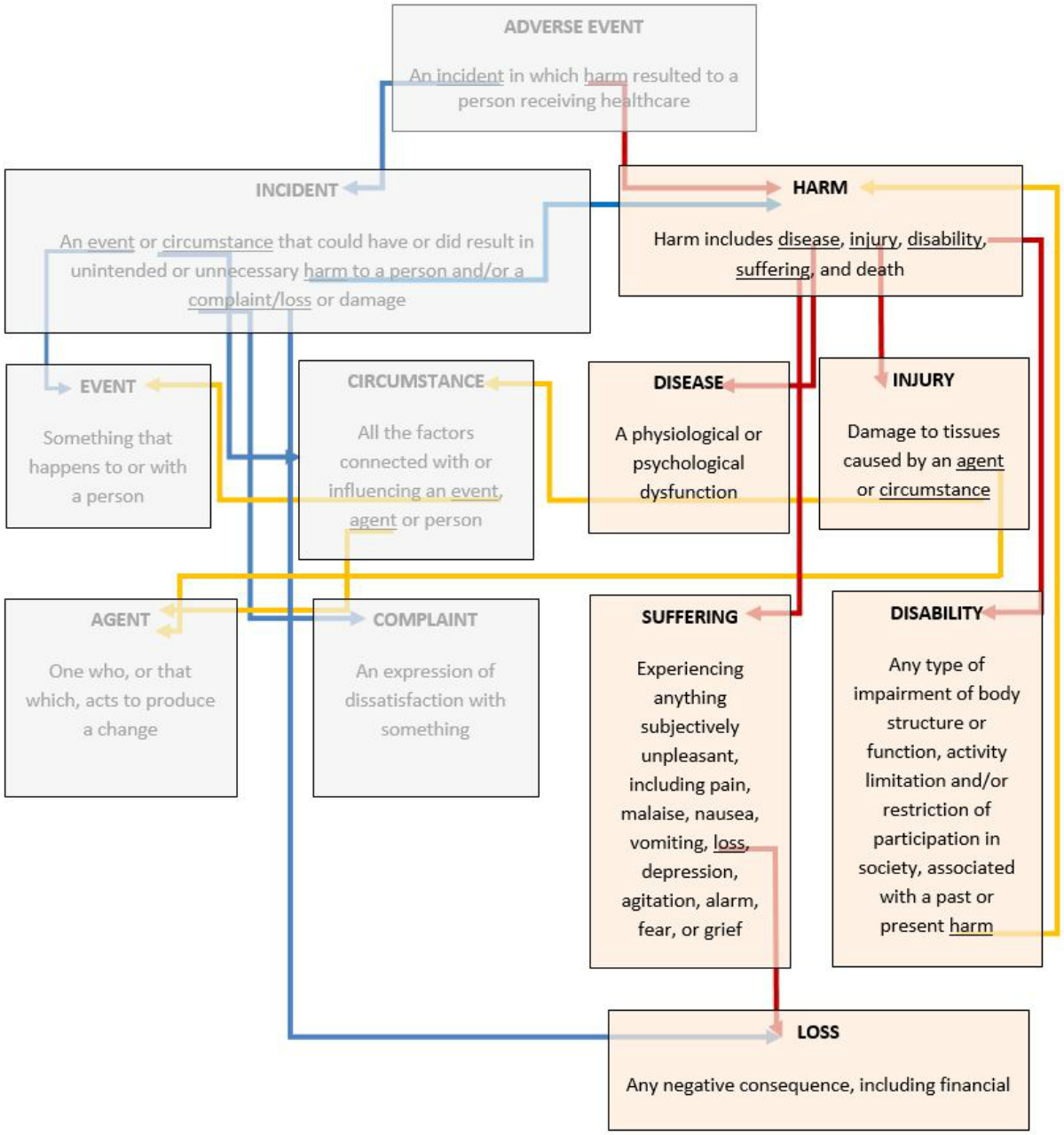
Practices will receive the results from their practice as soon as their patient reviews are complete, and at the end of the study they will be advised of the final results.

Definitions of Outcomes and Explanatory Variables

Patient Harm

Patient harm is defined as physical, emotional, or financial negative consequences to patients directly arising from health care, beyond the usual consequences of care and not attributable to patients' health condition. Figure 2 shows our operational definition of patient harm, derived from work undertaken by the Australian Council for Safety and Quality in Health Care [23].

Figure 2. Relationship between patient safety terms. Red arrows indicate relationships between key terms addressed in this study. Blue arrows and opaque boxes indicate definitions and relationships between terms that are not the subject of this study. Yellow arrows indicate where terms are used to describe both "incidents" and "harm."



Harm Preventability

Harm preventability assessment requires GP insight. While some harms are clearly preventable (eg, a patient with a history of specific adverse drug reaction experiencing another adverse reaction after being prescribed the same medicine) or not preventable (eg, a patient having an adverse reaction to an appropriately prescribed drug, without a previous history of such reactions), there is a considerable gray area in general practice, where risks and benefits of treatments have to be balanced and sometimes harm is knowingly risked in the interests of avoiding potentially greater or more permanent harm [24]. We will use the standard of a "reasonable" doctor to focus reviewers' consideration of preventability, as in hospital records review studies [3,9] and our feasibility study. Preventability will be coded using the definitions developed by McKay et al [25] as "not preventable and originated in secondary care," "preventable and originated in secondary care OR not preventable and originated in primary care," "potentially preventable and originated in primary care," "preventable and originated in primary care," or "not preventable, standard treatment."

Harm Severity

Harm severity will also be reviewed by the GP investigators, who will make subjective assessments of severity from "minor" to "severe" (Table 1). We will collect data specifically on whether harms resulted in death, hospital admission, emergency department contacts, additional general practice visits, or additional treatments.

Table 1. Harm severity assessment with examples.

Harm severity	Examples
Minor	Minor drug adverse effects (eg, nausea, rash), grazes, bruises and lacerations, and inconvenience to patients caused by processes of care, such as being given the wrong prescription.
Moderate	Ongoing morbidity attributable to omissions in care management (eg, ongoing poor diabetes control, untreated anemia, repeated abortions) and fracture of minor bones (eg, ribs).
Severe	Severe harms include renal failure, pulmonary embolism, myocardial infarction, peptic ulcer perforation, delayed cancer diagnosis, morphine overdose, and fracture of long bones.
Death	Death

Practice Size

Practice size is defined by the number of registered patients, rather than the number of clinicians, an approach used in some other studies [26,27]. Small, medium-sized, and large general practices are defined in Figure 1 by tertiles of total number of enrolled patients in all New Zealand practices. There will be some heterogeneity between practices within each size group. In theory, random selection of practices will even out the effects of this heterogeneity.

We considered the effect of the few New Zealand general practices that do not employ any GPs at the time of selection. The number of these practices is unknown. We assume that all such practices will fall into the "small" size group and the random selection process will allow their entry into the study sample. We will collect descriptive data from study practices, including staff composition, to allow analysis of differences between practice types in terms of harm probability or severity.

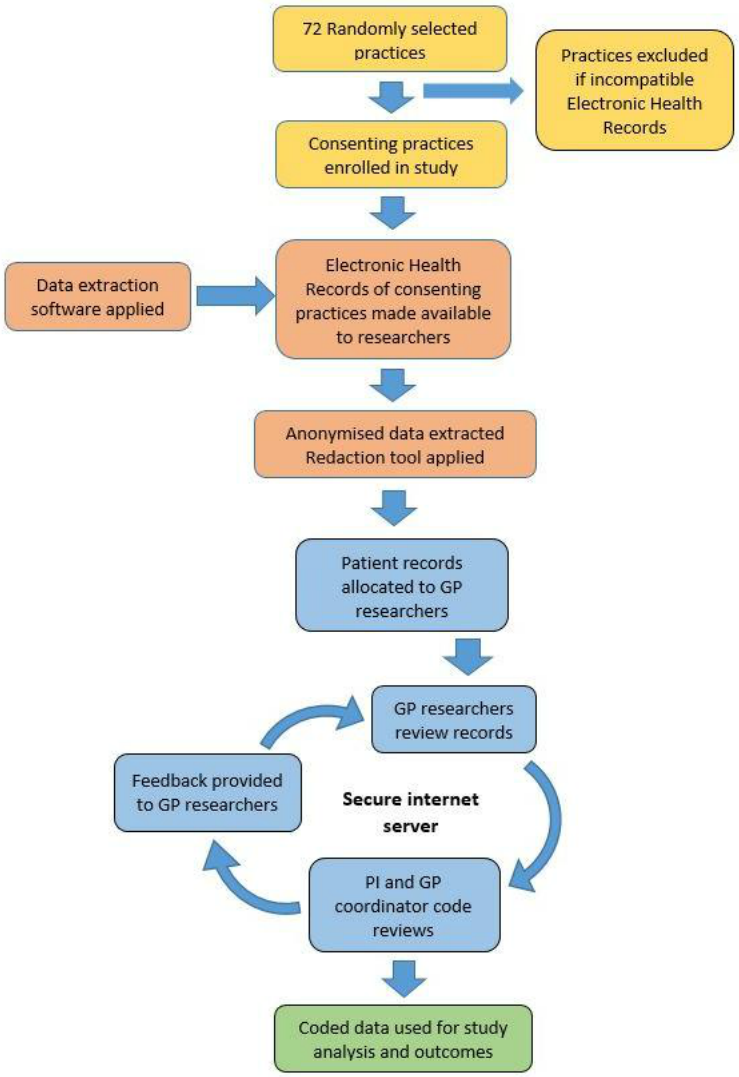
Rurality

Rurality is defined in New Zealand by the Rural Ranking Score developed in 1995 as an objective measure for allocating public funding to support the recruitment and retention of rural GPs and to assist the provision of after-hours care in rural and remote communities. By this measure, practices with a score of >35 capture the features of rurality that make them substantially different from urban general practices. Therefore, we will collect data about study practices' Rural Ranking Score, if they have one, and we will also define rural and urban practices by their addresses in locations meeting the Statistics New Zealand definitions of urban and rural [28], with one exception. Practices in "independent urban communities" will be included in the *rural* general practice group as independent urban communities are smaller centers without many of the specialty services provided by large hospitals [29]. Many of the patients of general practices in these towns live in surrounding rural areas.

Collection of Study Patient Records

Figure 3 shows the study's data processes. Study patients' records will be extracted electronically from the computer systems of participating general practices. Extracted patient records will include the dates for, and notes about every contact with the practice, all prescriptions and investigation results, and discharge summaries from hospitals. We may be unable to review referral letters and some other important information that is stored in portable document format (".pdf"). Extracted data will be reviewed and used to complete the study data form. The anonymized extracted records, along with reviewers' assessments of harm, will be sent to the Dunedin School of Medicine, Department of General Practice and Rural Health.

Figure 3. Flowchart of study processes. Color key: yellow=practice engagement, orange=data extraction, blue=data review, and green=analysis. GP: general practitioner; PI: principal investigator.



Data and Missing Data

Descriptive data will be collected from the general study practices at enrollment, including practice location (using both the Rural Ranking Scale and Statistics New Zealand definitions), size, services available, clinical staff composition, and clinical hours worked. This information will be held separately from the patient records and will not be visible to the GP reviewers.

Specially programmed software will interrogate the electronic health records of study practices, make a random selection of patients, and extract 3 years of data from these patients' records. Extracted patient records will be allocated to reviewers, who will access them via a secure website. Security of personal information is recognized by strict privacy legislation in New Zealand [30], so no identifiable patient information will be collected. Patients will be allocated a numeric study identifier. Deidentifying redaction software will be used to strip names and addresses from records, as far as possible. Dates of birth will not be collected but patients' ages (in years) during each study year will be recorded. Each record will have a data form attached, which will include study identifiers for the patient and practice, patients' age, sex, ethnicity, and social deprivation using the geographically based NZDep Index. Free text will be used to record each harm that patients experience during the 3 study years, with drop-down boxes to record the preventability and severity of each harm. Multiple harms may be recorded for each patient. Where no harm details are entered by GP reviewers, patients will be recorded as having "no harm."

As all study data are drawn from general practice records, their completeness will depend on the processes used in each practice. Our experience is that age, sex, event dates, prescriptions, and investigation results are almost always 100% complete as these data are ensured by the software. Ethnicity is variably recorded: we expect this to be missing from about 40% of records. The content of free text medical records depends entirely on the idiosyncratic practices of doctors and nurses: sometimes very detailed descriptions of patients' journeys through health care are provided, but sometimes descriptions are sketchy.

As the goal of the study is to determine from general practice records the epidemiology of harm in a way that can be generalized to all New Zealand general practices, we plan to

unconditionally accept for review all randomly selected records from participating practices. The only absolute requirement is that they are electronic records on software compatible with our extraction tool.

Data Coding and Checking

We found from the feasibility study that harms were seldom explicitly stated in the records but were recognizable to GPs who were able to interpret patients' journeys through the health care system after reading their general practice records.

All patient records reviews will be conducted by GPs who are currently clinically active. There are 8 GP reviewers distributed throughout New Zealand, including 5 who reviewed records in the feasibility study. Reviewer training includes an 8-hour interactive workshop before data collection, annual face-to-face meetings, reviews are critiqued and discussed in an online forum, monthly individual feedback is provided to each reviewer, and all reviewers have the opportunity to seek clarification about their work with the pharmacologist and study coordinators.

Most records in the proposed study will be reviewed by only 1 GP investigator, but a 5% random sample of records will have blinded review by a second GP to check concordance and identify areas where additional clarification and training may be needed (450 patient records). This was considered a sufficient number for reviewers to learn where discordant interpretations might happen and to develop consensus for frequently encountered harms. A final decision will be made by consensus. The blinded reviews will occur early in the study to ensure consistency between reviewers. GP investigators will be randomly allocated patient records to complete from any study practice, excluding practices from localities where the GP investigator has recently or currently worked.

Reviewers' free-text notes describing patient harms will be coded by the principal investigator (SMD) and the GP coordinator (SL) using the international clinically validated Medical Dictionary for Regulatory Activities (MedDRA) 18.0. This dictionary was chosen for its scope of classifications. SMD and SL will code all harms together, working collaboratively to obtain consensus.

Because most harms in the feasibility study were related to medications, and in order to assist a sensitivity analysis, a pharmacologist will rereview a randomly selected 5% of study records searching specifically for medicine-related harms that may have been missed by the GP investigators owing to their lack of specific expertise in pharmaceuticals use and toxicology.

Statistical Analysis

Survey data statistical analysis tools appropriate for the sampling design will be used by the study's biostatistician (AS) to analyze abstracted data. These are the "svy" group of tools in Stata. Sampling weights will be used to accommodate the study design features that allow, for example, a higher probability of selecting a larger practice into the sample but a lower probability of selecting a patient from large practices for records review. Probabilities of harm, harm types, harm severity, and harm preventability will be calculated overall and for each practice group. Rates will be calculated using as denominators all patients, consultations, medications, and other health care activities (such as surgery) relevant to each harm-related activity. The analysis will describe and adjust for patient characteristics and harm type. Other data (such as event dates) will be used to interpret harms in light of external events, to help reviewers understand the chronology of events, and to estimate probabilities of specific types of harm.

We will use a mixed model analysis (the "xtmixed" group of tools in Stata) to explore hypotheses relating to harm differences associated with rurality and size. Mixed effects modeling is also necessary to accommodate multiple harms (with multiple scores for preventability and severity) for some patients.

Ethics

Consent will be obtained from the general practices, not from individual patients. This research has been approved by the University of Otago human ethics committee (HD14/32). The Ngāi Tahu Research Consultation Committee has endorsed this research. As well as obtaining local ethics committee approval, we are seeking to have the researchers and participating practices protected by law, in the unlikely event our research reveals grievous malpractice. By the process set out in the Health Practitioners Competence Assurance Act 2003 [31], the Minister of Health will endorse the research as a protected Quality Assurance Activity, which protects the confidentiality of information and gives immunity from civil liability to people who carry out this research.

Results

Funding for the study has been obtained from the Health Research Council of New Zealand. We have enrolled 46 eligible general practices into the study and downloaded from these practices the electronic health records of 9078 patients. Records review is currently under way and the first results are expected to be submitted for publication in late 2017.

Discussion

Aspects of the Study

This study will address the lack of epidemiological knowledge of patient harms in general practice by a comprehensive analysis of general practice electronic health records. The random sampling of first practices and then patients within those practices means the results will be generalizable across New Zealand. Exclusion from the study of 3% of ineligible clinics and 20% of clinics with inaccessible patient data may bias the results. We will consider potential biases in interpretation of study results. The scope of the sample is broad enough to address concerns regarding selection bias, in terms of both patient numbers (9000) and study duration (3 years). Using clinically active GPs to review clinical records is a strength of the study. Concordance will be measured by double-blinded reviews. Coding will be reliable, as it will be done collaboratively by a clinically active GP who also has a reviewing role (SL) and a general practice researcher (SMD).

This study addresses an important gap in patient safety research, which to date has largely ignored harm occurring in general practice. It is powered to determine whether harms to patients systematically differ by rurality or by practice size, because this information will assist clinicians, organized general practice groups, and funding agencies to understand and ameliorate the specific safety risks of different types of general practice.

Perspectives

Information from the study will be of practical use to a wide variety of stakeholders. Patients will have new knowledge to inform decisions about treatment and type of practice to register in (with respect to size and location). The research will directly affect clinical decisions in general practices by alerting clinicians to the types of common and preventable patient harm likely in their specific type of practice (small, medium-sized, or large, and urban or rural). In addition, it will provide information at policy and organization levels. For example, it will inform public health safety agencies about the medicines commonly causing harm in the community (influencing decisions on their educational foci) and it will provide information to government and primary care groups about the relative safety of large and small practices, which may influence policy decisions regarding practice mergers.

Practical Applications From Study Results

Based in general practice, but including harm from other settings referenced in general practice records, this research will provide an epidemiological base to a general practice patient safety trigger tool that will help health care become safer for patients. Triggers are circumstances associated with a higher likelihood of preventable harm than other health care situations. Trigger tools are used as a focused way of measuring care safety improvements for particular groups of patients but can also be used as prompts to additional caution in patients with certain characteristics, which this study will identify. To be effective, triggers must be sensitive (capture most harm situations happening in general practices) and specific (so that GPs do not to have to spend time investigating situations seldom associated with harm). Widespread trigger tool use is the most likely way for GPs to identify remediable safety threats in their practices in the medium term and into the future, but in our feasibility study we found that only 20% of the harms identified from a random sample of records would have been identified by the NHS Trigger Tool: 80% of harms would not. We found that many existing triggers were neither sensitive nor specific and therefore of little practical use to New Zealand GPs.

The study's results will inform the development of triggers targeted to the most common and severe harmful situations patients experience in general practice. Although trigger tools are already recommended and used in several countries [32-34], they have typically not been grounded in epidemiological research. Instead, they have been based on opinions of high-risk areas of practice [32], so they may not be targeting the most problematic areas of practice. This is becoming apparent in hospital-based research [35] and is reflected in the results of our feasibility study. Protecting patients from health care–associated harm is important, and we intend for this study to advance that objective in general practice.

Conclusions

Harm may be a good signal of overall quality of primary care, but further research is needed before this can be stated with confidence. In most general practices, there is no capacity for the managerial oversight or complex investigations that feature in hospital-based systems to protect patient safety. To date, general practice in New Zealand has largely been excused from engagement in the patient safety agenda because of beliefs that the frequency of serious harms in general practice is low. The proposed research will objectively test this belief, find out what harms primary care patients experience, and use the results to develop strategies for reducing serious and common harms to patients. This is the first step to addressing patient safety in the setting where most people receive most of their health care and, perhaps, improve quality.

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Authors' Contributions

SMD is the Principal Investigator, who conceived the study and undertook its design and coordination. SL is the clinical coordinator and a reviewer for the study. SMD and SL wrote the first draft of the manuscript. KAW, KSE, WKC, MIW, SL, AWM, MWT, and DMR are the clinical reviewers and contributed to the final manuscript. AS provided biostatistical advice. JEH coordinated software development and will provide data management for the project. All authors participated in the development of the study methodology and reviewed the manuscript.

Conflicts of Interest

MWT is the CEO of BPAC Clinical Solutions, which provided IT support for this study.

Multimedia Appendix 1

Funding peer review report: Health Research Council of New Zealand.

[PDF File (Adobe PDF File), 609KB - resprot_v6i1e10_app1.pdf]

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Abbreviations

GP: general practitioner
MedDRA: Medical Dictionary for Regulatory Activities
NHI: National Health Index

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Protocol

Assessing the Efficacy of an App-Based Method of Family Planning: The Dot Study Protocol

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This is a corrected version. See correction statement: http://www.researchprotocols.org/2018/3/e9/

Abstract

Background: Some 222 million women worldwide have unmet needs for contraception; they want to avoid pregnancy, but are not using a contraceptive method, primarily because of concerns about side effects associated with most available methods. Expanding contraceptive options—particularly fertility awareness options that provide women with information about which days during their menstrual cycles they are likely to become pregnant if they have unprotected intercourse—has the potential to reduce unmet need. Making these methods available to women through their mobile phones can facilitate access. Indeed, many fertility awareness applications have been developed for smartphones, some of which are digital platforms for existing methods, requiring women to enter information about fertility signs such as basal body temperature and cervical secretions. Others are algorithms based on (unexplained) calculations of the fertile period of the menstrual cycle. Considering particularly this latter (largely untested) group, it is critical that these apps be subject to the same rigorous research as other contraceptive methods. Dynamic Optimal Timing, available via the Dot app as a free download for iPhone and Android devices, is one such method and the only one that has published the algorithm that forms its basis. It combines historical cycle data with a woman's own personal cycle history, continuing to accrue this information over time to identify her fertile period. While Dot has a theoretical failure rate of only 3 in 100 for preventing pregnancy with perfect use, its effectiveness in typical use has yet to be determined.

Objective: The study objective is to assess both perfect and typical use to determine the efficacy of the Dot app for pregnancy prevention.

Methods: To determine actual use efficacy, the Institute for Reproductive Health is partnering with Cycle Technologies, which developed the Dot app, to conduct a prospective efficacy trial, following 1200 women over the course of 13 menstrual cycles to assess pregnancy status over time. This paper outlines the protocol for this efficacy trial, following the Standard Protocol Items: Recommendations for Intervention Trials checklist, to provide an overview of the rationale, methodology, and analysis plan. Participants will be asked to provide daily sexual history data and periodically answer surveys administered through a call center or directly on their phone.

Results: Funding for the study was provided in 2013 under the United States Agency for International Development Fertility Awareness for Community Transformation project. Recruitment for the study will begin in January of 2017. The study is expected to last approximately 18 months, depending on recruitment. Findings on the study's primary outcomes are expected to be finalized by September 2018.

Conclusions: Reproducibility and transparency, important aspects of all research, are particularly critical in developing new approaches to research design. This protocol outlines the first study to prospectively test both the efficacy (correct use) and

effectiveness (actual use) of a pregnancy prevention app. This protocol and the processes it describes reflect the dynamic integration of mobile technologies, a call center, and Health Insurance Portability and Accountability Act–compliant study procedures. Future fertility app studies can build on our approaches to develop methodologies that can contribute to the evidence base around app-based methods of contraception.

ClinicalTrial: ClinicalTrials.gov NCT02833922; https://clinicaltrials.gov/ct2/show/NCT02833922 (Archived be WebCite at http://www.webcitation.org/6nDkr0e76)

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KEYWORDS

fertility; fertility awareness; family planning; contraception; natural family planning; reproductive health; mHealth; mobile health apps; study protocol

Introduction

Background

Current family planning options are not fully meeting the needs of women or men. Worldwide, some 222 million women want to avoid pregnancy but are not using family planning because of real or perceived side effects of methods or inaccurate perceptions of pregnancy risk at different points during their menstrual cycle or during breastfeeding [1]. The Family Planning 2020 (FP2020) goal of reaching 120 million additional women with family planning by 2020 is at its midpoint; new solutions to address unmet need are crucial to meeting this important milestone. Easy-to-use, affordable, fertility awareness-based methods, which can be made available through a variety of communication technologies, could fill a portion of this need.

Access to mobile phones, including smartphones, is increasing exponentially across the globe. According to the 2015 Ericsson Mobility Report, 2.6 billion people—25% of the world's population—currently have a smartphone. It is estimated that by 2020 6.1 billion people—70% of the world's population—will own a smartphone and that the vast majority (80%) of new smartphone subscriptions will come from Asia, the Pacific, the Middle East, and Africa [2]. In response to such large and diverse user bases, hundreds of thousands of smartphone apps have been developed and deployed, including more than 100,000 apps specifically focused on health issues [3]. Mobile phone apps have been shown to contribute to a range of positive health outcomes among people being treated for chronic conditions by providing information on frequently asked questions, reminders of appointments, medications, etc [4,5]. For family planning, smartphone apps also can provide timely information about specific contraceptive methods (how to use them, side effects, where to find services) and remind users about such actions as taking a pill or going for an injection [6].

However, fertility awareness-based methods, which require a woman to track her menstrual cycles and/or fertility symptoms but do not require a commodity or interaction with a provider, are the only methods that can be accessed entirely through a mobile app.

With these new technologies come new challenges. Currently, more than 1000 smartphone apps have been developed that focus on women's menstrual cycles. The majority of these apps are designed simply to track cycles or to assist in planning a pregnancy. Most are not appropriate for prevention of pregnancy, although, alarmingly, there is evidence that women are using these apps for this purpose [7].

It appears that many apps model cycle lengths with a normal distribution and then estimate the day of ovulation by fixing the luteal phase to be 13 or 14 days, with days around ovulation identified as fertile. There are a number of drawbacks to such an approach when used for pregnancy prevention. These normative models are insensitive to unusual cycle lengths and may be less accurate when few observations are available. There are additional problems with the assumption of the luteal phase length as constant, since from a biological perspective, this is untrue. Most importantly, this approach does not incorporate uncertainty inherent in estimating the day of ovulation.

There are few apps that are appropriate for pregnancy prevention. A recent study by Duane et al [8] found that only 6 apps that claimed to be appropriate for pregnancy prevention could correctly identify the fertile window. The majority of these accurate apps are simply electronic platforms for existing, scientifically validated fertility awareness methods (FAMs), such as the sympto-thermal method or the Creighton-Billings method. For users of these methods, apps can represent a helpful mechanism allowing for quicker, more immediate entry of events (such as cervical secretions and basal body temperature) and may allow for data aggregation over time. However, because the majority of these methods are reliant on user interpretation, use of such apps is recommended in conjunction with appropriate training by a facilitator certified in a particular FAM method.

A very small number of apps make claims as stand-alone methods of contraception that essentially live within the app itself. These apps combine women's personal fertility data (eg, period start date, basal body temperature) with proprietary algorithms in order to estimate times of high and low fertility within the menstrual cycle. Thus far, the existing literature on these apps has been limited to 3 studies.

The first study, assessing algorithm development and theoretical efficacy, was conducted on the Dot app in conjunction with the app developer, Cycle Technologies. The Dynamic Optimal Timing (DOT) algorithm for the Dot app was developed as a method of family planning that could be deployed on a mobile app platform without the need for any other assistive technology such as a basal body temperature thermometer. DOT's predictions are based on Bayesian statistical calculations using

pooled datasets of approximately 9000 cycles from several fertility studies to identify a woman's fertile window [9]. Using the Dot app, women only need to record their first day of menses each cycle. When a woman downloads the app, she indicates whether she is using it to avoid pregnancy, achieve pregnancy, or simply track her cycles. The information the app provides her depends on her purpose for using it. For women who are avoiding pregnancy, Dot flags high risk days as those days with estimated probabilities of pregnancy above 1% to 2.25%, depending on the number of cycles she has entered [9]. As more data are collected, DOT appropriately updates these estimates, modifying her fertile window using her personalized cycle history. A description of the approach and an estimate of its efficacy (which found an estimated failure rate of less than 3 pregnancies per 100 women years of exposure with correct use) was published in 2016 [9]. The authors point to the need for a prospective study to determine actual perfect and typical use efficacy for pregnancy avoidance.

