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Protocol

Serious Games for Improving Genetic Literacy and Genetic Risk Awareness in the General Public: Protocol for a Randomized Controlled Trial

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Abstract

Background: Genetic testing and genetic risk information are gaining importance in personalized medicine and disease prevention. However, progress in these fields does not reflect increased knowledge and awareness of genetic risk in the general public.

Objective: Our aim is to develop and test the efficacy of a suite of serious games, developed for mobile and Web platforms, in order to increase knowledge of basic genetic concepts and promote awareness of genetic risk management among lay people.

Methods: We developed a new ad-hoc game and modified an arcade game using mechanics suitable to explain genetic concepts. In addition, we developed an adventure game where players are immersed in virtual scenarios and manage genetic risk information to make health-related and interpersonal decisions and modulate their lifestyle. The pilot usability testing will be conducted with a convenience sample of 30 adults who will be categorized into 3 groups and assigned to one game each. Participants will be asked to report any positive or negative issues arising during the game. Subsequently, they will be asked to complete the Game Experience Questionnaire. Finally, a total of 60 teenagers and adults will be enrolled to assess knowledge transfer. Thirty participants will be assigned to the experimental group and asked to play the serious games, and 30 participants will be assigned to the control group and asked to read leaflets on the genetic concepts conveyed by the games. Participants of both groups will fill out a questionnaire before and after the intervention to assess their topic-specific knowledge of genetics. Furthermore, both groups will complete the self-efficacy questionnaire, which assesses the level of confidence in using genetic information.

Results: We obtained evidence of game usability in 2017. The data will be submitted to a peer-reviewed journal and used to improve the game design. Knowledge-transfer testing will begin in 2018, and we expect to collect preliminary data on the learning outcomes of serious games by December 2018.

Conclusions: It is important to educate the general public about the impact of genetics and genetic testing on disease prevention and the consequent decision-making implications. Without such knowledge, individuals are more likely to make uninformed decisions or handover all decisions regarding genetic testing to their doctors. Technological innovations such as serious games might become a valid instrument to support public education and empowerment.

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KEYWORDS

adventure games; cardiovascular risk; decision making; genetic literacy; genetic risk; heredity; knowledge transfer; mini-games; mutation; serious games

Introduction

Background

Genetic tests identify changes in chromosomes, genes, or proteins that may be related to an increased probability of inheriting or developing a disorder or disease [1]. Over the last 20 years, genetic tests have gained importance in personalized medicine and disease prevention and are usually prescribed by physicians to healthy individuals who have a family history of disease or patients who may have a disease resulting from a genetic mutation [2]. Since 2002 [3], people have been able to autonomously purchase genetic tests from the internet or local private companies that sell direct-to-consumer (DTC) genetic tests, which allows them to determine their genetic predisposition to diseases. The increasing success of such services indicates that people wish to obtain health information on their own even when it is not strictly required by their physicians or warranted by their family predisposition to certain illnesses [4].

Proponents of the DTC genetic test services argue that allowing consumers to calculate their relative risk of developing certain diseases may result in increased patient awareness, improved compliance with health-screening practices, and a better ability to make healthy lifestyle choices [5,6]. Despite these expectations, available data on the effects of DTC genetic tests on consumers are not encouraging. People face difficulties in understanding genetic risk information and its implications for health: On receiving their genetic results, patients sometimes experience unnecessary anxiety and emotional distress or make decisions about their health based on incomplete information that often results in increased health care costs [5-7]. Also, the expected changes are rarely executed in the consumers' lifestyle habits and usually restricted to the few weeks following the test [8-11]. Thus, the increased use of genetic tests does not reflect increased knowledge and awareness of genetic risk in the general public.

In the last few years, several attempts have been made to improve genetic knowledge among the public through different approaches such as the recent implementation of serious games like Touching Triton [12], Geniverse [13], and DNA Roulette [14]. Unfortunately, the current serious games on genetics are mostly intended for trainees in biology courses and medical practitioners (geneticists): They use technical language or focus on certain aspects of genetics such as the probabilistic nature of genomics and neglect the complexity of simplifying such information for the general public. The serious game approach is promising, as it represents a highly interactive medium that supplements traditional educational modalities. However, thus far, there are no available data on the effectiveness of existing serious games in increasing people's knowledge about genetic concepts.

