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Protocol

Development of a Virtual Reality Exposure Tool as Psychological Preparation for Elective Pediatric Day Care Surgery: Methodological Approach for a Randomized Controlled Trial

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Abstract

Background: Preoperative anxiety in children is highly prevalent and is associated with adverse outcomes. Existing psychosocial interventions to reduce preoperative anxiety are often aimed at distraction and are of limited efficacy. Gradual exposure is a far more effective way to reduce anxiety. Virtual reality (VR) provides a unique opportunity to gradually expose children to all aspects of the operating theater.

Objective: The aims of our study are (1) to develop a virtual reality exposure (VRE) tool to prepare children psychologically for surgery; and (2) to examine the efficacy of the VRE tool in a randomized controlled trial (RCT), in which VRE will be compared to care as usual (CAU).

Methods: The VRE tool is highly realistic and resembles the operating room environment accurately. With this tool, children will not only be able to explore the operating room environment, but also get accustomed to general anesthesia procedures. The PREoperative Virtual reality Intervention to Enhance Wellbeing (PREVIEW) study will be conducted. In this single-blinded RCT, 200 consecutive patients (aged 4 to 12 years) undergoing elective day care surgery for dental, oral, or ear-nose-throat problems, will be randomly allocated to the preoperative VRE intervention or CAU. The primary outcome is change in child state anxiety level between baseline and induction of anesthesia. Secondary outcome measures include child's postoperative anxiety, emergence delirium, postoperative pain, use of analgesics, health care use, and pre- and postoperative parental anxiety.

Results: The VRE tool has been developed. Participant recruitment began March 2017 and is expected to be completed by September 2018.

Conclusions: To our knowledge, this is the first RCT evaluating the effect of a VRE tool to prepare children for surgery. The VRE intervention is expected to significantly diminish preoperative anxiety, postoperative pain, and the use of postoperative

analgesics in pediatric patients. The tool could create a less stressful experience for both children and their parents, in line with the modern emphasis on patient- and family-centered care.

Trial Registration: Netherlands Trial Registry: NTR6116; <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6116> (Archived by WebCite at <http://www.webcitation.org/6ryke7aep>)

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KEYWORDS

virtual reality; pediatric; anxiety; surgery; anesthesia; intervention; exposure; randomized controlled trial

Introduction

Fifty to 70% of children experience elevated levels of anxiety and distress prior to surgery [1,2]. Preoperatively, anxious children are more often agitated, sad, emotional, less cooperative, and more resistant compared to children who are not anxious [3,4]. Preoperative anxiety is also associated with a higher incidence of emergence delirium, more intense and prolonged pain postoperatively, and poorer recovery [3,5,6]. A child's operation is also a stressful experience for parents and parental fear has been shown to intensify children's preoperative anxiety [7,8]. Anxious children undergoing surgery, as well as their parents, are even at risk for a posttraumatic stress disorder [9]. These adverse outcomes underscore the urgent need to develop effective strategies to minimize preoperative anxiety in children.

Education programs have proven to be effective in reducing children's preoperative anxiety. Nonetheless, a recent systematic review by Copanitsanou and Valkeapää indicated that education seems to have a negative effect on younger children's anxiety [10]. Other complementary methods for reducing preoperative anxiety in children predominantly focus on distraction, for instance, watching a video, listening to music, playing video games, or distraction by clowns [11-14]. However, scientific literature shows that gradual exposure is a much more effective way to reduce anxiety in children than mere distraction [15]. Due to busy clinical practices and the daily use of surgery rooms, exposing children to all pre- and postoperative aspects is often not feasible.

Virtual reality exposure (VRE) offers the possibility to expose children of different ages to a highly realistic virtual environment that mimics the operating theater of a hospital. Children can get accustomed not only to the operating environment, but also to the procedures associated with anesthesia. VRE has already been shown to be effective as a treatment for specific phobias in children, such as a fear of heights or a fear of flying [16]. To the best of our knowledge, the efficacy of VRE to prepare children for general anesthesia and surgery has not yet been studied. Furthermore, Cochrane reviews showed that most studies examining interventions for induction of anesthesia in children are small and of poor quality [17,18]. As such, high-quality randomized controlled trials (RCTs) are needed.

The aims of the PREoperative Virtual reality Intervention to Enhance Wellbeing (PREVIEW) study are (1) to develop a VRE tool to prepare children for surgery; and (2) to conduct an

RCT to test the effectiveness of the VRE tool in children undergoing elective day care surgery.

Methods

Virtual Reality Design

The VRE tool encompasses a highly realistic virtual environment that replicates the operating theater of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands.

A multidisciplinary team, consisting of child life specialists, child psychologists, a child psychiatrist, anesthesiologists, a three-dimensional (3D) acting director, and a 3D project manager designed the script of the VRE. Working together with specialized virtual reality (VR) developers and animators, multiple 3D characters, asset, and environment artists created the scenery and character modeling.

During the design and development phases, team meetings were held to review the process and make any necessary adjustments. Overall, the main goal was to create a dynamic and interactive environment that will prepare children for surgery under general anesthesia, in a realistic and child-friendly manner. Once the VR software was created, it was pilot tested in healthy children (N=10). Based on the observations and responses of the pilot test, final adjustments were made.

Technical Specifications

Hardware Details

All 3D characters in the virtual environment were modeled after pediatric anesthesiology employees who had undergone motion capture recording with professional Vicon Motion Systems Ltd equipment (Vicon Motion Systems Ltd). Vicon Vantage cameras were used for body motion capture and the Vicon Cara system, including 4 high resolution high speed cameras and a custom head rig, were used for facial motion capture.

The virtual environment is presented via an HTC Vive headset, using room-scale technology, which allows the user to navigate naturally. Real world awareness is created through a 110 degrees field of view for captivating immersion. The Vive features 32 sensors for 360 degrees motion tracking, a 2160 by 1200 combined resolution, and a 90 Hz refresh rate. With 2 wireless, motion-tracked handheld Vive controllers, each containing 24 sensors, users can interact with precision and experience immersive environments. The headset is connected to a custom computer with an Intel Core i7-5820K processor and a NVIDIA GeForce GTX 1080 graphics card.

Software Details

All software used is of professional quality and well known in the film, game, and VR industry. Vicon Blade II software, which is compatible with the Vicon camera systems, is used for body motion capture, whereas Vicon Cara Live and Vicon Cara Post are used for facial motion capture. Blade II provides real-time visualization, in which multiple range of motion sequences, and thus multiple people, can be captured simultaneously. Cara Live is used during setup and capture, while Cara Post automatically identifies and tracks the markers, applied on a human face, over time, creating a 3D point representation of the markers.

With RealityCapture, accurate and realistic 3D models are created out of photographs. 3ds Max and Maya 2016 are digital tools used for creating complex 3D animations and models. Autodesk MotionBuilder 2016 Service Pack 1 is also used for 3D character animation. Mudbox 2016 and Zbrush 4R7 are tools used for high resolution 3D sculpting. Everything comes together in the game engine Unreal Engine 4.13.

Virtual Reality Storyline

The duration of the VRE intervention is approximately 15 minutes. We developed one version for 4- to 7-year-old children and one for 8- to 12-year-old children such that the explanations of the procedures can be attuned to the child's developmental

level. We used 8 as the cut-off point between the versions because this age represents a key period in children's brain development with respect to cognitive flexibility and information processing [19].

The VR storyline begins in the holding area, where the child is sitting on a hospital bed (Figure 1). A receptionist welcomes the child and shows him/her a video with extra information on a virtual tablet. The video explains that one of the child's parents will stay with him/her all the time and shows the hospital gowns the child and parent will be wearing to surgery. After the video, the child in the hospital bed is transported into the corridor of the operating theater by an anesthesiologist and a nurse anesthetist (Figure 2). The bed is taken into the operating room via the surgery preparation room. The child can point at different instruments, such as the oxygen saturation monitor, blood pressure cuff, and anesthesia mask, with a motion tracked controller so that the nurse anesthetist can explain what they are used for (Figure 3). Next, the child moves itself onto the surgery bed where the anesthetic preparation takes place. These preparations are explained at this stage. The program is able to show both intravenous and inhalational induction. After induction, the operating room fades out and the recovery room fades in (Figure 4). Finally, the anesthetist nurse shows another video on a virtual tablet, which explains what kind of feelings the child might experience after surgery, such as pain or nausea.

Figure 1. The virtual reality holding area.



Figure 2. Transportation through the corridor of the operating theater in virtual reality.



Figure 3. The virtual reality operating room.



Figure 4. The recovery room in virtual reality.

Study Design

The PREVIEW study is a single-center, single-blinded RCT carried out in the Erasmus MC-Sophia Children's Hospital, by the departments of Child and Adolescent Psychiatry/Psychology, Pediatric Anesthesiology, and Maxillofacial, Dental, and Ear-Nose-Throat (ENT) Surgery. This RCT involves a psychosocial intervention (VRE preparation) versus care as usual (CAU) in 4- to 12-year-old children undergoing elective day care dental, oral, or ENT surgery (N=200). CAU involves children being recommended by their anesthesiologist during the preoperative screening consultation to watch the informative online movie of the Erasmus MC-Sophia Children's Hospital about general anesthesia prior to surgery.

Inclusion and Exclusion Criteria

Eligible participants are all consecutive pediatric patients (aged 4 to 12 years) undergoing elective day care surgery (ie, dental, oral, or ENT surgery) at the Erasmus MC-Sophia Children's Hospital, between March 2017 and August 2018. Exclusion criteria are mental retardation, inability of parents to read or write Dutch, epilepsy, visual impairment, or poor general health, indicated by an American Society of Anesthesiologists (ASA) classification of IV or more.

Patient Recruitment and Procedure

Eligible patients and their parents will be informed about the study by phone and, if interested, receive the patient information folder (PIF) by email. Participation will be voluntary and all data will be anonymized. Both parents will be asked to provide written informed consent. Patients who are 12 years old will also be asked to provide written informed consent themselves. Children under 12 years old will give their permission orally.

After informed consent is provided, children will be randomly allocated to the VRE intervention (N=100) or CAU (N=100) group at hospital admission. Randomization will be stratified

by age group (4- to 7- or 8- to 12-years-old), and type of surgery (ie, oral and maxillofacial surgeries, tonsil and adenoidectomy, tympanostomy tubes, or other ear surgeries). The researchers and operating staff will be blinded to group allocation. The research assistant will not be blinded, since he/she will be guiding the intervention. This will take place in a separate room, in the presence of an accompanying parent. Un-blinding takes place if patients are excluded from the study and after the final assessment of the last included patient.

Assessments will be carried out at the following time points: (1) T1, admission to the hospital, before possible intervention; (2) T2, after the VRE intervention or after CAU, in the holding area; (3) T3, during induction of anesthesia, in the operating room; (4) T4, postoperatively, in the recovery room; and (5) T5, 3 days after surgery, at home.

Sample Size

To conduct a repeated measures analysis of variance (ANOVA) with 4 time points (ie, T1, T2, T4, and T5) for self-reported child anxiety, Cohen *f* of 0.25, an alpha of .05 (2-tailed), and a power of .85, a sample size of 200 patients is needed (100 patients per group). To perform regression analyses with 6 predictor variables, a small to medium effect size, and a power of .85, a sample size of 100 patients in the intervention group is sufficient.

Outcome Measures

An overview of the study design and variables at each time point are provided in Figure 5. The primary outcome is change in child state anxiety level between baseline (T1) and induction of anesthesia (T3), evaluated by a psychologist trained in the administration of the modified Yale Preoperative Anxiety Scale (mYPAS) [20,21]. The mYPAS is a commonly used observational tool consisting of 27 items divided into 5 domains:

activity, emotional expressivity, state of arousal, vocalization, and use of parents.

Multiple secondary state anxiety outcomes will be examined. Children will indicate their level of anxiety with a Visual Analogue Scale (VAS) at different time points (T1, T2, T4, and T5) [22]. Moreover, situational parental anxiety, both pre- and postoperatively will be self-reported using the state anxiety form (20 items) of the State-Trait Anxiety Inventory (STAI) at T1 and T3 [23,24]. Either the psychologist (T1 to T3) or the recovery nurse (T4) will assess parental anxiety with the VAS.

Postoperative pain will be reported with 3 different instruments. The revised Faces Pain Scale (FPS-r) is a self-report measure designed for children to indicate pain intensity [25]. This measure will be used at T4 and T5. A recovery nurse, trained in administering the Face, Legs, Activity, Cry, and Consolability (FLACC) scale, will assess pain intensity at T4 [26,27]. This scale assesses nonverbal indicators of pain. The Parents' Postoperative Pain Measure (PPPM) will be completed by parents at T5 [28].

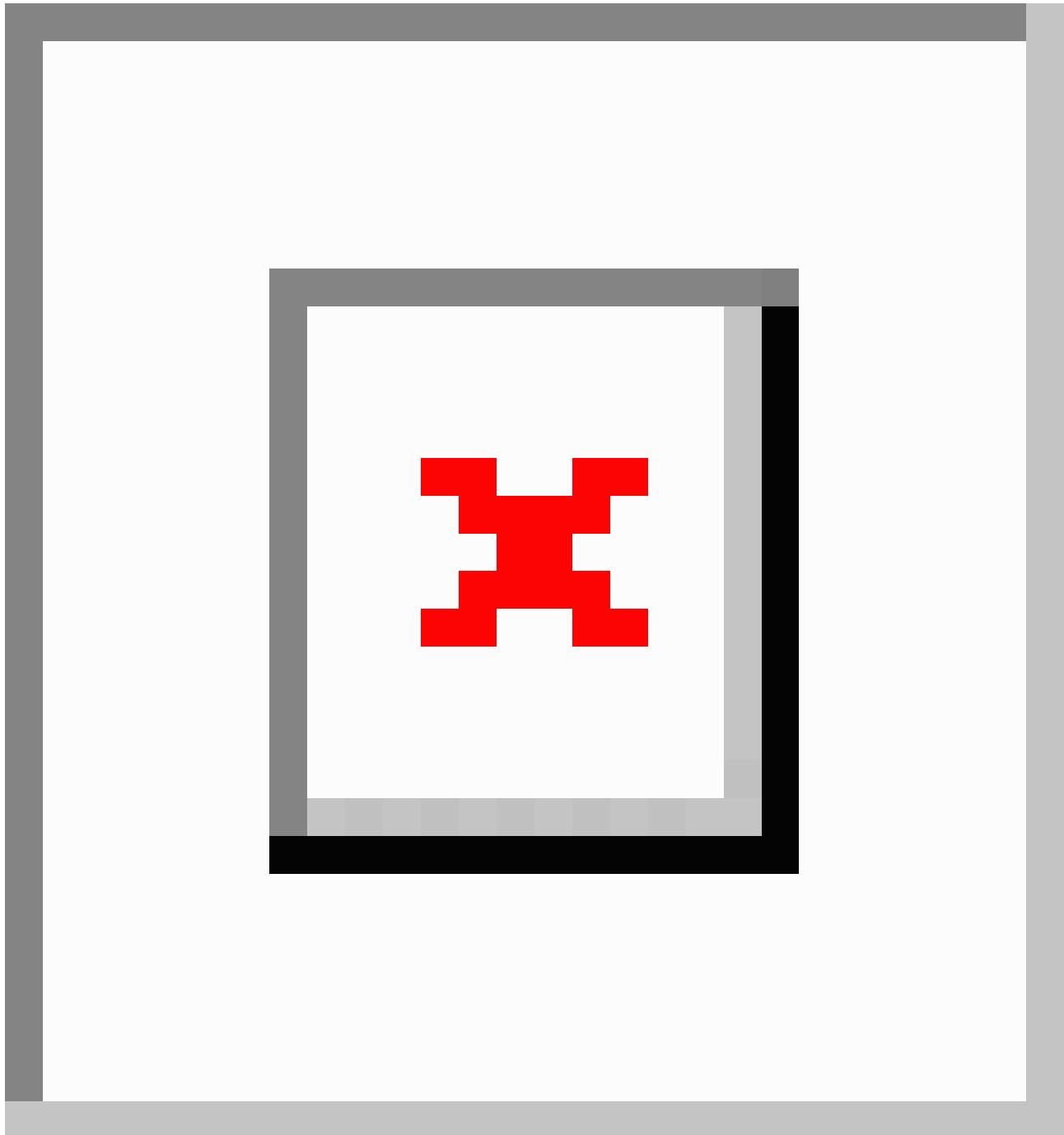
Emergence delirium will be measured with the Pediatric Anesthesia Emergency Delirium (PAED) scale by the recovery nurse at T4 [29,30]. Finally, information regarding use of analgesics and healthcare use will be extracted from medical records.

Several factors associated with situational anxiety will be assessed because these may influence the efficacy of the VRE. Putative predictors are socioeconomic status, age, sex, type of surgery, preoperative child, and parental trait anxiety. Child trait anxiety will be assessed by parents with the Child Behavior Checklist (CBCL) at T1 [31]. Parental trait anxiety will be self-reported using the trait anxiety form (20 items) of the STAI.

Statistical Analyses

To examine the effect of the intervention on the primary outcome, a repeated measures ANOVA will be conducted with child state anxiety level at T1 (baseline state anxiety) and T3 (anxiety during induction of anesthesia) as within variables and group (VRE versus CAU) as between variables.

Figure 5. Flow chart of the study design with outcomes, instruments, and informants at each time point.



For the secondary outcome measures, repeated measures ANOVA will be conducted with situational parental anxiety at T1 and T3 as within variables and group as between variables. Also, repeated measures ANOVAs will be performed using postoperative pain at T4 (in the recovery room) and T5 (at home) as outcomes, with group as between variables. The effect of the intervention on emergence delirium at T4 will be examined with an analysis of covariance (ANCOVA). Age and sex effects will be accounted for in all analysis.

Multiple linear regression analyses will be performed with change in child state anxiety between T1 and T3 and change in pain between T4 and T5 as outcomes. Predictor variables (ie, socioeconomic status, age, sex, type of surgery, preoperative child, and preoperative parental trait anxiety) will be included

into the linear models to identify which factors influence VRE efficacy.

Ethical Considerations

This study has been approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2016-626). The study will be conducted according to the Helsinki Declaration.

Results

The development of the VRE tool was finalized and participant recruitment began March 2017. The study to evaluate the efficacy of the VRE will be open for recruitment until September 2018. Data will be analyzed and scientific papers will be submitted for publication in the subsequent year.

Discussion

Principal Findings

There is a need to improve the psychological preparation of pediatric patients, as well as their parents, for surgery since elevated anxiety levels are highly prevalent. VRE has already been shown to be effective as a treatment for specific phobias in children. However, despite the fast-growing field of VR in medical care, the application of a VRE tool to reduce anxiety for surgical procedures in children has not been systematically studied. Since VR is a promising tool for improvement in health outcomes, high quality studies investigating innovative VR interventions are needed.

Here, we describe the development of a psychosocial VR intervention and the PREVIEW trial designed to test its efficacy. We expect the VRE to optimize the preparation of children for surgery under general anesthesia and diminish far-reaching maladaptive consequences, both psychologically and medically.

Strengths and Limitations

In regular medical care, the explanations given to parents and children regarding surgery and anesthesia are mostly verbal of nature. VRE is primarily a visual, non-verbal intervention, so it can have a surplus value for young children, non-verbal children, and for children and parents who do not speak or fully

comprehend their second language. Creating a less stressful experience for both children and their parents is in line with the emphasis on patient- and family-centered care [32]. Moreover, if VRE is proven to be effective, this easy to use tool can be implemented into standard medical care, engaging in secondary prevention. We would like to emphasize that, even with the use of modern technology, education provided by healthcare professionals of both pediatric patients and their parents is still absolutely necessary, especially for older children.

A limitation of our study is that it involves children undergoing elective day care surgery (more specifically, dental, oral, and ENT surgery). Therefore, the results of this study might not be generalizable to other types of surgeries.

Conclusion

Preoperative anxiety in children is highly prevalent and there is a need to develop more effective strategies to reduce this anxiety. VRE is a promising tool to prepare pediatric patients for surgery in a child-friendly and efficacious way. We demonstrated that the development of a highly realistic virtual environment that replicates the operating theater is possible with the collaboration of a multidisciplinary team. We are now examining the efficacy of the VRE tool by means of an RCT. By focusing on preparing children for anesthesia and surgery with an innovative VRE tool, instead of distracting them, we hope to improve clinical and psychological outcomes.

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Conflicts of Interest

None declared.

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Abbreviations

3D: Three-Dimensional
ANOVA: Analysis of Variance
CAU: Care As Usual
CBCL: Child Behavior Checklist

ENT: Ear-Nose-Throat
FLACC: Face, Legs, Activity, Cry, and Consolability
FPS: Faces Pain Scale
mYPAS: modified Yale Preoperative Anxiety Scale
PAED: Pediatric Anesthesia Emergency Delirium
PPPM: Parents' Postoperative Pain Measure
PREVIEW: PREoperative Virtual reality Intervention to Enhance Wellbeing
RCT: Randomized Controlled Trial
STAI: State-Trait Anxiety Inventory
STAIC: State-Trait Anxiety Inventory for Children
VAS: Visual Analogue Scale
VR: Virtual Reality
VRE: Virtual Reality Exposure

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Protocol

A Multi-Level, Mobile-Enabled Intervention to Promote Physical Activity in Older Adults in the Primary Care Setting (iCanFit 2.0): Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Most older adults do not adhere to the US Centers for Disease Control physical activity guidelines; their physical inactivity contributes to overweight and multiple chronic conditions. An urgent need exists for effective physical activity-promotion programs for the large number of older adults in the United States.

Objective: This study presents the development of the intervention and trial protocol of iCanFit 2.0, a multi-level, mobile-enabled, physical activity-promotion program developed for overweight older adults in primary care settings.

Methods: The iCanFit 2.0 program was developed based on our prior mHealth intervention programs, qualitative interviews with older patients in a primary care clinic, and iterative discussions with key stakeholders. We will test the efficacy of iCanFit 2.0 through a cluster randomized controlled trial in six pairs of primary care clinics.

Results: The proposed protocol received a high score in a National Institutes of Health review, but was not funded due to limited funding sources. We are seeking other funding sources to conduct the project.

Conclusions: The iCanFit 2.0 program is one of the first multi-level, mobile-enabled, physical activity-promotion programs for older adults in a primary care setting. The development process has actively involved older patients and other key stakeholders. The patients, primary care providers, health coaches, and family and friends were engaged in the program using a low-cost, off-the-shelf mobile tool. Such low-cost, multi-level programs can potentially address the high prevalence of physical inactivity in older adults.

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KEYWORDS

iCanFit; older adults; mHealth intervention; intervention development; intervention trial; primary care

Introduction

The benefits of regular physical activity on the well-being of older adults are well established. Even small increases in physical activity at a population level could have far-reaching positive impacts on chronic diseases such as diabetes, cardiovascular diseases, and several cancers [1-3]. The US

Centers for Disease Control and Prevention and the American College of Sports Medicine have recommended 150 minutes of moderate-to-vigorous physical activity (MVPA) per week [4]; however, less than 5% of American older adults adhere to the guideline [5-7]. Physical inactivity is associated with high prevalence of overweight (60%) and chronic conditions (80%) in this population [8]. As the elderly population continues to

grow—13% of the US population will be older than 65 years of age by 2020 [8]—an urgent need exists for physical activity-promotion programs that can reach a large population of older adults efficiently.

Increasing older adults' physical activity, especially MVPA, is challenging. Literature suggests that effective physical activity-promotion programs are those built upon social and behavioral theories and practices, extend beyond the individual-level factors, and incorporate social and health care support [9–11]. When promoting physical activity in older adults, multi-level intervention programs that promote physical activity through goal setting and tracking at the individual level, social support at the interpersonal level, continuous monitoring at the health care level, and positive social norms at the community level are more likely to have sustainable effects [10–13].

More than 67% of older Americans (65 years or older) use the Internet and 42% own a mobile phone [14]; the digital divide in older adults has narrowed in the past decade [15]. The high rates of owning mobile tools suggest feasibility of mobile-based physical activity interventions. Mobile-based programs can reach a large number of patients efficiently; such programs can be easily tailored to individual needs and integrated into the health care system where electronic health records (EHRs) have been widely adopted [16–18]. In fact, a growing number of mobile-based, physical activity-promotion programs have been developed and tested in older adults [19,20]. However, recent reviews of existing programs have shown inconclusive evidence. While some studies report significant efficacy, others suggest minimal benefits, especially compared to usual care [20,21]. These programs, which typically used simple texting or short message service (SMS) text messaging to deliver reminders, had only short-term effects [22,23]. Some programs have required participants to use newly developed websites or mobile apps, thus limiting the population reach [10,21]. Despite inconclusive evidence from mobile-based, physical activity-promotion programs, reviews of existing literature have revealed some common characteristics of successful physical activity programs. They typically (1) incorporate the patient as an active participant in goal setting and tracking, (2) are based on behavioral and socioecological theory, (3) emphasize problem solving and the use of social support, and (4) provide both proactive and follow-up support [3,10,24]. Literature also documents the importance of social support, especially support from friends and family in mobile-based, physical activity-promotion programs [25].

Older adults tend to have more trust in their primary care providers (PCPs), or *general practitioners* in some countries, compared to other populations [26]. American older adults see their PCPs at least every 6 months [27]. Thus, the primary care clinics provide an ideal setting for delivering physical activity-promotion programs to older adults. Many PCPs, however, do not counsel their patients for physical activity promotion; they either have to address other medical complaints raised by the patients or they see no necessity of bringing up physical activity in the consultation with patients [28]. Our recent interviews with PCPs found that most physicians assumed patients understood the importance of physical activity and the lack of regular physical activity was due to patients' insufficient

motivation [29,30]. A recent BMJ systematic review identified only 15 trials conducted in primary care organizations and the most typical intervention was a one-time simple counseling session by a PCP or nurse [13]. More research is therefore needed to explore the efficacy of theory-guided, physical activity-promotion programs in primary care settings.

We aim to address the literature gaps noted above by proposing a multi-level, mobile-enabled, physical activity-promotion program called *iCanFit 2.0* in a primary care setting. Guided by socioecological theory, the iCanFit 2.0 program incorporates PCPs and health coaches in behavioral goal setting and continuous support for the patients. The intervention will exert effects at the individual, interpersonal, health care, and community levels. Mobile tools will facilitate patient-provider communication, enhance motivation, and provide ongoing feedback and social support to promote physical activity, as shown in Figure 1. To test the efficacy of iCanFit 2.0, we also designed a cluster randomized controlled trial (RCT) in a large health care organization.

Methods

Development of iCanFit 2.0

Overview

The development of the iCanFit 2.0 program was based on the following data sources and processes: (1) Preliminary studies with older adults in primary care settings and mHealth interventions including the iCanFit Web app, (2) qualitative interviews with older patients in a primary care clinic prior to this design, and (3) iterative discussions with stakeholders.

Preliminary Studies

From 2011 to 2015, we conducted the following formative research and mHealth interventions on physical activity promotion among older adults:

1. Assessment of overweight patients' barriers to physical activity from the perspectives of PCPs. Through online surveys with 57 PCPs and focus groups with 49 PCPs, we learned that PCPs were aware of the importance of counseling older patients regarding physical activity and identified lack of motivation and social support as major barriers to regular physical activity [28–30].
2. Use of the iPod Touch for patient health behavior assessment and patient-provider communication. We developed an app on the iPod Touch—before the iPad was released—so patients could complete a brief health behavior assessment (HBA) on a touch screen while waiting for appointments with a PCP. A colorful chart report was generated instantly (see [Multimedia Appendix 1](#)). When the patient walked into the appointment with a PCP, the report became a natural conversation starter and facilitated patient-provider communication and collaborative goal setting. We piloted this app with 109 patients in a primary care clinic and the results showed that 30% of the participants reported that their PCP discussed the report with them, 24% established behavioral goals with him or her as a result of the discussion, and 90% related positive

experiences with using mobile tools to generate an HBA report [31].

3. Development and testing of the iCanFit interactive website for older adults. With the goal to promote physical activity in older cancer survivors, we developed an interactive website called iCanFit. We conducted three phases of research: formative research with key stakeholders [32], usability testing of the website with target users [33], and an efficacy trial with older cancer survivors [34]. The users of iCanFit reported high levels of usefulness and satisfaction. Participants reported a higher level of quality of life (effect size=0.35) and a higher level of physical activity (effect size=0.45) following the use of the iCanFit Web app [34].

Qualitative Interviews With Older Diabetes Patients in a Primary Care Clinic

The initial design of iCanFit 2.0 was the combination of the HBA tablet app and the interactive iCanFit Web app. As the initial design of iCanFit 2.0 evolved, we conducted qualitative interviews with 103 older diabetes patients in a primary care clinic. Considering most older adults have multiple chronic conditions, our preliminary studies focused on different chronic conditions to ensure that iCanFit 2.0 can serve the needs of a large number of older adults. The mean age of the participants in the qualitative interviews was 50 years and the mean years of living with diabetes was 10 years. Most of these older patients used the Internet and more than half had a mobile phone. They had positive attitudes toward a mobile-based, physical activity-promotion program and offered many suggestions and concerns for the design of iCanFit 2.0.

Iterative Discussions With Key Stakeholders to Refine the Design

After 10 years working in healthy aging and chronic disease management, we have established rapport with local

communities and health care organizations; we have also always engaged key stakeholders in the intervention design, implementation, and evaluation. In designing iCanFit 2.0, we had a series of group discussions with our key stakeholders. We brought our initial design to the meeting and obtained their feedback; the iterative process continued until a satisfactory protocol was agreed upon by all key stakeholders. The current design of iCanFit 2.0 reflects the inputs from our target patients and other key stakeholders and is substantially different from the original design.

Community Engagement

Prior to completion of protocol design and project implementation, a Community Advisory Board (CAB) will be established, consisting of older patients, community leaders, health care providers, and administrators. At least five members of the CAB will be older patients. The CAB will have 10 members and vote on a director and a secretary. The CAB will meet with the project team every month in the first 6 months of the project and every 6 months afterward. The CAB will offer gatekeeper and stakeholder concerns as well as recommendations on program design, feasibility issues, implementation, and evaluation strategies; it will also help the research team interpret findings and advise on how to translate research findings into sustainable programs.

Intervention Trial

Overview

The intervention trial compares the effectiveness of the iCanFit 2.0 intervention program with a comparator program among overweight older adults in a primary care setting. To achieve this goal, we will conduct a cluster RCT in 12 family medicine clinics (six pairs) in Central Texas, USA. In each pair of comparable clinics, one will be randomized to the intervention group and one to the control group (see [Figure 2](#)).

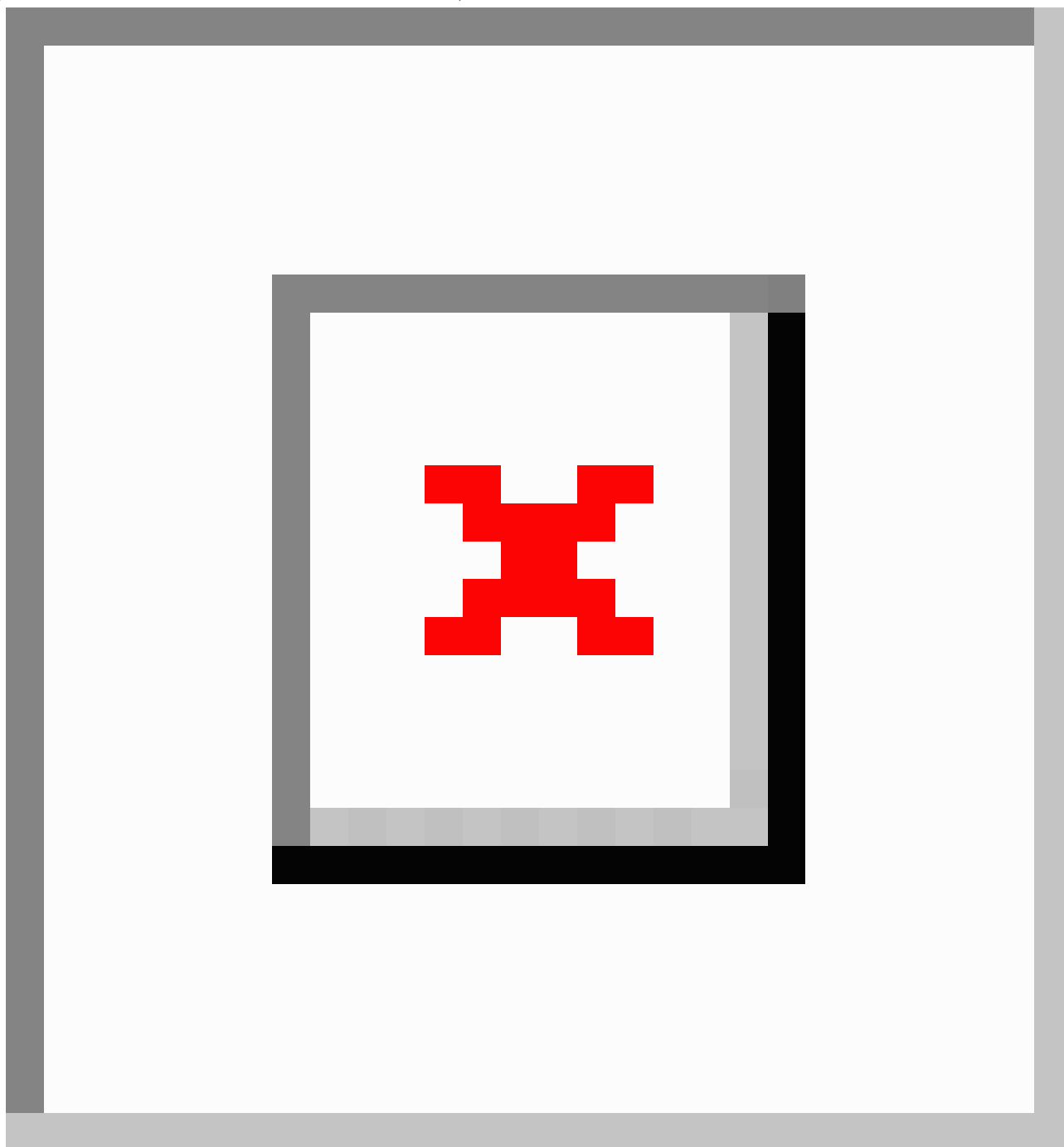
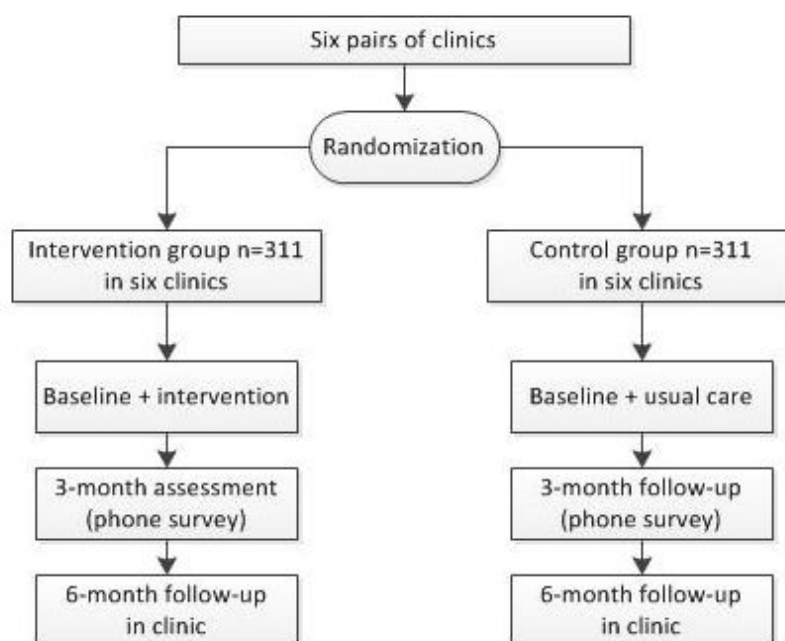
Figure 1. Theoretical framework of the multi-level intervention, iCanFit 2.0.

Figure 2. Intervention trial flowchart.

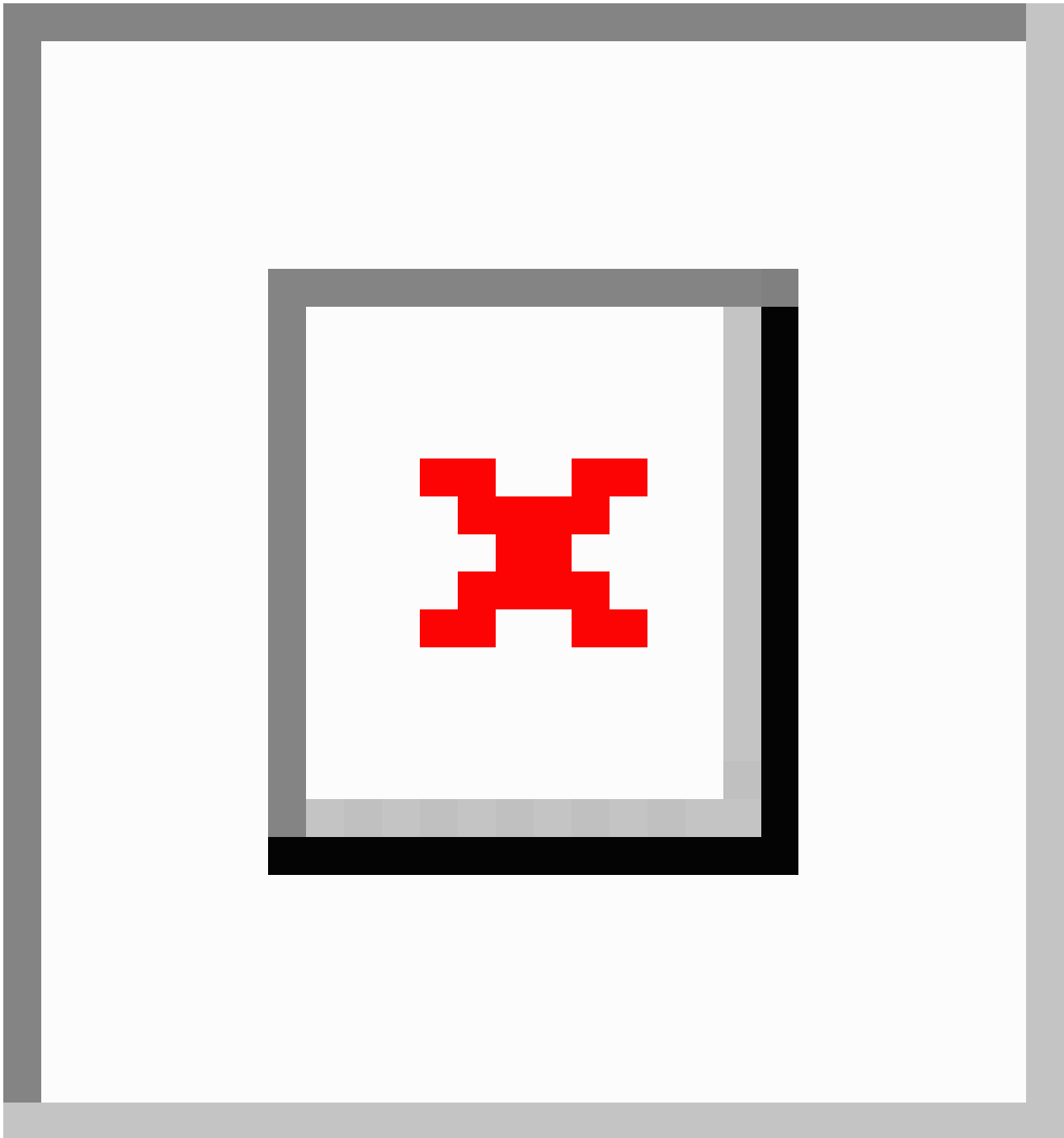
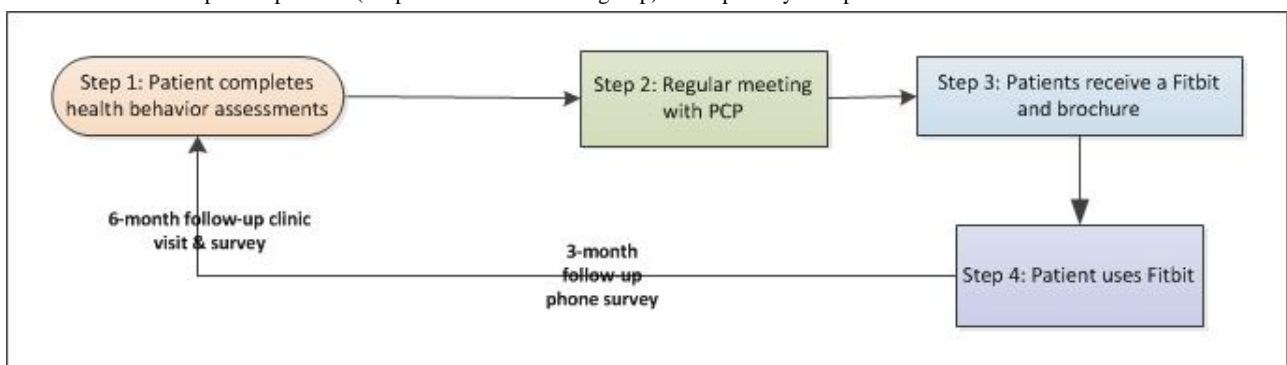
Study Sites and Sources of Patients

We will conduct the proposed trial in 12 family medicine clinics that belong to a large university-affiliated, integrated health care system in Central Texas. These clinics were selected because of their similarity in patient demographics, clinic operation, and service coverage. The 12 clinics will be grouped into six pairs. Clinics in each pair have been selected to have similar characteristics of size (ie, number of patient visits per year) and number of overweight older adults as well as situated miles apart to reduce possible contamination of the intervention. We will use a randomization table to assign the two clinics in each pair into the intervention group or the control group.

iCanFit 2.0 Intervention Protocol

As illustrated in [Figure 3](#), the iCanFit 2.0 intervention protocol includes four steps. First, after the eligible participants complete the informed consent forms, they will complete an HBA on an iPad (see [Multimedia Appendix 1](#) for sample screenshots), which takes about 15 minutes. Right after completion, patients will receive a printed copy of the HBA summary report with colorful charts of their current level of physical activity compared to the recommended physical activity levels (see sample summary reports in [Multimedia Appendix 1](#)). Meanwhile, the same report will be printed out in the office of the PCP with whom the patient has an appointment. Second, the patient brings the HBA report into his/her appointment with the PCP and the report serves as a natural conversation starter to facilitate patient-provider communication and joint goal setting. Third, right after the patient's appointment with the

PCP in the primary care clinic, a health coach will meet with the patient, further explain the HBA report, and ensure the patient has set a long-term physical activity goal, if the patient has not set one with the PCP. The health coach will give the patient a Fitbit Flex 2 (Fitbit Inc) (see [Multimedia Appendix 2](#) and section below about the device) and demonstrate how to use the device. The health coach will also help the patient to create an account on the iCanFit online community. The health coach will advise on how to set short-term (eg, weekly) goals, track and sync data, share progress with family and friends via Facebook, and obtain personalized feedback on the iCanFit online community. The counseling session will last 30 minutes; a photo-illustrative brochure with instructions on how to use the Fitbit as well as account information and reminders will be given to the patient. Fourth, the health coach will constantly monitor patients' use of the Fitbit and iCanFit online community. Patients will receive incentives (eg, online badges, virtual coins, and honor levels) for meeting physical activity goals and updating their progress. Any questions posted on the iCanFit online community will be answered by the health coach within 12 hours. If a patient is "idle" for 2 weeks, the health coach will call the patient to offer help and address the patient's barriers. Patients will also receive a brochure of safety tips (see [Multimedia Appendix 3](#)), which details possible adverse events during exercise and how to take action depending on the situation. For adverse events that need immediate medical attention, patients are advised to go to the nearest emergency room. For nonurgent matters, they can contact the health coach, who can assist with scheduling a clinic appointment with the patient's PCP.

Figure 3. Process of iCanFit 2.0 intervention. PCP: primary care provider.**Figure 4.** Process of comparator protocol (for patients in the control group). PCP: primary care provider.

Comparator

The patients in the control group will receive usual care enhanced with a Fitbit Flex 2, as shown in [Multimedia Appendix 2](#). The Fitbit Flex 2 was released in 2016, costs US \$75, and weighs a quarter of an ounce. It is compatible with iPhones and Android phones, only needs to charge once a week, syncs automatically with mobile phones within 20 feet, and easily syncs to a computer with a USB port. It tracks steps taken, stairs climbed, calories burned, distance travelled, and sleep time. [Figure 4](#) illustrates the process of the comparator protocol. After eligible patients provide informed consent, they will first complete an HBA on an iPad while waiting for their appointment. Unlike patients in the intervention group, patients in the control group will not receive any reports from their HBA; after their appointment with the PCP, they will receive a Fitbit Flex 2 and a brochure explaining how to use the Fitbit and the benefits of regular physical activity. Patients in the control group will not be given any information about the iCanFit online community; neither will they receive counseling or monitoring from health coaches. Similar to the intervention group, control group patients will receive the safety tips of exercise brochure.

Recruitment of Patients

Eligibility of participants includes the following: (1) 60 years of age or older, (2) body mass index (BMI) of 25 kg/m² or higher, (3) have no medical condition prohibiting regular physical activity as shown in the EHR, (4) have access to the Internet through a computer or mobile phone, and (5) have a phone that can receive SMS text messages or phone calls. Based on our prior experience of recruiting participants for mHealth interventions in primary care settings and the consideration of minimal interruption of daily operation of the clinic, we will recruit participants as follows: in the EHR system, patients who are 60 years of age or older, have a BMI of 25 kg/m² or higher, and have no medical condition that prohibits them from exercise will be *flagged*. When a flagged patient checks in for his/her appointment, a health coach will be notified, who will approach the patient and explain the purpose of the project and check if the patient meets all the criteria. Eligible patients will be invited to participate in the study. Participation is completely voluntary; if the patient declines to participate, we will take notes regarding the patient's demographic information for future analysis. If the patient agrees to participate, she/he will complete the informed consent form and be able to begin the study at the very visit when they are recruited. In case some patients agree to participate but cannot start the study at that visit, we will schedule another visit for these patients to start the study within a month.

Program Fidelity

We will take the following measures to ensure the program is delivered with high quality and good fidelity. First, all research staff will receive 2 months of intensive, project-specific training on research ethics, intervention design, and project implementation. They will also receive training on interviewing patients and research conduct at the family medicine clinics where the intervention will take place. Health coaches will receive additional training on how to interact with patients, how to demonstrate the use of the Fitbit Flex 2, and how to set

short-term goals and track progress on the iCanFit online community. They will practice health coaching with patient representatives from our CAB until satisfactory performance is demonstrated. We will also have refresher training once a year during the project implementation. Second, health coaches will counsel patients under the supervision of a registered nurse; an experienced nurse will randomly check these counseling sessions and provide timely feedback. As part of quality control, our CAB will conduct site visits quarterly throughout the study. Third, the principal investigators of the project will work in the participating clinics for quality assurance and address any issues that may come up during the trial.

Patient Retention

To ensure we retain most of the patients during the intervention trial, the following measures were proposed. First, we will explain to the participants the longitudinal nature of the study during the informed consent and the fact that they will have a phone survey in 3 months and a follow-up clinic visit in 6 months. Second, 2 weeks prior to the follow-up survey or visit, we will remind the participants via SMS text message or phone call and help them schedule the appointment at their convenience. Third, for patients who do not comply with the intervention protocol, for example, do not wear the Fitbit constantly or do not sync the data in a timely fashion, we will send friendly reminders via SMS text message and motivate them with positive outcomes of physical activity and social support from the iCanFit community. Patients who continuously ignore our reminders and invitations—for 2 consecutive weeks—will be considered dropouts. We expect a 20% attrition rate at 6 months. Fourth, some participants might lose their Fitbit device during the trial. We will immediately replace a Fitbit if lost. Based on our prior experiences [35,36], less than 5% of participants may lose the mobile device during the trial. Finally, some overweight older adults may report discomfort in exercise. During the counseling by the health coach at baseline, we will advise participants to slowly increase their physical activity level and to monitor their heart rates. All participants will have a brochure of safety tips (see [Multimedia Appendix 3](#)) outlining typical adverse events and how to take appropriate actions in case of such an event. The patient is advised to go to the nearest emergency room for an event that needs immediate care. For nonurgent issues that require consultation with a PCP, the health coach will assist to schedule an appointment.

Outcome Evaluation

Outcome Measures and Sources of Data

The evaluation of the iCanFit, physical activity-promotion program will be based on three datasets:

1. HBA surveys collected using the iPad at baseline and two follow-up surveys. As shown in [Table 1](#), the survey includes demographic information, technology use and eHealth literacy [37], current level of physical activity [38], quality of life [39], patient-provider communication [40], perceived support from the health care team [41], and perceived social support for physical activity from the community [42]. All of these measures are based on validated scales with good

validity and reliability. The first follow-up is a phone survey 3 months after baseline and the second follow-up is a clinic visit 6 months after baseline. This arrangement is based on the consideration that all overweight older adults are asked to visit their PCP at least every 6 months [27].

2. Fitbit data. Two types of Fitbit data will be collected for evaluation: physical activity data recorded on Fitbit and patient interactions with the health coaches and peers in the iCanFit online community.
3. Clinic data. We will collect patients' weight and adverse events related to participating in the study from the EHRs at the clinic visits at baseline and at the 6-month follow-up.

Power and Sample Size Calculations

The primary outcome of the study is the total minutes of MVPA per week. MVPA is measured as "very active" and "fairly active" on Fitbit. The secondary outcome of the study is the patient's self-report quality of life, measured by the 12-Item Short Form Survey [39]. We hypothesize the effect size of the iCanFit 2.0 to be 0.25, based on a prior Fitbit intervention trial [43]. Following the procedure developed by Cohen, the calculation of sample size is carried out in three steps by assuming a .05 significance level to achieve the power of 0.8 [44]. First, we assume that two independent samples can be obtained for the same size n_1 each. Then the total sample size is $n=2 \times n_1$. In this ideal scenario, the total sample size $n=398$ is required to detect the effect size $d=0.25$ between the two population means. Second, because the randomization occurs at the clinic level, we need to consider the clustering effect. Previous similar research suggests a small clustering effect due to multiple patients per physician, but virtually no clustering effect between patients with different physicians in the same clinic [45]. We assume that if the intraclass correlation coefficient (ICC) per patient is equal to .05, and that ICC per physician is equal to 0, then equation 1 holds:

$$ICC = (1 + ICC_{\text{patient}}) \times (1 + ICC_{\text{physician}}) - 1 = .05 \quad (1)$$

Thus, the design effect is as follows in equation 2:

$$D = 1 + (m - 1) \times ICC \quad (2)$$

where m is the average number of patients per physician in our effective sample. If we restrict m to be no more than 6, then $D = 1 + 5 \times .05 = 1.25$. We would need a sample size of 498 (ie, 398×1.25) after factoring in cluster effects. Third, based on our prior study of RCT primary care settings [36], we assume the attrition rate to be 0.2 after 12 months, thus the required sample size at baseline is 622 in total (ie, $498 / [1 - 0.2]$), or 52 patients per clinic on average. We will recruit no fewer than 30 and no more than 70 patients from each participating clinic.

Data Analysis Plan

Our analysis has been planned to correspond to the study's main aim. We will begin with exploratory data analyses. Demographic and baseline characteristics for the participants will be summarized using descriptive statistics overall and by intervention and control groups to assess baseline comparability.

Prior to analyses, we will check continuous outcome distributions and apply normalizing transformation where needed.

Our main goal is to test the hypothesis that patients in the intervention group will have more MVPA per week than the control group. To test this hypothesis, we will compare major outcomes between the intervention and control groups. We will implement multi-level regression models (eg, hierarchical linear models and mixed-effect models). Multi-level regression models are needed to account for an ICC that results from clinic-level observations [45]. Patients' observations over time are nested within PCPs, and PCPs are nested within clinics.

Equation 3 presents an example of a multi-level regression model for a continuous outcome Y_{ijt} , on clinic i , PCP j , and time point t . Our analyses will also include background characteristics that are not included in equation 3 for the sake of brevity. Two predictors, time (TIME) and intervention group (INTV), are classified as 1=iCanFit and 0=control. The multi-level regression model is given as follows:

$$Y_{ijt} = \alpha_0 + INTV_i \times \alpha_1 + TIME_{ijt} \times \alpha_2 + INTV_i \times TIME_{ijt} \times \alpha_3 + \zeta_{ij} + \epsilon_{ijt} \quad (3)$$

where α_0 , α_1 , α_2 , and α_3 are the fixed effects, ζ_{ij} is a random effect (ie, random intercept) for each PCP in each clinic, and ϵ_{ijt} is the residual error for repeated observations over time. The random effect is assumed to be normally distributed with mean zero. The residual error is assumed to be multivariate normally distributed across repeated observations, with mean zero and a covariance matrix that models the autocorrelation among repeated observations [46]. We will examine model fit statistics to choose an appropriate covariance structure. Hypothesis testing will be carried out to test for intervention effects on the outcome of interest over time. Referring to equation 3, this is equivalent to testing the hypothesis $H_0: \alpha_3 = 0$. If higher outcome values are desirable, then a positive significant α_3 parameter indicates a positive intervention effect (ie, we reject $H_0: \alpha_3 = 0$). We will use the SAS version 9.0 (SAS Institute Inc) PROC MIXED procedure and PROC GLIMMIX procedure to fit multi-level models to continuous and binary data, respectively.

We will also apply structural equation modeling (SEM) to examine the extent to which the intervention takes effect at individual, interpersonal, health care, and community levels as shown in Figure 1. Models will be constructed to measure direct and indirect effects. We will also analyze whether increased MVPA is a mediator for improved clinical outcomes. Latent variables are similar to random effects, accounting for nested observations. We will use Mplus version 3.1 (Muthén & Muthén) to fit SEM for continuous and binary data [47,48].

Results

The proposed protocol received a high score in a National Institutes of Health review, but was not funded due to limited funding sources. We are seeking other funding sources to conduct the project.

Table 1. Data collected and instruments used in the survey.

Domain	Scale or indicators	Data collection mode	Number of items
Demographics	Age, gender, race/ethnicity, marital status, education, income, insurance, chronic conditions, and perceived health	Survey with patients at baseline	11
Technology use	eHealth literacy scale (E-HEALS), $\alpha=.78$ [37]	Survey with patients at baseline	11
Physical activity	International Physical Activity Questionnaire, $\alpha=.76$ [38]	Surveys with patients at baseline and follow-up	4
Quality of life (primary outcome)	12-Item Short Form Survey, $\alpha=.81$ [39]	Surveys with patients at baseline and follow-up	12
Patient-physician communication	Provider Patient Communication Scale, $\alpha=.80$ [40]	Surveys with patients at baseline and follow-up	4
Support from health care team	Patient Assessment of Chronic Illness Care (PACIC), $\alpha=.79$ [41]	Surveys with patients at baseline and follow-up	11
Support from broader community	Perceived social support for diet and exercise, $\alpha=.78$ [42]	Surveys with patients at baseline and follow-up	9
Total minutes of exercise per week	Total minutes of moderate-to-vigorous physical activity a week	Fitbit	Varies
Patient-provider communication	Number of questions sent by patient	iCanFit community	Varies
Patient engagement	Frequency of log-ins, syncs, and communication with iCanFit community and health coach	iCanFit community and follow-up survey	Varies
Moderate-to-vigorous physical activity (primary outcome)	Total minutes of moderate-to-vigorous physical activity a week	Fitbit	1
Overall experience with the iCanFit program	Experience of the intervention and follow-up, intention of continuing use of Fitbit and iCanFit community, and suggestions for improving the program	Follow-up survey	Varies
Secondary clinic outcomes	Weight, chronic condition, and number of sickness clinic visits and adverse events	Medical records	4

Discussion

The iCanFit 2.0 intervention protocol has the following four strengths:

1. It is a mobile-enabled, multi-level intervention. Most existing mobile-based, physical activity-promotion programs are individual oriented and expect users to change behaviors after using the mobile tool; the complex social environment for behavioral change and maintenance has not been addressed [5,10,25]. The iCanFit 2.0 involves patients, PCPs, health coaches, and family and friends throughout the process instead of simply targeting the patients alone, thus shifting the focus from just a mobile tool to using mobile tools to foster a social environment for behavioral change and maintenance.
2. The intervention delivery is compatible with normal clinic operation. The implementation of our program is designed to fit the normal operation of the primary care clinics. For example, instead of recruiting eligible patients through mail or phone invitation [49], we will flag eligible participants in the EHR system; when these flagged patients come to visit their PCP for clinic appointments, they will be invited to participate in the study. While waiting for their appointments, patients will complete a brief HBA; immediately generated reports via the office Wi-Fi system will be sent to both patient and PCP for better patient-provider communication. Health coaches will use mobile tools for continuous monitoring, not only reducing the burden of the PCPs but also increasing service efficiency and patient outreach. Because the majority of older adults typically see their PCPs at least every 6 months [27], we set our follow-up clinic visit at 6 months. These implementation strategies will allow the proposed intervention to be sustainable and scalable.
3. The program uses the low-cost, off-the-shelf mobile device, Fitbit, for older adults. Many existing mHealth interventions have typically used newly developed mobile apps, which resulted in limited scalability and sustainability of the program [19,21]. We chose to use the Fitbit Flex 2 because of its low cost, ease of use, high compatibility, and documented reliability and validity [35,50,51].
4. The participants in the control group also receive a Fitbit Flex 2, allowing us to test the intervention effect of iCanFit 2.0 versus the mobile device alone.

The iCanFit 2.0 program also has the following limitations:

1. iCanFit 2.0 is a complex intervention with multiple components; it requires buy-in from the primary care clinics and especially the PCPs. It also requires skilled coordination and joint efforts by multiple parties.
2. iCanFit 2.0 needs well-trained health coaches for counseling and monitoring of the patients.
3. Some older patients may not have Internet access either via computers or mobile phones and, therefore, may not be able to join the study.

4. 4. The control group does not have regular monitoring and social support and may suffer a higher rate of attrition.
5. 5. The iCanFit online community needs active users to maintain the positive social norm, which may be challenging for older adults. It merits further study on how to further engage older adults and obtain social support online.

Despite these limitations, to the best of our knowledge, the iCanFit 2.0 intervention will be one of the first multi-level, mobile-enabled, physical activity-promotion programs for older adults in a primary care setting. It was built upon our 10 years of research of a mobile-based intervention to promote physical activity in older adults. We have engaged patients and other key stakeholders throughout the design and will continue to do so in the intervention trial.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Health behavior assessment screenshots and sample reports.

[[PDF File \(Adobe PDF File\), 611KB - resprot_v6i9e183_app1.pdf](#)]

Multimedia Appendix 2

Fitbit Flex 2 illustration and features.

[[JPG File, 12KB - resprot_v6i9e183_app2.jpg](#)]

Multimedia Appendix 3

Safety tips brochure.

[[PDF File \(Adobe PDF File\), 42KB - resprot_v6i9e183_app3.pdf](#)]

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Abbreviations

BMI: body mass index
CAB: Community Advisory Board
E-HEALS: eHealth literacy scale
EHR: electronic health record
HBA: health behavior assessment
ICC: intraclass correlation coefficient
MVPA: moderate-to-vigorous physical activity
PACIC: Patient Assessment of Chronic Illness Care
PCP: primary care provider
PESCA: Program to Enhance Scholarly and Creative Activities

RCT: randomized controlled trial
SEM: structural equation modeling
SMS: short message service

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Protocol

Using Smart Technology to Improve Outcomes in Myocardial Infarction Patients: Rationale and Design of a Protocol for a Randomized Controlled Trial, The Box

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Abstract

Background: Recent evidence suggests that frequent monitoring using smartphone-compatible wearable technologies might improve clinical effectiveness and patient satisfaction of care.

Objective: The aim of this study is to investigate the clinical effectiveness and patient satisfaction of a smart technology intervention in patients admitted with a ST elevation myocardial infarction (STEMI) or non-ST acute coronary syndrome (NST-ACS).

Methods: In this single center, open, randomized controlled trial patients who suffered from STEMI or NST-ACS will be randomized 1:1 to an intervention group or control group. Both groups will be followed up to one year after the index event. The intervention group will take daily measurements with a smartphone-compatible electrocardiogram device, blood pressure (BP) monitor, weight scale, and activity tracker. Furthermore, two of four outpatient clinic visits will be replaced by electronic visits (1 and 6 months after index event). The control group will receive regular care, consisting of four outpatient clinic visits (1, 3, 6, and 12 months after index event). All patients will be asked to fill in validated questionnaires about patient satisfaction, quality of life, propensity of medication adherence, and physical activity.

Results: The primary outcome of this trial will be percentage of patients with controlled BP. Secondary outcomes include patient satisfaction, health care utilization, major adverse cardiac events, medication adherence, physical activity, quality of life, and percentage of patients in which a sustained arrhythmia is detected.

Conclusions: Smart technology could potentially improve care in postmyocardial infarction patients. This trial will investigate whether usage of smart technology can improve clinical- and cost-effectiveness of care.

Trial Registration: Clinicaltrials.gov NCT02976376; <https://clinicaltrials.gov/ct2/show/NCT02976376> (Archived by WebCite at <http://www.webcitation.org/6tcvAdbdH>)

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KEYWORDS

telemedicine; myocardial infarction; hypertension

Introduction

Current European Society of Cardiology guidelines on secondary prevention in patients with sustained ST elevation myocardial infarction (STEMI) or acute coronary syndrome without persistent ST elevation (non-ST acute coronary syndrome; NST-ACS) recommend tight blood pressure (BP) control, weight control, and adequate physical activity after discharge from the hospital, as well as regular electrocardiograms (ECGs) [1,2]. In current practice, these patients regularly visit outpatient clinics in the first year after their initial hospitalization, where the patient is interviewed, weighed, an ECG is recorded, BP is measured, lifestyle advices are given, and pharmaceutical treatment is evaluated [3]. In this situation, patients must be physically present at the outpatient clinic [3], which might pose a burden to the patient, especially in remote areas [4]. Furthermore, this process necessitates trained health care staff, which increases their workload.

Recent advances in information and communication technologies have enabled remote monitoring of vital signs and remote doctor-patient contacts (together encompassing part of the broad concept of *telemedicine*) [5-9]. In recent years, a number of smartphone-compatible wearables have received a European Conformity (CE)-mark and Food and Drug Administration (FDA) clearance, and are available for over-the-counter sale in the European Union and the United States [10]. Some of these smartphone-compatible wearables allow for the measurement of (depending on the type of wearable) the number of steps taken per day, BP, weight, and the recording of an ECG. The devices are easy-to-use and do not require the assistance of trained health care staff. Results of measurements are communicated with smartphone apps tailored to the specific device. Data is uploaded via the Internet to servers belonging to the manufacturers of the devices [10,11].

Recent research in various patient populations suggests that telemedicine might improve clinical effectiveness and patient satisfaction of care [12,13]. Remote and more frequent monitoring with subsequent therapy changes has been shown to improve clinical outcomes of patients with uncontrolled hypertension (achieving 18.4% more patients with controlled

BP) [12] and with type 2 diabetes mellitus (a statistically significant 0.37% reduction in hemoglobin A1c) [13]. Furthermore, remote video contact moments, in which the doctor and patient communicate via a video connection, are potentially time-saving for patients [14,15]. One study found that office visits required an average of 50 minutes of a patient's time, while electronic visits only required 22 minutes on average [15].

We therefore hypothesize that telemedicine improves clinical effectiveness and patient satisfaction of care in the follow-up of STEMI and NST-ACS patients. Thus, the aim of this study is to investigate the clinical effectiveness and patient satisfaction of a smart technology intervention in patients after being admitted with a STEMI or NST-ACS. In this paper, the rationale and design of this open, single center, randomized controlled trial (RCT) are presented.

Methods

Study Design (Design, Randomization, and Follow-Up)

The Box is a single-center open RCT, and is a parallel group study. The study will be conducted at the Leiden University Medical Center (LUMC), a tertiary care hospital in Leiden, The Netherlands. The trial is registered under clinical trial number NCT02976376 (Clinicaltrials.gov) and NL56453.058.16 (Toetsingonline.nl). After inclusion, patients will be randomized 1:1 to either *The Box* (intervention group) or to regular follow-up (control group). Block randomization per 10 participants will be performed. Randomization will be stratified per primary diagnosis (STEMI or NST-ACS) and per age (<50, 51-60, 61-70, 71-80, and >80 years). A website will be used to generate randomization lists [16].

Patient Population

Patients who are admitted to the cardiology department of the LUMC with STEMI [1] or NST-ACS [2] will be eligible for participation. Patients with a STEMI or NST-ACS who match the inclusion and exclusion criteria will be approached for participation in the protocol within 24 hours after primary percutaneous coronary intervention (PCI). The maximum time between primary PCI and study inclusion is 96 hours. All inclusion and exclusion criteria are listed in [Textbox 1](#).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patient is admitted with acute myocardial infarction
- Patient is able to communicate in English or Dutch

Exclusion criteria

- Body Mass Index >35 kg/m²
- Included in another RCT
- Does not have wireless Internet access at home
- Less than 18 years old
- Considered an incapacitated adult (this decision is left to the discretion of the responsible cardiologist)
- Pregnant
- Unwilling to sign the informed consent form

Regular Follow-Up

Since 2004, the department of Cardiology of the LUMC has a dedicated care track for patients with STEMI or NST-ACS. Details about this protocol have been described previously by Liem et al [3]. Briefly, patients with signs and symptoms that are possibly related to a myocardial infarction are referred to a PCI center. Upon arrival, patients are immediately transferred to the catheterization department, where primary PCI of the culprit lesion is performed. Before discharge, patients are given written and oral information on the importance of medication adherence and lifestyle advices, in accordance with the European Guidelines on cardiovascular disease prevention in clinical practice [17].

After approximately 48-hours, patients are discharged from the hospital. The standard follow-up during the first year after discharge includes four outpatient clinic visits:

1. *Approximately 1 month after STEMI or NST-ACS.* This visit includes: a BP measurement; a 10-second, 12-lead ECG; laboratory testing (including kidney function, renal

function, and lipid spectrum); and an interview with a doctor or nurse practitioner.