The other 2 studies were conducted on the Natural Cycles mobile app. Natural Cycles, which uses a proprietary algorithm described as being based on quantum physics, calculates fertility using basal body temperature (taken by the user on an external thermometer) and date of menstruation. The investigators found a 0.05% probability that the app would provide a false safe "green" and calculated typical use Pearl Index rate at 7 per 100 women years in a retrospective study [10]. As the authors acknowledge, the study was limited by its design, short time-frame, incomplete information about sexual intercourse frequency, and inability to verify all data entered into the app [10], reflecting the complexities of conducting an efficacy study on an app-based contraceptive method.

As more app-based methods debut in the mobile health, or mHealth, world, there is a growing need to establish standards of practice by which these methods can be evaluated. Prospective trials, which follow women over time to establish perfect and typical use rates, have long been the gold standard of contraceptive development [11]. However, unlike contraceptive devices or pills, app-based methods pose new opportunities and challenges in conducting such trials. Mobile technology expands opportunities to collect data in real time, potentially increasing the accuracy of self-report. Additionally, recruitment for efficacy trials using mobile technology can potentially capture broader geographies, as anyone who uses a particular mobile device could potentially be recruited, which may result in increased generalizability of study results. However, the challenges of identifying, recruiting, and retaining participant populations through mobile studies are well documented in the mHealth literature [12-15]. Challenges may be exacerbated when the study subject matter is around sensitive information such as sexual activity.

This paper details the protocol of a study assessing the effectiveness and efficacy of the Dot app in preventing pregnancy in reproductive-aged women in the United States. This trial is unique for several reasons. First, it is the first prospective efficacy trial conducted on an app-based method of family planning. Secondly, the deployment of this trial involves the development of a research enhancement to the app itself, which is activated when participants are consented into the study. Finally, the majority of data, including study-specific sexual activity and survey data, are collected through the app. In sharing this protocol, we attempt to outline our efforts to capitalize on some of the opportunities and address some of the challenges of conducting research via mobile apps. Our interest is to provide ongoing information about the development of this study, enhance transparency, and increase communication and dissemination around best practices for mobile research.

Aims and Objectives

The aim of this efficacy study is to assess the Dot app as a new method of app-based contraception. The objectives for this study include (1) obtaining perfect and typical use pregnancy rates for users of Dot; (2) understanding how user interaction with the method is influenced by aspects such as demographics, social support, relationship support, and fertility awareness; and (3) assessing user preferences and best practices for conducting mobile contraceptive research.

Methods

Overview

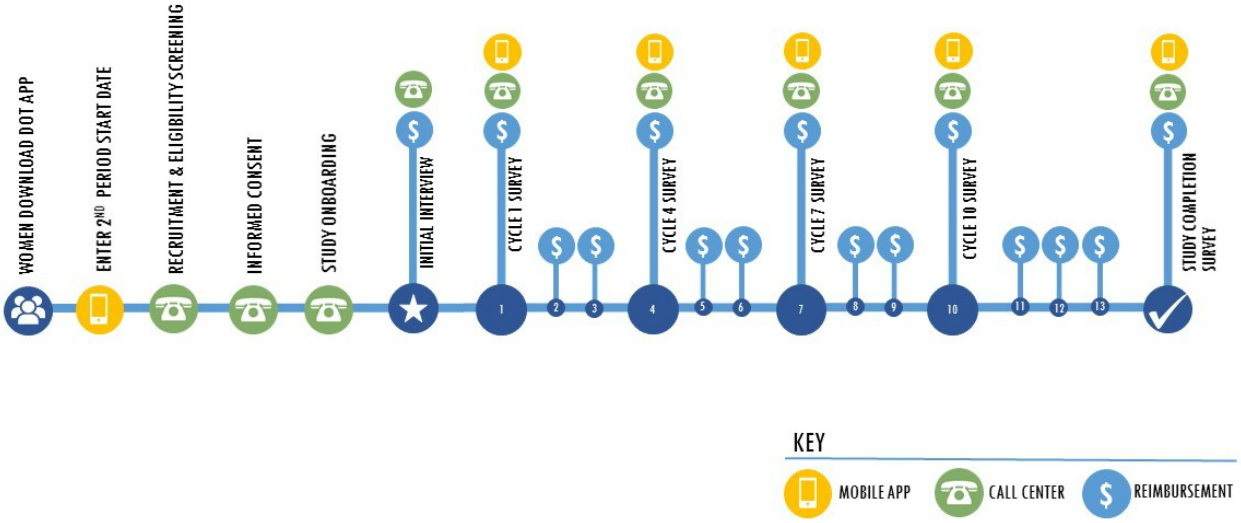
The format of this efficacy protocol adheres to Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines [16].

This prospective, longitudinal, nonrandomized trial will be conducted on a cohort of women in the United States who download Dot on their Android phones with the objective of preventing pregnancy. While we would have preferred a randomized design, this was not possible. There is no other app with an established efficacy to which we could make reasonable comparison, either because no such study has been done or because behavioral components of using other apps are different from using Dot in ways that are likely to affect the characteristics of users and study retention. Even the CycleBeads app, which requires the same user inputs as the Dot app (period start date), is only appropriate for women with a more restricted cycle length range and variability. Thus, we are conducting a nonrandomized study. This study received ethical approval from the Georgetown University's Institutional Review Board in May 2016 and is registered at ClinicalTrials.gov (NCT02833922).

In all other respects, we followed the Trussell and Kost guidelines for contraceptive efficacy studies [11]. Data collection, participant enrollment, and pregnancy definition are all influenced by their recommendations. Their guidelines also affect the way we will analyze the data, assessing both perfect and typical use, using life-table analysis (in additional to establishing a Pearl index), and observing women for up to 13 cycles of use. The approach has been adapted to meet the requirements of an app-based fertility awareness method. As there is virtually no experience conducting an app-based efficacy study for a method women access on their own prior to being recruited for the study, we will also attempt to minimize loss to follow-up by engaging women over time via the app and through communication with a call center. We will count pregnancies as reported by the woman, inquiring about her pregnancy status as soon as she fails to enter her period start date at the expected time to minimize undercounting

pregnancies. Pregnancy results will be reported via a completed home pregnancy test kit, provided by mail, to the study team by women who believe they are or might be pregnant. While ideally we would enter women into the study the day they begin using Dot, it is not possible logistically, due to the structure of the app (a woman can download and begin using Dot on any day of her cycle by entering the day her most recent period started).Because they need to enter the study at the beginning of a cycle (to ensure they are not pregnant prior to entering the study and to obtain a complete history of sexual intercourse throughout the cycle), women will be recruited when they enter their second period start date. A brief visual illustration of the study timeline can be seen in Figure 1.

Figure 1. Dot study timeline.



Recruitment

Study participants will be initially recruited from the pool of women who choose to download the app to an Android phone to prevent pregnancy, as determined when they select “prevent pregnancy” as their mode of use. Upon the entry of their second period start date, women who have chosen to use Dot for pregnancy prevention will receive a pop-up message within the Dot app notifying them of the study and asking them if they are interested in participating.

Eligibility Criteria

To be eligible to use the app to prevent pregnancy, participants must meet the following criteria:

- Self-reported usual cycle length of 20 to 40 days with less than 10 days variation
- Have not used hormonal contraceptives during their 3 most recent cycles

To be eligible for the study, participants must, in addition to meeting the Dot eligibility criteria

- Be between the ages of 18 and 39 years at the time of admission and live in the United States
- Be potentially at risk of pregnancy (ie, sexually active with a male partner)
- Be willing to install a password or biometric protection on their app for security purposes

Breastfeeding women can be admitted into the study upon meeting all other criteria if they have delivered at least 6 months ago and had at least 3 menstrual cycles postpartum. Women who do not meet one or more of these criteria will be excluded from the study.

Screening

Upon receiving the initial recruitment message, users who are interested in participating will be provided with a prescreening questionnaire within the app. If women meet these prescreening criteria, they will be contacted by a call center representative, who will conduct a full eligibility screening.

Consent

The call center study representative will review the informed consent document with potential participants. Women will also have the informed consent document available on their phones. Upon reviewing the consent, women will be asked to verbally consent and to electronically consent via the app.

Study Onboarding

Women who are consented into the study will be informed that the research enhancement component of the app will be activated on their phone. Study staff will review data collection processes and will collect some baseline demographic data from the study participant. This will allow us to begin building a profile of our study population and to analyze the data to highlight similarities and differences among participants with different characteristics.

Data Collection Methods

As part of the study, participants will be asked to provide daily sexual history information (whether they had intercourse on a particular day and if so, whether they also used a barrier method or emergency contraception) and their period start dates. They also will be asked to complete 4 brief surveys that will be distributed throughout the course of the study. Sexual history and period start date information will be collected exclusively through the app, but participants will have the choice to

self-complete the surveys within the app or to be contacted by a study representative who can administer them.

Exit Procedures

There are several circumstances under which participants may be exited from the study. Women whose cycles no longer meet the necessary criteria to use Dot (eg, experience short [<20 days], long [>40 days], or highly variable cycle lengths) will be exited from the study. Women who no longer wish to participate in the study or to use Dot will also be exited. Upon exiting the study, the research enhancement feature in the app will be disabled and all study elements removed. Participants will retain all cycle history data that they have entered into the app while participating in the study.

Pregnancy Procedures

On the 41st day of a cycle, participants who have not yet entered a new period start date will receive a pop-up within the app asking them to either (1) enter a new date, (2) confirm that they are experiencing a long cycle, (3) confirm that they no longer wish to participate in the study, or (4) confirm that they think they may be pregnant. If a participant believes she might be pregnant, she will be directed to contact the study representative within 48 hours. Study representatives will send 2 (EPT brand) pregnancy tests to participants to confirm pregnancy. If the first pregnancy test is negative, participants will be instructed to wait an additional 5 days and take the second pregnancy test. Both pregnancy tests will be sent back to the study center in a prepaid mailing envelope for confirmation, and women will be exited from the study. Alternately, women can also contact the study representative if they had unprotected sex and believe they might be pregnant, which will again trigger the pregnancy exit protocol.

Outcome Measures

Pregnancy status is the primary outcome measure. Because the study intends to provide both a perfect use and typical use failure rate, it is critical that for all pregnancies we determine whether it occurred as a result of intercourse on a day Dot identifies as fertile or infertile and if the intercourse resulting in pregnancy was protected (by use of a barrier method) or unprotected. We will review the intercourse data entered by the participant for the cycle in which pregnancy occurred and annotate pregnancies as resulting from (1) unprotected intercourse on a day Dot identified as fertile, (2) unprotected intercourse on a day Dot identified as nonfertile with no intercourse or only protected intercourse on a day identified as fertile, (3) protected intercourse on a day Dot identified as fertile with no intercourse on an identified fertile day, or (4) protected intercourse on a day Dot identified as nonfertile with no intercourse on a day identified as fertile. While there is a small possibility that pregnancy could result from protected or unprotected intercourse on a nonfertile day in a cycle with only protected intercourse on a fertile day, it is not possible to determine with the data we will be able to collect for this study.

The main secondary outcome is discontinuation of use of the Dot app for pregnancy prevention (to become pregnant, because participants are no longer sexually active, or because they prefer another method of family planning) or discontinuation from the study (because their cycle length is outside the range or variability covered by Dot, they chooses to leave the study, or they are lost to follow-up).

Data Management, Forms, Entry, Transmission, and Editing

The technical architecture for the Dot study will use cloud services provided by Amazon Web Service (AWS). The Institute for Reproductive Health (IRH) technical solution will be hosted within the northern Virginia region, as it is one of the largest AWS regions, as well as within the same geographical area as Georgetown University and the IRH offices. AWS provides a simple and streamlined way to access servers, storage, and databases over the Internet. There are no physical study site locations where participants will interact with study staff; study data will be collected through the app transmitted via transport layer security (TLS) and encrypted and stored in AWS DynamoDB, which is a scalable, highly available storage solution from AWS. Figure 2 illustrates the cloud-based architecture which will be used to collect and host research data. Furthermore, range checks along with a data dictionary will be used to enforce the integrity of the data. Participants will be able to modify their daily sexual history and period start date data within the current menstrual cycle. Once the menstrual cycle has been completed, the data will be considered locked for the study purposes.

Data Discrepancy Inquiries and Reports

Data will be reviewed periodically and checked for consistency and to identify any missing data. A number of standard analytic reports on various aspects, such as recruitment, study status, survey completion, and other relevant data points, will be developed and run through the system throughout the duration of the study.

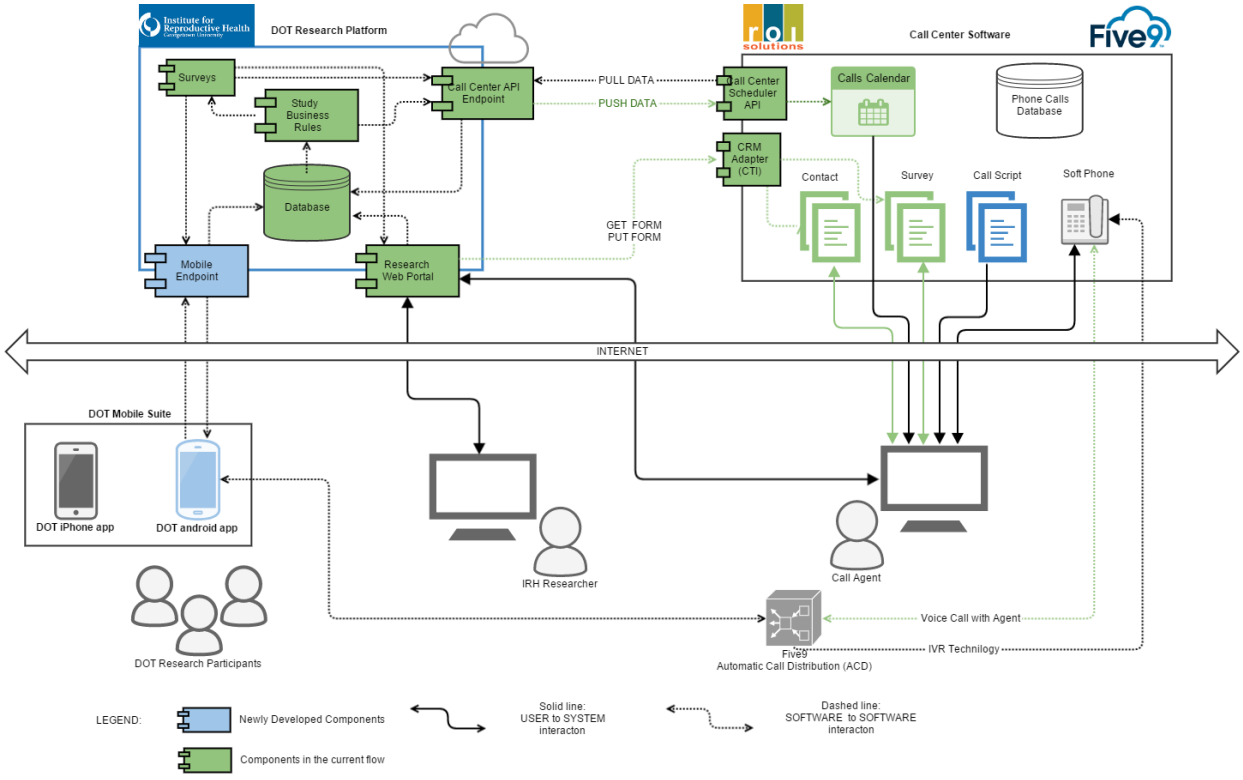
Security and Backup

All data in transit will be secured by https/TLS. Data at rest will be secured using a variety of encryption methods, including Amazon Elastic Block Store encryption and Relational Database Service encryption. The AWS ecosystem consists of distributed and fully redundant data centers strategically located throughout the United States. The AWS storage solution will deliver highly scalable and reliable cloud storage for backup and recovery. Data backups have been configured based on the research design and information needs; however they will be performed using a combination of incremental and full backups.

Description of Hardware

Each computer is configured per Georgetown University's university information system security standards with passwords settings, secure imaging, and computer firewall software. The desktop systems are Dell Latitudes E5470/E7250 and Lenovo X1 Carbon Thinkpads operating on a Windows 7 enterprise. Symantec Endpoint protection and Malwarebytes Anti-Malware Premiums will be used as the main personal computer anti-virus software.

Figure 2. Illustration of cloud-based architecture for the Dot study.



Confidentiality

Several steps will be taken throughout the course of the study to ensure participant confidentiality. Women who agree to participate must agree to set a passcode for the app so that the app and study data are protected. All study data will be pushed, pulled, and stored in accordance with or exceeding Health Insurance Portability and Accountability Act compliance standards set forth by Georgetown University.

Sample Size

Our estimated sample size, given 80% power, 95% confidence levels, and an assumed relative risk of 3, is 432 participants [17]. However, our sample size decision-making was also influenced by considerations for study attrition, which is a significant concern in longitudinal, web-based research [10,18]. We factored in previously identified variables negatively affecting attrition, such as marital status [19], younger-aged study participants [20], and research on a mobile platform [21], which are known attributes of our proposed research cohort. Given these factors, we see a need to enroll a significantly larger number of women to ensure that a sufficient number of women complete 13 cycles of study participation and to allow for the calculation of valid efficacy and effectiveness rates. Based on the rate of discontinuation in the Standard Days Method efficacy study (54.4%) and the higher potential for attrition in this particular study, we plan to overpower the proposed study by recruiting up to 2000 women and enrolling 1200 women. Quarterly, the IRH study team will evaluate the discontinuation rate and determine whether new or additional recruitment efforts for the study will be deployed [22]. We will also examine characteristics of participants who exit our study to identify potential threats to external and internal study validity.

Outcome Analyses

To address questions related to efficacy/effectiveness, we will use a prospective, single-arm design following women from their first full cycle of Dot use, as identified when women enter the start of their second period and continuing for up to 13 cycles (14th period start date). We will apply single-decrement multicensoring life tables to calculate Dot efficacy (probability of nonpregnancy status) and rates of continuation (women-months of method use). Censoring cycles will facilitate the use of more cycles in outcome analysis, while accounting for issues of missing data or loss to follow-up [23].

Dot efficacy will be assessed by typical use (correct plus incorrect use resulting in pregnancy) and method failure (correct use resulting in pregnancy) pregnancy rates. The unit of analysis will be the cycle and pregnancies recorded by cycle of Dot use. Both life tables and a Pearl Index (number of pregnancies per 100 women-years) will be calculated. A 95% CI will be calculated and the SE computed [24,25].

Women's cycles will be censored if

- They choose to discontinue from the study or are lost to follow up
- They report an experience that restricts their provision of data (eg, loss of cell phone, moving to an area with no coverage)

Periodically, we will examine the pattern of discontinuation and censored data to identify potential biases in study participation. In accordance with standard life table analyses assumptions, we will assume that there are no changes in participation over time, that data are simply missing, that the experience of individuals who are lost to follow-up is the same

as the experience of those who are followed, and that both pregnancy and study discontinuation of the participants occurs uniformly within the interval [26].

A series of descriptive statistics will be calculated to contextualize the questions outlined above regarding user profiles, ability to correctly use the method and the app, previous method use, and user satisfaction.

Results

Funding for the study was provided in 2013 under the United States Agency for International Development (USAID) Fertility Awareness for Community Transformation (FACT) project. Recruitment for the study will begin in January 2017. The study is expected to last approximately 18 months, depending on recruitment. Findings on the study's primary outcomes are expected to be finalized by September 2018.

Discussion

The main aims of the Dot efficacy study are to estimate the efficacy and effectiveness of the Dot app for pregnancy prevention. The findings from this trial will represent the first prospective efficacy trial conducted on an app-based method of family planning. This is an essential step in developing a research base to support the use of these methods as part of the existing contraceptive method mix and identifying lessons for establishing best practices to guide future research on similar apps. A stronger evidence base for fertility awareness apps will serve both the global family planning community and consumers who wish to use these methods but have little concrete information on their efficacy.

In addition to our main objectives, our study will also attempt to answer additional questions around several relevant topics to both reproductive health and to mHealth research. The real-time nature of data collection methods via mobile phone can contribute to ongoing research questions about fertility awareness methods in general, including important questions around sexual activity decisions during the fertile time, changes in couple communication over the course of fertility awareness method use, and changing reproductive goals. Additionally, we intend to assess several components of mHealth research more broadly, specifically around participant recruitment and retention questions such as research participant engagement, gamification of research, and data questions, such as which methods of data collection participants prefer (phone/instant messaging/in-app surveys). Our findings will contribute to the broader mHealth research agenda assessing these important questions.

Our study involves the creation of a supplemental research enhancement that overlays and is activated within an existing commercial app. Collaboration between research institutes and commercial app developers represents a potentially exciting opportunity in mHealth. Yet, such collaborations require significant deliberations around how to develop and implement quality research studies in a way that maintains app fidelity and doesn't inhibit user experience. We anticipate that our experiences and findings will also provide insights into the opportunities and challenges of collaboration and can provide recommendations for future research/developer partnerships.

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Authors' Contributions

VJ and DS developed the study upon which this paper is based. VJ, DS, and RS all contributed to the institutional review board–approved study protocol upon which this paper is based. DS developed the initial analytic approach and sample size calculations. All authors contributed to the writing and editing of this manuscript.

Conflicts of Interest

The product under investigation (the Dynamic Optional Timing [DOT] app) is the property of Cycle Technologies, Inc, a for-profit corporation based in Washington, DC. The CEO of Cycle Technologies is Leslie Heyer (née Jennings), who is the daughter of Victoria Jennings, one of the co-authors of this article. The efficacy study on DOT uses funds from a research grant awarded to the Institute for Reproductive Health at Georgetown. Cycle Technologies Inc or their employees do not receive any licensing fees, honoraria, or financial contributions related to the study.

Multimedia Appendix 1

CONSORT-EHEALTH checklist V1.6.2 [27].

[PDF File (Adobe PDF File), 523KB - resprot_v6i1e5_app1.pdf]

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Abbreviations

AWS: Amazon Web Service
DOT: Dynamic Optimal Timing
FACT: Fertility Awareness for Community Transformation
FAM: fertility awareness method
FP2020: Family Planning 2020
IRH: Institute for Reproductive Health
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
TLS: transport layer security
USAID: United States Agency for International Development

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Protocol

Pre-Exposure Prophylaxis (PrEP) as an Additional Tool for HIV Prevention Among Men Who Have Sex With Men in Belgium: The Be-PrEP-ared Study Protocol

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is a promising and effective tool to prevent HIV. With the approval of Truvada as daily PrEP by the European Commission in August 2016, individual European Member states prepare themselves for PrEP implementation following the examples of France and Norway. However, context-specific data to guide optimal implementation is currently lacking.

Objective: With this demonstration project we evaluate whether daily and event-driven PrEP, provided within a comprehensive prevention package, is a feasible and acceptable additional prevention tool for men who have sex with men (MSM) at high risk of acquiring HIV in Belgium. The study's primary objective is to document the uptake, acceptability, and adherence to both daily and event-driven PrEP, while several secondary objectives have been formulated including impact of PrEP use on sexual behavior.

Methods: The Be-PrEP-ared study is a phase 3, single-site, open-label prospective cohort study with a large social science component embedded in the trial. A total of 200 participants choose between daily or event-driven PrEP use and may switch, discontinue, or restart their regimen at the 3-monthly visits for a duration of 18 months. Data are collected on several platforms: an electronic case report form, a Web-based tool where participants register their sexual behavior and pill use, a more detailed electronic self-administered questionnaire completed during study visits on a tablet computer, and in-depth interviews among a selected sample of participants. To answer the primary objective, the recruitment rate, (un)safe sex behavior during the last 6 months, percentage of reported intention to use PrEP in the future, retention rates in different regimens, and attitudes towards PrEP use will be analyzed. Adherence will be monitored using self-reported adherence, pill count, tenofovir drug levels in blood samples, and the perceived skills to adhere.

Results: All participants are currently enrolled, and the last study visit is planned to take place around Q3 2018.

Conclusions: As PrEP is not yet available in Belgium for use, this study will provide insights into how to optimally implement PrEP within the current health care provision and will shape national and European guidelines with regard to the place of PrEP in HIV prevention strategies.

ClinicalTrial: EU Clinical Trial 2015-000054-37; https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000054-37/BE (Archived by WebCite at http://www.webcitation.org/6nacjSdmM).

(JMIR Res Protoc 2017;6(1):e11) doi:10.2196/resprot.6767

KEYWORDS

pre-exposure prophylaxis; HIV prevention; MSM; Belgium; daily; event-driven; demonstration project; acceptability; adherence

Introduction

Pre-exposure prophylaxis (PrEP) using Truvada (emtricitabine/tenofovir disoproxil fumarate) is a promising addition to the field of HIV prevention. Several clinical trials among men who have sex with men (MSM) at high risk of HIV infection have shown that daily PrEP is effective in preventing HIV when taken correctly [1-3]. Within the European context, the UK-based PROUD clinical trial examined daily use, whereas the French Ipergay study tested event-driven PrEP (ie, on demand, before and after anticipated sex). Both trials yielded significant protection effects (86% reduction in incident HIV) [4,5], showing that PrEP is a very promising tool to prevent HIV within this high-risk population.

Daily Truvada use for PrEP was approved by the Food and Drug Administration (FDA) in the United States as early as July 2012 [6]. As of September 2015, the World Health Organization (WHO) recommended that people at substantial risk of HIV infection should be offered PrEP as part of combination prevention approaches [7]. The European HIV prevention landscape is also changing rapidly. In November 2015, daily and event-driven Truvada as PrEP, in combination with safer sex practices, was approved in France [8]. After recommendation by the European Medicines Agency (EMA), the European Commission approved once-daily Truvada as PrEP in combination with safer sex practices in August 2016 [9,10]. Norway joined France by providing PrEP free of charge to at-risk groups in October 2016, and the United Kingdom will make PrEP available in the context of a large clinical study in mid-2017 [11,12]. While European PrEP guidelines are available, they provide little detail and remain general, and large-scale implementation guidelines are lacking [13]. Therefore context-specific experiences with PrEP delivery that can help to shape appropriate recommendations are urgently needed.

The number of MSM in Belgium is estimated to be around 106,000, which is 4.2% of the total male population [14]. As in many western European countries, MSM represent a high-risk population for both HIV and other sexually transmitted infections (STIs) including gonorrhea, syphilis, and chlamydia infection. In 2013, 61% of all registered STIs in men in Belgium were reported among MSM (sentinel surveillance) [15]. Since 2002, there is a trend of increasing numbers of new HIV infections among MSM, who represented 50% of the 1001 newly registered HIV infections in Belgium in 2015 [16]. A venue-based, cross-sectional study was conducted in 2009-2010 among 649 MSM in 2 Flemish cities in Belgium, Antwerp and Ghent, and revealed HIV prevalences as high as 14.5% in cruising venues to 4.9% in more general gay venues to 1.4% at younger MSM venues [17].

PrEP is a potential game-changer for the HIV epidemic among MSM in Western Europe including Belgium, but little is known about how PrEP will be used and how different regimens will influence sexual behavior and lifestyles of MSM.

The overall aim of this study is to provide the necessary data to shape Belgian and European guidelines with regard to the place of PrEP in strengthening HIV prevention. To this end, the following primary and secondary study objectives have been formulated.

The primary study objectives are as follows:

- To document the current preventive needs of MSM at high risk of acquiring HIV, including the uptake, acceptability, and feasibility of using PrEP daily or event-driven
- To evaluate adherence to the 2 different PrEP regimens

The secondary objectives can be found in Textbox 1.

Textbox 1. Secondary objectives of the Be-PrEP-ared study.