2. *Approximately 3 months after STEMI or NST-ACS.* This visit includes: a BP measurement; a 10-second, 12-lead ECG; stress echo; a 24-hour Holter ECG, and an interview with a doctor or nurse practitioner.
3. *Approximately 6 months after STEMI or NST-ACS.* This visit includes: a BP measurement, a 10-second, 12-lead ECG; a 24-hour Holter ECG; laboratory testing (including kidney function, renal function, and lipid spectrum); a transthoracic echocardiogram (TTE); and an interview with a doctor or nurse practitioner.
4. *Approximately 12 months after STEMI or NST-ACS.* This visit includes: a BP measurement, a 10-second, 12-lead ECG; laboratory testing (including kidney function, renal function, and lipid spectrum); a TTE; and an interview with a doctor or nurse practitioner.

Patients who are randomized to regular follow-up receive the same care as patients who do not participate in the study. A flowchart of regular follow-up is detailed in Figure 1.

Figure 1. MISSION, follow-up of patients who suffered from STEMI or NST-ACS. BP: blood pressure; ECG: electrocardiogram; NP: nurse practitioner; TTE: transthoracic echocardiogram.

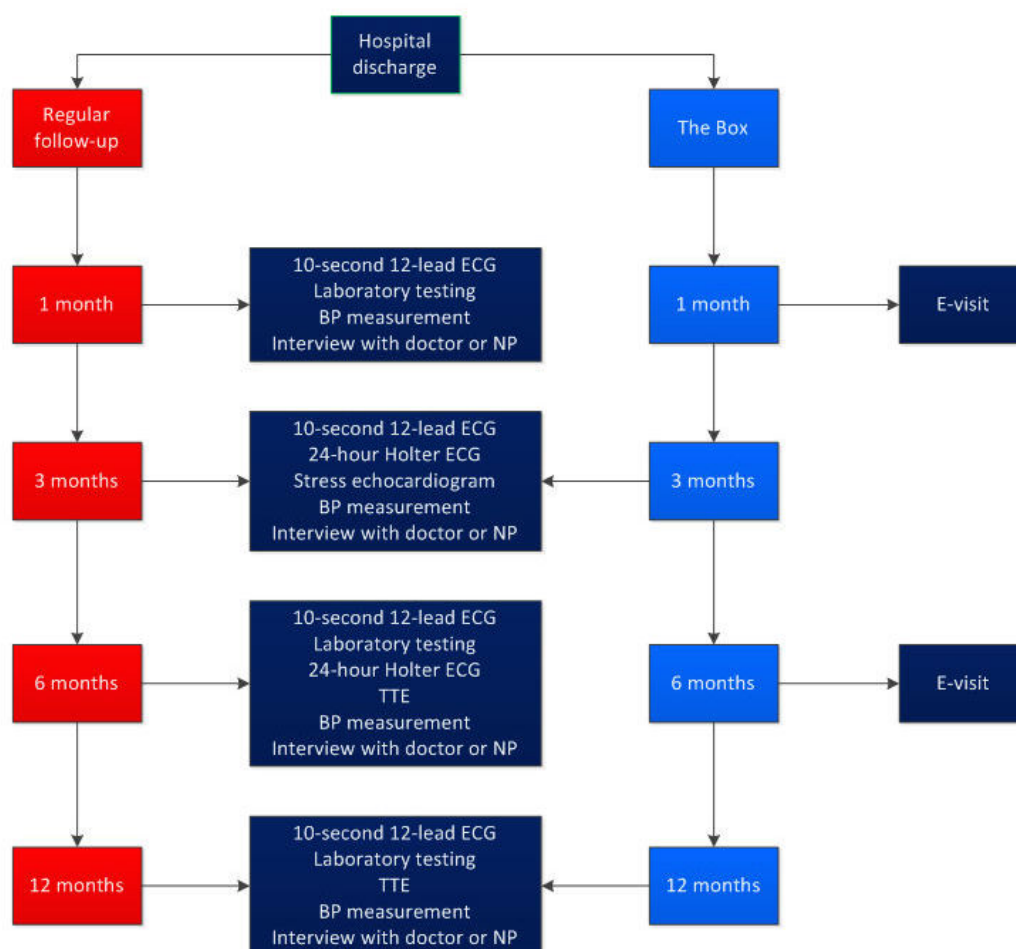


Figure 2. The Box.

The Box

When randomized to *The Box* (Figure 2), patients will receive a box containing a weight scale, BP monitor, activity tracker, and a wearable ECG device. Patients will receive *The Box* before discharge and will be given the same written and oral information on the importance of medication adherence and lifestyle advices as the control group, in accordance with the European Guidelines on cardiovascular disease prevention in clinical practice [17]. The necessary apps will be downloaded on the patient's smartphone; necessary accounts will be created and the installation of the devices will be carried out by a health care professional dedicated to the project. Afterwards, patients will be given oral instructions on the usage of the devices: they will be instructed to measure BP in a sitting position after five minutes of resting. The device should be applied to the left upper arm. Patients will be instructed to rest their left forearm on a table. Furthermore, a manual explaining the usage of the wearables (described below) will be handed over with *The Box*. Instruction videos are also available on YouTube. Patients who do not own a smartphone or tablet with iOS or Android OS but are willing to participate and be randomized to *The Box* will receive a smartphone. Patients will be instructed to use their own wireless Internet access (eg, home WiFi network). No mobile data network plan will be provided with the smartphone.

Patients will be instructed to record a single lead ECG, measure BP, and record their weight daily, preferably at the same time of day. Furthermore, participants will be asked to record a single lead ECG if any symptoms of possible cardiac origin occur (as interpreted by the patient). Lastly, patients will be instructed to

wear their activity tracker during the day to track their daily number of steps, and at night to track the duration and quality of sleep. Patients will be told that measurements will be checked on a daily basis and that they will be contacted in cases of predefined data irregularities. Patients will be explicitly told that they cannot rely on the devices of *The Box* in emergency situations.

In addition to daily measurements, the first and third of the four standard outpatient clinic visits will be replaced by an electronic visit, in which the patient will communicate with the doctor or nurse practitioner via a secured video connection. The content of the interview will be comparable to the content of a regular outpatient clinic visit. The same doctors and nurse practitioners will perform the regular outpatient clinic visits and the digital outpatient clinic visits. In the intervention group, the 10-second 12-lead ECG and the laboratory testing one month after the index event will not be performed. Moreover, the 10-second 12-lead ECG, the 24-hour Holter ECG, laboratory testing, and the TTE 6 months after the index event will not be performed (Figure 1).

Devices

All devices used for this study are noninvasive, battery powered, smartphone-compatible devices. All devices have a CE-mark, are approved by the United States FDA, and are allowed for over-the-counter sale in the European Union and the United States. The installation and usage of the devices are so intuitive that no medical staff needs to assist when the devices are used by the patient.

The usage of the devices requires a smartphone or tablet with Android Operating System (OS; Google, Mountain View, California, USA) or iOS (Apple Computers, Cupertino, CA, USA). The devices communicate with a dedicated mobile app on the smartphone or tablet, which can be downloaded from the App Store (iOS) or Play Store (Android). The data from the measurements are stored on the smartphone or tablet and uploaded to the app manufacturer's servers (the cloud), which are located in Europe. An Internet connection (eg, WiFi, 3G, or 4G) is required to synchronize with the cloud. Measurements can be done while the smartphone or tablet is offline. In these cases, the results of the measurements are stored on the smartphone or tablet, and uploaded to the server when the smartphone is reconnected to the Internet.

Electrocardiogram Device

The ECG device (AliveCor, AliveCor Inc., San Francisco, CA, USA) contains two electrodes. The device communicates with the AliveCor app. The ECG device allows the user to record a 30-second single lead ECG. To record an ECG, the patient must position two or three fingers of the right hand on one electrode and two or three fingers of the left hand on the other electrode. The device is to be held within approximately 1 to 30 centimeters of the smartphone. An ultrasound signal is sent from the ECG device to the smartphone. This signal is then converted to a live single lead ECG that is subsequently shown on the smartphone screen [7,10].

After 30 seconds, an automated algorithm in the app calculates the R-R intervals and formulates a diagnosis, varying from *normal* to *possible atrial fibrillation* to *undetermined*, on the screen [10]. The patient then has the ability to add notes, and is requested to report any symptoms (if present) before saving the ECG.

Blood Pressure Monitor

The BP monitor (Withings S.A., Issy les Moulineaux, France) is a smartphone-compatible, battery operated oscillometric BP cuff. The device allows the user to measure systolic BP, diastolic BP, and heart rate. The device is applied around the left or right upper arm (depending on the patient's preference). Upon pushing the button on the cuff, a connection is made with the smartphone via Bluetooth. The inflation and deflation of the cuff is automated and can be initiated via the dedicated Withings

Health Mate app (for iOS and Android) on the smartphone. The average duration of a measurement is approximately 20 seconds. After inflation and deflation, the systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate are shown on the smartphone screen.

The Weight Scale

The weight scale (Withings S.A., Issy les Moulineaux, France) allows the patient to track weight, fat percentage, heart rate, and ambient CO₂ parts per million. To measure all four parameters, the patient must stand on the weight scale. While standing on the weight scale, the patient must select their own account. The results are shown on a screen on the weight scale, and are automatically uploaded via the Internet to the Withings server.

Activity Tracker

The activity tracker (Pulse Ox, Withings S.A., Issy les Moulineaux, France) allows the patient to track the number of steps taken per day. The device is the size of a thumb and can be attached to the wrist or belt, and also allows the patient to track duration and quality of sleep. Steps are automatically tracked. The measurement results are sent via Bluetooth to a dedicated smartphone app, which is compatible with iOS and Android OS.

Storage of the ECGs

Single lead ECGs, generated by the single lead ECG device, are stored in the cloud. The system offers patients the ability to connect their personal account with a physician's account. The physician can then review the ECGs made by patients linked to their account, including the diagnosis given by the app's algorithm and the symptoms reported by the patient. The automated diagnosis algorithm has a reported sensitivity of 97% and a specificity of 98% for the detection of atrial fibrillation [7]. ECGs that are classified by AliveCor as *possible atrial fibrillation* and *undetermined* will subsequently be checked by a project-dedicated health care professional in our department. A patient will be contacted if a previously undiagnosed arrhythmia is seen or if a patient repeatedly reports symptoms. A flowchart of the storage of the ECGs is shown in Figure 3. An example of a portable document format (PDF) ECG showing sinus rhythm generated by the ECG device is shown in Figure 4. An example of a PDF ECG showing atrial fibrillation generated by the ECG device is shown in Figure 5.

Figure 3. Data integration of single lead electrocardiograms. Company A is the ECG manufacturer. ECG: electrocardiogram.

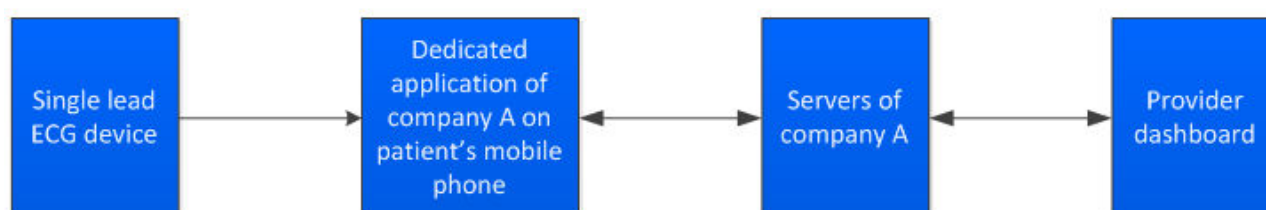


Figure 4. A PDF generated by the ECG device, showing sinus rhythm.

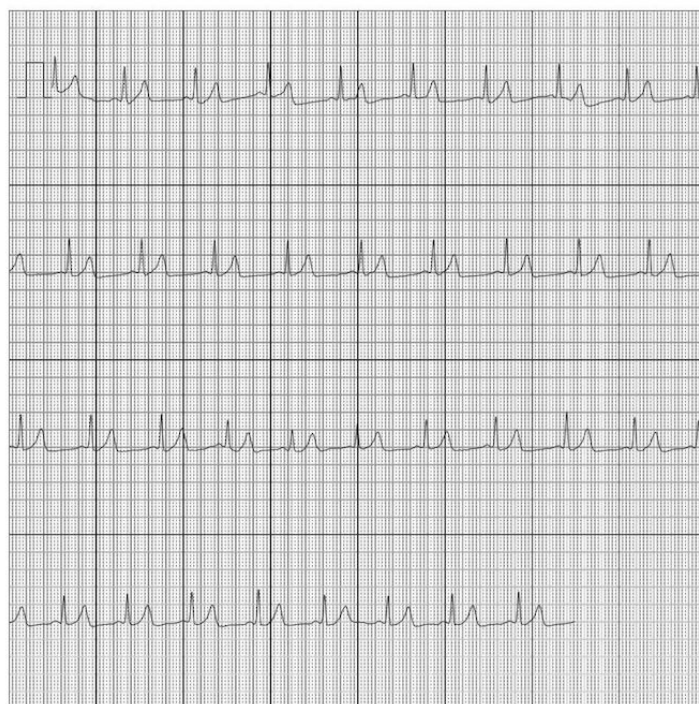
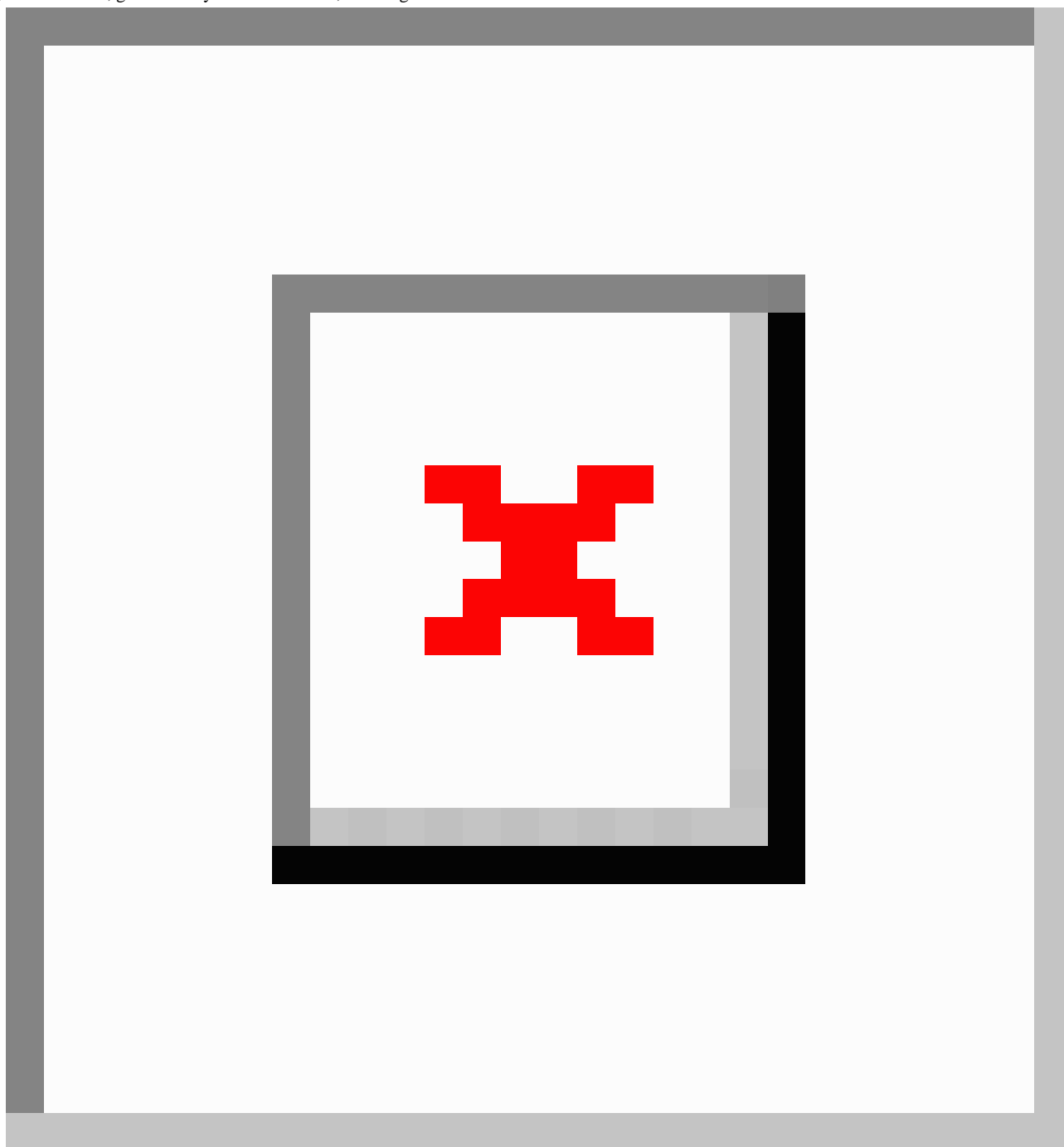


Figure 5. A PDF, generated by the ECG device, showing atrial fibrillation.



Data Integration in Electronic Medical Records

The measurement results from the weight scale, BP monitor, and activity tracker will be stored on the manufacturer's server (Withings S.A., Issy les Moulineaux, France). Data will be extracted from the Withings server and integrated in the department's dedicated electronic medical record (EMR; EPD-Vision, Department of Cardiology, LUMC, The

Netherlands). An automated algorithm searches for predefined irregularities in the data ([Textbox 2](#)). Data can subsequently be displayed in graphic format to facilitate trend analysis. A flowchart of the storage of BP, weight, and activity data is displayed in [Figure 6](#). If bugs arise in this system, a software developer who works at the Department of Cardiology will fix the bug.

Textbox 2. Warnings generated by the dedicated system.

BP monitor

- If a patient has not sent BP results for more than 7 consecutive days
- If the heart rate is >100 beats per minute
- If the SBP is >139
- If the DBP is > 89
- If the SBP is 10 mmHg higher than last measurement
- If the DBP is 5 mmHg higher than last measurement
- If the SBP is 10 mmHg higher than 7 measurements before
- If the DBP is 5 mmHg higher than 7 measurements before
- If the SBP is 10 mmHg lower than last measurement
- If the DBP is 5 mmHg lower than last measurement
- If the SBP is 10 mmHg lower than 7 measurements before
- If the DBP is 5 mmHg lower than 7 measurements before

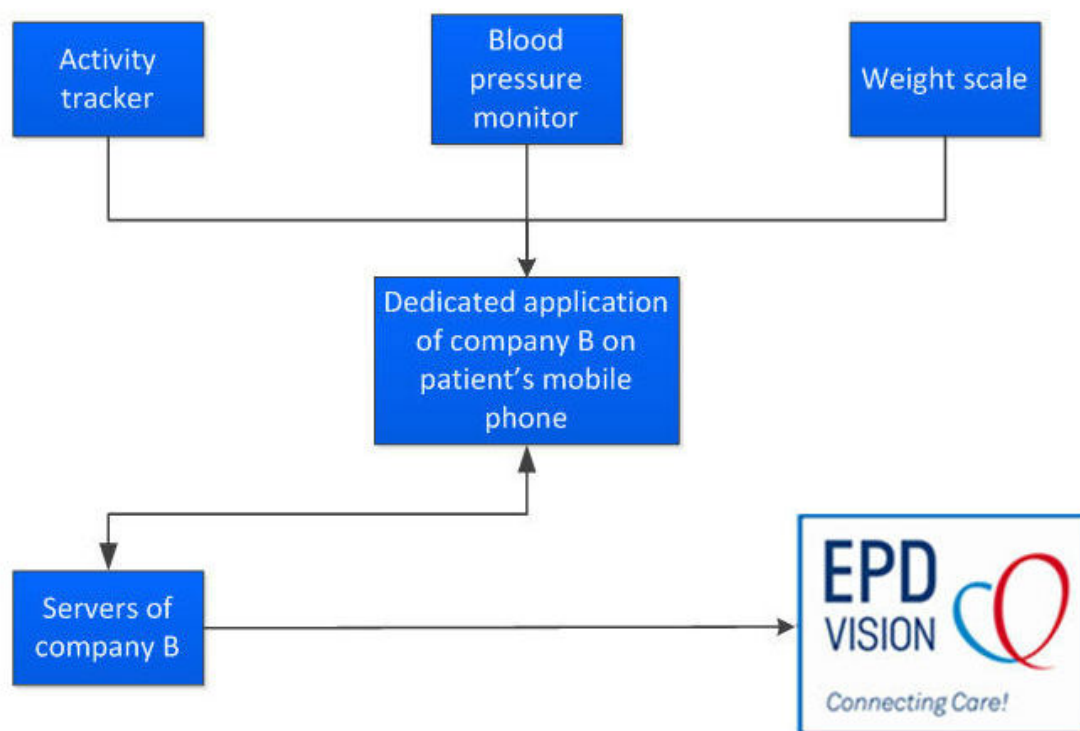
Weight scale

- If a patient has not sent measurements for more than 7 consecutive days
- If the weight is more than 2 kg higher than last measurement
- If the weight is more than 3 kg higher than 7 measurements before
- If the weight is more than 2 kg lower than last measurement
- If the weight is more than 3 kg lower than 7 measurements before

Activity tracker

- If a patient has not sent measurements for more than 7 consecutive days

Figure 6. Data integration of the activity tracker, weight scale, and BP monitor in the department's Cardiology Information System "EPD-Vision". Company B is the manufacturer of the activity tracker, blood pressure monitor, and weight scale.



Reasons to Contact Patients

Data will be checked daily by a project-dedicated health care professional. When prespecified irregularities are seen in the data, a patient will be contacted within 48 hours by email or phone. These data irregularities are standardized and shown in [Textbox 2](#).

Reasons to Adjust Therapeutic Regimen

Data will be discussed by the data reviewer and the patient's treating physician or nurse practitioner. There are several reasons to contact the patient, which are detailed below.

BP Monitor

Warnings generated by the system on the basis of BP measurements will be reviewed by a project-dedicated health care professional. The reason to change medication will be left to the discretion of the treating physician.

Single Lead Electrocardiogram

In cases of newly diagnosed arrhythmias lasting at least 30 seconds (eg, atrial fibrillation, atrial flutter, nodal or ventricular escape rhythms, ventricular tachycardias) or at least 4 newly diagnosed asymptomatic premature ventricular contractions, a 24-Hour Holter ECG will be performed. Patients noting chest pain or shortness of breath as symptoms will be contacted for an interview by telephone. The decision to change medication or to refer the patient for invasive therapy will be left to the discretion of the treating physician.

Weight

Weight will not be a primary reason to change a therapeutic regimen. Patients can be given lifestyle advice, depending on their height, weight, and estimated fat percentage; this will only be done at scheduled outpatient clinic visits.

Activity

Activity tracking data is not a primary reason to change a therapeutic regimen. Patients can be advised to exercise more or less, depending on the data; this will only be done at scheduled outpatient clinic visits.

Nonadherence

If a patient does not send measurements from any of their four devices for 21 consecutive days, they will be considered nonadherent. A standardized email will be sent to the patient, stating that measurements have not been received and that they are urged to contact the hospital in case of any technical difficulties. If no answer is received within 21 days or no measurements are seen within 21 days, the patient will be called by telephone. Any technical difficulties or objections by the patient will be assessed and solved if possible. After this phone call, if the patient starts sending measurements, they will be considered adherent again. This patient will be sent a standardized email in case they become nonadherent again. If the patient does not start sending measurements, they will not

be approached again by email or by telephone to try to affect their nonadherence. However, this patient will not be excluded from the trial, and will still be followed-up according to *The Box* protocol. If patients notify the hospital that they want to have regular outpatient clinic visits, they will be followed-up according to the regular follow-up protocol.

Questionnaires

All patients, in both the intervention and control groups, will be asked to fill-in a short form health questionnaire (SF-36) [18], a patient satisfaction questionnaire [19], a medication adherence questionnaire, and an International Physical Activity Questionnaire (IPAQ; to assess the patient's level of physical activity) [20]. These questionnaires will be used within one month after myocardial infarction, six months after myocardial infarction, and twelve months after myocardial infarction.

Privacy of Study Participants

To anonymize the data, patients will receive an email address consisting of a study code, which they can use to create their Withings and AliveCor accounts. The corresponding names will be kept in a separate, password-protected database.

Ethical Conduct

The study is approved by the Hospital's Medical Ethics Committee (P16.070). All procedures will be conducted in accordance with the principles of the Declaration of Helsinki (version 10, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice. Written offline informed consent will be obtained from all participants. The devices used in this study and described above have been approved by our Hospital's Instrumentation Department. All devices are CE-marked and are available for sale in the European Union. All devices have been purchased by our department for this study. No manufacturer has a role in the study design, data collection, statistical analysis, or writing of the manuscript. No financial support was received for this study from any device manufacturer. All devices are provided to study participants who are randomized to *The Box* group free of charge.

Study Withdrawal

Patients who are randomized to *The Box* group can be withdrawn from the study if they are either nonadherent (as discussed above) or if they themselves wish to withdraw from the study. Patients who withdraw from regular follow-up are considered lost to follow-up.

Results

Study Outcomes

The primary outcome of this study is the percentage of patients with normalized BP (defined as SBP <140 mmHg and DBP <90 mmHg), as measured at the 12-month outpatient clinic visit. Secondary outcomes of this study are detailed in [Textbox 3](#).

Textbox 3. Secondary outcome measures.

1. The percentage of patients with controlled BP (defined as SBP <140 mmHg and DBP <90 mmHg), as measured at the 3-month outpatient clinic visit.
2. Patient satisfaction, as assessed by the patient satisfaction questionnaire [18].
3. Health care utilization, defined as an outpatient clinic visit, emergency care visit, or admission for any reason. This factor will be measured via questionnaires and verified by EMR data.
4. Major Adverse Cardiac Events (MACEs)
 - a. Death of any cause
 - b. Cardiac death
 - c. Recurrent STEMI
 - d. Recurrent NST-ACS
 - e. Revascularization
 - f. Hospitalization for heart failure
 - g. Transient Ischemic Attack
 - h. Ischemic stroke
5. Propensity of medication adherence, measured by the 8-item Morisky Medication Adherence Scale (MMAS-8) [21].
6. Physical activity, as measured by the iPAQ [20].
7. Quality of life, measured by the SF-36 [19].
8. Percentage of patients in which a previously unknown sustained arrhythmia (>30 seconds) is detected.
9. Cost-effectiveness, expressed as the incremental cost-effectiveness ratio.

Economic Analysis

To assess the cost-effectiveness of the intervention, costs per quality adjusted life year (QALY) will be calculated. The analysis will be performed from a societal perspective with a time horizon of one year. Patients will receive a health care resource use questionnaire at 6 months and 12 months. In this questionnaire, a patient will be asked to fill in their total health care utilization, such as outpatient clinic visits, emergency visits, admissions for any reason, and visits to the general practitioner. All outpatient clinic visits, emergency visits, and admissions for any reason reported in the questionnaire will be verified by EMR data. In the same questionnaire, the patient will be asked to fill in total medication use. All health care and medication use will be multiplied with standard cost prices to calculate costs [22]. To calculate indirect costs, patients will be asked to note absence from paid and unpaid work. Productivity costs will be calculated using the friction cost method. Absence will again be multiplied against standard cost prices [22]. QALYs will be calculated from utility scores from the SF-36 questionnaire, which will be administered at baseline, 1 month, 6 months, and 12 months [19,23]. Finally, costs and QALYs in both groups will be compared. It is our hypothesis that societal costs will be lower in the intervention group.

Statistical Analyses

A power calculation was done using R software [24], which is based on a comparison of two proportions of patients with controlled BP (defined as an SBP of 139 mmHg or less and a DBP of 89 mmHg or less). We hypothesize that in the *The Box* group, 95% of the patients will achieve controlled BP, while in the control group, 75% will achieve controlled BP [25]. For this

calculation, an alpha of 0.05, a beta of 0.20, and a margin of 0.07 were chosen, yielding a sample size of 200 patients.

Data will be analyzed according to the intention-to-treat principle. Causes of missing data will be tabulated ([Multimedia Appendix 1](#)). The percentage of missing data is expected to be low. Therefore, complete case analyses will be done. Analyses will be based on the missing-at-random assumption. If the percentage of missing values exceeds 7%, multiple imputation will be applied in the analysis of the data.

After finishing the study (defined as the last patient's last visit), the proportion of patients with controlled BP will be compared with a Chi-square test. Logistic regression might be done if serious imbalances of baseline variables exist, to correct for potential confounding variables. Percentages of patients with controlled BP at three months (secondary outcome 1), and percentages of patients in which a previously unknown sustained arrhythmia is detected, will also be compared with a Chi-square test.

Scores of questionnaires (patient satisfaction questionnaire, MMAS-8 scale, iPAQ questionnaire, and SF-36 questionnaire) and health care utilization will be compared using an independent t-test. Major Adverse Cardiac Events (MACEs) will only be reported. As the study is underpowered, no statistics will be done on MACEs. The numbers will be hypothesis-generating.

Discussion

In this paper, we presented the rationale and design of a single-center, open, RCT. With this trial, we will evaluate the

clinical effectiveness of a smart technology intervention in patients with STEMI and NST-ACS.

Clinical Effectiveness

It is expected that with daily monitoring of ECG, BP, weight, and steps, data will allow for early detection of high BP and the development of arrhythmias. For this study, the percentage of patients with controlled BP at 12 months has been chosen as primary outcome. Controlled BP is associated with lower risks of death, recurrent PCI, and stroke in patients who suffered from ACS. Therefore, the European guidelines recommend tight BP control via medication and lifestyle advice.

Percentages of 1-year mortality after STEMI or NST-ACS vary, but have been reported to be under 10% [26]. With a sample size of 200, it is expected that this study is underpowered to detect a significant difference in mortality between the intervention group and control group. It is emphasized that it is not the primary objective of this study to demonstrate a difference in mortality. This study is intended to investigate whether regular monitoring of clinical parameters (including BP) can lead to better control of those parameters, therefore improving surrogate outcomes in these patients.

Patient Compliance

All devices used in the intervention group are designed for the consumer market. Patients will receive assistance with installation of the devices. After measurements, data will automatically be transferred to the hospital. It is expected that this automation will help to facilitate accurate and timely transmission, which might enhance patient compliance. To test this hypothesis, all reminders sent to patients for not having measured their data will be monitored. “No-shows” at digital outpatient clinic visits, and at the physical outpatient clinic visits, will be monitored as well. It is hypothesized that there will be no significant difference in the percentage of “no-shows” between the digital outpatient clinic visits and the physical outpatient clinic visits.

Patient Satisfaction

During the study, patient satisfaction will be monitored via a validated questionnaire [18]. In this study, by design, patients in the intervention group will monitor ECG, BP, and weight more intensively. This increased frequency of monitoring has potential clinical benefits, such as having early detection of high BP or arrhythmias, as well as allowing patients to see and interpret their own data. This approach might enhance patient satisfaction of care. Conversely, daily monitoring might pose

a burden to the patient, both physically (as patients must take time to perform the measurements) as well as mentally (as they might associate monitoring with their illness).

Health Care Utilization

A concern regarding smart technology interventions is the fear that patients, given their nonmedical background and their perceived inability to interpret medical data correctly, increase the number of contact points with hospitals, leading to more outpatient clinic visits and emergency department visits. This issue could therefore lead to higher burdens on both patients and health care staff, without improving clinical outcomes. Scientific evidence describing the relationship between increased monitoring frequency and health care utilization is scarce. Patients participating in this study will receive clear instructions about the usage of the devices, as well as the reasons for the hospital to contact the patients. It is therefore expected that health care utilization will not be higher in the intervention group.

Generalizability

Patients with a STEMI or NST-ACS who match the inclusion and exclusion criteria will be eligible for participation. Patients who do not own a smartphone will not be excluded from the RCT, but patients who do not have Internet access at home will be excluded. This factor might affect generalizability. However, as 97% of the Dutch population has Internet access [27], it is expected that this exclusion criterion only slightly affects generalizability. The fact that a smartphone will be used for remote monitoring might affect generalizability as well. Previous literature has indicated that smartphone literacy decreases with age [28]. Furthermore, patients who do own a smartphone might refuse to participate as well, for various reasons [29]. It is also known that patients who participate in RCTs have different demographics than patients who do not [30]; it is therefore expected that generalizability will be affected. However, it is emphasized that this factor might partly be due to the involvement of smartphone technology and partly inherent to the RCT study design in general. As patients are given a smartphone in case they do not own one, and technical support is provided, generalizability issues will be kept to a minimum.

Conclusion

In summary, the rationale and design of an RCT is presented to investigate whether a smart technology intervention can increase clinical effectiveness and patient satisfaction in the follow-up of STEMI or NST-ACS patients.

Acknowledgments

This is an investigator initiated study. All devices have been purchased for this study. No financial support will be received from either manufacturer.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Example of how causes of missing data will be tabulated.

[[PDF File \(Adobe PDF File\), 6KB - resprot_v6i9e186_app1.pdf](#)]

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Abbreviations

BP: blood pressure
CE: European Conformity
DBP: diastolic blood pressure
ECG: electrocardiogram
EMR: electronic medical record
FDA: Food and Drug Administration
iPAQ: International Physical Activity Questionnaire
LUMC: Leiden University Medical Center
MACE: Major Adverse Cardiac Event
MMAS: 8-item Morisky Medication Adherence Scale
NST-ACS: non-ST acute coronary syndrome
OS: operating system
PCI: percutaneous coronary intervention
PDF: portable document format
QALY: quality adjusted life year
RCT: randomized controlled trial
SBP: systolic blood pressure
SF-36: short form health questionnaire
STEMI: ST elevation myocardial infarction

TTE: transthoracic echocardiogram

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Protocol

Assessing the Efficacy and Safety of an 11 β -Hydroxysteroid Dehydrogenase Type 1 Inhibitor (AZD4017) in the Idiopathic Intracranial Hypertension Drug Trial, IIH:DT: Clinical Methods and Design for a Phase II Randomized Controlled Trial

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Abstract

Background: Idiopathic intracranial hypertension (IIH) is a condition with few effective management options. So far, there have been no randomized controlled trials evaluating new treatments in IIH.

Objectives: The purpose of this paper is to outline the trial design for the Idiopathic Intracranial Hypertension Drug Trial (IIH:DT), assessing an innovative medical treatment in IIH and the rationale for the chosen trial methodology.

Methods: IIH:DT is a phase II double-blind randomized placebo-controlled trial recruiting 30 female participants with active IIH (intracranial pressure >25cm H₂O and papilledema). Participants are randomized in a 1:1 ratio to 12 weeks of either AZD4017, an 11 β -hydroxysteroid dehydrogenase type 1 inhibitor, or a matching placebo. They receive either 400 mg of AZD4017 or placebo twice daily. Participants are followed up at Weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16 postrandomization. The primary outcome is to examine the effect of AZD4017 on intracranial pressure, measured by lumbar puncture, over 12 weeks. Secondary outcome measures include IIH symptoms, visual function, papilledema, headache measures, safety, and tolerability. Cerebrospinal fluid, serum, plasma, urine, and adipose tissue are also taken for exploratory outcomes.

Results: All participants were recruited between April 2014 and August 2016.

Conclusions: IIH:DT is the first phase II double-blind randomized placebo-controlled trial assessing the efficacy and safety of the novel pharmacological intervention, AZD4017, for the treatment of IIH.

Trial Registration: Clinicaltrials.gov NCT02017444; <https://clinicaltrials.gov/ct2/show/NCT02017444> (Archived by WebCite at <http://www.webcitation.org/6tVHesN6s>)

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KEYWORDS

11beta-HSD1; randomised controlled trial; clinical protocol; idiopathic intracranial hypertension; clinical trials, Phase II

Introduction

Idiopathic intracranial hypertension (IIH), also known as benign intracranial hypertension or pseudotumor cerebri, is a condition of unknown etiology characterized by elevated intracranial pressure (ICP) and papilledema. IIH typically affects young obese females of child-bearing age, causing disabling daily headaches and visual loss. Among this population, the incidence of IIH is 12-20 per 100,000 [1,2] (0.5-2 per 100,000 in the general population [3,4]). In line with the global obesity epidemic, the incidence of IIH is expected to rise and consequently contribute to significant morbidity in young obese females.

A 2015 Cochrane review identified two randomized controlled trials (RCTs) assessing the use of acetazolamide in IIH [5]. The review included the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), which demonstrated beneficial effects of acetazolamide in IIH patients with mild visual loss [6], and a UK pilot study of acetazolamide [7]. Previous studies have highlighted elevated attrition rates [5] possibly due to drug side effects, which include paresthesia and gastrointestinal symptoms. The Cochrane review concluded that there was insufficient evidence to support the use of acetazolamide and that further well-designed RCTs are required [5].

For progressive or acute deterioration of vision in IIH, surgical techniques such as cerebrospinal fluid (CSF) shunting, optic nerve sheath fenestration, or venous sinus stenting have been used to prevent blindness. However, there is limited evidence to support these surgical interventions.

A 2010 prospective cohort study evaluated the effect of a low-calorie diet to promote weight loss in the treatment of IIH. The resulting dietary weight loss led to improvements in ICP, headaches, and vision [8]. Although weight loss is generally advised, the management of IIH varies considerably owing to a lack of supporting evidence [9,10]. Meaningful and sustained weight loss is also difficult to achieve. Consequently, alternative approaches are needed.

In the first phase II RCT in IIH ever conducted, the Idiopathic Intracranial Hypertension Drug Trial (IIH:DT) will assess whether the 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor AZD4017 is a safe and effective treatment for IIH.

Scientific Background

The intracellular enzyme 11 β -HSD1 converts inactive cortisone to active cortisol, amplifying local glucocorticoid availability independent of systemic circulating cortisol. AZD4017 is an oral selective, competitive inhibitor of 11 β -HSD1 originally developed as a potential treatment for diabetes mellitus type 2, obesity, and metabolic syndrome.

Glucocorticoid metabolism has previously been characterized in IIH subjects before and after therapeutic weight reduction (loss of 15.7 kg [SD 8.0] of body weight) [8]. Global 11 β -HSD1 activity decreased with weight loss as assessed by the urinary THF+allo-THF:THE ratio measured by gas chromatography/mass spectroscopy. Importantly, there was a

relationship between the therapeutic reduction in ICP and the decrease in global 11 β -HSD1 activity ($r=.504$, $P=.03$) [11].

These data not only highlight the potential link between 11 β -HSD1 activity and ICP but offer the opportunity to test our hypothesis that specific inhibition of 11 β -HSD1 will decrease ICP in IIH participants, opening an entirely novel therapeutic avenue.

Disordered CSF dynamics have been suspected of causing the raised ICP seen in IIH. The choroid plexus is the principle contributor to CSF production, which is ultimately driven by the sodium potassium ATPase (Na⁺K⁺ATPase) pump. Sodium transport creates an osmotic gradient driving water into the CSF [12]. Increasing the level of fluid within a closed system in turn increases ICP.

Aqueous humor produced by the ocular ciliary epithelium in the eye occurs by a mechanism analogous to CSF secretion in the choroid plexus, an embryologically related tissue [13]. A nonselective 11 β -HSD inhibitor, carbenoxolone, was assessed in lowering ocular hypertension over 4 days of treatment, demonstrating a 10% (mean pressure: baseline 22.7, treatment 20.5, placebo 21.6; $P=.001$) reduction in intraocular pressure compared to placebo. Inhibition of intracellular cortisol conversion within the ocular ciliary epithelium led to a decrease in sodium transport and a reduction in the osmotic gradient. As a consequence, water movement into the aqueous humor also decreased [14]. A similar process may occur at the choroid plexus with CSF secretion.

Safety Considerations

AZD4017 is a fully reversible, competitive inhibitor of 11 β -HSD1. It has been tested in two animal models: rats and nonhuman primates. The drug was found to be an effective inhibitor of 11 β -HSD1 in human and nonhuman primates but a poor inhibitor in other animals [15]. AZD4017 was also tested in five phase I and II human clinical trials assessing the drug in healthy males, obesity, diabetes mellitus type 2, and raised intraocular pressure. The following safety considerations were found.

Liver

In animal models, reversible hypertrophy of the liver was observed in rats, which was adaptive rather than degenerative. However, nothing was noted in the cynomolgus monkey. Elevated transaminases, without concomitant rise in bilirubin, were observed in a few human subjects treated with AZD4017 in the multiple-ascending dose study. The findings were reversible on drug discontinuation, and no subjects were clinically symptomatic [15].

We hypothesize that specific inhibition of 11 β -HSD1 will decrease ICP and consequently improve the symptoms and signs of IIH, providing a new pharmacological treatment for IIH.

Hypothalamic-Pituitary Axis

There were adrenal changes in the animal models, but these were considered adaptive rather than adverse. In the clinical studies, increases in adrenocorticotropin and dehydroepiandrosterone- sulphate were seen, indicating an

activation of the hypothalamic, pituitary, adrenal (HPA) axis. However, serum cortisol and testosterone levels were unchanged. There was no sign of adrenal insufficiency detected in humans [15].

Thyroid

Adaptive thyroid changes were seen in rats. In humans, there was no difference in thyroid hormones between AZD4017 and placebo-treated subjects. Despite this, thyroid function will be monitored owing to the preclinical results [15].

Trial Objectives

The purpose of this paper is to outline the design considerations for IIH:DT. The aims of the trial are to assess the efficacy, safety, and tolerability of the selective 11 β -HSD1 inhibitor AZD4017 for the treatment of IIH.

Methods

Trial Design

IIH:DT is a multicenter phase II double-blind randomized, placebo-controlled trial in the United Kingdom comparing 12 weeks of treatment with 400 mg AZD4017 twice daily with a matching placebo in 30 female participants with active IIH (intracranial pressure [ICP] >25cm H₂O and papilledema). Participants are followed up for 16 weeks. The primary outcome examines the effect of AZD4017 on ICP, measured by lumbar puncture (LP), over 12 weeks (see Figure 1). An initial prescreening includes papilledema assessment and a blood test. Potential participants are invited to a screening 7-30 days later where an LP is performed. If eligible, random allocation to either AZD4017 or placebo occurs. Following 12 weeks of treatment, a repeat LP is performed. A final follow-up visit is then attended at Week 16.

Recruitment

The aim of the trial was to recruit 30 participants (see sample size below) from four National Health Service (NHS) trusts across the United Kingdom between April 2014 and August 2016. Patient lists are screened before ophthalmology and research clinics, and those meeting the basic eligibility criteria approached at their appointment to determine their interest in trial participation. Consent is taken from willing patients to undertake prescreening. Prescreening consists of slit lamp examination for papilledema (Frisen grading ≥ 1) and a blood test to determine initial eligibility (see Table 1). If they continue to meet the eligibility criteria, they are asked to complete a 7-day headache diary (see Multimedia Appendix 1) and provide a 24-hour urine sample for glucocorticoid metabolite analysis. Participants are asked to return for a screening visit at least 7 days after their prescreening visit (see Trial Visits for further information).

Eligibility

Patients are recruited based on the presence of active IIH, either newly diagnosed or a long-standing diagnosis, with any degree of visual loss and fulfillment of the trial inclusion and exclusion criteria (Table 1; [16]). As IIH predominantly affects obese females of child-bearing age, this will be the focus of the trial. Males and children tend to present differently with atypical features and may have an alternative pathogenesis [17] and so are excluded.

During the trial, the HPA hormones are monitored. We have excluded those on glucocorticoid and other hormonal medications as this may confound monitoring of the HPA axis. Those on mild topical steroid preparations or on inhaled steroids for asthma have been included as the systemic levels are low. The inclusion of IIH patients on acetazolamide and other diuretics is permitted if the participant is on a stable dose.

Figure 1. IIH:DT trial design.

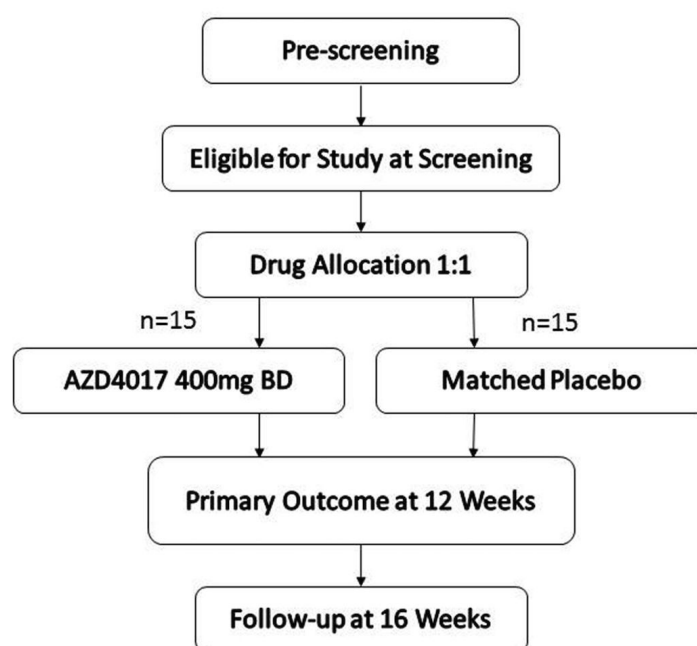


Table 1. Inclusion and exclusion criteria for IIH:DT.

Criteria	Description
Inclusion	<p>Provision of informed consent prior to any study specific procedures</p> <p>Female patients 18-55 years</p> <p>Diagnosis of IIH by the Modified Dandy criteria [16] with active disease (papilledema [Frisen grade ≥ 1] and significantly raised ICP $> 25 \text{ cm H}_2\text{O}$) and normal brain imaging during previous routine diagnostic work-up (evaluated by either magnetic resonance venography or computed tomography with venography)</p> <p>Participants must be willing to use one form of highly effective nonhormonal contraception. Participants must agree to undergo a urine pregnancy test at screening and at monthly intervals until the final follow-up visit 4 weeks after discontinuation of study treatment.</p> <p>Participants are able to continue other medications to treat their IIH (eg, acetazolamide, diuretics) but this dose should remain fixed throughout the study. Acetazolamide may be taken but the participant must be on a stable dose.</p> <p>Must be able to understand the consent form and comply with study requirements</p>
Exclusion	<p>Optic nerve sheath fenestration (as distortion of the optic nerve may prevent accurate assessment of their disease state). Participants who have had previous failed CSF shunting will be eligible for enrollment if they fulfill all other enrollment criteria.</p> <p>Abnormal neurological examination (aside from papilledema and consequent visual loss or VI nerve palsy)</p> <p>Unable to perform a visual field reliably</p> <p>Positive urine dipstick pregnancy test or planning to conceive in the 4 study months.</p> <p>Have estimated Glomerular Filtration Rate calculated by Modification of Diet in Renal Disease equation of $< 60 \text{ ml/min/1.73m}^2$</p> <p>Have any endocrine disorder, eg, thyroid dysfunction. Those with polycystic ovary syndrome will be included in the trial as there is a known association with IIH. Diabetes will not exclude participants.</p> <p>Suspicion of or known Gilbert's disease</p> <p>Creatine kinase $> 2 \times$ upper limit of normal on 2 consecutive measurements</p> <p>Alanine transaminase and/or aspartate transaminase $> 2 \times$ upper limit of normal</p> <p>Alkaline phosphatase $>$ upper limit of normal</p> <p>Bilirubin (total) $> 2 \times$ upper limit of normal</p> <p>Must not have donated blood within 2 months of screening and avoid further donation for 4 months following the study</p> <p>Participant is, at the time of signing the informed consent, a user of recreational or illicit drugs (including marijuana) or has had a recent history (within the last year) of drug or alcohol abuse or dependence, in the opinion of the investigator</p> <p>Pregnant or breastfeeding mother, unless willing to discontinue breastfeeding by baseline visit</p> <p>Have uncontrolled systemic hypertension (blood pressure > 160 systolic on 3 successive measurements on the screening visit</p> <p>Are receiving systemic (including vaginal/rectal) glucocorticoid treatment at the time of the screening visit</p> <p>Are taking any hormone-based medication, including hormone contraceptives (but not including intrauterine system/hormonal coil), at the time of screening</p> <p>Are taking probenecid at the time of screening visit</p> <p>Have any screening laboratory abnormality that, in the investigator's judgement, is considered to be clinically significant or any screening laboratory value that is outside the sponsor-specified ranges at screening; testing may be repeated once to see if the value returns to within the range, but any laboratory abnormality must be resolved prior to the baseline visit</p> <p>History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the subject at risk because of participation in the study or influence the results or the subject's ability to participate in the study. Specifically, a diagnosis of any inflammatory disorder that might reasonably need treatment with glucocorticoids during the course of the study should be considered for exclusion.</p> <p>History or presence of significant gastrointestinal, hepatic^a, or renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs</p> <p>Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of the Investigational Medicinal Product as judged by the investigator</p> <p>Have been involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study sites)</p> <p>Have participated in any other interventional studies within 1 month prior to the screening visit. Participation in the IIH national database or other observational studies will not prevent enrollment to this study.</p> <p>Previous randomization for treatment in this study</p>

^aA history of steatosis will not be considered an exclusion criterion.

Ethics, Regulatory Approvals, and Dissemination

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments), the Data Protection Act 1998, Human Tissue Act 2008, Human Tissue (Scotland) Act 2006, and Guidelines for Good Clinical Practice.

This trial will be carried out under a Clinical Trial Authorization (CTA) in accordance with the Medicines for Human Use Clinical Trials regulations. IIH:DT was approved by the National Research Ethics Committee York and Humber–Leeds West on November 19, 2013 (13/YH/0366), and received CTA for the use of investigational medicinal product on January 21, 2014. IIH:DT is sponsored by the University of Birmingham (RG 13-022). IIH:DT is registered on clinicaltrials.gov (NCT02017444) and the European Clinical Trials Database (EudraCT Number: 2013-003643-31.)

Results will be disseminated through internal reports, relevant conferences, peer-reviewed scientific journals, and online publications. No personally identifiable data will be published. Participants and general practitioners will be informed of results through a summary scientific report available through the trial website.

Trial Drug and Placebo

The dose to be used in this trial is 400 mg taken as two 200 mg tablets, twice daily. Doses are taken 12 hours apart, typically around 7 a.m. and 7 p.m. each day. Participants take the trial medication for 12 weeks.

AZD4017 has been well tolerated in previous phase I and II studies. The largest single dose used has been 1200 mg for 9 days and the longest duration of use has been 28 days at 400 mg twice daily [15]. A 12-week treatment period is considered sufficient to see sustained inhibition of 11 β -HSD1 by AZD4017 and potentially changes in ICP. This duration is longer than previous treatment with AZD4017; therefore, safety as well as drug efficacy is a key outcome.

AZD4017 is compared to placebo rather than a current treatment of IIH. During trial design and registration, there was no evidence supporting the use of any particular medical treatment for IIH [18]. While IIH:DT has been recruiting, new evidence emerged demonstrating the efficacy of acetazolamide in IIH patients with mild visual loss [6]. However, a recent systematic review suggested the evidence was inconclusive [5]. In addition, the IIH patient cohort included in this trial will include moderate to severe visual deficits. For these reasons, a placebo is still considered the optimal comparator for this trial.

Discontinuation of the trial drug can occur for a number of reasons: a clinically significant serious adverse event, deterioration in their IIH requiring CSF diversion surgery, severe noncompliance, hepatotoxicity, and muscle toxicity.

In the situation of very raised liver enzymes—alanine transaminase and/or aspartate transaminase >5 times the upper

limit of normal (ULN) and/or bilirubin >2 times ULN and/or Hy's Law criteria met—any time after randomization, the underlying cause for the liver enzyme elevation will be evaluated. If there is no improvement after 7 days or if the liver enzyme abnormality continues to worsen, depending on the clinical severity, then the treatment will be stopped. Subjects will also discontinue the trial drug if they fulfill all of Hy's Law criteria for 2 weeks. The trial will be stopped completely if more than one Hy's Law case persists for 2 weeks or more than three subjects (10%) meet the liver stopping criteria, unless another cause of liver enzyme abnormality is identified in these subjects.

Randomization

Randomization has been performed by the contract manufacturing organization (Almac) supplying and coding the trial medication on behalf of AstraZeneca. Block randomization was used so that each block of trial numbers contains a random assignment of equal numbers of active and placebo treatment allocations.

Drug allocation takes place if the participant is confirmed to be eligible at the end of the screening visit and consents to enter the trial. The next available trial number is given to the participant in order. A drug pack, containing either AZD4017 or placebo, is identified by the designated trial number and will be provided to the patient on a monthly basis during the 12-week treatment period.

Sample Size

We aimed to recruit 30 participants to allow for a sample size of 24 participants (12 per arm), with a 20% allowance for dropouts, which would allow 90% power ($\alpha=.05$) to detect a difference of 14% in ICP (assuming a standard deviation of 10% for ICP).

Outcomes

Primary Outcome

The primary outcome examines the effect of AZD4017 on ICP from baseline to 12 weeks postrandomization. ICP was chosen as the primary outcome to reflect the hypothesized action of AZD4017 inhibition of 11 β -HSD1 with consequent reduction in CSF secretion and ICP.

Secondary Outcomes

Raised ICP underlies the symptoms and signs of IIH, thus alterations in ICP should result in clinical fluctuations. The following secondary outcomes are recorded:

- IIH symptoms (presence or absence of tinnitus, visual loss, diplopia, visual obscurations, and headache)
- IIH visual function in both eyes (measured by log of the minimum angle of resolution charts to assess visual acuity, automated perimetry [Humphrey 24-2 central threshold] to measure the visual field mean deviation and MARs charts to evaluate contrast sensitivity)
- papilledema is evaluated using spectral domain optical coherence tomography (Spectralis, Heidelberg Engineering)

- and fundal photographs with Frisen classification (by masked neuro-ophthalmologists) to grade the images
- headache-associated disability through the headache impact test-6 score (HIT 6), headache severity, frequency, and the use of analgesia (days/weeks)
- anthropological measures (blood pressure, body mass index, waist/hip ratio)
- safety and tolerability profile of AZD4017 through adverse event reporting and safety bloods (see [Table 2](#))

Exploratory Outcomes

Exploratory studies evaluate the ability of AZD4017 to inhibit 11 β -HSD1 in IIH patients through evaluation of:

- hepatic 11 β -HSD1 activity by prednisone administration to measure prednisolone levels over 4 hours
- global 11 β -HSD1 activity through urinary glucocorticoid metabolites

- 11 β -HSD1 activity in subcutaneous adipose tissue following cortisone incubation ex vivo
- plasma and CSF drug levels and pharmacokinetic analysis
- cortisone and cortisol in serum and CSF

In addition, dual-energy x-ray absorptiometry (DXA) scanning is used to assess body habitus.

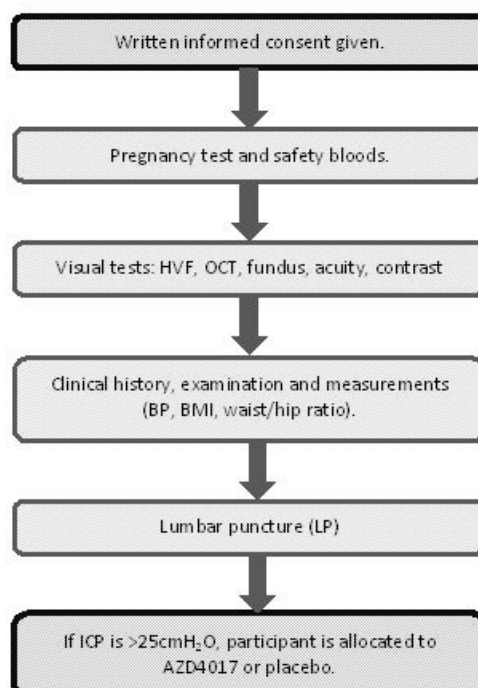
Trial Visits

Screening

A screening visit is attended between 7 and 30 days after successful prescreening. Participants are then assessed over 1 day or a split visit (see [Figure 2](#)). Following informed consent, a general history and examination as well as a neurological assessment is performed. A urinary pregnancy test and blood samples are taken followed by visual tests, DXA scanning, an LP, and fat biopsy. If the participant is eligible following screening, the data collected will be used as baseline data.

Table 2. A timeline of study visits and the outcome tests performed at each visit. Safety bloods include renal function (urea, creatinine, and electrolytes), liver function (aspartate transaminase, alanine transferase, bilirubin, albumin, alkaline phosphatase, gamma-glutamyl transferase), thyroid function (thyroid stimulating hormone free thyroxine), and creatine kinase.

Outcome	Measure	Weeks										
		0	1	2	3	4	6	8	10	12	16	
Primary outcome												
ICP	Lumbar puncture	X									X	
Secondary outcomes												
Anthropometric measures	Body mass index, blood pressure, waist/hip, body composition	X									X	X
IIH symptoms	Pulsatile tinnitus, visual loss, diplopia, visual obscurations	X									X	X
Visual function	Visual acuity, contrast sensitivity	X									X	X
	Humphrey visual field (24-2)	X									X	X
Papilledema	Optical coherence tomography	X									X	X
	Retinal photographs	X									X	X
Headache	HIT-6, headache index, analgesia use	X									X	X
Medical assessment	History, +/- examination, compliance	X	X	X	X	X	X	X	X		X	X
	Safety bloods	X	X			X		X			X	X
	Pregnancy test	X	X			X		X			X	X
Exploratory outcomes												
Global 11β-HSD1 activity	24-hour urine	X	X			X		X			X	X
Hepatic 11β-HSD1 activity	Prednisone to prednisolone measurements in serum	X									X	
Adipose 11β-HSD1 activity	Subcutaneous adipose biopsy	X									X	
Body habitus	DXA	X									X	
Pharmacokinetic analysis	Plasma and CSF	X	X								X	

Figure 2. Overview of the screening visit.

Subsequent Visits

The treatment period is 12 weeks. Participants will be assessed at 1, 2, 3, 4, 6, 8, 10, 12, and 16 weeks (see Table 2). All visits will determine adverse events and treatment compliance. Visits 1, 4, 8, 12, and 16 will require safety and hormone bloods as well as a urinary pregnancy test. The 12-week visit will repeat the screening visit. Following 4 weeks off the trial drug, patients will be assessed at 16 weeks for visual tests, headaches, bloods, IIH symptoms, and adverse events. The follow-up visit at Week 16 is deemed sufficient time for the effects of the trial drug to have dissipated. Any relapses in IIH-related symptoms are then determined.

Statistical Methods

The primary analysis of efficacy is based on the full analysis set, as defined by ICH guidance document *E9: Statistical Principles for Clinical Trials*. This analysis adheres as closely as possible to the intention-to-treat ideal and is based on data from all randomized participants with participants analyzed in the treatment group to which they were randomized.

Primary and Secondary Outcome Analyses

The primary comparison groups are composed of those randomized to AZD4017 versus placebo. For all major outcome measures, summary statistics and differences between groups (eg, mean differences) will be presented with 95% confidence intervals and *P* values from two-sided tests. No adjustment for multiple comparisons will be made.

The primary outcome examines the effect of AZD4017 on ICP from baseline to 12 weeks postrandomization. Data will be reported with means and standard deviations or medians and ranges for nonparametric data. The ICP at 12 weeks for the two trial arms will be compared using a linear regression model with baseline ICP included as a covariate in the model.

Secondary outcome measures are analyzed at 12 and 16 weeks. The majority of secondary outcomes are continuous data items, which will be analyzed as per the primary outcome. For the visual function data that are collected in both eyes, it is expected that the participant's data will be correlated, so the primary analyses will use data from both eyes and will be analyzed using a linear mixed model, with participants included as a random effect. The visual function data for each eye will also be analyzed separately as per the primary outcome, but this will be a secondary analysis. The IIH symptom data is binary and will be analyzed using log-binomial models with baseline symptom included in the model as a covariate.

Study Withdrawal

Participants are free to withdraw from the study at any time. Such participants will always be asked about the reason(s) and the presence of any adverse events. If the participant is withdrawn from the trial by the investigator for any reason at any visit during the study, assessments for the early discontinuation visit will be completed during that visit, and the withdrawn participant asked to return for Visit 12 between 83 and 97 days, inclusive.

If the participant needs to be withdrawn from the active treatment phase between trial visits for safety reasons, trial medication will be stopped immediately and the participant will be instructed to attend the next arranged clinic visit, which will be treated as an early discontinuation visit. If it is considered appropriate by the investigator, more frequent or additional follow-up visits can be scheduled (if willing, the participant will be asked to attend the 12-week final trial visit). Withdrawn participants will not be replaced.

Monitoring

Adverse Event Reporting

All serious adverse events (SAEs) must be reported, whether or not considered causally related to the trial drug or to study procedures. A clinician must assess the severity, causality, and expectedness of the SAE. If the event is considered to be related to the study drug, then the SAE will be classed as a serious adverse reaction (SAR). If the SAR is listed in the safety information of AZD4017, then it is listed as expected and included in the ongoing safety review of the study. If it is not an expected SAR for AZD4017, then it is listed as a suspected unexpected serious adverse reaction (SUSAR). The trial team will then be contacted to unblind the subject's medication allocation. A fatal or life-threatening SUSAR will be reported to the Medicines and Healthcare Products Regulatory Agency and the research ethics committee within 7 days.

Unblinding

Investigators and subjects are unaware whether the product is AZD4017 or placebo (double-blinded); this information is held by local pharmacies in the form of scratchcards detailing the trial number and a scratch-off panel. Unblinding can take place in the case of a SUSAR and in medical emergencies, when knowing the treatment will change the management of the patient.

Monitoring Committees

A trial steering committee made up of independent members (including the chair) and trial team members provides oversight of the trial. An independent data monitoring committee (DMC) monitors unblinded efficacy and safety reports. If there are any major safety concerns, the DMC can recommend early discontinuation of the trial.

Results

The trial opened March 2014 with the first patient recruited April 2014. Additional sites were opened at the Walton Centre, Liverpool (January 2016), Southern General Hospital, Glasgow (March 2016), and Royal Hallamshire Hospital, Sheffield (April 2016) to facilitate recruitment. The DMC and trial steering committee meet regularly to monitor the course of the IIH:DT. The trial results are expected in September 2017.

Discussion

Principal Considerations

Recruitment to IIH:DT was completed in August 2016. Results from the trial are still awaited. The two RCTs evaluating IIH treatments completed thus far have investigated an established drug, acetazolamide. IIH:DT is the first to assess the efficacy of a new drug treatment, an 11 β -HSD1 inhibitor (AZD4017), not tested in IIH before. More importantly, it aims to establish the safety profile of AZD4017 in IIH. Safety monitoring involves regular safety bloods and adverse event recording. These are performed in accordance with prior AZD4017 study results. This is the longest period of time the drug has been administered to humans. Positive safety results will provide important information for future trials using AZD4017.

Conclusions

IIH is in need of new treatments. IIH:DT is the first phase II double-blinded randomized placebo-controlled trial in IIH. It assesses a novel therapeutic pathway through inhibition of 11 β -HSD1 by the drug AZD4017. In addition to the primary outcome of ICP, a range of secondary outcomes including visual function, headache, and papilledema will be assessed. IIH:DT aims to establish initial evidence of efficacy and safety that could lead to a future large phase III study using AZD4017 in IIH.

Acknowledgments

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Authors' Contributions

AS and PN conceptualized and designed the study. AS and KM ran the study and recruited patients to the study. RO, CR, RW, and NI are staff within the coordinating center at the BCTU. RO and CR are part of the neurosciences trial management team, and RW and NI are on the statistics team. All authors helped write the paper.

Conflicts of Interest

AstraZeneca provided this study (through their chosen contract manufacturing organization, Almac) with the trial medication, AZD4017 and placebo. However, they were not involved in any part of the design or implementation of the study, apart from aspects of safety, and have no influence over its course.

Multimedia Appendix 1

IIH:DT headache diary.

[PDF File (Adobe PDF File), 48KB - [resprot_v6i9e181_app1.pdf](#)]

Multimedia Appendix 2

UK Medical Research Council (MRC) Reviewer comments.

[PDF File (Adobe PDF File), 19KB - [resprot_v6i9e181_app2.pdf](#)]

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Abbreviations

BCTU: Birmingham Clinical Trials Unit
CSF: cerebrospinal fluid
CTA: clinical trial authorization
DMC: data monitoring committee
DXA: dual-energy x-ray absorptiometry
HIT-6: headache impact test 6
HPA: hypothalamic, pituitary, adrenal
11 β -HSD1: 11beta-hydroxysteroid dehydrogenase type 1
ICP: intracranial pressure
IIH: idiopathic intracranial hypertension
IIH:DT: Idiopathic Intracranial Hypertension Drug Trial
IIHTT: Idiopathic Intracranial Hypertension Treatment Trial
LP: lumbar puncture
MRC: Medical Research Council
NHS: National Health Service
RCT: randomized controlled trial
SAE: serious adverse event
SAR: serious adverse reaction
SUSAR: suspected unexpected serious adverse reaction

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Protocol

Protocol for Co-Design, Development, and Open Trial of a Prototype Game-Based eHealth Intervention to Treat Anxiety in Young People With Long-Term Physical Conditions

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Abstract

Background: Approximately 10% to 12% of New Zealand young people (and 21% of Maori young people) have long-term physical conditions and are more likely to develop psychological problems, particularly anxiety and depression. Delayed treatment leads to worse management of physical conditions, school absence, and poorer long-term outcomes. Recently, electronic health (eHealth) interventions have been shown to be as good as face-to-face therapy and biofeedback techniques have been shown to enhance relaxation during the treatment of anxiety. In addition, young people with long-term physical conditions have expressed a preference for more technologically based support, including game-based interventions, to deal with psychological issues, particularly anxiety.

Objective: The aim of this study is to develop a prototype game-based eHealth intervention to address anxiety in young people with long-term physical conditions. The game will be based on the principles of cognitive behavior therapy (CBT) and will integrate a module of biofeedback-based relaxation.

Methods: During the first phase of the study, up to 48 young people with long-term physical conditions aged 13 to 18 years, attending a tertiary pediatric hospital will be invited to participate in a 3-stage series of co-design workshops. Following the design, development, and refinement of a working prototype, during the second phase of the study, a further 20 young people with long-term physical conditions and anxiety will be recruited from the same location to participate in an open pilot trial to evaluate its acceptability, usability, and preliminary efficacy.

Results: Changes in anxiety will be measured using the Generalized Anxiety Disorder 7-item scale (GAD-7) and the Spence Child Anxiety Scales (SCAS) at the end of every module (recommended to be completed weekly), post intervention, and 3 months later. Usability of the intervention will be measured using the System Usability Scale (SUS) and by measuring frequency and quantity of use of the intervention. Acceptability of the intervention will be assessed using brief, open-ended questionnaires and semi-structured interviews, the data from which will be analyzed using a general inductive approach. Recruitment to the study commenced in January 2017 and data collection will be completed by the end of December 2017.

Conclusions: If acceptable and useful, this game-based eHealth intervention may offer a cost-effective and clinically useful intervention for addressing the psychological needs of over 16,000 young people with long term health conditions in New Zealand.

Trial Registration: Australian New Zealand Clinical Trials Network Registry (ANZCTR): ACTRN12616001253493p; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=371443> (Archived by WebCite at <http://www.webcitation.org/6sYB716lf>)

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KEYWORDS

long-term physical conditions; chronic illness; anxiety; eHealth; gaming; young people; treatment; cognitive behavior therapy; biofeedback

Introduction

Long-term physical conditions are increasingly common in children and young people and those that last more than 3 months and impair functioning affect 10% to 12% of children globally [1]. These conditions include asthma, diabetes, epilepsy, and obesity, among others [2,3]. The prevalence of long-term physical conditions in childhood is increasing [4] and in some high-income countries, due to improvements in hygiene, immunization, and access to medical care, it is greater than that of acute illness [5].

Psychological problems, especially anxiety, are more likely in these individuals such that long-term physical conditions in children have consistently been associated with an increased risk of psychological problems [6-11], particularly anxiety which has been identified in up to 40% of these individuals [12]. The likelihood of anxiety is related to young people's developmentally linked internal ability to manage stress, to family factors, and the cumulative allostatic load-related impact of illness and treatment, particularly distress and pain [13,14]. Anxiety and other psychological problems can occur during or even following the completion of medical (eg, cancer) treatment [15] and may be associated with school absence, poor academic performance, and lower health-related quality of life [16,17]. Left untreated, anxiety disorders tend to have a chronic and unremitting course [18] and tend to increase the risk for adult psychiatric disorders, including depression and substance use disorders [19].

Access to, and effectiveness of, treatments for these problems are currently limited. Psychological problems are traditionally addressed using psychotherapies such as cognitive behavior therapy (CBT) and pharmacotherapy (eg, anxiolytic or antidepressant medication). There is limited evidence that these therapies are effective for children with long-term physical conditions [20]. Psychotherapies are often not accessible and although 60% of children with anxiety who receive CBT show an adequate treatment response [21], there does appear to be room for improving current treatment.

With the increasing popularity of smart technology, release of app-based interventions, and calls from international organizations such as The Lancet Global Mental Health Group [22] for the introduction of innovative and accessible cognitive and behavioral strategies to treat anxiety, depressive, and other common mental health problems, electronic health (eHealth) interventions may have a useful role to play in addressing common mental health problems in young people with long-term physical conditions. Health games, such as Smart, Positive, Active, Realistic, X-factor Thoughts (SPARX) [23], have already been shown to be as good as face to face treatment for addressing depression in young people. Similar interventions such as Body Signs, Relaxation, Active Helpful Thoughts, Victory Over Your Fears, Enjoy (BRAVE) online [24] exist to treat anxiety but are not focused on health-related anxieties and

are not widely available outside Australia. During a recent investigation by Thabrew and colleagues, young people with long-term physical conditions identified anxiety as the most significant psychological issue that they face. Together with their families and clinicians, they confirmed limited knowledge of and access to eHealth interventions and expressed support for the development of eHealth interventions targeted towards their needs [25].

Traditional psychological therapies often include a component of psychologically or chemically induced relaxation and there is increasing evidence that newer, more technologically-based forms of therapy, such as biofeedback, may achieve similar results, either alone or in combination with traditional therapies [26]. Furthermore, some biofeedback interventions have already been combined with game-based technology to reduce stress or treat behavior disorders [27]. Biofeedback involves the use of electrical or electro-mechanical equipment to measure physiologic processes occurring in a person and then feed this information back to them to develop a greater awareness and ability to control changes within their bodies with and without equipment [28] and improve health and performance [29]. There are a number of types of biofeedback including heart rate variability (HRV), electroencephalography (EEG), and pneumography (PNG). HRV is already used by some pediatric mental health teams in New Zealand (personal communication from Dr Louise Webster, Starship Hospital, Auckland) and a recent systematic review by Dr Thabrew supported further research into HRV biofeedback as a treatment for anxiety (in press).

The aims of this study are (1) to develop a prototype game-based eHealth intervention for treating anxiety in young people with long-term physical conditions via co-design with end-users at Starship Hospital; (2) to evaluate the acceptability of this intervention with its intended audience; (3) to evaluate the utility of this intervention with its intended audience; (4) to evaluate the efficacy of this intervention in a preliminary manner; and (5) to evaluate the feasibility of delivery of this intervention with its intended audience.

Methods

Research Strategy

The study will employ a mixed-methods design to co-design, produce, and test a prototype game-based eHealth intervention for treating anxiety in young people with long-term physical conditions.

Study Design

The study will involve 2 phases. During the first phase, a prototype game-based eHealth intervention will be designed and refined via a co-design process with young people with long-term physical conditions attending a tertiary pediatric hospital in Auckland, New Zealand. Three stages of iterative consultation are planned, with 4 focus groups of up to 12

participants at each stage. At least one focus group at each stage will be arranged for Māori young people to ensure that, in the spirit of biculturalism, the intervention is culturally acceptable to them. By the end of this phase, a working prototype that is ready for pilot testing will be created and refined to ensure it is compatible with end-user expectations. During the second phase, an open pilot trial will be undertaken with 20 young people with long-term physical conditions and anxiety from the same hospital. Each will be loaned a portable device (iPad or similar tablet) on which the prototype intervention, questionnaires, and scales will be preloaded. They will be given up to 8 weeks to complete the intervention at a speed and frequency of their choosing.

Study Population

Up to 48 young people with long-term physical conditions who are either inpatients or outpatients attending a tertiary pediatric hospital in Auckland, New Zealand will participate in focus groups during each stage of the first phase. Following this, 20 young people will then participate in the second phase, open trial.

Inclusion Criteria

Young people will be included in the first phase of the study if they are aged between 13 to 18 years, have any long-term physical condition over 3 months duration (eg, asthma, diabetes, cancer, cystic fibrosis), are of any ethnicity, do and do not have a known anxiety disorder, do or do not have any co-morbid mental health condition, can intellectually and physically use the device and intervention, and if they understand English and are able to provide informed consent or assent. Young people will be included in the second phase of the study if they meet all of the above criteria and have any symptoms of anxiety (not necessarily a diagnosed anxiety disorder).

Exclusion Criteria

Young people will be excluded from participation if they do not meet all of the inclusion criteria, if they have an intellectual disability or cannot speak English, or if they have recently undertaken or are undertaking CBT or other forms of psychotherapy, biofeedback therapy, or pharmacotherapy with anxiolytic medication, as these may confound the effectiveness of the prototype game-based eHealth intervention.

Intervention

The prototype game-based eHealth intervention that will be co-designed with young people with long-term physical conditions will be a 4 to 8 module online, game-based intervention. Its content will be based on the principles of CBT and include an integrated or associated biofeedback-based relaxation component. It is anticipated that modules will take between 30 to 60 minutes each to be completed. Key elements that will be included are education about anxiety and coping strategies for anxiety, using one's body (relaxation strategies), mind (recognizing unhelpful thoughts and cognitive restructuring), and actions (including graded exposure) to beat anxiety. The precise format and look of the prototype game-based eHealth intervention will be designed in conjunction with end users. The prototype intervention will be stored on a

portable tablet, rather than available online or via a mobile app. Due to the co-design process that is being planned, the precise form and content of the intervention is not yet fully defined. However, key CBT-based principles including psychoeducation, relaxation, graded exposure to feared stimuli, and cognitive restructuring will be included. Further refinement of the intervention is likely on the basis of feedback from the pilot trial.

Outcome Measures

The primary outcomes of the study are (1) acceptability of the prototype intervention, (ie, is the content and format acceptable to users), as assessed via a semi-structured interview following completion of the study at 8 weeks; (2) utility of the intervention (ie, is it useful), as assessed using the System Utility Scale (SUS) [30] following completion of the intervention at 8 weeks; and (3) feasibility of the intervention (ie, is it easy to deliver in a hospital/home setting), as assessed via a semi-structured interview following completion of the study at 8 weeks.

The secondary outcome of the study is efficacy (ie, does the intervention reduce anxiety and related issues). This will be assessed by measuring changes over time in the Generalized Anxiety Disorder, 7-item (GAD-7) [31], Spence Children's Anxiety Scale (SCAS) [32], and the Pediatric Quality of Life Inventory (PedsQL) [33], as outlined in the schedule below (Table 1). The GAD-7 is a newer, brief scale for measuring anxiety that may be useful to incorporate into the final version of the intervention for ease of completion. The SCAS is a well-validated, 46-item self-report scale measuring child anxiety via an overall score and 6 subscales for panic/agoraphobia, social phobia, separation anxiety, obsessions/compulsions, fear of physical injury, and generalized anxiety. It has sound psychometric properties with internal consistency reported at 0.92 for the total child score. The PedsQL is a well-validated, 23-item self or parent report scale measuring quality of life. It has good internal consistency (0.88 for total scale), validity, and acceptability. It reliably distinguishes between healthy children and those with acute or long-term physical conditions.

Statistical Methodology

Quantitative data will be analyzed using Microsoft Excel and Statistical Software Package (SPSS). Analyses will include basic descriptive statistics (eg, number of sessions completed, number of times device accessed, duration of use, changes in anxiety score, and demographic characteristics of the sample). McNemar's chi-square tests and *t* tests will be used to assess the statistical significance of changes in anxiety scores over time. *P* values of less than .05 will be taken to indicate statistical significance and 95% confidence intervals will be used to establish the extent of any difference between pre- and post-measures. A sample size of 20 will enable detection of changes within the study group with effect sizes of 0.65 or more as statistically significance (alpha .05 with 80% power). Qualitative data will be analyzed using a general inductive approach. Collated text analyzed to identify emerging themes, which will then be independently coded by one researcher and a subset of 30% of results, will be cross-coded. NVIVO software will be used to handle transcripts.

Table 1. Schedule of assessment procedures.

	Baseline	During intervention	Post intervention	3-month follow-up
Demographics	Yes			
GAD-7 ^a	Yes	At the completion of each module	Yes	Yes
SCAS ^b	Yes	At the completion of each module	Yes	Yes
PedsQL ^c	Yes		Yes	
SUS ^d			Yes	
Online tracking		As used		
Semi-structured questionnaire			Yes	Yes

^aGAD-7: Generalized Anxiety Disorder, 7-item.

^bSCAS: Spence Children's Anxiety Scale.

^cPedsQL: Pediatric Quality of Life Inventory.

^dSUS: System Utility Scale.

Table 2. Timelines of the study.

Phase	Tasks	Timeframe
Phase 1	Ethics approval, securing of funding	September 2016 to December 2016
	Prototype development via co-design with young people and in conjunction with software company and engineers	January 2017 to December 2017
Phase 2	Recruitment of participants for open trial	September 2017 to December 2017
	Open trial	January 2018 to June 2018
	Analysis of results, write-up, and dissemination of study results	July 2018 to December 2018

Timeline

The expected timelines of the study are shown in [Table 2](#).

Equipment Required

An initial working CBT-based prototype intervention will be created in conjunction with a software developer and computer engineer. Biofeedback will be applied via a crude and cost-effective hybrid (most likely an existing HRV-based device that is not fully integrated into the new CBT-based intervention, but used with it). Study participants will be loaned an iPad or similar device on which the necessary technology and analysis software has been pre-loaded.

Ethics and Consent

This study received ethics approval from the New Zealand Health and Disability Ethics Committee (16/CEN/136) on the 30th of September 2016. Invitations to the co-design focus groups and pilot study will be forwarded to potential participants through clinicians at Starship Hospital to minimize coercion by direct approach. Consent will be obtained directly for those over 16 years of age and via their parents with participant assent for those under 16 years of age. Participants will be free to discontinue engagement at any stage without consequence and this will be made clear to them. Should any unanticipated distress occur during participation, immediate referral will be undertaken to the hospital-based pediatric consult liaison (mental health) team. Data will be presented in a de-identified manner and will be securely stored for 10 years as per University of Auckland regulations.

Results

Participant recruitment for the first phase of this study commenced in January 2017 and recruitment of participants for the second phase of the study will commence in September 2017. Completion of recruitment is anticipated to occur in June 2018 and analysis of results will be undertaken by December 2018.

Discussion

Principal Findings

Anxiety disorders are among the top causes of disability adjusted life years (DALYs) in New Zealand [34] and are the most common type of mental disorder of childhood with a prevalence of 11% in international cohorts [35]. Based on 2013 New Zealand census data [36], we estimate there are over 400,000 young people aged 12 to 18 years in New Zealand. If 10% of them have a long-term physical condition, and up to 40% of this cohort is at risk of an anxiety disorder, that means that over 16,000 children in New Zealand could directly benefit from an intervention that is specifically designed for their needs.

Following the completion of this study, the prototype new game-based eHealth intervention will be refined into a final version for testing in a randomized controlled trial (RCT). If shown in this subsequent study to be clinically effective and acceptable in its final form, it is hoped that the intervention may be hosted on a national eHealth platform and will be made

available free of charge to young people in New Zealand. This is currently the case with SPARX, a computerized intervention for depression, but this is contingent on funding from the Ministry of Health.

Conclusion

The potential health impact of this intervention includes improved access to an acceptable and evidence-based treatment for anxiety in young people with long-term physical conditions and an improvement in the management of both psychological and physical conditions. The potential social impact of such an intervention includes improved functioning for young people with long-term physical conditions by means of reduced school

absence, improved social integration, and better relationships with family and clinical teams.

Short-term, the potential economic impact of such an intervention includes reduced cost of intervention (compared to face to face treatment) and reduced parental time off work. Long-term, direct improvements in psychological welfare and indirect improvements in physical welfare are likely to lead to improved chances of completed education and employment. From a service delivery point of view, this intervention could address current resource limitations of mental health services to address the needs of young people with long-term physical conditions.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavior therapy

eHealth: electronic health

GAD-7: Generalized Anxiety Disorder, 7-item

HRV: heart rate variability

PedsQL: Pediatric Quality of Life Scale

SCAS: Spence Children's Anxiety Scale

SPARX: Smart, Positive, Active, Realistic, X-Factor Thoughts

SUS: System Usability Scale

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Protocol

Comparing the Effects of Oral Contraceptives Containing Levonorgestrel With Products Containing Antiandrogenic Progestins on Clinical, Hormonal, and Metabolic Parameters and Quality of Life in Women With Polycystic Ovary Syndrome: Crossover Randomized Controlled Trial Protocol

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Abstract

Background: Oral contraceptives (OCs) have been used as a first-line option for medical treatment in women with polycystic ovary syndrome (PCOS). Despite theoretical superiority of products containing antiandrogenic progestins compared to OCs containing levonorgestrel (LNG), the clinical advantage of these compounds remains unclear.

Objective: The aim of this study was to compare the effects of OCs containing LNG with products containing antiandrogenic progestins including cyproterone acetate, drospirenone, and desogestrel on clinical, hormonal, and metabolic parameters and quality of life in women with PCOS.

Methods: We conducted a 6-arm crossover randomized controlled trial with each arm including OCs containing LNG and one of those 3 OCs containing antiandrogenic progestins. The anthropometric and clinical manifestations and hormonal and biochemical parameters of participants were assessed at 6 time points including baseline, after washout period, and 3 and 6 months after intervention.

Results: The study is ongoing and follow-up of recruited women will continue until 2018.

Conclusions: This study will provide scientific evidence on comparability of OCs with the various progesterones that will assist in decision making taking into account cost effectiveness.

Trial Registration: Iranian Registry of Clinical Trials IRCT201702071281N2; <http://www.irct.ir/searchresult.php?keyword=&id=1281&number=2&prt=12869&total=10&m=1> (Archived by WebCite at <http://www.webcitation.org/6tSP8FNWo>)

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KEYWORDS

polycystic ovary syndrome; oral contraceptives; randomized controlled trial; progestin

Introduction

Polycystic ovary syndrome (PCOS), the most common endocrine and metabolic disorder [1-3], which affects between 5% and 10% of reproductive age women [4,5], is characterized by chronic oligo-ovulation or anovulation and hyperandrogenism resulting in infertility, menstrual irregularities, hirsutism, acne, and alopecia [6,7]. PCOS is associated with an increased risk of metabolic disorders such as obesity, dyslipidemia, hyperinsulinemia, insulin resistance, and metabolic disturbances, which increase the risk of diabetes mellitus and cardiovascular disease [8-12]. Previous studies report that certain aspects of PCOS have negative effects on the health-related quality of life for these women [13,14].

Oral contraceptives (OCs) are frequently recommended as first-line medical treatment for the long-term management of menstrual disturbances and hyperandrogenism manifestations in women with PCOS who do not seek pregnancy [15-18]. The remedial effect of OCs is attributed to the suppression of pituitary gonadotropin secretion and a decrease in androgen secretion [19,20]; in addition, the estrogen component of these compounds increases circulating levels of sex hormone-binding globulin (SHBG), which decreases androgen bioavailability [1,21]. Moreover, the progestin component of some of the new generation of OCs inhibits 5 α -reductase activity and acts as an antagonist at the androgen receptor level [21,22], theoretically resulting in an increase in antiandrogenic activity [23]. Despite theoretical advantages of OCs with antiandrogenic properties from compounds such as cyproterone acetate (CA), drospirenone (DRSP), desogestrel (DSG), and ethinyl estradiol (EE) compared to OCs containing levonorgestrel (LNG) [1,24], clinical advantages of these compounds remain unclear [25].

In addition to the antiandrogenic effect of OCs, their metabolic effect is one of the main issues in OC therapy in patients with PCOS [26]. In fact, some studies have raised concerns regarding the potential adverse cardiovascular and metabolic effects of OCs in women with PCOS [2,27-30], including worsening insulin resistance and glucose tolerance and potential adverse effects on lipid patterns. It is also unclear whether the metabolic effects of OCs on PCOS are reduced by the use of certain progestin compounds. Despite the theoretical antiandrogenic advantage of the new generation of OCs, their possible metabolic adverse effects may be a serious threat [31].

Several studies that assessed the effectiveness of OCs on clinical, biochemical, and metabolic profiles in PCOS patients have reported conflicting findings [1,10,15,16,32-35]. However, a limited number of studies have compared the effects of the various OC products on different aspects of PCOS; the majority of these studies did not assess effects of OCs containing LNG.

Accordingly, in this crossover randomized controlled clinical trial, we aimed to compare the effects of OCs containing LNG

with products containing antiandrogenic progestins on the clinical, hormonal, and metabolic aspects and quality of life of reproductive-age women with PCOS.

We hypothesize that in PCOS patients, OCs containing antiandrogenic progestins including DRSP, CA, and DSG have no advantage over products containing LNG on the clinical, hormonal, and metabolic profiles of these women or on their quality of life.

Methods**Overview of Study Design and Procedures**

This study is a single institution crossover randomized controlled clinical trial with 6 treatment groups (A, B, C, D, E, and F) that commenced in February 2016. Our study design was based on the Consolidated Standards of Reporting Trials (CONSORT) requirements [36]. The research team included a gynecologist, midwife, endocrinologist, epidemiologist, and statistician. The trial was conducted at the endocrinology clinic of the Research Institute for Endocrine Sciences (RIES) of the Shahid Beheshti University of Medical Sciences, Tehran, Iran. Figure 1 presents an overview of the study protocol. Participants were recruited through 4 primary sources: online through professional social networks and referrals from municipal health centers, private clinics, and the Tehran Lipid and Glucose Study (TLGS). The trial was conducted at an endocrine outpatient clinic.

Before entering the study, the purpose of the protocol was clearly explained to the patients and written informed consent was obtained from all women enrolled. All eligible patients were randomly assigned to treatment groups (Figure 2). Patients in each of the groups alternately received OCs containing LNG or a product containing antiandrogenic progestins including CA, DRSP, DSG, or EE for 6 months. There was a washout period of 6 to 8 weeks between the 2 treatments. Clinical, hormonal, metabolic, and quality of life assessments were assessed at the time of recruitment and again at follow-ups. Hence, each patient was assessed for clinical and biochemical measurements at 6 time points: before the first treatment (baseline 1), after taking the first treatment for 3 months, after taking the first treatment for 6 months, 6 to 8 weeks after stopping the first treatment (baseline 2), after taking the second treatment for 3 months, and after taking the second treatment for 6 months (see Table 1).

Baseline fasting (for at least 9 hours) blood samples were collected between days 3 and 5 of the spontaneous menstrual cycle or progesterone-induced menstrual bleeding. Follow-up visits for blood sampling and clinical assessment were performed at 3 to 7 days after using last tablet. All sera were stored at -80°C until the time of testing. Following completion of the study (samples and data collection), all data will be analyzed using Stata software (StataCorp LLC).

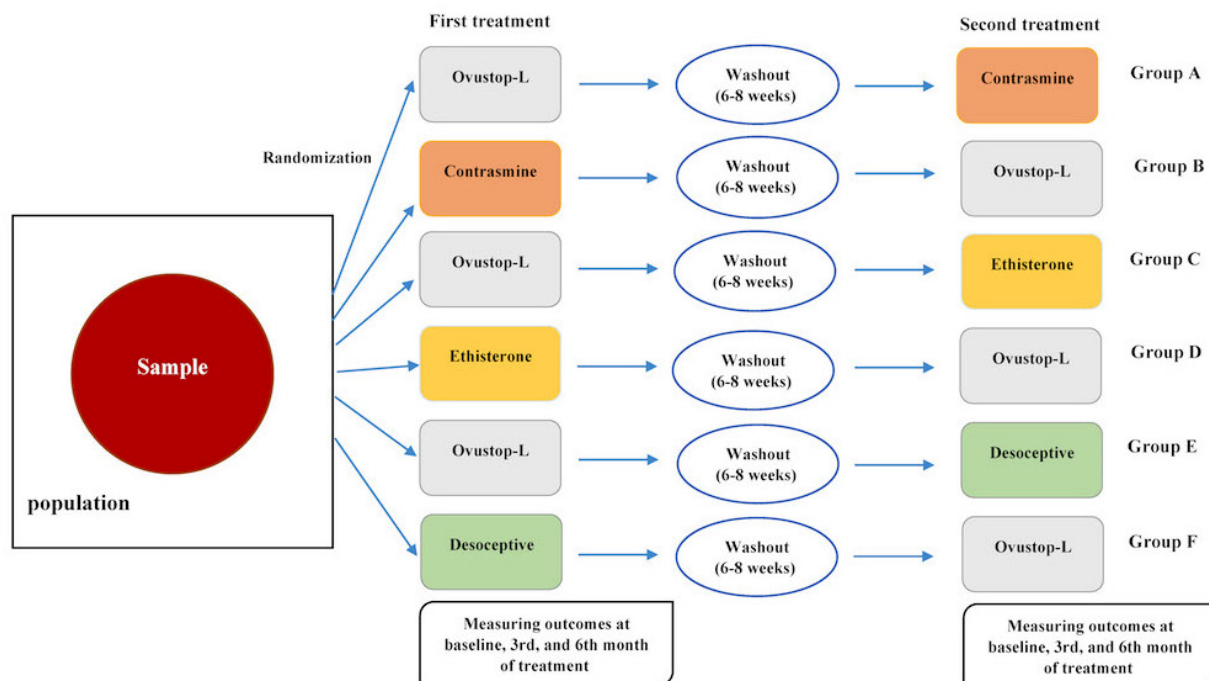
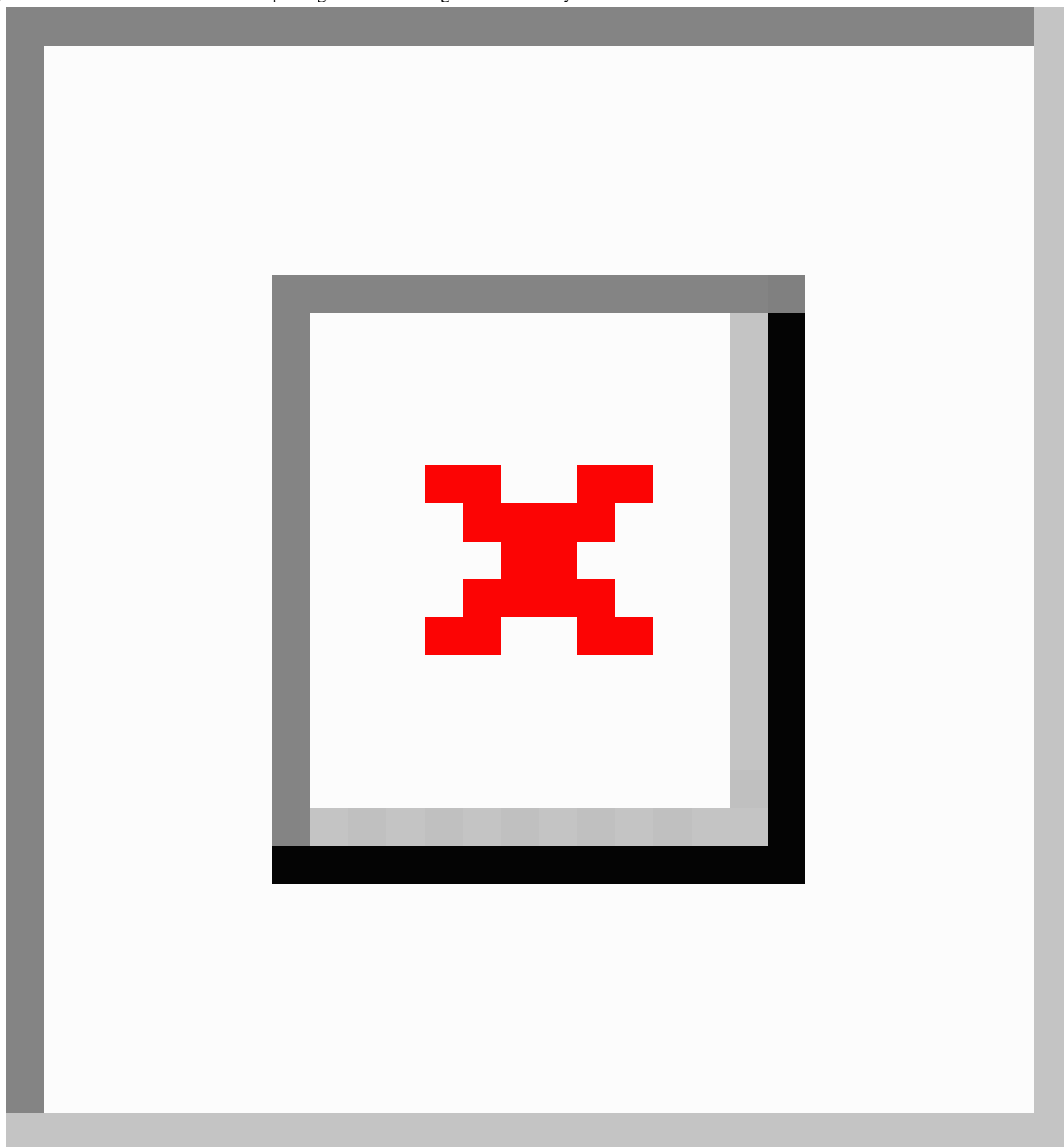
Figure 1. Overview of study design.

Figure 2. Consolidated Standard of Reporting Trials flow diagram of the study.

Ethical Considerations

Approval was obtained from the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (ethics code IR.SBMU.PHNM.1395.649). The trial is registered at the Iran Registry of Clinical Trials [IRCT201702071281N2].

Written informed consent was obtained from eligible participants after the content was clearly explained to the subjects by the trial assistant. All research tools, including questionnaires, will be completely anonymous; a unique code will, however, be included in each form in order to manage further references. All information on participants will be securely stored and only accessible to authenticated trial team members.

Participants

Women with PCOS (age range 18 to 45 years) were recruited at the endocrine outpatient clinic of the RIES of the Shahid Beheshti University of Medical Sciences, Tehran, Iran, by publicly advertising in the community or by referral from physicians or other clinicians. PCOS was diagnosed according to the 2006 criteria from the Androgen Excess Society (AES) (hirsutism or hyperandrogenemia and oligo-ovulation/anovulation or polycystic ovaries with exclusion of other androgen excess or related disorders) [37]. Patients testing positive for secondary etiologies including hyperprolactinemia, thyroid dysfunction, Cushing syndrome, congenital adrenal hyperplasia, and virilizing tumors were excluded from the study. Inclusion criteria were normal fasting plasma glucose (<100

mg/dL), normal cardiometabolic system, and normal hepatic function; all patients were nonsmokers and had negative pregnancy tests before enrollment. None of the women had taken medications known to affect plasma sex steroids for at least 3 months before the study. None of the patients planned to become pregnant or had had contraindications with the use of OCs.

Exclusion criteria were history of use of an exogenous hormonal agent within past 3 months; systemic disease such as cardiovascular disorder, renal disease, or liver disease; endocrinopathies including diabetes mellitus, thyroid dysfunction, hyperprolactinemia, and Cushing syndrome; contraindications to OCs; use of any medication related to PCOS such as hormonal, insulin sensitizer, or antiandrogen drugs within the previous 3 months; willingness for pregnancy; smoking; or any serious side effects of contraceptive use such as thrombosis, jaundice, or hepatic disorders. We excluded current study participants if they were unable to actively continue the cooperation required due to sickness, pregnancy, etc. Patients could terminate participation in the study for any reason. Patients who discontinued intervention for ≥ 2 months were excluded from the analyses.

Interventions

In this study, patients were randomly assigned to treatment groups with interventions using different OC products:

- Group A: first treatment—EE 30 μ g + LNG 0.15 mg daily for 6 months; second treatment—EE 30 μ g + DRSP 3 mg daily for 6 months
- Group B: first treatment—EE 30 μ g + DRSP 3 mg daily for 6 months; second treatment—EE 30 μ g + LNG 0.15 mg daily for 6 months
- Group C: first treatment—EE 30 μ g + LNG 0.15 mg daily for 6 months; second treatment—EE 35 μ g + CA 2 mg daily for 6 months
- Group D: first treatment—EE 35 μ g + CA 2 mg daily for 6 months; second treatment—EE 30 μ g + LNG 0.15 mg daily for 6 months
- Group E: first treatment—EE 30 μ g + LNG 0.15 mg daily for 6 months; second treatment—EE 30 μ g + DSG 150 μ g daily for 6 months
- Group F: first treatment—EE 30 μ g + DSG 150 μ g daily for 6 months; second treatment—EE 30 μ g + LNG 0.15 mg daily for 6 months

All participants received EE 30 μ g + LNG 0.15 mg as the standard treatment. To eliminate carryover effect of treatments, a washout period of 6 to 8 weeks was in place between 2 treatments (Figure 2). Interventions were performed by a trained midwife with the assistance of another person who was aware of the type of intervention.

Study Outcomes

Outcome measures were collected at 6 time points: before treatments, after washout period, and after 3 and 6 months of treatments (Table 1).

Only one person conducted clinical assessments of participants, and she was blinded to groups to minimize any assessor effects. Biochemical measurements were performed by an expert laboratory technician under the supervision of a laboratory sciences specialist.

In this trial, the primary outcomes were free androgen index (FAI) and homeostasis model assessment–insulin resistance (HOMA-IR). Secondary outcomes were modified Ferriman-Gallwey score (FG); acne; regularity of menstrual cycles; blood pressure; androgenic profiles including follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (tT), SHBG, androstendione (A4), and dehydroepiandrosterone sulfate (DHEAS); metabolic profiles including fasting blood sugar (FBS) fasting insulin, HOMA-IR, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C); and quality of life assessed by Health-Related Quality of Life Questionnaire for Polycystic Ovary Syndrome (PCOSQ-50) [13].

Table 1. Schedule of clinical and biochemical assessments.

Item	Baseline 1	At 3rd month of treatment	At 6th month of treatments	Baseline 2 (after washout period)	At 3rd month of treatment	At 6th month of treatment
Demographic characteristics	x					
Age, marital, educational, and occupational status						
Menstrual history						
Age of menarche	x					
Last menstrual period	x	x	x	x	x	x
Interval between menstrual cycles	x	x	x	x	x	x
Amenorrhea history	x					
Medical and family history						
Chief complaints (infertility, hirsutism, menstrual irregularity, acne, alopecia)	x					
Duration of PCOS ^a diagnosis	x					
History of previous treatments	x					
Hair removal methods	x	x	x	x	x	x
Past medical history	x					
Family history	x					
Anthropometric and blood pressure measurements						
Height	x					
Weight	x	x	x	x	x	x
Waist circumference	x	x	x	x	x	x
Hip circumference	x	x	x	x	x	x
Wrist circumference	x	x	x	x	x	x
Blood pressure	x	x	x	x	x	x
Clinical hyperandrogenism symptom assessments						
FG ^b score	x	x	x	x	x	x
Acne	x	x	x	x	x	x
Androgenic alopecia	x	x	x	x	x	x
Laboratory assessments						
Hormonal parameters (FSH ^c , LH ^d , tT ^e , FAI ^f , SHBG ^g , A4 ^h , DHEAS ⁱ)	x	x	x	x	x	x
Metabolic parameters (FBS ^j , fasting insulin, HOMA-IR ^k , TG ^l , TC ^m , LDL-C ⁿ , HDL-C ^o)	x	x	x	x	x	x
Quality of life	x	x	x	x	x	x
Ultrasound assessment	x					

^aPCOS: polycystic ovary syndrome.^bFG: Ferriman-Gallwey score.^cFSH: follicle-stimulating hormone.^dLH: luteinizing hormone.^etT: total testosterone.^fFAI: free androgen index.^gSHBG: sex hormone-binding globulin.

^hA4: androstenedione.

ⁱDHEAS: dehydroepiandrosterone sulfate.

^jFBS: fasting blood sugar.

^kHOMA-IR: homeostatic model assessment–insulin resistance.

^lTG: triglycerides.

^mTC: total cholesterol.

ⁿLDL-C: low-density lipoprotein cholesterol.

^oHDL-C: high-density lipoprotein cholesterol.

Clinical Assessment

In this study, a single trained midwife in the endocrinology clinic under supervision of a reproductive endocrinologist assessed the anthropometric parameters, menstrual cycles, hirsutism, acne, alopecia, and acanthosis nigricans in participants at baselines and follow-ups. She was blinded to type of treatment.

Patient weights were measured when they were minimally clothed using a digital scale (Seca 707, Seca GmbH) and rounded to the nearest 100 grams. Height was measured without shoes in the standing position with shoulders in normal alignment using a tape measure. Waist circumference was measured with an unstretched tape measure at the level of umbilicus without any pressure to the body surface and recorded to the nearest 0.1 cm. Hip circumference was measured at the level of anterior superior iliac spine without any pressure to the body surface. Wrist circumference was measured similarly. Body mass index was calculated as weight in kilograms (kg) divided by height squared (m^2). Systolic and diastolic blood pressure were measured twice on the right arm with the patient in a seated position by a qualified midwife with a standard mercury sphygmomanometer after the subject sat for 15 minutes; the mean of these 2 measurements was recorded.

All patients were evaluated for regularity of menstrual cycles. Those who had intervals of menstrual cycle more than 35 days were diagnosed as having oligomenorrhea, less than 22 days as polymenorrhea, and those with absence of menstrual periods for 6 months or longer as amenorrhea [37,38]. Spotting was assessed and registered.

In this study, the FG score was used for determining the density of terminal hair at 9 different body sites: upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh; this scoring system grades excess terminal body or facial hair growth based on a scale of 0 (absence of terminal hairs) to 4 (frank virilization), and a total score of 8 or more is considered as hirsutism [39,40]. Participants were asked to refrain from shaving or using other depilatory methods in the month before evaluation to improve accuracy of assessment.

The severity of acne was classified according to a grading system based on the number of lesions and their spread on the face, back, and chest: mild—comedones (clogged hair follicles often similar to pustules that do not have any inflammation)

present; moderate—the number of erythematous and popular moderate lesions was from 10 to 40 or number of pustules was from 10 to 40 (especially on the face); moderate to severe—the number of multiple and numerous papules and pustules was from 40 to 100 often accompanied by comedones in numbers of 40 to 100 on the face, upper chest, and back; severe—nodulocystic acne with painful nodules or pustules frequently observed on the chest and face and accompanied by smaller papules, pustules, and comedones [41].

To diagnose androgenic alopecia in participants, we used the following classification, which was presented by Ludwig [42] in Germany:

- Grade I: perceptible thinning of the hair on the crown limited in the front by a line situated 1 to 3 cm behind the frontal hair line
- Grade II: pronounced rarefaction of the hair on the crown within the area seen in Grade I
- Grade III: complete baldness (total denudation) within the area seen in Grades I and II

In addition, we will assess the common side effects of OCs during and after follow-ups (Table 2).

Hormonal Assay

FSH and LH will be measured by immunoradimetric assay (IRMA) (Institute of Isotopes Co Ltd) using the Wallac Wizard gamma counter (GMI Inc); tT, A4, and DHEAS will be measured by enzyme immunoassay (EIA) (Diagnostics Biochem Canada Inc). SHBG will be measured by immunoenzymometric assay (IEMA) (Mercodia AB); all enzyme-linked immunosorbent assay (ELISA) tests were performed using the Sunrise ELISA reader (Tecan Trading AG); and FAI will be calculated using the formula $[tT(nmol/L) \times 100 / SHBG(nmol/L)]$.

Biochemical hyperandrogenemia will be identified if FAI, DHEAS, or A4 levels are in the upper 95th percentile ($tT=0.89$ ng/mL, $A4=2.9$ ng/mL, $DHEAS=179$ $\mu g/dL$, $FAI=5.39$) considering the women studied were not on any hormonal medication and had no clinical evidence of hyperandrogenism and menstrual dysfunction. Hyperandrogenism was determined as clinical hyperandrogenism and/or biochemical hyperandrogenemia [43].

Inter- and intra-assay coefficients of variation for all hormonal measurements will be defined.

Table 2. A comparison of the common side effects of oral contraceptives in polycystic ovary syndrome patients.

Side effects	Type of treatment			
	OC ^a containing LNG ^b	OC containing CA ^c	OC containing DRSP ^d	OC containing DSG ^e
Headache	x	x	x	x
Dizziness	x	x	x	x
Nausea	x	x	x	x
Vomiting	x	x	x	x
Breast pain/tenderness	x	x	x	x
Spotting	x	x	x	x

^aOC: oral contraceptive.^bLNG: levonorgestrel.^cCA: cyproterone.^dDRSP: drospirenone.^eDSG: desogestrel.

Metabolic Assessment

FBS will be measured using the glucose oxidase method (Pars Azmun Co). HOMA-IR will be calculated using electrochemiluminescent immunoassay (ECLIA). Normal range of HOMA-IR is determined in the Iranian population by using ECLIA method with a cut-off of 2.63 [44]. TG levels will be measured using the enzymatic colorimetric method with glycerol phosphate oxidase (Pars Azmun Co). TC level will be determined using enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase (Pars Azmun Co). Level of HDL-C will be determined after precipitation of apolipoprotein β with phosphotungstic acid and enzymatic colorimetric method (Pars Azmun Co). LDL-C level will be calculated using enzymatic colorimetric method (Pars Azmun Co) [45]. Serum insulin concentration will be measured using ECLIA method (Roche Diagnostics) [46]. Albumin will be measured using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase (Pars Azmun Co). Inter- and intra-assay coefficients of variation for all metabolic measurement will be defined.

Ultrasound Assessment

Ultrasound examination of the uterus and ovaries was performed using a 6-MHz transvaginal transducer or a 4-MHz transabdominal transducer in cases where sociocultural constraints precluded a vaginal approach for ultrasonography. Sonography was performed at the first baseline visit when the blood samples were collected. Endometrial thickness, ovarian volume, number, diameter, and distribution of the follicles were recorded. The ovaries were considered as polycystic when observed as having increased ovarian size and/or at least 10 follicular cysts measuring 2 to 9 mm [47].

Quality of Life Assessment

The PCOSQ-50, developed by Nasiri-Amiri et al [13], was used to evaluate the quality of life of recruited participants. This questionnaire includes 50 items in the following 6 domains:

psychosocial and emotional, fertility, sexual function, obesity and menstrual disorders, and coping. Items were scored based on the 5-point Likert scale.

Sample Size

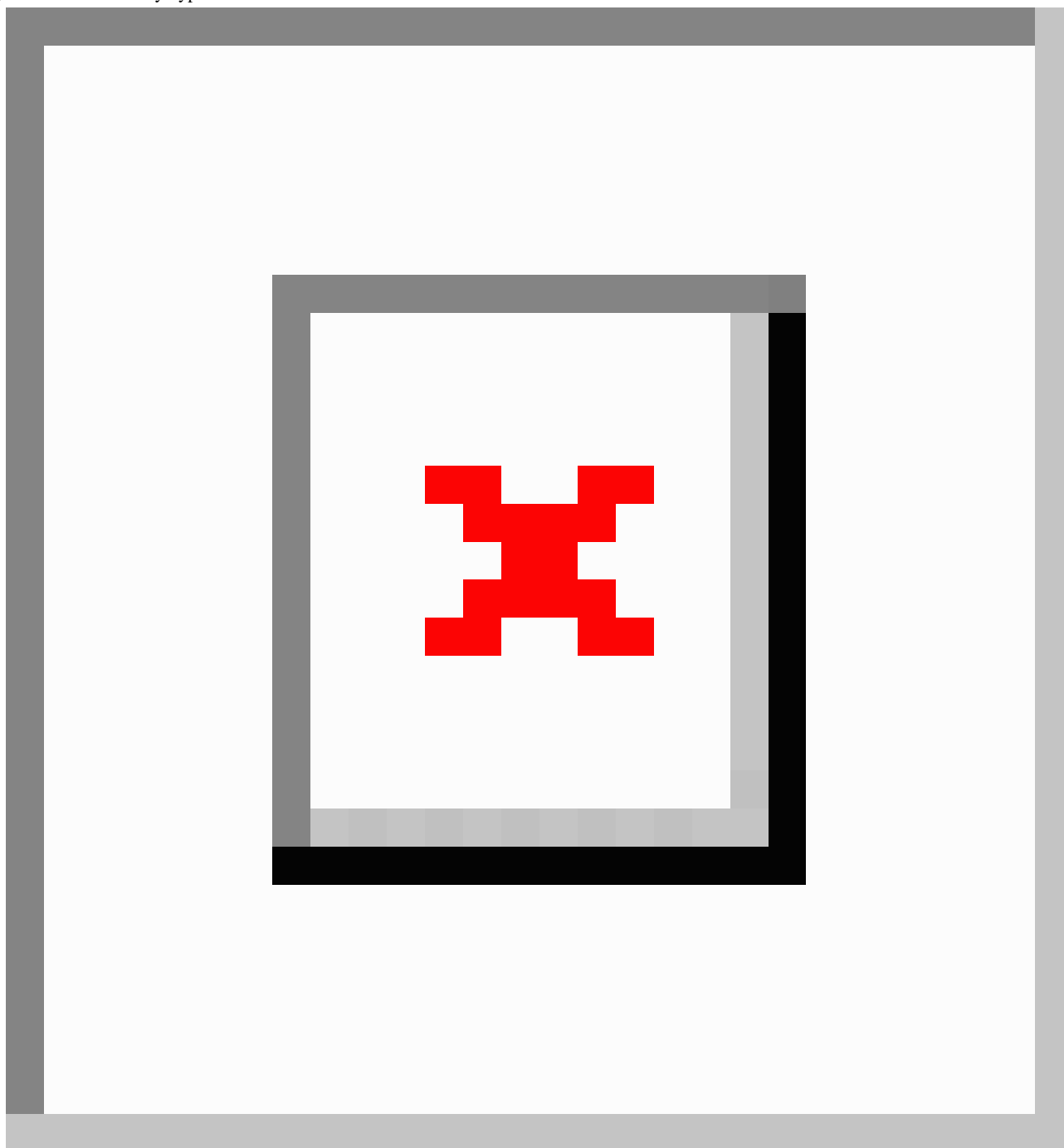
To show that the OCs containing LNG are clinically as effective as those containing antiandrogenic progestins including DRSP, CA, EE, and DSG, we used a noninferiority hypothesis as seen in Figure 3, where μ_T is the mean of the test drug, μ_S is the mean of standard therapy, and δ is a difference of clinical importance. By rejecting the null hypothesis, we conclude that the difference between the test drug and the standard therapy is less than a clinically meaningful difference (ie, δ), and therefore the test drug is as effective as the standard therapy [48].

We considered 80% power, 0.05 type I error, and $\Delta = 0.52$, where Δ is defined as the difference of mean of test drug and standard therapy minus difference of clinical importance divided by standard deviation, as seen in Figure 4. Sample size was calculated from the table introduced by sample size calculations in clinical research, as seen in Figure 5 [49].

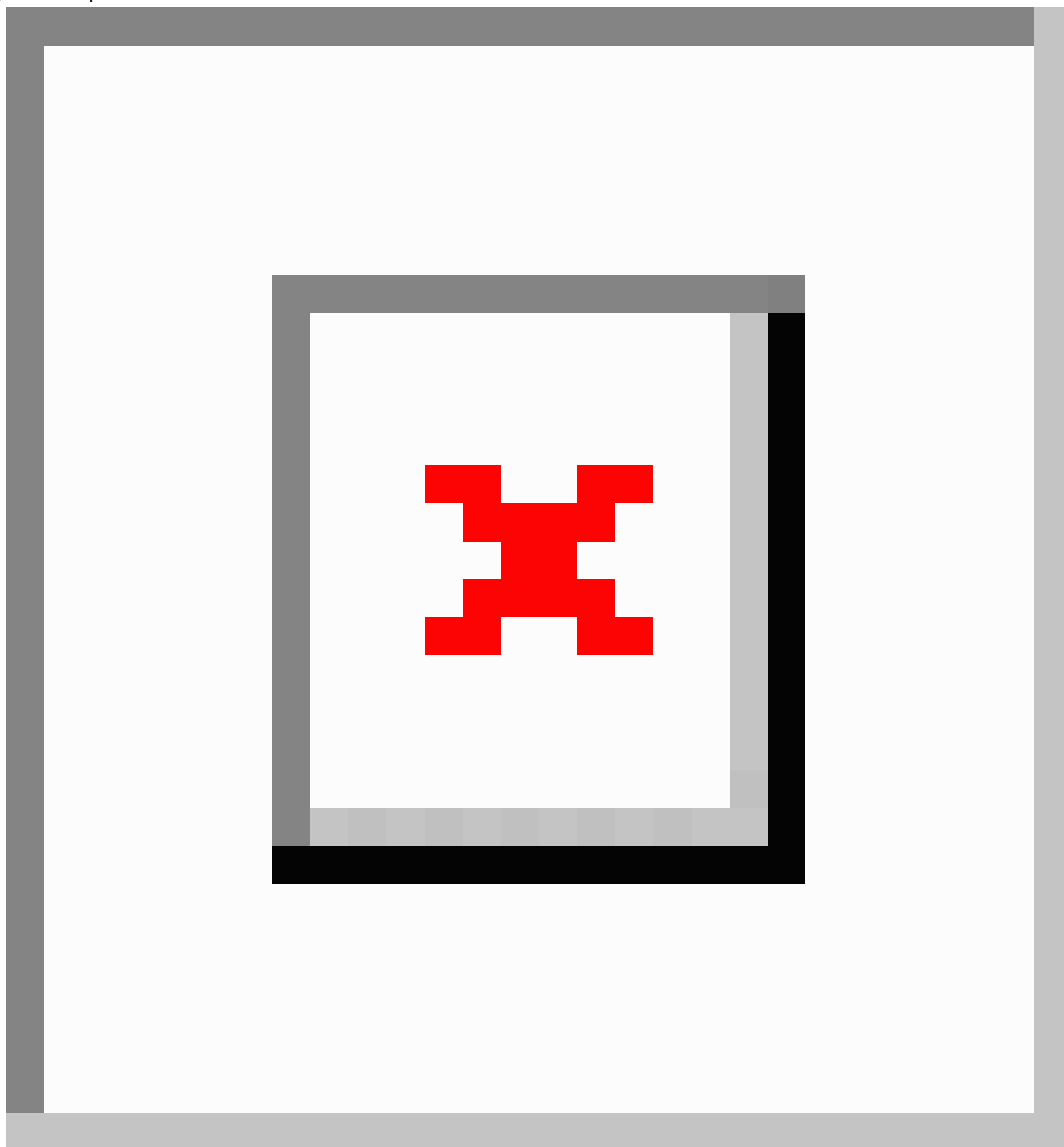
We estimated 25 samples were needed for each group, with 150 total samples needed. Considering 25% withdrawal, we will need 200 cases.

Randomization and Blinding

A blocking or stratification random allocation with a block size of 6 using a computer-based random number generator was prepared to assign participants to treatment groups. The randomization sequence was prepared before the trial, initiated by an independent statistician. For those patients meeting the inclusion criteria and providing informed consent, the research assistant assigned the next randomization sequence according to the schedule. Although participants couldn't be blinded to treatment type because the artifact was obvious, both clinical examiner and data analyst were blinded to participant groups during the trial.

Figure 3. Noninferiority hypothesis.**Figure 4.** Standardized difference of observational and clinical mean difference.

$$\theta = (\epsilon - \delta) / \sigma, \epsilon = \mu_S - \mu_T$$

Figure 5. Sample size formula.

Statistical Analysis

Descriptive statistics will be reported appropriately; normality assumptions will be tested per case by Kolmogorov-Smirnov or Shapiro-Wilk tests. A crossover study is a longitudinal study type in which participants receive treatments in different phases. Therefore, we will use repeated measures which are correlated. We will use statistical analysis appropriate for correlated measures such as generalized estimated equations or repeated-measurement designs to find the differences between treatments. This will be done after finishing the second phase. In addition, in first phase of study, we will estimate between-group differences using generalized linear models. A washout period was taken into account although carryover effect

(residual effect) will be tested at the beginning of the analysis via appropriate statistical tests like *t* tests presented by Fleiss [50]. Statistical analysis will be performed using the software package Stata version 12 (StataCorp LLC).

Results

This trial began enrollment in February 2016, and 200 participants are currently enrolled as planned. Recruitment of participants and follow-ups are still ongoing, and preliminary results are expected to be published in 2018.

Discussion

This study presents a protocol for a crossover randomized controlled trial to compare the effects of OCs containing LNG with products containing antiandrogenic progestins including CA, DRSP, EE, and DSG on clinical, hormonal, and metabolic findings and quality of life of reproductive-age women with PCOS. To our knowledge, this is the first trial with crossover design to compare the effects of different OCs on various clinical and biochemical aspects of PCOS. Results of this study will empower clinicians with evidence-based recommendations regarding treatment options and follow-up duration.

Different approaches have been used to treat patients with PCOS. Use of OCs is one of the most common treatment options for improving clinical and biochemical findings of PCOS [21,51]. It is well known that improvement in clinical signs of PCOS usually begins after 3 to 6 months of therapy, but because hair follicles have a half-life of up to 6 months, lifelong therapy may be needed to prevent recurrence [16,52]. In this study, patients were treated with OCs for a 6-month period in each phase.

To minimize selection bias, we enrolled patients from different settings such as professional social networks and municipal health centers, private clinics, and from among participants of the TLGS. These settings were located in different districts of Tehran. All patients who met the eligibility criteria were included in the study. Adolescent and premenopausal patients were not included in the trial because of different clinical and hormonal statuses in these periods.

An important strength of this study is its crossover design, in which the interventions under investigation are evaluated within the same patients, eliminating between-subject variability [53]. We designed this study and its methodological issues such as allocation, blinding, flow diagrams, patient preference, and carryover effects based on guidelines reported in the CONSORT statement [36]. This clinical trial is a head-to-head trial that permits patients to receive multiple treatments; hence, it can express preferences for or against particular treatments.

This study has limitations. Patients may drop out after the first intervention period and not receive a second treatment. This makes within-subject comparison impossible and is particularly important if withdrawal is related to side effects. We expect a considerable rate of loss to follow-up. To eliminate carryover effects, a washout period of 6 to 8 weeks was scheduled between treatments. Considering carryover effects of treatments across study periods can potentially distort the results obtained during the second treatment and the observed treatment effects will depend upon the order in which they will be received, hence we designed 6 treatment arms with different treatment orders. We intend to assess side effects of treatments. Considering our patients were diagnosed by AES criteria, our results may not be generalizable for those minor phenotypes diagnosed using Rotterdam criteria.

Finally, it is important to note that this project and its design are novel in the management of PCOS. If OCs containing LNG are as effective as OCs containing CA, DRSP, EE, or DSG without safety concerns, they may be recommended as a cost-effective first-line treatment for patients who suffer from the symptoms of PCOS. Therefore, we predict that the findings of this clinical trial will provide useful information for clinicians.

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Authors' Contributions

MA was involved in the study conception and design and data collection, carried out the sample analysis and interpretation of data, and drafted the manuscript. FRT was involved in the study conception and design and carried out the analysis and interpretation of data, managed the literature search, and drafted the manuscript. FN participated in the study conception and design, carried out the analysis and interpretation of data, drafted the manuscript, and wrote critical revisions. DK participated in the study design and analysis and helped to draft the manuscript. RB participated in statistical analyses and randomization design. MT will contribute to interpreting laboratory tests. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

A4: androstenedione
AES: Androgen Excess Society
CA: cyproterone
CONSORT: Consolidated Standards of Reporting Trials
DHEAS: dehydroepiandrosterone sulfate
DRSP: drospirenone
DSG: desogestrel
ECLIA: electrochemiluminescent immunoassay
EE: ethinyl estradiol
EIA: enzyme immunoassay
ELISA: enzyme-linked immunosorbent assay
FAI: free androgen index
FBS: fasting blood sugar
FG: Ferriman-Gallwey score
FSH: follicle-stimulating hormone
HDL-C: high-density lipoprotein cholesterol
HOMA-IR: homeostatic model assessment–insulin resistance
IEMA: immunoenzymometric assay
IRMA: immunoradimetric assay
LDL-C: low-density lipoprotein cholesterol
LH: luteinizing hormone
LNG: levonorgestrel
OC: oral contraceptive
PCOS: polycystic ovary syndrome
PCOSQ-50: Health-Related Quality of Life Questionnaire for Polycystic Ovary Syndrome
RIES: Research Institute for Endocrine Studies
SHBG: sex hormone-binding globulin
TC: total cholesterol
TLGS: Tehran Lipid and Glucose Study
TG: triglycerides
tT: total testosterone

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Protocol

Legacy Effect of Delayed Blood Pressure-Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute Cardiovascular Disease Risk: Protocol for a Systematic Review

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Abstract

Background: Many national and international guidelines recommend that the initiation of blood pressure (BP)-lowering drug treatment for the primary prevention of cardiovascular disease (CVD) should no longer be based on BP level alone, but on absolute cardiovascular risk. While BP-lowering drug treatment is beneficial in high-risk individuals at any level of elevated BP, clinicians are concerned about legacy effects on patients with low-to-moderate risk and mildly elevated BP who remain “untreated”.

Objective: We aim to investigate the legacy effect of delayed BP-lowering pharmacotherapy in middle-aged individuals (45-65 years) with mildly elevated BP (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) stratified by absolute risk for primary prevention of CVD, but particularly in the low-risk (<10% five-year absolute risk) group.

Methods: Randomized trials of BP-lowering therapy versus placebo or pretreated subjects in active comparator studies with posttrial follow-up will be identified using a 2-step process. First, randomized trials of BP-lowering therapy will be identified by (1) retrieving the references of trials included in published systematic reviews of BP-lowering therapy, (2) retrieving studies published by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), and (3) checking studies referenced in the 1993 World Health Organization/International Society of Hypertension meeting memorandum on BP management. Posttrial follow-up studies will then be identified by forward citation searching the randomized trials identified in step 1 through Web of Science. The search will include randomized controlled trials with at least 1-year in-trial period and a posttrial follow-up phase. Age is the major determinant of absolute cardiovascular risk, so the participants in our review will be restricted to middle-aged adults who are more likely to have a lower cardiovascular risk profile. The primary outcome will be all-cause mortality. Secondary outcomes will include cardiovascular mortality, fatal stroke, fatal myocardial infarction, and death due to heart failure.

Results: The searches for existing systematic reviews and BPLTTC studies were piloted and modified. The study is expected to be completed before June 2018.

Conclusions: The findings of this study will contribute to the body of knowledge concerning the beneficial, neutral, or harmful effects of delayed BP-lowering drug treatment on the primary prevention of CVD in patients with mildly elevated BP and low-to-moderate CVD risk.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews: CRD42017058414; https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058414 (Archived by WebCite® at <http://www.webcitation.org/6t6sa8O2Q>)

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KEYWORDS

legacy effect; high blood pressure; cardiovascular disease

Introduction

Despite improvements in the management of cardiovascular disease (CVD) over the past five decades, it remains the leading cause of death and disability in the world [1]. CVD was responsible for approximately 17.5 million deaths worldwide in 2012 [1]. In updated guidelines for the primary prevention of CVD from Australasia [2,3], the United Kingdom [4], and Europe [5], blood pressure (BP)-lowering pharmacotherapy is indicated by absolute CVD risk, not BP level alone. In contrast, the US guideline (the Eighth Joint National Committee) [6] is still heavily focused on BP level and age, despite the fact that BP-lowering therapy is beneficial for the reduction of CVD mortality and morbidity at sufficiently high CVD absolute risk, regardless of the level of BP elevation [7]. The use of BP-lowering drug treatment in high-risk settings has achieved consensus in Australasian [2,3], European [5], and the US guidelines [6]. In low-risk individuals, BP-lowering drugs are not recommended by guidelines in Australia [2], New Zealand [3] or the United Kingdom [4], unless BP exceeds a level of 160/100 mmHg, whereas the European [5] and US [6] guidelines recommended an early initiation at a BP level of 140/90 mmHg. However, both approaches raised many concerns from clinicians and a gap still exists between guidelines and clinical practice [8].

An international expert consultation was recently performed to solve the controversy of whether adults with grade 1 hypertension (<140/90 mmHg) and low-to-moderate CVD risk should be treated by drug therapy [9]. Morales-Salinas et al [9] recommended an early initiation of BP-lowering pharmacotherapy primarily from the results of the Heart Outcomes Prevention Evaluation (HOPE-3) trial [10] and a meta-analysis by Thomopoulos et al [11] for adults with grade 1 hypertension and moderate CVD risk; however, the two studies were likely to include a number of high-risk participants. In the HOPE-3 trial [10], participants with an INTERHEART risk score higher than 16 (a value of 16 or higher indicates a high CVD risk) accounted for 32.5% of the total sample [12]. In the meta-analysis by Thomopoulos et al [11], the CVD risk was calculated by CVD death rate in the control group, while the CVD risk score used in most guidelines is for fatal and nonfatal CVD events. Thus, the benefits of BP-lowering pharmacotherapy in low-to-moderate-risk individuals remain unclear, as opposed to the benefits achieved by treating high risk individuals. Most clinicians use BP-lowering pharmacotherapy based on BP criteria alone, due to the perceived potential risk of irreversible target organ damage (the “legacy effect”) for delayed therapy [5]. Studies that would help us to answer this question include those that have extended

follow-up in the posttrial period. Such studies include the Systolic Hypertension in the Elderly Program trial [13] of approximately 22 years, the Hypertension Detection and Follow-Up Program [14] of 8.3 years, and the second Australian National Blood Pressure study [15] of 10.6 years. Participants in these studies are still likely to be at high baseline risk of CVD due to the advanced age and diabetic status in the inclusion criteria of the trials [13-15]. Hence, the concern of legacy effects on low-to-moderate-risk individuals has not been addressed. Age is the most important determinant of adverse cardiovascular risk, so the participants in our review are restricted to middle-aged adults who are more likely to have a broader cardiovascular risk profile. Therefore, in this systematic review and meta-analysis, we will investigate the effects of BP-lowering drug treatments in middle-aged individuals with mildly elevated BP, stratified by absolute CVD risk.

Methods

Review Objectives

Aim 1

We will conduct a systematic review and meta-analysis of published and unpublished studies of randomized placebo control trials with a posttrial follow-up phase that included middle-aged participants without overt CVD, and examine these studies for CVD mortality and all-cause mortality.

Aim 2

We will conduct a subgroup analysis (where possible) of participants in these trials classified as low-, moderate-, and high-absolute CVD risk by the Framingham Risk Score (FRS) used in the Australia guideline [2], or the risk calculator used by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [16] which uses routine clinical information if information on cholesterol levels is not available for fatal and nonfatal CVD events and all-cause mortality. We will conduct an individual patient data meta-analysis, if data are available.

Primary Null Hypothesis

There will be no significant difference in CVD mortality or all-cause mortality between patients who have drug therapy initiated earlier (active treatment arm) versus delayed or not initiated (control arm) in individuals at low-absolute CVD risk.

Secondary Hypotheses

Hypothesis 1

There will be no significant difference in CVD mortality or all-cause mortality between patients who have drug therapy

initiated earlier (active treatment arm) versus delayed or not initiated (control arm) in individuals at moderate-absolute CVD risk.

Hypothesis 2

There will be no significant difference in CVD mortality or all-cause mortality between patients who have drug therapy initiated earlier (active treatment arm) versus delayed or not initiated (control arm) in individuals at high-absolute CVD risk.

Hypothesis 3

In-trial CVD events (fatal and nonfatal) will be incremental by risk classification estimated by FRS or equivalent risk calculated at baseline.

Criteria for Considering Studies in the Review

Population

The study will include men and nonpregnant women from 45 to 65 years of age. At least 80% of participants from each trial must have had mildly elevated BP at baseline, defined as a systolic BP of 140- 159 mmHg and/or diastolic BP 90- 99 mmHg. Furthermore, all included participants must not have exhibited any history of CVD at baseline: myocardial infarction, angina pectoris, coronary bypass surgery, coronary angioplasty, stroke, transient ischaemic attack, carotid endarterectomy, surgery for peripheral vascular disease, intermittent claudication or renal failure (creatinine >1.5 times the upper limit of normal). If trials included participants different than those of interest (eg, secondary prevention, moderately-elevated or highly-elevated BP), we will attempt to access individual patient data and subsequently select participants that meet specific criteria.

Intervention

The study will focus on all types of BP-lowering drugs, except for some types that have limited clinical use due to the risk of side effects and availability (eg, ganglion blockers, reserpine, rauwolfia).

Comparison

The study will compare the effects of BP-lowering drug treatments in active treatment groups versus control treatment groups. However, if comparative trials with two active comparators had an extended posttrial follow-up phase and individual data are available, we will perform a legacy effect analysis per Nelson et al [15]. We will reclassify participants into *previous treatment* (early treatment) groups and *treatment naïve* (delayed treatment) groups. The *previous treatment* group will include participants who were on BP-lowering drug treatments at trial registration and then went on a specific drug withdrawal program. The *treatment naïve* group will include those who were not on any treatments at trial registration.

Outcomes

Primary outcomes will include all-cause mortality in both randomization and follow-up periods. Secondary outcomes will include CVD mortality (defined as deaths due to stroke, myocardial infarction, and heart failure), fatal stroke, fatal myocardial infarction, and fatal heart failure. Nonfatal CVD events will be included if the measurements of outcomes are

similar between trials. Vital status in posttrial periods must be assessed by national death databases or equivalent records.

Study Design

Randomized controlled trials with at least 1-year in-trial period and a posttrial follow-up phase.

Language

No restriction (English and non-English studies).

Publication Type

Published and unpublished studies reported in peer-reviewed journals, reports, conference abstracts, and theses.

Search Methods for Identification of Studies

Randomized trials of BP-lowering therapies versus placebo or active comparator with posttrial follow-up periods will be identified using a 2-step process. First, randomized trials of BP-lowering therapy will be identified by (1) retrieving the references of trials included in published systematic reviews of BP-lowering therapy, (2) retrieving studies published by the BPLTTC, and (3) checking studies referenced in the 1993 WHO/ISH (World Health Organization/International Society of Hypertension) meeting memorandum on BP management [17]. To identify existing systematic reviews, we will search Medline Ovid using a combination of Medical Subject Headings and text word terms for BP-lowering regimes and high BP with a systematic review filter (see [Multimedia Appendix 1](#)). Web of Science will be used to retrieve the references of studies cited by the systematic reviews, and these will be exported to an Endnote file. To identify studies from the BPLTTC, a text word search in the title, abstract, and author fields will be conducted in Ovid Medline and the retrieved references will be exported to the Endnote file. Web of Science will be used to retrieve the references of studies cited in the WHO/ISH meeting memorandum and these will be exported to the Endnote file. After removing duplications, the Endnote file will be screened to identify randomized trials of BP-lowering therapies versus placebo or active comparators. In the second step of the search, posttrial follow-up studies will be identified by forward citation searching the randomized trials identified in step 1. Web of Science will be used for forward citation searches of each of the original trials, with the citations exported to another Endnote file. After the removal of duplications in the Endnote file, the file will be searched using terms related to extended follow-up (see [Multimedia Appendix 2](#)). The resulting titles and abstracts will be screened independently by two reviewers using the review eligibility criteria.

Study Selection

First, two independent reviewers will screen a small sample of papers found in the search to revise any unclear or inappropriate inclusion criteria. In the full selection process, two reviewers will independently scan the results of the search and determine the eligibility of the studies. In the initial screening of titles and abstracts, the studies will be included if they meet the inclusion criteria or they do not have enough information for exclusion. Rejected citations will be recorded and classified as irrelevant studies. All potentially relevant articles will be screened through full text for a final decision. If a paper does not have sufficient

information to assess eligibility, we will attempt to contact the authors; the paper will be classified as a *potentially relevant article* and checked in sensitivity analyses if authors do not reply after one month. If we identify trials that meet our inclusion criteria but lack data on the posttrial follow-up period, we will run a forward citation search from those studies. If a study has multiple citations, we will report separate citations but analyze these reports as a single study. We will also liaise with the BPLTTC for any individual patient data from trials meeting our inclusion criteria.

Textbox 1. Information required for data extraction.

General information: reviewer performing data extraction, date of data extraction, and identification features of the study (eg, record number, authors, article title, type of publication, country of origin, the source of funding)

Study characteristics: aims of the study, study design, study inclusion and exclusion criteria, recruitment procedures (details of randomization, blinding), and unit of allocation (participant, GP practice)

Participant characteristics: baseline characteristics (age, gender, ethnicity, socioeconomic status, comorbidities, systolic BP, diastolic BP, weight, height, smoking status, serum total cholesterol, serum creatinine level), and the number of participants in active treatment group and control group

Intervention and setting: type and dose of BP-lowering regimen

Outcome data:

- For each outcome: whether reported, definition, length of follow-up, number of events, number of participants in each event, odds ratio, risk ratio, and hazard ratio
- For both intervention groups: number of participants enrolled; number of participants included in analysis; and number of withdrawals, exclusions, and lost to follow-up

Type of analysis used in the study: intention to treat or per protocol

Data Extraction and Quality Assessment

Data extraction forms (detailed in [Textbox 1](#)) and quality assessment forms will be piloted on a small group of studies. Two reviewers will independently perform data extraction and quality assessment in the prespecified form. If any disagreements arise, the reviewers will discuss consensus or consult with the third reviewer. A report of correction or amendments to the prespecified form will be recorded.