- To study the impact of pre-exposure prophylaxis (PrEP) use on other preventive strategies such as condom use
- To study the impact of PrEP use on sexually transmitted infection (STI) trends
- To study the safety of daily and event-driven use of PrEP
- To document real-life effectiveness of PrEP use on HIV seroconversion and treatment-related resistance
- To evaluate the feasibility of 3-monthly HIV testing using oral fluid self-sampling testing

Methods

Study Design

The Be-PrEP-ared project is a single-site, open-label prospective cohort study with a nested qualitative component. It takes place in the HIV/STI clinic of the Institute of Tropical Medicine (ITM), Antwerp, Belgium. A total of 200 MSM at high risk of acquiring HIV were enrolled and are being followed up for 18 months, with 3-monthly follow-up (FU) visits. Truvada is being provided to them as part of a comprehensive HIV prevention

package including regular HIV/STI testing and basic adherence and sexual health counseling.

Participants

Eligibility is assessed using the inclusion and exclusion criteria as shown in Textbox 2.

Textbox 2. Selection criteria of the Be-PrEP-ared study.

Inclusion criteria:

- Able and willing to provide written informed consent
- Born to male sex (including transgender females)
- Aged 18 years or more
- Had sex with a man in the last 12 months
- HIV negative (confirmed at enrollment)
- Reporting at least 1 criterion for high risk:
  - Condomless anal intercourse in the last 6 months with a casual partner with unknown HIV status or HIV positive status
  - A sexually transmitted infection episode in the last 6 months
  - Having taken post-exposure prophylaxis in the last 6 months
- Able and willing to participate in the project as required by the protocol for 18 months
- Motivated to strengthen prevention efforts, including willingness in starting to use pre-exposure prophylaxis

Exclusion criteria:

- Having symptoms or clinical signs consistent with acute HIV infection
- Being allergic to the active substances or any of the excipients
- Having an estimated creatinine clearance of <60 mL/minute/1.73 m² according to the CKD-Epi formula (Chronic Kidney Disease Epidemiology Collaboration)
- Having an active hepatitis B infection
- Taking HIV post-exposure prophylaxis
- Participating in other clinical studies (phase I-III) or another research project related to HIV and antiretroviral therapy

Sample Size

Given the provided funding, we included 200 MSM at high risk of acquiring HIV. The sample size was determined to estimate the proportion of participants who are nonadherent. Using the normal approximation for the calculation of the 95% confidence interval and using the worst-case value for proportion of nonadherence of 0.5 with 200 participants, the proportion of nonadherence can be estimated to a precision of 7%.

Participant Recruitment

The project has been advertised by websites of various community-based gay and sexual health organizations and their respective social network sites and person-to-person promotion of the project. Referral to the project is also done by health care providers at the HIV/STI clinic at ITM. Potential participants were invited to preregister on the project website [18] where details about study participation were also provided. Registered candidates were then invited for a screening visit at the clinic in random order so that they were not invited in the same order as they registered with the exception of the last candidates, who were invited on a “first come first served” basis.

Investigational Product

Truvada is used for PrEP in this trial. One daily film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil fumarate.

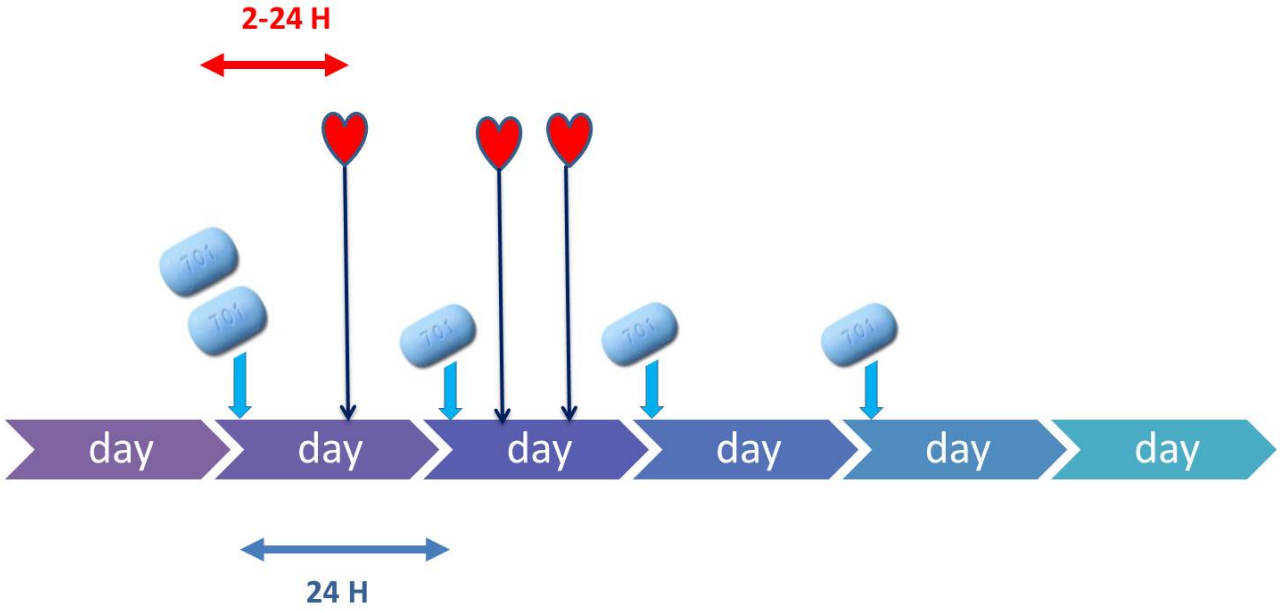
When eligible, participants can self-select between 2 different PrEP dosing regimens:

- A pill every 24 hours (further referred to as daily)
- Starting dose before anticipated sex and 1 pill daily during a sexual active episode (further referred to as event-driven). This is the regimen which has been described by the Ipergay protocol (Figure 1) [4]:
  - A dose of 2 pills between 2 and 24 hours before having sex (or 1 pill if the most recent dose was taken between 1 and 6 days ago)
  - A tablet of Truvada every 24 hours (starting when the first 2 tablets are taken) during the period of sexual activity including after the last sexual intercourse
  - Finally, a last dose of 1 tablet of Truvada approximately 24 hours later
  - Tablets need to be taken every 24 hours with a window period of 2 hours before or after the scheduled time.

All participants, irrespective of their regimen, can opt to switch regimen and to discontinue or to (re)start using PrEP at every

FU visit at the HIV/STI clinic at ITM. Before being given a new supply, the participant must be confirmed to be HIV negative using HIV point-of-care tests.

Figure 1. Event-driven scheme (adapted from the Ipergay protocol).



Study Visits

All participants are followed up for 18 months and will undergo a total of 9 prescheduled visits corresponding to screening, enrollment, FU month 1, and 6 3-monthly FU visits. During every prescheduled visit, participants see a social scientist (or social science assistant), a study nurse, and a physician.

Table 1 summarizes the study procedures. At the screening visit after written informed consent is obtained, study staff collects data on basic sociodemographics and current sexual behavior with special attention to high risk criteria (see Textbox 2); performs a physical examination with special attention to symptoms of an acute HIV infection; collects blood, urine, anal, and pharyngeal samples for kidney, liver, HIV, and STI testing; and performs preventive counseling.

The participant is invited to come back to the clinic within 2 weeks to confirm eligibility, including a reassessment of symptoms of acute HIV infection, relevant medical history, and current medication and recreational drug use. When eligible, the participant receives 1 box of 30 Truvada tablets, and the different PrEP regimens are discussed. Detailed information on PrEP use, adherence counseling, and preventive sexual health counseling is provided. Study staff explains the use of an online diary to collect data on sexual activity and adherence throughout study participation. The participant is also instructed to complete a self-administered questionnaire on a tablet computer.

At every follow-up visit, adverse events and concomitant medication are documented and a physical examination and HIV testing are performed. In addition, participants are screened for STIs every 3 months. Oral fluid samples are taken every 3 months using the Intercept i2 collection device (OraSure Technologies Inc) for future HIV testing. PrEP-related toxicity is monitored, adherence and prevention counseling is provided, and PrEP use is discussed. The participant takes the leftover Truvada back to the clinic and gets a refill to cover the needs until the next visit, with a maximum of 90 tablets. Intra- and extracellular drug level assessment of tenofovir or tenofovir diphosphate is performed at month 1 and month 3. Afterward, drug level monitoring will only take place for a proportion of daily users and some interesting event-driven users at the end of the study.

At FU month 15, specific counseling will address the impact of discontinuing PrEP use and will support participants in developing personal risk reduction solutions, since PrEP may not be available and reimbursed after individual completion of the study.

Different methods are being used to measure adherence: online diary, pill counts, questionnaire, and drug level assessment. Results of these measurements will be triangulated to assess adherence. When a participant is diagnosed with an STI, treatment will be given according to national guidelines.

Table 1. Schedule of assessments.

Procedures	Screening (1-2 weeks prior)	Enrollment (day 0)	FU[a] month 1	FU month 3, 6, 9, 12, 15	FU month 18
Informed consent	X				
Relevant medical history		X			
Current/concomitant medication		X	X	X	X
Adverse events			X	X	X
Diary collection			X	X	X
HIV rapid test	X		X	X	X
HIV antigen test	X		X	X	X
Syphilis	X			X	X
HSV-2[b]	X			X[c]	X[d]
Hepatitis B	X				X
Hepatitis C	X			X[c]	X[d]
Creatinine	X			X	X
Phosphate	X				X
ALT/AST[e]	X				X
Proteinuria	X			X	X
CT/NG/MG/TV[f] (urine)	X			X	X
Anorectal and pharyngeal swab for CT/NG/MG/TV	X			X	X
Oral fluid collection				X	X
Drug level testing (blood/hair)			X	X	X
Provide Truvada		X	X	X	
IDI[g] (subsample of men)			X	X[h]	X
Questionnaire		X	X	X	X
Preventive sexual health counseling	X	X	X	X	X
Adherence counseling		X	X	X	X

[a]FU: follow-up.

[b]HSV-2: herpes simplex-2 virus.

[c]Will only be done using a look-back procedure when the final visit is positive to determine the time of infection more accurately, if funding permits.

[d]Only when screening visit result was negative.

[e]ALT/AST: alanine transaminase/aspartate transaminase.

[f]CT/NG/MG/TV: *Chlamydia trachomatis* / *Neisseria gonorrhoeae* / *Mycoplasma genitalium* / *Trichomonas vaginalis*.

[g]IDI: in-depth interview.

[h]Only month 9.

Online Diary

The participant is asked to complete an online diary with information regarding pill intake, number of rectal and oral sex acts, and an individual risk assessment of acquiring HIV for each day participated in the study. A Web platform is created where participants can log in with a personal account using their smartphone, laptop, or other devices. They are instructed to complete the online diary every day or at least twice a week to limit recall bias. At every visit, and more clearly emphasized at the month 1 visit, the social scientist or designee examines all diaries for completion to allow for optimal data collection and verifies whether participants encountered problems or difficulties or unclear procedures when completing the online diary. Participants also receive an email when they have not completed their diary for more than 7 days. Event-driven users are able to complete the diary only during sexual active periods. In addition, a paper version is available if preferred. Finally, an audit trail is available.

Questionnaire

At the enrollment visit, a detailed electronic self-administered and standardized questionnaire collects data on sociodemographic characteristics, well-being, sexual lifestyle,

sexual behaviors, and determinants related to HIV risk, as well as motivations for (not) choosing either PrEP dosing regimen. It was based on similar questionnaires used in other PrEP studies or HIV prevention and sexual behavior research among MSM. The questionnaire was pilot-tested before study initiation among 7 MSM, and their suggestions were incorporated into the final version. It was translated and back-translated in 3 different languages: Dutch, French, and English. At the FU visits, a shortened version is used assessing adherence, recent sexual behavior, and reasons for switching PrEP dosing regimen if applicable. At FU month 9, a more comprehensive questionnaire is used reassessing several measures of the enrollment questionnaire (eg, well-being). At FU month 18, a questionnaire is used similar to FU month 9 that includes questions assessing participant experiences of and attitudes toward using and receiving PrEP, for which the content will be informed by the in-depth interviews (IDIs) and their experiences of study participation such as the collection of oral fluid for HIV testing.

In-Depth Interviews

To explore participant prevention needs, their preferences for and attitudes toward PrEP use (ie, regimen choice and decision making), user experiences, and perceived influences on their sex lives, 35 to 40 IDIs are conducted throughout the project. All interviews are conducted by a social scientist with expertise in qualitative research after obtaining informed consent. The data collection and analysis is guided by an inductive approach based on grounded theory [19,20]. The topic guide is developed within the study team and is amended where necessary to improve data collection and account for an iterative qualitative data collection approach without losing consistency [21]. Dutch- or English-speaking participants are purposely selected based on information-rich events (eg, switching PrEP regimen) and availability. Triangulating the results of the IDIs with other quantitative data from the trial will allow for improving validity of the overall study results.

Laboratory Procedures

Table 2 provides an overview of all laboratory tests that are performed in the study. All testing is performed at ITM except for drug level testing which is performed at the University Hospital of Gent, Belgium. Dry blood spots (DBS) are taken at every visit where blood is taken and stored together with oral fluid and hair samples (when consented) for future HIV testing or drug level testing.

Table 2. Be-PrEP-ared laboratory procedures.

To be tested	Kind of test
HIV	See Figure 2
Syphilis	RPR[a] (Macro-Vue, BD) and TPA (Vitros 5600) /TPPA[b] (Fujirebio)
Hepatitis B	HBsAg/HBsAb[c], HBcIg/HBcIgM[d] (Vitros 5600)
Hepatitis C	Antibody Hepatitis C (Vitros 5600)
Biochemistry: AST/ALT[e], creatinine, and phosphorus	Creatinine clearance calculated using CKD-Epi[f] formula (Vitros 5600)
Proteinuria	Urine dipstick (Siemens Hema-Combistix)
Chlamydia trachomatis (CT) / *Neisseria gonorrhoeae (NG)*	Abbott Real Time *CT* / *NG* with confirmation by in-house PCR[g]
Mycoplasma genitalium (MG) / *Trichomonas vaginalis (TV)*	In-house PCR for *MG* and Diagenode (S-DiaMGTV) for *TV*
Herpes simplex virus-2 (HSV-2)	Kalon HSV Type 2 IgG
Plasma and upper layer packed cell drug level testing	Thermo Scientific Q-Exactive hybrid quadrupole–Orbitrap mass spectrometer (LC-MS/MS[h] system)
HIV-1 resistance	RNA sequencing
HIV-1 viral load	Cobas 4800 (Roche)

[a]RPR: rapid plasma reagin.

[b]TPA/TPPA: *Treponema pallidum* assay/ *Treponema pallidum* particle agglutination assay.

[c]HBsAg/HBsAb: hepatitis B surface antigen/hepatitis B surface antibody.

[d]HBcIg/HBcIgM: total hepatitis B core antibody/hepatitis B core IgM antibody.

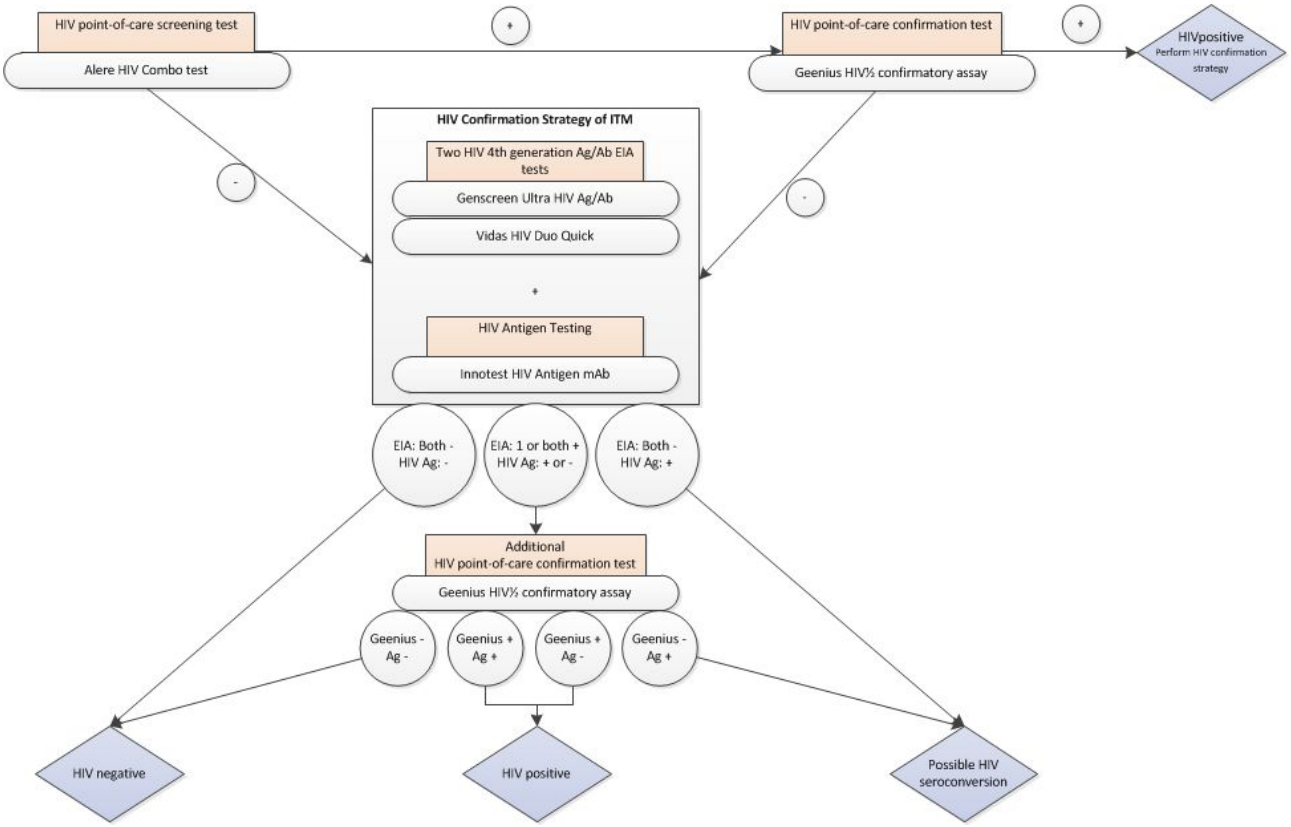
[e]AST/ALT: aspartate transaminase/alanine transaminase.

[f]CKD-Epi: Chronic Kidney Disease Epidemiology Collaboration.

[g]PCR: polymerase chain reaction.

[h]LC-MS/MS: liquid chromatography coupled with tandem mass spectrometry.

Figure 2. HIV algorithm in the study.



HIV Seroconverter Procedures

If a participant becomes HIV positive during the study, he is discontinued immediately from the study but is followed up for safety. In this case, study staff collects all unused pills, conducts the final visit procedures including resistance and viral load testing, discusses the pros and cons of early ARV therapy, and refers the participant to an AIDS reference center of choice for linkage to HIV care.

Safety

Safety and tolerability of Truvada is evaluated by recording adverse events (AEs) and grading laboratory and vital signs evaluations in the electronic case report form (eCRF) starting from enrollment until the final visit. Severity, causality, and outcome are also assessed by the study physician. Any event that occurred before the enrollment visit is documented as medical history. All AEs are followed up until resolution to the extent possible. An HIV infection is not considered a serious adverse event (SAE). Due to the possible renal adverse effects of Truvada, elevations in serum creatinine are monitored closely. Truvada will be interrupted when creatinine clearance is below 60 mL/minute/1.73 m² and will be permanently discontinued when the clearance stays below 50 mL/minute/1.73 m² after repeat testing.

All SAEs whether or not deemed drug-related or expected are reported within 24 hours (1 working day) to the sponsor (ITM). Line listings of all reported SAEs are sent to the concerned ethics committee (EC) and the Belgian Competent Authority (CA) on a yearly basis. In addition, all fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) need to be reported to the Belgian CA and to the concerned EC within 7 days. Nonfatal and non–life-threatening SUSARs must be reported within 15 days. Gilead Sciences is notified immediately in case of SUSARs and will receive SAE listings every 2 weeks.

No formal data safety monitoring board (DSMB) has been set up due the fact that this drug is widely used and approved for treatment and prevention of HIV infection by the FDA and EMA. However, an independent data safety monitor has been appointed to review all SAE reports. In case of major safety concerns, this monitor may advise the sponsor to halt recruitment of the trial and/or organize a formal DSMB with a complete overview of the available safety data.

Data Collection

Databases

Due to the project's mixed methods approach, 4 different types of databases have been set up:

- A clinical trial database was programmed and validated prior to project start: an eCRF developed in the Good Clinical Practice (GCP)-compliant clinical trial software MACRO (InferMed, United Kingdom) with CFR 21 Part 11 in-built consistency checks is used.
- An online survey database is used for the questionnaires (using Survey to Go mobile survey software from Dooblo for the development of the online questionnaires).
- The online diary data is stored on a secured and password-protected Web platform that was created for the purpose of this project.
- The interview data from the IDIs is stored using a computer-assisted software program for data storage and analysis (NVivo 10.0, QSR International).

Confidentiality and Security of Trial Participant Data

Private information on trial participants is handled confidentially. Only the participant identification number, initials, and date of birth are captured in the eCRF and all other study documentation. Name and contact data for each participant is kept separately, and access to them is limited to the authorized study staff. The same confidentiality rules apply for all study documents and electronic files. The computers and eCRFs are only accessible by the study staff with personal username and password. The online diary and survey data are stored on secured servers only accessible to the researchers.

Data Analysis

End Points

The uptake, acceptability, and feasibility of using PrEP will be examined by the end points documented in Textbox 3.

Textbox 3. End points of the Be-PrEP-ared study.

Preventive needs:

- Recruitment rate (number of screened participants/number of registered on study-specific website)
- (Un)safe sex behavior during the last 6 months
- Percentage of reported intention to use pre-exposure prophylaxis (PrEP) in the future at final visit
- Retention rates in the different regimens
- Attitudes towards PrEP use: satisfaction and motivation for future use

Adherence:

- (In)consistent pill take, percentage of days with no pill taken/days on which a pill should have been taken
- Tenofovir drug levels in blood and/or hair samples
- Perceived skills to adhere, including self-efficacy

Impact of PrEP use on other preventive strategies:

- Number of sex partners
- Self-reported condom use
- Sex under influence (alcohol, drugs)

Impact of PrEP use on sexually transmitted infection (STI) trends (descriptive analyses only):

- STI incidence and trends: *Chlamydia trachomatis* / *Neisseria gonorrhoeae*, *Mycoplasma genitalium* / *Trichomonas vaginalis*, herpes simplex virus-2, syphilis, and hepatitis C

Safety of the different regimens of PrEP use:

- Rate of adverse events related to PrEP

Real-life effectiveness of PrEP use:

- Incidence of HIV infection by regimen
- Genotypic viral resistance

Feasibility of oral fluid self-sampling testing:

- Feasibility

A mixed method analysis of quantitative and qualitative end points will be conducted by triangulating the results from both data collection types.

Clinical Data Analysis

The study design is observational, and all analyses will be descriptive. As participants may change regimens, a single participant may be included in different regimens over time and contribute to person-months of daily, event-driven, or no use in the analyses.

Adherence may be dichotomized as adherent/nonadherent and is defined in general as the proportion of pills the participant needed to take that were actually taken. The number of pills actually taken is calculated based on self-reporting through the diary. Different indicators for adherence will be used for each of the regimens and per 3 months:

- Adherence to regimen: number of pills taken/number of pills which should have been taken according to the PrEP dosing regimen.
- Estimated proportion of covered sex acts: number of sex acts covered with PrEP/number of sex acts. This indicator will be calculated separately for high-risk sexual activities and low-risk sexual activities. High-risk sexual activities are defined as anal intercourse without a condom with a

partner of unknown HIV status or known to be HIV positive with detectable virus load.

Exploratory analysis of predictors of retention on PrEP or (non)adherence may be performed using regression models (linear, logistic, or Cox-regression). Different groups may be considered for analysis depending on the change of regimen: group remaining on daily use, group remaining on event-driven, group changing from daily to event-driven, and group changing from event-driven to daily use.

All nonserious and serious AEs will be grouped according to a prespecified side-effect coding system and tabulated. The number of subjects experiencing any AE, any SAE, and any drug-related SAE will be summarized by PrEP regimen.

Questionnaire Data Analysis

Analysis of the questionnaire data will be mainly descriptive, using uni- and bivariate statistical analyses. Depending on the results, multivariable statistical models and longitudinal analyses may be used. All computations will be done using SPSS version 23.0 (IBM Corp).

Interview Data Analysis

Interview data will be analyzed inductively based on grounded theory principles using multiple, independent coders. They will establish a data-driven codebook. This approach ensures triangulation from different perspectives [19,20] and thus improves data validity.

Ethics and Quality Assurance

The protocol and all study documents were reviewed and approved by the Institutional Review Board (IRB) of the ITM, the EC of the University Hospital of Antwerp, and the CA of Belgium. No study activities were performed before approval from all these bodies. Amendments to the protocol must be approved by the sponsor and by the concerned IRB, EC, and CA. Yearly updates are sent to all of these bodies. The study is carried out according to the principles stated in the Declaration of Helsinki as amended in 2013 and any further updates, all applicable national and international regulations, and according to the most recent International Conference on Harmonization (ICH) and WHO GCP guidelines. All laboratory activities are conducted in accordance with Good Clinical Laboratory Practices (GCLP) and EN-ISO (International Organisation for Standardization) 15189.

The study is monitored in accordance with regulations applicable to clinical trials, including ICH-GCP and GCLP requirements, and sponsor-specific monitoring and source data verification standard operating procedures. A trial management group is in charge of the day-to-day management of the clinical study.

Informed Consent

Before any study procedures took place, participants were asked to provide written informed consent.

Community Advisory Board

A Community Advisory Board (CAB) was set up with representatives from local and regional MSM community and health organizations and Belgian MSM prevention experts to ensure that the demonstration project meets the target group's needs. The researchers consult with this CAB twice yearly or more often if needed. Its main purposes are to assist in recruiting participants; to ensure proper feedback of the project results to the community; and to assist in safeguarding the community's ethical, social, and cultural norms.

Results

The clinical trial part of the study has been registered in the EudraCT database (EudraCT 2015-000054-37). A total of 200 participants were enrolled on December 12, 2016. The last participant's last visit will take place around Q2 2018.

Discussion

Given EMA's recent approval of PrEP and recent national developments, we assume that PrEP will soon be available and may even be (partially) reimbursable in Belgium. Our study results will be useful for PrEP implementation as part of overall HIV combination prevention (eg, screening guidelines for PrEP eligibility). Given the mixed method approach and longitudinal data collection, this study will provide insights into factors influencing PrEP use and choice of regimen—as participants are able to switch dosing regimen or to discontinue—and how it relates to user perspectives. Actual PrEP use may shift and be influenced by several factors such as users' self-perceived risk for HIV, actual user experience with PrEP, PrEP adherence, and perceived impact on sexuality. These findings could have important implications for HIV prevention policies and health care expenditure.

To our knowledge, the Be-PrEP-ared study is, together with the AMPrEP project of Amsterdam, the first study investigating the uptake of different PrEP dosing regimens at the choice of the participant [22]. Moreover, the study is novel in longitudinally exploring the preferences for and experiences of using the different regimens or discontinuing and restarting PrEP. Allowing participants to adapt PrEP use and different regimens to better suit periods of perceived high risk of HIV infection is novel and could lead to important insights into the need for PrEP within this high-risk population. Furthermore, such insights are crucial for developing appropriate adherence counseling guidelines and an optimal integration of PrEP within the already existing tools for HIV prevention.

One major strength of this project is its strong mixed methods approach, allowing for methodological triangulating of the various data sources and for exploring MSM's prevention needs in depth. This will lead to an improved understanding of the uptake and acceptability of PrEP use within the current context and greatly improves the validity of the results [23].

Moreover, the mixed methods approach will lead to important in-depth insights about and knowledge of adherence to PrEP, one of the key outcomes of the project. In our study we combine different methods to assess adherence to PrEP. We test drug levels of tenofovir and tenofovir diphosphate immediately in plasma and upper layer packed cells at FU month 1 and FU month 3. With intracellular tenofovir diphosphate, an assessment of the adherence over the past 2 to 4 weeks can be made and

"white-coat adherence" (ie, only taking PrEP just before the study visit) can be detected [24]. In addition, DBS and hair are also stored for future emtricitabine/tenofovir disoproxil fumarate therapeutic drug monitoring testing to reflect longer term windows of exposure when funding is available. Furthermore, the online diary will lead to improved insights into the number and timing of pills taken throughout the study, whereas the questionnaire and online diary will explore attitudes towards adherence to the medication.

Another strength is the participation of and close communication with health care providers and members of the HIV prevention and MSM community in Belgium through the CAB. The use of the CAB not only helps to raise awareness about the study and to more efficiently disseminate the results of the study, it is also crucial in developing study procedures and implementation guidelines that are sensitive to those who will be using PrEP [25,26].

The number of MSM who registered for participation in the first 3 weeks of launching the registration study website (ie, 196 in total) shows that there is an interest for PrEP within this population. However, interpreting the registration rate as a measure for PrEP acceptability would remain difficult: we did not overly promote study registration after the initial 3 weeks as it was clear that the desired number of participants would be reached; not all possible candidates may thus have been aware of the study and some may have anticipated not being able to participate in the study due to the promoted consultation hours (ie, during office hours) or may have been unwilling due to setting-related reasons (eg, distance to the clinic).

The slow recruitment rate was mainly due to limited staff resources (ie, limited availability of study physicians) resulting in approximately 4 screenings per week. This could be an important limitation, as those enrolled first could differ from those enrolled last (ie, as PrEP use is at least 1 year apart) and thus would not be comparable. Media coverage or PrEP availability, changing sexual norms within the community, and related factors may have had a different influence on participants. However, the study may reflect actual willingness to use PrEP and allows for exploring how an evolving HIV prevention landscape including access to PrEP affects individual PrEP uptake and adherence. Moreover, it cannot be excluded that individual differences between the start and end of the study will be the result of similar influences rather than PrEP use on its own.

Conducting a demonstration project such as Be-PrEP-ared may in itself have an impact on HIV prevention that goes beyond providing ARV medication to participants. It has reinforced collaborations with community organizations and health care providers and can help in increasing PrEP awareness and influence policy on HIV prevention. In the wake of Be-PrEP-ared, various substudies have already started in Belgium such as a survey among health care providers to assess their PrEP knowledge, attitudes, and willingness to prescribe. New studies are being set up in this evolving field, which will be important to allow for crossnational research. To develop a good understanding of how to optimally implement and provide PrEP integrated into the existing health care structures, new research will be of paramount importance.

In conclusion, results from this study will contribute to a better understanding of PrEP users' experiences including their choices for specific PrEP regimens. The findings will help to inform appropriate delivery strategies for the roll-out of PrEP and for policy makers to consider financial reimbursement of PrEP in Belgium.

Acknowledgments

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Authors' Contributions

Irith De Baetselier, Thijs Reyniers, and Bea Vuylsteke wrote the first draft of the manuscript where Irith De Baetselier focused on the clinical part and Thijs Reyniers on the social aspects of the study. All authors revised, edited, and approved the present version of the manuscript. The Be-PrEP-ared study group is performing the study: Laura Albers, Maureen Aerts, and Kurt Van Lent (study-nurses); Kristien Wouters and Chris Kenyon (study physicians); Bea Vuylsteke (principal investigator); Thijs Reyniers (social coordinator); Irith De Baetselier and Vicky Cuylaerts (clinical and laboratory coordinators); Bart Smekens and Céline Schurmans (clinical monitors); Harry Van Loen and Hanne Landuyt (data management and review); Jozefien Buyze (statistician); and Marie Laga as coordinating investigator. Jozefien Buyze, Tania Crucitti, Irith De Baetselier, Katrien Fransen, Chris Kenyon, Marie Laga, Christiana Nöstlinger, Thijs Reyniers, Céline Schurmans, Marjan Van Esbroeck, Harry Van Loen, Jef Verellen, Bea Vuylsteke, and Kristien Wouters conceptualized the protocol.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
ALT/AST: alanine transaminase/aspartate transaminase
ARV: antiretroviral
CA: Competent Authority
CAB: Community Advisory Board
CT: Chlamydia trachomatis
DBS: dry blood spot
DSMB: data and safety monitoring board
EC: ethics committee
eCRF: electronic case report form
EMA: European Medicines Agency
FDA: Food and Drug Administration
FU: follow-up
GCLP: Good Clinical Laboratory Practices
GCP: Good Clinical Practices
HBV: hepatitis B virus
HCV: hepatitis C virus
HSV-2: herpes simplex-2 virus
ICH: International Conference on Harmonization
IDI: in-depth interview
IRB: Institutional Review Board
ISO: International Organisation for Standardization
ITM: Institute of Tropical Medicine
MSM: men who have sex with men
MG: Mycoplasma genitalium
NG: Neisseria gonorrhoeae
PrEP: pre-exposure prophylaxis
SAE: serious adverse event
STI: sexually transmitted infection
SUSAR: suspected unexpected serious adverse reaction
TV: Trichomonas vaginalis
WHO: World Health Organization

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Protocol

Leveraging Electronic Health Care Record Information to Measure Pressure Ulcer Risk in Veterans With Spinal Cord Injury: A Longitudinal Study Protocol

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Abstract

Background: Pressure ulcers (PrUs) are a frequent, serious, and costly complication for veterans with spinal cord injury (SCI). The health care team should periodically identify PrU risk, although there is no tool in the literature that has been found to be reliable, valid, and sensitive enough to assess risk in this vulnerable population.

Objective: The immediate goal is to develop a risk assessment model that validly estimates the probability of developing a PrU. The long-term goal is to assist veterans with SCI and their providers in preventing PrUs through an automated system of risk assessment integrated into the veteran's electronic health record (EHR).

Methods: This 5-year longitudinal, retrospective, cohort study targets 12,344 veterans with SCI who were cared for in the Veterans Health Administration (VHA) in fiscal year (FY) 2009 and had no record of a PrU in the prior 12 months. Potential risk factors identified in the literature were reviewed by an expert panel that prioritized factors and determined if these were found in structured data or unstructured form in narrative clinical notes for FY 2009-2013. These data are from the VHA enterprise Corporate Data Warehouse that is derived from the EHR structured (ie, coded in database/table) or narrative (ie, text in clinical notes) data for FY 2009-2013.

Results: This study is ongoing and final results are expected in 2017. Thus far, the expert panel reviewed the initial list of risk factors extracted from the literature; the panel recommended additions and omissions and provided insights about the format in

which the documentation of the risk factors might exist in the EHR. This list was then iteratively refined through review and discussed with individual experts in the field. The cohort for the study was then identified, and all structured, unstructured, and semistructured data were extracted. Annotation schemas were developed, samples of documents were extracted, and annotations are ongoing. Operational definitions of structured data elements have been created and steps to create an analytic dataset are underway.

Conclusions: To our knowledge, this is the largest cohort employed to identify PrU risk factors in the United States. It also represents the first time natural language processing and statistical text mining will be used to expand the number of variables available for analysis. A major strength of this quantitative study is that all VHA SCI centers were included in the analysis, reducing potential for selection bias and providing increased power for complex statistical analyses. This longitudinal study will eventually result in a risk prediction tool to assess PrU risk that is reliable and valid, and that is sensitive to this vulnerable population.

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KEYWORDS

natural language processing; pressure ulcer; risk assessment; spinal cord injury; text mining

Introduction

Background

The pressure ulcer (PrU) is one of the most significant complications in veterans with spinal cord injury (SCI) in terms of morbidity, mortality, quality of life, and cost of care. The Veterans Health Administration (VHA) has the largest single network of SCI care in the United States providing a full range of care to more than 27,000 veterans. Services by the VHA are delivered through a "hub and spoke" system of care, extending from 24 regional SCI centers, offering primary and specialty care by interdisciplinary teams, to the 135 SCI patient-aligned care teams. These teams are typically comprised of an SCI coordinator (usually a social worker), a nurse, and physician, or support clinics at local VHA medical facilities [1].

The total cost of discharges for veterans with an SCI in the VHA who were discharged from a designated SCI system of care facility (ie, treating-bed section of SCI) with a primary admitting diagnosis of a PrU was over US $300 million for fiscal years (FYs) 2011-2012. In this time period, veterans with SCI who were discharged from SCI facilities with the primary admitting diagnosis of a PrU—in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 707.00-707.09 series—accounted for 64.1% (US $304M/US $474M) of the total costs for SCI discharges in the VHA (Veterans Health Administration, Managerial Cost Accounting System Discharge Pyramid Report, 2015.06.18). Stroupe and colleagues found that the cost of PrU-related hospitalizations for 150 veterans with SCI in the VHA over a 3-year period was approximately US $9 million and total health care costs were US $87,639 higher for patients with PrUs than those without (US $113,579 vs US $25,940, respectively) [2].

Current clinical practice guidelines for PrU prevention and treatment state that all patients should be assessed for risk of developing PrU using a valid, reliable, and sensitive tool [3,4]. The Braden Risk Assessment Scale [5,6], developed to predict risk in general inpatients, is presently used throughout the VHA for inpatients and outpatients. There is often a ceiling effect with most or all persons with SCI being identified at a high-risk level using the Braden Scale. Surveys conducted between 2008 and 2010 by the VHA External Peer Review Program at VHA Spinal Cord Injury and Disorder (SCI/D) Centers found that 91.3% of those measured in SCI were identified as being at high risk for PrU using the Braden Scale.

Reliability and sensitivity have not been fully established for existing tools in persons with SCI [7] despite the unique characteristics of this population (eg, lack of sensation and muscle wasting) [3]. Salzberg and colleagues devised a risk assessment scale specific to the SCI population; although used in a few SCI/D Centers [8], the psychometrics of this tool are limited [9,10].

This 5-year retrospective cohort study will leverage data available in the VHA's electronic health record (EHR) to develop SCI-specific predictive models that can be used to better identify risk for PrUs. The new model will enable targeted prevention strategies, thereby reducing the burden of this serious complication on veterans, their caregivers, and the health care system.

Scientific Rationale

Despite widespread implementation of risk assessment tools for PrUs, the incidence of PrUs among veterans with SCI has remained stable. Furthermore, there has been an increase in PrUs in the general population. Data from the Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality (AHRQ), identified a national increase of almost 80% in PrUs in 2006 compared with 1993; SCI was a frequent comorbidity (29.2%) of those hospitalized with a PrU [11].

In pilot work, we found that the majority of potential PrU risk factors identified in our review were available in the EHR in structured, unstructured, or semistructured data. Structured data, the easiest to extract, are precoded (ie, value or meaning is assigned) and stored in database tables such as the ICD-9-CM codes. Recent studies have shown that it is possible to develop valid risk models based on structured data in the EHR [12-14]. Semistructured data are text formatted into tables, templates, lists, and other documents. Extraction of such data is often difficult because it is commonly embedded within the unstructured clinical narrative and the presentation format is not standardized. Unstructured data are text that is formatted in

traditional sentences and paragraphs. It is commonly considered the most difficult data to extract because natural language provides multiple methods of communicating the same essential information.

Recent studies have also shown that natural language processing (NLP) techniques can be used to extract risk and decision-making information from clinical text [15-17]. Natural language processing research focuses on developing computational models for understanding natural language [18]. The specific NLP technique employed varies depending on whether the text is semistructured or unstructured. The NLP techniques are used to extract and encode specifically targeted information in text (ie, information extraction [IE]) and convert it to structured data, which can then be readily used in risk assessment.

Aims and Hypotheses

The goal of this study is to develop an improved SCI PrU risk model to better predict level of risk, guide preventive practices, and ultimately maximize the patient's clinical outcomes. The resultant risk model, tailored to veterans with SCI, should promote adoption into clinical practice.

We will test two hypotheses to compare a model based on the commonly used Braden Scale versus (1) a risk model developed using structured data alone and (2) a model using both structured and NLP (ie, semistructured and unstructured) data. A third hypothesis will test the added value of NLP-based data over structured data. The hypotheses are as follows:

1. Hypothesis 1: The risk model using structured data alone will predict the development of PrUs better than the model based on the Braden Scale.

2. Hypothesis 2: The risk model based on combined structured and NLP data will predict the development of PrUs better than the model based on the Braden Scale.

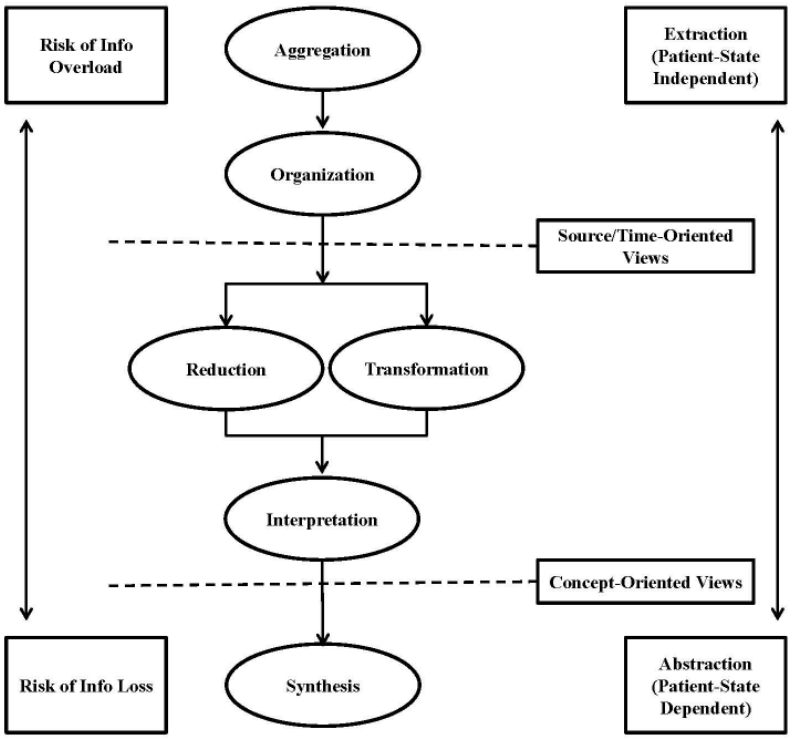
3. Hypothesis 3: The risk model based on combined structured and NLP data will predict the development of PrUs better than the model based on structured data alone.

Conceptual Framework

In developing this protocol, we employ the Aggregation, Organization, Reduction, Transformation, Interpretation, and Synthesis (AORTIS) model of understanding clinical summarization in both computer-independent and computer-supported clinical tasks [19]. Using this framework, "clinical summarization" is any act that can be carried out by a health care team member who utilizes patient and clinical information to create a structured data summary, which in turn supports clinical tasks.

In our conceptual model, any or all of the steps to produce a concise and accurate summary could be performed by either a clinician or an automated system. The model was designed to be sequential, with the output from one step providing input into the next, and task dependent, with the content of each step varying based on the clinical task that the summary was designed to support (see Figure 1). In this study, we include many but not all of the steps of the model to employ AORTIS.

Figure 1. The model used to understand clinical summarization in both computer-independent and computer-supported clinical tasks. Info: information.



In AORTIS, data are organized around the specific clinical situation, development of a PrU. This expedites IE and clinical decision making but requires the application of a significant clinical knowledge base. The process of identifying and extracting the necessary data from structured data or text represents activities related to aggregation and organization. The application of NLP programs represents the reduction and transformation of complex text data, which was not readily computable, into structured data elements that could be included in prediction models. The development of prediction models represents the interpretation and synthesis of these data, which could be presented to clinicians for interpretation.

Methods

Overview

This is a 5-year longitudinal, retrospective, inception, cohort study targeting veterans with SCI. This research was approved by the Department of Research and Development, James A Haley Veterans' Hospital, and the VHA Central Institutional Review Board. As described below, the study is ongoing. Each section describes the current status of the study activities as complete, ongoing, or planned.

Expert Panel—Complete

An expert panel meeting was held in March 2014 to discuss PrU risk factors. The goal of the panel was to identify factors that were likely present in the EHR and could be used to develop improved risk models for PrU development. Participants included two physicians specializing in care for veterans with SCI, three nurse researchers, a wound care specialist, an SCI outcomes registry coordinator, a physical therapist, a dietitian, and a social worker. All members of the expert panel had multiple years of experience in managing persons with PrUs and SCI. Members of the study team also attended the expert panel meeting. Results of the expert panel were iteratively reviewed and refined by two additional physicians and a nurse specializing in research and treatment of PrUs in veterans with SCI.

Variables Selection and Definition—Ongoing

The dependent variable for this study will be documentation of the occurrence of a PrU in the EHR within 1 year (ie, 1-year incidence risk of PrU). The definition of the presence of a PrU used for case identification is based on ICD-9-CM codes (707.0-707.9) and the application of the classification algorithm based on text analysis or a combination of these two sources, depending on what is found to be more accurate. The potential independent variables for this study include the risk factors that were identified through a literature review and validated by expert panel discussion. The final list of potential risk factors, with input from the expert panel, will be extracted from multiple tables in the EHR, or from semistructured and unstructured text notes, for use in analysis. Three sets of candidate predictors based on data sources will be generated to develop each risk model: (1) structured data extracted directly from the EHR, (2) Braden scores, and (3) a combination of existing structured data and data extracted from text through the NLP processes.

The investigators conducted a comprehensive literature review generating a list of approximately 50 potential independent variables or risk factors (eg, demographics, diseases status, comorbidities, health behaviors, psychosocial factors, and home care). This list was reviewed by the expert panel for logical consistency, completeness, clinical relevance, and whether they were modifiable or not. The panel identified high-priority risk factors and discussed practical considerations including where the risk factor might be located in the EHR, how reliable these data might be, and alternative ways to document risk factors. Subsequently, persistent moisture on the skin, the type of living situation of the patient, evidence of malnutrition, and documentation that the patient took steps to redistribute their weight during the day were targeted as risk factors available in unstructured data. Structured data contained elements of the Braden Scale, lab values, and other variables (see Table 1). Several coding systems are used to classify structured data variables, including the ICD-9-CM, Logical Identifiers Names and Codes (LOINC), and the Healthcare Common Procedural Coding System (HCPCS). International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes were not implemented in the VHA until after the end of this study and are not used.

Sample and Sampling—Complete

Using VHA data in its Corporate Data Warehouse obtained through its Veterans Affairs Informatics and Computing Infrastructure (VINCI), we identified an inception cohort (N=12,344) of veterans with SCI who received care in the VHA in FY 2009, but had no PrU in the 12 months prior to 2009 based on recorded ICD-9-CM codes. This group was considered free of PrUs for the purpose of the study. All structured hospital discharges (N=4090), outpatient encounters (N=5,202,804), and text data (N=9,888,245) for the cohort for FY 2009-2013 (October 1, 2008-September 30, 2013) were obtained through the VINCI. Veterans from this cohort were classified as having a PrU (ie, PrU+) or not having a PrU (ie, PrU-) during the study period based on both structured and text data. A total of 3860 PrUs were identified based on structured data and 829 based on text data alone, resulting in a total incidence of 4689 (4689/12,344, 37.99%) across the study period.

Table 1. Risk factors categorized by structured, semistructured, and unstructured data sources.

Data source	Risk factor	Description or definition
Structured	Age	Age in years
	Gender	Male/female
	Race/ethnicity	Race/ethnicity
	Education level	Highest level of education
	VHA[a] eligibility	VHA category, service connection
	Body weight	Body mass index, most recent weight, or change in weight
	Patient status	Inpatient/outpatient when pressure ulcer develops
	Pattern of preventive care	Consistency of annual well-patient exam
	Cognitive dysfunction	ICD-9-CM[b] codes (ie, traumatic brain injury, dementia, and Alzheimer's disease)
	Comorbidities—psychological	ICD-9-CM codes (ie, depression, anxiety, and posttraumatic stress disorder)
	Comorbidities—physical	ICD-9-CM codes (ie, diabetes mellitus, pulmonary disease, cardiac disease, renal disease, peripheral vascular disease, anemia, deep vein thrombosis, cancer, infection, lower extremity fractures, spasticity, autonomic dysreflexia, hypotension, and heterotopic ossification)
	Laboratory analysis	LOINC[c] codes for lab values (ie, C-reactive protein, white blood cells, erythrocyte sedimentation rate, renal function, hemoglobin, hematocrit, albumin, and prealbumin)
	Medications	VHA formulary to identify chemotherapeutics, steroids, and benzodiazepines
	Surgery	ICD-9-CM codes of surgical procedures within previous 6 months of pressure ulcer development (administrative data)
	VHA-issued equipment	HCPCS[d] codes for wheelchair cushion, bed support surface, and other equipment
	Telehealth	Distant observation of skin integrity
Semistructured	Motor/sensory assessment	American Spinal Cord Injury Association (ASIA) classification of SCI[e] (eg, ASIA A= *Complete* injury of spinal cord)
	Level of injury	Cervical (C1-C8), thoracic (T1-T12), lumbar (L1-L5), and sacral (S1-S5)
	Alcohol use	Alcohol Use Disorders Identification Test—Consumption (AUDIT-C)
	Tobacco use	Current/former/nonsmoker
	Caregiver resources	Receiving aid and attendant, VHA-supported/reimbursed bowel/bladder care
	Duration of SCI	Years since injury/onset
	Sensation[f]	Ability to feel and relieve discomfort
	Moisture[f]	Exposure to moisture on trunk (ie, bowel/bladder leakage/accidents due to management or lack of containment, diarrhea, and diaphoresis)
	Mobility[f]	Ability to relieve pressure on high-risk areas (eg, trunk and heels)
	Activity[f]	Level of activity (ie, ability to get out of bed and ambulation)
	Nutrition[f]	Food intake malnutrition, undernutrition, and moderate/severe compromise
	Friction and shear[f]	Ability to minimize resistance between two parallel surfaces (ie, bed linens and skin)
	Living situation	Living arrangements (eg, alone, immediate family, extended family, roommate, and group setting)
Unstructured	Noncompliance with pressure redistribution	Patient refusal/decline to turn in bed
	Pain	Numeric pain rating scale (1-10) when pressure ulcer develops
	Pressure ulcer history	Previous pressure ulcer

[a]VHA: Veterans Health Administration.

[b]ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.

[c]LOINC: Logical Identifiers Names and Codes.

[d]HCPCS: Healthcare Common Procedural Coding System.

[e]SCI: spinal cord injury.

[f]Element of the Braden Scale.

Data Extraction and Synthesis (Structured Data)—Ongoing

To determine whether the targeted structured variables were present in a patient's record, we identified lists of codes (ie, ICD-9-CM codes) to operationally define the variables. When available, definitions employed by the VHA Support Service Center (VSSC), a centralized reporting portal, were used. The VSSC provides data summaries to VHA administrators and policy makers regarding business operations, clinical care, quality performance, and resource management. Otherwise, operational definitions were obtained from the AHRQ's HCUP Clinical Classifications Software [20] or the Centers for Medicare and Medicaid Services definitions. Extraction routines were used to identify each occurrence of the variable in the patient's record. These data were then transformed into single elements in the analytic data table based on clinically relevant temporal considerations. For example, some comorbidities such as diabetes were considered chronic conditions, while others such as fractures were framed in a 1-year period.

Data Extraction and Synthesis (Unstructured and Semistructured Data)

We will employ NLP techniques to extract targeted information from the documents in the EHR. This will be accomplished using the following steps.

Step 1: Create Reference Standard—Complete

Large samples of documents (approximately 2000) will be extracted from the larger corpus of documents. A human-annotated (ie, chart review) corpus will be developed, which will be used as a reference standard to train and evaluate NLP algorithms. An annotation schema was developed, which defines the classes of concepts based on the variables reviewed by the expert panel. The concepts will be annotated in each document in the corpus by two clinicians and adjudicated by a third clinical expert. Interrater reliability will be evaluated by calculating interannotator agreement. Agreement between the two annotators will be evaluated by calculating the *F* measure, proposed by Hripcsak and Rothschild [21], against the final reference that will be adjudicated by our clinical expert.

Step 2: Extract Information From Unstructured and Semistructured Text Data—Ongoing

We will use the annotated reference set of documents to develop and evaluate distinct methods to extract information from unstructured and semistructured text.

Step 2a

The General Architecture for Text Engineering (GATE) software will be used to create an NLP pipeline to extract the information from the unstructured text data [22]. The results of the NLP pipeline will be iteratively compared to the annotated terms from the reference standard on 70% of the documents. The remaining 30% of the documents will be used to validate the best model. This will enable the pipeline to be iteratively refined to more accurately identify the potential predicators located in the narrative documents.

Step 2b

We will develop an NLP system for semistructured text data. The composition of semistructured text presents unique challenges to NLP, making information extraction especially challenging [23,24]. Semistructured text consists of short, simple phrases that are not grammatically correct.

A traditional grammatical NLP system may fail to negate the presence of moisture for the patient. While this "structure" aids readability, it hinders traditional grammatical NLP systems. However, this "structure" makes rule-based systems using regular expressions a viable alternative for extracting targeted information. Thus, we will employ a custom-developed, rule-based system using named entities- and structural-based regular expressions, which will also be developed and evaluated using an annotated reference set of documents.

Data Analysis—Planned

Three separate predictive models of PrU occurrence based on each set of predictors in each hypothesis will be developed using R statistical program version 3.3.2 (The R Foundation). To prepare, the distribution of each continuous predictor will be examined and variable transformation will be carried out as appropriate to approximate normality (eg, log transformation of skewed data). However, to avoid information loss, no continuous variable will be categorized in an initial prognostic model. Using the generalized additive model (GAM) approach, a bivariate logistic regression will be performed to test potential nonlinearity between each continuous candidate predictor and the binary PrU outcome [25]. This will provide further guidance for appropriate transformation needed for the predictor.

The analytic data sample (N=12,344) will be randomly divided into two groups in the ratio of 70% (n=8641) for derivation and 30% (n=3703) for validation. The randomization will be stratified by site, age group, and gender to increase similarity in the distribution of both validation and derivation random samples.

Model Development

An automated model selection procedure will be performed with the R package *glmulti* [26] to select variables and interaction terms in a logistic regression model of PrU status in the training sample. The automated model selection procedure will return a set of *n* best models, ranked by their information criteria values as well as estimating importance scores for the predictors. Thus, it offers us the flexibility to select from the set a more parsimonious or more intuitively reasonable final model that is context based. Another consideration is for the final prognostic model to include variables that could be easily assessed in practice and with minimal burden on the respondent SCI patients. The fully specified prognostic model will eventually be part of an automated decision support system.

The clinical utility of the risk scores will be evaluated for different risk thresholds and the sensitivity, specificity, positive predictive value, and negative predictive value will be included as performance measures in the automated output. In addition, a separate listing of risk factors will be provided for each risk model and ranked by their rounded Z-scores (or standardized regression coefficients). A higher Z-score implies a more "important" contribution of that variable in the model. These lists will assist the clinicians in prioritizing what variables to assess. Each product will be accompanied with appropriate complete operational definitions and scoring instructions.