Quality Assessment

The risk of bias will be assessed by two reviewers following the Cochrane Risk of bias tool [18] which includes the following criteria: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants, personnel, and outcome (performance and detection bias); and incomplete outcome data (attrition bias). The bias will be assessed as unclear, low-risk, or high-risk. Publication bias will be judged by observing the asymmetry of funnel plots; if they are asymmetric, contour-enhanced funnel plots will then be analyzed to examine whether publication bias alone caused the asymmetry. We will also use Egger's meta-regression model to assess the relationship between the observed effect sizes and the size of studies [19].

Data Synthesis and Analysis

After pooling all eligible studies, we will design a fixed-effect model and assess the heterogeneity by visually inspecting the forest plots, Chi-squared tests, and I^2 tests. Statistical heterogeneity will be recorded when the studies' confidence intervals exhibit poor overlap, the P-value of the test of heterogeneity is 0.1 or lower, or the I^2 value is 0.5 or greater. In these cases, we will also perform an analysis using a random-effects model. All trial endpoints will be treated as dichotomous variables and grouped by time from randomization. In the fixed-effect model, the Mantel-Haenszel method model will be used to combine risk ratios of each outcome [20]. We will conduct a subgroup analysis in which available risk calculators will be used to stratify participants by the baseline absolute CVD risk for fatal and nonfatal CVD events. In a

sensitivity analysis, each study will be removed (one at a time) to assess the impact of each study on the pooled outcomes. The Cochrane software (Revman) [21] will be used for meta-analysis, selective reporting, and other sources of bias.

Ethics and Dissemination

This systematic review will analyze nonidentifiable data; thus, a formal ethics approval is unlikely to be crucial. The study protocol was registered with the International Prospective Register of Systematic Review (PROSPERO) with the reference number CRD42017058414. The current study will contribute a chapter of a PhD thesis (CH).

Results

We are currently in the process of developing the search strategy. The search in Medline via Ovid has been piloted and modified. The analysis is expected to complete before June 2018.

Discussion

Given the strong beliefs held by many clinicians that early treatment of elevated BP is necessary to prevent CVD events, it is not possible to conduct a randomized controlled trial of early versus late treatment at present. This is particularly true for patients with mildly elevated BP and low CVD risk, as studies would require a large sample size of participants or a long follow-up period because approximately 10% of CVD events are expected to occur within 10 years. In addition, clinicians are questioning the real benefits, adverse effects, and

medical costs of the life-long intervention of BP-lowering drug treatment. The findings of this study will contribute to the body of knowledge concerning the beneficial, neutral, or harmful effects of delayed BP-lowering drug treatment in patients with mildly elevated BP and low-to-moderate CVD risk.

Limitations

Due to the changes in definitions of CVD and diagnostic methods used over time, we predict that it will be difficult to combine these outcomes in a meta-analysis. This issue inherently generates bias in selection, detection, attrition, and reporting.

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Conflicts of Interest

MRN has served on an advisory board for AMGEN in the last 5 years. All other authors declare no conflicts of interest.

Multimedia Appendix 1

Search strategy developed for Medline via Ovid to identify existing systematics review.

[PDF File (Adobe PDF File), 22KB - [resprot_v6i9e177_app1.pdf](#)]

Multimedia Appendix 2

Search terms related to extended follow-up.

[PDF File (Adobe PDF File), 19KB - [resprot_v6i9e177_app2.pdf](#)]

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Abbreviations

BP: blood pressure

BPLTTC: Blood Pressure Lowering Treatment Trialists' Collaboration

CVD: cardiovascular disease

FRS: Framingham Risk Score

HOPE-3: Heart Outcomes Prevention Evaluation trial

WHO/ISH: World Health Organization/International Society of Hypertension

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Protocol

Health Information National Trends Survey in American Sign Language (HINTS-ASL): Protocol for the Cultural Adaptation and Linguistic Validation of a National Survey

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Abstract

Background: The Health Information National Trends Survey (HINTS) collects nationally representative data about the American's public use of health-related information. This survey is available in English and Spanish, but not in American Sign Language (ASL). Thus, the exclusion of ASL users from these national health information survey studies has led to a significant gap in knowledge of Internet usage for health information access in this underserved and understudied population.

Objective: The objectives of this study are (1) to culturally adapt and linguistically translate the HINTS items to ASL (HINTS-ASL); and (2) to gather information about deaf people's health information seeking behaviors across technology-mediated platforms.

Methods: We modified the standard procedures developed at the US National Center for Health Statistics Cognitive Survey Laboratory to culturally adapt and translate HINTS items to ASL. Cognitive interviews were conducted to assess clarity and delivery of these HINTS-ASL items. Final ASL video items were uploaded to a protected online survey website. The HINTS-ASL online survey has been administered to over 1350 deaf adults (ages 18 to 90 and up) who use ASL. Data collection is ongoing and includes deaf adult signers across the United States.

Results: Some items from HINTS item bank required cultural adaptation for use with deaf people who use accessible services or technology. A separate item bank for deaf-related experiences was created, reflecting deaf-specific technology such as sharing health-related ASL videos through social network sites and using video remote interpreting services in health settings. After data collection is complete, we will conduct a series of analyses on deaf people's health information seeking behaviors across technology-mediated platforms.

Conclusions: HINTS-ASL is an accessible health information national trends survey, which includes a culturally appropriate set of items that are relevant to the experiences of deaf people who use ASL. The final HINTS-ASL product will be available for public use upon completion of this study.

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KEYWORDS

HINTS; health information seeking; American Sign Language; signed language; cultural adaptation; translation; health surveillance; survey

Introduction

The Health Information National Trends Survey (HINTS) is a survey of people's health information seeking behaviors, including technology mediated sources. HINTS has previously been used for baseline data/endpoints in health communication studies and as outcome measures in several human-computer interaction studies [1]. Instruments are available in English and Spanish [2]. The methodology for translation includes an iterative process of forward and back translation, independent reviews by bilingual experts, and pretesting on a population with characteristics similar to the population to be assessed.

There are currently over 200 published papers using HINTS and over 50,000 participant responses collected. However, HINTS is not available in American Sign Language (ASL) yet, thus excluding deaf adult signers from health communication research. This exclusion has led to a significant gap in knowledge of Internet usage for health information access in this underserved and understudied population. With National Institutes of Health (NIH) funding, we were able to culturally adapt and translate a set of HINTS items to ASL. We also added items that were unique to the deaf signers' experiences with seeking health information and communicating with health professionals. For example, we included items that asked deaf people about their experiences with using video relay interpreting (VRI) services in medical settings. We also included questions about the modality of communication that they used with their healthcare providers. This is the first nationwide survey that is accessible in ASL and includes items that are culturally relevant to deaf people's health communication experiences.

This paper describes the cultural adaptation methods used to make existing HINTS items applicable to deaf people. In addition, we describe the linguistic translation methods to translate HINTS items to ASL. We produced an accessible health information seeking survey in ASL (HINTS-ASL) and a culturally appropriate set of items that are relevant to the experiences of deaf adults.

Methods

To make the HINTS survey accessible in order to gather data for the deaf population in America, we obtained approval from the National Cancer Institute (NCI) HINTS group to translate the items to ASL. Because existing HINTS items were originally written and validated in the general population, we followed the cultural adaptation process to ensure that these items are relevant and can be answered by deaf users of accessible technology and services.

Addition of New Deaf Health Experience Items and the Cultural Adaptation of Existing HINTS Items

We reviewed HINTS items that required cultural adaptation for deaf people who use accessible technology and services. Some items from the social media section required cultural adaptation for use with deaf people who use accessible services or technology. An example of an original item taken from HINTS and its culturally adapted item is shown below.

Sometimes people use the Internet to connect with other people online through social networks like Facebook or Twitter. This is often called "social media". In the last 12 months, have you used the Internet to write in an online diary or blog (ie, Web log)? [Original question]

In the last 12 months, have you used the Internet to write in a status update on Facebook or to share ASL vlogs? [Adapted question]

Another example of an original HINTS item, "In general, how much would you 'trust' information about health or medical topics from each of the following?" required cultural adaptation and translation to be consistent with the TRUST and CONFIDENT sign, which is similar in handshape, location, orientation, and movement [3]. This sign was also used in "Overall, how 'confident' are you that you could get advice or information about health or medical topics if you needed it?" The research team met and discussed this issue and came up with the solution of adding a sign of "believe" along with "trust". We then tested its translation with deaf ASL users who have high school education or lower. All translations were shown online using HINTS-ASL layout (Figures 1 and 2). Each participant played the question and then the response options, all in ASL. No English texts were shown in this testing phase. These participants answered the questions without any difficulty, which validates the linguistic translation of those questions.

New items reflecting deaf-related experiences were added to the existing HINTS item bank, reflecting deaf-specific technology such as VRI services in health settings. A team of experts from national organizations working with deaf people—the National Association of the Deaf, Telecommunications Inc. and the Rehabilitation Engineering Research Center at Gallaudet University—used case studies to draft items related to video remote interpreting and VRI services for health purposes. Each item was evaluated for nomination for inclusion in the survey if it met the following criteria: (1) the item should measure a single target concept, and (2) the item should be relevant to deaf people's experiences. If the item content was too narrow to have universal applicability to the deaf population that uses ASL, the item was revised or removed. All deaf-related items were tested for cultural relevancy with deaf ASL users.

One of the items that was found to be problematic in ASL translation was "What is your hearing level in your better ear?" The translation of that question was riddled with difficulty, because the phrase "better ear" doesn't have a direct translation in ASL. Another problem was the typical responses used by audiologists in measuring hearing would be mild, moderate, severe, and profound. The original question in ASL was "Point-to-both-ears, which better, level what?" The problem with the framing of that question, according to the cognitive interviews, was that the respondents would say that they're not sure and that both ears are deaf, period. They did not know what "level" they were deaf at and that they were simply deaf. One participant said: "I'm 100% deaf in both ears!" and another felt this was an inappropriate question. This led us to think that questions about hearing levels can easily be confused with questions about their cultural identity (eg, deaf, hard-of-hearing,

or hearing). This question was then removed from the questionnaire because it was not culturally compatible. In lieu of this audiological-specific question, we used the following more culturally acceptable question:

If a person speaks to you through a combination of listening and/or lip-reading in a quiet room, how much can you understand what the person says?

This included a response set of:

All of what they said.

Most of what they said.

Some to little of what they said.

Did not understand what they said.

Participants in the debriefing process did not indicate any concerns for this question and it was used in lieu of the audiological question to collect information from the participants about their perceived access to auditory information.

The items that are included in the deaf experience item bank are shown in [Textbox 1](#).

Textbox 1. Deaf experience item bank.

Items
Are any of your immediate family members deaf or hard of hearing?
Which immediate family member is deaf or hard of hearing?
When you were a teenager (between 12 and 18 years old), how well did you understand what your parents said?
How do you communicate with your doctor, nurse, or health professional that you see the most?
Most of the times, the interpreter was... [on site or through VRI]
If you had to choose one, how do you prefer to use an interpreter in health settings?
How would you rate the quality of VRI services you received in healthcare settings in the past 12 months?
Overall, how would you rate the quality of interpreting services you received on site in healthcare settings in the past 12 months?
Overall, how well did you understand your ASL interpreters at your healthcare appointments in the past 12 months?
Overall, how well did the ASL interpreters at your healthcare appointments in the past 12 months understand you?
Have you used video relay services (VRS) to contact your doctor, health insurance, or any medical service?
How often do you struggle or get frustrated when you used VRS to contact your doctor, health insurance or any medical service?
Please think about your most recent frustrating experience with using VRS to contact your doctor, health insurance, or any medical service. What was the main reason for this frustration?
Do you feel having an onsite interpreter in the doctor's office will interfere with your disclosure of health information with the doctor?
Do you feel having a VRI will interfere with your disclosure of health information with the doctor?
If a person speaks to you through a combination of listening and/or lip-reading in a quiet room, how much can you understand what the person says?
Which language do you prefer or feel comfortable using?
What do you identify yourself as? Culturally Deaf, deaf, hard of hearing, or hearing?

Figure 1. Lung cancer answer option with medical illustration.

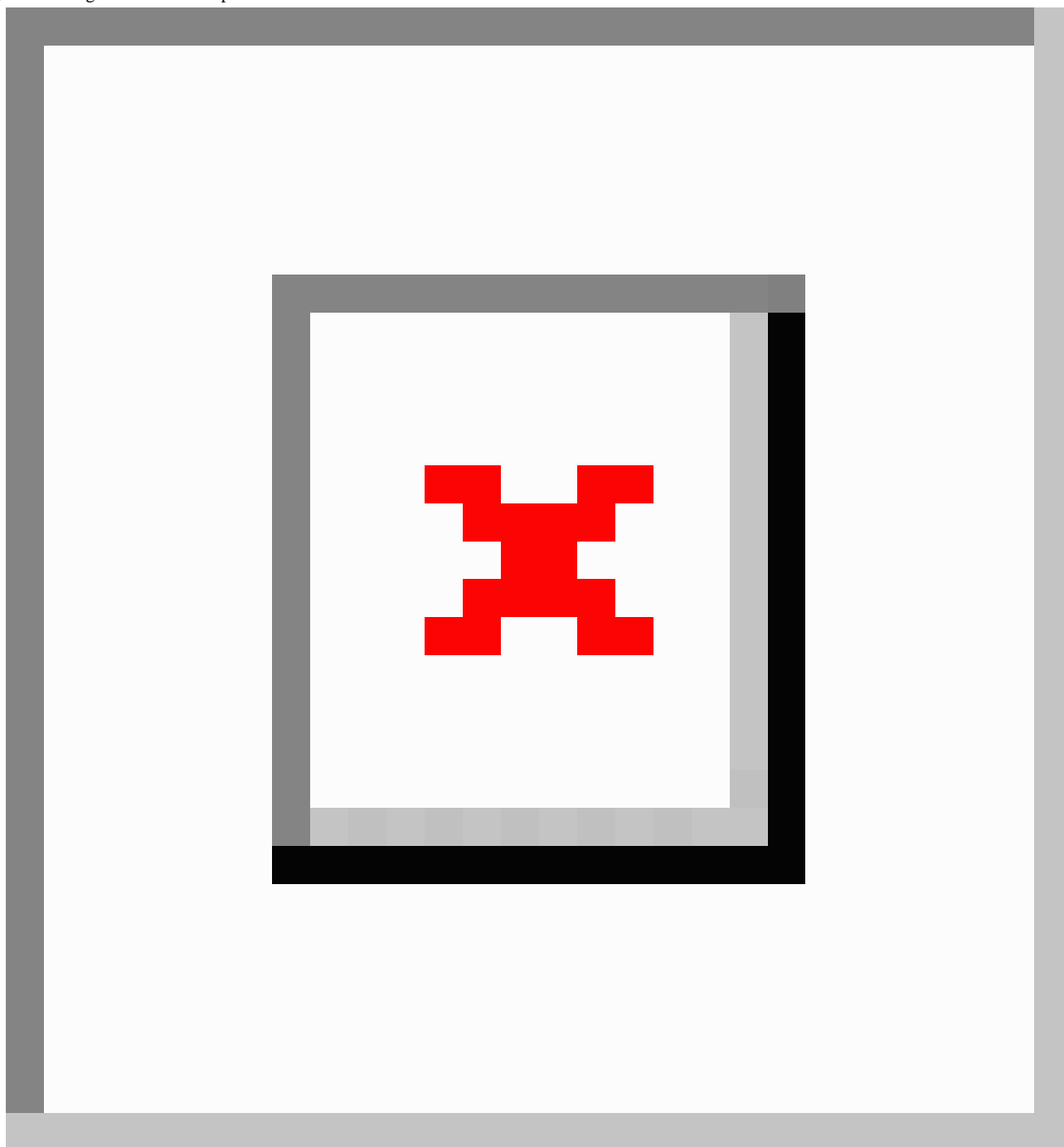
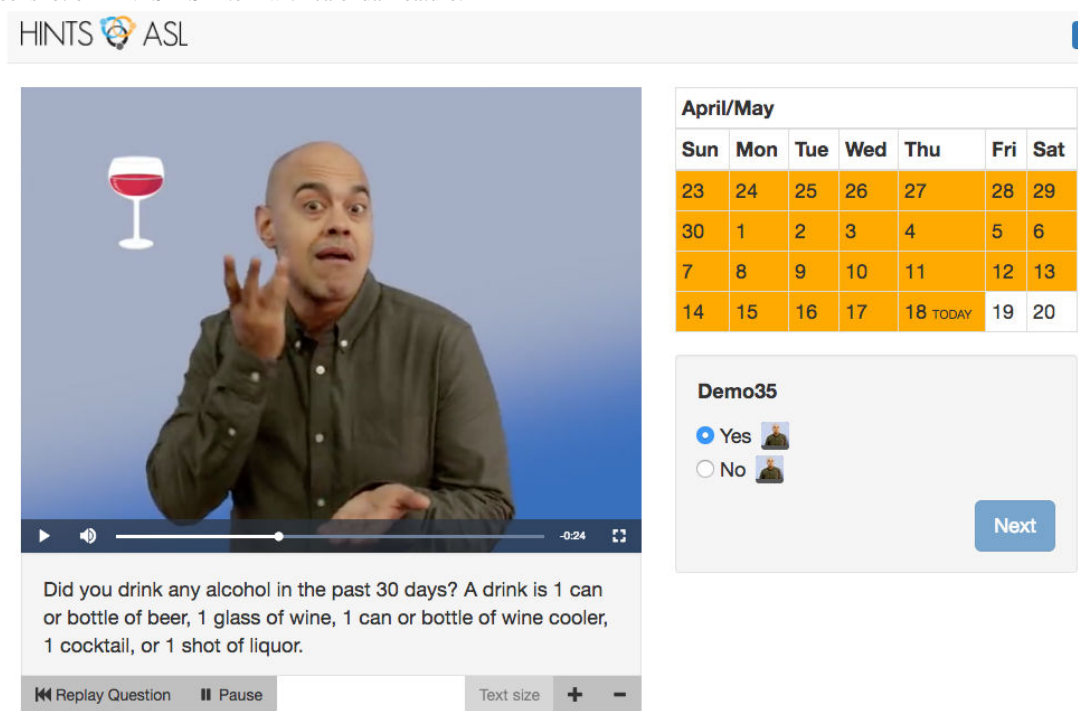


Figure 2. Screenshot of HINTS-ASL item with calendar feature.

Linguistic Validation and Translation

The backward and forward translators involved in this project were deaf native signers, born to parents who were deaf or had older deaf siblings and thus were exposed to ASL since birth. They were also proficient in English. The translation team consisted of 2 forward translation consultants (A and B) and a backward translation consultant. All were bilingual in ASL and English with experience translating test items. The concept of linguistic validation was explained to the team in detail before working on the translations. Forward translation consultant A was given a list of HINTS items in English to be translated to ASL. A video camera was used to record the translation. A backward translator viewed forward translation A's videos and wrote down the equivalent items in English. A reconciliation of items was then performed by the principal investigator. Items that failed the reconciliation process were then passed over to forward translation consultant B who translated these items to ASL using a video camera. The backward translator viewed translation B's ASL videos and made further corrections to the back-translated English items. A deaf oncology nurse who is bilingual in ASL and English reviewed the translations to ensure concept equivalence of cancer-related items were delivered in ASL. A native ASL user with background training in ASL linguistics assumed the model signer role for the final HINTS-ASL version.

The final HINTS-ASL items included grammatically correct ASL, for example, including a question marker at the end indicated by raising the eyebrows. These subtle changes in facial expressions convey important linguistic information in ASL and the equivalence in spoken English would include the raising of pitch at the end of a sentence to indicate a question. Other linguistic and cultural modifications to the translations included the questions regarding the timeline, such as in the last 12

months. The research team felt that "last 12 months" in English should be converted to "since 1 year" in ASL, due to the concern that the participants may misinterpret "last 12 months" as January of the past year, even if the year has not fully ended. Those new phrases in ASL were tested during the cognitive debriefing sessions and responses supported the alternate word choices. All timeline questions were then modified to the culturally and linguistically appropriate phrases of "since 1 year" in ASL.

Cognitive Debriefing

The goals of the cognitive debriefing interviews were to assess whether (1) the respondents understood the intent of the HINTS-ASL questions; and (2) the questions were both culturally acceptable and contextually relevant to deaf signers' experiences. The English version of the survey items on ASL video clips were not shown to the participants to ensure focus on the clarity of ASL items. If the participant had any difficulty with understanding the items, the interviewer provided alternative words or concepts, or asked the person to propose improvements. By having the test items audited and validated by members of the target language community—the deaf community—they align with Harris and colleagues' terms of ethics on how a researcher can ethically work within the deaf community, a marginalized group [4].

As an effort to save cost in re-filming and re-editing ASL video clips, an open-ended cognitive interview approach with the HINTS-ASL items was utilized, allowing time for follow-up, clarification, and expansion on the test items with the respondents if and when needed. A native speaker of ASL and a Certified Deaf Interpreter (CDI) with a doctoral degree in educational linguistics, specializing in ASL discourse with an extensive background in ASL pedagogy, translation, and interpretation led this process. As a CDI, she has significant

experience working with a variety of clients ranging from those who are semi-lingual to multilingual in multiple sign languages in medical, mental, and health-related settings.

Following approval from human participants review board and after written consent was obtained from participants, 1- to 2-hour cognitive debriefing interviews were conducted with a target linguistic community of deaf people who use ASL primarily and have a high school degree or less. Involving members of the deaf community with high school education or less in this cognitive debriefing process also helps to ensure the test items are understood by the greater majority of the deaf community, increasing the reliability and validity of the test items across a larger number of participants. Cognitive debriefing was performed through 3 waves of face-to-face interview sessions with 4 to 5 ASL signers per wave. Each wave included both male and female signers with a high school degree or lower.

Web-Based App Development and Testing

AllOut Marketing, Inc. was contracted to iteratively develop the Web-based app and the user interface testing was done at the authors' institution. Since the videos were signed in ASL, the human-computer interaction played a significant role in having participants not only understand what the question is asking, but also feeling comfortable with the visual layout on the screen. In the user experience sessions, participants often asked the research staff to clarify what or where a "kidney" was, or what a "regular dial-up telephone line" looked like. When the researcher asked how it could be improved, they recommended visual aid to be placed adjacent to the signer. We incorporated their feedback to improve the video (Figure 1). The pictures helped greatly with the clarity and understanding of the questions in the next wave of user experience sessions.

A person who listens or reads French may respond to questions similarly to a person who listens or reads English. A deaf person who uses ASL should not be viewed differently from those readers as far as giving certain information. The only difference is that the deaf person sees the ASL videos on the computer and selects responses on the screen. The hearing person sees the English/French words on a paper and marks responses. Sign languages are not permanently embedded on the screen and are ephemeral, requiring the participant to press a button to play the question (or option) again to review information that was presented. In other words, after you watch a person narrate a question or a sentence, the information disappears. Languages that have a written version can be permanently left on the screen and easily revisited as one reads the options and then looks back at the question if needed. This type of question format was not as viable in ASL, due to its ephemeral nature, and needed to be repeated for each option. For instance:

In general, how much would you trust information about cancer from a doctor?

In general, how much would you trust information about cancer from family or friends?

Therefore, the online survey app was designed to allow replays of the question and response options.

An item example, which offers an option of watching the ASL version of the item on a video or turning the video off for greater

emphasis on the English text, is shown in Figure 2. A highlighted calendar next to the video and English text provided added visual information on the range of days that the experience or symptom may have or may not have occurred. Participants could also pause the video to take a closer or longer look at the image before proceeding to answer. The final HINTS-ASL was pre-tested with 4 deaf adults to determine whether the survey is of a suitable length to avoid participant burden. Then the Web-based app was finalized and prepared for administration in future studies.

Administration

All research staff who participated in administering surveys were required to complete human participants training and were trained in conducting informed consents. The interviewers were also trained to know each question asked in the survey and how to correctly translate them into ASL without losing the meaning of the original English question. When prospective participants expressed interests in taking the survey, they were asked to watch informed consent in ASL and provide written consent if they wished to participate. The researcher then met with the participant to review their rights. Participants were assured that all information provided by them will be kept confidential and access to their data was controlled by the principal investigator. The participants were also informed that the interviewers did not have access to the dataset and could not see the participants' responses. Deaf participants were also told that, for dissemination purposes, results were presented in aggregate so that no person is identifiable.

A purposive sampling method was used to ensure similar distribution of key demographic characteristics such as US region, age, and education. The US census was used to determine estimates for each region, age group, and education level. We gathered information on deaf-specific demographics as well. Through channels targeting the Deaf community, we solicited participation using methods that we have used in the past with success, including distributing flyers, through word of mouth in the community, community centers and churches, deaf organizations, creating a Facebook page for the study, and in local or statewide deaf-oriented listserves. Communication with community recruiters and interested participants also took place through community events, email, Facebook, and Facetime/videophone.

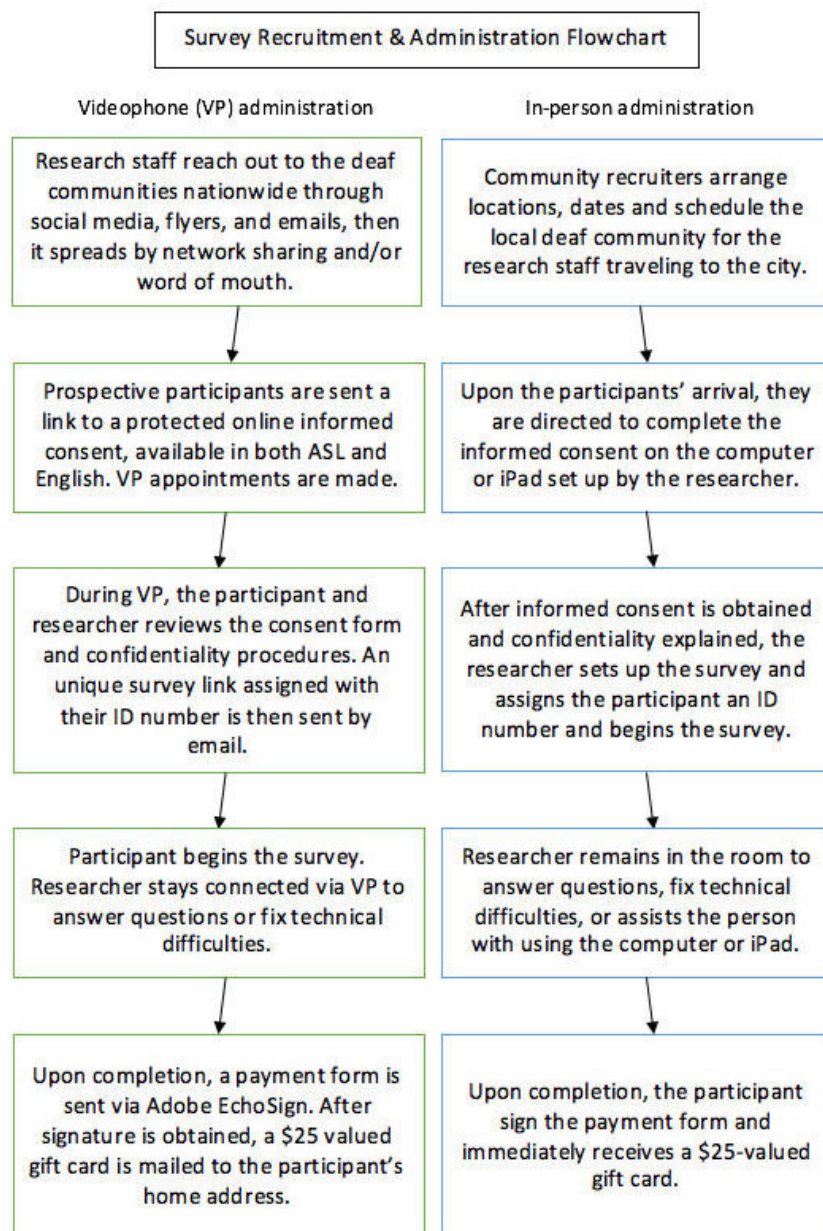
Data was collected in ASL by one of the following methods to meet the needs of the diverse deaf sample: (1) interviewer-guided survey in person; or (2) interviewer-guided survey by videophone. For the first method, interview-guided survey in person, the respondent may have opted to view the questions in ASL and enter responses directly while the interviewer stands by to aid if required or to have the interviewer ask the questions and then enter the participant's responses. For the second method, the interview-guided survey by videophone, the interviewer checked in with the participant to ensure they understood the informed consent that was shown through ASL videos online and briefly reviewed their rights that were explained in the informed consent. When the participant was ready to begin the survey, the interviewer sent the survey link via email. The interviewer remained visible on videophone to

answer questions during the session, including immediate assistance of technical difficulties.

On average, it took approximately 45 to 60 minutes to complete the online survey. Upon completion, each participant was

compensated a US \$25 gift card as a gratuity for their time and participation. The flowchart procedure for each method is shown in Figure 3.

Figure 3. Flowchart for survey administration and recruitment.



Results

Data collection is ongoing. At the time of this publication, a total of 1356 deaf adults provided informed consent and took the survey. An unweighted summary of the demographic data is shown in Table 1. A large number came from the South (39.90%, 541/1356), followed by West (26.18%, 355/1356), Northeast (10.77%, 146/1356), and Midwestern (23.16%, 314/1356). Within the sample ranging from 18 to 95 years old that had a mean age of 50 (SD 18) years, the 18 to 34 age group had the largest number of participants (32.60%, 442/1356) followed by the 35 to 49 age group (25.22%, 342/1356). Half of the HINTS-ASL sample had a college degree. This sample

included 16.15% (219/1356) who self-identified as lesbian, gay, or bisexual and 36.43% (494/1356) who were people of color. When asked about the hearing status of the respondent's parents, 23.38% (317/1356) reported having parents who are deaf.

Approximately 38.79% (526/1356) earned less than US \$35,000. Nearly 87.09% (1181/1356) of the deaf sample reported having health insurance coverage and 62.54% (848/1356) had a healthcare provider that they see regularly. Although most of the sample (66.96%, 908/1356) reported having been told by their healthcare provider to have a medical diagnosis (ie, hypertension, diabetes, depression/anxiety disorder, etc), and many rated their health as "good" (34.59%, 469/1356) or "very good" (37.54%, 509/1356).

Table 1. Sociodemographic characteristics (N=1356).

Characteristic	n (% ^a)
Age in years, mean (SD)	50 (18)
Gender	
Male	567 (41.81%)
Female	776 (57.23%)
Missing/did not answer	13 (0.96%)
Age group, years	
18-34	442 (32.60%)
35-49	343 (25.29%)
50-64	325 (23.97 %)
65-74	172 (12.68%)
75 and over	74 (5.46%)
Ethnicity/race	
Hispanic	189 (13.94%)
Non-Hispanic White	845 (62.32%)
Non-Hispanic Black or African American	156 (11.50%)
Other	149 (10.99%)
Missing/did not answer	17 (1.25%)
Geographic location	
Northeast	146 (10.77%)
South	541 (39.90%)
Midwestern	314 (23.16%)
West	355 (26.18%)
Education	
Less than high school	54 (3.98%)
High school graduate	331 (24.41%)
Some college	301 (22.20%)
College graduate	667 (49.19%)
Missing/did not answer	3 (0.22%)
Preferred language	
ASL ^b	716 (52.80%)
Both ASL and English	624 (46.02%)
Missing/did not answer	16 (1.18%)
Occupation	
Employed	663 (48.89%)
Unemployed	126 (9.29%)
Homemaker	62 (4.57%)
Student	164 (12.17%)
Retired	259 (19.10%)
Disabled	37 (2.73%)
Other	11 (0.81%)
Missing/did not answer	34 (2.51%)

Characteristic	n (% ^a)
Personal history of cancer	
Yes	175 (12.91%)
No	1129 (83.26%)
Missing/did not answer	51 (3.76%)

^aUnweighted percent.

^bASL: American Sign Language.

Discussion

Transformative Research Paradigm

The additional step of conducting cognitive interviews prior to translations was rooted in the transformative paradigm [5], where researchers incorporate elements of social justice and human rights in the research process by involving the target community in the validation of the survey items. In the transformative research paradigm, researchers make explicit the issue of power and who holds the power, but also explicitly identify the process of sharing ownership of the research process with the research team, participants, and the target community [6,7]. In any research involving the deaf community, deaf people must be involved in every step of the research, and not simply as research assistants [4]. In the case of the HINTS-ASL research project, almost all members of the research team were deaf and led by a primary investigator who is deaf and bilingual in ASL and English. The hierarchical structure typically associated with research was destabilized in this project, and made more equal in this process where the deaf primary investigator, being a person of color, worked closely with a deaf team of experts, with at least half of the research team members being deaf people of color. These experts worked closely with

members of the deaf community to ensure that the survey items in ASL were still accessible to and understood by deaf signers who have high school education or lower. These deaf community members who participated in evaluating the ASL items have high school degree or lower. All investigations in indigenous communities, such as the deaf community, should be done with the deaf community's consent and with the deaf community's joint control and guidance [8], conditions of which were met in this study.

The involvement of participants in this process is transformative for both the research team and the participants because it redistributes the power back to the community by having the participants provide input on the test items. Regardless of the results, the research team, participants, and the community were in some ways transformed by the research process, hence the name of the transformative research paradigm [5].

Conclusion

HINTS-ASL is an accessible health information national trends survey, which includes a culturally appropriate set of items that are relevant to the experiences of deaf people who use ASL. The final HINTS-ASL product will be available for public use upon completion of this study.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review report.

[PDF File (Adobe PDF File), 15KB - [resprot_v6i9e172_app1.pdf](#)]

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Abbreviations

ASL: American Sign Language

CDI: Certified Deaf Interpreter

HINTS: Health Information National Trends Survey

HINTS-ASL: Health Information National Trends Survey in American Sign Language

NIDCD: National Institute on Deafness and Other Communication Disorders

NIH: National Institutes of Health

VRI: video relay interpreting

VRS: video relay services

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Protocol

Study of Methods for Assessing Research Topic Elicitation and pRioritization (SMARTER): Study Protocol to Compare Qualitative Research Methods and Advance Patient Engagement in Research

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Abstract

Background: Involving patients as partners in research is a defining characteristic of patient-centered outcomes research (PCOR). While patients' experiential knowledge of a health condition or treatment may yield research priorities not reflected by researchers and policy makers, the methods for identifying and effectively collaborating with patients are still evolving. Patient registries and crowdsourcing may offer ease of access and convenience to both researchers and patients. Surveys and focus groups, including online modalities, have been described for prioritizing research topics. However, little is known about how these different methods compare in producing consistent priorities and similar perceptions of engagement quality among participants.

Objective: The aims of this study are (1) to compare how different engagement methods used to elicit patient priorities for research perform as measured by rankings for priorities generated and participant satisfaction; and (2) to determine characteristics of individuals choosing to participate in research prioritization activities.

Methods: Participants in the Back pain Outcomes using Longitudinal Data (BOLD) patient registry, established to evaluate the natural history of back pain among individuals 65 years and older, and participants on the Amazon Mechanical Turk (MTurk) crowdsourcing platform, to provide input on priorities for research via a questionnaire, are invited. For BOLD participants, we subsequently randomize interested respondents to 1 of 3 interactive prioritization activities to further develop priorities: a Delphi panel, an online crowd voting activity, or an in-person facilitated prioritization activity using nominal group technique (NGT). Participants involved in each activity complete a survey to evaluate the quality of the experience and a subset of these participants discuss their experience further in an interview. Descriptive statistics are used to characterize the rankings produced by each method and compare the top 5 rated topics resulting from each prioritization activity. We use rank-ordered logistic regression models to identify associations of the ranked priority topics with baseline patient characteristics. We analyze responses to the

evaluation using a mixed-methods approach wherein we tabulate responses to Likert-scale questions and use content analysis to enumerate themes emerging from interviews for the 3 activities.

Results: In Phase I, we invite approximately 3000 BOLD participants and 500 Amazon MTurk workers to complete a research topic prioritization survey. Based on these results, we include additional topics into a subsequent prioritization survey. In Phase II, we invite BOLD participants to join 1 of 3 activities: 90 participants for Delphi panel, 100 participants for crowd voting, and 60 participants for focus groups. Of the Phase II participants, 30 will be interviewed to evaluate the activities.

Conclusions: This study informs decisions about how to conduct outreach to patient registry participants for providing input on research priorities, how individuals 65 years and older wish to participate in engagement activities, and how different research prioritization methods compare in terms of rankings generated and participant satisfaction.

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KEYWORDS

patient involvement; qualitative research; research priorities; back pain

Introduction

The direct involvement of patients as partners in research is a defining characteristic of patient-centered outcomes research (PCOR). Involvement of patients throughout the research process—starting with the identification of the research question—ensures that the research conducted centers on evidence gaps that patients face when making decisions about their healthcare. Without patient representation, research agendas do not align with information needs of greatest importance to patients [1]. Funding agencies, government organizations, and advocacy organizations at the local, national, and international levels often establish priorities for future research and funding using diverse approaches with varying levels of patient involvement in the process [2-6]. Despite the time and resources dedicated to this important effort, little is known about how different prioritization methods compare in participant experience and priorities generated.

One barrier cited for greater patient involvement is the ability to identify patients interested and able to participate in research activities [2]. Traditionally, representatives from formal patient advocacy organizations provide the patient perspective in priority-setting activities, yet such formal representation is not always available and may represent a different perspective than that of the broader patient community.

One example is low back pain (LBP), one of the most important causes of functional limitations and disability worldwide [7,8]. Despite the prevalence of LBP, national patient advocacy organizations focused on this health condition do not exist. In this scenario, as with other diseases and health conditions without formal patient organization representation, research agendas are often set without the patient perspective fully represented.

Patient registries provide an opportunity to address this gap. Patient registries are developed to collect data on a defined patient population with a specific disease or condition. To better understand the effectiveness, safety, and cost-effectiveness of interventions for older patients with low back pain, the Back pain Outcomes using Longitudinal Data (BOLD) study, funded in 2010 by the Agency for Healthcare Research and Quality, established a large, community-based registry of older patients with LBP [9]. Leveraging this research infrastructure provides

one potential avenue for involving patients in topic prioritization, yet little is known about the feasibility or predictors of participation in this process. Newer approaches to involvement, such as social media and crowdsourcing platforms, are also emerging as ways to expand outreach and obtain input from broader audiences. For example, Amazon created a crowdsourcing Internet marketplace, Mechanical Turk (MTurk), which allows individuals to participate in activities—a number driven by research interests [10]. Further exploration of how these communities support PCOR is needed.

With Patient-Centered Outcomes Research Institute (PCORI) funding, we aim to compare different methods for obtaining input from patients on future research topics in both participant experience and priorities generated. We will test the hypotheses that the different methods produce similar rankings for research priorities but differ in participant-rated experience with methods with greater participant interaction receiving better ratings. This 2-phase study first assesses participant characteristics and research priorities from 2 populations: participants in the BOLD registry and participants from the MTurk platform. In the second phase, different interactive methods engaging patients in research prioritization among BOLD registry participants are compared.

Methods

Patient Engagement in the Research Process

Patient engagement is a core component of PCOR processes with the goal of improving the quality and relevance of research [4]. Patient engagement in this study occurs through direct involvement of a patient partner on the research team (Ms Scott), discussions with patient advisors at each site, and outreach to the CERTAIN Patient Advisory Network Back Pain Research Patient Advisory Group [11], a committee established by researchers at the University of Washington (UW) for the purpose of supporting patient engagement across a number of ongoing research initiatives, including BOLD. Our patient partner participates in all research team meetings as an equal member in all decisions. Patient partners at BOLD study sites assist with iterative study material development. Finally, input on study activities is obtained through quarterly meetings held with the CERTAIN Patient Advisory Network Back Pain Research Patient Advisory Group, a group of 10 individuals

with back pain who convene to discuss a number of ongoing and developing research projects. Standing time on the agenda allows for study updates, requested input on study activities, and general discussion about results and findings.

Study Overview

This is a 2-phase study (Figure 1). The first phase elicits research priorities from 2 different patient populations (the BOLD registry and MTurk) via questionnaire. The second phase uses random assignment of BOLD registry respondents from Phase I to participate in 1 of 3 subsequent prioritization activities: (1) focus group using nominal group technique (NGT), (2) modified Delphi process, and (3) online crowd voting. These methods vary in the level of interaction between participants and mode of involvement. During each activity, participants convene to review and prioritize the list of topics (both existing and newly generated) from Phase I.

Institutional Review Board Approval

The institutional review boards (IRBs) at all collaborating institutions (UW, Henry Ford Health System [HFHS], and Kaiser Permanente, Northern California [KPNC]) reviewed and approved the protocols for this study.

Phase I Study Procedures

Participant Eligibility and Recruitment

The BOLD registry consists of older adults with back pain. The inclusion and exclusion criteria for BOLD is presented in Textbox 1. Two of the original 3 BOLD clinical sites, KPNC and HFHS in Detroit, MI, participated in the Study of Methods for Assessing Research Topic Elicitation and pRioritization

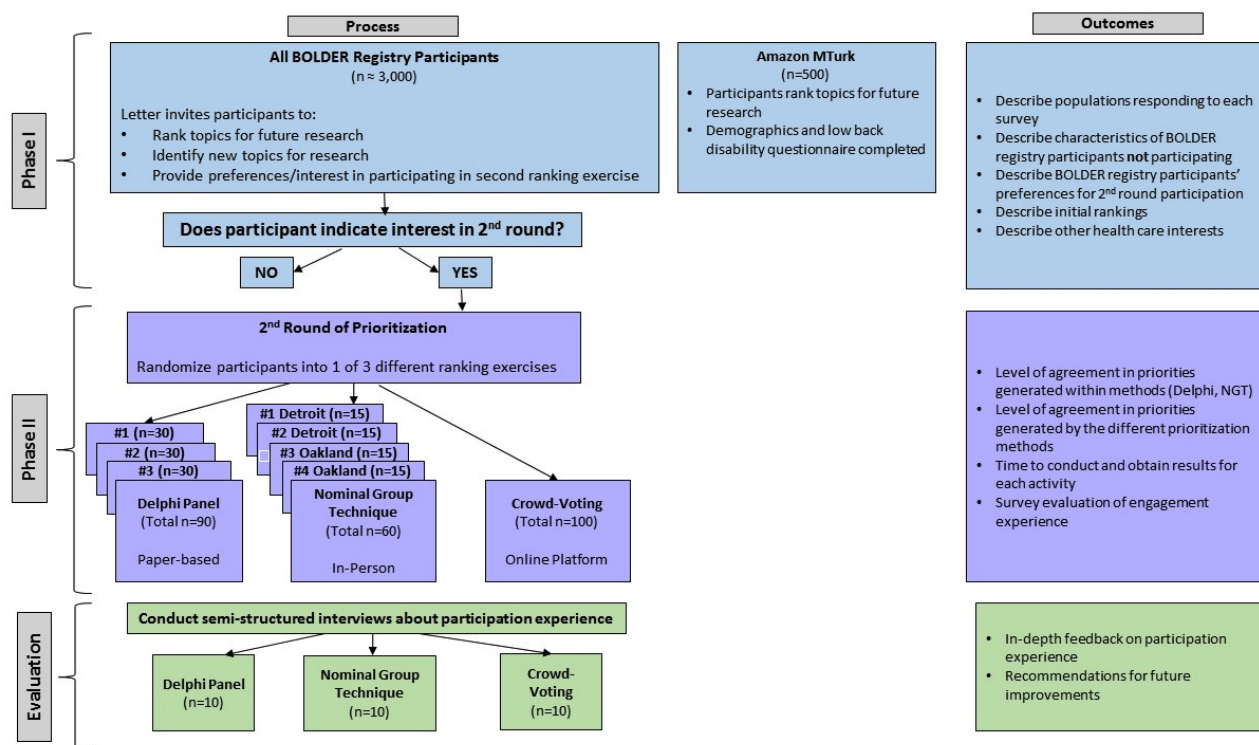
(SMARTER) study [9]. The sites represent diversity in patient demographics and clinical experience [9]. At the time of the SMARTER study initiation, a total of 4131 patients were enrolled in the BOLD registry (3164 at Kaiser and 967 at Henry Ford), with a 1-year follow-up retention rate of 85%. BOLD registry participants at the 2 participating sites (KPNC and HFHS) with current contact information completing 24-month follow-up are eligible to participate in the prioritization activity.

MTurk

The Amazon MTurk platform provides access to an online community interested in providing input on an array of activities, including research, requests for completion of basic tasks, and participation in opinion polls [10]. MTurk reports more than 500,000 registered users (MTurk workers) throughout the world.

MTurk workers with an active account registered in the United States are eligible to participate in the crowdsourcing prioritization activity. MTurk workers screen for the prioritization activity or human intelligence task (HIT) through a questionnaire accessed through the MTurk platform. The posted HIT to prioritize research topics in LBP will offer workers US \$0.10 for completing the initial screening questionnaire and once approved, an additional US \$0.75 to complete the prioritization task. Incentives are directly credited to the participants' Amazon account. Workers selecting to complete our HIT first complete the Roland Morris Disability Questionnaire (RDQ) [12], a validated measure for back pain, and the primary patient-reported outcome measure in the BOLD registry. Participants who score a 7 or greater on the RDQ are invited to continue and complete a topic prioritization activity.

Figure 1. Study overview.



Textbox 1. BOLD registry inclusion and exclusion criteria.

Criteria

- Inclusion criteria
 - Age 65 years and greater
 - Primary care visit for back pain based on ICD9 code
- Exclusion criteria
 - Healthcare encounter for back pain within 6 months
 - Previously contacted for registry participation
 - Prior lumbar spine surgery
 - Developmental spine deformities
 - Inflammatory spondyloarthropathy
 - History of cancer within the past 5 years excluding non-melanomatous skin cancer
 - History of HIV within past 5 years
 - No telephone
 - Planning on leaving health system within the next 12 months
 - Unable to understand English
 - Severe mental impairment that would interfere with answering questions

Questionnaire Development

Materials developed for this study include the invitation for participation, instructions, and a prioritization questionnaire. Invitation letters include a short introduction to PCOR, explanation of the study goals, and a list of research topics for prioritization adapted from topics identified and published in 2013 by back pain primary care clinicians and researchers [13]. Instructions guide participants to review the list, provide (if desired) up to 5 additional topics not listed, and from this list, rank their top 5 research topic priorities. Participants are instructed to rank their highest priority with the number 1.

Data Collection**BOLD Registry**

Research coordinators at each site approach recruitment by mailing questionnaires to all eligible participants enrolled from their respective health system. Participants have the option to submit responses via postage paid mail or to complete the questionnaire by phone. Participants not responding within 14 days of initial outreach (returned questionnaire or opt-out form) receive a follow-up phone call from BOLD research coordinators. All responses are entered into a secure and encrypted system maintained at the registry site.

MTurk

Eligible MTurk workers complete a topic prioritization questionnaire through a unique survey link. Participants review the list of priorities (identical to those provided to the participants from the BOLD registry), provide (if desired) up

to 5 additional topics not listed and from this list, rank their top 5 research topic priorities. In addition to the topic prioritization, workers provide basic demographic information (Textbox 2). Inclusion of the unique MTurk identification code is optional but required for payment to the appropriate MTurk account. The HIT closes after 1 month or once 500 HITs are completed.

Data Management

The UW serves as the Data Coordination Center for the BOLD registry and serves in the same capacity for this study. The UW Data Coordination Center coordinates the recruitment and follow-up of study participants across sites and provides a common infrastructure for the management of study data. Research coordinators receive all returned questionnaires and enter data into Research Electronic Data Capture (REDCap) [14], a software platform specifically designed for electronic data capture in research studies.

Phase II Study Procedures**Participant Eligibility and Recruitment**

Participants from BOLD Phase I indicating willingness to participate in a second, interactive topic prioritization activity are eligible for randomization into 1 of 3 different activities: focus groups using NGT, a 2-round modified Delphi process, or an online crowd voting activity. We randomize eligible participants taking into account individual preference for activity. The MTurk platform prohibits the collection of identifiable information, thus, MTurk participants are excluded from Phase II activities [15].

Textbox 2. Demographic information collected for participants.

Demographic information

- Age
- Sex
- Race
 - Caucasian
 - Black or African American
 - Asian
 - Native American Indian, Native Alaskan, Native Hawaiian or other Pacific Islander
 - Other
- Ethnicity
 - Hispanic
 - Non-Hispanic
- Education
 - Less than high school graduate
 - High school grad or obtained General Education Development (GED)
 - Some college
 - Vocational, technical, trade, or associate's degree
 - 4-year college graduate
 - Professional or graduate degree
- Employment
 - Employed, full time
 - Employed, part time
 - Not employed, looking for work
 - Unable to work, not employed, not looking for work
 - Retired
- Marital status
 - Married
 - Living with a partner
 - Divorced/separated

UW research staff recruit participants randomized to each activity by phone approximately 6 weeks prior to the planned start of each activity. For recruitment calls, study staff describe the activity that the participant is invited to join, including the purpose, the goals of the activity, what occurs during the activity, the expected time commitment, the participants' role in the activity, and incentives for participation. Recruitment continues until capacity is reached for all planned engagement activities. We exclude participants for Web-based engagement (ie, crowd voting) if they do not have ready access to a computer or an active email address. Research staff will contact consented participants at 2 weeks and again 2 days prior to the activity as a reminder of the event and to answer any questions.

Priority-Setting Activities Overview

Standard materials developed for all activities include a common-language overview of the project, goals for the activity, and instructions on the ranking process. In addition, each participant receives a full list of topics ranked during Phase I appended with new topics identified by participants. Excluding descriptions of and instructions for each specific activity, all preparation materials are designed for consistent messaging across all methods to reduce variation in external factors that could influence the experience or outcomes. All participants complete a consent form and brief demographic form prior to the prioritization activity ([Textbox 2](#)).

Focus Group with Nominal Group Technique

Focus group with NGT is a structured group discussion method used to generate consensus [16,17]. The method combines individual work and thought for idea generation with structured interactive group discussion [2,18]. In this manner, each individual develops and contributes ideas ensuring that no one perspective dominates the discussion or activity. We plan to hold in-person focus groups at each study site with up to 30 participants from each site (10 people per group). Priority lists will be produced in multiple rounds during the focus groups. We plan to audio-record and transcribe the focus groups. Participants receive US \$100 at the conclusion of the activity for an expected 4 hours total time for participation, including preparation time.

Modified Delphi

Modified Delphi uses a series of questionnaires with controlled feedback to systematically and efficiently obtain input from respondents with desired knowledge and experience in a given area [16,17,19]. Unlike focus groups with NGT, the Delphi method does not require in-person interaction, rather it uses written responses to exchange ideas and information [18]. For the purpose of this activity, we adopt a common practice and modify the method to 2 rounds in which the initial questionnaire provides topics for ranking rather than generating them de novo. We plan to conduct 3 modified Delphi activities among 3 different groups, with each group consisting of 30 participants. Conducting 3 separate modified Delphi activities allows for assessment of how this method performs across randomized samples. In the first round, we provide participants with a list of prioritized topics plus newly identified topics from Phase I with instructions to indicate importance of individual topics using a 5-point Likert scale. When all completed questionnaires are received back from all participants within a group, UW investigators summarize the findings and develop a second questionnaire to send back to participants. During the second round, participants review the prioritized list generated by the group in the first round and revise their rating of the topics, should they choose to do so. Participants receive US \$50 at the conclusion of the activity for an expected 2 hours total time for participation, including preparation time.

Online Crowd Voting

Online crowd voting uses an Internet community platform allowing participants the opportunity to submit ideas, vote on existing ideas, and interact with others through online discussion. The crowd voting activity brings together up to 100 people with LBP for online discussion and voting through a secure Internet-based program called IdeaScale [20]. This activity occurs over the course of 1 month. Participants create accounts to access the online private community allowing the opportunity to vote on topics for LBP research, discuss topics that are posted, and share new topics. Participants will be asked to sign in to the community at least twice over the course of the 1-month time period. Minimal group moderation led by study staff will occur over the course of the activity to support community involvement. Participants receive US \$25 at the conclusion of the activity for an expected 1-hour total time for participation including preparation time.

Evaluation

Participants evaluate the quality of experience and perceived effectiveness of each method for generating topics. Evaluation questions assess how effective each method performs in meeting overarching goals of PCOR as trustworthy, fair, balanced, legitimate, respectful, and accountable [3,21]. Questions evaluating process and outcomes include items adapted from work by Van De Ven and Delbecq [18] as part of a comparative effectiveness analysis of group decision-making processes, participant ratings on perceived satisfaction with the number of topics generated, and perception that the group process is an effective way to provide input. We plan to include open-ended questions to elicit input on the aspects that participants liked most and least for each engagement activity and if participation resulted in a change in priorities ranked. Participants of the modified Delphi process and crowd voting activity receive the questionnaire via mail or the Internet at the end of the prioritization activity. Individuals participating in the focus group receive the evaluation questionnaire in person immediately following the activity.

Finally, participants are invited to provide additional feedback via a phone interview to elicit in-depth feedback on experience and satisfaction with involvement. Up to 30 interviews with participants from each of the different interactive engagement activities (ie, 10 Delphi participants, 10 focus group participants, and 10 crowd voting participants) participate in interviews. We select interviewees representing a range (negative and positive) of responses from the evaluation questionnaire. We record interviews, with consent, for transcription purposes.

Data Management

Data collected in Phase II includes focus group transcripts, Delphi surveys, online crowd voting activity, evaluation surveys, demographic surveys, and evaluation interview transcripts. Audio recordings and transcriptions of focus group discussions and evaluation interviews are stored on a secure and encrypted system maintained at UW. UW research staff enter Delphi survey data directly into a REDCap database. IdeaScale exports data from the online community at the conclusion of the activity for upload into the study database.

Analysis

Phase I

We plan to describe the characteristics of the populations participating in each prioritization activity, including the initial paper-based questionnaire mailed to all BOLD registry participants and MTurk activity. We will evaluate, compare, and describe the characteristics of BOLD registry patients who elect to participate further compared to those who do not. Patient characteristics will include geographic location, age group (65 to 74, 75 to 80, greater than 80 years), gender, pain as measured by the 0 to 10 point numeric rating scale (NRS), disability as measured by the RDQ, education, marital status, and duration of pain.

Phase II

We will describe the characteristics of the populations participating in each prioritization activity (focus group with

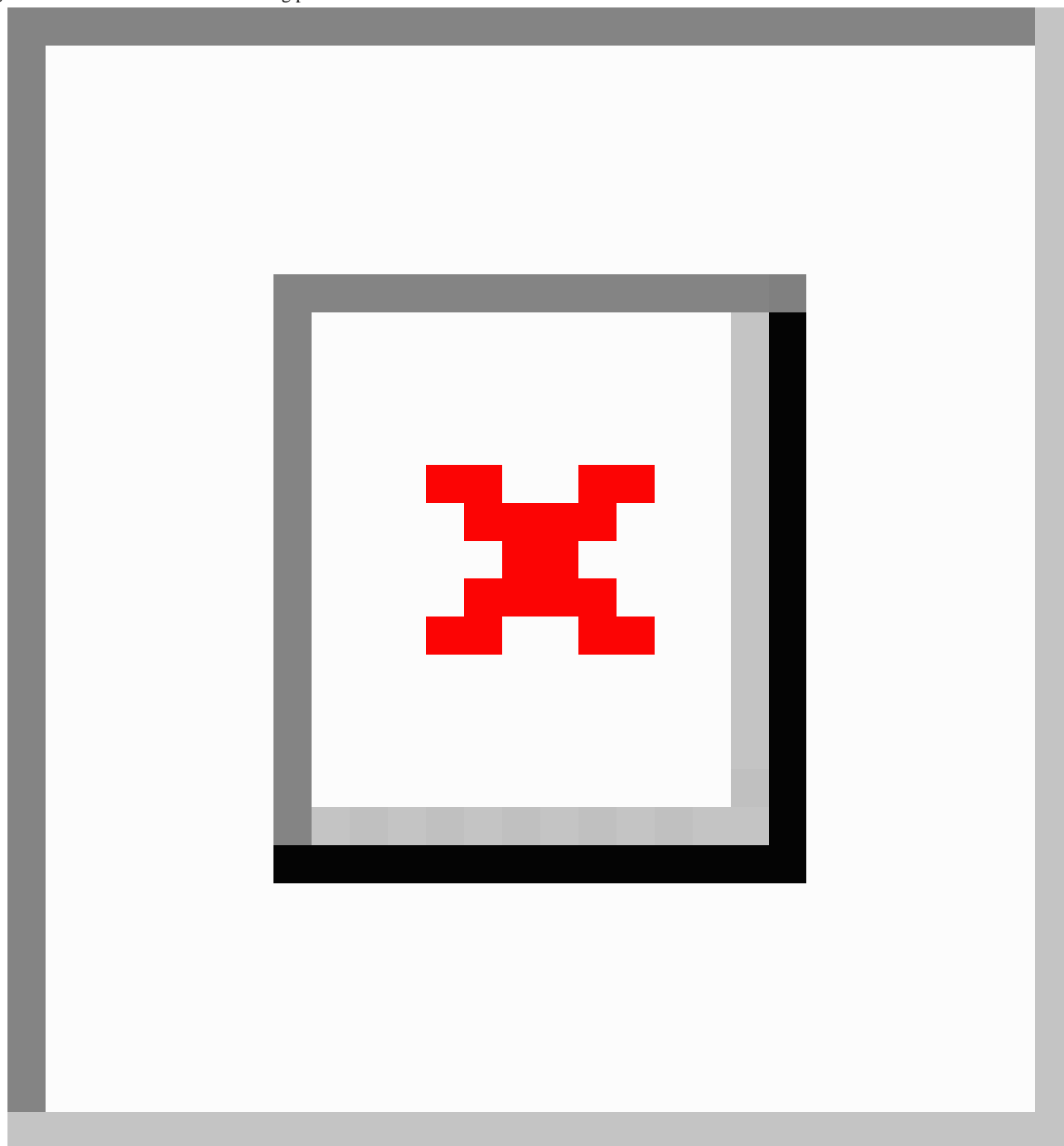
NGT, modified Delphi process, and crowd voting). To identify potential bias among those who choose to participate versus those who do not, we will analyze the characteristics of non-responders in the different groups compared to responders across Phase II activities. We will evaluate the primary hypothesis that the different methods produce similar priorities by comparing the top 5 highest rated topics resulting from each prioritization activity using descriptive statistics. We will use rank-ordered logistic regression models to identify associations of the ranked priority topics with baseline patient characteristics. In addition, we will report on the number and type of new topics identified by respondents in each activity.

We will evaluate the secondary hypothesis that participants will prefer methods with greater participant interaction as defined both by in-person interaction and ability to engage in discussion with other participants (focus groups with NGT greater than online crowd voting greater than modified Delphi process

greater than mailed survey) through analysis of Likert-scale questions using descriptive statistics for each activity. We will conduct a directed content analysis of transcribed interviews to better understand participant experiences and perceptions of prioritization activities.

Results

We provide an overview of our anticipated recruitment ([Figure 1](#)). In Phase I, we will invite approximately 3000 BOLD participants and 500 Amazon MTurk workers to complete a research topic prioritization survey. Based on these results, we will include additional topics into a subsequent prioritization survey. In Phase II, we will invite BOLD participants to join 1 of 3 activities: 90 participants for Delphi panel, 60 participants for focus groups, 100 participants for crowd voting ([Figure 2](#)). Of the Phase II participants, 30 will be interviewed to evaluate the activities.

Figure 2. Screenshot of the crowd voting platform.

Discussion

Principal Findings

This study assesses how different methods perform in generating reproducible research prioritization lists, and perhaps more importantly, in participants' perception of the quality of the engagement experience. Such comparative studies are rare [18]. Two methods—the focus groups with NGT and modified Delphi process—are well described in the literature and are among the most commonly used methods [2,16,17]. The third, crowd voting, is a novel approach and reflects increasing interest in how Internet-based platforms may enhance survey methods to reach a large and diverse population to generate data while allowing for group interaction [2,22]. This study allows for

comparison across different prioritization methods in generating similar results and perceptions of participant's experience.

The intent of our proposed study is to add to the evidence to further support the conduct of priority-setting activities involving patients to inform the development and planning of research agendas. This is an area of growing focus. For example, the James Lind Alliance, a United Kingdom-based initiative established in 2004, brings together patients, caregivers, and clinicians for the purpose of identifying and prioritizing research priorities [23]. The PCORI brings together patients, caregivers, clinicians, and other healthcare stakeholders to identify priorities to shape areas for research funding. Our hope is to inform new methodological standards on involving patients in research

activities and for topic prioritization, important building blocks for PCOR.

Two methods proposed in this study—crowdsourcing and crowd voting—are innovative. Crowdsourcing via the Internet is appealing in its ability to rapidly obtain responses from a broad and potentially diverse population [22,24]. Crowd voting, one example of crowdsourcing using open-source platforms, allows for interaction among participants through polling and open comments. This approach invokes transparency, as participants are able to view the activity and results as they unfold. Crowdsourcing requires minimal infrastructure to develop and permits rapid deployment [24]. In a previous study soliciting participants from MTurk, 500 eligible responses were obtained within 1 week [24]. These features make it appealing as a substitute for traditional survey-based methods that often require significant resources and time for distributing and collecting responses. Developing evidence using this novel approach and comparing it to older methods will advance and improve PCOR methods by incorporating emerging technologies into the research armamentarium. Further, if the PCOR field is going to embrace new technologies, we need to understand how they operate, particularly in older populations.

This study also explores how patient registries facilitate patient input and involvement in research outside of consented activities. Patient registries are organized to systematically collect data on a defined population to support clinical, research, and/or policy endeavors. When properly designed, registries provide important insight on the natural progression of disease and allow for assessment of the effectiveness or post-market safety of medications or devices as examples. Registry organizers and participants dedicate valuable time and effort to develop these important resources—learning with and from participants to support future work seems a natural next step.

Patient engagement is a core component of PCOR with the goal of improving the quality and relevance of research. Early involvement of our patient-partner during the research proposal development shaped early versions of the study protocol. Subsequent to receiving funding, her participation in research team meetings to further refine the protocol and design directly shaped the approach for recruitment and retention. For example, early plans included a token incentive of US \$1 along with the initial prioritization questionnaire to participants. Based on Ms Scott's input that this could demonstrate a perceived value to the importance of a patient's perspective, the decision was made to instead place the funds towards staff-led outreach. Further,

her involvement shaped the patient-facing materials. An important change made based on Ms Scott's observations included a reorder of the listed priorities presented in the questionnaire. Initial drafts of the topics started with content about employment and work-related issues. As a retired person herself, Ms Scott recommended we change the order of priorities to avoid initial participant impressions that the questionnaire is not relevant as the majority of BOLD participants are over 70 years of age and no longer working. Other recommended changes to initial drafts included reducing the number of pages, increasing font size, clarifying instructions, and reducing technical terminology to improve comprehension.

One limitation of patient registries is the defined inclusion and exclusion criteria. The BOLD registry includes only individuals 65 years and older from integrated healthcare systems and thus, findings from the prioritization activities may not reflect experiences of younger individuals receiving care in different environments and health systems. Conducting a prioritization activity among non-BOLD registry participants (MTurk) allows for assessing generalizability and comparability with other methods. Mailed surveys and MTurk are similar in that participants are invited to participate to rank research priorities void of interaction with other participants. In this study, one difference is that for BOLD registry participants, the prioritization activity is conducted using traditional paper-based survey methods whereas MTurk is conducted online and is open to a broader and more heterogeneous audience for participation. Differences may exist between individuals choosing to participate versus those who do not. While we have the ability to assess these differences among BOLD registry participants, similar demographic and clinical information is not available for the MTurk population. Further, the MTurk platform policies prohibit collecting personal information, thus involving MTurk participants in Phase II activities is not possible. This limits the use of crowdsourcing platforms, such as MTurk, to non-interactive activities.

Conclusion

This study provides a unique and rare opportunity to compare qualitative research methods, and to our knowledge, is the first study assessing such methods for the purposes of advancing patient engagement in research. Findings from the SMARTER study will provide funders, researchers, policy-makers, and organizations involving patients in the process of generating and prioritizing research evidence about how different approaches compare.

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Authors' Contributions

DCL, BAC, MRS, TCE, DLP, and JGJ developed the original concept of the study. ALA, DRN, ZB, SOL, and ART participated in the design and protocol development of SMARTER. All authors read and approved the manuscript as written.

Conflicts of Interest

DCL, MRS, TCL, DLP, DRN, ALA, ZB, ART, and SOL report no competing interests. JGJ serves as a consultant for HealthHelp, a radiology benefits management company. He is a co-founder and stockholder of PhysioSonics, a high intensity focused ultrasound company. In the past 3 years he has served as a consultant for UpToDate (Wolters-Kluwer) and as a consulting medical editor for Google. BAC is a cofounder of C-SATS, an online system for appraising technical skills and technique through crowdsourcing. However, the present work was not affiliated with or did not benefit C-SATS in any way.

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Abbreviations

BOLD: Back pain Outcomes using Longitudinal Data

HFHS: Henry Ford Health System

HIT: human intelligence task

KPNC: Kaiser Permanente, Northern California

LBP: low back pain

MTurk: Mechanical Turk

NGT: nominal group technique

PCOR: patient-centered outcomes research

PCORI: Patient-Centered Outcomes Research Institute

RDQ: Roland Morris Disability Questionnaire

REDCap: Research Electronic Data Capture

SMARTER: Study of Methods for Assessing Research Topic Elicitation and pRioritization

UW: University of Washington

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Proposal

Cancer Predisposition Cascade Screening for Hereditary Breast/Ovarian Cancer and Lynch Syndromes in Switzerland: Study Protocol

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Abstract

Background: Breast, colorectal, ovarian, and endometrial cancers constitute approximately 30% of newly diagnosed cancer cases in Switzerland, affecting more than 12,000 individuals annually. Hundreds of these patients are likely to carry germline pathogenic variants associated with hereditary breast ovarian cancer (HBOC) or Lynch syndrome (LS). Genetic services (counseling and testing) for hereditary susceptibility to cancer can prevent many cancer diagnoses and deaths through early identification and risk management.