Data analysis will be focused on testing two hypotheses that compare the ability of the current standard risk assessment measure—Braden Scale—with models based on structure data alone and in combination with data extracted from text. Comparisons will be made between a pair of risk models to test each hypothesis using exactly the same veterans from the validating sample. Our priority will be to develop models with low false positive rate (ie, the rate at which negative instances are incorrectly classified as having PrU). This consideration will guide how any two competing risk models (ie, classifiers) will be compared using the receiver operating characteristic (ROC) curve analysis. The logistic model will output proper probability scores from which a full ROC curve will be generated for each classifier with overlay in one plot. Generally, a higher calculated total area under the curve (AUC) implies a better prognostic performance. However, when comparing two classifiers, it is possible for the classifier with a higher total AUC to show poorer local performance in our priority region. Therefore, we will assess classifier performance in the overall AUC as well as partial AUC (pAUC) in our priority local region of low false positive rate. The classifier that has a higher sensitivity (ie, true positive rate) in the priority region has superior local performance. That is, an appropriate pAUC will also be computed in addition to the standard full AUC.

Both discrimination and calibration will be investigated as validation measures for each prognostic model using the validation sample. The better discriminating models have higher AUC and pAUC values based on their CIs (ie, better able to distinguish between patients with SCI who have and do not have PrU). To assess calibration, the predictions of each model will be compared with the veterans' actual outcomes in the validation sample by performing the Hosmer-Lemeshow test using the hoslem.test function in the Resource Selection library of R. To ensure that the overall type I error rate of α is maintained, first, we will repeatedly sample from each model and calculate the Hosmer-Lemeshow *P* value 1000 times, and calculate the proportion of *P* values less than .05 (ie, type I error rate should be no greater than 5%).

A graphical approach will be used to compliment the Hosmer-Lemeshow test since it has been known to be sensitive to sample size. For the graphical method, first, the sample will be divided into 10 risk groups of equal size with each group having similar model predicted probabilities. Next, the observed proportions of PrUs will be plotted against predicted probabilities for these groups with one smooth curve fit (eg, lowess) as well as a linear fit to the data points. We anticipate that the observed and predicted occurrence of PrUs will be similar across the risk groups. A perfect calibration (ie, perfect agreement between the predicted and observed outcomes) will produce a calibration line with an intercept and slope of 0 and 1, respectively [27-29]. The smooth curve will be added to reveal differential calibration among risk deciles, if present.

We expect the validation study to span across different domains (eg, inpatient vs outpatient, site, age group, and gender) as this provided the strongest evidence of generalizability of the prediction rule to new patients [30]. Since stratified randomization ensured a similar case mix within each of our samples—derivation and validation—and both samples were representative of our population of interest, we believe that the results of our validation tests will serve as strong evidence of generalizability.

Results

The study is ongoing with results expected in 2017. The expert panel met and reviewed the initial list of risk factors based on the literature review (see Table 1). They made recommendations for additions and deletions and provided insight into where, and in what format, the documentation of the risk factors might exist in the EHR. This list was then iteratively refined through review and discussion with individual experts in the field. The cohort for the study has been identified and all structured, unstructured, and semistructured data have been exported into a relational database for analysis. A description of the cohort is provided in Table 2.

The cohort is almost exclusively male (11,796/12,344, 95.56%), with 68.96% (8513/12,344) being white and 19.64% (2424/12,344) being black or African American. The mean age of the cohort was 58 years (SD 14) with more than half (6782/12,344, 54.94%) being between 50 and 69 years of age. Approximately half (6873/12,344, 55.68%) reported being married.

Annotation schemas have been developed, samples of documents have been extracted, and annotation and adjudication are ongoing. Table 3 outlines the variable targeted through the annotation process.

Table 2. Description of study cohort (N=12,344).

Characteristic	n (%)
Gender	
Female	548 (4.44)
Male	11,796 (95.56)
Race	
Asian	74 (0.60)
Black or African American	2424 (19.64)
Native Hawaiian or other Pacific Islander	1 (0.01)
White	8513 (68.96)
Other	28 (0.23)
Unknown by patient/missing	1214 (9.83)
Ethnicity	
Hispanic or Latino	939 (7.61)
Non-Hispanic or non-Latino	10,723 (86.87)
Unknown by patient/missing	82 (0.66)
Age group, years	
<21	24 (0.19)
21-30	491 (3.98)
31-40	824 (6.68)
41-50	1854 (15.02)
51-60	3753 (30.40)
61-70	3120 (25.28)
71-80	1540 (12.48)
81-90	701 (5.68)
>90	36 (0.29)
Missing	1 (0.01)
Marital status	
Single/never married	2354 (19.07)
Married	6125 (49.62)
Divorced	3097 (25.09)
Widow/widowed	560 (4.54)
Unknown/missing	187 (1.51)

Table 3. Pressure ulcer (PrU) annotation schemas.

Task	Variable	Attributes	Description	Example text spans
Annotation task 1	Pressure ulcer	Pressure ulcer	Text indicating presence of a PrU	Pressure ulcer, skin sore, decubitus ulcer
		Stage	Stage of the PrU	Stage 1, stage 2, unable to stage, stage 3-4
		Laterality	Right, left, bilateral, midline, not applicable, unspecified	Right, left, lower extremity
		Location	Anatomic location of PrU	Coccyx, heel, trochanter, sacrum, ankle, ischial
		Orientation	Medial, lateral, proximal, distal, dorsum, plantar, anterior, superior, posterior, inferior, unspecified	Bilateral
		Temporality	Date: date of examination Duration: span of time since PrU discovered	Sept 10, 2009, approximately one year
		Assertion	Modifiers: historical, recurrent, negated, hypothetical, not PrU, unspecified	Healed pressure ulcer, history of pressure ulcers, no pressure ulcers, if pressure ulcers develop
	Noncompliance	None	Documentation of noncompliance with pressure release	Patient refuses to turn because of pain
	In label	None	PrU mentions within section labels in documents (ie, are not indications of a PrU)	Pressure ulcer protocol Pressure ulcer education
Annotation task 2	Living situation (LS)	LS cue	Key phrase indicating presence of LS	Living at, living with, address, living arrangements
		LS main	Actual value assigned to LS (ie, alone, nuclear family, extended family, roommate, group, homeless)	Mother's residence, girlfriend, half way house, caregiver, spouse
	Malnutrition (MN)	MN cue	Key phrase indicating presence of MN	Nutrition status:
		MN main	Actual value assigned to MN	Moderately compromised, severely compromised
	Moisture (MO)	MO cue	Key phrase indicating statement about MO	Moisture: Constantly moist:
		MO main	Text indicating presence of MO (ie, fecal, urinary, sweat)	Multiple loose stools, copious amounts foul purulent drainage, night sweats, perspiration, urine
		Assertion	Modifiers: asserted, historical, hypothetical, negation, not patient, uncertain	Was, prior medical history, nutrition risk, manage, []a, history of
Annotation task 3	Template components	Header	Title line naming the template	Braden Scale, ASIAb score
		Item label	Label for individual assessment items	Moisture, turgor, color, temp
		Item score	Value (text or number) assigned to item	Moist, red, 4, 0
		Total label	Text identifying the summed score	Total score:
		Total score	Final value for the assessment	30, high risk
		Whole template	Offsets from block of text identifying template boundaries	132-165

[a]These empty brackets would be generated by the system and placed in a progress note when a check box was left blank in a template in the electronic medical record system.

[b]ASIA: American Spinal Cord Injury Association.

The annotation process was split into three tasks to allow for sampling of different types of documents, depending on the targeted variables. This also reduces the cognitive burden for the annotators in each of the tasks. In the first task, the emphasis is on identifying attributes of the pressure ulcers and on any documentation of patient noncompliance with steps to reduce pressure ulcers, such as pressure release. In the second task, the primary targets were the patients' living situation, whether there

was any evidence of malnutrition, and whether there was evidence of ongoing moisture on the skin. Annotation for each of the targeted variables included both a *cue* (phrase indicating presence) for the variable and the actual value assigned to the variable. The third annotation task was slightly different in that it emphasized labeling of the structural component of semistructured text (stored in templates). This information will allow for targeted extraction of the information contained in the template. Operational definitions of ICD-9-CM codes are being created. Once all of the various data are defined and extracted, they will be combined into an analytic dataset for development of risk models.

Discussion

When completed, the results of this study will provide clinicians in the VHA system with a PrU risk assessment model specific to veterans with SCI. As part of the study, the predictive ability of the new model will be compared directly with that of the Braden Scale, the current risk assessment. Also, individual items on the Braden Scale will be tested for inclusion in the model. This will provide clinicians with information about the clinical utility of the new model. Initially, the new model will be distributed in the form of a simple stand-alone desktop computer program; however, our long-term goal is to deploy the risk assessment as an automated, integrated part of the VHA EHR. Clinicians could use the improved risk model to (1) maximize the impact of expensive resources for prevention of PrU (eg, specialty mattress and paid caregiver) by identifying those veterans at highest risk, (2) justify allocation of staffing resources (eg, home health care or telehealth), and (3) institute policies (eg, frequency of turning the veteran in bed). Further, we believe this study represents a model of how to leverage information from the EHR for risk assessment that could be applied to other clinical problems.

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Authors' Contributions

SL made substantial contributions to the conception and design of the work and interpretation of data. He is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and he will have final approval of the version to be published. SST made substantial contributions to the conception and design of the work and drafted and revised the paper critically for important intellectual content. SS and GPC made substantial contributions to the conception and design of the work and revised it critically for important intellectual content. DKF, JM, PT, LM, and GTG made substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work. MEM made substantial contributions to the conception and design of the work and interpretation of data.

Conflicts of Interest

None declared.

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
AORTIS: Aggregation, Organization, Reduction, Transformation, Interpretation, and Synthesis

ASIA: American Spinal Cord Injury Association
AUC: area under the curve
AUDIT-C: Alcohol Use Disorders Identification Test—Consumption
EHR: electronic health record
FY: fiscal year
GAM: generalized additive model
GATE: General Architecture for Text Engineering
HCPCS: Healthcare Common Procedural Coding System
HCUP: Healthcare Cost and Utilization Project
hx: history
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification
IE: information extraction
info: information
LOINC: Logical Identifiers Names and Codes
LS: living situation
MN: malnutrition
MO: moisture
NLP: natural language processing
pAUC: partial area under the curve
PrU: pressure ulcer
PrU+: presence of a pressure ulcer
PrU-: absence of a pressure ulcer
ROC: receiver operating characteristic
SCI: spinal cord injury
SCI/D: Spinal Cord Injury and Disorder
VHA: Veterans Health Administration
VINCI: Veterans Affairs Informatics and Computing Infrastructure
VSSC: VHA Support Service Center

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Protocol

Adaptation, Implementation Plan, and Evaluation of an Online Tobacco Cessation Training Program for Health Care Professionals in Three Spanish-Speaking Latin American Countries: Protocol of the Fruitful Study

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Abstract

Background: Tobacco cessation training programs to treat tobacco dependence have measureable effects on patients' smoking. Tobacco consumption in low- and middle-income countries (LMICs) is high and slowly decreasing, but these countries usually lack measures to face the epidemic, including tobacco cessation training programs for health professionals and organizations. Based on a previous online smoking cessation training program for hospital workers in Spain, the Fruitful Study aims to increase smoking cessation knowledge, attitudes, self-confidence, and performance interventions among health care professionals of three Spanish-speaking low- and middle-income Latin American and Caribbean (LAC) countries.

Objective: The purpose of this paper is to describe the methodology and evaluation strategy of the Fruitful Study intended to adapt, implement, and test the effectiveness of an online, evidence-based tobacco cessation training program addressed to health professionals from Bolivia, Guatemala, and Paraguay.

Methods: This study will use a mixed-methods design with a pre-post evaluation (quantitative approach) and in-depth interviews and focus groups (qualitative approach). The main outcomes will be (1) participants' attitudes, knowledge, and behaviors before and after the training; and (2) the level of implementation of tobacco control policies within the hospitals before and after the training.

Results: To date, adaptation of the materials, study enrollment, and training activities have been completed. During the adaptation, the main mismatches were language background and content adaptation. Several aids were developed to enable students' training

enrollment, including access to computers, support from technicians, and reminders to correctly complete the course. Follow-up data collection is in progress. We have enrolled 281 hospital workers. Results are expected at the beginning of 2017 and will be reported in two follow-up papers: one about the formative evaluation and the other about the summative evaluation.

Conclusions: There is a need to learn more about the cultural and content elements that should be modified when an online tobacco cessation training program is adapted to new contexts. Special attention should be given to the personal and material resources that could make the implementation possible. Results from the Fruitful Study may offer a new approach to adapting programs to LMICs in order to offer education solutions with the use of emerging and growing communication technologies.

ClinicalTrial: Clinicaltrials.gov NCT02718872; https://clinicaltrials.gov/ct2/show/NCT02718872 (Archived by WebCite at http://www.webcitation.org/6mjihsgE2)

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KEYWORDS

tobacco cessation; online; training; low- and middle-income countries; policies

Introduction

Background

Tobacco use remains a global public health concern; annually it causes 6 million preventable deaths [1]. The tobacco consumption epidemic is shifting to low- and medium-income countries (LMICs) such as some countries in the Latin American and Caribbean (LAC) region [2]. Currently, more than 120 million smokers live in these countries [3]; half of them will develop a tobacco-related disease and consequently will require medical care.

In the LAC region, smoking rates vary by country, sex, and socio-economic status [4,5]. In some low-income countries, such as Bolivia, Guatemala, and Paraguay, smoking rates are 10 percentage points higher than the rest of the LAC countries [6]. Thus, among men, smoking prevalence ranges from 42% (in Bolivia) to 22.9% (in Paraguay) [7]. Among women, the prevalence is lower, but it is rapidly increasing, confirming the alarming feminization of the epidemic in LAC countries [7]. In the overall region, smoking-related mortality accounts for 16% of total mortality [7], and according to the World Health Organization (WHO), smoking-related deaths will increase by 700% by 2030 [8]. The report points out that the epidemic can be curbed by implementing comprehensive tobacco control measures embraced by the WHO Framework Convention on Tobacco Control (WHO-FCTC) [9]. These measures have demonstrated the reduction of tobacco use and the increase of awareness of its hazards [9]. Guatemala, Paraguay, and Bolivia signed the WHO-FCTC early on, and have implemented some tobacco control measures, including smoke-free legislation (according to the WHO-FCTC Article 8) in workplaces and public places, including health care services. However, smoking cessation services (Article 14) have not received the same recognition and attention [5]. As a consequence, smoking cessation interventions are not well spread among health care services within these countries. Smokers are frequent users of health care services, and their contact with the health system might be an adequate “teachable moment” for quitting [10]. Indeed, according to studies conducted in the United States between 60% and 70% of patients make an attempt to quit while they are hospitalized [11]. However, in spite of these favorable conditions, evidence-based cessation programs are hardly available in LAC countries [12]. The most common barriers to incorporating tobacco cessation interventions into hospitals involve lack of training, expertise, and time. In addition, organizational and financial constraints threaten the suitability of smoking cessation interventions [6].

In LAC countries smoking consumption among health care professionals is still similar to that of the general population [13,14], and most doctors and nurses acknowledge that they have not received formal training in smoking cessation during their undergraduate or graduate training [14]. Generally, they state little confidence in its effectiveness to help their patients to stop smoking. Training facilitates having a more positive attitude on smoking cessation [15] and helps to increase the performance of smoking cessation interventions [16]. Given that about 70% of smokers visit health services over the course of a year, the lost opportunities to intervene remain significant [3]. Frequently, providers believe that smoking cessation is extremely important, but also extremely difficult due to a serious communication gap between doctors and patients that jeopardizes the opportunities to support smokers to quit [17].

Implementation research recommends addressing organizational constraints in order to overcome executive barriers when the cessation messages are delivered such as lack of time, support, and resources [18,19]. Training programs obtain higher impact and sustainability when they are fostered by organizations that allocate time, promote key champions, and provide implementation materials and resources [20,21]. At the organizational level, the chief executive should endorse the initiative and disseminate this endorsement through senior management meetings and routine communication mechanisms. In addition, an implementation committee led by a champion and members of the executive board should establish a feasible execution plan. Following this strategy, tobacco cessation training programs would better sway professional norms and promote the implementation of smoking cessation services.

In the literature, there are several conceptual training models that exhibit significant heterogeneity [22]. For example, online courses allow for distance-learning, are cost-efficient, and provide modes to teach and reinforce counseling skills that often can be difficult to convey in traditional classroom settings [23,24]. Moreover, online training has clear potential to meet large-scale training dissemination needs. Compared with classroom instruction, online training offers greater learner

accessibility, increased convenience, and greater scalability [22]. Previous online tobacco cessation training courses have demonstrated an increase in the health provider's skills to counsel patients on tobacco cessation [16,25,26]. Although there are several distant learning tobacco cessation training programs the majority have been developed and evaluated in English-speaking countries. A recent review on online tobacco dependence treatment training programs (all in English) found that 17 out of the 24 courses evaluated failed to meet minimal quality standards. The authors suggested improving instructional design elements, such as teaching effectiveness, learning strategies, instructor's role and assessment, and evaluation [27].

Using previously established programs can save time and money while increasing the likelihood of achieving successful outcomes [27]. In addition, research training initiatives have been suggested to increase capacity-building efforts, in particular within developing countries [22]. However, the evidence of distant learning training from high-income countries (HICs) may not be directly applicable to LMICs and may need cultural and content adaptations. Research is needed to develop and understand how best to implement effective smoking cessation strategies in LMICs, especially in resource-poor environments where access to health care providers are limited.

Conceptual Framework

Adaptation implies not only to the replication or translation of a program but to the process of adjusting a program to reduce mismatches between its characteristics and the new context in which it is to be implemented. Adapting a tobacco cessation education program should take into account the treatment regulation of each country, the existing guidance and proceedings, and the dynamics of the health organization [3]. Card et al [28] propose science-based pragmatic steps to adapt an existing program to new contexts based on the following steps: (1) select a suitable, effective program; (2) gather the original program materials; (3) develop a program model; (4) identify the program score components and best-practice characteristics; (5) identify and categorize mismatches between the original program model or materials and the new context; (6) adapt the original program model, if warranted; and (7) adapt the original program materials. To fill the gap of the lack of tobacco cessation training programs in Spanish-speaking LAC countries, we designed the "Fruitful study."

Prior Work

We selected the ongoing Brief Intervention for Smoking Cessation Training Program from the Catalan Institute of Oncology (ICO) as the baseline program and created a partnership between ICO and three hospitals from Bolivia, Paraguay, and Guatemala to first adapt and later disseminate the course. We intend to increase the capacity-building of the implicated organizations that will ultimately initiate a cascade of change within their countries [29]. Our training is intended to be a vehicle for the systematic dissemination of the clinical practice guidelines for treating tobacco dependence in hospitalized and ambulatory smoker patients.

The purpose of this paper is to describe the methodology and evaluation strategy of the Fruitful Study research protocol intended to adapt, implement, and test the effectiveness of an online, evidence-based tobacco cessation training program addressed to health professionals from Bolivia, Guatemala, and Paraguay.

Research Objectives

The primary research goal of the Fruitful Study is to evaluate the impact of an online, evidence-based tobacco cessation training program aimed to increase smoking cessation knowledge, attitudes, self-confidence, and performance interventions among health care professionals of three Spanish-speaking low- and middle-income LAC countries (Bolivia, Guatemala, and Paraguay).

Hypothesis

Our primary hypothesis is the participants in the online tobacco cessation training program will increase their tobacco-related knowledge, attitudes, and behaviors by the 6-month follow-up, as compared to baseline conditions prior to the training. Our secondary hypothesis is that participating hospitals will exhibit greater tobacco control progression, commitment, and implementation of tobacco cessation services.

Methods

Study Design

The Fruitful Study is a 2-year mixed-method (qualitative and quantitative) study conducted in one hospital in each of the three participant countries (Bolivia, Guatemala, and Paraguay).

For the quantitative approach, a pre-post design will be used to (1) assess participants' attitudes, knowledge, and behaviors before and after the training using a questionnaire (Tool 1); and (2) measure the level of implementation of tobacco control policies within the participant hospitals before and after the training using the Self-Audit Questionnaire (SAQ) (Tool 2). For the qualitative approach, focus groups and in-depth interviews of key persons will be used. With this methodology we aim to (1) explore the experience of adapting the training program in each of the participant hospitals; (2) ascertain participants' experience undertaking the training program; and (3) understand the opportunities and barriers of undertaking online smoking cessation training programs in the participant countries. With the results of the focus groups, the research team aims to identify any difficulties in accessing and completing the course and to make the necessary improvements.

Participants

The two main participant units from each organization are students and the hospitals themselves. The participant hospitals were selected because they had previously collaborated with the Training Unit of the ICO in training their health professionals in either electronic learning (e-learning) or in-person courses. The selected hospitals and their characteristics are shown in Table 1.

Table 1. Characteristics of the selected hospitals.

Hospital	Country	Type of hospital	Workers, n	Beds, n
Instituto Oncológico del Oriente Boliviano de Santa Cruz de la Sierra	Bolivia	Public, urban oncology hospital	359	79
Instituto de Cancerología y Hospital Dr Bernardo del Valle	Guatemala	University, public, urban oncology hospital	300	108
Instituto Nacional de Enfermedades Respiratorias y del Ambiente (INERAM)	Paraguay	University, public, respiratory hospital	746	151

Student participants were all health professionals and paraprofessional staff from the three participant hospitals. All health providers in the selected hospitals, including nurses, doctors, and other health professionals were invited to enroll in the training. Each local coordinator recruited participants from a variety of units and departments over a 6-month period through informative sessions, leaflets, and posters (designed to inform about the training program).

Procedure and Timeline

Selecting a Suitable and Effective Training Program

The selected original training program was chosen because it was shaped using evidence-based guides, was originally designed for Spanish hospitals (culturally and organizationally similar to LAC hospitals), and is addressed to hospital workers. Furthermore, offering the course through an online platform has clear potential to reduce cost and increase training coverage within participant hospitals in less time.

The original course was developed in the online platform e-oncologia based on the in-person courses offered during the last 10 years by the Tobacco Control Unit of the ICO. The theoretical framework underpinning the training program is the Stages of Change Model [30], and the curriculum was developed with the content of numerous meta-analysis and clinical practice guidelines [16,31-34] (Figure 1). We created a fully referenced, online curriculum, with feedback from an expert advisory group that oriented the instructional design to ensure the course content was palatable for an online format and aligned with the learning objectives. The goals and program components (strategies, activities, services, etc) are depicted in Figure 2. The final curriculum content of the "Brief Intervention for Smoking Cessation Training Program" is composed of 4 modules (Textbox 1).

Textbox 1. The 4 modules of the Brief Intervention for Smoking Cessation Training Program

Modules

- Module 1 describes the tobacco epidemic, tobacco-related morbidity and mortality, second hand smoke, and measures included in the MPOWER strategy to tackle smoking.
- Module 2 provides orientation on how to assess the smoker, how to assess tobacco dependence and willingness to quit, and evaluate smoker self-efficacy, previous quit attempts, previous relapses, and so on.
- Module 3 introduces the efficacy of the different levels of attention and treatment orientations (eg, cognitive behavioral, psychodynamic, medication management) and presents the clinical settings where the intervention is possible (eg, inpatient, outpatient, ambulatory treatments). It explains in detail the 5As intervention model.
- Module 4 explains in detail the different tobacco cessation treatments available (nicotine replacement, bupropion, varenicline, and other treatments). It also provides orientation about the follow-up, strategies to improve the adherence of the treatment, how to identify withdrawal symptoms, how to deal with relapses, and so on.

This online training program includes (1) slides; (2) review exercises; (3) cases of 4 patients differing in demographics, diagnostic, stages of change, setting; and (4) problem solving exercises. The training provides several materials including slides, online tutorials with an expert tutor, recommended readings, patient cessation brochures, a therapeutic pocket guideline, and an organizational recommendation model to facilitate the implementation of tobacco cessation services in the hospital setting.

The original online course was firstly tested by 10 voluntary participants in Catalonia (Spain). Evaluation of the tobacco cessation program was thereafter tested in the ICO by 150 health professionals. This pilot test proved the acceptability of the training model, the adequacy of its contents, and obtained a high level of satisfaction in the trainees. This training initiative has also been shown to increase the level of implementation of tobacco control in Catalan hospitals (according to the SAQ) [35] and the engagement of health professionals [36,37], thus making them part of the solution. This course has been accredited by the Council of Oncology in Europe (ACOE) in support of Continuing Medical Education for physicians. Since its launch in November 2012 to June 2014 more than 1000 Catalan health professionals have taken this course.

Based on literature regarding attrition among online learners [38], and our own experience delivering online training to Catalan health workers, we anticipate that roughly 50% of participants will complete all components of the proposed activities.

Figure 1. Conceptual framework.

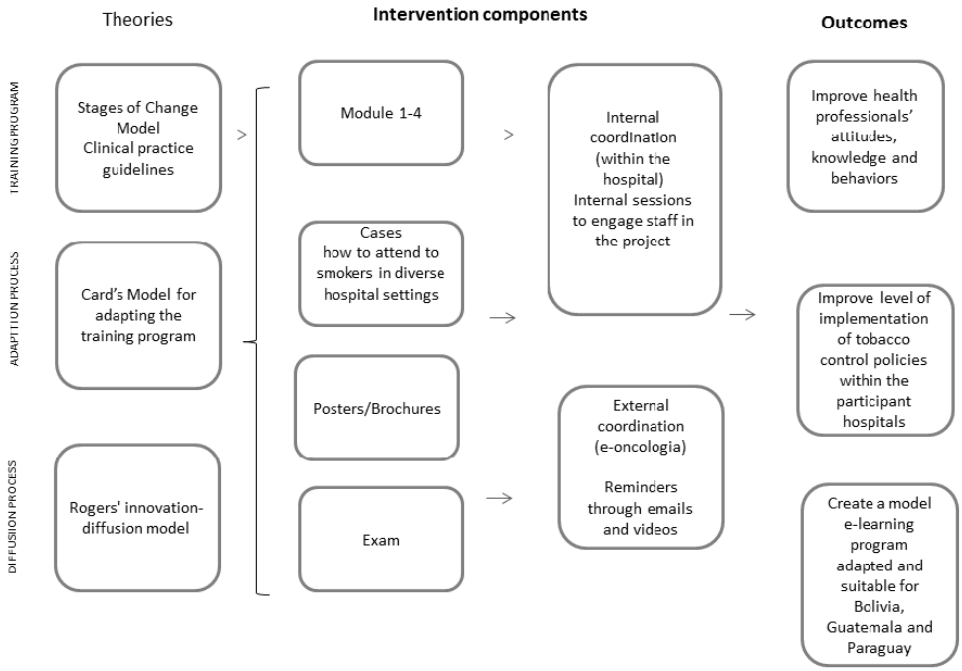
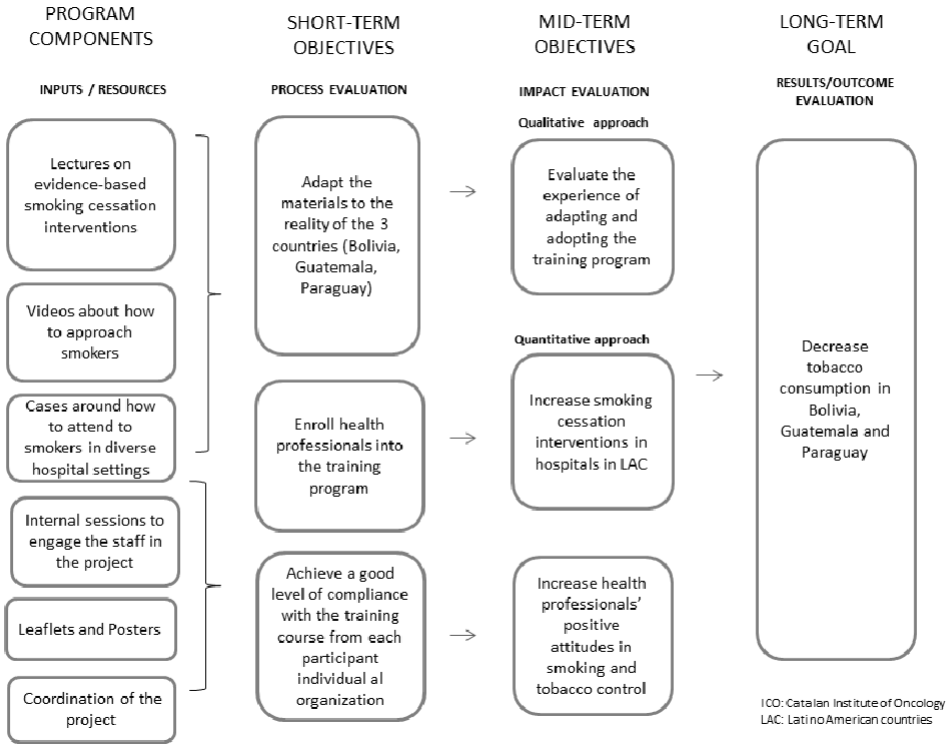


Figure 2. Program model.



Adaptation of the Material

The adaptation has been done with local partners and other stakeholders. First, a group of professionals with extensive experience in tobacco control in their country were selected for identifying and categorizing mismatches between the original materials and the new context. Experts expressed that the goal and objectives were aligned with the original program model (Figure 2). Since they approved the interface and the images employed as culturally acceptable, the same layout was used. However, we detected some mismatches (Textbox 2) that were modified in a version that was pilot tested by 8 to 10 volunteers in each country.

Textbox 2. Identified mismatches that were later modified and pilot tested

Mismatches

- Language background and literacy level in some of the terms used:

  The course was in Spanish from Spain, and the Spanish spoken in Bolivia, Guatemala, and Paraguay differs somewhat with respect to vocabulary, some expressions, and in some cases even in grammar structures.

- Description of the epidemiology smoking in Model 1:

  The original version included the situation in Spain, whereas the adapted version included the most updated data in Bolivia, Guatemala, and Paraguay.

- Tobacco cessation pharmacological treatment in Module 4 (nicotine replacement therapy, bupropion, varenicline) and settings where tobacco prevention and cessation services are performed in Spain (primary care, hospitals, quitlines, etc) were adapted to the current resources in each country.

- In case studies, the clinical simulations demonstrate the cultural characteristics of each country.

- Questions and answers of the assessment and evaluation were also changed according to the adapted contents.

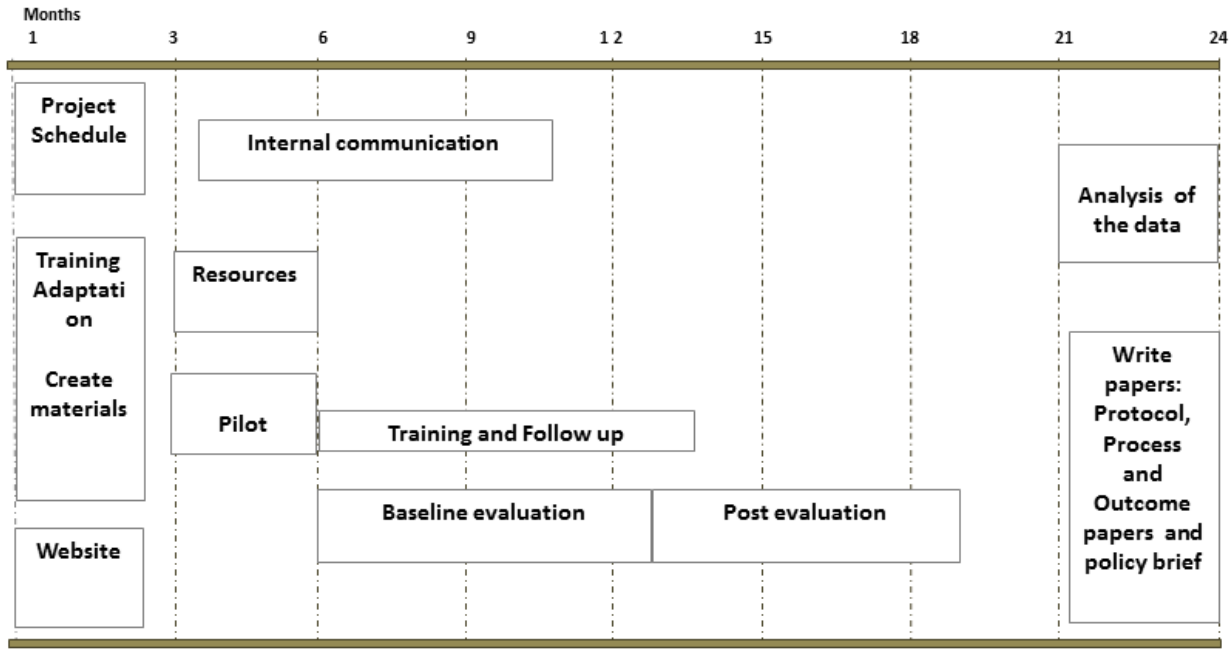
Several aids were necessary in order to enroll students. Thus, local investigators suggested a double registration method through the online platform consisting of an independent method (first one) by which students generated their own credentials and a second one assisted by a computer technician who created the login credentials and helped them in the usage of platform. The second method was necessary since many students had little or no experience in pursuing online education.

Implementation Plan

This study is expected to last 24 months (from November 2014 to November 2016). Information on the various activities is depicted in the event planning timeline (Figure 3).

This paper was written during the 18th month of the study when the post-evaluation data was being gathered. During the training (months 6 to 13), each participant had 1 month to fill in the baseline evaluation, complete the online training, and take the exam. Participants were monitored by local coordinators that acted as champions and encouraged participants to enroll and complete the course. Coordinators set monthly meetings with personnel from the different units and services to increase the number of participants and support those enrolled to complete the course. In addition, during the implementation, coordinators from each hospital offered assistance to students with little or no computer skills. Technical support was mainly used by less educated health professionals (assistants and support health professionals) and older workers who were less familiar with the use of computers. They offered their assistance in logging into the online platform, filling out the questionnaires, completing the evaluation, as well as other technical support-related issues. Participants' progress was monitored in real-time on the Web platform. The project coordinator at the ICO sent biweekly reports of the participants' progress to coordinators, and if necessary personal emails and videos that motivated the students to finish the course and complete the evaluations. Participants accessed the course using their electronic devices (mobile phones, tablets or computers) or the ones provided by their hospitals during and after working shifts. The hospitals from Guatemala and Paraguay made a library available with computers to facilitate students' enrolment before or after their working hours. The hospital from Bolivia provided a computer room in which students had access to the course and the support of a technician during specific hours of the day. Therefore, the participating hospitals facilitated computer and Internet access at the workplace.

Figure 3. Event planning timeline.



Evaluation Design

To design the evaluation we applied the conceptual frame for continuing medical education (CME) conceived by Moore et al [39] that fosters meaningful approaches to address the issues of health professional competence and performance. From the 7-level outcome framework, we employed those from level 1 to level 5 as follows: (1) participation (measured by coverage fulfillment of the course); (2) satisfaction (measured through a satisfaction questionnaire); (3) A-learning and B-learning procedural and declarative knowledge (measured using a pre-post test of knowledge); (4) competence (measured using a pre-post self-report on competence); and (5) performance (measured using a pre-post self-evaluation report of performance). In the evaluation formative and summative assessments will be used.

Formative Evaluation

The formative evaluation will assess the adoption, implementation, and maintenance of the training program. We will measure program coverage, completion rates, fidelity with the training program, usage of the materials, and the satisfaction with the training. We will use qualitative (focus groups and interviews) and quantitative methods to gather this information. The indicators linked to the performance of the program are (2) number of participants; (2) characteristics of the participants (profession, units, sex, age); (3) number of hours dedicated to the training program; (4) program performance and fidelity to the curriculum plan (whether the students completed all the modules, the exercises as planned); (5) service utilization or dosage use of the training (time applied for undertaking the course, number of downloads of the materials, etc); and (6) opinions, experience, perceptions, and satisfaction with the training course.

Summative Evaluation

We will investigate the short and intermediate outcomes by measuring the impact of the smoking cessation training program within the participant hospitals using quantitative methods (pre-post design). This will include the level of implementation of tobacco control policies within the participant hospitals before and after the training by using the SAQ (Q1) and participants' attitudes, knowledge, and behaviors before and after the training using a questionnaire (Q2).

Instruments

Tool 1

To assess differences in tobacco control polices implemented within the hospitals we will use the European Network of Smoke free Hospitals (ENSH) SAQ [35]. This tool was developed for the ENSH-Global Network for Tobacco Healthcare Services. The questionnaire is composed of the following 10 policy standards: (1) commitment (6 items); (2) communication (4 items); (3) education and training (4 items); (4) identification and cessation support (8 items); (5) tobacco control (5 items); (6) environment (6 items); (7) healthy workplace (5 items); (8) health promotion (1 item); (9) compliance monitoring (2 item); and (10) and policy implementation (1 item). Each item is scored 1 (not implemented), 2 (less than half of the aspects are implemented), 3 (more than half are implemented), or 4 (fully implemented). The maximum score of the ENSH SAQ is 168 points, calculated as the sum of the 10 standards [35]. At baseline, the SAQ provides information on the tobacco control policies undertaken within the organization. Once it is used to monitor the project, the instrument detects the fulfilled standards and the areas for improvement.

Tool 2

Trainers' attitudes, knowledge, and behaviors will be assessed using a questionnaire composed of 63-items. The

website-delivered questionnaire is emailed to the participants at baseline and 3 months after finishing the training. The questionnaire, designed by Sheffer et al [40], takes 30 to 40 minutes to complete. The questionnaire gathers information about the provider's sex, tobacco use history, previous tobacco cessation education, level of pro-activity addressing tobacco use, and perceived success in helping patients stop using tobacco [40]. Perceived knowledge and attitudes about treatment of tobacco use will be determined by assessing the levels of (1) motivation; (2) knowledge about tobacco cessation; (3) self-efficacy; (4) importance of providing tobacco use interventions; (5) effectiveness of interventions; (6) importance of barriers; (7) readiness; and (8) level of tobacco cessation intervention provided assessed by the 5A's model, an evidence-based framework that helps health professionals to structure smoking cessation interventions by identifying all smokers and offering support to help them quit. The 5A's model consists of 5 components: ask, advice, assess, assist, and arrange follow-up. All items are assessed on a discrete scale from 0 (none or not at all) to 10 (the most possible). The pre-test will be administered immediately prior to the training. The post-training assessment is composed of a 37-item questionnaire assessing providers' knowledge, attitudes, and behaviors, as assessed in the pre-test.

Focus Groups

Each participant country will carry out at least 5 focus groups with hospital workers enrolled and not enrolled in the course. Participants will be volunteers. The focus groups will consist of homogenous working categories to avoid possible reticence of some participants to openly talk in the presence of their supervisors. In each country focus groups will be conducted by external local qualitative researchers that will follow the same protocol.

Data Analysis

Descriptive statistics will be used for the quantitative indicators. The quantitative variables will be summarized using means and other central tendency measurements, whereas the qualitative data will be summarized by computing their frequencies and percentages. The qualitative indicators gathered by the qualitative methods (focus groups and interviews) will be summarized using the classical content analysis approach (creating codes and chunks of information and the researcher complements the codes with description of this code). Analysis of the data will be validated by informants to increase the reliability of the data [41].

Usual statistics will be used to describe the sample and non-parametric tests will be used for pre-post comparisons for tobacco control policies (measured by Tool 1) and the trainees' knowledge, attitudes, and behaviors (measured by the Tool 2). In addition, a validity and reliability test of both instruments is planned.

Sample Size

Based on literature regarding gains of training [27,40], we anticipate an increase of 40% in health professionals' level of knowledge, attitudes, and perception in tobacco cessation from baseline to 6 months. Given this estimate, we will need a minimum of 43 participants per hospital, (total 129, alpha=.05, beta=.1, and 15% dropouts). However, we expect at least an overall enrollment of 300 professionals (100 per hospital).

Results

We have enrolled 281 hospital workers (105 from Bolivia, 88 from Guatemala, and 88 from Paraguay). The overall average completion rate is 66.2% (186/281). At the time of submission of this paper, data collection for the post-evaluation was underway. Evaluations will finish in November 2016 and results are expected by the beginning of 2017. Results of this study will be reported in two follow-up papers: one about the formative evaluation and the other about the summative evaluation.

Discussion

Principal Findings

We will consider a good level of coverage of the training program if at least 50% of the enrolled health professionals in each hospital conclude the training program. We will measure the engagement of the training program with the focus groups and key informant interviews. We anticipate that hospitals will increase their tobacco control policies by 20% to 30% according to the SAQ. In addition, we anticipate that health professionals' level of knowledge, attitudes, and perception in tobacco cessation will increase to 30% to 40%.

Limitations and Strengths

Health professionals and paraprofessional staff from the three countries will be invited to voluntarily participate in the project. We will be able to determine whether the recruitment process used by each coordinator affects both the number of participants recruited and the commitment to start and finish on time. We hypothesize that as they agree to join, they will be highly motivated to pursue the course and we expect many of them to succeed on their own. However, participants may have varying levels of computer skills and Internet usage that could affect their course enrollment and progression. Online training programs also require devices for their use (ie, computers, tablets or mobile phones with app capabilities) and a high speed Internet connection. Although Internet services and technological devices are rapidly growing in low-income countries [42] it may not be the same as in HICs. Nevertheless, the course could be followed by these platforms facilitating the connectivity among users (tablets, mobile phones) being able to complete the training program at home or in their working hospitals. We foresee that many of the students will be using mobile phones as their primary access to the course, because mobile phones are more accessible in these countries than computers [42]. Furthermore, the participants could have different knowledge in smoking cessation interventions within participant hospitals and among the different countries. This could make comparisons among participant countries very interesting. The fact that we included baseline and post-intervention evaluations will permit the evaluation of these differences.

Comparison With Prior Work

According to a paper by Ng et al [43] tobacco use in these three countries is decreasing at a slower pace than in developed countries. Furthermore, tobacco cessation services have been poorly implemented in these countries [5] mainly because of the lack of knowledge and skills of health providers, difficulty to ground tobacco cessation interventions in health care organizations, and lack of working groups and leaders on this topic [6]. Online education in tobacco cessation might be the solution to provide evidence-based treatment for tobacco dependence in these countries because it is cost efficient and can reach remote locations. Most of the existing smoking cessation training programs have been designed in HICs and are available only in English [27]. Nevertheless, the process of spreading new learning approaches requires cultural and content adaptations that require reviewing whether the material and examples are applicable to the new target group [44]. To our knowledge this is the first study that tests the feasibility and effectiveness of implementing an online smoking cessation training program addressed to health care providers in Bolivia, Guatemala, and Paraguay. We thus consider this study approach innovative because (1) it adapts a straightforward smoking cessation training program through an online platform addressed to all hospital workforce levels (from doctors, nurses, and assistance personnel) of three LMICs in LACs; (2) it applies an organizational model in LACs to promote smoking cessation training within the organization; and (3) it evaluates its impact using quantitative and qualitative methods from the individual level (by measuring students' knowledge, attitude, and behavior gains before and after the training) to an organizational level by measuring whether the organization has increased tobacco control policies before and after the training. Moreover, facilitators and barriers of implementation will be evaluated by using focus groups and in-depth interviewers to key people involved in the project.

It is for these reasons that the methods and results of Fruitful Study may offer a new approach to adapt and implement programs to LMICs countries in order to offer education solutions through the use of emerging and growing communication technologies.

Conclusions

It is critical to develop distant learning programs to train health workers in tobacco cessation in LMIC where opportunities for continuing education are scant and sometimes not well adapted to the reality of their contexts. This study will show whether it is possible to adapt and implement an online course in developing countries. In addition, we will determine how best to implement effective distant-learning strategies in organizations belonging to LMIC, especially to detect what resources and aids are required to make the training possible in all levels of the workforce. Finally, we will measure whether the training program will increase knowledge, attitudes, and perception in tobacco cessation among participants and will produce changes in tobacco control policies at the organizational level.

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Authors' Contributions

CMM and EF conceived the project. CMM coordinated the contents of the program. EF and AC co-designed the study, oversee the training content, and supervise the day to day activities. OG and MM manage the technical support with the online platform. MAA, CS, and PC are the project leaders in their hospitals and are responsible for advancing the project activities as scheduled.

Conflicts of Interest

None declared.

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Abbreviations

ENSH: European Network of Smoke free Hospitals
ICO: Catalan Institute of Oncology
HIC: high-income country
LAC: Latin American and Caribbean
LMIC: low- and middle-income country
SAQ: Self-Audit Questionnaire
WHO: World Health Organization
WHO-FCTC: WHO Framework Convention on Tobacco Control

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Original Paper

The Epital Care Model: A New Person-Centered Model of Technology-Enabled Integrated Care for People With Long Term Conditions

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Abstract

Background: There is worldwide recognition that the future provision of health care requires a reorganization of provision of care, with increased empowerment and engagement of patients, along with skilled health professionals delivering services that are coordinated across sectors and organizations that provide health care. Technology may be a way to enable the creation of a coherent, cocreative, person-centered method to provide health care for individuals with one or more long-term conditions (LTCs). It remains to be determined how a new care model can be introduced that supports the intentions of the World Health Organization (WHO) to have integrated people-centered care.

Objective: To design, pilot, and test feasibility of a model of health care for people with LTCs based on a cocreative, iterative, and stepwise process in a way that recognizes the need for person-centered care, and embraces the use of digital technology.

Methods: The overall research method was inspired by action research and used an agile, iterative approach. In 2012, a living lab was established in a Danish municipality which allowed for the freedom of redesigning health care processes. As the first step, a wide group of stakeholders was gathered to create a layout for the reorganization of services and development of technology, based on established principles for innovative management of people with chronic conditions. The next three steps were (1) a proof of concept in 2012, (2) a pilot study, and (3) a feasibility study from 2013 to 2015, in which a total of 93 chronic obstructive pulmonary disease (COPD) patients were enrolled. Citizens were provided a tablet-based solution for remote follow-up and communication purposes, and access to a 24/7 response and coordination center that coordinated both virtual and face-to-face support for COPD management. In step five the initial model was extended with elements that support continuity of care. Beginning in the autumn of 2013, 1102 frail elderly individuals were included and offered two additional services: an outgoing acute medical team and a local subacute bed function.

Results: Based on the findings from the iterative process, and evolving technology and workflow solutions, we propose a robust and feasible model that can provide a framework for developing solutions to support an active life with one or more LTCs. The

resulting Epital Care Model (ECM) consists of six stages, and serves as a template for how a digitally-enhanced health service can be provided based on patients' medical needs. The model is designed to be a proactive, preventive, and monitoring health care system that involves individuals in the management of their own health conditions.

Conclusions: The ECM is in accordance with WHO's framework for integrated people-centered health services, and may serve as a framework for the development of new technologies and provide a template for future reorganization.

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KEYWORDS

integrated care; technology enabled; innovative care; chronic obstructive pulmonary disease (COPD); frail

Introduction

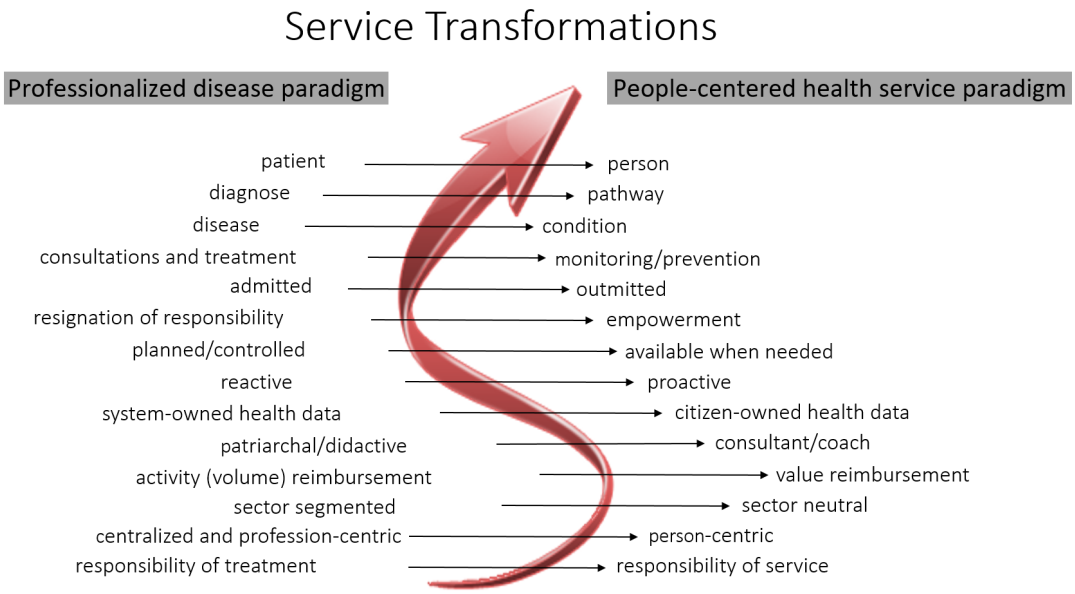
For more than half a century it has been recognized that people living with chronic illness need to develop the knowledge and understanding of their conditions. This knowledge provides patients with the means to recognize the appropriate changes in behavior that will improve self-management of their conditions with support from their doctors, allied health professionals, and others in their environment [1,2]. In response to this need, more effective approaches for people with long-term conditions (LTCs) have been developed. One example is the Chronic Care Model (CCM) [3], which was further extended by the World Health Organization (WHO), resulting in the Innovative Care for Chronic Conditions (ICCC) Care Model [4]. During the last decade, many health care organizations have published experiences of reorganization, new business models, new frameworks, and various levels of service transformations to improve care for those with LTCs [5-11].

The main focus of most of these initiatives is to reorganize the way that health care is provided, support people in the management of their own conditions, incorporate caregivers into supporting care, and use a more holistic approach to care [12,13]. This paradigm shift has led to a redesign of services, new tasks for the workforce, and integrated care programs covering different sectors to achieve alignment of programs across sectors, involvement of patients and their relatives, and moving initiatives closer to people's communities. Although a number of initiatives inspired by the CCM and ICCC have been implemented, the benefits of system reorganization and incorporating the full advantage of digital health remains to be demonstrated on a larger scale.

In response to this need, we present a project that has the overall aim to fill this gap by demonstrating how the entire care process can be redesigned with electronic health (eHealth) tools. This paper outlines the voyage from vision and ideology to a translation of fully functional transformed health care service. Our idea of a person-centric health care system based on the *personalized health paradigm* follows the road map of service transformations shown in Figure 1. The final result aims to be a proactive, preventive, and monitoring health care system that involves individuals managing their own health and conditions.

The overall goals of this project are to (1) provide an understanding of how provision of health care can be designed for people with LTCs by taking advantage of technology, and then (2) based on these findings, propose a new prehospital care model. To achieve the first goal, the first part of this paper, the Methods section, is organized as a step-wise process in which eHealth technology is systematically brought into the design, pilot, and feasibility phases in the development of a novel eHealth driven socio-technical care system. In the second part of this paper, the Results section, we present the Epital Care Model (ECM), which has emerged from the project.

Figure 1. A roadmap for service transformation in healthcare systems. To assist both the individuals and their health care providers, there is an emergent need to develop advanced information and communications technology systems and services for personalized care that may support such transformations.



Methods

Establishment of a Living Lab

The ECM project was initiated in early 2011, based on knowledge gathered during two previous projects: The Capital Region of Denmark's development of clinical digital paths for chronic conditions (Kronikerprojekt 5; *K5*) and the *Virtual Hospital* [14,15].

K5 was initiated by the Capital Region of Denmark in 2010, and supported by the Danish Ministry of Health. This initiative resulted in a service model for how three chronic conditions (chronic obstructive pulmonary disease [COPD], ischemic heart disease, and type 2 diabetes mellitus) could be planned digitally. The study demonstrated that it was possible for all health professional stakeholders to interact and coordinate via a digitalized individual plan that contained an updated list with planned health services in a cross-sectorial setup [14]. The model was tested with prototypes and clinical users representing all sectors [14].

In the *Virtual Hospital* study, patients with acute exacerbation of COPD were admitted to a hospital within 24 hours and were randomized to be either *admitted* or *outmitted* [15]. The results suggest that rather than being hospitalized, COPD patients can be treated at home using telehealth technology in combination with an organizational and service redesign, without increasing mortality. The study also demonstrated that individuals need introduction to new ways to manage their condition before they become acutely ill and distressed. Furthermore, if patients are introduced to enhancing technology that increases autonomy and coping, patients are (to a certain extent) reluctant to part with these aides [16].

Inspired by these findings and two other Danish projects [17,18] that demonstrated the benefits of telemedicine support for COPD patients, we assembled a group of stakeholders from the municipality of Lyngby-Taarbæk, in the Capital Region of Denmark. The goal of this initiative was to develop a living learning lab isolated from the existing conventional health care systems, which allows for innovative and disruptive thinking on how to deliver health care [19].

In Denmark, health care provision is organized in three structures: the regions, that run the hospitals and contracts with general practitioners (GPs); the municipalities, that have the responsibilities of rehabilitation and home care; and GPs, who are private doctors working by contract for the regions, taking care of a certain number of people in their community. GPs can be organized in single or group practices [20]. The management of people with chronic conditions is constantly evolving, with strategies being updated every year. The latest update was published in 2016 and is based upon seven recent shared-care projects, including the project reported here [21]. Currently, people with LTCs are handled according to regional clinical pathways, which are designed in accordance with national guidelines [22]. The GP is the coordinator and primarily sees the patients. The hospitals follow the people with more severe conditions and the municipalities are only involved for people with a need of home care, or those who are referred to a standardized rehabilitation program.

The technological infrastructure for national health care is based on a backbone governed by the Danish Health Care Communication Network (MedCom), which is a national infrastructure that enables standardized communication between all official health organizations [23]. MedCom offers a set of standardized communication services, such as a referral from the GP to the hospital or a discharge letter from the hospital to the GP. Additionally, patient data is presented in a national health portal [24], which offers patients and their relatives access to health data and information about clinical conditions with three days of delay. The municipalities have their own care records, which exchange data with the hospital systems and GPs via MedCom communication services. The messages are exchanged in EDIFACT or XML formats. Most health care

services are free for everybody and the economy is governed by rates for the hospitals and a fee for service reimbursement system for the GPs. The municipalities also reimburse 34% of the hospitals' costs related to patient admissions (up to 2000 Euros). A reduction in outpatient visits or patient admissions will therefore result in savings for both hospitals and municipalities. These saving may not materialize for the hospitals. Conversely, a reduction of hospital bed days may increase the costs for the municipalities due to patients spending more days in their own homes, thereby increasing needs for homecare.

The Theoretical Approach

This project was initiated as a collaborative learning process with noncontractual participation from enterprises and patient associations. Access to a relevant clinical setting was provided through an agreement between the first author (KP) and the mayor of Lyngby-Taarbæk municipality in 2011. The project was designed to be an iterative process, aimed to create collaborative learning, performed by practitioners and with the researchers taking an active role in the project. The process was inspired by action research [25], the agile manifesto [26] with the Scrum model, and the *plan-do-check-act* approach [27], which all build on the same core principles: plan, action, observe, evaluate, reflect, and then iterate. The final stage resulted in a model of how people with LTCs can be managed in a prehospital setting. Originally the project was designed to have four steps, but during this project we decided a fifth step was needed.

The Process

Step 1: Initialization

The initial objectives of the ECM project were

1. To introduce methods, technology, equipment, and organization to support COPD patients to detect potential exacerbation of their disease, in order to establish appropriate early intervention.

2. To set up a management system for acute exacerbations, primarily based on virtual monitoring and remote communication facilitated by telehealth technology, in order to supervise and support self-management.

3. To involve other health care providers in a way that supports explicit patient needs, and is not constrained by official roles or affiliations, to ensure a seamless patient pathway.