Objective: Cascade screening is the systematic identification and testing of relatives of a known mutation carrier. It determines whether asymptomatic relatives also carry the known variant, needing management options to reduce future harmful outcomes. Specific aims of the CASCADE study are to (1) survey index cases with HBOC or LS from clinic-based genetic testing records and determine their current cancer status and surveillance practices, needs for coordination of medical care, psychosocial needs, patient-provider and patient-family communication, quality of life, and willingness to serve as advocates for cancer genetic

services to blood relatives, (2) survey first- and second-degree relatives and first-cousins identified from pedigrees or family history records of HBOC and LS index cases and determine their current cancer and mutation status, cancer surveillance practices, needs for coordination of medical care, barriers and facilitators to using cancer genetic services, psychosocial needs, patient-provider and patient-family communication, quality of life, and willingness to participate in a study designed to increase use of cancer genetic services, and (3) explore the influence of patient-provider communication about genetic cancer risk on patient-family communication and the acceptability of a family-based communication, coping, and decision support intervention with focus group(s) of mutation carriers and relatives.

Methods: CASCADE is a longitudinal study using surveys (online or paper/pencil) and focus groups, designed to elicit factors that enhance cascade genetic testing for HBOC and LS in Switzerland. Repeated observations are the optimal way for assessing these outcomes. Focus groups will examine barriers in patient-provider and patient-family communication, and the acceptability of a family-based communication, coping, and decision-support intervention. The survey will be developed in English, translated into three languages (German, French, and Italian), and back-translated into English, except for scales with validated versions in these languages.

Results: Descriptive analyses will include calculating means, standard deviations, frequencies, and percentages of variables and participant descriptors. Bivariate analyses (Pearson correlations, chi-square test for differences in proportions, and t test for differences in means) will assess associations between demographics and clinical characteristics. Regression analyses will incorporate generalized estimating equations for pairing index cases with their relatives and explore whether predictors are in direct, mediating, or moderating relationship to an outcome. Focus group data will be transcribed verbatim and analyzed for common themes.

Conclusions: Robust evidence from basic science and descriptive population-based studies in Switzerland support the necessity of cascade screening for genetic predisposition to HBOC and LS. CASCADE is designed to address translation of this knowledge into public health interventions.

Trial Registration: ClinicalTrials.gov NCT03124212; <https://clinicaltrials.gov/ct2/show/NCT03124212> (Archived by WebCite at <http://www.webcitation.org/6tKZnNDBt>)

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KEYWORDS

public health genetics; public health interventions; family communication; cancer surveillance; patient-provider communication; quality of life; psychosocial support; family-based interventions

Introduction

Breast, colorectal, ovarian, and endometrial cancers constitute approximately 30% of newly diagnosed cancer cases in Switzerland, affecting more than 12,000 individuals annually [1]. About 2%-15% of incident cases are associated with known hereditary cancer syndromes. Several hundred Swiss patients diagnosed with any of these cancers are likely to carry known pathogenic germline variants [2]. Approximately 5-10% of breast cancer cases and 10%-15% of epithelial ovarian cancer cases develop due to single gene mutations that are passed down in the family, such as the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes [3,4]. Germline *BRCA* mutations are associated with most hereditary breast and ovarian cancer (HBOC) cases. Women with *BRCA* mutations have a 55%-70% risk of breast cancer and 17%-59% risk of ovarian cancer by age 70, while the corresponding lifetime risks in the general population are 12% and 1.3%, respectively [5-7]. HBOC cases have an increased risk of cancer at a younger age, often before recommendations for routine screening apply [8,9]. The prevalence of *BRCA* mutations varies considerably among ethnic groups and geographical areas. In Caucasian populations, the prevalence of *BRCA* pathogenic variants is estimated at 1:400 to 1:500, whereas the frequency of three founder mutations in the Ashkenazi Jewish population is 1:40 [10-12]. About 21% of Swiss breast cancer patients are diagnosed younger than 50 years old, which may indicate genetic susceptibility [13,14].

Lynch syndrome (LS), previously known as hereditary nonpolyposis colorectal cancer, is an inherited disorder, associated with 22%-74% lifetime risk for colorectal cancer, 14%-71% risk for endometrial cancer, 3%-22% risk for ovarian cancer, up to 13% risk for gastric cancer, and up to 25% risk for urothelial cancer [15]. LS accounts for about 2%-5% of colorectal cancer and endometrial cancer burden, as well as increased risk for several other malignancies including gastric, ovarian, small bowel, urinary and biliary tract, pancreatic, and sebaceous gland tumors [16]. Individuals with LS have a 10%-74% risk of colorectal cancer, and a 14%-71% risk of endometrial cancer by age 70, while the corresponding rates in the general population are 5.5% and 2.7%, respectively [17,18]. A hallmark of LS is early age of onset, usually before the age of 50 at which recommendations for routine screening apply [15,19]. Most LS-related tumors are characterized by a high level of microsatellite instability (MSI-H), which is distinctive of cancers with a defective DNA mismatch repair (MMR) mechanism [20]. Diagnosis of LS involves a sequential process including prescreening with MSI testing and immunohistochemistry analysis to determine expression of the main MMR proteins (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in tumor tissues. Additional *MLH1* promoter methylation testing eliminates the possibility of loss of *MLH1* expression due to epigenetic mechanisms or identification of a somatic *BRAF* pathogenic variant (c.1799T>A/p.V600E). In the case of pathological prescreening results, germline analyses of two or

more MMR genes (*MLH1/PMS2* and/or *MSH2/MSH6*) and search for *EPCAM* deletions confirm the diagnosis. Germline mutations in the *MLH1* and *MSH2* genes account for up to 90% of LS cases, whereas *MSH6* and *PMS2* mutations account for most of the remaining cases [21]. The Amsterdam Criteria II and Revised Bethesda Guidelines are used in clinical practice for identifying individuals concerned about LS [22]. These guidelines are not sensitive enough and may miss up to 30% of LS cases [23]. Even if the population prevalence of LS is estimated at 1:440 [24], LS is vastly underdiagnosed compared to HBOC.

Germline mutations connected to HBOC and LS are inherited in an autosomal dominant manner. De novo mutations are rare in these syndromes. For every identified mutation carrier, there are multiple family members who may carry the same mutation. First- and second-degree relatives and first cousins of known carriers have 50%, 25%, and 12.5% probability for inheriting the respective cancer predisposition. The availability of cancer genetic services (counseling and testing) for HBOC and LS is a significant milestone for effective cancer prevention and control [25]. When a pathogenic variant is identified, relatives can be tested with 100% accuracy [26]. Genetic counseling can educate patients and cancer-free individuals about cancer risk and management options according to mutation status. Physicians' attitudes [27] and coverage of cost of tests and gene panels by health insurance influence whether genetic testing is performed or not [28].

A Swiss study reported that about 11% of all breast cancer patients and 25% of those with a strong family history used genetic services [29]. These figures are lower for LS-related colorectal and endometrial cancer patients, suggesting that many Swiss mutation carriers and their family members may not benefit from advances in health care technology and medical diagnostics. HBOC and LS patients are at an increased risk of secondary cancers and can benefit from intensive surveillance, pharmacoprevention, or prophylactic surgery. Prophylactic surgery such as mastectomy, bilateral salpingo-oophorectomy, and hysterectomy should be discussed with women affected with HBOC or LS [30]. Subtotal colectomy can be considered for LS patients with colorectal cancer [18]. Family members who test positive benefit from high-risk management care starting at age 25-30, or 10 years before the earliest age of breast cancer onset in the family. This care can include annual breast magnetic resonance imaging, mammograms, pelvic ultrasound for women (HBOC) [31], and annual colonoscopy starting at age 20-25, or 2-5 years before the earliest age of colorectal cancer onset in the family, whichever comes first (LS) [15,18]. Implementing clinical recommendations and providing high-quality surveillance to patients during survivorship requires excellent coordination of health care services provided in high-risk clinics [32-35].

Mutation carriers identified through complete genetic analyses are asked to communicate test results to relatives and encourage them to use genetic services. This process is highly variable from family to family, with less than 40% of high-risk relatives using genetic services, suggesting a lack of effective communication [36,37]. Lack of understanding of genetic information combined with family conflicts most likely inhibits

disclosure of test results to relatives [38,39]. In Switzerland, the Federal Act on Human Genetic Testing (HGTA) is the legal regulation that directly applies to the clinical practice of genetic analysis. HGTA states that a physician is not allowed to disclose genetic test results to anyone except the tested individual or their legal representative. Results can be disclosed to family members, spouses, or partners only with the explicit consent of the tested individual. If the tested individual refuses to disclose this information, if they are deceased, have disappeared, or are unable to consent in the absence of an authorized delegate, the physician can seek help from the expert commission on professional confidentiality. The physician may apply to the appropriate cantonal authority to be released from the duty of professional secrecy if protecting the overriding interests of the family members, spouse, or partner requires that they receive this information. Cantonal authorities may also request an opinion from the Expert Commission for Human Genetic Testing [40]. Interventions designed to facilitate patient-provider and patient-family communication can enhance understanding of genetic information and facilitate the disclosure of test results from carriers to relatives and can contribute to more effective management of hereditary cancer. Several such interventions have been developed and tested in the United States [41-51] but should be adapted before they can be implemented in Switzerland, due to cultural and possibly legal differences.

Cascade screening is the sequential process of identifying and testing blood relatives of a known mutation carrier to determine if additional individuals carry the pathogenic variant, and proposing preventive and other clinical management options to reduce morbidity and mortality [52]. Cascade screening also reassures non-carrier relatives and excludes them from intensive surveillance, making it cost-effective and contributing to personalized medicine [53]. The Centers for Disease Control and Prevention, Office for Public Health Genomics issued evidence-based recommendations justifying genetic testing in affected individuals and relatives when there is a known family history of HBOC or other *BRCA*-related cancers, LS-related colorectal cancer, or familial hypercholesterolemia (FH). These are Tier 1 genetic conditions suitable to promoting translation of scientific breakthroughs in genetics to public health [54]. There are currently no systematic efforts to apply cascade screening for Tier 1 genetic conditions among the general population in Europe apart from the Netherlands, which successfully implemented a cascade screening program for FH. The implementation of this pioneering public health program helped identify more than 28,000 asymptomatic cases [55] and provides proof-of-concept that cascade screening can be applied in other settings [56].

Robust evidence from basic science and descriptive population-based studies in Switzerland support the necessity of cascade screening for HBOC and LS [57-67]. However, there are currently no interventions to translate this knowledge into public health. Researchers know little about the cancer status and surveillance behaviors of mutation carriers and their relatives, and their needs for psychosocial, patient-provider, and family communication support. This is especially important over time, as little is known about decisional regret associated with genetic testing, communication, and support after the

pathogenic variant has been identified in some family members but not in others, as well as impact on quality of life. A better understanding is needed of the overall response of the Swiss health care system to mutation carriers' needs for long-term coordination of cancer surveillance and prevention. Finally, there are no interventions culturally tailored for Swiss families and designed to enhance patient-provider and patient-family communication, coping, and provide decisional support.

Establishing a registry with families harboring germline pathogenic variants associated with HBOC and LS and the collection of cancer surveillance and psychosocial data over time will greatly assist in finding sustainable solutions and developing cutting-edge interventions that optimize the health care system. However, establishing cascade screening for HBOC and LS and promoting interventions for communicating hereditary cancer risks pose several challenges at the medical and social level, requiring interprofessional collaboration with stakeholders from basic research, the health care system, and social science. In response to this challenge, the Swiss Cancer Genetic Predisposition Cascade Screening Consortium was assembled in 2015 with stakeholders from various disciplines (ie, basic science, epidemiology, medicine, nursing, psychology, public health, and sociology) to conduct the CASCADE study and examine the feasibility of establishing a family-based registry and a cohort with HBOC and LS mutation-harboring families.

The specific aims of the CASCADE study are to (1) survey index cases with HBOC or LS from clinic-based genetic testing records and determine their current cancer status and surveillance practices, needs for coordination of medical care, psychosocial needs, patient-provider and patient-family communication, quality of life, and willingness to serve as advocates for cancer genetic services to blood relatives, (2) survey blood relatives identified from pedigrees or family history records of HBOC and LS index cases and determine their current cancer and mutation status, cancer surveillance practices, needs for coordination of medical care, barriers and facilitators to using cancer genetic services, psychosocial needs, patient-provider and patient-family communication, quality of life, and willingness to participate in a study designed to increase use of cancer genetic services, and (3) explore the influence of patient-provider communication about genetic cancer risk on patient-family communication and the acceptability of a family-based communication, coping, and decision support intervention with focus group(s) of mutation carriers and relatives.

Methods

Design

CASCADE is a longitudinal study using surveys and focus groups, designed to elicit factors that enhance cascade genetic testing for HBOC and LS in Switzerland. The CASCADE study will contact known mutation carriers for HBOC and LS and systematically identify and contact their relatives to determine if they have had genetic testing, if they also carry the pathogenic variant, and how they manage their risk for hereditary cancer. Repeated observations are the optimal way for assessing these outcomes. The study will also use focus groups to examine the acceptability of a family communication, coping, and decision support intervention (Phase I). [Table 1](#) presents a detailed description of assessments conducted for the study. The study protocol has been approved by the local ethics committee, while approval from ethics committees in other cantons is underway. The study will be carried out according to principles described in the Declaration of Helsinki and applicable Swiss laws and Swiss regulatory authority requirements.

Setting

This multicenter study involves contributions from oncology and genetic testing centers from three linguistic regions of Switzerland (German-, French-, and Italian-speaking). Medical directors of clinical sites are either co-principal investigators (co-PIs) or site co-investigators and will oversee recruitment procedures according to the study protocol. The PI will oversee the scientific integrity of the study, including recruitment, data collection, and data analyses. These findings will be compiled and communicated to clinical sites.

Sample and Sample Size

The CASCADE study targets individuals who have been identified through genetic testing as carrying a pathogenic germline variant associated either with HBOC or LS and their relatives (first- and second-degree, and first cousins). [Textbox 1](#) describes applicable inclusion and exclusion criteria. Index cases include male and female cancer patients and cancer-free individuals. Cancer risk associated with HBOC and LS does not apply to children, thus, the study will include only adults (≥ 18 years old). Decisions to undergo genetic testing for these conditions are made by adults deemed competent to provide informed consent and should be undertaken after individuals participate in consultation regarding the benefits and drawbacks of genetic testing. Vulnerable participants (eg, those living in nursing homes) will be excluded because they may not be able to consent to genetic testing or follow recommended cancer surveillance or preventive measures. Critically ill patients will be excluded from recruiting relatives and from focus groups to avoid increasing subject burden.

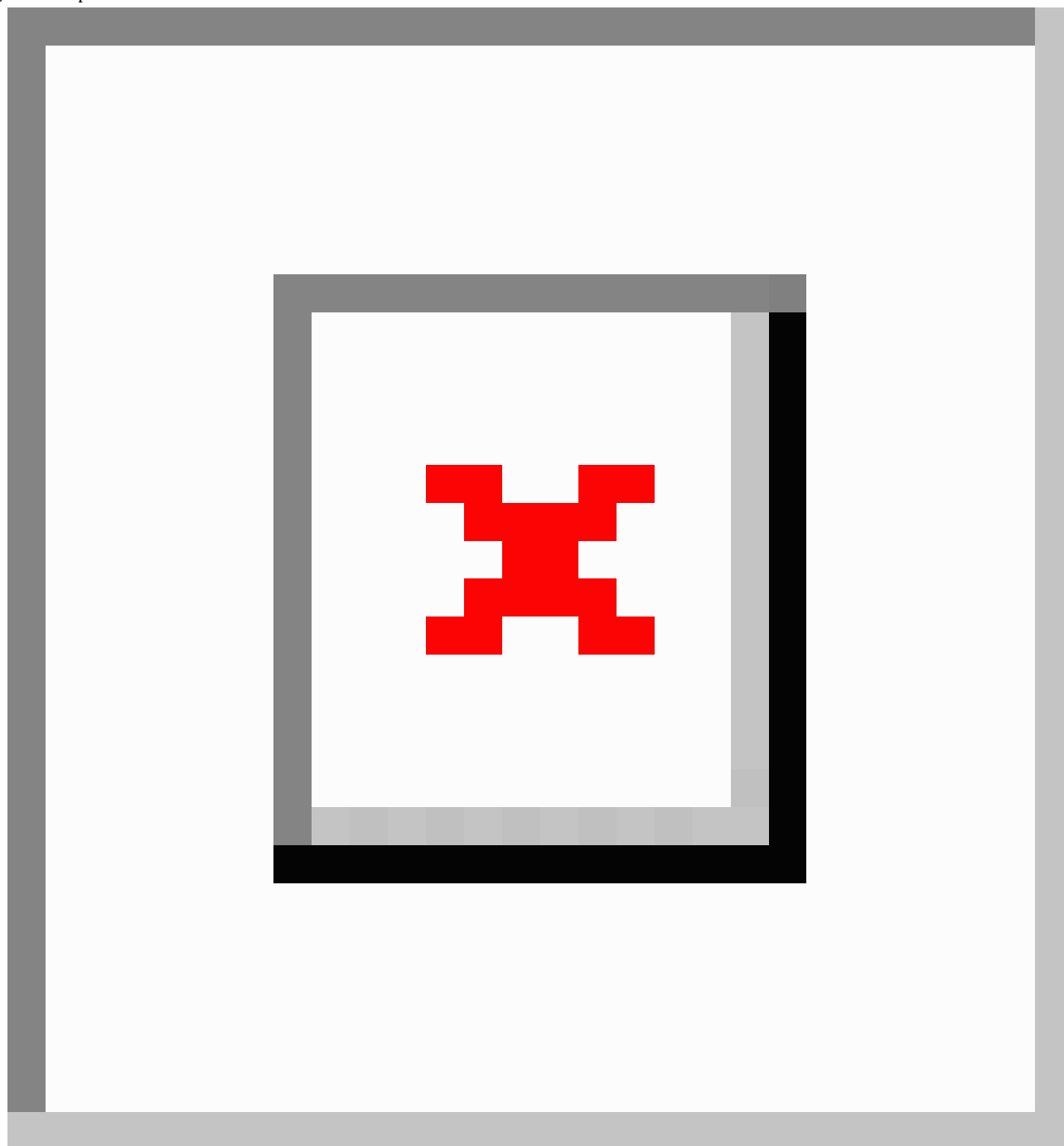
Table 1. Flow of assessments for the CASCADE study.

Phase and steps	Tasks/Procedures	Data
Selection of eligible index cases		
Random selection of families	Each clinical site provides the principal investigator (PI) with a list of the family identifications (IDs) determined by the clinical site as harboring a pathogenic germline variant. The PI randomly selects 35% of family IDs from the list with computer-generated numbers. The number of selected family IDs at each site is based on total number of family IDs at the clinical site and stratification for representative sampling.	No identifiable data for index cases are shared with the PI.
Identification of eligible index cases	Through pedigrees and family history records, each site coordinator identifies index cases (1st family member to be identified as a carrier of a germline pathogenic variant) and determines whether they can be contacted (ie, alive and living in Switzerland). If an index case cannot be contacted, site coordinators identify 1st degree relatives who carry the familial pathogenic variant, randomly select one of them (computer-generated numbers), and determine whether they can be contacted. The process is repeated until an eligible mutation carrier is identified that can initiate cascade screening in the family.	Clinical sites collect minimal data (except identifiable data) for all index cases, regardless of whether they can be reached or not. Minimum data include gender, age, mutation, cancer type, age at diagnosis, stage, age tested, alive, place of residence, preferred language.
Recruitment of eligible index cases		
Recruitment package to index cases	The medical director of each clinical site (co-PI or site co-investigator) and the site coordinator mail recruitment packages to index cases. If the index case did not receive genetic counseling at the testing site, then the recruitment package is sent to the referring physician who is asked to pass it on. Three attempts will be made to contact index cases. The medical director will inform treating oncologists about the participation of index cases.	Unique identification coding scheme enabling identifying index cases, site they were recruited from, and type of hereditary cancer syndrome (HBOC or LS). Dates recruitment packages were sent to physicians, dates the response from Index cases was received, and recruitment attempts made.
Engagement of index cases in the CASCADE study	The site coordinator receives the informed consent or participation refusal form from index cases. Index cases accepting participation receive the CASCADE survey in their preferred language and format (paper/pencil or online) from the PI. The PI creates a coding key for identifying participants and the Clinical Trials Unit creates a coding key for variables assessed in the CASCADE survey.	Identifiable information for index cases accepting participation is passed on from site coordinators to the PI. Response rate from index cases, acceptance to participate in various stages of the CASCADE study, reasons for nonparticipation and preferred language and format for survey.
Survey from index cases	The PI and the data management team receive the completed survey from index cases either in paper/pencil or online.	Assessment of data quality in each format (eg, percent missing data, outliers). Assessment of instrument reliability (Cronbach alpha and principal component analysis). Number of eligible relatives. Number of eligible relatives the index case is willing to invite. Characteristics of relatives reported by the index case. CASCADE study outcomes.
Recruitment of eligible blood relatives		
Identification of eligible relatives	Based on index cases' response to the CASCADE survey, the PI identifies eligible blood relatives the index case is willing to invite. Information about relatives is cross-referenced with pedigrees and family history information from clinical sites.	Number of relatives and degree of relationship to the index case (1st or 2nd degree relative, or 1st cousin).
Recruitment package to eligible relatives	The PI prepares recruitment packages for relatives and a personalized letter for each index case, explaining the recruitment process and asking them to pass on recruitment packages to relatives.	Unique identification coding scheme enabling matching members of the same family.

Phase and steps	Tasks/Procedures	Data
Engagement of eligible relatives in the CASCADE study	The PI receives informed consents or participation refusal forms from relatives. Relatives accepting participation receive the CASCADE survey in their preferred language and format (paper/pencil or on-line).	Response rate from relatives, acceptance to participate in various arms of the CASCADE study, reasons for nonparticipation and preferred language and format for survey completion.
Survey from relatives	The PI and the data manager receive the completed survey from relatives either in paper/pencil or on-line form.	Assessment of data quality in each format (eg, percent missing data, outliers). Assessment of instrument reliability (Cronbach alpha and principal component analysis). Number of eligible relatives willing to invite. CASCADE study outcomes.
Focus groups		
Selection of index cases and relatives	A purposeful sample of index cases and relatives accepting participation in focus groups will be selected by the qualitative methodologist and the PI.	Characteristics of index cases invited in the focus groups (preferred language, gender, mutation, type of cancer). Characteristics of families invited in the focus groups (level of support and communication).
Invitation letters for focus groups	The PI in collaboration with the qualitative methodologist will send invitation letters initially to index cases and then to families selected for the focus groups.	Acceptance rate.
Focus groups	Focus groups are organized and completed under the auspices of the qualitative methodologist.	Narrative data from focus groups.

Textbox 1. Characteristics of the target populations.

Inclusion criteria
<ul style="list-style-type: none"> • Living carriers of germline pathogenic variants associated with HBOC and LS, and their relatives (1st and 2nd degree, and 1st cousins) • Have at least one living blood relative • Both genders • Age ≥18 years old • Mentally/physically able to provide informed consent • Cancer patients and cancer-free individuals • Can read/speak German or French or Italian or English • Currently living in Switzerland
Exclusion criteria
<ul style="list-style-type: none"> • Carriers of unclassified genetic variants in <i>BRCA1</i>, <i>BRCA2</i> or <i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, <i>PMS2</i>, <i>EPCAM</i> genes • Currently not living in Switzerland • Critically ill patients not able to complete the survey • Not able to provide an informed consent • Institutionalized (eg, nursing homes) or incarcerated

Figure 1. Expected recruitment of index cases.

Estimates of sample size are based on the PI's experience, consultations with medical directors of clinical sites, and assuming average prevalence rates of 5% for hereditary breast cancer and 2-5% for hereditary colorectal cancer (the two most common manifestations of HBOC and LS), respectively. Assuming that it is feasible to recruit 10% of mutation carriers from each participating clinic, 300 index cases will be targeted for inclusion within 12 months. It is expected that around 70% of approached index cases will accept participation, meaning that 495 index cases need to be approached to reach 305. It is estimated that from each index case we will identify 2.5 relatives. Assuming a response rate of 50% among relatives, we expect to recruit approximately 381 relatives. [Figure 1](#)

presents the CONSORT [68] diagram for recruitment of expected index cases and relatives.

Recruitment Procedures for Index Cases

Participating Swiss clinical sites will record the total number of mutation-harboring families for HBOC or LS. A dedicated staff person at each clinical site, the site coordinator, will identify eligible index cases (ie, first person in the family identified as carrying a germline pathogenic variant associated with HBOC or LS), determine whether they can be contacted or not, and initiate and monitor the recruitment process. Selection of mutation-harboring families from each clinical site will involve the following steps:

1. Each site creates a list with IDs (eg, 001..., 350) corresponding to each index case and a family with a pathogenic variant.
2. The ID list is sent to the PI, who selects approximately 35% of cases with the assistance of a computer-generated random list. Identifiable information is not released until the index case accepts participation through signing an informed consent form.
3. Site coordinators retrieve the medical charts of selected index cases and decide whether the cases can be contacted by determining living status and residence.
4. If the index case is not available, then site coordinators identify first-degree relatives, who have also been identified through genetic testing as carriers of the familial pathogenic variant, and randomly (computer-generated list) select one of them.
5. Steps 3 and 4 are repeated until an index case who can be the initial contact person for the family is identified. If this process yields no results, the next family is selected.
6. All information obtained from each step is recorded, including minimum information for index cases. Minimum information includes demographics (age, gender), clinical history (tumor type, age at diagnosis, stage), and genetic testing results (including MSI and IHC tumor testing for LS patients) and is obtained from medical records. Index cases are recruited to the CASCADE study by the medical director of the respective site.

Index cases will be mailed an information letter, two copies of the informed consent form, two copies of a participation refusal form, and a stamped self-addressed envelope to return their response to the clinical site. Index cases will be informed about the objectives of the CASCADE study, participation requirements, the study plan, confidentiality, and associated risk and benefits through the informed consent form, which explicitly requires their agreement to (1) complete the CASCADE survey, (2) contact one or more of their blood relatives for the study, (3) be contacted once a year for 5 years and provide updated information about their health, and (4) participate alone or with a blood relative in a focus group. Index cases can participate in all or in some of the above study steps. The information letter explains that the minimum requirement for taking part in the CASCADE study is to complete the self-administered survey once. The refusal form asks nonparticipating index cases the reason for their refusal; this information is necessary for the validity of the study.

Site coordinators will determine whether the identified index case can be contacted or not by investigating whether they are alive and whether they live in Switzerland through hospital and civil records. If the recruitment package is returned undelivered, additional address verification methods will be used to locate a new residence. If the index case cannot be contacted a priori, coordinators will determine whether a first-degree relative can be the new index case for the family. Three attempts will be made to contact index cases for each family. If the study receives no response 6 weeks after the third attempt, a new family will be selected to preserve required sample size. Index cases will be recruited to the CASCADE study on a consecutive ongoing basis. Site coordinators will review pedigrees and family history

of index cases who accept participation to extract demographic and medical information and to record all blood relatives (first- and second-degree relatives and first cousins). Index cases will be asked to complete a self-administered survey.

When an index case has not received genetic counseling at the participating center, the invitation package for the CASCADE study will be sent by the referring physician. This is necessary because some clinical sites perform only genetic testing and the referring physician is considered the medical person who has direct knowledge of index case's genetic testing results. Site coordinators and the PI will keep track of the recruitment process. Referring physicians will make three recruitment attempts by mailing a new invitation package every 6 weeks if the index case does not respond to the invitation (either positively or negatively). Contact information (address, telephone, email) of the PI and the medical director will be provided in the information letter, so that index cases can request further information about the study at any point. A signed informed consent will be requested prior to index case's enrollment as a prerequisite for engagement in the CASCADE study.

Recruitment Procedures for Relatives

In order to alleviate ethical concerns associated with contacting blood relatives (ie, first- and second-degree relatives, and first cousins) without their explicit consent, the CASCADE study will approach them through index cases and will approach only relatives the index case is willing to contact. This recruitment method has been used in previous family-based studies with very good recruitment outcomes [69,70]. Index cases will be mailed recruitment packages to pass on to their relatives, including an information letter, two copies of the informed consent form, two copies of the participation refusal form, and a stamped self-addressed envelope for relatives to return their response to the PI. Relatives' identifiable information will not be released to the PI. By returning a signed informed consent, the relative indicates willingness to participate and releases their identifiable information to the PI. Once this information is available, a recruiter will contact them to ascertain eligibility. If relatives do not respond after 6 weeks, the PI will contact the index case asking them to pass on a reminder letter to the nonresponding relative. If this effort yields no response, there will be no further attempts to contact the relative. Relatives agreeing to participate will receive a similar survey as the index case, asking if they are willing to (1) invite additional relatives to the CASCADE study, (2) be contacted once a year for 5 years and provide updated information about their health, and (3) participate alone or with a blood relative in a focus group. Relatives can also participate in all or some of the above study steps.

Recruitment Procedures for Focus Groups

Two series of focus groups will be organized to explore the (1) difficulties associated with patient-provider communication regarding genetic cancer risk, (2) difficulties associated with patient-family communication regarding the pathogenic mutation, (3) mutual influence of patient-provider and patient-family communication, and (4) acceptability of a family-based intervention designed to enhance communication,

coping, and decision making for genetic testing. A purposeful sample of index cases and relatives will be selected from individuals who agreed to participate in focus groups. The sampling method will be based on the expertise of the qualitative methodologist from interviews with Swiss *BRCA* carriers [32,33,71] and the PI's experience conducting focus groups with US *BRCA* families. Segmentation strategy will guide sampling methods and the composition of the focus groups. Each focus group will be relatively homogeneous, while the full set will include several potentially distinct perspectives [72]. Focus groups will include 5-10 participants. Male and female cancer patients and cancer-free individuals will be selected to represent HBOC and LS.

It is expected that data saturation will be reached with 6-10 focus groups including about 30-60 carriers and 30-60 relatives. The first series of focus groups will include only mutation carriers stratified according to level of family communication (high, intermediate, low). These focus groups will explore the difficulties in patient-provider and patient-family communication, and the interrelatedness of these two types of communication. The second series of focus groups will include carriers and relatives and will explore the acceptability of an intervention designed to facilitate communication of test results among family members, helpful coping mechanisms, and decision making for genetic testing. Two sampling methods are envisioned. One method involves several members of the same family who can be invited together; the other involves 3-4 family pairs consisting of one carrier and one relative, which will be homogeneous in terms of gender, health status, etc. The sampling method of the second series of focus groups will be informed by responses to the CASCADE survey and findings from the first series of focus groups.

Data Collection and Data Management

The CASCADE survey will be developed in English, translated into three languages (German, French, and Italian), and back-translated into English by professional translators, except for scales with validated versions in these languages (eg, 12-Item Short Form Health Survey [SF-12]). Discrepancies will be resolved by the PI with the collaboration of the translators and the co-investigators. Index cases and relatives will be given the choice to complete the CASCADE survey either as paper/pencil or using an online platform. The content of the paper/pencil and online survey are identical. Participants who choose to complete the survey online will receive an access code and will be instructed how to log into a secure Web platform. If a survey is missing important information (eg, number of relatives the index case is willing to contact), research personnel will contact participants to ascertain it.

No identifying information, such as name and address, is collected with paper/pencil or online surveys. Each index case is given a code; for example, G001-IC stands for an index case selected from the Geneva clinic with the family study code 001. Relatives recruited from this index case will be coded G001-R1, G001-R2, etc, to establish the link between family members. This code will be used for surveys, consent forms, refusal forms, and correspondence letters to match participants to the correct family unit and maintain the study's internal validity. The PI

and coordinators will keep logs with these codes. The coding key will be kept in a password-protected computer file and will be available to the PI, members of the Swiss Cancer Genetic Predisposition Cascade Screening Consortium, and key personnel. The code will be broken only to avert an immediate risk to the health of the person, in cases of withdrawal from the study, or when there is a legal basis.

All study data will be collected and stored in a secure database and handled by the data management team from the Clinical Trials Unit, University Hospital, Basel (CTU Basel). The online survey will be implemented using LimeSurvey, installed on a separate server, and exclusively used for the study. Lime Survey is an established app to perform online surveys. The system (server and data) is integrated in a regular backup process. Data transfer from and to the Web-based survey system are encrypted using secure sockets layer/transport layer security (SSL/TLS). The secure database will be used for data collection and to track returned surveys. Data entered for paper/pencil surveys will be double-checked for accuracy. The usability of the paper/pencil or online survey will be assessed based on number of individuals who choose either mode, percent of missing data, etc. Many items are parts of multi-item scales and are anticipated to correlate with each other. The reliability of these scales will be tested using principal component analyses and Cronbach alpha coefficients. Scales with $\alpha \geq .71$ will be used. On completion of approximately 30 surveys, scale psychometrics will be examined. For any given scale that shows less than required psychometric properties (ie, Cronbach $\alpha < .71$ and factor analysis indicates item loadings $< 10\%$ compared to item loadings in the original scale), a revision of the translated scale will be undertaken. This will allow comparisons of scale reliability based on delivery mode and will establish whether the survey can be administered interchangeably.

Health-related and personal data collected for the CASCADE study are confidential; coding will safeguard participants' confidentiality. All study documents will be archived in the PI's office. Site-related documents will be archived at the office of each medical director. Administrative data are accessible only by authorized personnel and data managers from CTU Basel. Direct access to documents will be permitted for monitoring, audits, or inspections. Ethics committee members, members of the Swiss Cancer Genetic Predisposition Cascade Screening Consortium, the statistician, and key personnel will have access to project plan, dataset, statistical code, etc, during and after the study (publication, dissemination). Paper/pencil surveys will be stored in a separate research office in the PI's building for 5 years and then destroyed by shredding. Once all data have been collected, the complete dataset and survey setup will be exported by CTU Basel and transferred to the PI and the statistician via a secure channel. The survey system (including database) will be purged after the end of the study. The PI will archive the electronic data for a minimum of 10 years.

Outcomes

Table 2 [73-89] describes primary outcomes for index cases and relatives and the scales used to assess them. The feasibility of establishing a family-based registry will be assessed using the number of mutation-harboring families associated with

HBOC and LS from each clinical site, the number of relatives identified from pedigrees and family history, index cases' response rate to the CASCADE survey, the number of relatives each index case is willing to invite, relatives' response rate to the CASCADE survey, and the willingness of index cases and

relatives to be contacted once a year for 5 years. Additional outcomes include assessing acceptance rates of paper/pencil and online platform and quality of data (eg, percent missing values).

Table 2. Scales used in the CASCADE survey.

Concepts	Scale	Index case	Relatives
Demographics	Age, gender, education, employment status (previously used) [73]	✓	✓
Health history			
Comorbidities	Chronic conditions associated with mobility, cardiovascular disease, diabetes, anxiety, depression Self-reported list (yes/no) (previously used) [73]	✓	✓
Reproductive history (females)	Risk factors associated with the Gail model [74,75] Self-reported	✓	✓
Alcohol, tobacco, physical activity	Self-reported (previously used) [76]	✓	✓
Cancer-related			
Cancer diagnoses	Type of cancer, age of onset Self-reported list (previously used) [73]	✓	✓
Surgery	Surgeries associated with HBOC & LS Prophylactic surgeries Self-reported (previously used) [29]	✓	✓
Surveillance behaviors	Surveillance for cancers associated with HBOC & LS Surveillance for common cancers Investigating tool developed per the American Society of Clinical Oncology guidelines [77] (previously used) [73] Barriers & facilitators (previously used) [73] Coordination of medical care (multiple choices) High out-of-pocket costs (yes/no)	✓	✓
Family history	Family history in 1st and 2nd degree relatives & 1st cousins – type of cancer, age of onset (previously used) [73]	✓	✓
Psychosocial needs			
Fear of cancer recurrence	Concerns About Recurrence Scale [78] 4 items, 7-point Likert scale	✓	✓
Perceived cancer risk	Perceived Risk for Developing Cancer [79] 1 item, 10 points with verbal anchors	✓	✓
Decisional conflict	Decisional Conflict associated with genetic testing [80] 16 items, 7-point Likert scale		✓
Decisional regret	Decisional Regret associated with genetic testing [81] 5 items, 7-point Likert scale	✓	
Coping with stressful events	Brief Cope [82] 25 items, 7-point Likert scale	✓	✓
Self-efficacy	Self-efficacy dealing with cancer [83] 14 items, 7-point Likert scale Self-efficacy – use genetic services (counseling & testing) [83] 1 item, 7-point Likert scale	✓	✓
Knowledge	Breast & Ovarian Cancer Risk Factor Knowledge Index [84,85] 17 items (True, False, Don't Know) Knowledge of Breast Cancer Genetics Scale [70] 12 items (True, False, Don't Know) LS Risk Factors & Inheritance Investigator developed 19 items (True, False, Don't Know)	✓	✓

Concepts	Scale	Index case	Relatives
Communication			
Physician	Need for physician communication about mutation Investigator developed 10 items, 7-point Likert scale	✓	
Family	Mutuality & Interpersonal Sensitivity [86] 15 items, 7-point Likert scale	✓	✓
	Family Support in Illness [73,87] 10 items, 7-point Likert scale	✓	✓
	Communication with children & relatives about mutation (previously used) [29] 17 items (multiple choice)	✓	
Genetic services			
Genetic services	Barriers & facilitators (previously used) [29,88] 11 items, 7-point Likert scale & 22 items (multiple choice)	✓	✓
Genetic testing	Had genetic testing (yes/no) Self-reported	✓	✓
Referral	Source & involvement (previously used) [29] 16 items (multiple choice)	✓	
Quality of Life	SF-12 [89] Physical component & Mental component	✓	✓

Data Analyses

Selection bias will be minimized by random selection of mutation-harboring families in each clinical site from three linguistic regions of Switzerland. Stratification will ensure selection of an equal proportion of index cases from clinical sites that offer genetic services for both syndromes. The study will try to recruit all index cases from clinical sites including fewer than 100 mutation-harboring HBOC/LS families to ensure a representative sample.

All statistical analyses will be conducted in licensed software packages, including Microsoft Excel, SPSS (IBM), and R. For all statistical tests, significance will be set at two-sided $\alpha=0.05$. Data values will be examined for legality (within appropriate range) using histograms and box plots and corrected when possible. Descriptive analyses will include calculating means, standard deviations, frequencies, and percentages of variables and participant descriptors. Bivariate analyses (Pearson correlations, chi-square test for differences in proportions, and *t* test for differences in means) will assess associations between demographics and clinical characteristics. Regression analyses will incorporate generalized estimating equations for pairing index cases with their relatives and explore to what extent predictors are in direct, mediating, or moderating relationship to an outcome.

The following comparisons will take place: between index cases and relatives, between HBOC and LS, between men and women, cancer patients versus cancer-free individuals, participants with children versus those with no children, between different age groups and different cancer diagnoses. Data from participants

who withdraw will be kept in the study to ensure the internal validity of the study. Missing data from multi-item scales will be addressed with multiple imputations using R software if they exceed 5% of observations and if they are less than 25% for each specific scale. Scale reliability will be assessed with Cronbach alpha and principle component analyses. Deviations from the planned analyses are not foreseen. The study statistician will review and approve any deviations from the original statistical plan if necessary.

Narrative data from focus groups will be recorded and transcribed verbatim to allow data management and content examination. Thematic analyses to inductively classify data in concepts and categories, as these emerge through an interpretive process, will be carried out under the guidance of the qualitative methodologist [90]. Focus group participants will be shown a prototype of a family-based intervention as a PowerPoint presentation. Then they will be asked if they like the intervention, if they find it useful, and how it can be improved. Acceptability of the intervention will be assessed with a short survey using 7-point Likert-type items (1=Low to 7=High) asking overall satisfaction with the content, format and appearance of the program, and whether it can help with family communication, coping, and decision making. The survey assesses six acceptability items: ease of use, clarity, appropriate length, appropriate level of detail, able to hold interest, and satisfaction.

Results

This study is currently recruiting participants.

Discussion

Principal Considerations

Cancer predisposition cascade genetic screening combines personalized medicine and public health. Once a mutation carrier for HBOC or Lynch syndrome is identified, evidence-based interventions are available that can reduce the risk of adverse health outcomes in entire cohorts of relatives [91]. This approach is cost-effective for Tier 1 genetic conditions, leading to reduced medical and insurance coverage costs (eg, treatment and hospitalization expenses) [92-94]. Cascade screening for FH applied in the Netherlands identified thousands of mutation carriers for the disorder and has been subsidized by the Dutch government since 2015 [95,96]. Similar programs for FH have also been implemented in Scotland and Wales [97,98].

Availability of genetic testing created an increasing demand for coordination of health care services and risk communication among index cases and relatives. Knowledge of hereditary risk can serve as an information tool to reduce cancer morbidity and mortality. This necessitates the establishment of family-based registries that systematically record genetic information. Currently, this information is fragmented and dispersed across Swiss clinical sites. The establishment of high-risk clinics would allow synergistic approaches in cancer surveillance and medical

care offered to these families. Effective data sharing and dissemination across disciplines is mandatory for increasing the impact of genetic screening, ensure resource allocation, and facilitate health care policy and decision making.

Conclusion

CASCADE study will promote multidisciplinary research in public health genetics at the cutting edge of medicine with strong translational application. This has significant potential to enhance the development of high-quality comprehensive support systems to improve use of cancer genetic services and facilitate patient involvement in health care decisions. The long-term outcome of this program is the development and implementation of new models for systematic surveillance and detection of individuals at risk for hereditary cancer in Switzerland. Immediate outcomes are the assessment of current use of cancer genetic services and evaluation of the public health impact of HBOC and LS. The CASCADE study will document the needs of mutation-harboring families, including barriers and facilitators to accessing cancer genetic services, and will promote use of family history for genetic risk assessment. The study will also provide information for the acceptability of an intervention that will potentially increase genetic literacy, expand understanding of health care technologies, and reduce HBOC- and LS-related morbidity and mortality in Switzerland.

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Conflicts of Interest

None declared.

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Abbreviations

BRCA1: breast cancer 1
BRCA2: breast cancer 2
CTU: Clinical Trial Unit
FH: familial hypercholesterolemia
HBOC: hereditary breast/ovarian cancer syndrome
HFTA: Federal Act on Human Genetic Testing
LS: Lynch syndrome
MMR: mismatch repair
MSI-H: microsatellite instability

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Protocol

Protocol for Usability Testing and Validation of the ISO Draft International Standard 19223 for Lung Ventilators

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Abstract

Background: Clinicians, such as respiratory therapists and physicians, are often required to set up pieces of medical equipment that use inconsistent terminology. Current lung ventilator terminology that is used by different manufacturers contributes to the risk of usage errors, and in turn the risk of ventilator-associated lung injuries and other conditions. Human factors and communication issues are often associated with ventilator-related sentinel events, and inconsistent ventilator terminology compounds these issues. This paper describes our proposed protocol, which will be implemented at the University of Waterloo, Canada when this project is externally funded.

Objective: We propose to determine whether a standardized vocabulary improves the ease of use, safety, and utility as it relates to the usability of medical devices, compared to legacy medical devices from multiple manufacturers, which use different terms.

Methods: We hypothesize that usage errors by clinicians will be lower when standardization is consistently applied by all manufacturers. The proposed study will experimentally examine the impact of standardized nomenclature on performance declines in the use of an unfamiliar ventilator product in clinically relevant scenarios. Participants will be respiratory therapy practitioners and trainees, and we propose studying approximately 60 participants.

Results: The work reported here is in the proposal phase. Once the protocol is implemented, we will report the results in a follow-up paper.

Conclusions: The proposed study will help us better understand the effects of standardization on medical device usability. The study will also help identify any terms in the International Organization for Standardization (ISO) Draft International Standard (DIS) 19223 that may be associated with recurrent errors. Amendments to the standard will be proposed if recurrent errors are identified. This report contributes a protocol that can be used to assess the effect of standardization in any given domain that involves equipment, multiple manufacturers, inconsistent vocabulary, symbology, audio tones, or patterns in interface navigation. Second, the protocol can be used to experimentally evaluate the ISO DIS 19223 for its effectiveness, as researchers around the world may wish to conduct such tests and compare results.

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KEYWORDS

usability; terminology; standardization; lung ventilators

Introduction

Lung ventilators are frequently used in health care, and over 300,000 patients are ventilated in the United States every year [1]. However, the use of lung ventilators is associated with a number of complications and usage errors. While usage errors by clinicians can result in inadequate ventilation, overventilation, barotrauma, or patient-ventilator asynchrony, they can also worsen complications generally associated with ventilators, including ventilator-associated pneumonia, sepsis, psychological distress, acute respiratory distress syndrome, and pulmonary edema (all of which can increase the risk of patient disability and death) [1]. Moreover, medical device manufacturers use inconsistent nomenclature on user interfaces of lung ventilators. For example, the term *continuous mandatory ventilation* (CMV) can have different meanings on different ventilator models [2]. Similarly, a mode for volume-targeted pressure-controlled ventilation has five different names on different ventilator products (see Table 1, first row). While several such inconsistencies in terminology between different ventilator models exist (Table 1), there has also been considerable debate on the correctness of some of the terms used by manufacturers, and the extent to which terms can be intuitively interpreted by clinician users [3]. The discrepant nature of ventilator terminology is a factor underlying increased training costs and human errors, and is an impediment to communication between clinicians, electronic health records, and ventilators. Henzler [4] suggests that partial ventilatory support modes are ill defined, and studies conducted on these modes are difficult to interpret or compare, which necessitates new and precise definitions and taxonomies for ventilation modes. Human factors and communication issues are the two most frequent root causes underlying ventilator-related sentinel events that occurred between 2004 and 2015, which were reported to The Joint Commission [5]. According to The Joint Commission, a sentinel event is an event that results in patient mortality, permanent harm, or severe harm of temporary nature requiring intervention to sustain life; additionally, a sentinel event is not primarily related to the affected patient's illness or underlying condition [5]. The discrepant nomenclature of existing lung ventilators is an issue that is inseparable from human factors, communication, and training.

The main objective of our study is to determine the ease of use, safety, and utility of standardized vocabulary as it relates to the usability of medical devices, compared to legacy medical devices from different manufacturers. We will focus specifically on lung ventilators and the "ISO Draft International Standard 19223 – Lung Ventilators and related equipment – Vocabulary and Semantics" [6]. An International Organization for Standardization (ISO) subcommittee has been working to standardize vocabulary for lung ventilators since 2006; the ISO Draft International Standard (DIS) 19223 is under development, and it may soon become an ISO standard. Our study will evaluate terms defined in the ISO DIS 19223 in the context of their use with lung ventilator user interfaces. The proposed research protocol aims to assess whether terms defined in the ISO DIS 19223 improve the usability of lung ventilators.

Little work has been done to evaluate the impact of a standardized terminology on the usability of medical devices, especially on transitions across heterogeneous devices from different manufacturers. Bakhshi-Raiez et al [7] tested the usability of a clinical information system that incorporated the Systematized Nomenclature of Medicine - Clinical Terms (SNOMED CT) in the registration of reasons for admissions into intensive care. The protocol involved a three-month on-site implementation of SNOMED CT, usability evaluations before and after the implementation, and 16 intensive care unit (ICU) physicians as participants [7]. However, the protocol did not involve comparing multiple heterogeneous systems or comparisons of two or more nomenclature systems [7]. Juvé-Udina [8] reported a usability evaluation of the Architecture, Interface, Terminology, Information, Nursing, and Knowledge (ATIC) terminology for the documentation of nursing diagnoses. The study involved a longitudinal design involving two hospitals and electronic records incorporating the ATIC terminology [8]. A limitation of this protocol is that it mainly focuses on the frequency and completeness of a terminology rather than efficiency, accuracy, or error rate. The Juvé-Udina protocol is not applicable in the evaluation of a nomenclature system intended to be used across heterogeneous devices [8]. Rosenbloom et al [9] proposed a model to evaluate clinical terminology used in the interaction between humans and structured clinical data. The model prescribes several terminology attributes (eg, concept coverage, term accuracy, term expressivity) and usability factors, including correctness, completeness, efficiency, and user satisfaction [9]. However, the model focuses on the evaluation of medical terminology rather than user interface(s) incorporating a given terminology, and the model does not prescribe a protocol for comparing several systems that incorporate alternative terminologies [9]. Morita et al [10] reported a study comparing the safety and user experience of four ventilator models; although their experimental protocol is informative for usability studies involving ventilators, their design is not concerned with nomenclature standardization. Therefore, our protocol to evaluate the usability of a standardized nomenclature applicable across user interfaces of several heterogeneous devices would be a contribution, and the protocol would be applicable in other terminology-related usability studies.

Usability is associated with task performance, which is in turn associated with risk of complications and ventilator-associated lung injuries. Our proposed study will experimentally examine differences in task performance (ie, human error rate, task completion times) and error type (emerging from the use of a standardized versus nonstandardized nomenclature) on lung ventilator user interfaces in clinically relevant scenarios. Our research question and hypothesis are stated as follows: *If medical device manufacturers consistently incorporate a standardized nomenclature, will there be fewer usage errors committed by clinicians operating medical devices unfamiliar to them after some training on the standardized nomenclature? And: Usage errors with unfamiliar medical devices will be lower when mode naming standardization is consistently applied on medical devices produced by all manufacturers.*

Table 1. Translation of terms between vocabularies.

Description	Type	Term in ISO DIS 19223	Term in PB-840	GE Engstrom
Mode in which pressure is adjusted from inflation to inflation, and a set target volume is delivered	Mode	Volume-targeted pressure control (vtPC)	Volume Control Plus (VC+)	Pressure Control Ventilation - Volume Guaranteed (PCV-VG)
Sleep apnea breathing therapy mode	Mode	Continuous positive airway pressure (CPAP)	Spontaneous (SPONT)	Continuous Positive Airway Pressure/Pressure Support Ventilation (CPAP/PSV)
Mode in which two pressure levels are set for spontaneous breathing	Mode	Bi-level positive airway pressure (also bi-level PAP or BPAP)	BiLevel	BiLevel
Ventilation-pattern in which a selected inflation-type (which is the primary inflation) is initiated at a set rate. Patient-trigger events may lead to additional primary inflations beyond the set rate	Mode class	Assist/Control Ventilation	Assist/control mode	“Assist control” mode is available through Volume Controlled Ventilation (VCV), Pressure Controlled Ventilation (PCV), Pressure Controlled Ventilation - Volume Guaranteed (PCV-VG) modes only
Ventilation-pattern in which a selected inflation-type (which is the primary inflation) is initiated at a set rate; patient trigger events cause support inflations in which spontaneous breathing may occur; primary inflations are synchronized with any spontaneous breathing through “synchronization windows”	Mode class	Synchronized intermittent mandatory ventilation (SIMV)	SIMV, “mandatory breaths” can be volume or pressure-based	Several modes on - Synchronized Intermittent Mandatory Ventilation (SIMV) are present in the Engstrom; SIMV Pressure Controlled (SIMV-PC), SIMV Volume Controlled (SIMV-VC), and SIMV Pressure Controlled, Volume Guaranteed (SIMV-PCVG). SIMV-VC, SIMV-PC, and SIMV-PCVG use a “trigger window” which is different from “synchronization windows” mentioned in the ISO DIS 19223
Baseline airway-pressure (BAP) or pressure level set above ambient pressure at which unassisted breathing may occur, and/or inflations may be superimposed	Setting	Baseline airway-pressure (BAP)	Positive end-expiratory pressure (PEEP)	PEEP
Higher pressure level in the Bi-Level Mode	Setting	BAP _H	PEEP _H	Phigh
Lower pressure level in the Bi-Level Mode	Setting	BAP	PEEP _L	Plow
High PEEP time or Inspiratory Time	Setting	BAP _H Time or t _H	T _H	Thigh
Low PEEP time or Expiratory Time	Setting	BAP Time or t _L	T _L	Tlow
Setting for duration of inspiratory phase	Setting	Inspiratory Time or t _I	T _I	Tinsp
Setting or measured quantity for airway pressure in an inspiratory or inflation phase	Setting, measured quantity	Inspiratory Pressure	P _I	Pinsp
Tidal Volume	Setting	V _T	V _T	Tidal Volume or TV

To test this hypothesis, the proposed experimental study will compare performance declines resulting from the use of an unfamiliar ventilator model. These declines will be compared between two groups: a group of clinical participants provided with legacy ventilator models, and a group of clinical participants provided with ventilator models that are modified to include standardized nomenclature. The experiment will consider user interfaces on two types of ventilator models: one

familiar to clinical participants and one unfamiliar to clinical participants. Multiple manufacturers provide lung ventilators, so clinicians (eg, respiratory therapists) within a given geographic region become trained and familiarized only with a subset of the lung ventilators that the global market is capable of providing. However, clinicians may encounter unfamiliar lung ventilators on an occasional basis. For each ventilator model's user interface, a variant will be developed in which the

original layout and navigational structure will be retained, while replacing its nomenclature with the ISO DIS 19223.

The familiar ventilator model will be the Puritan Bennett 840 (PB-840), and the unfamiliar model will be the General Electric (GE) Engstrom Carestation (referred to in this paper as *Engstrom*). The two ventilator models differ in the extent to which respiratory therapy trainees and practitioners are familiar with their interfaces and nomenclature systems. The comparison will provide insights on benefits or difficulties with the use of the ISO DIS 19223 on ventilator user interfaces. A related objective of our proposed study is to identify any terms in the ISO DIS 19223 associated with a high rate of human error. Such terms, if any, should be used with caution on instruction manuals and interfaces.

Relevance to Patient Care

Usability of medical devices is of direct relevance to patient care. It is common for ventilators from several different manufacturers (with different terminology) to be used in hospital departments or different hospital units within a hospital system; this leads to increased risk in patient care [11]. Patients being mechanically ventilated are transported between different health care settings that include homes, emergency departments, long-term care facilities, and ICUs. These movements require clinicians to be able to switch between different nomenclature systems in life-or-death situations; during transitions of care, inconsistent terminology has resulted in clinicians losing valuable time in handoffs that involve translating ventilator use instructions [2]. Clinicians are often required to use ventilators unfamiliar to them, and inconsistent nomenclature contributes to the risk of ventilator-associated lung injury. There is a high risk of mortality in patients being mechanically ventilated who have an acute lung injury: the mortality is 24% for patients 15 to 19 years of age and 60% for patients 85 years or older [1]. There are many causes for ventilator-related sentinel events; however, human factors and communication issues were the most common factors underlying such events that occurred between 2004 and 2015, according to The Joint Commission [5].

Human factors and communication issues are inseparable from the issue of nomenclature inconsistency. The development of an ISO standard for lung ventilator nomenclature is a positive step towards mitigating patient safety risk with the use of lung ventilators. Our research protocol (and eventual study to evaluate the ISO DIS 19223) will help us better understand the potential benefits and barriers, if any, in the incorporation of the ISO DIS 19223 in lung ventilators.

The results of our proposed study will be valuable in the adoption of the ISO DIS 19223 in lung ventilators and in training programs and manuals. When the ISO DIS 19223 becomes widely used, insights from our proposed study will be useful to interface designers of lung ventilators. The proposed study plans to recruit experienced respiratory therapists, so any frequently recurring error(s) associated with specific ISO DIS 19223 term(s) may be of interest in clinician education, in manuals, and in the design of training materials incorporating the ISO DIS 19223. This proposed study will also provide insights about relationships between operator mental models, device

nomenclature, and operator error types, which would be a useful human factor contribution applicable to other types of medical devices and instruments.

Present State of Knowledge and Practice

Lung ventilator models differ between manufacturers in terms of nomenclature. Differences are seen in definitions of various ventilation modes and other terminology, which affects training costs and human error in health care settings. The complexity of lung ventilators in use is a factor underlying patient complications and ventilator-associated lung injury. As an example of an adverse event, a 28-year-old in a neurological ICU was having difficulties with his/her ventilator; a respiratory therapist from a cardiothoracic ICU attending to this patient decided to change settings on the ventilator to improve the patient's oxygen saturation [2]. This action resulted in barotrauma and deteriorated the condition of the patient; later, the respiratory therapist stated that he was not familiar with the ventilator and that the one (familiar to him) in his unit was different [2]. Adverse events like this necessitate the adoption of a standardized nomenclature system and require clinicians to become familiarized with the standardized terminology. As the current state of ventilator nomenclature is in disorder, human error associated with issues in communication, human factors, usability, and training cannot be mitigated unless a standardized terminology is implemented across manufacturers. The implementation of the standardized terminology would significantly benefit from a study focusing on assessing its usability and on the identification of any potential terms associated with conflict, frequent error, or misinterpretation.

As an example of conflict resulting from current inconsistencies in terminology, the term “breath” sometimes refers to an inflation performed by a lung ventilator, leading to ambiguity with the use of manuals and descriptions [12]; for disambiguation, it is argued that ventilators do not “breathe”, and the term “inflation” be used for referring to work done by a ventilator filling air in a patient's lungs [12]. In 2010, there were at least 34 ventilator models using 174 unique terms for ventilation modes [13]. Additionally, terms for settings and modes are often abbreviated, which makes it more difficult for clinicians to familiarize themselves with an unknown ventilator model [14]. This example only provides an estimate of the extent of complexity and disorder with the current ventilator vocabularies in use.

Chatburn [11] stressed the need for a standardized vocabulary and taxonomy in lung ventilators to develop a better understanding about their scope and capabilities; the lack of a standardized vocabulary or nomenclature has jeopardized delivery of care, clinician training, and ventilator sales [11]. Chatburn provides a ventilator mode taxonomy that has been reportedly published for 15 years [11]. However, Chatburn's terminology has not kept pace with changes in technology and the emergence of new modes and settings in lung ventilators. Therefore, an ISO subcommittee was formed to create an ISO standard.

In a 2014 Association for the Advancement of Medical Instrumentation/Food and Drug Administration summit on ventilator technology, it was noted that gaps exist in current

clinical training for ventilator use and in the current state of ventilator terminology [2]. The lack of a, “simple, common, usable ventilator taxonomy including nomenclature” was reiterated by Dr. Steven Dain [2]. A number of related barriers in communication between ventilators and ancillary systems, and an inconsistent understanding of ventilator terminology, were highlighted [2]. A summit presenter noted that in the St. Louis region, five ventilator models in use had five different terms that referred to the same mode for *volume-targeted pressure controlled ventilation*. User interface issues (eg, interface layouts and navigation) were cited in addition to issues in model use competency, and in the setup of ventilators and alarm conditions [2]. It was noted that several barriers exist in training clinicians on lung ventilator models; this includes inadequate incentives to attend training programs conducted by manufacturers [2].

Advances in the standardization of lung ventilator nomenclature will have the most impact if user interfaces on lung ventilators and manuals adopt the standardized nomenclature. There has been no research done to examine or compare the effectiveness of two or more nomenclature systems in lung ventilators. The effectiveness of user interfaces is captured in the construct of usability. Therefore, usability is being incorporated in the proposed study to understand the potential impact that a standardized terminology could have. Usability is a multi-faceted construct that takes into consideration efficiency, errors, memorability, learnability, and satisfaction [15]. We believe that all components of usability are relevant in terms of evaluating the effects of adopting a standardized nomenclature.

In summary, our paper reports an experimental protocol to evaluate a standardized nomenclature system for a medical device, and the evaluation will determine the extent to which the standardized nomenclature facilitates the work of clinicians in situations in which the clinician would need to operate an unfamiliar medical device. The evaluation will take clinician error, performance, and usability into consideration. The medical device we will focus on is the lung ventilator, and the standardized nomenclature is the ISO DIS 19223.

Methods

To test our hypothesis pertaining to nomenclature in medical equipment, the proposed research protocol focuses on lung ventilators while planning to involve respiratory therapy practitioners and trainees. The study will involve at least two lung ventilator models, one of which would be less popular in practice in the region of study, while the other would have a high level of familiarity due to common practice among clinical practitioners and trainees in the region of study. Mockups of interfaces on these ventilator models will be developed. Additionally, for each ventilator model being considered in the study, a variant incorporating the terminology in the ISO DIS 19223 will be developed. This protocol will involve the following tasks: (1) *development of materials - training, mockups, and scenarios*, (2) *vetting and refinement of materials*, (3) *recruitment of clinical participants*, (4) *experiment*, and (5) *analysis*.

Task 1: Development of Materials - Training, Mockups, and Scenarios

In Task 1, we will develop mockups of the *familiar* PB-840 ventilator and the *unfamiliar* GE Engstrom Carestation. The contrast in familiarity is expected in the targeted participant sample in the region of study. Based on our interaction with subject matter experts, one of these products is less commonly used in the market within the region of study. A ventilator mockup is a scaled-down simulator that will consist of a series of screens on the ventilator that allows input-driven transitions between screens. Each screen will be similar to that of the corresponding ventilator. The Department of Systems Design Engineering at the University of Waterloo has a PB-840 ventilator and a GE Engstrom Carestation. These ventilators were provided for educational and research use by Puritan Bennett and GE.

There will be a total of four mockups (PB-840, PB-840-ISO, Engstrom, and Engstrom-ISO), as a variant for each model will be developed using of the ISO DIS 19223 nomenclature. In Phase 1, we will also prepare 10 clinically relevant scenarios, of which seven will be routine scenarios and three will be nonroutine critical scenarios. Each scenario will require the participant to specify or change modes and/or settings on a ventilator mockup. The training materials will be designed to familiarize participants with the ventilator mockups. Training materials for the PB-840, the GE Engstrom Carestation, and their ISO-standard variants will be prepared. Definitions of terms used on the ventilators will not be provided in training.

Task 2: Vetting and Refinement of Materials

The objective of this task is to get feedback on experimental materials (ie, clinical scenarios, mockups) and the experimental protocol. This feedback will be elicited from experienced respiratory therapists and we will use the feedback to refine the experimental materials and protocol. The task will mainly involve a pilot run of the main experiment with think-alouds and unstructured interviews. We will recruit approximately 12 experienced respiratory therapists [10] and instructors from the respiratory therapy program at Conestoga College. The pilot trial and feedback will be used to make modifications in the materials. We will request that participants pay attention to the following areas: (1) comprehensibility of scenario descriptions and discovery of any ambiguities; (2) identification of scenarios that are too difficult to solve by experienced respiratory therapists (we will remove or modify any scenarios for which accurate answers cannot be obtained for most respiratory therapists in the control condition); (3) do the mockups appropriately represent the user interfaces of the PB-840 and the GE Engstrom Carestation?; and (4) is it easy to follow the training, and what would be the appropriate training time for familiarization with the ISO DIS 19223 or that of the unfamiliar ventilator model?

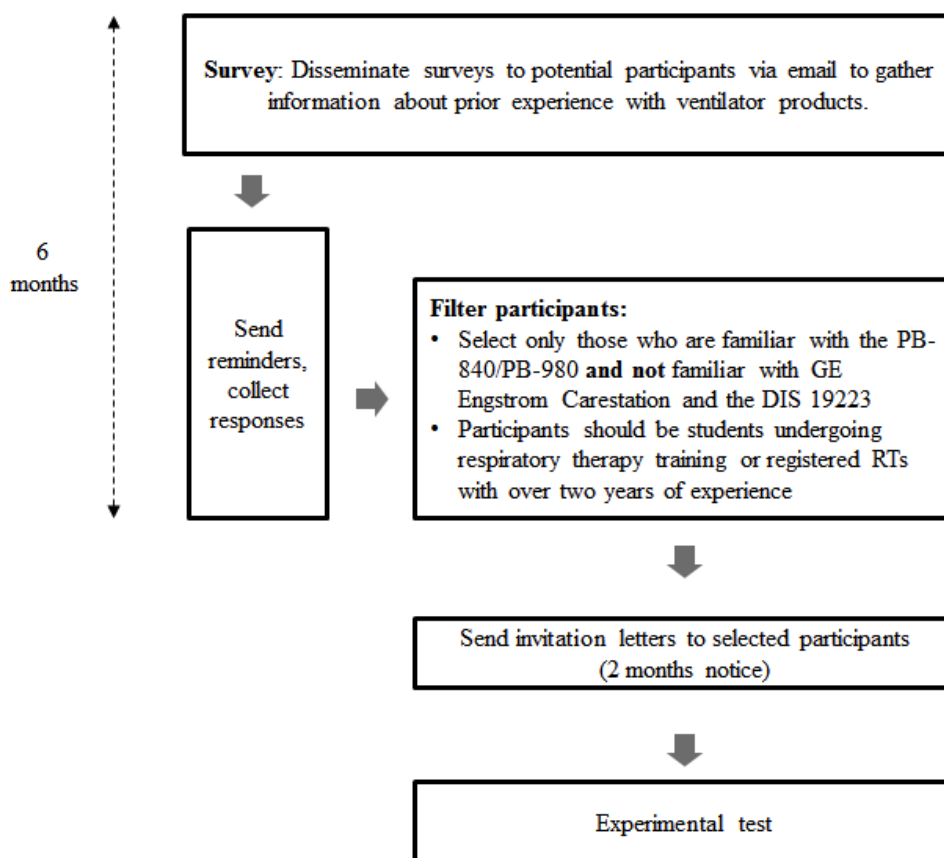
Task 3: Recruitment of Clinical Participants

We plan to recruit 60 participants with training and/or clinical experience with ventilators. A power analysis was conducted with G*Power. Considering a medium effect size (effect size f of .25), alpha of .05, power of .80, and the assumption of a

moderate correlation ($r=.5$) between performance measures across ventilator types, the required sample size is estimated to be 48 participants. However, participant data may need to be excluded due to performance considerations or technical issues. Therefore, a target participant pool of 60 would be appropriate for this study. This sample will consist of 30 students undergoing training in respiratory therapy and 30 registered respiratory therapists who have been in practice for over two years. This timeframe is equal to (or higher than) the experience level of *Therapist II* in the American Association for Respiratory Care's career ladder model; *Therapist I* is considered to be entry-level [16]. A between-subjects design is required as a participant's experience in one condition can influence results in another condition if a within-subjects design is implemented. The assignment of a participant to either group will be randomly determined, subject to gender and experience balancing. This approach will result in four groups of 15 participants: trainee-control, trainee-ISO, therapist-control, and therapist-ISO.