4. To design all services to support self-directed, health-literate, and empowered people with COPD.

The team represented: conventional health care services; small, medium, and large enterprises; patient representatives; and researchers. The participants formed an informal network whose goal was to develop a people-centered digitally supported environment that could provide health services, health care, and other resources to support people to take care of their own health. The project was initially limited to COPD, as it is a condition in which an abundant experience with telehealth solutions exist and deteriorations are easy to follow with telemonitoring equipment [28]. The project was organized within the organizational setting of the municipality of Lyngby-Taarbæk.

In 2012, the organization consisted of a communication center that managed the home care of frail patients referred to home care and responded to their alarms. The center did not offer interaction regarding clinical conditions or home monitoring. All medical issues were referred to the patients' GPs, emergency services, or hospital services.

All participants were invited to weekly meetings and interest groups were formed with specific focuses (eg, empowerment, technology, and research); this process is reported elsewhere [19,29]. A number of enterprises committed themselves to the development of an information and communications technology (ICT) solution to monitor and register data. The resulting platform served as the infrastructure for the proof of concept (POC).

Step 2: Proof of Concept

The POC was a platform to test and develop the usability of the digital solution. This testing was carried out together with seven people with COPD from May to July 2012. The digital literacy of participants was also evaluated and usability tests were performed [30].

The telemonitoring devices used in the POC were the same as the ones used in the *Virtual Hospital* study [15]. An algorithm based on the self-monitored data set of the persons/patients was developed to detect deterioration of the condition using a traffic light format. Variation in patterns triggered attention to the nurses in the communication center by a shift in the color code: green, yellow, or red. A red color of current condition then caused a further action, comprised of an examination by a virtual contact to the person with a detailed analysis of the underlying data. If needed, the electronic doctor (eDoctor) was involved in supervision to initiate one of three medical interventions, depending on the severity of the exacerbation.

Step 3: Design of Feasibility Study

The design of the feasibility study was based on inputs from the POC, as well as stakeholders, and was initiated at the end of 2012. The response to the POC involved health care staff and entailed the adjustment of the user interface for those with COPD, and training of nurses who received calls at the existing call center. These nurses and others organized the Response and Coordination Center (RCC) functionality and developed a prototype of a medical first aid box (see Figure 2) with five different medications for treating acute exacerbations. Ordering, delivery, and renewal of medication packages was streamlined as a new service together with the local pharmacies, as was the first step of an electronic prescription.

Figure 2. Prototype of medical first aid box containing (1) short acting beta2-agonist for inhalation, (2) corticosteriods for inhalation, (3) anxiolytics (tablets), (4) prednisolone (tablets), (5a) container for sputum sample, (5b) envelope for sending sputum sample, and (6) antibiotics.

Step 4 (A & B): Kick-Off and Feasibility Study

This project was based on a RCC with access to an on-call pulmonary specialist and equipment designed for home monitoring that was delivered to the participating citizens. The organization and development was based on an iterative process with the aim to support citizens with COPD in managing their own health and in handling exacerbations. The core components were

1. A tablet with software enabling contact with the RCC by video conference, and visualization of the citizen's condition by algorithms showing indicators of deterioration with an auto-generated written feedback system.

2. Equipment for participants to monitor their own health (eg, spirometer, pulse oximeter).

Box with medicine to be used when exacerbations occurred, to avoid delays in initiation of treatments.

3. 24/7 RCC nurse with access to an eDoctor specialized in respiratory medicine.

4. Optional services by referral (eg, health coaching, dietitian, physiotherapist supporting and motivating behavioral change, and setting of new goals).

The project included services to support the processes, the RCC, and the person with COPD:

1. An eDoctor service for all patients, and to support the RCC nurses.

2. An e-technical service team, for installation, patient education, and support of the equipment.

3. Pharmacies responsible for delivery of medication boxes and advice.

4. An empowerment network consisting of a small sized personal health coaching enterprise, a dietician, and a physiotherapist from the municipality. Each member was available for consultations on a weekly basis.

All services were connected by a software platform that had interfaces designed for both participants and health professional users. In January 2013, staff were trained and the services were organized. Recruitment through rehabilitation centers, patient associations, and leaflets resulted in the first participants being enrolled in April 2013. The feasibility study continued until December 2015.

A total of 93 persons with COPD were recruited, educated, and followed (32/93, 34% male; 61/93, 66% female; mean age 73.9 and mean forced expiratory volume = 1.1 liters/second). The patients were included after a consultation by the eDoctor was performed at the patient's home, including a clinical examination and a stratification of their COPD in accordance with the Global Initiative for Chronic Obstructive Lung Disease guidelines and a subsequent evaluation by the e-technical service team. The participants were only included if they were deemed eligible, based on an evaluation of their cognitive function (Mini-Mental State Examination score above 22) and were able to cooperate and communicate with the technology.

The services provided support for active and independent living. When needed, or due to exacerbations of symptoms, more interaction with the RCC occurred with both nurses and eDoctors, who were available by virtual connection. Participants could monitor their health when they chose to, and were able to discuss their condition with nurses who were supported by the eDoctors. This approach led to a degree of active and independent living, which for some of the participants resulted in a new experience of freedom, so much so that several participants felt able to leave their homes and even travel.

As a result of the feasibility study, the following changes were made: (1) the software for the user interface was programmed as open source to enable dissemination of the code without license restrictions; (2) a second generation of the software was developed as a cocreative process between clinicians and vendors; and (3) an eDoctor clinic was established to have a legal point of entry for the medical doctors, prescriptions, and diagnostic work in this cross-sectorial setting.

Step 5: Extension of Prehospital Care Services

By the end of 2013, it was clear that the eHealth organization that had been developed had the capacity to include more extensive services than just COPD follow-up. In the last (and unanticipated) phase, we developed a new eHealth-supported service that provided in-home clinical evaluation and treatment for the following frequent conditions among frail elderly patients: urinary infection, pneumonia, COPD in exacerbation, dehydration, constipation and diarrhea, and confusion and dizziness.

The service structure was in place in September 2013, and was enhanced to include four in-house Subacute Surveillance Beds within the municipal care center, and in June 2014 also included a Mobile Acute Team (MAT). In addition, a business case was developed to convince local politicians that the project had the potential to be cost-effective, as it would reduce the number of hospitalizations by more than 40%. The business case builds on unpublished data from another project led by the first author (KP) at the Frederiksberg Hospital.

The Mobile Acute Team

This new service sent MAT nurses to the frail participants' homes when acute problems were detected. The team included five specially trained nurses certified to manage the conditions mentioned above. The eDoctors from the project developed clinical guidelines for the team based on the Capital Region's guidelines for the management of hospitalized patients, which was adapted to settings outside the hospital.

Individuals in need of a clinical evaluation could be referred to the MAT team by GPs or nurses in the municipality service, or those located at nursing homes. Those patients referred were offered an evaluation that included a medical history, clinical examination, registration of early warning score, paraclinical tests with routine blood samples and blood gas analyses, and collection of sputum and urine for investigation. The samples were collected on-site by the MAT nurse and sent to a small municipality lab for analysis. All results were immediately discussed with the eDoctor.

The MAT can administer intravenous fluids for rehydration, initialize peroral medical treatment in collaboration with the eDoctor service, and administer nebulizers for inhalation therapy for COPD. The MAT service resulted in four different clinical paths: (1) finalizing the evaluation and treatment, and referral to the participant's GP for follow up; (2) a follow up plan for a period, in which the participant is regularly evaluated by the nurses and an eDoctor; (3) referral to the Subacute Surveillance Place (SAP) unit, for participants to have immediate access to a health professional, be evaluated regularly, and see a doctor within 24 hours; or (4) referral to a hospital for more thorough assessment and treatment.

The Subacute Surveillance Place

The SAP had the main purposes of being an alternative to admission to hospital, and having the potential of increasing quality of life for participants with acute deteriorations. The goal was to train and increase the competence of the municipality nurses to enable them to take care of uncomplicated medical conditions while being supervised by the eDoctors, with the intention of preventing unnecessary costly hospital admissions. Four in-house beds were established and five nurses were certified to handle the treatment, observation, and care of the patients (based on guidelines).

Upon arrival, patients went through a standardized medical examination, including history and clinical examination by the nurse, and supplemented with paraclinical tests. The results were confirmed with the eDoctor and relevant treatment regimens were initiated. Within 24 hours the patients were physically seen by a medical doctor for further planning.

Between September 2013 and December 2015, 168 participants were admitted to the SAP, and the MAT team performed 2007 home visits for 1102 different individuals.

Proposal of a Whole-System Approach for Management of People With One or More Chronic Conditions

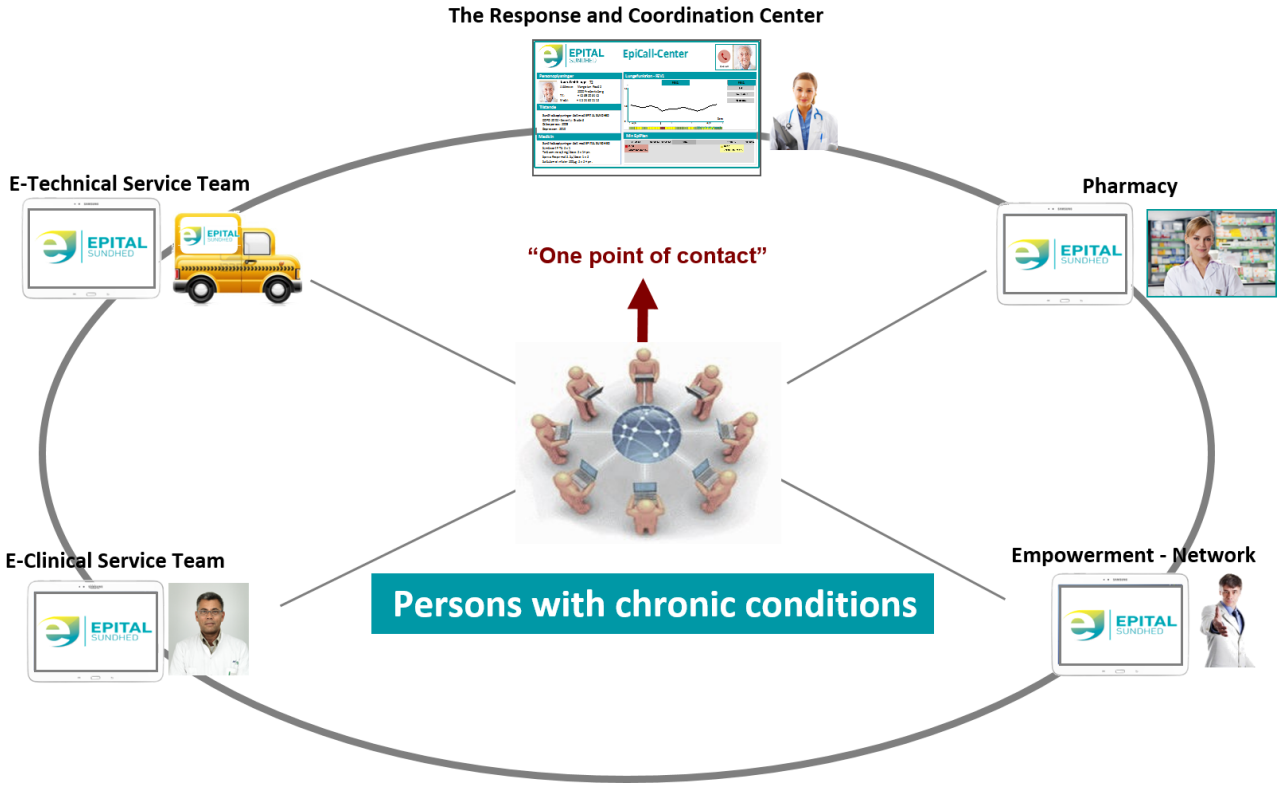
The evolutionary process described above was intended to be disruptive, and occurred outside the established system. This experience has led us to propose a new model for organizing and providing health care for people with one or more LTCs. The proposed model is in alignment with Wagner's CCM, WHO's ICCC, and the newer WHO framework for integrated people-centered health services [11]. The key characteristics are to provide accessibility with a model that is not overly complex, and is intended to be less costly than current models.

Results

Figure 3 outlines the principles of the ECM, and can be conceptualized as a step-wise increase in the care resources that are made available in response to increased care needs. All care is person-centered, which in the ECM means that the patient is in control of care goals, care plans, and changes in care plans.

Each stage of the funnel builds on the former stages. The patient will move back and forth in the funnel depending on their current health condition. The patient voluntarily monitors his/her health condition, and transmits their health status to the RCC by ICT-communication on the mobile tablet. The tablet supports relevant sensors, self-reports, and video communication with the RCC. The RCC responds to changes in health status, according to the agreements made with the patient, as they are recorded in their individual care plan. The RCC responds and triages unanticipated or emergency requests together with the patient, with a primary focus of uncovering the citizen's and informal caregiver's needs.

Figure 3. Epital Care Model services in the proof of concept and feasibility study.



Stage 0: Citizens With Undiagnosed/Unknown Long-Term Conditions

This segment of the population is invisible and therefore not connected to the ECM service network. The focus here is on early detection of potential diseases. The GPs and patient organizations/networks are likely to play an essential role at this stage.

Stage 1: Active and Independent Living

In this stage citizens live their life connected to the ECM services in accordance with their personal needs, values, and preferences. This stage is possible even in the face of serious health issues. Support for the active informed patient, in terms of self-management support, is fundamental both here and at all other stages of the funnel. The local pharmacies offer regular evaluation of prescriptions for enrolled individuals. Enrolled citizens have an acute medicine box with prescribed medication for acute exacerbations, which allows the eDoctor to initiate urgent treatment at home. The participants are offered free use of the empowerment network services.

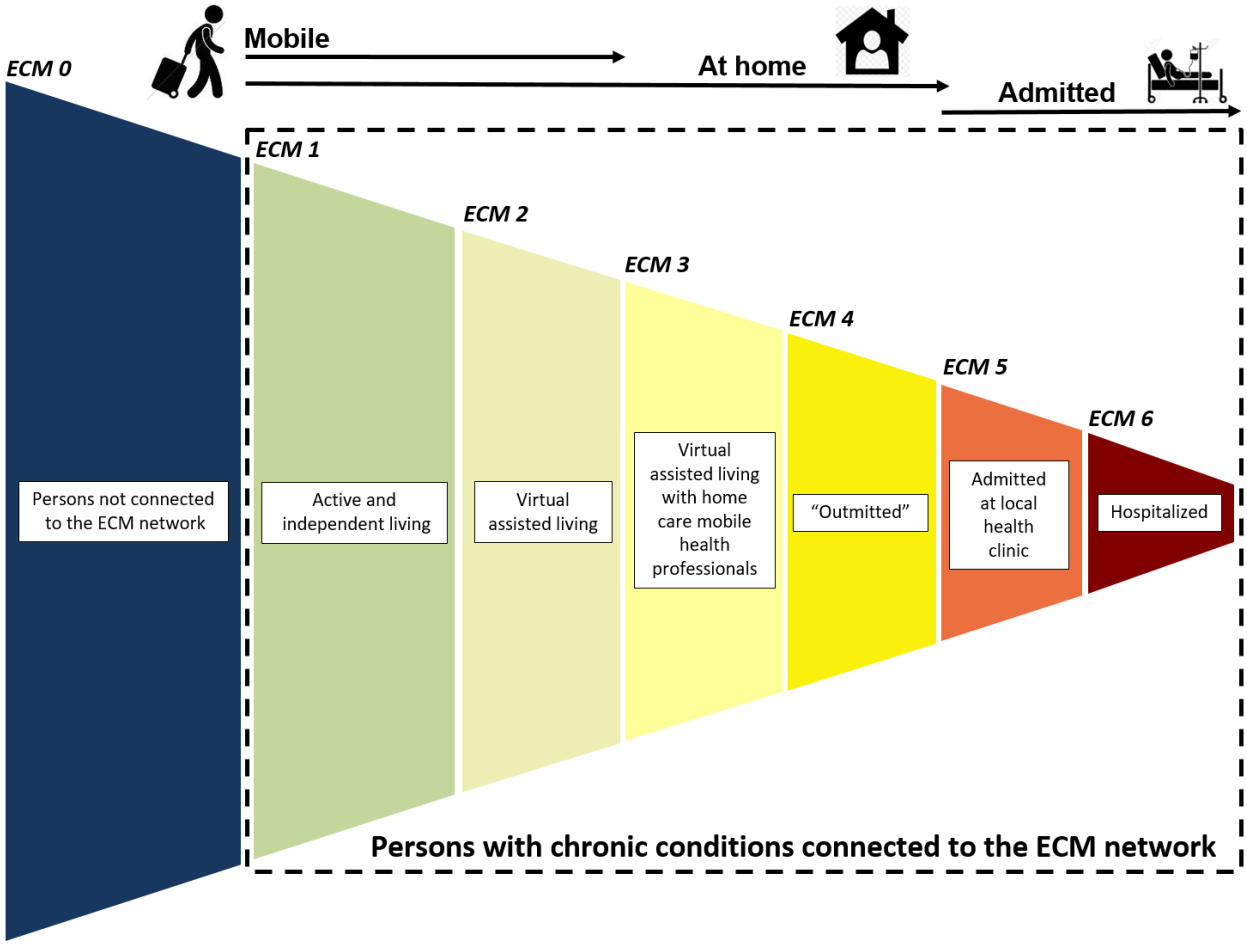
Stage 2: Virtual Assisted Living

The participant makes use of virtual support through *one-point-of-contact* with immediate response and 24/7 availability, also including indirect access to the eDoctor . The RCC provides e-consultations with relevant health professionals. Proactive treatment may be started using the acute medicine box.

Stage 3: Virtual Assisted Living With Assistance From Home Care Mobile Health Professionals

Virtual assistance is added with mobile support in the participant's home, such as physical visits from the MAT (see Figure 4). The empowerment network can still be used in this stage, and all stages listed above.

Figure 4. The Epital Care Model illustrated as a funnel.



Stage 4: Outmitted at Home

The goal is to enable the participant to stay in their home as long as possible without compromising safety. Treatment, monitoring, and follow-up by both virtual and mobile teams can be intensified, corresponding to an inpatient setting. The eDoctors play an essential role in this setting, being proactively available virtually and responsible for the treatment in the citizen's home, while having the MAT nurses as the *eyes and hands* at the point of care in the home. The empowerment network is not activated in stages 4 and 5, in which services are switching towards traditional health care deliveries.

Stage 5: Admitted at Local Health Clinic

If required, the participant is moved to a local health clinic (SAP) equipped with basic hospital facilities, including 24/7 physical availability of certified ECM health professionals.

Stage 6: Hospital

If the former services and efforts are insufficient, the citizen is admitted to hospital with specialized health care services. An implementation of the model is the service that is currently integrated into the ECM in Lyngby-Taarbæk, as shown in Figure 5. The concept involves the following organizational elements of health care, all of which are supported by advanced ICT technology:

1. A 24/7 RCC responds to all requests for service and coordinates the delivery of services. The RCC also supports the participant's plan and is responsible for data coordination. Nurses and social care specialists staff the RCC.

2. Empowerment network services are delivered either as e-services at home through digital tools (ie, training, health coaching, and dietary support), or as personal or group sessions via electronic video communication channels.

3. An e-technical service team is able to support participants' needs at home with regard to installing technology and training with the technology. The service team also brings medicine cases and collects laboratory tests that are performed at home.

4. The E-Clinical Service Team, including an eDoctor, is responsible for the execution of all clinical services in the total system. Preferably the clinical team works via the electronic channels, but uses the media as necessary to guarantee the best possible support of participant decisions, including home visits. Ultimately, specialist guidance can be available for the citizen, if needed.

5. The pharmacy provides support by disseminating information to participants and training patients in the use of medicine, and produces and delivers the medicine required.

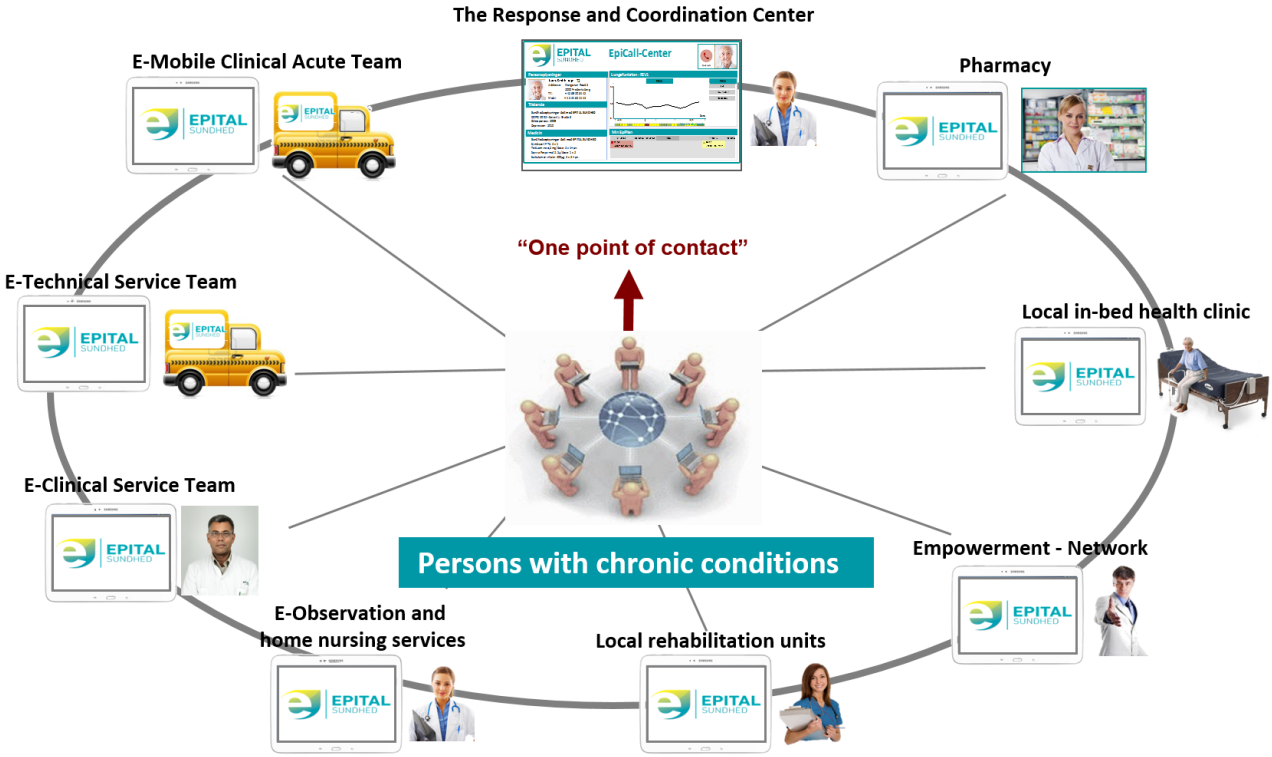
6. An observation service, coordinated by the RCC, which is capable of online observation of measurements from home care instruments connected to the citizens' home technology. This service is designed to seamlessly take control upon the participant's request.

7. An outgoing team of specialized nurses provide home nursing. These nurses are skilled in preventive treatment, if health is deteriorating rapidly and threatening the possibility of hospitalization.

8. Local rehabilitation units ensure rehabilitation when wanted and needed.

9. A local in-bed clinic service, for citizens who cannot continue at home.

Figure 5. Full scale Epital Care Model services: the health services that are embedded in the Epital Care Model covering ECM 1-5.



Epital Care Model-Compliant Technology Setup

Appropriate technology is a prerequisite for a health care system to become ECM-compliant. The technology must be able to support the core ECM services, the ECM actors, and their collaboration and coordination. As a consequence, various tools, devices, and ICT functionalities must be available for the ECM actors. At all times, it is mandatory to keep an alignment between services, actors, and functionality of the technologies.

The core processes of the ECM are briefly described in Table 1.

Actors are persons or digital agents who are characterized by their role, organizational and employment relations, authorization, certification, health literacy, and capabilities. The central actors of an ECM network are described in Table 2.

To execute the ECM services in an easy and appropriate way, the actors must have access to a set of ICT devices and functionalities that are shown in Table 3.

Table 1. Core Epital Care Model (ECM) services.

Process type	Short description
Inclusion and stratification	All participants are offered: general health information; clinical examination for diagnosis, stratification, and medical information; and delivery and education in using ECM equipment, including acute medicine box.
Self-monitoring	The self-monitoring process includes the measurement and acquisition of relevant information in context. Examples include recurrent self-monitoring of pulmonary function, temperature, and pulse. These measurements need to be integrated into daily living. The self-monitored data is the fundamental resource that enables all others activities in the ECM network to be stratified.
Supervision	The Response and Coordination Center (RCC) monitors and supervises the connected population; this includes surveillance functions that can detect persons at risk for developing subacute complications and acute deteriorations, in order to initiate preventive and proactive interventions.
Contact	All participants can contact the RCC at any time, or be contacted if the RCC registers any deterioration. The contact can be text-based (asynchronous communication), via telephone, or via videoconference (synchronous communication). Depending on the RCC's assessment of the situation, a contact may be followed by an advisory consultation, a visit for more assistance, or initiation of medical treatment.
Clinical examination	The clinical examination can be either physical or virtual if video-based communication is possible. The clinical examination will vary in structure but always includes a clinical conclusion based on the content and findings at hand, and will be documented in the medical record.
Treatment	Medical treatment is always preceded by monitoring and a clinical examination. A medical treatment is typically a process involving a prescription of medication and a timeline with follow up consultations, either physically (ECM >2) or virtually (ECM=2).
Pharmacy services	The pharmacy services include ordering, packing, and delivering prescribed medicine, as well as maintenance of the content of the acute medicine box.
Technical service	Technical services include delivery, maintenance, user education, and problem solving activities regarding the ECM-connected person's equipment.
Paraclinical investigation	Paraclinical services include diagnostic procedures of different kinds (eg, blood sampling and analysis, urine tests, and electrocardiogram).
Health coaching services	Health coach services are consultations (or a series of consultations) for empowering a person.

Table 2. Epital Care Model (ECM) actors.

Actor type	Short description
Person	An ECM-connected person is an individual with one or more chronic conditions who is a member of an ECM network. The person gradually moves to be a patient when the context shifts from ECM1 (active and independent living) towards ECM6 (hospitalized living).
Response and Coordination Center nurse	The Response and Coordination Center (RCC) nurse is the coordinator of the ECM network. The RCC nurse conducts population monitoring, initiates proactive contacts to ECM connected persons at risk, and coordinates the services in treatment for acute deteriorations. The RCC nurse is always backed up by a responsible eDoctor regarding prescriptions and decision making.
Mobile Acute Team nurse	Mobile Acute Team nurses are trained and certified in handling frail people, in collaboration with the eDoctors; this includes clinical assessment and investigations.
Subacute Surveillance Place nurse	Subacute Surveillance Place nurses are municipality nurses who are qualified to take care of the patients in the subunit.
eDoctor	The eDoctor is a medical doctor combining a medical specialty (typically general practitioner or internal medicine) with a specialization in eHealth. The eDoctor is capable of taking treatment responsibility in the ECM network, which includes virtual treatments according to the context filters in the ECM funnel.

Table 3. Information and communications technology functionality and devices.

ICT/device type	Short description
eHealth-box	The eHealth box is delivered to all Epital Care Model (ECM)-connected persons and contains: (1) an Android tablet with the ECM Health Navigator (Appinux) that contains a condition app (which includes an algorithm for triaging a data set regarding lung function measures) and the ability to video conference with *one point of contact* to the Response and Coordination Center (RCC); (2) a spirometer; (3) a pulse oximeter, included in the facility to measure pulse activity; (4) a thermometer; and (5) a medical first aid box.
Epital Care Model medical record (EpiProcess)	EpiProcess is a process-oriented shared care system that enables the eDoctor and the RCC nurses to input into the same system and coordinate their activities, particularly with respect to exacerbation treatments and follow-ups. EpiProcess is integrated with the Health Navigator, enabling the RCC and eDoctor to evaluate or react on the ECM population's self-monitored data.
Municipality Care Record (Avaleo)	The municipality of Lyngby-Taarbæk has a care record system (Avaleo) which is used for those who receive municipality health care services. EpiProcess can communicate with the Avaleo system via MedCom messages.
Messaging (MedCom) and the Health Communication Network	All activities that involve medical treatment are electronically communicated to the general practitioner through standardized MedCom messages generated by EpiProcess.
National Medication Service (FMK)	FMK is a national medication service for coordinating updated information about all medicine related to persons [31]. FMK was not available at the time of the feasibility study, and prescribed medicine had to be documented in both the EpiProcess and the eDoctor systems.