The experimental apparatus (including mockups) will be implemented for portability, and experiments may be conducted at several potential sites. We will approach students undergoing respiratory therapy training in Conestoga College. Experienced respiratory therapists will be recruited from hospitals and professional associations such as the Canadian Society for Respiratory Therapists and the Respiratory Therapy Society of Ontario. We may also approach practitioners via a booth setup in a conference focused in respiratory therapy. For both novice and experienced participants, inclusion criteria pertaining to prior experience with ventilator models from specific manufacturers will be applied. We will first distribute surveys to potential participants, wait for their responses, and select participants based on their familiarity with lung ventilator models from specific manufacturers. Figure 1 provides an overview of the planned timeline for recruiting clinical participants.

Figure 1. Planned timeline for recruitment of clinical participants. PB-840: Puritan Bennett 840 ventilator; GE: General Electric; DIS: Draft International Standard; RT: respiratory therapist.



Textbox 1. Independent and dependent experimental variables.

Dependent Variables

- Response accuracy: number of inaccurate mode or setting selections (in a scenario set of 10 scenarios)
- Average time for completion (taken across ten scenarios in one set)
- Responses to subjective ratings on interface evaluation questionnaire [17]

Independent Variables

- *Nomenclature type (between participants)*; Levels: Control versus ISO-Standard
- *Ventilator type (within participants)*; Levels: Familiar (PB-840) versus Unfamiliar (Engstrom)
- *Skill level (between participants)*; Levels: trainees versus experienced respiratory therapists

Task 4: Experiment

The experiment is designed to simulate situations in which a clinician undergoes a transition from familiar to unfamiliar equipment, as such situations could give rise to clinician errors. Participants (both trainees and therapists) will be randomly placed in one of two groups: the control group or the ISO group. A summary of the experimental variables is presented in Textbox 1. Each group will experience a change of ventilators part way through the study, thereby modeling a transition from familiar to unfamiliar equipment in clinical settings. The control group will interact with existing nomenclature (similar to interactions in contemporary clinical settings) on each ventilator model. The ISO group will interact with the ISO DIS 19223 on each ventilator model. Therefore, the control group will first train on the PB-840 (with current manufacturer nomenclature), work on scenarios with the PB-840, and transition to the Engstrom (with current manufacturer nomenclature) after a short Engstrom training session. The ISO group will first train on the PB-840-ISO, work on scenarios with the PB-840-ISO, and transition to the Engstrom-ISO after a short Engstrom training session. These training sessions are intended to be very short. Thirty participants will be placed in each group (control and ISO), and each group will have an equal number of respiratory therapy students and registered respiratory therapists.

Experimental sessions may be videotaped, with the camera focused on the mockup screens only. All participants will be required to perform 10 scenarios on each ventilator model, which will include seven common scenarios that are routine in clinical settings and three emergency/nonroutine scenarios. Nonroutine scenarios or nonroutine events are events that would appear to be atypical to health care providers, may cause disruptions in the process of care delivery, and may result in cognitive deliberation in addition to what a routine event may demand; they also represent a class of events broader than *adverse events* [18]. Nonroutine events or scenarios can be helpful in capturing dysfunctional aspects of a clinical system or its perils [18], and could challenge cognitive processes and decision making [19]. Examples of routine scenarios are listed below; however, the scenarios in the final experiment will be different from the examples.

Example Scenario A

Set up the ventilator to the mode in which two pressure levels are set for spontaneous breathing, wherein the upper pressure should be set to 20 cmH₂O, lower pressure set to 7 cmH₂O, time at upper pressure should be 1.5 seconds, breathing rate set to 10, and percentage of oxygen by volume set to 28%. On the ventilator provided to you, change the settings to what would be appropriate for the patient.

Example Scenario B

Change the ventilator mode to the one in which pressure control inflations should be initiated at a rate of 10 while additional patient-trigger events would increase inflations of the selected type (ie, pressure control). Set inspiratory pressure to 15 cmH₂O and baseline pressure at 5cmH₂O above ambient pressure. The percentage of oxygen by volume should be 30%.

Participants will be instructed to respond to each scenario using their ventilator mockups, one at a time, and a time limit will be provided for each scenario. We will log start and end times for each scenario, which will be used to calculate response times for each scenario. When a participant does not respond accurately in a given scenario, the experimenter will probe the participant with questions. The inaccurate responses will also be recorded for analysis. Responses to these probes will be audio recorded, and they will be used to classify the error(s) based on Rasmussen's error classification [20]. We may also use Reason's classification [21] as suggested by the International Electrotechnical Commission [22]. At the end of each experimental session, participants will be required to complete a questionnaire to evaluate the interface. The evaluation questionnaire will be based on the one used by Salyer (67.7, page 1558) [17]. Salyer's questionnaire will be modified to better suit the purpose of our evaluation protocol. Additionally, we will debrief the participants about the purpose of our study and about the possibility that vocabulary on future ventilator models may be standardized. The debriefing for the control group will include information about the nomenclature system in the ISO DIS 19223. In the debriefings, groups will be informed about how their ventilator interfaces differed from those in the other group.

Figure 2. Timeline of an experimental session for the experiment. Each experimental session is expected to last approximately 80 minutes, including time for demographic surveys. PB-840: Puritan Bennett 840 ventilator; ISO: International Organization for Standardization; DIS: Draft International Standard; S: scenario set.

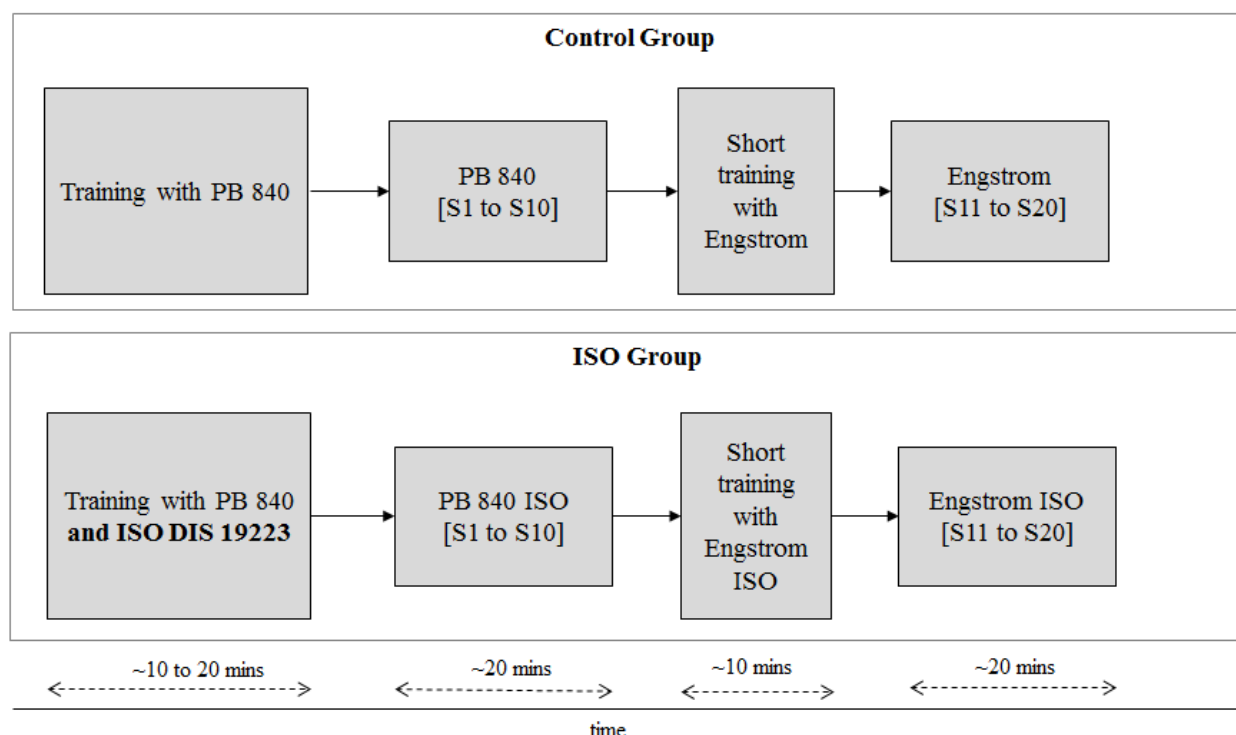


Figure 2 provides a summary of the planned timeline for an experimental session. Participants in the ISO group will be trained on the ISO DIS 19223. This training will familiarize participants with the terminology; however, participants will not be presented with a conversion table such as Table 1 that maps the ISO DIS 19223 to any manufacturer-specific terms. The scenario set (S1 to S10) on the PB-840 will be very similar to the scenario set (S11 to S20) on the Engstrom, to allow comparison of performance on the two types of ventilator models. Each scenario in the S1 to S10 set will have a corresponding scenario in the S11 to S20 set; however, the order of presenting these scenarios will be different.

Task 5: Analysis and Reporting

Task 5 consists of statistical analyses and a qualitative analysis. The statistical analyses will mainly involve response times, accuracy, and subjective ratings, and will focus on performance differences between groups and ventilator types. We will run a mixed factorial analysis of variance to detect differences of statistical significance across groups and ventilator types. We will also apply statistical tests to detect any potential relationships between task performance and experience. Verbal responses to probe questions will be qualitatively analyzed [23]. The results of our proposed study will influence the ISO DIS 19223 standard for lung ventilators, and guide training programs and manuals provided by manufacturers. The insights will be useful to interface designers for lung ventilators. Additionally, frequently recurring errors associated with specific ISO DIS 19223 terms (if any) will be informative to the standards committee. We will also use the information from this study to provide guidance to respiratory therapists, colleges, and hospitals

on how to manage the transition to ISO standard instrumentation.

Results

The work reported here is in the proposal phase. Once the protocol is implemented, we will report the results in a follow-up paper.

Discussion

Executing the Protocol

In a number of domains in which time-critical tasks are performed with complex equipment, health care providers may be required to occasionally work with various manufacturers' models of equipment with which providers are unfamiliar. During such transitions, providers must cope with unfamiliar symbology, terminology, proprietary manufacturers' terms, audio tones, or patterns in interface navigation. Such transitions can be a cause for error, potentially leading to hazardous situations that result in environmental damage, patient morbidity, or mortality. To mitigate the risk of human error, efforts can be made to standardize terminology for instruction manuals, displays, and controls (eg, alarm signals of differing equipment used in critical care). Previous attempts to assess the usability of medical systems incorporating a specific terminology in the context of operation in realistic settings have been limited [7,24,25]. The protocol reported in our paper can be used to assess the role of standardization in mitigating the risk of human error in the use of devices that incorporate standardized terminology. This protocol provides templates for participant

recruitment and experimental design. The protocol is also applicable in the evaluation of the vocabulary of terms proposed by the ISO DIS 19223 for lung ventilators. The proposed standardized vocabulary may have potential benefits for the usability of lung ventilators, and researchers around the world may be interested in performing similar studies to assess the potential benefits of the ISO DIS 19223. Medical equipment usability studies are required by many countries to obtain a license to sell the product in that country. The protocol reported here will assist researchers in recruiting participants and in designing the experiments to evaluate usability. Additionally, [Table 1](#) provides a list of equivalent terms across those in the ISO DIS 19223 [6], the PB-840 [24], and the Engstrom [25]. [Table 1](#) would be useful in designing studies involving these vocabularies. More information can be found in conversion tables provided by the Emergency Care Research Institute [26]; these tables provide comparisons across five terminologies, not including the ISO DIS 19223. The results from multiple studies informed by this protocol would help us understand potential benefits and difficulties associated with the use of the ISO DIS 19223.

Limitations

We would like to indicate a few limitations in our protocol. Replication of this protocol for a planned experimental study in an industry or university laboratory would not be bound by the same limitations. First, there is a limit on the number of ventilator models that we can integrate into our study. The protocol reported in our paper includes only two ventilator models (PB-840 and the GE Engstrom). However, it is recommended to include more ventilator models, and we may include more ventilator(s) depending on availability of other ventilators and industry participation. Second, we will be using mockups, although it would be ideal to use the actual medical devices that have the ability to record data. Finally, nurses and clinicians other than respiratory therapists are not included in our protocol. Nurses may be regular operators of lung ventilators in some developing countries, and the inclusion of such nurses in an experimental protocol may be beneficial. A follow-up study can also be conducted to compare nurses with respiratory therapists.

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Conflicts of Interest

None declared.

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Abbreviations

ATIC: Architecture, Interface, Terminology, Information, Nursing, and Knowledge
BAP: baseline airway-pressure
CPAP: continuous positive airway pressure
DIS: Draft International Standard
GE: General Electric
ICU: intensive care unit
ISO: International Organization for Standardization
PB-840: Puritan Bennett 840 ventilator
PCV: Pressure Controlled Ventilation
PCV-VG: Pressure Controlled Ventilation - Volume Guaranteed
PEEP: positive end-expiratory pressure
SIMV: Synchronized Intermittent Mandatory Ventilation (in the ISO DIS 19223) or Synchronous Intermittent Mandatory Ventilation (in the PB-840)
SIMV-PC: Synchronized Intermittent Mandatory Ventilation - Pressure Controlled
SIMV-PCVG: Synchronized Intermittent Mandatory Ventilation - Pressure Controlled, Volume Guaranteed
SIMV-VC: Synchronized Intermittent Mandatory Ventilation - Volume Controlled
SNOMED CT: Systematized Nomenclature of Medicine - Clinical Terms

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Original Paper

Influence of Information and Communication Technologies on the Resilience and Coping of Sexual and Gender Minority Youth in the United States and Canada (Project #Queery): Mixed Methods Survey

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Abstract

Background: Sexual and gender minority youth are a population in peril, exemplified by their disproportionate risk of negative experiences and outcomes. Sexual and gender minority youth may be particularly active users of information and communication technologies (ICTs), and it is important to identify the potential contributions of ICTs to their resilience and well-being.

Objective: Our aim was to (1) investigate the use of ICTs by sexual and gender minority youth, (2) identify the ways that ICTs influence the resilience and coping of sexual and gender minority youth, focusing on promotion of well-being through self-guided support-seeking (particularly using mobile devices), (3) develop a contextually relevant theoretical conceptualization of resilience incorporating minority stress and ecological approaches, (4) generate best practices and materials that are accessible to multiple interested groups, and (5) identify whether video narratives are a viable alternative to collect qualitative responses in Web-based surveys for youth.

Methods: Mixed methods, cross-sectional data (N=6309) were collected via a Web-based survey from across the United States and Canada from March-July 2016. The sample was generated using a multipronged, targeted recruitment approach using Web-based strategies and consists of self-identified English-speaking sexual and gender minority youth aged 14-29 with technological literacy sufficient to complete the Web-based survey. The survey was divided into eight sections: (1) essential demographics, (2) ICT usage, (3) health and mental health, (4) coping and resilience, (5) sexual and gender minority youth identities and engagement, (6) fandom communities, (7) nonessential demographics, and (8) a video submission (optional, n=108). The option of a 3-5 minute video submission represents a new research innovation in Web-based survey research.

Results: Data collection is complete (N=6309), and analyses are ongoing. Proposed analyses include (1) structural equation modeling of quantitative data, (2) grounded theory analysis of qualitative data, and (3) an integrative, mixed methods analysis using a data transformation design. Theoretical and methodological triangulation of analyses integrates an interwoven pattern of results into a comprehensive picture of a phenomenon. Results will be reported in 2017 and 2018.

Conclusions: This research study will provide critical insights into the emerging use of ICTs by sexual and gender minority youth and identify intervention strategies to improve their well-being and reduce risks encountered by this vulnerable population. Implications for practice, research, and knowledge translation are provided.

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KEYWORDS

mixed methods; survey; grounded theory; sexuality; LGBTQ; gender; sexual orientation; gay; transgender; youth; Internet; online; information and communication technologies

Introduction

Information and Communication Technologies

Information and communication technologies (ICTs) are offline (eg, televisions, phones) and online (eg, Internet, social media) technologies that facilitate communication and sharing of information, including mobile devices (eg, mobile phones, tablets) [1]. ICTs have the potential to promote resilience and coping among youth [2]. In the United States, 92% of adolescents (age 13-17) are online daily [3], and 97% of young adults (age 18-29) use the Internet [4]. In Canada, 99% of youth (age 16-24) use the Internet [5]. Global expansion in ICT use is expected to lead to improved education and economic opportunities for youth [6], yet whether this is true of socially marginalized populations remains unknown. The rapid uptake of ICTs represents a promising evolution for accessible interventions [7]. Youth in crisis may turn to online ICTs for support before interventions such as hotlines or social services [8]. There remains a lack of research on the potential positive impacts of increased ICT usage by sexual and gender minority youth.

Sexual and Gender Minority Youth

Sexual and gender minority youth are youth who identify as gay, lesbian, queer, bisexual, transgender, and other nonmajority sexual and gender identities. They are a population in peril, as exemplified by disproportionate risk of negative experiences and outcomes, such as familial rejection [9], social exclusion [10], depression [11,12], and low academic achievement [13,14]. Such risks result in accumulation of high overall levels of stress [15]. Sexual and gender minority youth are also more likely to endure emotional and behavioral stressors (eg, isolation, violence, victimization) [16-19]. Such experiences exacerbate vulnerability to negative outcomes. Opportunities to foster resilience and coping are critical to sexual and gender minority youth health and well-being. Resilience is defined as the ability to adapt constructively to risk exposure [20], while coping refers to dynamic and conscious actions to regulate behavior in the face of stress [21].

Sexual and gender minority youth are particularly active Internet users compared to their non-sexual and gender minority youth peers [22], often relying on ICTs for sexual and gender minority information and resources [23,24]. There are risks related to ICT use for sexual and gender minority youth, such as increased likelihood of online bullying and harassment [22]. However, there are potential beneficial contributions of these technologies to sexual and gender minority youth resilience and coping that are important to understand. The use of ICTs to engage in

self-guided support seeking (ie, using ICTs to independently address one's own challenges) requires further investigation.

Study Objectives

This study, Project #Queery, will (1) investigate the use of ICTs by sexual and gender minority youth, (2) identify ways that ICTs influence the resilience and coping of sexual and gender minority youth, focusing on promotion of well-being through self-guided support-seeking (particularly using mobile devices), (3) develop a contextually relevant theoretical conceptualization of resilience incorporating minority stress and ecological approaches, and (4) generate best practices and materials that are accessible to various stakeholder groups (eg, youth, service providers, policy makers). Additionally, using an innovative data collection design, this study will (5) identify whether video narratives are a viable alternative to collect qualitative responses in Web-based surveys for youth. A Web-based survey, open from March-July 2016, generated a sample of 6309 English-speaking sexual and gender minority youth participants aged 14-29 from across the United States and Canada. Data are currently being cleaned and analyzed. The purpose of this paper is to detail the research protocol of Project #Queery, including study design, recruitment strategies, data collection procedures, proposed mixed methods and integrative analyses, as well as planned knowledge mobilization activities.

Methods

Study Team

The Project #Queery Study Team consists of (1) a principal investigator, (2) two co-investigators, (3) a research coordinator, and (4) a multidisciplinary advisory group. The advisory group included the co-investigators, two international academic collaborators, several social service practitioners working with sexual and gender minority youth, and a number of sexual and gender minority youth. The advisory group provided insight during measure development, tested the data collection tools, and will provide additional support throughout analyses, dissemination, and knowledge mobilization. The principal investigator and the research coordinator managed the advisory group, as well as a research team of 5-7 research assistants, with ongoing input from the co-investigators. Research assistants were students from all degree levels (ie, bachelors, masters, and doctoral) and were selected for their research skills or knowledge of the target population. Research assistants completed a variety of tasks, including outreach and recruitment, measure development, data collection and management, website and social media development and maintenance, literature searches

and reviews, data cleaning and mixed methods analyses, and dissemination activities.

Ethics and Consent

Prior to completing the Web-based survey all participants, regardless of age, read and independently accepted a Web-based statement of informed consent. Parental consent was not required. Participants who opted to submit a video at the end of the survey read and accepted an additional statement of informed consent prior to completing that section. Obtaining independent informed consent from participants under age 18 may pose challenges [25]. This approach may be justified in specific situations, such as where seeking parental consent may put youth at risk. In the case of Project #Queery, requiring parental consent would have potentially put some participants at risk of exposure regarding their sexual and gender minority youth status [26,27]. The University of Toronto Research Ethics Board approved the protocol for this study, including approving the independent consent procedure for participants under age 18 (ie, waiving the parental consent requirement). Consent materials should be age-appropriate and easy to understand [26]. In Project #Queery, all consent materials were assessed for grade-level readability (using Readable.io) to ensure they were understandable to the youngest participants. Additionally, animated videos explaining each consent statement (ie, survey and video) were provided. Videos were produced using online video animation platform GoAnimate and were implemented to increase participants' understanding of the study [28].

All standard elements were included in the Web-based informed consent, including an introduction to the study and the estimated time required to complete the survey. Participants were not required to provide identifiable details (other than an email address). Research assistants were available by email, as well as via study accounts on Facebook, Instagram, Twitter, Tumblr, Reddit, and YouTube. Platforms permitted direct/private messaging. National sexual and gender minority youth resources in both the United States and Canada were listed at the end of the survey, and contact information for the principal investigator was provided for more personalized resources. Participants were also asked if they needed immediate help directly after answering challenging questions (eg, self-harm, suicidal ideation) and were provided with immediate access to the aforementioned national sexual and gender minority youth resources [26].

Data Collection

A Web-based, cross-sectional open survey of sexual and gender minority youth was employed containing a combination of quantitative measures and qualitative questions, as well as enabling the opportunity to provide a video response. The study logo (Project #Queery) and institutional logos (Factor-Inwentash Faculty of Social Work, University of Toronto) were displayed. This research used digital delivery because (1) sexual and gender minority youth are avid users of ICTs, so it is a naturally occurring location for intervention [2,22], (2) youth prefer this approach [29], (3) Web-based research is cost effective [26], and (4) sexual and gender minority youth not present in other systems of care may be captured [30]. Only highly secure and encrypted data collection platforms were used (ie, Qualtrics,

WeTransfer). Since data collection was completed, data have been encrypted and kept on secure computer drives. The survey was tested for usability and functionality, including vetting by the advisory group.

Following participation, sexual and gender minority youth had the option to enter into a raffle for a variety of prizes. These include e-gift cards to Amazon or iTunes (100 cards at Can \$25, two cards at Can \$250), as well as five iPad Minis. Participants were required to provide only an email address to enter the raffle. The number of raffle entries participants received depended on the completeness of their data. Additional prizes were provided for completing the optional fandom and video sections to encourage participation. Fandom refers to communities of individuals with personal connections to particular media objects. Participants who completed a survey received one raffle entry. Participants who also completed a video received a second raffle entry (and entry into a specific draw for an iPad Mini just for video participants). Fandom participants were entered into a specific draw for a Can \$100 e-gift card. Raffle winners were selected using a random number table; all prizes were distributed online.

Recruitment

A multipronged, targeted recruitment approach using Web-based, purposive, venue-based strategies was used to recruit a diverse, convenience sample of sexual and gender minority youth:

e-Flyers and participation emails were distributed to agencies and organizations serving sexual and gender minority youth in every state in the United States, and every province and territory in Canada. Over 950 groups were contacted (most multiple times).

Approximately 70 Facebook groups (eg, regional Pride pages, pages for campus groups) were directly messaged encouraging them to ask their communities to participate. Communities were also contacted on other social media platforms (eg, Tumblr, Reddit).

Promoted (paid) posts were employed using Facebook's Ad Manager to reach approximately 98,000 people on Facebook and Instagram. Several of these posts targeted particular locations and communities in an effort to generate a geographically broad and diverse sample [27].

An animated YouTube commercial, produced using GoAnimate, was released. The process of developing and using animated videos in research with youth is described in detail elsewhere [28]. As random sampling is not feasible in hard-to-reach, stigmatized populations [31], existing relationships between the research team and organizations serving sexual and gender minority youth helped identify appropriate recruitment pathways. Limited paper flyering was completed in Ontario, Canada.

Survey

Participants (N=6309) completed a 30-45 minute Web-based survey hosted on Qualtrics, a method often used in youth research [26]. Web-based data collection is preferred by adolescents and has been suggested for effectively accessing

marginalized populations, including sexual and gender minority youth [26,29,32]. The survey was divided into eight sections: (1) essential demographics, (2) ICT usage, (3) health and mental health, (4) coping and resilience, (5) sexual and gender minority youth identities and engagement, (6) fandom communities, (7) nonessential demographics, and (8) a video submission (optional). Adaptive questioning (where survey items are only conditionally displayed) [33] was used. A “back button” was available to allow participants to revise their answers. Participants were also able to return to their survey and make changes or complete additional survey items for up to 1 week. Unique site visitation was determined via the provided email address, as Internet protocol addresses were not collected [33]. Each page contained a maximum of five questions. The questionnaire was a maximum of 40 pages, provided that participants viewed every question. The retention rate through to the last section of the survey (nonessential demographics) was 76.22% (4809/6309).

Measures

Measures incorporated into various sections of the survey included:

1. Demographics (Sections 1 and 7): Developed for Project #Queery, Section 1 contained essential demographics, including measures of age, gender identity, sexual orientation, race and ethnicity, current geographic location (eg, country, state/province), and education attainment (eg, high school, college, university) and educational status (eg, student, nonstudent). Section 7 contained demographics that were deemed important, but less essential to the core research questions, including community type (eg, city, town, rural), employment status (eg, part-time, full-time), country of birth, duration in country of residence, socioeconomic status (eg, parent occupation), living situation, and family religiosity.
2. ICT Usage (Section 2): This was created specifically for Project #Queery and informed by the format and content of the Pew Internet & American Life child and adolescent ICT surveys. Datasets are available on the Pew website.

Questions included active hours online per day, devices used and their capabilities (eg, phone, text, WiFi, data), and favorite social media sites and their impact.

3. Identity Development (Section 5): Generated for Project #Queery from a review of the literature on sexual and gender minority youth identity development [34-37], this section included questions on sexual attraction and relationship experiences, ages of realization and identification of sexual and gender minority status, outness and age(s) of coming out, and experiences in sexual and gender minority communities.
4. Fandom Communities (Section 6): Fandom refers to communities composed of individual fans with personal connections to various media objects (eg, television shows, movies franchises) [38,39]. This section asked about participation in fandom communities in online contexts.

Existing scale survey measures were also incorporated (see Table 1 [40-52]).

Video

Participants were given the opportunity to enter an open-ended textual response or upload a 3-5 minute video or audio recording in which they provide an example of how ICTs have facilitated their resilience and coping. This research innovation, suggested by sexual and gender minority youth in a previous study as an alternative to open-ended questions (often a part of adolescent surveys), represents an innovative multimedia approach to survey research. Participants who opted to provide a video (n=108) submitted files via WeTransfer, a Web-based file sending service that allows for the free encrypted transfer of files as large as 2GB. The paid version of the service (a “Plus Channel”) provided a personalized webpage where participants were directed to upload their files. All participants were required to provide (in addition to the video file) was a valid email address. The email address allowed the connection of participants’ videos to survey responses and raffle entries. Participants on mobile devices were able to upload files in any mobile Web browser.

Table 1. Scale survey measures.

Scale	Survey section	Items, n	Modifications
E-Health Literacy Scale [40]	3	3	5 items excluded
Diagnostic and Statistical Manual of Mental Disorders, V [41]	3	21	(1) Excluded 6 items from sections 9 (Psychosis) and 10 (Repetitive Thoughts and Behaviors). (2) Changed scale from 5-point (0-4) to 11-point (0-10).
Perceived Stress Scale [42,43]	4	10	No modifications
Adverse Childhood Experiences Scale [44]	3	10	Added an unsure response option
Internalized Queerness [45]	4	5	Replaced gay or homosexual with the word queer
Microaggressions [46]	4	9	From LGBQ Microaggressions on Campus Scale Used 5/15 items from interpersonal subscale and 3/5 items from environmental subscale
Child and Youth Resilience Measure-12 [47]	4	12	No modifications
Adolescent Coping Orientation for Problem Experiences [48,49]	4	20	34 items excluded
School Performance and Engagement [14,50]	4	5	From the Youth Risk Behavior Survey
Social Support Scales [51,52]	4	10	Used 5/9 items From Family Cohesion Scale and 5/9 items from Peer Support Scale

Table 2. Sexual orientations and gender identities (N=6309).

	n	%
Sexual orientations		
Pan umbrella ^a	1878	29.8
Bi umbrella ^b	1655	26.2
Queer	1321	20.9
Gay	988	15.7
Lesbian	983	15.6
Asexual (Ace) umbrella ^c	748	11.9
Not sure/Questioning	399	6.3
Other	153	2.4
Demi umbrella ^d	128	2.0
Straight/Heterosexual	122	1.9
Two-spirit	74	1.2
Gender identities		
Woman/Female	2592	41.1
Gender nonbinary/Nonconforming/Independent	1506	23.9
GenderQueer/GenderFluid	1230	19.5
Man/Male	1080	17.1
Trans man/Male	781	12.4
Other	171	2.7
Trans woman/Female	143	2.3
Agender	115	1.8
Two-spirit	90	1.4

^aPansexual, Panromantic, Pansensual.

^bBisexual, Biromantic.

^cAsexual, Aromatic, Grey Asexual, etc.

^dDemisexual, Demiromantic.

Sample

Participants were age 14-29 (\bar{x} = 18.19, SD 3.60) and were able to select multiple options (or write in their own response) for both sexual orientation and gender identity. Responses were complex and individual. For simplicity, a multitude of related sexual orientations were grouped into five overarching “umbrella” categories (Table 2). Participants were also able to choose multiple racial and ethnic categories. The sample was predominantly Caucasian/white (79.57%, 5020/6309), though other categories also provided robust numbers: Hispanic (8.24%, 520/6309), mixed/multiracial (7.31%, 461/6309), American Indian/First Nations (5.31%, 335/6309), Asian (including South and Southeast Asian) (5.14%, 324/6309), Black (4.20%, 265/6309), and Middle Eastern (1.0105%, 66/6309).

A third of the sample was from Canada (29.8399%, 1882/6309), while two thirds were from the United States (68.1516%, 4300/6309). A small number of participants came from outside these two countries (1.85%, 117/6309). Participants came from every state, province, and Canadian territory. The most

American respondents came from California (7.35%, 316/4300), New York (5.00%, 215/4300), Ohio (4.79%, 206/4300), Florida (4.35%, 187/4300), Illinois (4.05%, 174/4300), Pennsylvania (4.00%, 171/4300), and Texas (3.65%, 157/4300). The most Canadian respondents came from Ontario (38.47%, 724/18821892), Alberta (16.47%, 310/18821892), British Columbia (16.26%, 306/18821892), and Quebec (7.07%, 133/18821892).

Results

Proposed Quantitative Analyses

Quantitative survey data have been entered into SPSS 24 and descriptive analyses conducted. Structural equation modeling (SEM) techniques will be used during analyses as they account for measurement error and error correlations, as well as interactions and latent variables [53]. AMOS 18.0 will be used to generate a SEM model of the multivariate relationships and evaluate it using recommended fit indices [54]. More focused SEM analyses will also be conducted by specific variables (eg,

sexual orientation, gender and racialized identities; location; socioeconomic status) to identify commonalities and disparate patterns in ICT use, resilience, and coping.

Proposed Qualitative Analyses

Qualitative videos and textual open-ended responses will be imported into ATLAS.ti 7 and analyzed using a grounded theory approach [55]. Video clips will be directly analyzed, as ATLAS.ti permits coding of video data. The use of video data has been lauded as a means of enabling participant voice in context [56,57], as an innovative method of triangulation [58], and as a technique to detect meaning and emotions not captured in text [59]. Open and axial coding strategies will be used to generate codes and themes that will subsequently be used to form a grounded theory to describe the relationship between ICTs and well-being for sexual and gender minority youth. To enhance trustworthiness, independent coders (research assistants) will be trained to perform thematic analysis and employ the “constant comparison” method [55].

Proposed Integrative Analyses

A concurrent mixed methods analysis [60], using a data transformation design [61], will be used to effectively mine rich qualitative data while preserving the integrity of emergent qualitative themes. Multimethod research is ideal for resilience investigations [62] because such analytical integration addresses distinct multilevel protective processes (eg, individual, interpersonal, social, cultural) influencing resilience, resulting in more scientifically robust and culturally relevant theories [63]. This conceptual approach triangulates the data using investigator, theoretical, and methodological triangulation and creates a type of “ontological synthesis” that integrates an interwoven pattern of results into a comprehensive picture of interconnected phenomena [64].

Following full analysis of the qualitative findings, an integrative analytic process will be undertaken as follows:

1. The emergent themes developed from the grounded theory analysis will be quantitized (transforming qualitative data to a numerical form) to enhance the monomethod quantitative and qualitative results. For each participant’s textual response and/or video narrative, the presence or absence of each emergent theme of resilience and coping will be assigned a score of “1” or “0” [60].
2. Then an interrespondent matrix (ie, theme x youth) indicating which sexual and gender minority youth reflected each theme will be created [65].
3. A bivariate analysis of quantized responses (0 or 1) and selected demographic variables (eg, age, sexual orientation) will be conducted.
4. An exploratory factor analysis will determine constructs and results will generate metathemes (containing at least one emergent theme) that will contribute to a holistic theoretical understanding of resilience [66].

Discussion

Principal Considerations

Project #Queery will provide critical insights into sexual and gender minority youth’s use of ICTs. It is the first study into the relationship between ICT use, mental health and health, and coping and risk behaviors of sexual and gender minority youth populations with participants from every state and province in the United States and Canada. This sample of English-speaking sexual and gender minority youth aged 14-29 (N=6309) describe their experiences and perceptions through quantitative (measures) and qualitative (text and video) data. With its innovative Web-based recruitment and survey design, the study encouraged significant involvement from sexual and gender minority youth who may not have interaction with offline services and may be less likely to participate in research [26]. Data collection is complete, with results of proposed analyses anticipated in 2017 and 2018.

Strengths and Limitations

This project has several limitations, such as barriers to participation for sexual and gender minority youth who do not have access to ICTs or have literacy issues. That the sample is predominantly Caucasian/white (79.57%, 5020/6309) should also be acknowledged. In addition, this survey is fairly comprehensive and less accessible for sexual and gender minority youth who may not have had time to participate. Thus the results of this study will not be representative of all sexual and gender minority youth.

Despite these challenges, this project will develop an empirical understanding of the impact of ICTs on the well-being of sexual and gender minority youth, a socially vulnerable group who may be particularly active via ICTs [21]. Despite youth affinity for Web-based interventions [29,67,68], studies of their ICT use generally focus on problems (eg, online addiction, cyberbullying) [69,70] without adequate consideration of potential benefits. Online contexts are often welcoming spaces wherein youth may express themselves in ways not possible offline [71,72]. As sexual and gender minority youth frequently struggle with social exclusion and poor outcomes [9-15], understanding the potential of ICTs to minimize risks by promoting connections that help youth cope with and navigate their environment may significantly impact their lives [2]. This line of inquiry is critical to reducing the documented health and mental health disparities of sexual and gender minority youth. Emerging scholarship indicates sexual and gender minority youth benefit from ICTs [2,22-24,72] and supports our proposed analysis of the trends in use across a variety of subpopulations.

Conclusion

Project #Queery will offer guidance for the development of best practices in ICT use for sexual and gender minority youth by offering insight into youth perceptions and the role of their social contexts. Knowledge mobilization will ensure that study findings are utilized by professionals, participants, and community. Presentations at relevant educational and social service settings, as well as professional and academic conferences, will be pursued. Findings will be disseminated

through relevant academic journals and through the use of a series of 6-8 infographics to directly inform youth and practitioners. Results will be used to inform affirmative interventions to promote healthy coping of sexual and gender

minority youth both online and offline. As ICT use is increasingly ubiquitous among youth [3-6], understanding the impact on sexual and gender minority youth is crucial to inform tailored intervention approaches.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Grant reviews.

[PDF File (Adobe PDF File), 589KB - [resprot_v6i9e189_app1.pdf](#)]

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Abbreviations

ICT: information and communication technology

SEM: structural equation modeling

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Protocol

Influence of Fear of Pain and Coping Strategies on Health-Related Quality of Life and Patient-Anticipated Outcomes in Patients With Chronic Pain: Cross-Sectional Study Protocol

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Abstract

Background: Fear of pain and coping strategies are emotional-behavioral responses to pain and are known to play an important role in the development and maintenance of pain. It is highly likely that fear of pain and coping strategies influence each other, potentially affecting the course of chronic pain. To our knowledge, the relationship between pain, fear of pain and coping strategies, and how they influence patient-anticipated outcomes and health-related quality of life, have not been investigated.

Objective: The aims of this study are to test (1) if both fear of pain and/or coping strategies are sufficient causes for maintaining pain; and (2) whether fear of pain influences coping strategies and pain intensity. The study will also examine the impact of fear of pain and coping strategies on health-related quality of life and patient-anticipated outcomes.

Methods: The cross-sectional study will be conducted using an online survey. The Fear of Pain Questionnaire-III (FPQ-III), the Brief Coping Inventory (COPE), and EuroQoL-5d (EQ-5D) validated questionnaires will be used to collect data. Information pertaining to demographic factors, pain-related factors, and patient-anticipated outcomes will also be collected. The study has ethics approval from the Human Research Ethics Committee of the University of Adelaide. Study participants will be individuals aged 18 years and above who are experiencing chronic pain (ie, pain lasting more than 6 months). Effect measure modification technique (EMMM) will be used to examine if fear of pain acts as a moderator or mediator between coping strategies and pain. Simple and multinomial logistic regression analysis will be used to examine the effect of fear of pain and coping strategies on health-related quality of life and patient-anticipated outcomes.

Results: Recruitment began July 2017 and it is anticipated that data collection will be completed by October 2017. Findings from this study will help to extend our understanding of fear of pain and coping strategies, their interaction, and their impact on health-related quality of life and patient-anticipated outcomes.

Conclusions: Fear of pain and coping strategies have significant influence on the experience of chronic pain and its course. This study will help enhance our understanding of the relationship between fear of pain and coping strategies, which may help in developing patient-centered care practices.

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KEYWORDS

fear of pain; coping strategies; health-related quality of life; patient-anticipated outcomes; chronic pain

Introduction

Background

Chronic pain is a multifaceted, global health problem affecting nearly 1 in 5 individuals worldwide [1]. Its continuous presence has devastating effects on an individual's personal, social, and work life [2]. Chronic pain invades everyday functioning, communications, and interactions. Its complex presentations and etiology still perplex healthcare professionals and scientists. To improve our understanding of the variations in presentation of chronic pain, it is essential to understand the close interactions between various relevant psychosocial and physiological processes [3].

As proposed by the Gate Control Theory [3], sensory information from afferent neurons to transmission cells in the spinal cord is moderated by the substantia gelatinosa in the dorsal horn, which functions as a "pain gate." This gate can affect the transmission of the nociceptive signal by opening or closing. It is postulated that this gate is modulated not only by input from supraspinal centers but also by the thoughts, feelings, and behaviors of the patient. In other words, negative view (eg, focusing on pain and non-constructive thoughts), feelings (eg, sadness, helplessness, anger, hopelessness), and behaviors (eg, inactivity, smoking, sleep deprivation) can potentially "open" the gate, while positive thoughts, feelings, and behaviors can prevent the gate from "opening" [3].

Fear is defined as an emotional and behavioral reaction [4] to immediate threat or a past distressing event, and fear of pain is explained as an emotional and behavioral response to stimuli [5] that are or are perceived to be painful. Fear of pain may cause aversion to movement or activity, or escape in response to noxious stimuli [5]. These responses are believed to evolve from catastrophic thoughts and beliefs and negative interpretations of the potentially painful stimulus [6]. The manner in which an individual responds or reacts to pain is often influenced by their fear of pain and not by the pain itself [7,8]. This maladaptive response is believed to precede persistent pain and disability through a fear-avoidance cycle [6] and plays a vital role in initiating, developing, and sustaining pain [9]. Similarly, coping is also described as a psychological response exhibited by individuals when managing stressful events such as chronic pain [10]. The coping strategies employed in response to a stressor significantly determines psychological adjustment and well-being of the individual [11]. Several distinct coping styles have been recognized, such as approach and avoidance coping [12], problem-focused and emotion-focused coping [13], situational and dispositional coping [14], and active and passive coping [15]. Although these styles are independent, they show influence on mood, anxiety, depression, behavior, and clinical outcomes [15,16]. The psychological shift observed in chronic pain patients can be guided by these coping strategies [17].

It is plausible that distinct emotional-behavioural responses can not only keep the pain gate "open" or "closed", but can also likely influence and interact with each other affecting the course

of chronic pain. The level of fear of pain could influence the choice of coping strategies applied by patients with chronic pain and conversely. It is also likely that coping strategies could act as mediator of the effect of fear of pain. To our knowledge, the relationship between pain, fear of pain and coping strategies has not previously been investigated. How these emotional-behavioral responses affect health-related quality of life and outcomes in patients with chronic pain also remains unclear. A better understanding of how these factors influence and interact with each other will help build knowledge that will ultimately facilitate improved care for chronic pain sufferers.

Study Aim and Objectives

The aim of this study is to examine if there is an interaction between fear of pain and coping strategies and how this interaction influences patient-anticipated outcomes and health-related quality of life. We will also test the following hypotheses: (1) both fear of pain and coping strategies are sufficient causes for maintaining pain; and (2) fear of pain influences coping strategies and pain.

The specific objectives of this study are (1) to examine if fear of pain acts as a mediator or moderator between coping strategies and pain severity; (2) determine the common predictors of high fear of pain levels and passive coping strategies; (3) examine if fear of pain affects health-related quality of life and patient-anticipated outcomes reported by individuals experiencing chronic pain; and (4) examine if coping strategies affect health-related quality of life and patient-anticipated outcomes reported by individuals experiencing chronic pain.

Methods

Study Design

A cross-sectional design will be used to conduct this study. An online survey will be conducted as it is cost-effective and can reach a diverse group of populations regardless of geographical location. With an online survey, identical questions can be posed to all participants, which allows researchers to draw generalizable results tailored to patients with chronic pain.

Validated questionnaires will be used for this study, with the patient-anticipated outcomes assessment specifically designed after reviewing the literature and conducting discussions with researchers. The survey comprises the Fear of Pain Questionnaire-III (FPQ-III) [5], the Brief Coping Inventory (COPE) questionnaire [18], and EuroQol-5d (EQ-5D) [19]. The study will be administered via Survey Monkey. Ethical approval for this study was granted by the Human Research Ethics Committee of the University of Adelaide.

Selection Criteria

Participants aged 18 years and above who are experiencing pain for more than 6 months and have good comprehension of the English language will be invited to participate in this study.

Individuals younger than 18 years of age and experiencing chronic pain for less than 6 months will be ineligible.

Recruitment

The study will be advertised on the University of Adelaide website. Health-related organizations and patient forums popularly accessed by patients with chronic pain will be approached for advertising the survey—both within Australia and internationally—using the networks of the study authors. Invitation for the study will inform the interested participants of our inclusion and exclusion criteria and assure potential participants of anonymity (no personal information will be collected during any stage of the survey) and voluntary participation. No direct contact will be established with potential participants.

Consent

The invitation to take part in the study will include a Web link, which will take the participant to the information page of the survey. The information sheet will provide a description of the research team, purpose of the study, the type of questions asked in the survey, expected completion time, and contacts for

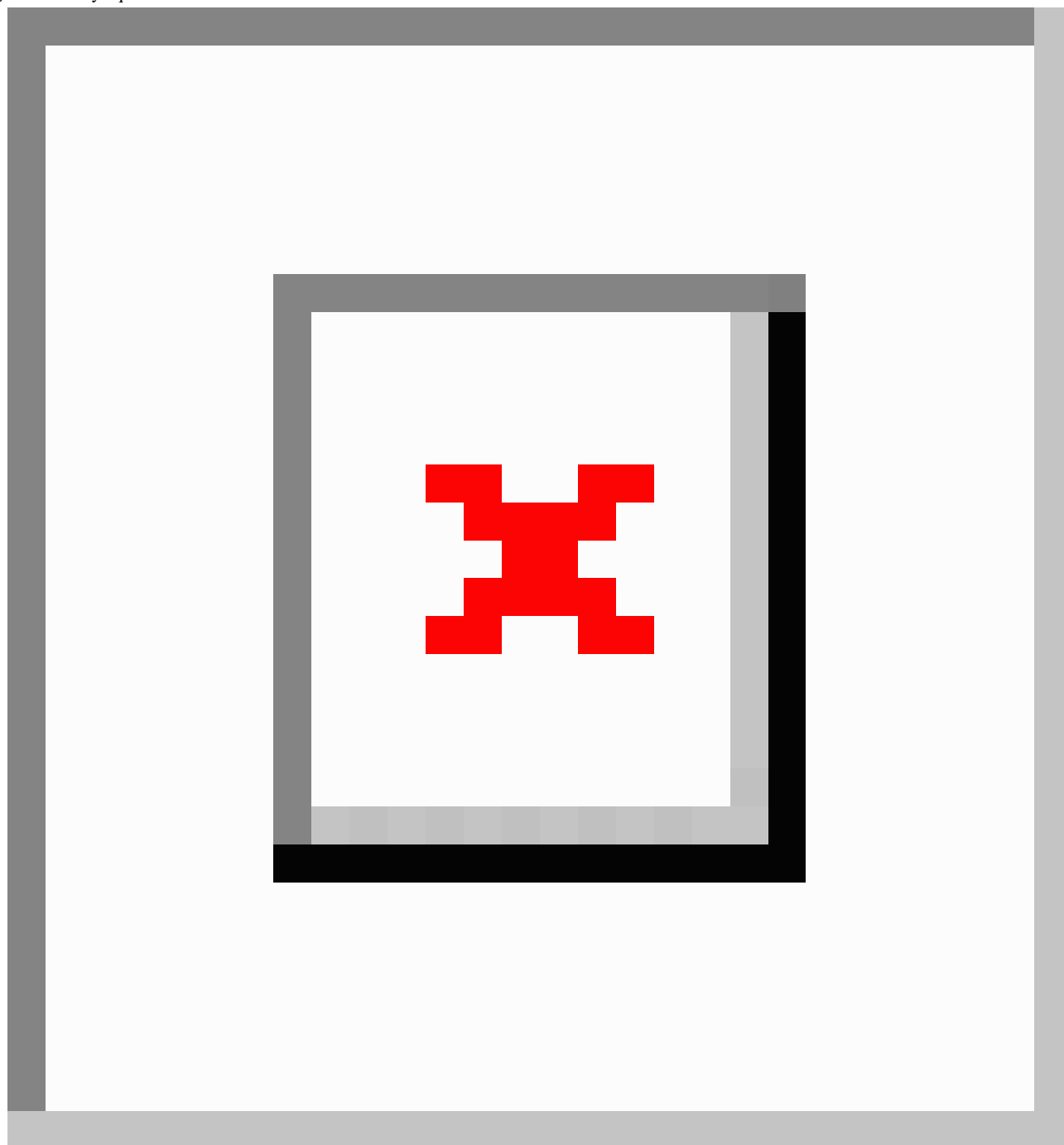
grievances or feedback. At the bottom of the information sheet, the participant will be asked to “click” a box as their consent to participate in the study. Only participants providing their consent will be directed to the survey page.

Data Storage and Handling

The data will be stored on a password-protected desktop computer located at the Australian Research Centre for Population Oral Health (ARCPOH). Because no information that could potentially identify the participant will be collected, the data will be completely anonymous. Any written information from the study will be stored on a password-controlled University of Adelaide computer, which itself is not accessible to the public. Only the listed authors will have access to the data collected.

Sample Size

Following the simple random sampling approach, a sample size of 480 is estimated for 95% confidence interval, with P equal to .5 and delta of .05 (Figure 1, equation a), where n is sample size, P is the estimated population proportion, and δ is the precision of the estimate.

Figure 1. Study equations.

Dependent Variables

Fear of Pain

The FPQ-III is a self-reporting scale that measures fear of severe pain, minor pain, and medical pain. The FPQ-III is a self-rating scale that measures fear of severe pain, minor pain, and medical pain. It uses a 5-point rating scale that measures fear across a range of situations which can trigger pain. The overall score (range 30 to 150) and subscale scores (range 10 to 50) will be calculated for every participant. The validity and reliability of FPQ-III has been confirmed through various studies [5,20-22].

Brief Coping Inventory Questionnaire

To examine the ways in which participants cope with everyday pain, the original version of the Brief COPE will be used [18]. The Brief COPE is based on the COPE inventory developed by Carver and colleagues [12]. It is a self-report scale measuring use of problem- and emotion-focused coping strategies across 14 different approaches (grouped into 14 different scales). Each item is scored using a 4-point Likert scale. As recommended by Carver et al [12], each scale will be recorded separately to determine its relationship with other variables. The validity and reliability of the Brief COPE questionnaire has been studied and confirmed by multiple studies performed in different countries and samples [23-26]. The Brief COPE was preferred over the original COPE questionnaire due to its concise format,

which requires less time for completion, thus preventing participant fatigue.

Independent Variables

Demographic Information

The survey will collect the following demographic information: age, sex, country of residence, metropolitan or non-metropolitan location, marital status, level of education, type and status of employment, and rating of family income in past 12 months (low, middle, and high income).

Information on Current Pain Problem

Information regarding most painful body part(s), diagnosis provided, and if the pain is related to an injury or accident with legal proceedings in process will also be collected.

European Quality of Life Questionnaire

The 5-level EQ-5D (EQ-5D-5L) [19] will be used to assess participants' subjective assessment of their physical, mental,

and social well-being. EQ-5D is a short report of health-related quality of life. It appraises movement, self-care, daily activities, pain/discomfort, anxiety/depression, and self-rated health state using a visual analogue scale (VAS). The questionnaire will be scored as recommended by the EQ-5D-5L committee. The reliability and validity of EQ-5D in various diseases has been shown by studies performed in different countries and populations [27-29].

Patient-Anticipated Outcomes

A detailed literature search was performed to understand the outcomes anticipated by individuals experiencing chronic pain. A total of 15 items were documented which were then grouped into the following domains: (1) pain-specific, (2) physiological, (3) social, (4) psychological, and (5) economical. Participants will be asked to select the 5 most expected outcomes from a list of outcomes (Textbox 1).

Textbox 1. Domains of clinical outcomes.

Domain
<ul style="list-style-type: none">• Pain-specific<ul style="list-style-type: none">• Reduce pain• Reduce amount of daily medications• Self-management of pain or discomfort• Physiological<ul style="list-style-type: none">• Improve sleep and concentration• Improve physical functioning- more walking, exercise, movement and strength• Less tiredness and fatigue• Social<ul style="list-style-type: none">• Plan a holiday/travel• Socialize more with family and friends• Pursue a hobby—cooking, gardening• Psychological<ul style="list-style-type: none">• Improve mood, less stress, anxiety and worry• Improve self-worth• Be optimistic about the future• Economical<ul style="list-style-type: none">• Go back to work/increase working hours and improve performance• Go back to studying• Improve financial earning

Statistical Analysis

STATA statistical software [30] will be used for all statistical analyses.

Objective 1:

To examine if fear of pain acts as a mediator or moderator between coping strategies and pain severity, we will test 2 hypotheses in this objective. The first hypothesis is depicted in Figure 2 and the second hypothesis is depicted in Figure 3. In

Figure 2, we hypothesize that both fear of pain and coping strategies are sufficient causes for maintaining pain. In other words, we hypothesize that fear of pain acts as a moderator between coping strategies and pain, where moderator is defined as the variable that has the potential to alter the strength of the causal relationship between exposure and outcome [31].

To examine if fear of pain acts as a moderator between coping strategies and pain we will use the effect measure modification technique (EMMM) as detailed by VanderWeele [32] (Figure 1, equation b) where X is exposure, Y is outcome, and Z is another exposure which is not an effect of X. Thereby, the effect of X (exposure) on Y (outcome) may vary across the subpopulations of Z (second exposure (ie, for some levels of the exposure x_0 and x_1)). Simply, the expected average change of the first exposure on the outcome is not constant within the realized values of the second exposure Z. Since it is sensitive to scale (eg, log [multiplicative] or linear additive), we will utilize the EMMM using both additive and multiplicative scales.

Alternatively, we also hypothesize that fear of pain influences coping strategies and pain (Figure 3). To test this second hypothesis we will conduct mediation analysis. From mediation analysis, we intend estimating the direct and indirect effects of fear of pain on pain. Direct and indirect effect effects will be estimated using the counterfactual theory. In counterfactual theory, we create the counter-to-the-fact scenarios and estimate the change in the outcome. Counterfactual theory is used as it allows us to estimate the marginal compared to the simple regressions, which only allows us to compute the conditional estimates [33]. In counterfactual theory, the direct estimate is the natural direct effect, and the indirect effect is the total indirect effect. The natural direct effect is the change in the potential outcome when the individual receives a treatment and the same individual does not receive treatment when the mediator is set to a counterfactual level. The total indirect effect is defined as the change in the potential outcome when treatment is set to the counterfactual level and the mediator is set to the observed and the counterfactual levels (Figure 1, equations c-e).

Figure 2. Hypothesis 1: fear of pain acts as a moderator between coping strategies and pain. X (exposure) is coping strategies; Y (outcome) is pain; Mo (moderator) is fear of pain.

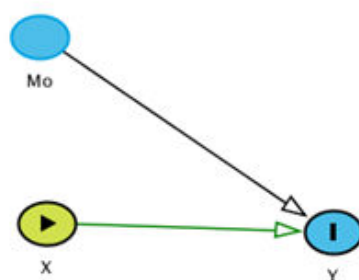
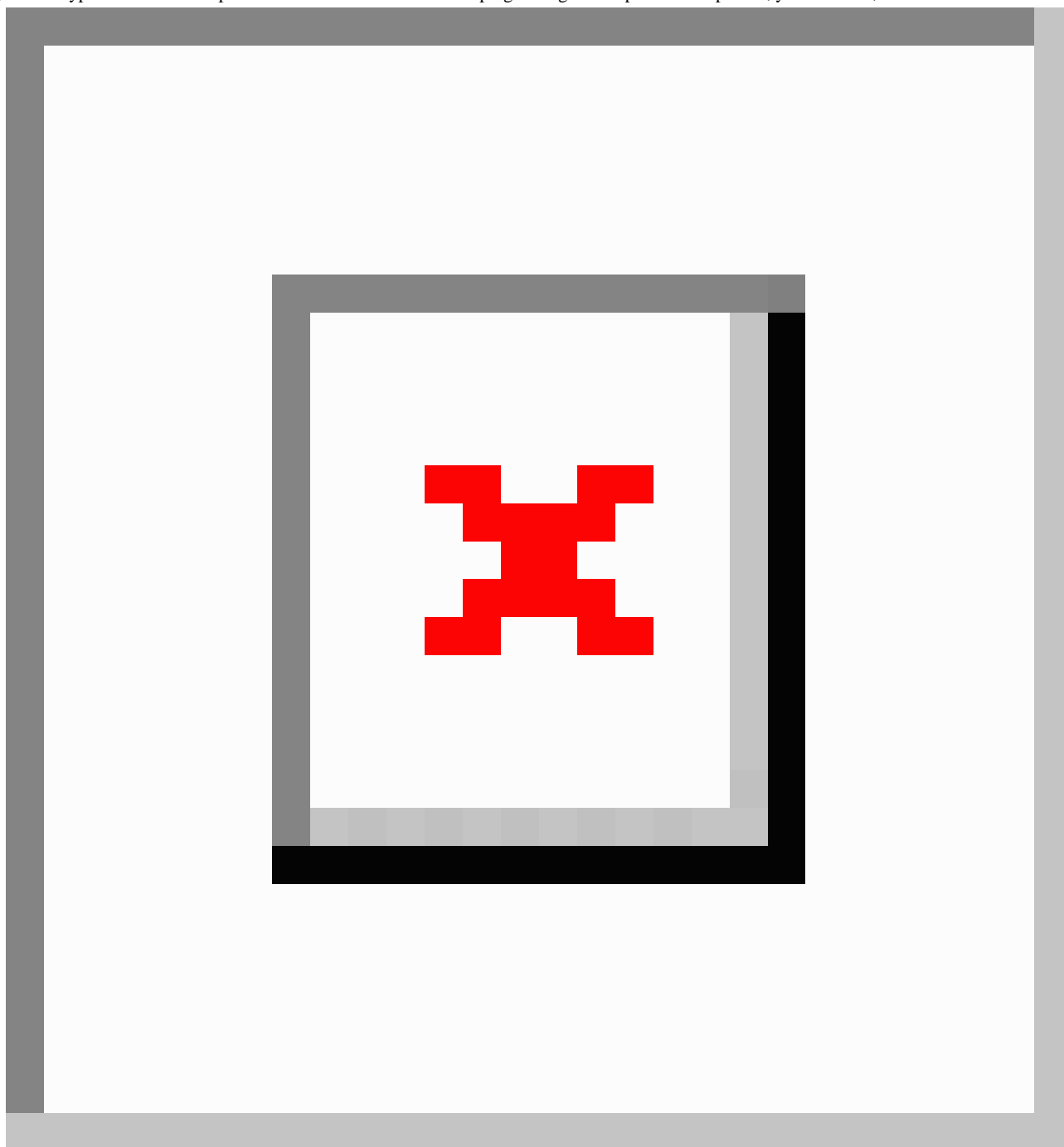


Figure 3. Hypothesis 2: fear of pain acts as a mediator between coping strategies and pain. x is exposure; y is outcome; M is mediator.



Objective 2

To determine the common predictors of high fear of pain and maladaptive coping strategies, we will conduct a simple logistic regression analysis because our outcome is measured as a binary variable.

Objective 3

Multinomial logistic regression modeling will be used to determine the effect of fear of pain on health-related quality of life and patient-anticipated outcomes. Multinomial logistic regression modeling will allow us to predict the probability of categorical membership on the dependent variable based on multiple independent variables [27].

Objective 4

Univariate logistic regression modeling will be used to determine the effect of coping strategies on health-related quality of life and patient-anticipated outcomes. All analyses will be adjusted for confounders such as age, sex, residential location (ie, metro, non-metro), marital status, employment status, and education. The entire sample will be described using simple descriptive statistics such as means, proportions and variances.

Dissemination

Findings from this study will be presented at conferences and public forums. The results will be published in peer-reviewed journals.

Results

Participant recruitment and data collection began July 2017 and it is anticipated that all data will be collected by October 2017. The findings from this study will help to extend our understanding of fear of pain and coping strategies, their interaction, and their impact on health-related quality of life and patient-anticipated outcomes.

Discussion

Principal Findings

This study aims to extend our understanding of key emotional behavioral responses observed in chronic pain patients: fear of pain and coping strategies. While previous studies have assessed their effect on treatment outcomes, their impact on and interaction with each other has not previously been examined. Considering that both fear of pain and adaptive or maladaptive coping could co-exist in chronic pain patients, their association is predictable. However, we hypothesize that fear of pain, which

can exist with or without a pain-causing event, can act as a mediator between the coping strategies and pain. It is anticipated that the study findings will help detect common predictors of fear of pain and adaptive versus maladaptive coping strategies, allowing healthcare professionals and researchers to build a management plan tailored to individual patient needs.

Limitations

Causal inferences will not be able to be drawn from our findings due to the cross-sectional study design. As the study may potentially have participants from different countries, it may lack specificity.

Conclusion

Enhancing our understanding of the interplay between fear of pain and coping strategies, and its effect on health-related quality of life and patient-anticipated outcomes, may increase understanding of how different psychosocial factors modify the course of chronic pain. It is also anticipated that the findings from this study may be helpful in developing patient-centered care strategies for chronic pain sufferers.

Conflicts of Interest

None declared.

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Abbreviations

COPE: Coping Inventory
EMMM: effect measure modification technique
EQ-5D: EuroQol-5d
EQ-5D-5L: 5-level EQ-5D
FPQ-III: Fear of Pain Questionnaire-III

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Protocol

The Paget Trial: A Multicenter, Observational Cohort Intervention Study for the Clinical Efficacy, Safety, and Immunological Response of Topical 5% Imiquimod Cream for Vulvar Paget Disease

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Abstract

Background: Vulvar Paget disease is a rare skin disorder, which is most common in postmenopausal Caucasian women. They usually present with an erythematous plaque that may show fine or typical “cake icing” scaling or ulceration that may cause itching, pain, irritation, or a burning sensation. Although most cases are noninvasive, vulvar Paget disease may be invasive or associated with an underlying vulvar or distant adenocarcinoma. The histological evidence of so-called “Paget cells” with abundant pale cytoplasm in the epithelium confirms the diagnosis. The origin of these Paget cells is still unclear. Treatment of choice is wide local excision with negative margins. Obtaining clear surgical margins is challenging and may lead to extensive and mutilating surgery. Even then, recurrence rates are high, ranging from 15% to 70%, which emphasizes the need for new treatment options. A number of case reports, retrospective case series, and one observational study have shown promising results using the topical immune response modifier imiquimod.

Objective: This study aims to investigate the efficacy, safety, and immunological response in patients with noninvasive vulvar Paget disease using a standardized treatment schedule with 5% imiquimod cream.

Methods: Topical 5% imiquimod cream might be an effective and safe treatment alternative for vulvar Paget disease. The Paget Trial is a multicenter observational cohort study including eight tertiary referral hospitals in the Netherlands. It is ethically

approved by the Medical-Ethical Committee of Arnhem-Nijmegen and registered in the Central Committee on Research Involving Human Subjects (CCMO) Register by as NL51648.091.14. Twenty patients with (recurrent) noninvasive vulvar Paget disease will be treated with topical 5% imiquimod cream three times a week for 16 weeks. The primary efficacy outcome is the reduction in lesion size at 12 weeks after end of treatment. Secondary outcomes are safety, immunological response, and quality of life. Safety will be assessed by evaluation of adverse events and tolerability of treatment. To evaluate the immunological response, various immunological markers will be tested on biopsy specimens taken before, during, and after treatment. Quality of life will be assessed with three questionnaires taken before, during, and after treatment.

Results: First results are expected in the summer of 2018.

Trial Registration: ClinicalTrials.gov NCT02385188; <https://clinicaltrials.gov/ct2/show/NCT02385188> (Archived by WebCite at <http://www.webcitation.org/6sXygHuhP>).

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KEYWORDS

Paget disease; extramammary Paget disease; vulvar Paget disease; imiquimod

Introduction

Cutaneous Paget disease was first described in a series of patients with nipple ulceration and an underlying breast carcinoma. This became known as mammary Paget disease (MPD) [1]. When the same condition was reported on the scrotum and vulva, these were named extramammary Paget disease (EMPD) [2,3].

The presence of so-called Paget cells in the basal layers of the epithelium is pathognomonic for this rare disease. The origin of these large cells with abundant clear, pale cytoplasm, which often contain mucin, remains unclear. The most common hypothesis is that Paget cells originate from adnexal structures, such as apocrine glands or multipotent stem cells in the basal layer of the epidermis [4,5]. Other theories suggest the anogenital area contains mammary-like glands or that Toker cells, also seen in the nipple in mammary Paget disease, are precursor cells for EMPD [6-8].

The incidence rate of EMPD is 0.11 per 100,000 person-years, based on an epidemiological study with data of the Netherlands Cancer Registry [9]. Vulvar Paget disease (VPD) causes pain, itching, or a burning sensation, and a skin lesion, which can be described as a scaling, erythematous plaque that sometimes shows ulceration. VPD typically presents in postmenopausal Caucasian women [8].

Vulvar Paget disease can be divided into primary VPD, which is cutaneous, and secondary VPD, which is noncutaneous. [Textbox 1](#) illustrates the different types of VPD [10].

Vulvar Paget disease is associated with different malignancies, mainly an underlying vulvar, intestinal, or urological malignancy, and breast cancer. Approximately 20% of patients are reported to have an associated malignancy in their history.

Therefore, screening for underlying carcinoma is advised, although there is no evidence for screening and no consensus on the extent of the additional diagnostic procedures [11,12].

Historically, the treatment of choice for VPD is wide local excision with clear margins, which is not always easy to realize on the vulva. Because Paget cells are found widely spread throughout the anogenital area, it is almost impossible to obtain clear surgical margins [13,14]. The recurrence rates of VPD are high: 15% to 70% independent of margin status. The risk of recurrence is highest in the first year after treatment [15]. To improve obtaining clear surgical margins, Mohs microsurgery has been evaluated for treatment of VPD. In Mohs microsurgery, the lesion is excised and the entire margin is examined immediately [16]. In case the margin is not clear, the excision is repeated, enlarging the circumference until the margins are clear. This technique may lead to lower recurrence rates [17]. However, large vulvar excisions may require plastic reconstruction.

Extensive vulvar surgery can cause permanent mutilation and functional impairment [18-22]. To address this problem, alternative treatment options such as photodynamic therapy, radiotherapy, chemotherapy, laser treatment, and recently topical 5% imiquimod cream have been used in patients with VPD with varying degrees of success [23-30].

Topical 5% imiquimod cream is an immune response modifier. It binds to toll-like receptor 7, inducing an innate and cell-mediated immune response [31]. It has antiviral and antitumor properties and is registered for the treatment of condylomata acuminata, actinic keratosis, and superficial basal cell carcinomas. Imiquimod also has shown to be effective for human papilloma virus-induced usual vulvar intraepithelial neoplasia [32,33]. The mechanism of action of imiquimod and local immunity in VPD are not known.

Textbox 1. Different types of vulvar Paget disease.**Primary EMPD (cutaneous)**

Type 1a: associated with noninvasive, intraepithelial disease

Type 1b: associated with invasive disease

Type 1c: associated with an underlying adenocarcinoma

Secondary EMPD (noncutaneous)

Type 2: EMPD originates from intestinal adenocarcinoma

Type 3: EMPD originates from urothelial carcinoma

More recently, a number of case reports, case series, and one observational trial that reported on the use of topical 5% imiquimod cream for VPD showed that imiquimod may be an effective treatment option [34,35]. A systematic review also concluded it is an effective alternative for VPD [36]. However, most studies described limited numbers of patients, various treatment schedules, and short follow-up periods. Therefore, it is impossible to pool data from previous studies to make final conclusions about the efficacy. The authors of the systematic review also mentioned the risk of publication bias: only positive results may be published retrospectively [36].

Objective

The objective of this study is to assess the clinical efficacy, safety, and local immunity of topical 5% imiquimod cream in patients with noninvasive VPD.

Methods**Study Design**

This study is a multicenter, prospective, open-label observational cohort study in patients with histologically proven, noninvasive VPD. Patients will be treated with topical 5% imiquimod cream three times a week for 16 weeks, with follow-up of one year after the end of treatment.

Study Setting

Because VPD is rare, with an estimated incidence of four to seven cases per year in the Netherlands, the trial will be carried out in seven tertiary referral hospitals with a vulvar clinic in the Netherlands. Vulvar clinics are outpatient multidisciplinary clinics with participation of both gynecologists and dermatologists who are specialized in disorders of the vulva.

Participating centers are Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam; Catharina Ziekenhuis, Eindhoven; Erasmus Medical Center, Rotterdam; Leiden University Medical Center; Radboudumc, Nijmegen; University Medical Center Groningen; and University Medical Center Utrecht.

Participants

All patients with histologically proven noninvasive cutaneous VPD visiting or referred to a participating clinic will be asked to participate in this study. We estimate to include one patient per center per year because of the rarity of the disease.

Inclusion criteria are noninvasive VPD (primary or recurrence after earlier surgery or imiquimod treatment more than 6 months previously), age 18 years and older, and willing and able to

comply with the protocol and provide informed consent in accordance with institutional and regulatory guidelines. Most patients are expected to be elderly, postmenopausal women, who may suffer from comorbidities. All patients will be instructed on how to apply the imiquimod cream by their clinician, according to the leaflet provided by the manufacturer, and using a mirror. If the patient is physically unable to apply the cream, a health care provider (eg, a nurse at the nursing home or via domiciliary care) will receive written instructions. If the patient consents, a printed photograph in which the affected skin is marked will be provided. Main exclusion criteria are current invasive VPD, underlying adenocarcinoma, and treatment of the vulva with topical 5% imiquimod cream during the last 6 months.

Sample Size

Based on the estimated incidence of VPD in the Netherlands, viability is set at 20 inclusions. Our sample size considerations are based on the response rate. The primary outcome variable is the response at 12 weeks after end of treatment with topical 5% imiquimod cream. The only observational study on this topic, at time of conception of this trial, reported a response in 9 of 10 women [35]. Assuming a complete response rate of 80%, a cohort size of 20 patients is sufficient to estimate the complete response rate with a standard error of 9%, using the normal approximation for the binomial distribution. Because we presume that the dropout rate will not exceed 20%, a maximum of 25 patients will be included. When 20 patients have been treated with topical 5% imiquimod cream for at least 8 weeks, we will stop recruitment.

Study Intervention

All patients will be treated with topical 5% imiquimod cream three times a week for 16 weeks. This treatment schedule is based on the treatment schedule for condylomata acuminata and on a previous randomized controlled trial of imiquimod 5% for usual vulvar intraepithelial neoplasia [31,33]. The healthy skin around the visible lesion can be protected with an indifferent basic ointment. Patients are allowed to use topical 3% lidocaine in Vaseline ointment if they experience pain at the application site. There must be a 1-hour interval between the application of different topical agents. Patients are also allowed to use paracetamol. In case of severe pain, when paracetamol and 3% lidocaine ointment are insufficient, it is permitted after consultation with the clinician to stop the treatment with topical 5% imiquimod cream for one week at a time. Patients are allowed to stop/delay treatment for a total of 3 weeks within the assigned treatment period.

Table 1. Study schedule presenting an overview of all study activities.

Study activities	0 w	Baseline	4 w	10 w	16 w	28 w	40 w	52 w	68 w
Before treatment									
Mapping and mammography	X								
Written informed consent	X								
Require histological samples (incl. mapping) and mammography results from referring hospital	X								
Imiquimod 5% cream									
		Start			Stop				
Consultation by phone				X					
Consultation at outpatient clinic of involved research clinic, containing:	X	X			X	X	X	X	X
Vulvar examination, measurement and photo documentation	X	X			X				X
VAS score	X	X	X	X	X	X	X	X	X
Tolerability questionnaire		X	X	X					
Biopsy	X		X			X			
EQ5D		X	X			X			
DLQI		X	X			X			
FSDS		X	X			X			
Review patient diary			X	X	X				

In case of a suspected secondary bacterial infection, fucidin cream or ointment 20 mg/g will be prescribed. The patient will apply the fucidin cream or ointment three times a day, according to the prescription. No other local products than imiquimod cream, lidocaine, indifferent moisturizers, or fucidin are allowed to be applied at the lesion site. On an individual basis, other topical products will be considered as a protocol violation.

Study Schedule

Patients will visit the clinic seven times during the study; the final visit will be 1 year after the end of treatment (Table 1). One consultation will take place by telephone. During these consultations, pain will be measured by means of the visual analog scale (VAS) score for pain. Pain, burning, and itching will be asked on a four-point Likert scale. During the visits, the clinical response will be evaluated by vulvar examination and bidimensional measurement of the visible lesions. The histological effect will be assessed by pathological assessment of the presence of Paget cells in the biopsy sample(s) taken 12 weeks after the end of treatment. All biopsy samples taken before, during, and after treatment will be taken around the same location. The site of the first biopsy is most likely the most evident lesion, causing a clinically visible lesion. The site of this biopsy will be recorded in the case report file to ensure other biopsies will be taken at the same area. Quality of life will be assessed before, during, and after treatment using three questionnaires on general health (EQ-5D), dermatological quality of life (Dermatology Quality of Life Index [DLQI]), and (if applicable) sexual functioning (Female Sexual Distress Scale [FSDS]).

Safety will be evaluated by documentation of all adverse effects, recorded by the clinician and by the patient in the patient diary.

The immunological effect will be assessed by comparing the results of additional immunohistochemistry stains performed

on all three samples taken around the same location at baseline, 4 weeks after start of treatment, and 12 weeks after end of treatment. All biopsies will be taken at approximately the same location to ensure the local microenvironment is as similar as possible in all samples. There are limited data on the tumor microenvironment in VPD; we are currently performing a separate pilot study to investigate the parameters in the immune infiltrate in VPD. We are investigating which immune cells are present in VPD, and will use this knowledge to further explore which immune cells respond to the topical imiquimod cream and the role they play in the origin and treatment of VPD. The results of this separate pilot study will be used to decide which markers will be investigated in the samples collected in the Paget Trial.

Study Endpoints

The main study outcome is clinical response. This will be assessed by determination of the reduction in lesion size 12 weeks after the end of treatment. This will ensure any local skin effects caused by treatment will be healed at time of examination. All measurements during the study will be conducted by the same trained and experienced local clinician. Photographs for documentation will be taken with a ruler alongside the lesions. The comparison between the lesion size at the start of treatment and 12 weeks after the end of treatment can lead to the following outcomes:

1. Complete response: defined as disappearance of the lesion and histological confirmation of disappearance;
2. Partial response: defined as decrease by $\geq 50\%$ of total lesion size;
3. No response: defined as $< 50\%$ decrease of total lesion size; or

4. Progressive disease: defined as $\geq 25\%$ increase of total lesion size or progression into invasive disease and/or adenocarcinoma.

Secondary outcomes are the safety, quality of life, and the assessment of local immunological response. These outcomes will be assessed according to the following criteria:

1. Safety: all adverse events that occur during the study will be collected by the clinician at every consultation (at the clinic or via telephone) and by the patient using a standardized patient diary.
2. Quality of life: results of the three questionnaires (EQ-5D, DLQI, and, if applicable, FSDS) taken before, during, and after treatment will be compared.

Local immunological response will be assessed by a set of markers, to be determined, in tissue samples obtained by vulvar biopsy before, during, and after treatment.

Statistical Analysis:

An intention-to-treat (ITT) and per protocol (PP) analysis will be performed. The population included in the ITT analysis is defined as all patients that have started treatment with topical 5% imiquimod cream. The PP analysis will include patients that have completed treatment with topical 5% imiquimod cream according to protocol. Two-tailed P values $< .05$ will be considered statistically significant. Our primary study parameter is the clinical response to topical 5% imiquimod cream. Twelve weeks after the end of treatment, the clinician will examine the vulva of the patient and assign the patient in one of the response categories as defined previously. Estimates of the percentage responders per response category will be presented with corresponding 95% confidence intervals. The relation between treatment duration and dose versus response will be explored. Safety will be analyzed in a descriptive manner, presenting all adverse events (local and systemic) in all participants treated with topical 5% imiquimod cream. Also, the use of painkillers, lidocaine ointment, and discontinuation of treatment will be reported.

Quality of life will be assessed by three questionnaires. The EQ-5D results will be converted to the crosswalk index values, using the Crosswalk Index Value Calculator [37]. The DLQI results will be categorized according to the instruction manual, ranging from “no effect at all on patient’s life” to “extremely large effect on patient’s life” [38]. The result of the FSDS is the sum of the answers. Descriptive statistics will be used to present the change outcomes during treatment versus before treatment, and after treatment versus before treatment. A subanalysis of responders and nonresponders will be conducted.

The immunological results will be counted and compared between the different biopsy samples. These data will be reported in a descriptive manner.

Ethics

This study will be conducted according to the principles of the Declaration of Helsinki (2008) and the Medical Research Involving Human Subjects Act (Dutch: WMO). The protocol has been medical-ethically approved by the Medical-Ethical Committee of Arnhem-Nijmegen to be conducted in all seven

centers (NL51648.091.14). Before enrollment to the study, written informed consent will be obtained from all patients.

Results

The study opened for enrollment in January 2015. Currently, 17 patients are participating in this trial. The first results are expected in the summer of 2018.

Discussion

Currently, this study is the first prospective study examining the clinical efficacy of topical 5% imiquimod cream in patients with noninvasive VPD using a standardized treatment schedule over 16 weeks. In addition, this study will also be the first to investigate the safety, quality of life, and immunological response of 5% imiquimod cream therapy in patients with VPD.

Until now, about 25 retrospective case series have been published on this topic. These studies show high success rates. The effectiveness of topical 5% imiquimod cream for VPD in these cases might be overrated due to publication bias in these retrospective cases. Most of the retrospective series have used different treatment schedules. The prospective trial of Marchitelli et al [35] used a different treatment schedule per patient. In most case studies, treatment was continued until the patient obtained a complete response. The pilot study by Cowan et al [34] investigated the clinical response after 12 weeks of treatment in eight patients with noninvasive VPD. Patients applied the cream three times a week. Six patients had a clinical and histological complete response; the other two had a partial response with histological persistence. In our study, all 20 consecutive patients will be treated according to the same treatment schedule: three times a week for 16 weeks. Currently, there are no guidelines for topical 5% imiquimod treatment for VPD. We based the treatment schedule on the treatment schedule for condylomata acuminata because this is a registered indication and therefore we consider this treatment schedule to be safe for genital skin [31]. Furthermore, VPD may be considered a vulvar premalignancy, and the same treatment schedule is used in a previous randomized controlled trial of imiquimod 5% for usual vulvar intraepithelial neoplasia [33].

There are very limited data concerning the influence of VPD on everyday life of the patient. It is reported that vulvar surgery may contribute to decreased quality of life and sexual functioning compared to healthy patients. As VPD has high recurrence rates, we assume (repetitive) surgical treatment may have significant psychosexual effects on patients. Topical treatment with 5% imiquimod cream will not induce scarring nor will it alter the anatomy of the vulva. Because there is a lack of data on this specific topic, we will investigate quality of life with three different questionnaires before, during, and after treatment.

The mechanism of action and immunological effects of 5% imiquimod cream in VPD are uncertain. It is likely that imiquimod’s immune modulating effect induces a local immune response resulting in clearance of the Paget cells. Investigating the immunological response in biopsy specimens taken before, during, and after treatment will provide insight in the local

effects of imiquimod in the skin and also in the underlying mechanisms of action. Unfortunately, there is no current literature on this topic. Therefore, we are conducting a pilot study, investigating the microenvironment of VPD, to assess which markers may be valuable in understanding the immunological response in VPD.

In conclusion, VPD remains an elusive disease. Surgery has been the treatment of choice for over a century. Due to high

recurrence rates and the vulnerable patient population affected by the disease, there is a need for other less-invasive treatment options. Topical 5% imiquimod cream may be an attractive alternative. Our trial will investigate the clinical efficacy of topical 5% imiquimod cream in 20 patients with a standardized treatment schedule. This study will also evaluate the safety, quality of life, and immunological response while using 5% imiquimod cream.

Authors' Contributions

JdH, CvH, MvP, MvB, MvS, KM, and MvdL were involved in the conception of the study. MvdL, KM, JB, TB, MvP, and JdH were involved in the design of the study. MvdL, KM, and JdH drafted the manuscript. JitH drafted the statistical methods and performed the sample size calculation. All authors are members of the study group; MvB, DB, CvH, MvP, BS, JdH, MvS, and EvD are local investigators at the participating centers. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

KM provides consulting services for Eucerin Beiersdorf NV, the Netherlands.

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Abbreviations

DLQI: Dermatology Quality of Life Index
EMPD: extramammary Paget disease
FSDS: Female Sexual Distress Scale
ITT: intention to treat

MPD: mammary Paget disease

PP: per protocol

VAS: visual analog scale

VPD: vulvar Paget disease

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Protocol

Understanding the Natural Progression of Spina Bifida: Prospective Study

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Abstract

Background: Spina bifida (SB) is monitored through birth defects surveillance across the United States and in most developed countries. Although much is known about the management of SB and its many comorbid conditions in affected individuals, there are few systematic, longitudinal studies on population-based cohorts of children or adults. The natural history of SB across the life course of persons with this condition is not well documented. Earlier identification of comorbidities and secondary conditions could allow for earlier intervention that might enhance the developmental trajectory for children with SB.

Objective: The purpose of this project was to assess the development, health, and condition progression by prospectively studying children who were born with SB in Arizona and Utah. In addition, the methodology used to collect the data would be evaluated and revised as appropriate.

Methods: Parents of children with SB aged 3-6 years were eligible to participate in the study, in English or Spanish. The actual recruitment process was closely documented. Data on medical history were collected from medical records; family functioning, child behaviors, self-care, mobility and functioning, and health and well-being from parent reports; and neuropsychological data from testing of the child.

Results: In total, 152 individuals with SB were identified as eligible and their parents were contacted by site personnel for enrollment in the study. Of those, 45 (29.6%) declined to participate and 6 (3.9%) consented but did not follow through. Among 101 parents willing to participate, 81 (80.2%) completed the full protocol and 20 (19.8%) completed the partial protocol. Utah enrolled 72.3% (73/101) of participants, predominately non-Hispanic (60/73, 82%) and male (47/73, 64%). Arizona enrolled 56% (28/50) of participants they had permission to contact, predominately Hispanic (18/28, 64%) and male (16/28, 57%).

Conclusions: We observed variance by site for recruitment, due to differences in identification and ascertainment of eligible cases and the required institutional review board processes. Restriction in recruitment and the proportion of minorities likely impacted participation rates in Arizona more than Utah.

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KEYWORDS

spina bifida; natural history; birth defect; disability; surveillance; recruitment

Introduction

Spina bifida (SB) is a neural tube defect that occurs in the first month after conception and involves a defect of variable severity in the developing spinal cord [1-3]. The term SB is an umbrella term and includes different types of spinal cord defects, of which myelomeningocele is the most frequent and the most involved. SB is monitored through birth defects surveillance across the United States and in most developed countries. A concerted public health emphasis on primary and secondary prevention has been associated with a decreased birth prevalence and improved health outcomes in individuals with SB [4]. In the United States, the estimated prevalence is 2-3 per 10,000 live births [5,6]. Although much is known about the management of SB and its many comorbid conditions in affected individuals, there are few systematic, longitudinal studies on population-based cohorts of children or adults. The natural history of SB across the life course of persons with this condition is not well documented [7,8].

Health, developmental, and school problems occur on a continuum for children with SB. Comorbidities (eg, hydrocephalus) are frequent [9] and because many body systems (eg, muscular/skeletal, renal/urinary) are affected simultaneously, SB is a complex condition to manage and treat. This complexity can be further compounded by the development of secondary conditions such as frequent urinary tract infections, pain, and depression [10,11]. Although more significant cognitive deficits may be apparent before the age of 3 years, the subtle learning and language problems common in children with SB [12] may not be identified by public school systems until children are 8-10 years old [13]. Assessment of learning and language problems may not occur until children are significantly behind their peers academically. Given that children with SB have such a high rate of school problems [14,15], the possibility of earlier identification (ie, ages 3-6 years) may allow for earlier academic and language interventions that enhance the academic performance and improve the developmental trajectory of the condition for these children.

In adulthood, individuals with SB have markedly wide ranges of outcomes in terms of physical function, social participation, and quality of life. Outcomes vary from full employment, successful relationships, and independent living (the typical goals of adulthood) to social isolation, depression, and under- or unemployment [16-18]. These outcomes, while partially determined by underlying health-related and cognitive issues (eg, shunt revisions, incontinence, mobility, challenges with executive function), are greatly influenced by the lived experience of the individual and by the environmental responses to the condition.

In 2010, the Centers for Disease Control and Prevention (CDC) announced a funding opportunity for a cooperative agreement entitled *A Prospective Assessment of the Development, Health, and Condition Progression in Young Children with Spina Bifida*. The purpose of this announcement was to assess the development, health, and condition progression by prospectively studying children who were born with SB. In addition, the

methodology used to collect the data would be evaluated and revised as appropriate. The approach and methodology to be used in this project was informed by a pilot project that was conducted in Georgia [7]. The funded applicants, Arizona (university) and Utah (health department) worked in collaboration with CDC to refine and finalize the research protocol. In this first publication since the project's conclusion, we describe and evaluate the methodology and recruitment process of the study.

Methods

Study Protocol

Prior to this study, CDC researchers and collaborators completed a pilot project to inform the current larger study [7]. The protocol used in the CDC pilot study served as a framework for the funding announcement. Because Utah and Arizona submitted separate applications in response to the funding announcement, a unified protocol was developed by both sites in the first year of the study. The two sites were tasked with identification, location, and recruitment of English- or Spanish-speaking parents with children with SB (International Classification of Diseases, Ninth Revision, Clinical Modification, codes 741.0, spina bifida with hydrocephalus and 741.9, spina bifida without hydrocephalus) born between September 1, 2004, and August 31, 2009, residing in one of the two catchment areas. Individuals living in nearby states were also recruited, but only if they attended an SB clinic at the participating sites. The birth date range was selected to ensure children were between 3 and 6 years at the time of enrollment in the study, which allowed the collection of extensive baseline data on health status, social, and cognitive development, of the children prior to entering school. Each child's parent was required to be over 18 years old and able and willing to sign the consent forms. Institutional review board (IRB) approvals were obtained separately at the two sites. Recruitment began in May 2011 and ended in September 2013.

Identification of Eligible Participants and the Recruitment Process

Children with birth defects were first identified from surveillance systems from both sites. IRBs at each site differed in how they allowed potential participants to be identified, contacted, and recruited; therefore, the recruitment processes varied between the two sites. In Utah, children with SB were identified using population-based statewide surveillance data from the Utah Birth Defect Network. Surveillance data included demographic and diagnostic information to determine case eligibility. All parents of eligible children were sent a recruitment letter from the Utah Department of Health introducing them to the study and inviting them to participate. Follow-up phone calls were made by the study coordinator approximately 7 days after the recruitment letter was sent to assess the parents' interest in participating in the study. Parents of eligible children with SB who were attending the SB clinic during the study period were also invited by the SB clinic staff to participate. Occasionally, eligible children with SB and their parents traveling from Utah's surrounding states (eg, Idaho, Wyoming, and Nevada) to attend the SB clinic in Salt Lake

City were invited to participate. Staff in Utah were not restricted in contact attempts or recruitment by their local IRB.

In Arizona, eligible children with SB were identified through the birth defects monitoring program, hospital discharge databases, SB multispecialty clinics, and the primary children's hospitals in Tucson and Phoenix to assemble the eligible population, including health and demographic characteristics of the children. The IRB for this site did not permit research staff to contact any patients without expressed consent; therefore, recruitment letters, emails, and Web announcements were sent advertising the study and providing contact information for self-enrollment through the Arizona Spina Bifida Association and from the Children's Rehabilitation Services program (Medicaid-funded program for children with physical disabilities). Staff at the Phoenix and Tucson multispecialty SB clinics were allowed to make phone calls to parents of active patients informing them about the study and requesting permission for research staff to contact them. Active recruitment was also performed during scheduled visits to clinics at the Tucson location. However, the IRB at the Phoenix location with the largest SB population only permitted making flyers available to potential participants and did not permit any direct recruitment. The primary IRB approval limited the contact with any family to three phone calls at each stage in the recruitment process.

Procedures and Measures Included

Parents were given two options to participate: (1) an in-person clinic visit with the child and family to complete neuropsychological assessments and parent surveys (ie, Full Protocol), or (2) a phone survey with mailed questionnaires to the parents (ie, Partial Protocol). Parents also had the option of a mailed questionnaire that could be completed and returned instead of either the in-person assessment or the phone interview. In all options, parents were asked consent to release their child's medical records for medical record abstraction. Medical record abstraction was performed at both sites to obtain detailed data on clinic visits and hospitalizations, surgeries, growth, and comorbid conditions. Medical record data at each site were stripped of personal identifiers and transmitted to the CDC for pooling into a central dataset.

The in-person visits to the clinics were conducted in either English or Spanish and took 2-3 hours to complete; the phone survey lasted approximately 30 minutes. Because of the length of time associated with the in-person clinic visit, study appointments had to be scheduled on a day other than the child's regular SB clinic visit. Gift cards of US \$50 were given to parents who participated in the full protocol as compensation for travel and time, and US \$25 gift cards were given to those who participated in the phone survey.

The survey included 120 items and covered topics regarding the child's medical issues, development and learning, nutrition and physical growth, mobility and functioning, general health,

and family demographic information. Although most of the survey items were created in the pilot project completed prior to the current study (with modifications for this specific study), many of the more generic items in the survey have previously been used in large national surveys, such as the Youth Risk Behavior Survey and the National Early Intervention Longitudinal Study. Parents who chose a phone interview were mailed the consent forms and medical records release form as well as five of the six self-administered questionnaires and were asked to complete them at home and send them back in the postage-paid envelope provided. One of the parent surveys (the Pediatric Evaluation Disability Index [PEDI]) was not mailed to the participants because the investigators considered it too difficult for parents to complete on their own. After the consent forms and surveys were completed and returned to the study coordinator, parents were contacted to schedule a time to participate in the phone survey.

At the beginning of each in-person study visit, the consent and parental permission forms and a medical record release form were presented to the parent and any questions or concerns were addressed. After the parent reviewed and signed these documents, the pediatric psychologist escorted the child into a separate room for neuropsychological testing. Parents were typically not in the exam room unless parental attendance was warranted according to the professional judgement of the clinician. The psychologist administered five assessments: the *Bracken Basic Concept Scale* Receptive (BBCS-R) [19], the *Differential Abilities Scale* 2nd Edition (DAS-2) [20], the NEUROPSYCHOLOGICAL Assessment (NEPSY) II [21], the *Peabody Picture Vocabulary Test*, 4th Edition [22], and the *Wide Range Assessment of Visual Motor Abilities* (WRAVMA) [23]. For Spanish-speaking participants, all documents, including the consent, parental permission, and medical records release forms, parent interview, parent surveys, and three of the five child assessments (DAS-2, BBCS-R, and WRAVMA) were conducted in Spanish. In Utah, a translator was available for appointments with Spanish speakers to assist in the completion of the study documents, the parent interview, and the parent surveys and administering the battery of neuropsychological assessments used in the study. In Arizona, which has a large Hispanic population, all appointments were conducted by bilingual professionals. While the child was completing testing, the study coordinator administered the study survey to the parents, which was the same questionnaire used in the phone survey. Parents were asked to complete six self-administered questionnaires addressing family functioning, child behaviors and personality, self-care, mobility, and functioning, and health and well-being: the *Adaptive Behavior Assessment System*, 2nd Edition [24]; the *Behavior Assessment System for Children*, 2nd Edition [25]; the *Behavior Rating Inventory* [26]; the *Child Health Questionnaire* [27]; McMaster Family Assessment [28]; and PEDI [29]. The battery of assessments and questionnaires is provided in Table 1.

Table 1. Key characteristics of the instruments used in the prospective study of spina bifida in children, 2011-2013.

Instrument	Age range	Items/ subtests	Domains tested	Administration	Language
Parent reported					
Adaptive Behavior Assessment System 2 nd Edition	0-89 yrs	241 items	Daily living skills 10 skill areas; Domains (1) social, (2) practical, & (3) conceptual	In-person, Mail	English, Spanish
Behavior Assessment System for Children 2 nd Edition Parent Rating Scales-Preschool	2-5 yrs	134 items	Behavior and self-perceptions of children and young adults ages 2-25 years. Only the Parent Rating Scales were included in this project, which measures adaptive and problem behaviors in the community and home setting.	In-person, Mail	English, Spanish
Behavior Assessment System for Children 2 nd Edition Parent Rating Scales-Child	6-11 yrs	160 items			
Behavior Rating Inventory of Executive Function - Preschool Version	2-5 yrs	63 items	Executive Function Subscales: (1) emotional control, (2) shift, (3) inhibit, (4) working memory, & (5) plan/organize	In-person, Mail	English, Spanish
Behavior Rating Inventory of Executive Function	5-18 yrs	86 items	Indices: (1) inhibitory self-control, (2) flexibility, & (3) emergent metacognition		
Child Health Questionnaire	5-18 yrs	50 items	Quality of life instrument measuring 14 unique physical and psychosocial concepts. The parent form (50 items) was used for this project	In-person, Mail	English, Spanish
McMaster Family Assessment Device (FAD)		12 items	The 12-item general functioning scale of the FAD was used for this study. Both unhealthy family functioning (negative) and healthy family functioning (positive) items are included	In-person, Mail	English, Spanish
Pediatric Evaluation of Disability Inventory	0.5-7.5 yrs	217 items	Functional abilities. Subdomains: (1) self-care, (2) mobility, & (3) social function. Parts: (1) functional skills, (2) caregiver assistance, & (3) modifications	In-person	English, Spanish
Study Survey		120 items	Project-specific questionnaire containing items in six domains: (1) medical concerns, (2) development & learning, (3) nutrition & physical growth, (4) mobility & functioning, (5) general health, & (6) family demographics	In-person, Telephone, Mail	English, Spanish
Psychologist administered					
BBCS-3:R	2:6-7:11 yrs	5 subtests	The School Readiness Composite was the only assessment from the BBCS-3:R used to assess children's knowledge of those readiness concepts that parents and preschool and kindergarten teachers traditionally teach children in preparation for formal education. The subtests included the following: colors, letters, numbers/counting, sizes/comparisons, and shapes.	In-person	English, Spanish
DAS-2	2:5-17:11 yrs	7 subtests	Cognitive abilities, 7 core subtests from early years battery: (1) verbal comprehension, (2) picture similarities, (3) naming vocabulary, (4) recall of objects, (5) pattern construction, (6) matrices, & (7) copying	In-person	English, Spanish
NEPSY II	3-16:11 yrs	3 subtests	The Comprehension of Instructions and the Word Generation subtests from the Language domain and the Sentence Repetition from the Memory and Learning domain were the only subtests administered	In-person	English
Peabody Picture Vocabulary Test 4 th Edition	2-6+	228 items	Measure of receptive vocabulary; included 228 test items each consisting of 4 full-color pictures as response options on a page	In-person	English
WRAVMA	3-17 yrs	2 subtests	Visual-motor integration; WRAVMA matching visual-spatial subtest; WRAVMA pegboard fine-motor subtest	In-person	English, Spanish

The Arizona IRB did not require consent for medical record abstraction of eligible cases, whereas the Utah IRB did. The medical records of consented children in Utah, and eligible

children in Arizona with or without consent, were abstracted at each site. Prior to the start of the project, the two sites and CDC agreed on a number of data elements to collect from the medical

records. This included birth and mortality data (if applicable), as well as demographic information (ie, insurance status at birth, maternal and paternal ages at birth, race/ethnicity, education, gravidity, plurality, marital status, and occupation status), newborn hearing evaluation results, SB level of lesion and type, visual acuity measurements, conditions secondary to SB, and growth parameters. Additionally, information was collected regarding clinic visits (ie, clinic type, provider, and visit reason), hospitalizations (ie, admit/discharge dates, hospitalization reason, and discharge diagnosis codes/text), and surgical history (ie, dates, surgery type, reason, and procedural and diagnosis codes). Medical record data from both sites were entered into an Access database created by the Arizona team specifically for the project. An abstraction manual was created to ensure uniformity and consistency among abstractors at both sites.

Results

The distributions of gender, race/ethnicity, type of primary insurance, and year of birth among children who participated and those who did not at each site are presented in Table 2. In

Utah, there were no differences between participants and nonparticipants on these variables. In Arizona, participants were more likely to be Hispanic ($P=.011$, Fisher's Exact Test). They were also more likely to have Medicaid as their primary insurance ($P<.013$, Fisher's Exact Test).

In Utah, recruitment letters were sent to all 92 parents of eligible children identified in the birth defects surveillance system. An additional 27 recruitment letters were re-sent either because the initial letter came back as undeliverable or the parent stated that they did not receive it when the study coordinator called to follow up. Of the 92 parents, 52 participated in the full protocol, 13 in the partial protocol, and 27 declined. Of the 10 eligible children who were identified from the SB clinic but not born in Utah and who were invited by the SB clinic director, 7 participated in the full protocol, 1 in the partial protocol, and 2 did not respond. Medical records of 70 of the 73 who participated in either the partial or full protocol were abstracted. For Utah, participants who completed the full protocol did not differ from those who completed only the partial protocol on gender, race/ethnicity, insurance type, and year of birth.

Table 2. Descriptive information for participants and nonparticipants, by site, in the prospective study of spina bifida in children, 2011-2013^a.

	Arizona, n (%)			Utah, n (%)		
	Partial (n=6)	Complete (n=22)	No participation (n=140)	Partial (n=14)	Complete (n=59)	No participation (n=29)
Gender						
Male	11 (50)	5 (83)	71 (51)	8 (11)	39 (53)	16 (55)
Female	11 (50)	1 (17)	68 (49)	6 (8)	20 (27)	11 (38)
Ambiguous			1 (1)	—		—
Missing	—	—		—		2 (7)
Race/Ethnicity						
White	7 (32)	1 (17)	59 (42)	14 (19)	46 (63)	17 (59)
Hispanic	13 (59)	5 (83)	57 (41)	—	10 (14)	9 (31)
Other	2 (10)	—	24 (17)	—	3 (4)	1 (3)
Missing	—	—		—	—	2 (7)
Primary insurance						
Private insurance	2 (9)	0 (0)	14 (10)	2 (3)	12 (16)	—
Medicaid/ Federal	11 (50)	3 (50)	32 (23)	2 (3)	12 (16)	—
Other	1 (5)	—	94 (67)	—	—	
Missing	8 (37)	3 (50)		10 (14)	35 (48)	29 (100)
Year of birth						
2004	—	—	8 (6)	—	1 (1)	2 (7)
2005	3 (11)	—	33 (24)	5 (7)	12 (16)	5 (17)
2006	1 (4)	4 (14)	27 (19)	2 (3)	10 (14)	6 (21)
2007	1 (4)	7 (25)	30 (21)	1 (1)	19 (26)	4 (14)
2008	1 (4)	7 (25)	24 (17)	4 (5)	10 (14)	6 (21)
2009	—	4 (4)	18 (13)	2 (3)	7 (10)	6 (21)

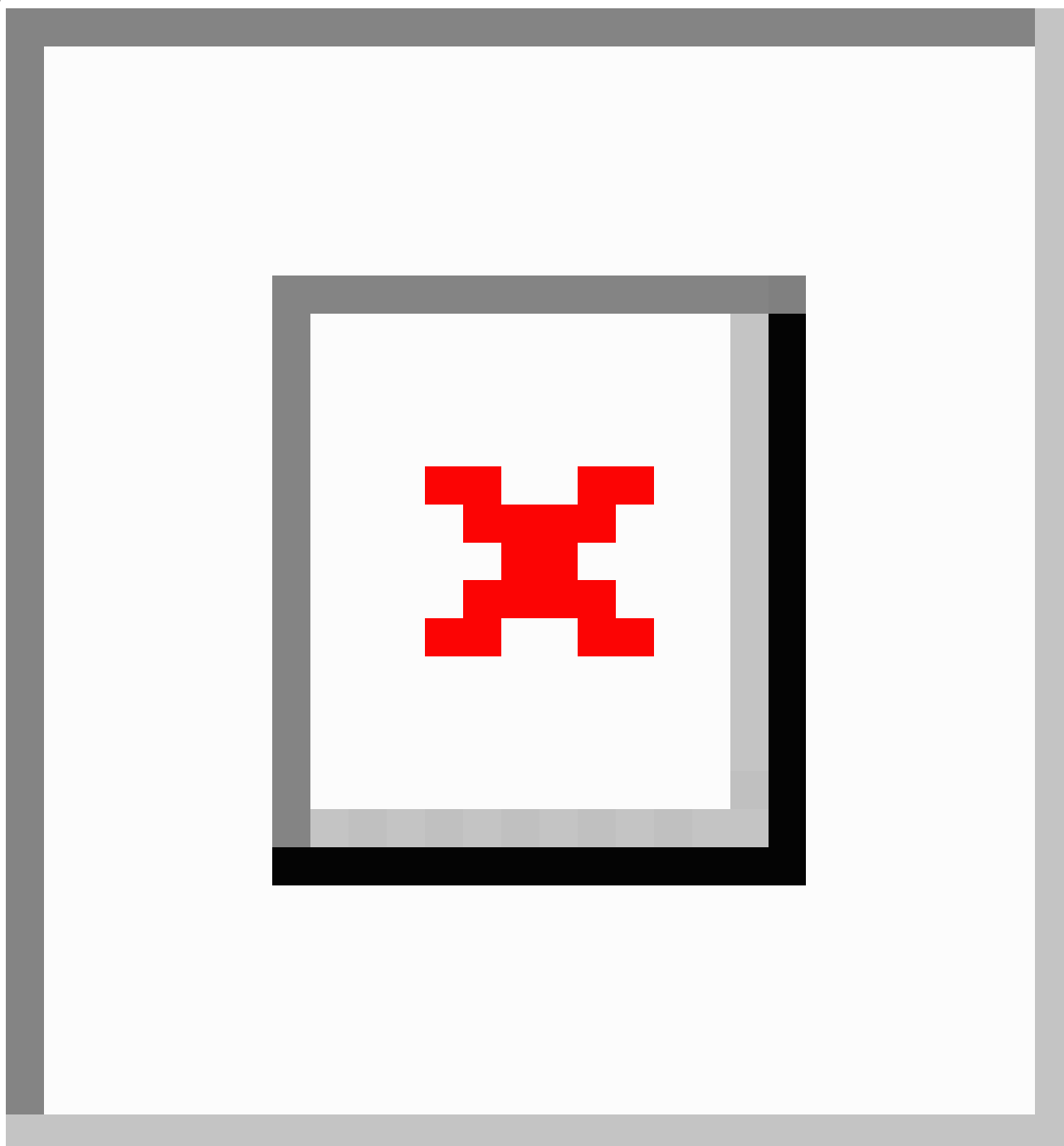
^aPercentages may not add to 100% due to rounding.

Of the 264 eligible children identified in Arizona, permission was granted by 50 families for the research staff to contact them directly. Of these, 23 participated in the full protocol and 5 in the partial protocol. Six consented to participate but did not participate in the study, and 16 declined. Because letters were sent through partners and not directly by the research team, the Arizona site staff could not collect information on the nonenrollees. It is assumed that the remaining 214 cases did not want to respond or the research staff had the wrong addresses. Medical records were abstracted for surveillance for the 214 cases, 96 of which had little or no medical record information and were assumed to live outside the catchment area. A flow chart of the results of the recruitment process is presented in

Figure 1. For Arizona, there were no differences between full and partial protocol participants on gender, insurance type, and race/ethnicity. However, the two groups differed on year of birth in that all of the participants born in 2005 completed partial protocol and all of the participants born in 2009 completed full protocol ($P=.022$, Fisher's Exact Test).

In total, 152 parents of eligible children were directly contacted by the research staff for enrollment in the study. Of those, 45 (29.6%) declined to participate, and 6 (3.9) consented but did not follow through with the study. Of the 101 parents who agreed to participate, 82 (81.1%) participated in the full protocol and 19 (18.8%) participated in the partial protocol.

Figure 1. Recruitment flow chart.



Discussion

Principal Findings

The aim of this project was to explore methods piloted by CDC to collect health, cognitive, and social development information for children with spina bifida by identifying eligible children in Arizona and Utah, and collecting similar data as in the pilot. In total, 814 children with SB, aged 3-6 years, were identified, of whom 366 (44.9%) were eligible to participate instead of 368 (45.2%). Medical records were abstracted on 188 (51.4%) of eligible participants. There were unexpected methodological challenges that arose due to differences in the sampling plan between sites, primarily due to differences in IRB permissions for study selection and to some participants' perception of the potential for adverse outcomes as a result of participation.

Differences in the approved sampling design between Utah and Arizona sites presented variation in study methodology. First, the sampling frame in Utah was a more comprehensive list of the eligible families than that of Arizona. Eligible participants in Utah were derived from a population-based state surveillance system, whereas those in Arizona were identified through varying sources that included a birth defects monitoring program, multispecialty clinics, and hospital databases. Therefore, Utah had greater target population representation in their sample and findings from their site may have greater generalizability and relevance to the interested Utah population. Second, Arizona was not allowed to actively recruit from their list of eligible participants. Although a common study methodology was agreed on between sites to evaluate parents and their children with SB, the difference in the processes permitted by the IRBs for the identification, ascertainment, and recruitment of eligible children with SB impacted Arizona's participation rate. Utah's population-based surveillance program within the Utah Department of Health was approved by the IRB to identify eligible children with SB and invite the parents directly to participate in this study. The IRB in Arizona permitted access to medical records of children whose parents were not contacted to participate; however, a challenge for the Arizona site was the inability to mail letters or directly recruit parents and their children from the SB specialty clinic. Thus, one lesson learned from this multisite study was that variance in sampling frame can impact study methodology and participant selection. In this research, the difference in permissible methods of contacting eligible participants affected the response rate in Arizona. The external validity of findings from Arizona is limited since the proportion of eligible participants who participated was low.

There are unique challenges to participating in research for individuals who have complex conditions. SB requires multidisciplinary care and services, which can be time-consuming and cumbersome for parents. Parents must devote significant time and resources to finding and utilizing health and educational services needed by their children. These demanding tasks may reduce the opportunities for participation in research, which could be seen as having no immediate or long-term benefit for their child. Yet having a child with a severe impairment—or the time constraint that might result—does not

explain the differential recruitment in the current study because this factor is not likely to differ between sites or states. In addition, those who found the in-person assessment to be too time-consuming had the option of participating by phone survey, which required less time commitment, and this option was offered at both sites. Given that the study was designed to be population-based, the different outcomes in recruitment in the two states may be the result of both the contrasting interpretations by the local IRBs of rules created to protect human subjects and the differences in the racial/ethnic composition and geographic distribution of the population between the two states.

Utah's population is relatively homogeneous, with non-Hispanic whites representing 79% and Hispanics 13% of the population [30]. Geographically, 75.5% of Utah's population lives within 50 miles north and south of Salt Lake City (known as the Wasatch Front) where the tertiary and subspecialty pediatric clinical services are located [31]. With medical care for children and adolescents centrally located within the state and the majority of residents living along the Wasatch Front, parents may be more likely to participate in studies that are based where this care is provided.

In Arizona, 90% of the population lives in urban areas, primarily in and around Phoenix and Tucson. Arizona has a unique racial/ethnic distribution of 57% non-Hispanic white, 31% Hispanic, and 4% Native American. Most pediatric specialty services can be accessed only at facilities in the Phoenix and Tucson metro areas. Since the population in Arizona lives primarily in the urban areas where the specialty clinics are located, it is more likely that there may be a cultural explanation to the low participation rate in Arizona. The principal investigator in Arizona observed that some Hispanic parents, when approached to participate by study recruiters, were reluctant to test their children because they felt that their children did not need another medical or cognitive label (author SR, personal communication, September 20, 2012). The fear of a stigmatizing label that could arise from poor performance on cognitive testing was likely a deterrent for these families. Additionally, if the principal investigator, a person trusted and known by the patients, explained the benefits and risks of the study, they were more likely to agree to participate. Feelings of discomfort and fear of loss of privacy have been recognized in other studies as reasons for low participation [32]. Some of these issues may apply to the population in this study.

Recruiting participants to engage in research can be demanding and some of the challenges are highlighted here. Difficulties recruiting and retaining individuals with specific conditions or diseases to participate, for example, in clinical trials and behavioral interventions have been discussed elsewhere [32-36]. For a study that is dependent on the successful recruitment of representative samples, considering the challenges of recruitment at participating sites early in the planning stage may have a positive impact. The researchers may be aware of the specific factors and contexts that may challenge their recruitment efforts and address what can be done to counteract these. Considering the potential for variation in project interpretation by local IRBs early in the development phase may also contribute to a

representative picture of the populations in the sites that participate.

Conclusion

A total of 101 children aged 3-6 years and their families participated in this project in Arizona and Utah. Parents completed a survey that inquired about their child's medical status, development and learning, nutrition and physical activity, mobility, general health, and family functioning. Medical records were abstracted for demographics, clinical characteristics, inpatient and outpatient encounters, and surgical

history. Children were assessed in the areas of social and cognitive development and visual/motor skills. Additionally, families were assessed in the areas of family functioning, child behavior and personality, self-care, mobility and functioning, and health and well-being. It is expected that findings from these assessments will highlight areas of deficit that may impact the development of the child and their success in school. Knowledge of these deficits and development of plans to address them may support a more developmentally appropriate trajectory for the population of children affected by SB.

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Conflicts of Interest

None declared.

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Abbreviations

BBCS-R: Bracken Basic Concept Scale Receptive
CDC: Centers for Disease Control and Prevention
DAS-2: Differential Abilities Scale 2nd Edition
FAD: McMaster Family Assessment Device
IRB: institutional review board
NEPSY: NEuroPSYchological Assessment
PEDI: Pediatric Evaluation Disability Index
SB: spina bifida
WRAVMA: Wide Range Assessment of Visual Motor Abilities

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Protocol

Educational Module Intervention for Radiographers to Reduce Repetition Rate of Routine Digital Chest Radiography in Makkah Region of Saudi Arabia Tertiary Hospitals: Protocol of a Quasi-Experimental Study

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Abstract

Background: Repetition of an image is a critical event in any radiology department. When the repetition rate of routine digital chest radiographs is high, radiation exposure of staff and patients is increased. In addition, repetition consumes the equipment's life span, thus affecting the annual budget of the department.

Objective: The aim of this study is to determine the impact of a printed educational module on reducing the repetition rate of routine digital chest radiography among radiographers in Makkah Region tertiary hospitals.

Methods: A quasi-experimental time series with a control group will be conducted in Makkah Region tertiary hospitals for 8 months starting in the second quarter of 2017. Four hospitals out of 5 in the region will be selected; 2 of them will be selected as the control group and the other 2 as the intervention group. Stratification and a simple random sampling technique will be used to sample 56 radiographers in each group. Pre- and postintervention assessments will be conducted to determine the radiographer knowledge, motivation, and skills and repetition rate of chest radiographs. Radiographs of the chest performed by sampled radiographers in the selected hospitals will be collected for 2 weeks before and after the intervention. A piloted questionnaire will be distributed and collected by a researcher in both groups. One-way multivariate analysis of variance and 2-way repeated multivariate analysis of variance will be used to analyze the data.

Results: It is expected that the repetition rate in the intervention group will decline after implementing the intervention and the change will be statistically significant ($P < .05$). Furthermore, it is expected that the knowledge, motivation, and skill levels in the intervention group will increase significantly among radiographers after implementation of the intervention ($P < .05$). Meanwhile, knowledge, motivation, and skills in the control group will not change.

Conclusions: A quasi-experimental time series with a control will be conducted to investigate the effect of printed educational material in reducing the repetition rate of routine digital chest radiographs among radiographers in tertiary hospitals in the Makkah Region of Saudi Arabia.

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KEYWORDS

repetition rate; intervention; radiographer; quasi-experimental; information motivation behavioral skills model

Introduction

Good quality images in routine radiography should provide an adequate picture of the body's anatomy. Failure to obtain a good quality image requires the radiograph to be repeated. According to Foos et al [1], the term "repetition" refers to redoing a radiograph of a patient that was deemed clinically unacceptable. Repetition of an image is a critical event in radiology. It is recommended that the repetition rate should not exceed 5% [2-7]. The Diagnostic Imaging Quality Assurance Committee recommends that the repetition of radiographs should not exceed 5% to 7% [8]. The American Association of Physicists in Medicine recommends keeping the repetition rate below 6%, and when it increases to 10%, corrective action should be conducted [9]. The Australian College of Radiologists recommends an acceptable repetition rate of 2% and not more than 5% [10].

A study by Khafaji and Hagi [11] reported high repetition rates of radiography in Saudi hospitals, averaging 14.9%, which is higher than the international standard. Another study reported the repetition rate in 3 Ministry of Health hospitals ranged from 7.4% to 9.7%. The same study revealed that chest radiographs have higher repetition rates compared to other radiological procedures [12]. Related to that, it was revealed that radiographer error is one of the factors that strongly contribute to the issue of the repetition [13,14].

The production of high-quality images is based on radiographer practices. According to the World Health Organization, practice is influenced by the level of knowledge, motivation, and skills [15]. A study conducted in Saudi Arabia by Alsharif et al [16] showed that there is poor knowledge among radiographers in identifying image error. Another study conducted in Saudi Arabia by Ahmed et al [17] revealed that there is variation in radiographer knowledge of radiation protection, with 58% of radiographers indicating poor knowledge. Additionally, it was revealed that the motivation level of radiographers is low and this affects production of high-quality images [18]. Lack of knowledge and motivation dramatically influence skill level. It has been exhibited that the increase in repetition rate is due to deficiencies in radiographer skills [19]. Radiographers with high skills tend to avoid errors in the imaging process. Skills include the ability to communicate properly with the patient and handling the equipment accurately.

Repeated radiographs have financial and health implications, especially because of increased exposure to radiation for both

staff and patients [12]. Khafaji and Hagi [11] and Khoshinani and Heidari [20] added that a high repetition rate in radiography consumes the digital equipment's lifetime by 2 months each year. This increases both staff workload and waiting time for the patient in addition to affecting the achievement of the organization's vision.

According to Almalki et al [21], most interventions conducted in previous studies are technical in nature. Despite that, those intervention studies show a positive impact on the repetition rate of digital radiography. However, radiographers were not included in the studies despite them being significant factors in the repetition rate.

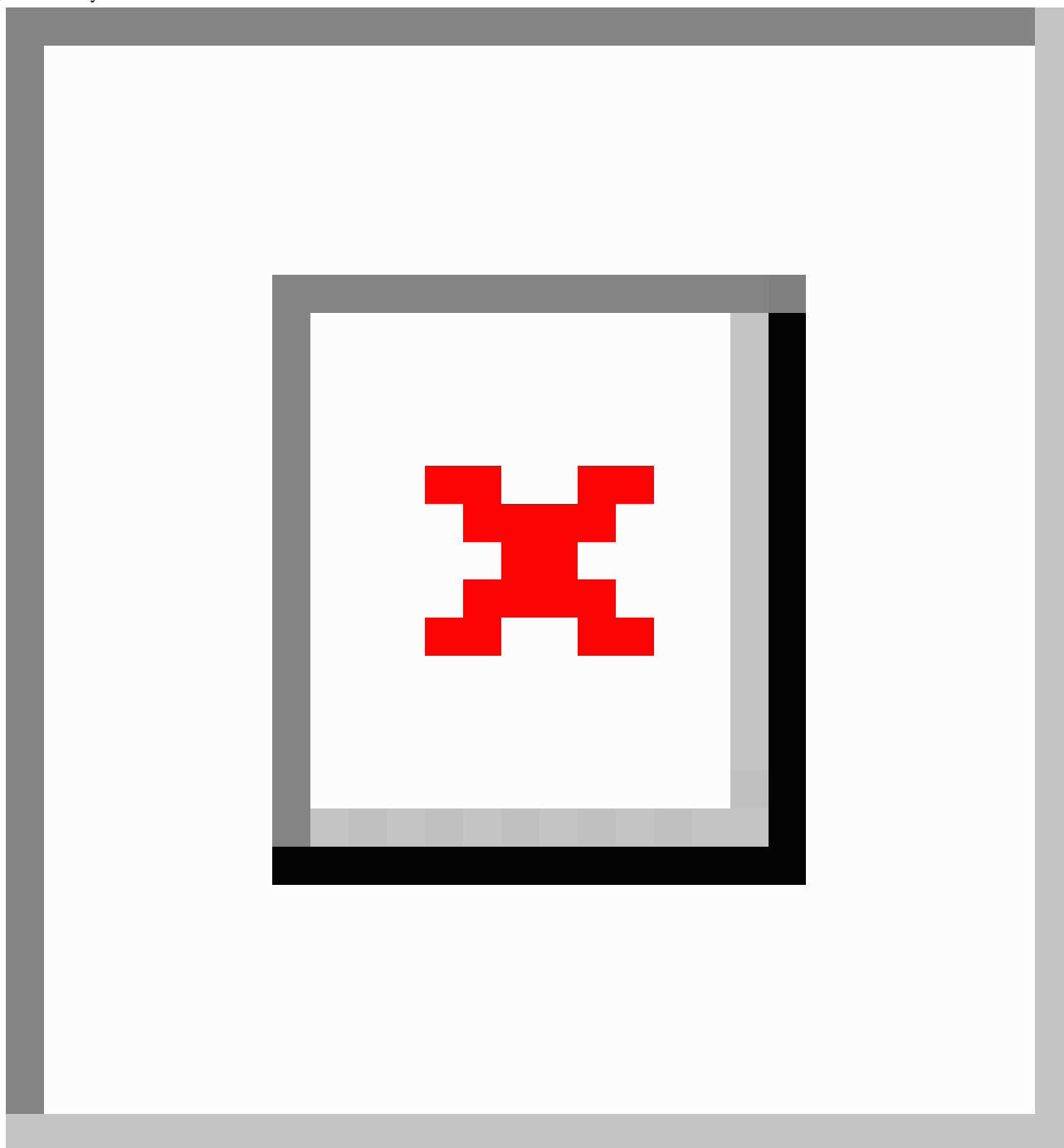
In general, the aim of this study is to develop, implement, and evaluate the impact of printed educational material in reducing the repetition rate of routine digital chest radiography among radiographers in Makkah Region tertiary hospitals.

Methods

Study Design

The design of this study is basically a quasi-experimental time series with a control group. This design was chosen because the intervention was recommended by other researchers [22,23]. A quasi-experimental study is the only design that could be applied in this study. The difficulty of randomizing by location and subject and the small number of the population make the quasi-experimental design suitable in this study [24]. In addition, there is difficulty in randomizing by subject to avoid potential contamination. Location is also a factor, since no 2 hospitals are similar.

The Makkah Region of Saudi Arabia was selected for the study because the problem has been ignored in the area and the repetition rate has not been periodically measured there [25,26]. Out of 5 hospitals, 4 will be selected to be in the study since randomization is not required in this type of study [27]. The hospitals involved are under the direction of Makkah Region health affairs. Two will be chosen as an intervention group and 2 as a control group. Preintervention assessment will be conducted in both groups at the same time during the second quarter of 2017. The intervention will be distributed to radiographers in the intervention group, and after 1 month, an assessment will be conducted. Six months after the implementation of intervention, a second postintervention assessment will be conducted. Figure 1 demonstrates the study flow.

Figure 1. Study flow.

Selection Criteria

The inclusion and exclusion criteria are based on the job description of a radiographer, since there are several tasks in routine radiography in the radiology department. Only radiographers who perform routine digital chest radiography will be included. Clerk radiographers, administrative radiographers of routine digital radiography, radiographers who are on long annual leave, and radiographers who are pregnant will be excluded. Non-Saudi radiographers will be excluded as well.

Recruitments

Sampling Methods

The method employed to sample radiographers is stratification followed by simple random sampling. The list of radiographers will be obtained from the radiographer in charge. After that, the inclusion and exclusion criteria will be applied to radiographers derived from the list. Then, radiographers will be stratified by gender, with male respondents representing 70% of the sample and female respondents forming 30%. After that, a software number generator will be used to select the targeted sample.

Matching

Matching has been used in research since the beginning of the 19th century [28]. Exact matching is the method that will be employed in this study. Stuart and Rubin [29] recommended the selection of the most common covariate that has an effect on the outcome in order to make matching possible. According to Loman [30], exact matching can be employed for up to 5 variables. Based on these principles, variables that underwent matching include gender, experience, education level, training, and the type of university from which a radiographer graduated.

Respondent characteristics will be obtained from the radiographers in charge in the control group. First, a sample from the intervention group will be randomly selected using a software number generator. Since the list of radiographers in the control group and the characteristics have already been obtained, exact matching can be performed. This method will help in making the groups comparable and similar in terms of confounder distribution.

Sample Size

We will use the formula by Lemeshow et al [31] to estimate the minimum sample size required in intervention studies and to test a hypothesis of proportion of 2 population problems in terms of the radiographers sample size (see Figure 2), where p_1 and

p_2 were obtained from a study by Moreira [32] to estimate the sample size of radiographers in each group and $Z_{1-\alpha}=1.96$, $Z_{1-\beta}=0.842$, p_1 is 0.63, p_2 is 0.88, and $p^-=0.755$. Figure 3 displays the sample size estimation of the secondary outcome variables.

According to Sullivan [33], the attrition rate (dropout) can be calculated by the formula (desired sample size)/(percent retained). Hence, for this study, a sample size of 56 for each group was targeted.

In terms of the repetition rate of routine digital chest radiographs sample size, the same formula was used, where p_1 and p_2 were obtained from the study of Zhang and Chu [34] to estimate the sample size of routine digital chest radiography in each group and $Z_{1-\alpha}=1.96$, $Z_{1-\beta}=0.842$, p_1 is 0.0584, p_2 is 0.087, and $p^-=0.0728$. Figure 4 displays the sample size estimation of the primary outcome variable.

According to Sullivan [33], the attrition rate that may occur due to any loss of chest images can be calculated by the formula (desired sample size)/(percent retained). The sample size of routine digital chest radiographs is 1618 for each group, and this number is expected to be reached within 2 weeks. Two weeks' time is similar to that used in the study conducted by Ahmed and Suliman [35].

Figure 2. Formula of sample size estimation to test a hypothesis of proportion of 2 populations.

$$n = \frac{(Z_{1-\alpha} \sqrt{2(P)(1-p)} + Z_{1-\beta} \sqrt{((P_1)(1-P_1) + (P_2)(1-P_2))})^2}{(P_1 - P_2)^2}$$

Figure 3. Sample size of the secondary outcomes.

$$n = \frac{(Z_{1-\alpha} \sqrt{2(0.755)(1-0.755)} + Z_{1-\beta} \sqrt{((0.63)(1-0.63) + (0.88)(1-0.88))})^2}{(0.63 - 0.88)^2} = 45$$

Figure 4. Sample size of the primary outcome.

$$n = \frac{(1.96 \sqrt{2(0.0728)(1-0.0728)} + 1.28 \sqrt{((0.0584)(1-0.0584) + (0.087)(1-0.087))})^2}{(0.0584 - 0.087)^2} = 1294$$

Instruments

A questionnaire developed by the researcher based on the information motivation behavioral skills model is one of the instruments that will be used to evaluate the level of radiographer knowledge about imaging, as well as the motivation and skills. It consists of close-ended questions and is divided into 2 sections: demographic data of the radiographer and domain of the radiographer's knowledge, motivation, and skills. Radiographers are expected to spend 5 minutes completing the questionnaire.

A check list was recommended and used in several studies around the world to measure the repetition rate of routine digital chest radiographs [8]. It is an international instrument. It

contains radiographer demographic data, number of radiographs performed by radiographer, number of repeated radiographs, and causes of repetition. It is completed by the researcher in order to obtain accurate results and overcome biases, using actual numbers. Therefore, its reliability does not need to be checked. Furthermore, studies conducted by Al-Malki et al [12] and Khafaji and Hagi [11] in Saudi Arabia used the same instrument. This means that the check list used in this study is valid.

In order to achieve accurate and precise results, the validity and readability of the questionnaire will be evaluated. Face validity will be ensured by an expert currently practicing to ensure the veracity of the meaning, wording, and sequences. Content validity will be ensured by lecturers working in the university

to ensure clarity, representation, and comprehensiveness. Furthermore, factor analysis will be conducted to ensure a structural correlation between variables and factors on the instruments. Finally, reliability through the Cronbach coefficient alpha will be conducted to ensure internal consistency.

Intervention

Piloted intervention will be used in this study. The intervention is in the form of printed educational material distributed to routine digital radiographers in the departments of intervention hospitals based on a specific module developed for the purpose of the study. The intervention module was developed from previous studies [36-39]. The education material was developed based on the information motivation behavioral skills model. This model has 4 constructs: information, motivation, skills, and behavioral change. This model was selected because it was recommended by another researcher to study the effect of self-efficacy, attitude, and knowledge on repetition. The intervention component comprises 3 sections. The first section touches on the background of the repetition issue and the importance of producing high-quality chest images. The second section encompasses the motivation issue of repetition and dose of radiation. The third section includes important skills that should be performed by a radiographer to reduce the repetition rate of chest images. Furthermore, the educational material discusses the issue of repeated radiography and the definition, repetition rate, international standard, causes of repetition, and the burden of repeated radiography to radiographers, patients, clinicians, and the organization. Anatomical parts which should be included in chest radiography will also be included in the education material.

Outcome Measure

Primary Outcome

The primary outcome of this research is the repetition rate of routine digital chest radiographs. It is the change of the behavior based on the information motivation behavioral skills model.

Secondary Outcome

The secondary outcome in this study is knowledge, motivation, and skills of radiographers. Based on the information motivation behavioral skills model, there are direct and indirect correlations between knowledge and behavioral change. There are also direct and indirect correlations between motivation and behavior change. Meanwhile, behavioral skills have a direct correlation with behavioral change.

Statistical Analysis

Data analysis in this study is divided into 2 parts: descriptive and inferential. Descriptive data will be calculated in order to compute the central tendency and dispersion to add valuable statistical information to the study. Inferential data analysis will be used to meet a specific objective. Chi-square, 1-way multivariate analysis of variance, 2-way repeated measure multivariate analysis of variance, and multivariate analysis of covariance are the statistical methods that will be used to test the hypothesis. *Cochran Q test* will be also employed to assess the difference in proportion. The level of significance will be set at $\alpha=0.05$, and all testing of hypotheses will be conducted

using 2-sided tailed hypotheses. The statistical program used is SPSS version 22 (IBM Corp).

Ethics Approval and Registration

Approval from the ethics committee of the faculty of Medicine and Health Sciences of the University Putra Malaysia was obtained (reference number EXP16 P160). Approval to conduct the study was also obtained from the Ministry of Health (reference number H-02-J002). Approvals from Makkah health affairs and the hospitals that are under study were also obtained. In addition, radiographers who will be involved in the study will sign a consent form.

Results

The researchers expect that the repetition rate and the radiographer knowledge, motivation, and skills in both the control and intervention groups before intervention are statistically not significant ($P>.05$). It is expected that a high repetition rate with a low level of knowledge, motivation, and skills in both groups will be found in the baseline data. We predict that after implementation of the educational material in intervention hospitals, the knowledge, motivation, and skills of radiographers will increase and the repetition rate will *reduce* ($P<.05$), but we do not expect the repetition rate, knowledge, motivation, and skills to change in the control group ($P>.05$). It is expected that the intervention will be effective to change the behavior and reduce the repetition rate of routine digital chest radiography ($P<.05$). The results are expected to be published in 2018.

Discussion

Summary

This quasi-experimental time series with control group aims to investigate the effect of printed educational material on radiographer knowledge, motivation, and skills and the radiography repetition rate.

Educating radiographers helps reduce the dose of radiation exposure on patients, decreases waiting time, and increases patient satisfaction. A reduction in the repetition rate decreases the dose of radiation and reduces the workload. This intervention is significant to the organization as it reduces the burden of equipment consumption and cost as well as assists the organization in achieving its vision and goals. In addition, implementing an educational program that focuses on reducing the repetition rate of radiographs has been highly recommended [12,40,41].

To our knowledge, this is the first study that combines 4 outcome variables—knowledge, motivation, skills, and the repetition rate of routine digital chest radiography—and aims to investigate the effect of using printed educational material on the repetition rate of routine digital chest radiography. Furthermore and based on our knowledge, this is the first study that analyzes the repetition rate among radiographers.

The intervention module will be made available in both English and Arabic languages, and participants can choose their preferred language to complete the sessions. The intervention

program was designed to be as brief as possible to increase readability. The printed educational material was selected because of the difficulty of assembling radiographers from different cities in one place at one time. There is a need to overcome the issue of bias to increase the credibility of the study. The quasi-experimental design is one of the strongest designs for this particular research.

Limitations

There are some limitations to this study beginning with the research design. The threat of internal validity mostly reduces the inference of causality due to the lack of randomization. However, the researcher will make the groups comparable and similar by using the exact matching technique. Another limitation is that the result cannot be generalized to all of the hospitals in the Makkah Region due to differences in hospital equipment, which may be conventional, computed, or direct forms of radiography. These modalities are totally different than the others, but the result can be generalized on tertiary hospitals in the region.

The printed education intervention could serve as a new modality to manage the critical event of repetition among

radiographers. The study aims to provide better recognition and management of the repetition rate of routine digital radiography through increasing knowledge, motivation, and skills. It also aims to educate and create awareness of the problem of repetition in radiography. There is a need to develop simple, brief, and effective interventions tailored to the needs of the radiology department to reduce the burden of repetition among radiographers.

Conclusion

To our knowledge, this study will be the first quasi-experimental time series study with a control group using a printed educational material intervention program for radiographers to investigate the repetition rate in chest radiography and radiographer knowledge, motivation, and skills. The results from this study will determine the effectiveness of the intervention in managing and decreasing the repetition rate of routine digital radiography among radiographers. If proven to be effective, the intervention can better serve the organization by assisting decision making in the radiology department to manage and reduce the burden caused by repetition.

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Conflicts of Interest

None declared.

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Original Paper

Effect of Caffeine on Attention and Alertness Measured in a Home-Setting, Using Web-Based Cognition Tests

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Abstract

Background: There is an increasing interest among nutritional researchers to perform lifestyle and nutritional intervention studies in a home setting instead of testing subjects in a clinical unit. The term used in other disciplines is 'ecological validity' stressing a realistic situation. This becomes more and more feasible because devices and self-tests that enable such studies are more commonly available. Here, we present such a study in which we reproduced the effect of caffeine on attention and alertness in an at-home setting.

Objective: The study was aimed to reproduce the effect of caffeine on attention and alertness using a Web-based study environment of subjects, at home, performing different Web-based cognition tests.

Methods: The study was designed as a randomized, placebo-controlled, double-blind, crossover study. Subjects were provided with coffee sachets (2 with and 2 without caffeine). They were also provided with a written instruction of the test days. Healthy volunteers consumed a cup of coffee after an overnight fast. Each intervention was repeated once. Before and 1 hour after coffee consumption subjects performed Web-based cognitive performance tests at home, which measured alertness and attention, established by 3 computerized tests provided by QuantifiedMind. Each test was performed for 5 minutes.

Results: Web-based recruitment was fast and efficient. Within 2 weeks, 102 subjects applied, of whom 70 were eligible. Of the 66 subjects who started the study, 53 completed all 4 test sessions (80%), indicating that they were able to perform the do it yourself tests, at home, correctly. The Go-No Go cognition test performed at home showed the same significant improvement in reaction time with caffeine as found in controlled studies in a metabolic ward ($P=.02$). For coding and N-back the second block was performed approximately 10% faster. No effect was seen on correctness.

Conclusions: The study showed that the effects of caffeine consumption on a cognition test in an at-home setting revealed similar results as in a controlled setting. The Go-No Go test applied showed improved results after caffeine intake, similar as seen in clinical trials. This type of study is a fast, reliable, economical, and easy way to demonstrate effectiveness of a supplement and is rapidly becoming a viable alternative for the classical randomized control trial to evaluate life style and nutritional interventions.

Trial Registration: Clinicaltrials.gov NCT02061982; <https://clinicaltrials.gov/ct2/show/NCT02061982> (Archived by WebCite at <https://clinicaltrials.gov/ct2/show/NCT02061982>)

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KEYWORDS

caffeine; at-home testing; cognition; EFSA claim

Introduction

There is increasing interest in the scientific research in measuring health parameters in a real-life setting instead of using a clinical unit, facilitated by using eHealth and mHealth. In medicine, mHealth for example is used in type 2 diabetics resulting in improved monitoring and diabetes management of patients themselves [1].

Many tests for measuring health parameters are commonly available in drug stores as well as Web-based, enabling self-measurement. In addition, many consumer devices are available that, with increasing reliability, measure health parameters. Calibration of these methods, uploading the data of these devices, privacy, and security of data health portals, are currently all important aspects to make these methods applicable for consumer health science.

Because more people have mobile phones, in which all sorts of applications are available, it is used for research too. Apps replace face-to-face contact [2] and enable testing in free-living subjects. At-home data collection could provide a better picture of real-life situations. Web-based data collection was reviewed by Swan [3] as an important emerging complement to clinical trials. Addition of a more standardized, organized design is recommended for more reliable data than by various crowdsourced data collections.

A recent systematic review [4] investigated the diversity and effectiveness of all sorts of digital interventions. Variability in type of interventions, definitions, outcome measures, and reporting of results of the different studies made interpretation of the results difficult. This finding stresses that a more guided manner of conducting these studies is beneficial. When structured in a clear protocol, this could be introduced for performing a randomized intervention trial in a real-life setting by consumers themselves. If successful, the costs for a clinical trial are no longer a substantial part of the budget for research. Moreover, the parameters of interest will be measured within the real-life setting where the tested product (or intervention) is ultimately aimed at being used by consumers at home. Examination of the effects in the real-life environment is known as 'ecological validation' [5].

Studies that are used for supporting nutrition and health claims are especially interesting for this approach. The European Food Safety Authority (EFSA) is verifying the scientific substantiation of the submitted claims on food products. Most of the studies that are used for supporting such claims have been conducted in a clinical setting; however, for these claims a real-life situation would be more suitable. In other words, the ecological validity of such studies can be questioned. Testing the effect of food products using materials and in the setting that is the best approximate of the real world, will also produce much more robust claims. An effect present in a less controlled environment as in real life, measured while there is more variation present, does really exist (less false positives). Although ecological validity of neuropsychological tests is under debate with respect to everyday cognitive skills as dependent upon the population tested, the approach used in the study, the experimenter conducting the tests, as well as the environment [5]; the

controlled 'office-based tests' (lab condition) on cognitive function alone do not give a complete picture of behavior. Real-world observations, or tests performed in a real-world setting improve executive function assessment [6].