Discussion

For more than half a century it has been realized that people with chronic conditions need to be involved in managing their own conditions through education and activities, which increase health literacy and agency, and facilitate changes in health behaviors [1,2,32]. In 1996, Wagner [3] focused on this issue and since then it has been repeatedly emphasized [4,12,33]. In 2016 the WHO concluded that we are still in need of models and solutions to support large scale implementation of integrated people-centered health services [11].

In this paper, we propose a new way to organize health services for people with chronic conditions. The model is based on a five-year period of action research involving organizational learning and a collaboration between a wide range of stakeholders. The ECM has addressed three great challenges: how to create a personal engagement, how to benefit from using technology, and how health care provision can be reorganized. The ECM integrates our learning from two projects with different approaches into one new model that supports people in all stages of their chronic conditions, and offers them an opportunity for active living. One approach is the involvement of people with COPD in monitoring and handling their condition, which is assisted by an RCC. The other approach is to manage individuals suffering from acute deteriorations with a significant risk for acute hospital admission. The most frequent causes of the acute deterioration include dehydration, infection, and other acute medical problems. Our learning has resulted in a fusion of the different approaches into one model, which may serve as a template or governance model for provision of health care to people with one or more LTCs, including the challenges of those struggling with multimorbidity and polypharmacy.

The ECM meets the requirements set out by Wagner in his proposed model for chronic care, as it both moves services closer to the individual in need, engages the participants, and includes technology to support the use of guidelines and decision making. The certification of nurses, and the way in which they work by delegation, instructions, and in dialogue with the eDoctors, also supports a changed role with new tasks. In this project, we have succeeded with a cocreative process and created organizational learning by including practitioners, academic researchers, the municipality, and other organizations.

The activities in ECM1-ECM3 have proven to be feasible and have been adopted by the involved stakeholders, and recognize that informed individuals should be encouraged and supported to make personal decisions related to their health. These decisions should be guided by their own values, and influenced (but not directed) by the health professionals' views, as recommended by Zoffmann et al [34,35].

The ECM demonstrates how technology may be used to get the best of the digital and real world to provide continuous care, thereby increasing agency and support for people to have an active and independent life, despite the burden of their chronic condition. To achieve the full benefits in ECM1 and ECM2, each participant must have a unit (such as a smartphone or tablet) with appropriate applications installed to support the management of their conditions. In ECM3-ECM5, the technology primarily supports the health professionals, but may still be used by the participants to communicate with the RCC and the connected caregivers.

It should be noted that the participants in the COPD project reported here were all able to interact with the RCC themselves and did not need support from relatives. A large-scale inclusion of people with LTCs may require that formal or informal caregivers assist them to achieve the full benefits of a given intervention, especially if the participants are cognitively impaired. Other disabilities can often be compensated by built-in accessibility tools in the devices. The training by the e-technical service team may also improve the performance of the participants by addressing particular needs in relation to their digital health literacy [36].

The model developed here may serve both as a template for development of new technologies for people with LTCs, and for future reorganization of health care. The model is generic and is not limited to a particular health organization or service

provider, but does require the individual to be actively engaged with services across multiple sectors. The ICT tools of the ECM were developed by three vendors, but the ECM service model is generic and can serve as a framework for other vendors and health care providers. The key is to implement proactive, person-centered solutions based on the principles of the CCM and ICCC, which are enabled by technology.

The innovation process was inspired by Clayton Christensen [19] and it was recognized from the start that this project would be a disruptive influence process working from outside the established system. During the project, the project group experienced restrictions due to legislation and the existing structures for provision of health care. Various strategies emerged, including the proactive and disruptive establishment of an eDoctor clinic, and the more reactive establishment of formal and informal contacts to institutions in the conventional health care system.

The initial intention to create a disruptive model for health care provision resulted in a model influenced by a normalization process [37]. The resulting ECM is not (as initially intended) a model for a parallel health care system, but serves to inform existing health care organizations about how to assist people with LTCs in managing their health in a proactive, people-centered, technology-enabled, and team-based manner. Although it may be difficult to make disruptive changes in a publicly-financed health care system, it is through a disruptive approach that fundamental change occurs in health care, which in turn has the capacity to lead to improved care and reduced costs.

The ECM has emerged from an empirical iterative research process involving public and private partners with wide contacts in the established health care system. The next step is to design a *migration* process of the ECM into other care contexts. This process has already started, and the project might have influenced the Danish national strategy, as the Danish government now focuses on decision support for elderly along with increased involvement of patients [21]. The core principles of ECM are also being used as inspiration for a Norwegian project involving three regional sites [38].

The ECM operationalizes two WHO policy papers [4,11]. It remains to be demonstrated to what extent the ECM will create beneficial outcomes and be economically beneficial. Results from the feasibility study are currently under evaluation. The ECM remains to be proven in a large-scale study that is designed to evaluate the overall benefits to people with LTCs. To facilitate the understanding of the proposed model, please refer to the screencast in Multimedia Appendix 1.

ECM has characteristics that enable the empowerment and engagement of people, reorganization of the provision of care, transformation of roles, and development of more skilled professionals by taking advantage of technology. This approach is in accordance with the intentions of the WHO's framework for integrated people-centered health services [11]. ECM may therefore be a model to assist vendors, health care organizations, and researchers with populating the WHO framework.

We welcome researchers and/or health care provider organizations to participate in the further development of both the ECM building blocks as well as the ECM. The core of the ECM is that each individual makes their own informed decisions, and are advised by the health care team and the services provided by the health care navigator. Hopefully the ECM, with its framework and an increasing number of health care providers and vendors, will move the health care sector from a specialist-centered, fragmented, patriarchal system to a person-centered, supporting, educating, and cocreative environment. This shift will support people with LTCs in living an independent and active life, and allow them to feel safe with the freedom of mobility. Our goal is not simply related to integrated care, but also relates to personalized care in the context of the individual's activities and preferences.

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KP, SV, JS, ASC, JSN, and LK organized the project initially, together with all the involved actors. KP, SV, and LK wrote the first draft of the paper. SN advised the Epital project group and contributed to the second draft. GB has been involved as a Norwegian partner since 2015 and has contributed to the original draft and the continued development of the manuscript. All authors have contributed to the final version of the manuscript and consent to the content.

Conflicts of Interest

Dr Klaus Phanareth and Dr Søren Vingtoft now own a company, Epital Health, which is based on the ECM insights regarding the implementation of the ECM. Mister Jørgen Svenstrup is the owner of a company, EmpowerMind, that provides coaching, including health coaching; this company has provided free health coaching for this project.

Multimedia Appendix 1

Screencast.

[MP4 File (MP4 Video), 110MB - resprot_v6i1e6_app1.mp4]

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Abbreviations

CCM: Chronic Care Model
COPD: chronic obstructive pulmonary disease
ECM: Epital Care Model
eDoctor: electronic doctor
eHealth: electronic health
GP: general practitioner
ICCC: Innovative Care for Chronic Conditions
ICT: information and communications technology
K5: Kronikerprojekt 5
LTC: long-term condition

MAT: Mobile Acute Team
POC: proof of concept
RCC: Response and Coordination Center
SAP: Subacute Surveillance Place
WHO: World Health Organization

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Original Paper

The Use of Social Media to Recruit Participants With Rare Conditions: Lynch Syndrome as an Example

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Abstract

Background: Social media is increasingly being used as a means of recruiting participants, particularly for investigators whose areas of interest involve rare conditions or hard-to-reach populations. However, much of the literature to date has focused on paid advertisement recruitment.

Objective: We used Lynch syndrome (LS), a rare hereditary cancer syndrome, as a model to demonstrate the successful partnership between researchers and a Web-based patient education and advocacy organization to facilitate participant recruitment.

Methods: Recruitment was undertaken in partnership with Lynch Syndrome International (LSI), an advocacy organization with a strong social media presence. After LSI published our study information, participants followed up via email or phone call. Following prescreening and consent, interested and eligible participants were then sent a secure survey link.

Results: Within 36 hours of a single Facebook post by the site administrators for LSI, over 150 individuals responded via phone or email. Sixty-five individuals were sent the survey link and 57 individuals completed the survey (88% response rate). Of note, these 57 individuals were geographically diverse within the Unites States, representing LS patients from 26 different states.

Conclusions: This approach has several advantages, including recruitment through a trusted source outside of a clinical setting, higher response rates, and cost-effectiveness with a small research team in a relatively short amount of time. Overall, social media recruitment with a trusted online partner can be highly effective in hard-to-reach clinical populations, such as patients with LS. However, this approach requires additional effort for eligibility screening.

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KEYWORDS

social media recruitment; Lynch syndrome; participation rates; response rates; data collection

Introduction

Historically, investigators with an interest in rare illnesses or hard-to-reach populations have relied on clinics or hospitals for access to potential research participants. However, individuals have become increasingly interested in using the Internet to seek health information, making social media a highly valuable recruitment tool. Patients, especially those with rare conditions, often use the Internet to build communities, find information, and establish a support network [1,2]. Facebook alone has an average of 1.09 billion daily users, and many patient education and advocacy organizations maintain an active social media presence [3,4]. Social media recruitment has been shown to increase accessibility of target populations along with willingness to participate in research [5]. Social media also has the potential to reach understudied and demographically-diverse populations at a higher yield compared to traditional recruitment methods [6].

Current literature indicates that social media and electronic medical records continue to expand the ways in which patients and providers connect with each other and/or communicate regarding health care decisions [7]. However, social media

recruitment, as currently documented in the literature, largely focuses on paid advertisements that attempt to recruit respondents directly to an online survey [8,9]. Additionally, there are some established concerns regarding social media recruitment (specifically privacy, access, security, cost, and the gathering of patient-reported outcomes) that are less of a concern in our study [10]. We recruited people who are actively engaged in social media that focuses on Lynch syndrome (LS), making both privacy and access to online communities less challenging. Security concerns that are documented in the existing literature are less relevant for this project, as the post on the Facebook page of Lynch Syndrome International (LSI; our community partner) provided us only with names and contact information [11]. Individuals responded to the Facebook post, and research staff were then responsible for screening participants for eligibility, obtaining consent, and sending a secure link to an anonymous survey. There were no costs associated with our recruitment methodology, as our Facebook post was free and the survey was security-enabled via Research Electronic Data Capture (REDCap [12]; explained in more detail below). Notably, our procedural differences in social media recruitment may result in a study population that is similar to existing study samples in hereditary cancer research (eg, more affluent, higher educated, and white). The primary difference between participants recruited through clinic-based methods and those recruited through social media was the inclusion of patients who were receiving care outside of major cancer centers when recruitment was completed through social media.

In this paper, we use LS, a rare hereditary cancer syndrome that predisposes an individual to a variety of cancers (including, but not limited to, colorectal, endometrial, and ovarian cancer [13,14]), as a model for successfully partnering with a Web-based patient education and advocacy organization for participant recruitment. We outline study details that can be replicated in other studies.

Methods

This study was approved by the Institutional Review Board of the Albany College of Pharmacy and Health Sciences. The entire recruitment process and outcomes are outlined in Figure 1. To be eligible for the study, individuals had to meet the following criteria: (1) at least 18 years of age, (2) able to read and speak English, (3) completion of genetic testing for an LS mutation; and (4) diagnosis of an LS mismatch repair mutation. Participants were recruited through LSI, a patient education and advocacy organization whose mission is to serve the LS community by providing support for families affected by this diagnosis, creating public awareness of the syndrome, educating the public and health care professionals about LS, and providing support for research [15]. The organization is founded and governed by LS survivors, their family members, and health care professionals who specialize in LS, making it a trusted source of information and interaction for LS patients and their families. The LSI website includes accurate and up-to-date diagnosis, treatment, and management information, as well as message boards [15]. LSI is active on social media, including Facebook and Twitter, and members of their community frequently post and respond to questions by other members, and discuss new LS-related research [4]. LSI provided a letter of support for the initial grant application and, prior to participant recruitment, the executive board of LSI reviewed the approved protocol and held a conference call with the Principal Investigator to discuss study aims and the recruitment plan. When all issues were resolved and the study was open for recruitment, LSI posted the announcement on their Facebook page, which established our credibility with the potential study population.

A Facebook post (Figure 2) directly from LSI was used for recruitment, and contained eligibility criteria and study details, such as study procedures, time commitment, and incentives. Interested individuals were given instructions to respond either via email or phone. To confirm eligibility, one member of the study team called potential participants to screen for study eligibility in the order that they responded; these calls lasted approximately 5-10 minutes. If the person did not answer, a voicemail was left and the next person on the list was called. After the participant was screened for eligibility, a secure survey link with instructions for completion was sent via REDCap, a browser-based electronic data capture software package, that allowed us to create and manage the online surveys and provided a mechanism for data capture in a quick, secure, Health Insurance Portability and Accountability Act-compliant manner. Our institution has a site license for REDCap and only personnel with approved access can access the survey data, which is held on a secure server that can only be accessed on campus by approved study personnel. Once a survey is initiated or completed in REDCap, the data is stored without being linked to the email address of the individual participant, leaving no identifiable information in the surveys. A separate secure system exists within REDCap that tracks when the survey links are opened and when surveys are completed, but the participant identification number is not linked to that system. All participants who completed the online questionnaire were mailed a US $25 gift card as compensation, and were called to schedule the in-depth, semistructured telephone interview. Participants who completed the qualitative interview were mailed a second US $25 gift card as compensation. Recruitment was discontinued when the survey link was sent to 65 potential participants, as a completion rate of approximately 75% was anticipated for both the survey and interview. This estimated completion rate was based on prior studies by our research team piloting this recruitment method; the estimated completion rate would result in a final sample size of 50. Research staff also maintained a relationship with both LSI and potential respondents by following-up two days after the initial call for participants with a *Thank You* post on Facebook (Figure 3). This post served three purposes. First, it communicated to individuals who had responded that we were systematically working through the responses and contacting potential participants. Second, it let new people who were just seeing the study information for the first time know that we had already surpassed the number of responses for the study sample size, thus decreasing the number of continued responses. Finally, it allowed anyone who was looking at the Facebook page to get a sense of the community response. These small gestures from research staff continue to build relationships, and ensure the possibility of future research, within this community.

Figure 1. Recruitment process and outcomes.

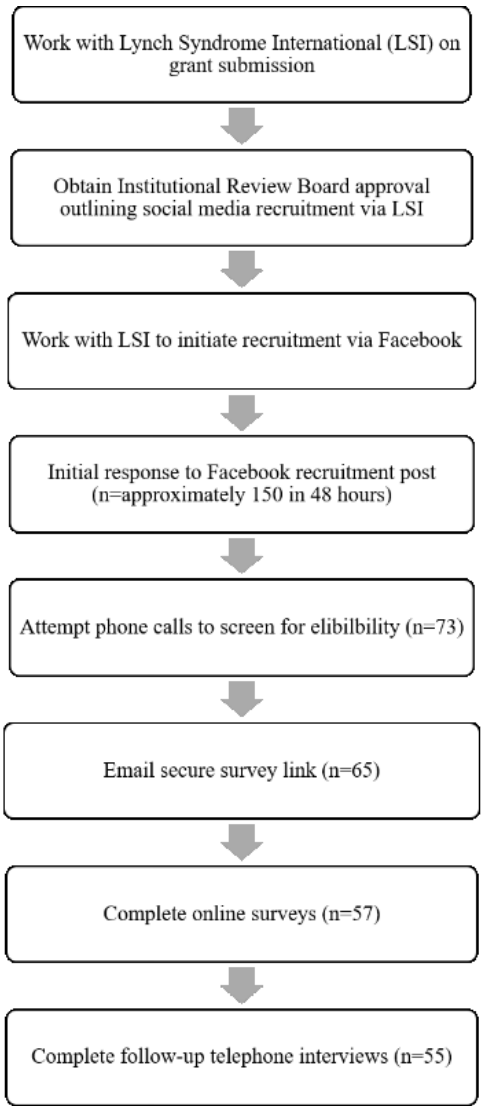


Figure 2. Facebook recruitment post.

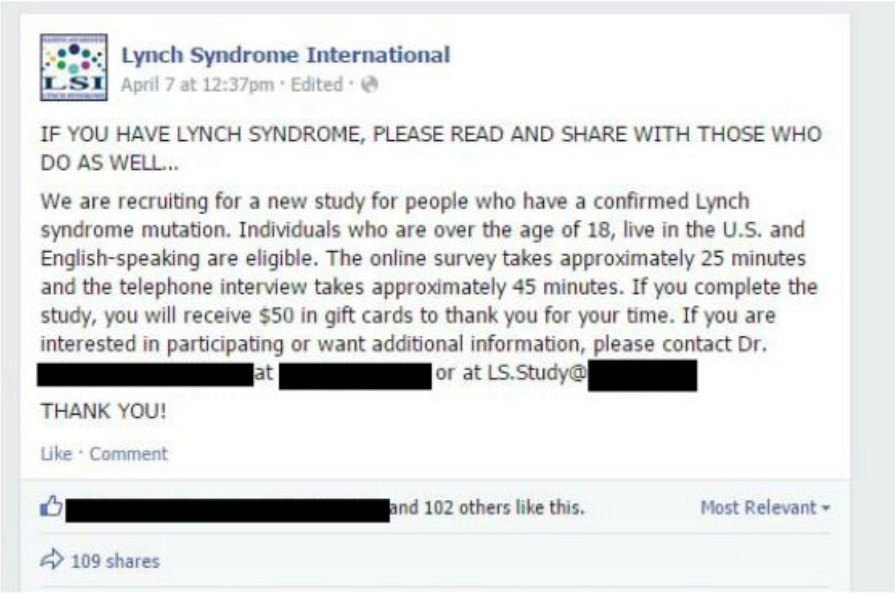
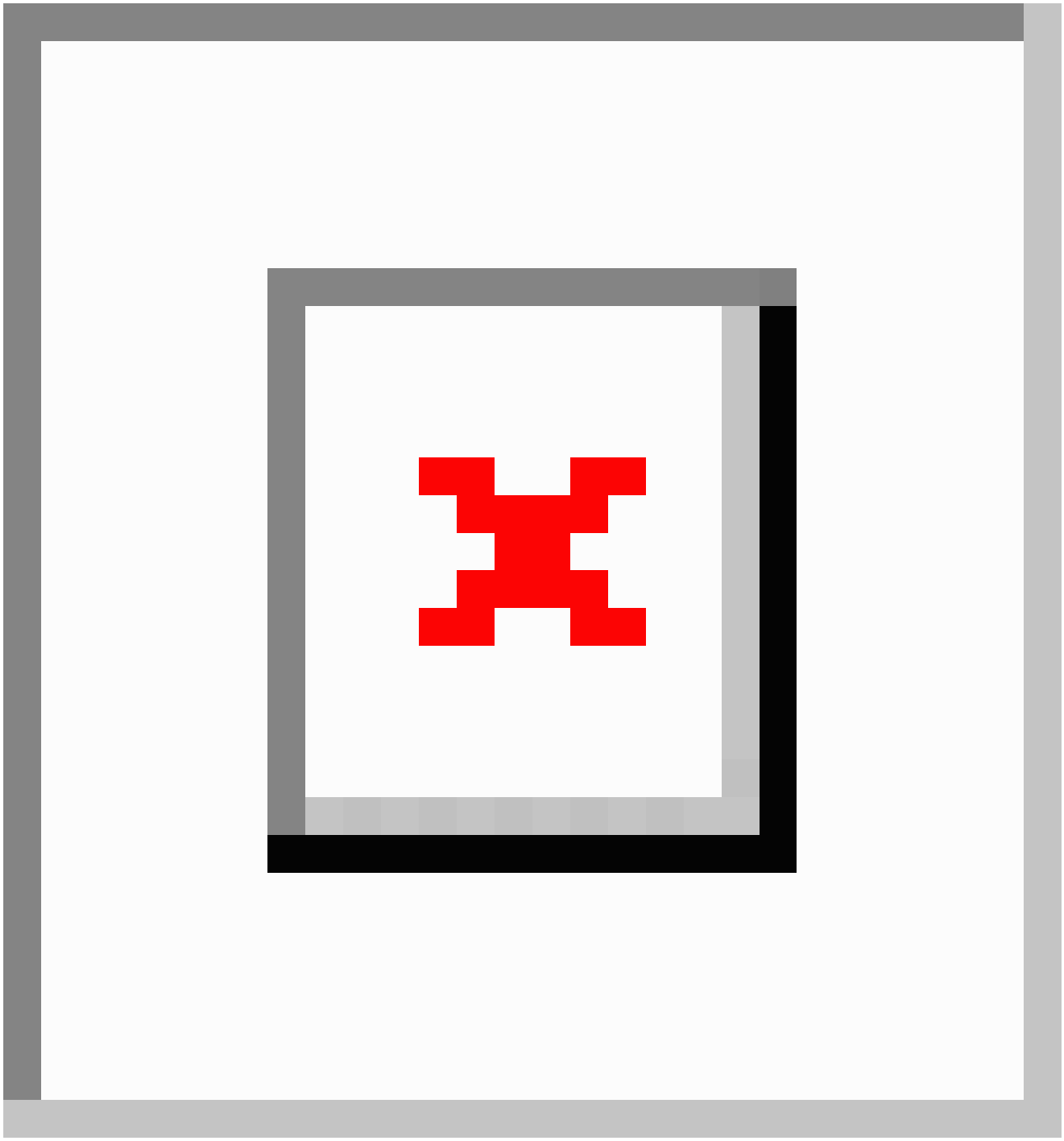


Figure 3. Thank you Facebook post.



Results

Within 36 hours of a single Facebook post by the site administrators of LSI, over 150 individuals responded via phone or email (Figure 1). One member of the research team (ABC) contacted 73 respondents to reach an anticipated final sample of 55 participants (75% overall response rate). Sixty-five of those individuals were sent the secure link; 57 participants completed the online survey, while 8 individuals did not (88% response rate). Of those 8 individuals, 6 did not finish, 1 did not consent, and 1 never opened the survey link. Follow-up interviews were conducted with 55 of the 57 participants who completed the survey (96% response rate); 2 individuals were not able to be contacted during the study period. As expected, the final sample of 55 participants was primarily female (n=41; 75%) and white (n=51; 93%). However, there was significant geographical diversity within the United States among participants, with 26 states represented in the final sample. There was also heterogeneity in terms of rural and urban communities and regions of the country. Additionally, approximately half of our sample were previvors (n=27; 49%), meaning that they have tested positive for an LS mutation but have not yet had a cancer diagnosis. This split between cancer survivors and previvors will allow us to study group differences in care transitions and provider satisfaction; this comparison is one we have not been able to do in prior studies due the difficulty of recruiting previvors when using traditional clinic-based methods.

The survey link was sent in three batches. The first batch was sent the day after the announcement was posted, the second was sent the following day, and the third was sent 5 days after the Facebook post. The average time for survey completion was 3 days (median=2; range=1-16) after receiving the survey link (responding on the same day was classified as 1 day to complete). The approved protocol stated that the research team would wait 2 weeks after survey completion to contact participants to set up the in-depth telephone interviews. The average number of days between survey completion and participation in the phone interview was 33 (range=21-42). Three members of the research team conducted the telephone interviews. The online survey took approximately 45 minutes to complete, however there was significant variability due to skip patterns and complexity of personal and family health history; the in-depth telephone interviews ranged in length from 25 minutes to 2 hours. Overall, the time from the initial call for participants to the completion of data collection (online survey and phone interview) was 45 days, which was significantly shorter than in prior studies by our research team in the same population.

Discussion

This study demonstrates the effectiveness of partnering with a patient education and advocacy organization to recruit participants with rare conditions or hard-to-reach populations. This method can be utilized outside of a traditional clinical setting and affords investigators who are not affiliated with major medical centers (and thus, without direct access to clinical populations) the opportunity to conduct valuable research in their target populations. However, the reputation of the community partner is a critical component. While this study did not directly obtain data on reasons for participation, participants did take the opportunity both during the eligibility screening call and telephone interview to informally discuss this topic. During those conversations, many participants cited their confidence in the merits of this study due to its endorsement and publicization by LSI. Respondents trusted that LSI had vetted the study appropriately prior to posting the call for participants. Stated simply, it appears that our recruitment may have been particularly successful because LSI is a respected and trusted organization within the LS population. However, given that these data were not systematically collected, further research is needed to determine how large of a role this factor played in our successful recruitment efforts.

Other advantages of this methodology are that it can be carried out with a small research team in a short amount of time. These factors are highly beneficial for pilot studies with small budgets or tight timelines. Notably, the response rate using social media recruitment was significantly higher than prior studies in the same population [16-18]. This result could be due to the two-step recruitment process, allowing researchers to screen for participants who were eligible while also establishing a personal connection. Posting an open recruitment call allowed individuals to opt-in to the study, and the subsequent telephone call to screen for eligibility provided potential participants with the opportunity to ask questions and gain a greater understanding of the study goals. This level of interaction, along with the validation of the community partner, appears to have increased participant commitment, as evidenced by our high response rate. In addition, in a climate of limited funding for research and the need to document the ability to connect to communities prior to applying for federal grant funding, this technique could be invaluable. Costs were limited to researcher time, incentives, postage, and transcription of the qualitative interviews. The institutional access to a secure online data collection tool was essential, as well as the partnership with LSI.

Researchers who utilize this methodology must be aware of the potential for participant bias. One potential concern is that respondents recruited through social media may not be representative of the entire population, which should be acknowledged when data are published; however, prior research has shown that participants recruited through social media tend to be more demographically diverse than traditional clinical populations [6]. In our experience, the participant demographics of individuals recruited through social media are similar to those recruited through traditional sources for hereditary cancer studies. However, both have been noted to over-represent individuals who are more highly educated, female, and white. In terms of increasing the heterogeneity of the study sample, the use of social media as a recruitment method allows researchers to reach individuals, such as previvors, who are receiving care in the community (as opposed to a single institution or comprehensive cancer center) and in geographically-diverse areas. Although this methodology does not fully address the broader bias in research participation for hereditary cancer populations, which merits continued discussion by researchers and clinicians, it is a step forward in terms of including individuals who would previously have been left out of these types of studies. Finally, concerns regarding privacy and security were procedurally minimized in this study. Patients were open about their health circumstances as part of the LSI online community, surveys were anonymized, and data were securely collected via REDCap. Future research could easily connect to clinical data via electronic health records in this same structure to combine patient-reported outcomes with the depth of clinical data.

Conclusions

Creating partnerships with Web-based patient education and advocacy organizations and social media recruitment are powerful tools for health researchers, especially those who study hard-to-reach populations. If utilized effectively, this recruitment method can open up research opportunities for investigators, particularly those who do not have direct access to clinical populations or are working with limited staff and budgets. It is also clear that the choice of community partner must resonate and have credibility with the population of interest. Organizations must have both an active social media presence, and be seen as valuable and trusted community resources, by potential participants. LSI provides connections, shares up-to-date health information, and provides education to LS patients; therefore, when a research opportunity was posed to potential participants via the LSI website, respondents trusted that the study has been properly vetted and were willing to share their opinions and experiences.

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Conflicts of Interest

None declared.

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Abbreviations

LS: Lynch syndrome
LSI: Lynch Syndrome International
REDCap: Research Electronic Data Capture

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