In the present study, we focus on the EFSA claim of caffeine, in which it is stated that 75 to 150 mg of caffeine increased alertness and attention [7]. In the EFSA document, numerous controlled studies are described in which an effect of caffeine on cognition tests was found. The control in these studies are mostly related to the sex and age of subjects, habitual smoking and drinking habits (regular coffee consumption), order of activities during the test days, the number of cognitive tests, fasting state, activities allowed in the test session, food and drinking rules prior to the tests, duration of caffeine deprivation, and so on [8-12].

Brice and Smith [8], who studied single and multiple coffee consumptions, found reduced reaction times. Already as a control of habitual coffee consumption, 1 cup of coffee hourly, the study was designed to compare one large single dose of caffeine versus multiple small doses of caffeine consumption. The test days were controlled for start time, number of doses provided, timing of consumption, and types of subjects (male, young, non-smoking). It was found that both regimes showed increased alertness and improved performance of cognition tasks. The authors therefore concluded that findings from large, single-dose studies could be applicable for normal consumption effect [8].

The level of deprivation of caffeine and smoking was studied by Fine [9], who concluded that due to caffeine deprivation, high-caffeine consumers showed poorer results on cognition tests. Restriction of caffeine and nicotine prior to testing is a normal standardization procedure, which may in itself affect the outcome [9]. But others found that even in subjects minimally deprived of caffeine with a low dose of 75 mg of caffeine, a performance enhancing effect was found in the lab 1 hour after consumption [10]. So cognitive performance improvement was found, even when no caffeine withdrawal is present [10].

In a study were habitual coffee consumers versus nonconsumers were tested, similar improvements were seen for caffeine consumption; both showed faster reaction times and improved mood [11].

Improvement of reaction time was also found in a study using a dose range of 32 to 256 mg of caffeine, in which for all caffeine consumption tests improved performance (more correct answers) and a 5% faster reaction time was present [12]. Control was present for the provision of test dose, caffeine consumption throughout the experiment, the order of the tasks, and the baseline practice sessions. It is concluded that although laboratory tasks, the objective benefits of caffeine could be useful in other settings, like automobile driving (although also simulated in a lab).

Establishing effects on attention and alertness require cognitive tests on reaction time and vigilance. These tests are available in various formats and sources, but are commonly only available on a local computer or network. Quantification of alertness and

cognition in an at-home setting, relevant tests require Internet-based and scientifically reliable applications. Quantified Mind is a project in the United States [13] that provides a wide range of cognition tests. Data collection on response time may however be a source of variation in itself due to differences in laptops and browsers used [14].

To study the feasibility of a real-world setting, a relatively simple study intervention should be chosen, of which the effect is well known and acknowledged, like the effect of caffeine on alertness and attention. Moreover, study subjects can perform a caffeine intervention at home with relatively minor effort on their daily habits. The required dose to be able to demonstrate an effect is within the normal range of daily use (at least 75-mg caffeine is required). This dosage corresponds with a cup of regular coffee and was used in the present study to test the at-home setting.

We therefore designed a randomized, double-blind study to repeat a classical randomized control trial as conducted for caffeine on cognitive function (EFSA claim), in which parameters are measured in a real-life, at-home setting instead of in a metabolic ward with a controlled setting.

The objective of the present study was to examine the reproducibility of caffeine on attention and alertness of subjects using a Web-based study environment with different cognition tests at home without contact with the subjects compared with results from controlled, clinical studies.

Methods

Subject Recruitment

In October 2013, subjects were recruited via 2 main Internet sites: Facebook and FoodLog, a popular food blog for (professional) people interested in food (research). Additional people were recruited via LinkedIn or by word of mouth. In total, 102 subjects showed their interest. The interested subjects were provided a study information document by email. There were 74 subjects who wanted to participate and were sent an informed consent form and a health and lifestyle questionnaire (hard copy). Subjects were eligible when healthy (according to questionnaire), ≥ 18 years of age, able to perform tests on the computer/laptop, moderate caffeine users, had no mental disorder or used medication for this, participated voluntarily, and sent a signed informed consent form. After completion and return of these documents, we had 70 eligible subjects (see [Multimedia Appendix 1](#)).

The EFSA caffeine claim document [7] showed that the caffeine tests were conducted with at least 35 subjects. To compensate for possible dropout of approximately 20%, we wanted to include at least 50 subjects.

Study Design

The study was designed as a randomized, placebo-controlled, double-blind, crossover study.

The subjects participated in 5 study days: 1 training day and 4 test days on which the interventions with placebo (decaf) or caffeine were measured, consuming 1 treatment per test day.

A complete training day preceded the tests to have the main learning effects in this first session, and start with all subjects at a rather similar learning level independent of their acquired testing skills. All 3 cognition tests were conducted similarly as on a normal test day (duration, type, and level of difficulty of the tests). The order of the cognition test was always the same (Coding test; Go-No Go; N-back).

Conduct of the Study

The eligible subjects were provided with 4 sachets of coffee (2 with decaf [coded A] and 2 with caffeine [coded B]) so they could prepare the coffee at home. The order of using the sachets was mentioned in a letter. Together with the coffee sachets, an instruction document was sent on how to prepare the coffee and the order of actions of the tests days with respect to timing of drinking and testing.

Subjects performed the tests in the morning after an overnight fast. After filling in a wellbeing questionnaire and the sleepiness scale, the subjects performed 3 cognition tests on his/her own personal computer or laptop. Then preparation and drinking of coffee was scheduled, and after 1 hour, the computer tests were conducted again. During the total period of the test (~1.5 hour), the subjects were not allowed to eat, drink, or smoke anything except for the coffee.

Information was provided to allow each test subject to perform the Web-based cognition tests. Website, user name, and passwords were provided and details of the tests were explained. Subjects with login problems could call or mail our helpdesk service.

Analysis of the provided coffee revealed that the caffeinated sachets contained 85 mg of caffeine. In the decaffeinated sachets 3 mg of caffeine was present.

The study was performed according to guidelines in the Declaration of Helsinki, and the institutional review board of Brabant, the Netherlands approved all procedures (NL 45382.028.13). Registration was done prior to the start of the study [NCT02061982]. The study was performed in November to December 2013.

Data Collection

Effects on alertness and attention were measured using 3 computerized cognitive tests provided by Quantified Mind. The 3 tests were performed by the subjects at $t=0$ (baseline, prior to coffee consumption) and $t=1$ hour in one go. Each test was performed for 5 minutes. During the training session the participants were instructed to get acquainted with the tasks. The 3 cognition tests used are described in [Multimedia Appendix 2](#).

Statistics

Each subject performed 2 placebo and 2 caffeine-coupled tests. Counterbalancing was applied to account for potential carry-over effects between subsequent test days as a result of learning, boredom, fatigue, and so on. This was done by dividing the full 4-day experiment into 2, 2-day blocks in which every subject received both decaf and caffeine. This resulted in 2 randomization schemes (ABAB and BABA), which were both

assigned to one-half of the study population each. As a result, potential carry-over effects were equally distributed over both treatment conditions.

Each cognition test revealed 2 data sets, reaction time and correctness of the responses. Separate analyses were performed on the reaction times and on the dichotomous true/false outcomes. Reaction times were analyzed using a repeated-measures analysis of the variance (ANOVA) with treatment (ie, caffeine or decaf), block (first or second 2 days of testing), and the treatment \times block interaction, as well as a random intercept for subject to account for correlations between repeated measures collected from individual subjects. True/false outcomes were analyzed with a repeated measures logistic regression model that also included treatment, block, and the treatment \times block interaction, and a random intercept for subject.

The residual plots of the data were checked for normal distribution of the data. For the reaction time data, the curves were not normally distributed and had to be log transformed first. The model assumptions were met enabling the use of ANOVA. The models provided estimates of the overall means per treatment condition and block as well as the interaction between these two. Differences between means were deemed significant when the corresponding 2-sided *P* value was below .05. All statistical analyses were conducted using SAS 9.2.

Results

Baseline Characteristics

Of the 70 subjects who started the study, we obtained a complete data set of all test sessions of 53 subjects. There were 17 subjects

(25%) who started the study but were unable to perform all tests days completely. Of the 53 subjects, 77% (41/53) were female and 23% (12/53) were male, with a mean age of 36 years (standard deviation, 14 years). In Table 1, a description of the baseline characteristics of the subjects is presented. The subjects had a high education level and showed a healthy lifestyle (low smoking rate; moderate alcohol consumption; physically active). Subjects were used to consuming coffee and tea regularly.

Of the cognition sessions performed by the participants, 10% to 20% were not completed. Some missing data was therefore present for A and B, but the model was able to use these incomplete data.

Responses with a reaction time under 200 ms and above 4000 ms were excluded from the analysis; the first were considered anticipatory, the second caused by something other than effortful cognitive processing. In total, these excluded responses accounted for 1.3% of all data points.

Cognition Tests

The 3 cognition tests used, revealed different reaction time frequency spectra, stressing the different types of cognition performance required for the test. The Go-No Go showed the fastest reaction time; Coding and N-back testing required more time for answering (see Figure 1 for reaction time spectrum of the tests). The ratio of correct and incorrect responses also illustrates the various levels of difficulty of the 3 tests (see Figure 2).

Figure 1. Reaction time frequencies (in ms) of the 3 cognition tests of the subjects: Coding (red), Go-NoGo (green), N-back (blue) test.

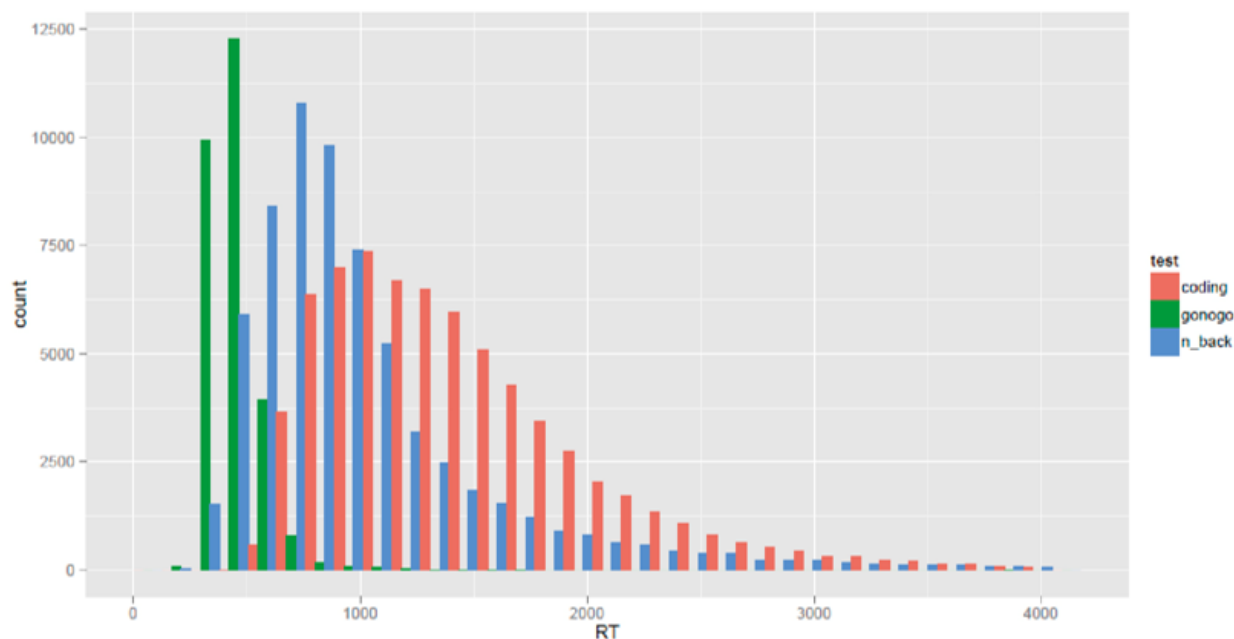
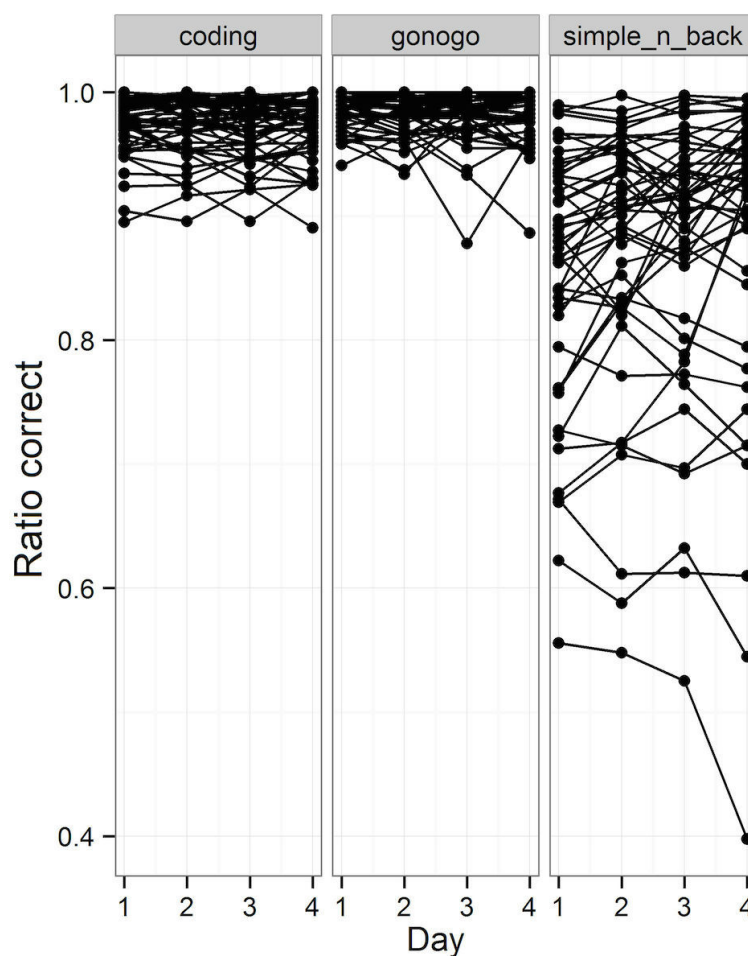


Table 1. Baseline characteristics of subjects (n=53).

Parameters and characteristics	n (%)
Age (years)	
All subjects 36 ± 14	53 (100)
Men: 36 ± 14	12 (23)
Women: 36 ± 14	41 (77)
Recruitment	
Facebook	16 (30)
FoodLog.nl	21 (40)
Other media	16 (30)
Daily physical activity: Dutch activity norm (.5 hours activity/day)	
Below Dutch norm	14 (26)
Met the Dutch norm	39 (74)
Alcohol consumption	
No	10 (19)
Yes	43 (81)
1–7 consumptions/week	36 (68)
8–14 consumptions/week	5 (9)
15–21 consumptions/week	2 (4)
Smoking habit	
Yes	6 (11)
No	47 (89)
Just stopped	4 (8)
Quit	15 (28)
Never	28 (53)
Habitual coffee consumption	
No	0 (0)
Yes	53 (100)
<7 cups/week	16 (30)
7–14 cups/week	18 (34)
>14 cups/week	19 (36)
Habitual tea consumption	
No	12 (23)
Yes	41 (77)
<7 cups/week	17 (32)
7–14 cups/week	12 (23)
>14 cups/week	12 (23)

Figure 2. Ratio correct responses of total responses of the three cognitive tests on the four test days: Coding, Go-NoGo, N-back tests.



Reaction Time

The reaction time results of the cognition tests performed 1 hour before consumption of the provided coffee sachets (baseline) and after coffee consumption (intervention) is presented in [Table 2](#).

A clear treatment effect of caffeine was present for the Go-No Go test after coffee consumption ($P<.001$), resulting in a faster response after caffeine intake. For the Coding and N-back tests this was not seen. For Coding, a block effect was present ($P<.001$) and for N-back an interaction effect was found ($P=.006$).

The baseline cognition data collected before coffee consumption did not show a treatment effect. An interaction was found for

Coding ($P=.001$) and for N-back ($P=.007$). For Go-No Go, a block effect was seen ($P=.005$).

Correct Responses

In [Table 3](#), the correct response index of the cognition tests performed 1 hour before consumption of the provided coffee sachets (baseline) and after coffee consumption (intervention) are presented. The data collected at baseline revealed a treatment effect ($P=.044$) for Coding, and a block effect for the N-back test ($P<.001$). The intervention of coffee consumption showed small reduction in correct answers for the Go-No Go test ($P=.004$) for the second block. Improvement of correct answers in the second block was seen for the N-back test ($P<.001$).

Table 2. Reaction time (in ms) at baseline and after coffee consumption for decaf and caffeine conditions.^a

Test and treatment	Baseline			Intervention		
	Block 1	Block 2	<i>P</i> value	Block 1	Block 2	<i>P</i> value
Coding						
Decaf	1506 ± 613	1413 ± 571	<.001 ^b	1483 ± 592	1405 ± 566	<.001 ^e
Caffeine	1506 ± 621	1401 ± 587		1465 ± 572	1397 ± 577	<.001 ^e
Go-No Go						
Decaf	436 ± 137	442 ± 117	.005 ^c	426 ± 102	434 ± 109	<.001 ^f
Caffeine	446 ± 121	423 ± 102		420 ± 95	418 ± 103	
N-Back						
Decaf	1093 ± 618	925 ± 506	.007 ^d	1013 ± 570	877 ± 487	.006 ^g
Caffeine	1089 ± 606	985 ± 567		1005 ± 580	917 ± 525	

^aAt baseline the coffee is not yet consumed, but it reflects the condition for that test day. Both coffee conditions were repeated and shown as block 1 and block 2 data.

^bTreatment × block interaction Coding Intervention.

^cBlock effect Go-No Go Intervention.

^dTreatment × block interaction for N-back; especially between block 1 and block 2 for both treatments.

^eBlock effect for Intervention.

^fTreatment effect of intervention.

^gInteraction effect of intervention.

Table 3. Correct response index at baseline and after coffee consumption for decaf and caffeine conditions.^a

Test and treatment	Baseline			Intervention		
	Block 1	Block 2	Statistics	Block 1	Block 2	Statistics
Coding						
Decaf	0.967 ± 0.177	0.966 ± 0.181	.044 ^b	0.973 ± 0.162	0.967 ± 0.178	
Caffeine	0.967 ± 0.179	0.972 ± 0.164	.044 ^b	0.967 ± 0.178	0.967 ± 0.177	
Go-No Go						
Decaf	0.981 ± 0.136	0.981 ± 0.136		0.985 ± 0.121	0.979 ± 0.142	.004 ^d
Caffeine	0.981 ± 0.136	0.981 ± 0.137		0.986 ± 0.118	0.981 ± 0.133	.004 ^d
N-Back						
Decaf	0.859 ± 0.348	0.877 ± 0.328	<.001 ^c	0.875 ± 0.330	0.887 ± 0.316	<.001 ^e
Caffeine	0.862 ± 0.345	0.876 ± 0.329	<.001 ^c	0.876 ± 0.329	0.879 ± 0.326	<.001 ^e

^aAt baseline the coffee is not yet consumed, but it reflects the condition for that test day. Both coffee conditions were repeated and shown as block 1 and block 2 data.

^bTreatment effect Coding baseline.

^cBlock effect for N-back baseline.

^dBlock effect for intervention.

^eBlock effect for intervention.

Discussion

Principal Results

For the first time to our knowledge, in the present study we describe the conduct of a human intervention study design (via use of the Internet) to test the effect of caffeine on cognition

(EFSA claim) in a real-world setting. Instead of using a clinical setting for conduction of the studies [8-12], participants were tested in their home environment. This study may be of importance for food companies to enable testing of their products in a more natural environment. The effect of caffeine on cognition was measured using 3 different tests, requesting different cognitive functions (attention, alertness, [visual]

memory). We found a significant treatment effect in the 'at-home condition', what may be interesting for ecological validity of the tested (food) product.

Our main finding was a faster reaction time in the Go-No Go test, as a result of caffeine consumption prior to the test. The test resulted in a significant finding even in an environment (at home) where more variation in the test conditions and performance measurements was anticipated. The significant difference in reaction time of 10 ms of decaf versus caffeine condition may not be meaningful in real life, but was similar to that found in the controlled condition [8]. The reduced reaction time of 330 to 320 ms [8] was already faster than in the present study, but a similar reduction was present. A very strict time protocol was used in the study of Brice and Smith [8], but was not precisely known in the present study because subjects perform the tests themselves at home. Smith and Rogers saw a similar improvement in reaction time as well (± 510 ms for placebo and ± 490 ms for 100-mg caffeine) [15]. The more pronounced effect found in the latter study might be a result of the fact that both habitual caffeine consumers, as well as caffeine abstainers were included in the study. In our study, only subjects habituated to coffee and tea consumption were included. This may explain the more pronounced effect in reaction time, because the effect in abstainers may be increased, although there is still debate whether abstainers show increased effects [15].

For this type of study, it is important to stress the amount of data available. The tests contain multiple tasks and are mostly performed for at least 5 minutes, resulting in thousands of data points for all subjects together. This explains the significant finding, although still a large standard deviation was present. This was in line with well-controlled lab trials [12,15,16].

The main difference from the well-controlled clinical trials [8-12] was the level of control of the conduct of the test day. Timing of the tests performed, product preparation, compliance, and conduct of the tests are performed according to protocol supervised by a research nurse able to correct the subject. At home, more variation will be present. In the present study, subjects were provided with an instruction how to prepare the drink, the timing of consumption, and performance of the tests; otherwise, too much variation may result in less interpretable results in these type of studies [4].

Internet and laptop differences may be a source of variation as well. In the study, we used the website of QuantifiedMind for standardized testing. So the software used was controlled. However, there may have been variation in the browser used, the central processor unit of the laptop [14]. This may give rise to additional variation in reaction time as was recently discussed. Restricted inclusion of type of laptop and browser should be beneficial for reduction in variation, but may be difficult with respect to recruitment of subjects.

The variation at home was exactly the item reported in the evaluation questionnaire by the participants; some deviations from the protocol were mentioned (minor time differences, nonfasting state, order of activities deviated). This means that there was indeed more variation present at home than in a controlled metabolic ward trial environment. This indicates that for this type of study less power is present and more subjects

need to be included to find significant effects. The number of subjects in controlled caffeine studies was 18 [8] and 24 [10]; our study was conducted with twice as many subjects, just to increase the power with this variation in outcomes and have ecological validity.

For the different cognition tests, we found that the significantly reduced reaction time for the second block illustrates that subjects were still on a learning curve at the test days. More training sessions than the 1 test day session and the training practices at each test day before the actual tests were performed, may provide better test conditions to measure differences due to a treatment intervention. The finding that a learning effect is still present and affecting reaction time, stresses the importance of training sessions in these types of studies. The design for an at-home cognition study should therefore contain multiple test days so that training will not affect the outcome of the test anymore or contain tests with less training effects (simple, straightforward tests).

Due to the randomized and balanced order of treatment in the study the learning effect is not affecting the outcome of the study.

Web-Based Recruitment and Subject Population

The websites used for recruiting subjects, resulted in a fast recruitment (Facebook and FoodLog) as was reported before [17]. Highly motivated subjects with an interest in food research showed interest in participation. Both websites revealed clearly highly educated subjects. The high education level and the healthy lifestyle of this group of subjects (see Table 1: low alcohol intake, low smoking percentage, high activity level; good computer skills) stressed the selectivity of our population. Nicholl [4] also recently reported that participants were predominantly female, white, well educated, and middle aged, and thus the wider applicability of digital self-management interventions remains uncertain. This is of importance for the introduction of the usability of these at-home tests. It may be not be applicable for the general population.

Also, our subject population showed a predominance of women in the study of 77% (41/53) versus 23% (12/53) men. The mean age of 36 ± 14 years further showed that we did not have a young group of subjects, both factors were in line with Nicholl [4] and indicate that we cannot generalize our results to the whole population.

At-Home Testing

To study the feasibility of the real-world setting, a relatively simple study intervention should be chosen, of which effect is well known. In addition, the study measurements should be able to be performed by volunteers at home when subjects conduct the protocol alone and unguided. At-home testing further requires computer-skilled subjects, a portal with adequate Web-based tests/questionnaires, and a helpdesk at the research site. The study procedures performed by the subjects need to be straightforward; products to be consumed must be sent in time and clearly coded.

In the study evaluation the subjects stressed that the cognition tests were easy to implement in their daily activity schedule.

The at-home study design therefore had a high compliance score. However, not all cognition tests used are applicable: the coding test was difficult and needed too much explanation, and is therefore not suitable to implement in an 'at-home setting'.

Strengths and Limitations

Many strengths can be identified in our study. The study was designed as a randomized controlled trial. The subjects were provided with clear instructions on how to perform the tests themselves at home. The decaf and caffeine coffee sachets looked similar and were coded and were both tested twice. Intake of which coffee sachet was consumed, was checked via the Internet. Some compliance questions were asked before the start of the tests. Cognitive baseline testing was included to examine day-to-day variation. These are all aspects of well-controlled studies.

There were some limitations in the study as well. In the evaluation of the study, it became clear that some subjects performed the study differently than prescribed (nonfasting state; time deviations; order of activities deviated). Therefore, it is known that these tests contained more variation than completely controlled clinical studies. Improvement of the prescribed conduct of the study may be visualization; besides written information, provision of instruction films may help a correct conduct of the tests or study at home.

The set up at home is therefore less suitable for strict or complicated study protocols. Easy research questions with simple read outs for data collection and adequate, tailored instructions are essential. A reduction in variation of conducting the study may be achieved by a Web-based check prior to the start of the tests to examine understanding of the protocol and conduct of the tests.

Another inherent limitation in this type of study is reliability of the selection criteria due to absence of face-to-face contact or even blood or physiological data because subjects are recruited via the Internet. The screening form can be manipulated and this again will result in more noise/variation of the subject data.

The fact that no control of the conduct is present, other than the electronic data obtained, is a clear limitation. Some control was present (electronic data, code of coffee sachet consumed), but subjects could manipulate the tests. Collection of a saliva sample in order to encourage compliance with the test instruction, but

not analyzing the sample as done by others [15] may limit this factor. This strategy may stimulate subjects to perform the study as correct as possible.

Implementation of webcam use to improve or monitor compliance may affect privacy too much, resulting in fewer subjects willing to participate. This may also be a technologic issue for subjects unable to upload movies.

A study design based on Internet websites requires skills with respect to computers and the Internet. Based on starting numbers in our study, 25% (17/70) of the subjects were not able to complete the tests or found the study too time consuming. The website built was not easy for subjects, because of the double login; after the login to the Do It Yourself (DIY) caffeine study, they needed to login on QuantifiedMind website separately. Of course, this can be improved both by better websites and better evaluation of computer skills prior to study performance.

Further study should also be done on the variation present in these types of studies. Now we have one large cloud of variation, but well-controlled examination of all kind of factors influencing the variation may provide insight into the amount of effect: the differences in time of testing, preparation, environment, people (children) present, fasting, eating the evening before, activities done before, and so on. Control of these factors may show what elements are of real importance affecting the outcome for at home testing.

Conclusions

In the present study, it is shown that a DIY study conducted at home is a valuable alternative for well-controlled studies.

On the Go-No Go cognition test, the DIY caffeine study presented showed a similar faster response as found in controlled studies in a metabolic ward as used in the EFSA claim for caffeine. Not all cognitive tests are sensitive enough or suitable for at-home testing. The learning effect present with cognitive tests, stress the importance of training sessions prior to actual testing. The limited control and the variation in conduct by subjects themselves at home, stress the use of the DIY design for simple, straightforward research questions, and a clear instruction protocol. The easier recruitment and the lower costs for conducting, make this type of design and attractive addition to the current randomized control trial portfolio.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Subject inclusion.

[[PDF File \(Adobe PDF File\), 344KB - resprot_v6i9e169_app1.pdf](#)]

Multimedia Appendix 2

Cognition tests.

[[PDF File \(Adobe PDF File\), 81KB - resprot_v6i9e169_app2.pdf](#)]

Multimedia Appendix 3

CONSORT-EHEALTH checklist (v1.6.1).

[[PDF File \(Adobe PDF File\), 510KB - resprot_v6i9e169_app3.pdf](#)]

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Abbreviations

ANOVA: analysis of the variance
DIY: do it yourself
EFSA: European Food Safety Authority

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Original Paper

The Adverse Drug Reactions from Patient Reports in Social Media Project: Five Major Challenges to Overcome to Operationalize Analysis and Efficiently Support Pharmacovigilance Process

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Abstract

Background: Adverse drug reactions (ADRs) are an important cause of morbidity and mortality. Classical Pharmacovigilance process is limited by underreporting which justifies the current interest in new knowledge sources such as social media. The Adverse Drug Reactions from Patient Reports in Social Media (ADR-PRISM) project aims to extract ADRs reported by patients in these media. We identified 5 major challenges to overcome to operationalize the analysis of patient posts: (1) variable quality of information on social media, (2) guarantee of data privacy, (3) response to pharmacovigilance expert expectations, (4) identification of relevant information within Web pages, and (5) robust and evolutive architecture.

Objective: This article aims to describe the current state of advancement of the ADR-PRISM project by focusing on the solutions we have chosen to address these 5 major challenges.

Methods: In this article, we propose methods and describe the advancement of this project on several aspects: (1) a quality driven approach for selecting relevant social media for the extraction of knowledge on potential ADRs, (2) an assessment of ethical issues and French regulation for the analysis of data on social media, (3) an analysis of pharmacovigilance expert requirements when reviewing patient posts on the Internet, (4) an extraction method based on natural language processing, pattern based matching, and selection of relevant medical concepts in reference terminologies, and (5) specifications of a component-based architecture for the monitoring system.

Results: Considering the 5 major challenges, we (1) selected a set of 21 validated criteria for selecting social media to support the extraction of potential ADRs, (2) proposed solutions to guarantee data privacy of patients posting on Internet, (3) took into

account pharmacovigilance expert requirements with use case diagrams and scenarios, (4) built domain-specific knowledge resources embedding a lexicon, morphological rules, context rules, semantic rules, syntactic rules, and post-analysis processing, and (5) proposed a component-based architecture that allows storage of big data and accessibility to third-party applications through Web services.

Conclusions: We demonstrated the feasibility of implementing a component-based architecture that allows collection of patient posts on the Internet, near real-time processing of those posts including annotation, and storage in big data structures. In the next steps, we will evaluate the posts identified by the system in social media to clarify the interest and relevance of such approach to improve conventional pharmacovigilance processes based on spontaneous reporting.

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KEYWORDS

pharmacovigilance; social media; big data; natural language processing; medical terminology

Introduction

Adverse drug reactions (ADR) are among the most frequent causes of death in industrialized countries [1]. For example, in the Netherlands, ADRs correspond to 140,000 hospital stays per year, which is more than the number of stays for myocardial infarction, and from 10,000 to 30,000 deaths per year are related to ADRs [2]. Due to methodological and patient selection limitations, clinical trials are not designed to detect all ADRs, requiring postmarketing surveillance or pharmacovigilance systems.

Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem” [3]. Pharmacovigilance therefore aims to alert about the potential risks of a drug: the detection or generation of a signal. According to Bégaud et al [4], “on average, no more than 5% of serious ADRs are actually reported.” Underreporting by health care professionals is therefore a limiting factor for the efficiency of pharmacovigilance processes. The collection of data directly from patients has been organized by the health authorities of several countries in the past. Studies have shown that some reports from patients can be of similar quality compared to health professionals [5], but reporting by patients remains limited due to lack of awareness of the reporting system.

In the era of Web 2.0, online social networking applications have become very popular, allowing users to communicate, interact, and share worldwide. These social media bridge the geographical and social gap between people, enabling them to share similar experiences, facilitating what is difficult in the real world. Patients using social media have grouped into communities to share a wide variety of personal medical experiences, including use of medicines and adverse reactions. The interactions between patients take many forms, including social networks, blogs, microblogs and discussion boards, emails, and chats, which are potential sources to explore. Extraction of such data and its integration in pharmacovigilance processes face 5 major challenges as depicted in Table 1.

Although research teams have already performed several experiments to extract knowledge from Web forums [6-8], the process is still not operably exploited by most pharmacovigilance teams from drug regulatory authorities and the pharmaceutical industry [9]. We assume the reason is that much effort has been devoted to identifying relevant information within patient posts, but supplementary developments are still required to build specific solutions for the other challenges.

The Adverse Drug Reactions from Patient Reports in Social Media (ADR-PRISM) project aims to develop a method to operationalize the analysis of patient posts in social media. This paper describes the current state of advancement of the ADR-PRISM project by focusing on the solutions we have chosen to respond to the 5 major challenges.

Table 1. Major challenges related to exploiting patient posts in pharmacovigilance.

Question	Challenge	Response? Process? Solution?
How to manage social media quality?	Variable quality of information on social media	Identify social media that present high-quality content regarding relevance and completeness of information for pharmacovigilance purposes
How to manage data privacy?	Guarantee of data privacy	Take into account data privacy of patients posting on the Internet
How to deal with pharmacovigilance main objectives?	Response to pharmacovigilance expert expectations	Identify the optimal framework where analysis of patient posts can usefully complement usual pharmacovigilance processes
How to identify relevant information within patient posts?	Identification and processing of relevant information (eg, drugs and adverse reactions) within Web pages	Extract, process, and render relevant information on drugs and their adverse reactions
How to manage scalability related to big data collection in social media?	Robust and evolutive architecture	Take into account the evolution of the platform and the high quantity of data available on the Internet that requires specific methods for big data collection and storage

Table 2. Proposed methods for meeting the 5 major challenges.

Challenge	Proposed method
Variable quality of information on social media	Design a scoring method that allows selection of high-quality social media
Guarantee of data privacy	Design a technical solution based on data minimization and access restriction that guarantees data privacy of patient posting on social media
Response to pharmacovigilance expert expectations	Study the pharmacovigilance expert requirements and formalize them in use case diagrams and usage scenarios
Identification and processing of relevant information (eg, drugs and adverse drug reactions) within Web pages	Enforce best practices based on specialized dictionaries, pattern-based matching, and natural language processing to detect drugs and their adverse reactions in patient posts
Robust and evolutive architecture	Build a component-based architecture that allows storage of big data and accessibility to third-party applications through Web services

Methods

Overcoming the Five Major Challenges

In order to overcome the 5 major challenges, we propose to apply the methods depicted in [Table 2](#).

Variable Quality of Information on Social Media

In order to carry out our study about the quality of information on social media, we first sought to identify potential sources of interest. An initial analysis was conducted exploring the functioning and content of a selected sample of websites as well as the behavior and interactions of their users [10].

To identify relevant forums for the project (ie, providing messages about drug use and safety), we conducted research through search engines such as Google with the terms “network,” “forum,” “health,” “patient,” and “medicine,” and 11 sites were identified.

In addition, to identify specialized forums about a disease or group of diseases, for example, we used the *Catalogue et Index des Sites Médicaux de langue Française* (CISMeF) website [11,12], a catalog and index of French language health resources on the Internet that conducts appraisals of the websites of patient associations. These websites were systematically covered by a medical librarian to identify forums, and 17 websites were identified. Forums strictly reserved for members or forums with very little activity (fewer than 10 messages in the current month) were excluded.

We identified, reviewed, and rated the websites according to 3 major criteria (number of visits, popularity of the website, and number of health and drug therapy-related posts) which we estimated using the following methods:

- Collection of total posts if it was indicated
- The website 1001forum [13], one of the most important French forums for indexers, to estimate the number of messages posted per day on each forum
- Google, Alexa [14], and Yoovi [15] to estimate the popularity, traffic, and overall activity of the forum

Finally, for all selected and specialized forums, a pharmacist checked the relevance of each mention of drugs corresponding to the theme of the forum.

A state-of-the-art search of the existing methodologies to assess the quality of the websites was carried out. This led to the

identification of the net scoring [16] method, among others [17], which enables the assessment of health websites. This tool, designed for the evaluation of websites but not specifically for forum evaluation, was used to perform a detailed analysis of 7 health websites and their forums among the sites initially identified in order to adapt the criteria of the net scoring grid to the evaluation of social media.

The evaluation of Twitter and Facebook as sources is currently being addressed, and their specific formats (eg, limitation of the number of digits to 140 for Twitter) necessitate a more specific analysis. Tweets are more difficult to interpret than posts in other social media that usually contain more information, but tweets have the advantage of being available in larger volumes. While the contribution of Twitter to pharmacovigilance has already been extensively evaluated, for example, by Bian et al [18], who concluded that “daily-life social networking data could help early detection of important patient safety issues,” little work has been performed with Facebook, which requires further investigation.

Guarantee of Data Privacy

ADR-PRISM established an ethics committee comprised of a medical doctor specializing in pharmacovigilance, an expert in the management of data privacy, and an epidemiologist to support the consortium in defining the policy for access, data recording, and respect for the privacy of personal information of patients describing an adverse effect on social media. The committee worked on a solution that was ethically acceptable and consistent from a legal point of view.

In parallel, a working group was created and studied the different possibilities for complying with the ethical and confidential aspects of data collection by organizing brainstorming sessions, participating in working groups and conferences on this theme, and consulting the outside advice of a lawyer specializing in the matter. The working group held several meetings with the expert in data privacy from the ethics committee.

Response to Pharmacovigilance Expert Expectations

We defined several use cases after a compilation and analysis of end-user requirements for the future system. Use cases have been written after thorough analysis of the context of the monitoring of health products, an analysis of foreseen end users of the platform, and the uses they may have of the tool. See [Table 3](#) for the definitions of the concepts of use case diagrams and usage scenarios.

Table 3. Definitions of use case diagram and usage scenario.

Definition	Example
Use case diagram	
Unified Modeling Language provides use case diagrams in order to specify and describe use cases. These are cases of the system (ie, a description of how the user interacts with the system). Use cases are generally organized in steps, which can be considered smaller usage components (and therefore can be described as discrete use cases).	An example of use case is the selection of a drug and/or an adverse reaction upon interaction with a form displayed by the system. Another use case is to read posts from social media for this selection.
Usage scenario	
Usage scenarios are circumstances in which a user will interact with the system. Multiple usage scenarios can be defined that can correspond to a single use case.	Making a pharmacovigilance survey is a usage scenario. Indeed, we can decompose the survey into smaller components to look for similar case reports in the national pharmacovigilance database, make a literature search, and perform a search in social media.

Identification and Processing of Relevant Information Within Web Pages

Information extraction is the process of extracting and analyzing information in order to discover buried knowledge, leading to intelligence from large volume of unstructured text content. Our extraction process involves several subtasks: (1) text preprocessing, including text formatting tasks, (2) morphosyntactic tagging, performed by the XeLDA (Naver Labs Corp) tagger, which identifies the language, splits the text into sentences and words, and attaches to them their lemma and part of speech category, (3) extraction rules compiled in semantic components, which model the relevant information to extract, and (4) postprocessing, to normalize the information extracted.

All analysis steps are packaged in components that build a Skill Cartridge (Expert System France SA). It can be imagined as a cascade of extraction modules that condense the textual data into meaning. The analysis is based on finite state technology [19].

Skill Cartridges are domain-specific knowledge resources that may embed lexicon, morphological rules, context rules, semantic rules, syntactic rules, and postanalysis processing. They are plugged into the Expert System Luxid (Expert System France SA) extraction server to perform annotations. The processing unit is the sentence. The information to be extracted by the Skill Cartridge is modeled according to the Luxid Data Model, which is made up of Luxid Objects. A Luxid Object is qualified by a type, either entity, relationship, or structure. Objects of the same type share the same behavior, meaning, and attributes. A type may have a parent type from which it inherits meaning, attributes, and behavior. A type is represented by the complete hierarchy like /entity/company or /relationship/biomedical/

activation. Entities can either stand alone or be related to each other by a relationship (which in general describes an action).

The Skill Cartridges use multilanguage dictionaries that assign concepts to words and phrases called entities. Each entity, in addition to its preferred label and its variants, may also have attributes. These are fields associated with the concept that contain additional information about the concept. For example, a concept “disease” may have the attribute “course” whose value is “acute.” All these entities are stored in the form of a concept tree. Some concepts have parents and/or children (eg, one can see the concept “neuropathy” as a child of the concept “neurological disease”).

Extraction rules, driven by targeted results, build relationships between defined concepts from the low level to a higher level. The extraction rules process consists in several read-outs, where the analyzed text is successively retagged. During each read-out, the tagged text is replaced by the corresponding concept. During successive read-outs, the extraction server does not see the text but the concepts. Skill Cartridges are used to annotate the messages using medical terminologies that detect a broad medical vocabulary and discern the concepts and semantic relationships related to drugs, associated adverse events, and all additional data that can be attached as the date, location, patient characteristics (age, gender, dosage, etc), characteristics of the medication (dose, frequency, duration, etc), and characteristics of the post (name of the forum, name of the thread, etc).

A working group has been created to develop a process to analyze data and extract some pharmacovigilance information and has identified 3 medical terminologies from the HeTOP terminology server (Health Terminology/Ontology Portal) [20,21] and data from the Vidal Drug Database for the project. The identified terminologies are shown in Table 4.

Table 4. Medical terminologies selected for feeding the dictionary for the data extraction task.

Short name	Long name	Content	Language	Number of concepts	Example	Reference
ATC	Anatomical Therapeutic Chemical Classification	Drugs classes and substances	FR/EN	4717	http://www.chu-rouen.fr/cis-mef/skos#ATC_CD_A/ anabolic agents for systemic use/ anabolic steroids/androstan derivatives/ androstanolone	[22]
MedDRA	Medical Dictionary for Regulatory Activities	Adverse drug reactions	FR/EN	74,413	MedDRA top tree/cardiac disorders/heart failures/cardiac failure/cardiac insufficiency	[23]
Racine Pharma	Roots of the pharmaceutical products	Short names of drugs	FR	5164	Ascorbic acid	manually produced
Vidal Drug Database	Drug database sold by the Vidal company	All the regulatory information about drugs	FR	40,227	XVII congenital malformations and chromosomal abnormalities/ Q00-Q07 congenital malformations of the nervous system/ Q00.0 anencephaly	[24]

In the ADR-PRISM project context, the Anatomical Therapeutic Chemical (ATC) classification enables drugs class and substance entities extraction. Racine Pharma enables extraction of common drug names and abbreviations used by patients. It is a terminology developed by CISMef from a file of French brand names where “racine” is the French word for “root.” A root corresponds to its brand name label without its strength or form or the name of the company in the case of a generic drug. This terminology is revised monthly according to new updates to the French public drug database. New potential roots are extracted by an informatics process and presented to a pharmacist for curation. Several roots are linked to their ATC code. This terminology is not currently available in open access. The Medical Dictionary for Regulatory Activities (MedDRA) identifies ADRs. Vidal data contains all the regulatory information about drugs (names, indications, contraindications, expected adverse reactions, dosage, posology, interactions, precautions, etc).

Robust and Evolutive Architecture

The method used to define the system architecture was based on the information system architectures part of the Open Group Architecture Framework. After having defined inputs and outputs provided by each partner of the ADR-PRISM consortium, data and application architecture have been combined to propose a service-oriented architecture. Regarding the storage software, a study comparing several solutions was conducted. Different big data storage technologies have been subject to the project constraints concerning relational or object-oriented database management system as well as non-structured query language solutions: columns oriented, documents oriented, key/value, graphs oriented, in-memory data grids, and triplestores.

The first prototype of the ADR-PRISM project is based on Expert System Luxid repository technology, in which both posts and their indexing metadata (structural metadata and semantic annotations coming from the annotation service) are stored in order to support the search and browse functionalities from Luxid: (1) keywords (full text search), (2) concepts (terms from the thesauri), and (3) relations linking the concepts.

Results

Variable Quality of Information on Social Media

The use of the net scoring tool, composed of 46 criteria, in the evaluation of Internet social media has been studied by Katsahian et al [10]. The results showed that the net scoring tool needed to be adapted, clarified, and simplified in order to obtain the most suitable and functional grid. The least relevant criteria were eliminated or grouped into new and more general criteria. The final resulting grid was composed of 21 equally weighted criteria (see [Multimedia Appendix 1](#)).

Guarantee of Data Privacy

The positioning of the project in terms of data processing, collection, and ethical compliance is complex in terms of current regulations and their evolution in the near future. In France, the Data Protection Act of January 6, 1978 (*Loi Informatique et Libertés*), applies as soon as there is automatic or nonautomatic data processing involving personal health data. Article 2 of the law defines personal health data as “any information relating to a physical person who is or can be identified, *directly or indirectly*, by *reference* to an *identification number* or to *one or more factors specific* to them” [25].

Article 8 of the law specifies that “the collection and processing of personal data that reveals, directly or indirectly, the racial and ethnic origins...of persons, or which concern their health or sexual life, is prohibited.” This article also defines exceptions to this law, for example, for “processing that relates to personal data that the concerned person has made public” or if the personal data are subject to an anonymization procedure which the French data protection authority, *Commission Nationale de l'Informatique et des Libertés* (CNIL), has earlier approved. In that case, the CNIL provides a specific procedure for processing in the scope of conventional pharmacovigilance (number AU-013 unique authorization of the CNIL).

One of the specificities of the ADR-PRISM project lies in the fact that its purposes and the data processing natively refer to several legal and sometimes conflicting environments. Indeed,

the analysis of social media to identify ADRs requires at least the following actions to proceed:

- Identification of data types that will be used (personal data, health data)
- Qualification of the data processing to be carried out (collection, treatment, preservation and storage, etc)
- An inventory of texts and regulations governing the operated data processing (French and European, including the decree on health care data hosting, etc)
- Obtaining the necessary authorizations

To respond to this complexity we have chosen an approach that involves:

- Breaking the global treatment related to the ADR-PRISM project into several treatment units that will then be positioned in a known and mastered legal framework
- Articulating the treatment units in order to match them to the global treatment

This approach, subject to the approval of the CNIL, led to the identification of 2 different treatment units:

- Data collection from forums. Data collected are considered as indirectly identifying data (as the pseudonym is collected). Data considered at this stage are the copy of data found on public forums and haven't been enriched by processing yet.
- Data processing and enrichment. Data are enriched by text mining analyses. Health data emerges at this stage from raw data.

This process relies on the creation of 2 different accesses to the database that will be granted to minimize the risk of reidentification:

- Regular access to the database through a process of data minimization that doesn't allow access to the verbatim text of the post, the author's pseudonym, and the name of the forum
- Restrictive access to the posts (cleaned by algorithms aiming to remove all directly identifying data before storage, such as email, telephone number, or addresses), the pseudonym, and the forum

This second access allows the treatment covered by the processing of personal data and data processing steps related to pharmacovigilance requirements (defined by number AU-013 single authorization of the CNIL). These include preserving the possibility of making contact with the author of the message describing the adverse reaction (via its account) to investigate the case report and if necessary to intervene for a medical emergency. This second access is the most sensitive, which explains why it benefits from the highest modalities of information security.

We have completed the process of computer data security with organizational procedures. In particular, we established a limited list of users allowed to benefit from the second restrictive access.

This list is controlled by a specific procedure established by the ethics committee and, in exceptional cases, additional special authorizations may be granted after study of the application by the ethics committee.

Response to Pharmacovigilance Expert Expectations

While the usage scenarios are numerous and depend on the monitored product or type of implementation monitoring method, the use cases related to the platform are relatively similar regardless of the context. For the user, the main usage scenario to use the ADR-PRISM platform will be to:

- Consult cases
- Filter the cases or make queries
- View results
- Select products or ADRs for active surveillance (manage alerts)
- Follow these and see new information on these products
- Be alerted of new cases
- Extract the results (data stream or aggregated tables)
- Identify new pharmacovigilance signals

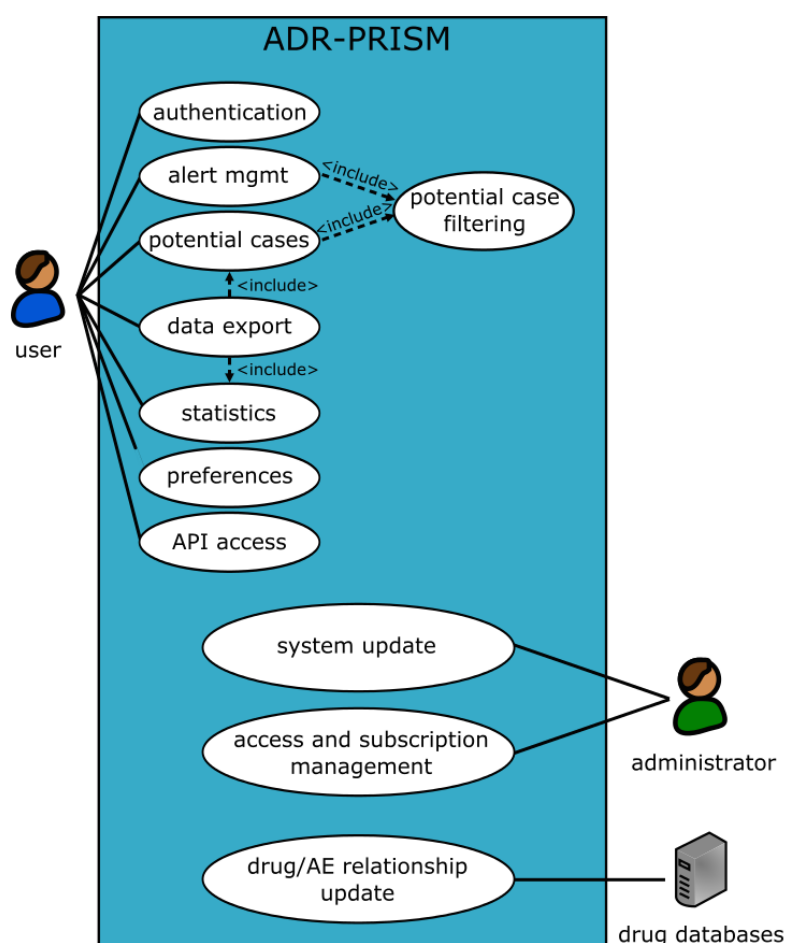
A total of 11 use cases have been described: 8 for the user, 2 for the administrator, and 1 for the update of drug/ADR relationships. Use case diagrams are depicted in [Figure 1](#). The user is a pharmacovigilance specialist who needs to review potential ADRs reported by patients in social media. The administrator is working in the back office of the ADR-PRISM platform in order to update the system and manage the user accounts.

Identification and Processing of Relevant Information Within Web Pages

As a result of the annotation, we obtained lists of medical entities coming from the different terminologies that have been automatically converted into the Expert System Skill Cartridges format. No manual work was done at this stage, only recommendations on incongruities and ambiguities. The extracted entities were symptoms, medications, patients, and pathologies.

Relationships based on extraction rules give information on the occurrence of an ADR which can be absent (the treatment is effective and does not cause adverse reaction) or present (the treatment causes adverse reactions), as depicted in [Table 5](#). To identify these reactions, the Skill Cartridge leverages the different thesauri and embeds specific extraction patterns and rules.

The extraction rules rely on trigger words coming from the terminologies and on semantic or syntactic patterns, which describe the syntactic phrases. A context rule expresses combinations relying on contextual triggers. A semantic rule consists of combinations of meaningful units of analysis (ie, concepts defined in previous rules). A syntactic rule consists of combinations of units relying on the syntactic structure and predication. Roles are associated to concepts depending on their function.

Figure 1. Use cases of the project.**Table 5.** Examples of drugs and adverse reactions extracted by the annotation.

Drug effects	Medical entity	Example
Present (ie, adverse reactions)	Drug: citalopram (Racine Pharma); Adverse reactions: insomnia, nausea (MedDRA ^a)	"Citalopram gave me the same <i>side effects</i> as setraline, <i>insomnia</i> and <i>nausea</i> ."
Absent	Drug: androcur (Racine Pharma); Adverse reactions: weight gain (MedDRA)	"My taking of <i>androcur</i> didn't have <i>weight gain</i> as a consequence."

^aMedDRA: Medical Dictionary for Regulatory Activities.

Robust and Evolutive Architecture

The ADR-PRISM information system fits well with the SaaS (software as a service) delivery model: it can be accessed by light clients such as Web browsers and is interoperable through the Web services it provides. A short overview of the ADR-PRISM information system is described in the technical architecture schema depicted in Figure 2.

Technically speaking, the ADR-PRISM component-based architecture is mainly composed of the following:

- Web scraping module: this crawling server provides Web services to launch the crawling of new posts of a given website from a given date and recover the cleaned content. Both Simple Object Access Protocol and Representational State Transfer are supported. The administrators of the crawling server punctually supply the crawling tool with
- Text annotation module: the Luxid Annotation server provides Web services to launch the automatic annotation of posts passed as parameter. The administrators of the annotation server punctually supply it with data from the terminology repositories to update the Skill Cartridges. After the call to this annotation service by the controller,

useful terminology data at this stage (names of the roots of medicinal products, for example). A specific parsing program is written for the filtering and cleaning process of each website. Inheritance is of course used for common functions. In addition to the post's textual content, metadata linked to the post are also delivered by this service. The result of the client call to the ADR-PRISM Web scraping service by the ADR-PRISM controller is stored in the common database for further purposes, such as text annotation service calls.

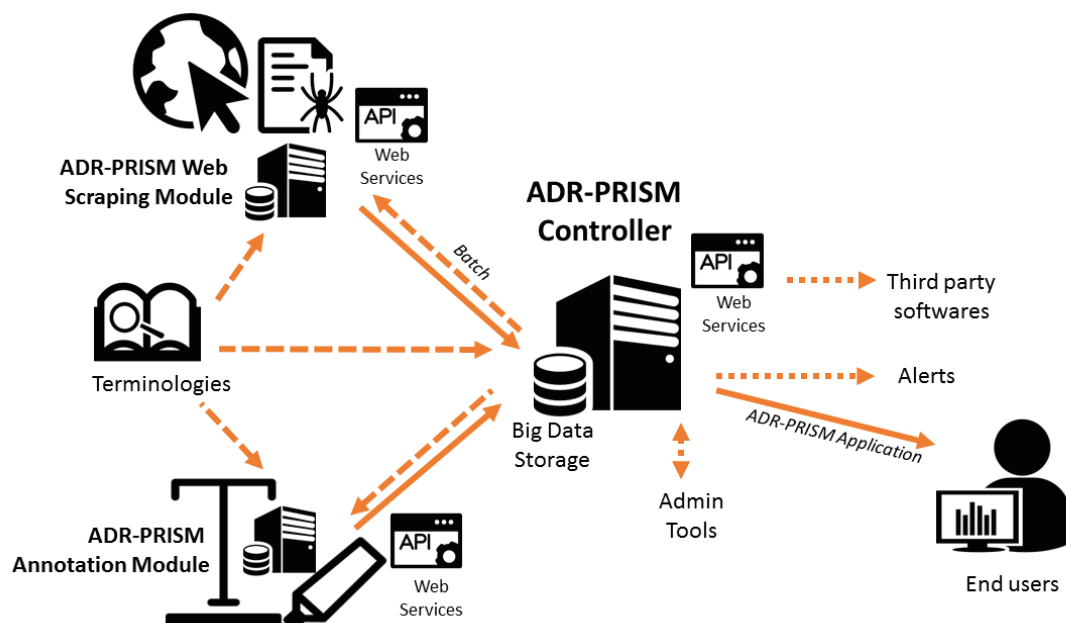
posts are labeled with known controlled vocabulary concepts (provided by terminology servers).

- Terminology standards: exports are made from the Vidal terminology servers and HeTOP [20]. The HeTOP portal includes more than 69 health terminologies and provides services to export those data with standard formats. These exports are loaded in the modules requiring terminological information scraping and annotation tools but also the common database (data source for the graphical user interface). Terminological data can be used in several steps of the ADR-PRISM information system: to preselect posts, to create a Skill Cartridge, or for data mining or querying purposes.
- Common database: this serves to host the data necessary to the ADR-PRISM application server, whether batch process (controller jobs) or graphical user interface. This database especially contains monitored URLs, forums related metadata (name, last analysis dates, etc), crawling results (threads and posts to annotate and related metadata), annotation results, terminological data, and necessary

information for the user interface (users, alerts, statistics, etc). The chosen solution for big data storage is PostgreSQL, which offers the best compromise for ADR-PRISM problematics—besides its proven reliability, it especially combines horizontal scalability features and advanced querying capabilities.

- Controller: this application server is a client of the data collection and annotation services. Batch processes are initiated at regular intervals: they consult the common database to respectively identify the URLs to process and posts to annotate, after which they query the required services and store the response in the database. Given that this batch process regularly launches the scraping, a lag can occur with the initial data in proportion of the time interval between each passage. The server also hosts the graphical interface Web application and the administration application. It also sends alerts to users according to their preferences and communicates through the interoperable Web services that allow access to the ADR-PRISM system-collected data for third-party applications.

Figure 2. The technical architecture of the Adverse Drug Reactions from Patient Reports in Social Media project.



Discussion

Principal Findings

In this paper we presented 5 major challenges that must be overcome to exploit patient posts as a complementary knowledge source for pharmacovigilance in professional settings such as drug regulatory agencies and the pharmaceutical industry. We expect that our proposals add new contributions to the field by taking into account some aspects that make sense when a software application processing large volumes of posts to support pharmacovigilance intends to be applied in an operational way: (1) developing a scoring method to evaluate the quality of information of social media, (2) guaranteeing safe application of data privacy thanks to data minimization and restricted control of access, (3) analyzing the pharmacovigilance expert's expectations to figure best practices to integrate this

complementary knowledge source consisting of selected posts on putative ADRs in current pharmacovigilance process, (4) developing a data dictionary, pattern-based matching, and natural language processing techniques for the efficient identification of relevant information on ADRs within Web pages, and (5) implementing a robust and evolutive architecture that allows storing big data from medical Web forums and access by third-party applications.

Comparison With Prior Work

Monitoring Tools for Drug Safety Using Patient Posts

Existing tools already exist for analyzing patient posts about drug use on the Internet like Treato IQ [26]. This tool aims to assess what patients say about their treatment (ie, the patient voice). This professional platform gives health and life science industries insight into what patients think about their brand.

Contrary to the ADR-PRISM project, the Treato main objective is more related to eReputation (the perception that Web users have about a brand, a company, or employees), and the platform is for pharmaceutical marketers and health care advertising and marketing agencies. ADR-PRISM aims to give regulatory agencies, pharmaceutical companies, and health care professionals insight about ADRs in social media, and its main objective is related to drug safety. Web Recognizing Adverse Drug Reactions (Web-RADR) is a European project that aims to recommend policies, frameworks, tools, and methodologies for the analysis of ADRs reported by patients in social media [27], but the consortium has not yet reported these recommendations.

Several points were partially or insufficiently documented by previous authors such as evaluation of social media, data privacy, and pharmacovigilance requirements. The technical architecture was usually implemented in previous works to allow a retrospective analysis based on a single extraction and did not support near real-time indexing, storage of big data, or interoperability with third-party applications that are desirable features in operational settings.

Variable Quality of Information on Social Media

It is expected that different social media may present different levels of quality of information about ADR descriptions. However, previous studies did not address issues related to measuring the quality of information of these social media (eg, selecting a Web forum containing threads about cancer in order to extract information on anticancer drugs [28]). Some tools exist to rate websites [17], but none of them has been designed to evaluate social media. We identified 21 criteria for evaluating social media in order to select those that present the most informative and relevant content to support pharmacovigilance processes with extraction and analysis of potentially interesting descriptions of ADRs.

Guarantee of Data Privacy

Data privacy was seldom discussed as an issue when extracting information from social media. A recent systematic review about attitudes toward ethics of researchers who explore data in social media showed very different approaches on whether social media should be seen as public or private space [29]. Indeed, one may believe that privacy does not apply online because information becomes public once it is posted, which allows access and use for research purposes, and that users should be responsible for preserving anonymity the way they manage their identity. Additionally, seeking consent from forums users is usually not feasible. There are still ethical issues in using social media for the extraction of new medical knowledge, the most important being that each patient posting on a forum should be guaranteed to keep his anonymity [30]. Considering data extraction for pharmacovigilance, anonymization was the main solution to guarantee data privacy such as implemented by Benton et al [28]. However, despite the anonymization process, patients may be reidentified a posteriori as described by Zimmer [31]; his analysis of a public release of anonymized Facebook data shows that a special mechanism should be implemented to limit access only to authorized personnel. This is the reason why we designed

procedures to guarantee that only data going through a step of data minimization should be accessible for analysis by registered end users, but we kept raw data accessible in very specific circumstances to allow contacting the patient if drug withdrawal was required for safety reasons.

Response to Pharmacovigilance Expert Expectations

In order that analysis of data retrieved from patient posts could be implemented in current pharmacovigilance processes, it is desirable to first describe these processes and to identify the pharmacovigilance evaluator requirements and expectations. We could identify these requirements in previous work only from a broad scope (ie, discussing issues related to underreporting and the need for a complementary knowledge source). We believe that previous works have insufficiently taken into account the way pharmacovigilance experts are working and how the new suggested methods should be complementary with current pharmacovigilance processes. We explored the pharmacovigilance experts' expectations and identified several issues that should be addressed by designing and implementing new functionalities supported by appropriate graphical user interface.

Identification and Processing of Relevant Information Within Web Pages

While other challenges were seldom described in previous work, identification of drugs and ADRs in Web pages was the main objective for studies focusing on extraction of relevant information from Web forums for pharmacovigilance. On one hand, several publications [28,32-35] only deal with cooccurrences of drug names and adverse reactions in messages from social media. On the other hand, some studies [18,36-41] went further and attempted to qualify the relationship between occurrences of drugs and adverse reactions. The following methods have been applied to patient posts in social media: specialized dictionaries [28,32,34,36-39,42-43], pattern-based matching [38], machine learning [18,37,42-44].

Our approach enforces best practices based on specialized dictionaries, pattern-based matching, and natural language processing. We selected 4 terminologies to feed the terminological services. One limit is that the Skill Cartridges are still in development, which prevents us from conducting a formal study in order to evaluate their performance and compare them with other approaches already described in previous work. However, results obtained by the current version of the Skill Cartridges are encouraging.

Robust and Evolutive Architecture

The number of posts extracted from forums was variable in previous work, ranging from small samples (<20,000 posts [32,40]) to larger extractions (over one million posts [28,33]). But none had to face big data issues except Bian et al [18], who collected 2 billion Tweets. We found only one article discussing specific technologies for storing large numbers of tweets with Hadoop and Apache Hive [45].

Moreover, these applications were based on a retrospective extraction of patient posts and did not take into account the requirement to automatically collect new posts on a regular

basis. We consider that extraction should be available through a near real-time indexing technique to allow analysis of patient posts in pharmacovigilance daily routine.

The barriers we had to overcome were (1) making the system robust and reliable (accelerating and securing Web services to be able to add and to rapidly evolve services and technological solutions without putting risk on the platform) and (2) opening the system to the outside to offer native interoperability by advancing from the software model to a large modular service platform. The ADR-PRISM platform supports storage of big data and access to third-party software through Web services and is based on a modular architecture consisting of different components to handle terminological, scraping, and annotation services.

Perspectives

Although the part of posts that describe personal experiences of an ADR may correspond to a very small subset of the available posts on the Internet, the large number of data sharing in social media makes such data valuable material for pharmacovigilance [46]. Analyzing patient narratives in discussion forums or blogs is important to explore patient-centered issues that may not be detected in other existing sources generated by health care professionals [47].

In the early stages of the ADR-PRISM project, we studied the requirements of final users and defined a technical architecture that allows the efficient extraction and exploitation of ADRs from social media. The consortium approach for guarantee of data privacy may change depending on new regulatory developments. In particular, the European general regulations on data protection will be taken into account when they apply. As the 21 criteria selected for evaluating the quality of social media are independent from the application domain, additional research would be necessary to determine those that allow identification of the most informative and relevant content to support pharmacovigilance processes with extraction and analysis of potentially interesting descriptions of ADRs.

Perspectives of annotation in patient posts are to evaluate the performance of the annotation module compared to previous

work and to take into account specific issues related to lay language [28,32,36,40,44]. An additional thesaurus containing patient language must be created in order to normalize the vocabulary found in the messages so that it can be recognized by medical reference thesauri. We will take into account the number of words between the detected drug and event as recent evidence shows that such distance can be used for identifying false positives and filter events that are likely to be ADRs [48].

A second prototype is being elaborated that provides a user interface for browsing documents and performing direct searches with the following functionalities: semantic facets that enable multidimensional navigation within documents and highlighting and definition of concepts within the text.

In the next steps, we will evaluate posts identified by the system in social media in order to clarify the interest and relevance of such an approach to improve conventional pharmacovigilance processes based on spontaneous reporting. Any pharmacovigilance system will be enabled to use the ADR-PRISM platform through Web services by selecting a specific drug, drug reaction, class of drug, or type of ADR. All potential ADRs will be extracted and filtered; a triage function at intake will help to identify case reports that have high potential, regarding the drug implicated or the reaction described, to enable a proactive surveillance. For example, the seriousness of the reaction will be assessed, adverse reactions concerning specific populations (pregnant women, etc) will be identified, and pharmacovigilance signals will be detected. Specific drug use may also be identified to detect possible cases of nonmedical use of pharmaceutical products [49].

Regarding languages processed by the ADR-PRISM system, the application scope of the project is focused on French and English data. But more languages could be added in the future (terminological data are multilingual; for example, MeSH or MedDRA are available respectively in 16 and 11 languages in HeTOP [21]). Other applications such as identification of counterfeiting and eReputation analysis for pharmaceutical companies should also be considered.

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Conflicts of Interest

The Vidal drug database is owned by the Vidal Company, which employs SP. The Luxid Annotation server and the Skill Cartridge are owned by the Expert System Company, which employs SGL and CH. Kappa Santé, the company that developed the Detec't tool that extracts data from posts related to potential ADRs in social media, employs CF, SS, and NT. CR, an employee of Atos, addressed issues related to guaranty of data privacy in this study. The other authors have no conflicts of interest to declare.

Multimedia Appendix 1

List of the 21 selected criteria for the evaluation grid.

[PDF File (Adobe PDF File), 21KB - [resprot_v6i9e179_app1.pdf](#)]

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Abbreviations

ADR: adverse drug reaction

ADR-PRISM: Adverse Drug Reactions from Patient Reports in Social Media

ATC: Anatomical Therapeutic Chemical Classification System

CISMeF: Catalogue et Index des Sites Médicaux de langue Française

CNIL: Commission Nationale de l'Informatique et des Libertés

HeTOP: Health Terminology/Ontology Portal

MedDRA: Medical Dictionary for Regulatory Activities

SaaS: Software as a Service

Web-RADR: Web Recognizing Adverse Drug Reactions

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