Primary Aim

This study aimed to evaluate the effectiveness of serious games in terms of the learning outcomes in the fields of genetics and genetic risk. In particular, we aimed to assess the learning impact of a suite of mini-games on participants' knowledge and understanding of basic genetic concepts and to determine the effect of an adventure game on participants' skills and perceived self-efficacy with regard to genetic risk management.

Secondary Aim

The secondary aim was to evaluate game-flow parameters for two mini-games and an adventure game.

Methods

Team and Target Population

Serious games were designed and developed by a multidisciplinary team of psycho-oncologists, computer scientists, and a science journalist. Through constructive discussion among different professionals in the field of genetics, accuracy and consistency of genetic contents such as a detailed description of heredity mechanisms were ensured. Genetic concepts were explained in a simple way and presented as interesting facts for laypeople, as described previously [15,16]. The choice of thematic concepts and game scenarios was based on the important cornerstones of genetics.

The target population comprised people interested in genetics, high-school students, and people who require or need to decide whether to undergo genetic counseling or a genetic test. The developed serious games are suitable for people aged 16-65 years, during which primary prevention has a high impact on the health status. Therefore, we recruited participants aged 16-65 years to include teenagers who start to learn more complex genetic principles (such as DNA structure, cell duplication, mutations, and gene interaction) during their high school years and older adults who are interested in playing games or still accustomed to playing games [17]. The research protocol was approved by the Institutional Review Board of the University of Milan and the Centre for Research Ethics & Bioethics at Uppsala University (leader of Mind the Risk project). The study was conducted according to the Helsinki Declaration.

Game Design and Learning and Educational Aspects of Serious Games

The new generations are raised in a digital world and have a natural attitude toward the digital language of computers, video games, and the internet. Young people, in particular, spend a significant amount of time playing computer games through which, they usually experience a high level of motivation and engagement. To them, traditional learning is an incredibly boring, effort-intensive, complex task [18].

To improve lay people's attention, motivation, and engagement in genetic concepts, challenging activities and clear educational goals were embedded in our games to guarantee pleasure and

"flow" (a situation of complete absorption or engagement [19-21]), which are relevant dimensions for the efficacy of serious games.

Learning can be viewed as both information acquisition and knowledge construction (ie, the ability to use new knowledge). An individual's ability to act appropriately in a given situation depends on his or her knowledge and knowledge-transfer ability in a particular situation. In our study, the serious games aimed to maximize genetic learning by presenting individuals with genetic information and having them apply this information to successfully proceed with the game.

Several components of our games stimulate the learning process. First, genetic concepts are introduced and explained in a conversational manner by a virtual narrator (Figure 1) during an initial interactive tutorial. The virtual narrator—SCI (Scientist)—accompanies the player through the tutorial, during which, the characters, elements, and main rules of the game are introduced and specific genetic mechanisms are discussed. Thereafter, during the game sessions, information, hints, and feedback are provided to prevent players from getting stuck during the game (due to the lack of understanding) or to fix some concepts explained in the tutorial. Immediately after listening and interacting with the SCI, the player has to overcome challenges, wherein he or she applies the basic concepts of genetics. Thus, the player has the opportunity to practice genetic concepts in the application to win the game.

When creating the game, we balanced the complexity of genetic concepts, the game challenge, and the required cognitive load by introducing different levels of difficulty, thereby alternating moments of challenge and reflection and providing hints through the SCI. This approach provided the players sufficient time to reflect and revisit the rules of the genetic mechanisms explained in the tutorial.

To successfully proceed with the adventure game and maintain the principal character in good health (see Game Description), players need to apply their learnings from the game session to each specific situation in the narration. Another important aspect of the serious game design was the provision of clear immediate feedback (audio and video) that reflected user performance. The player interacts with the game on the basis of the new genetic mechanisms he or she learned during the tutorial (testing) and determines the result of this interaction through immediate feedback (revision). The feedback guarantees the ability to understand the results of the action taken during the play session.

To create the serious game, we followed Piaget's Theory of Cognitive Development, with the principles of assimilation (the player fits "new information" about genetics into existing slots or categories he or she had before playing the game), accommodation (the player accommodates "new information" about genetics that does not fit into an existing slot or category), and cognitive disequilibrium (presence of contradictory beliefs) to support the learning process [22]. The challenges create a cognitive disequilibrium (a situation where new information is not immediately interpreted on the basis of existing categories), without exceeding the capacity of the player to succeed. The player tries to find a new equilibrium by modifying his or her cognitive patterns and incorporating the newly acquired knowledge.

Game Description

Two mini-games and an adventure game were developed for this study.

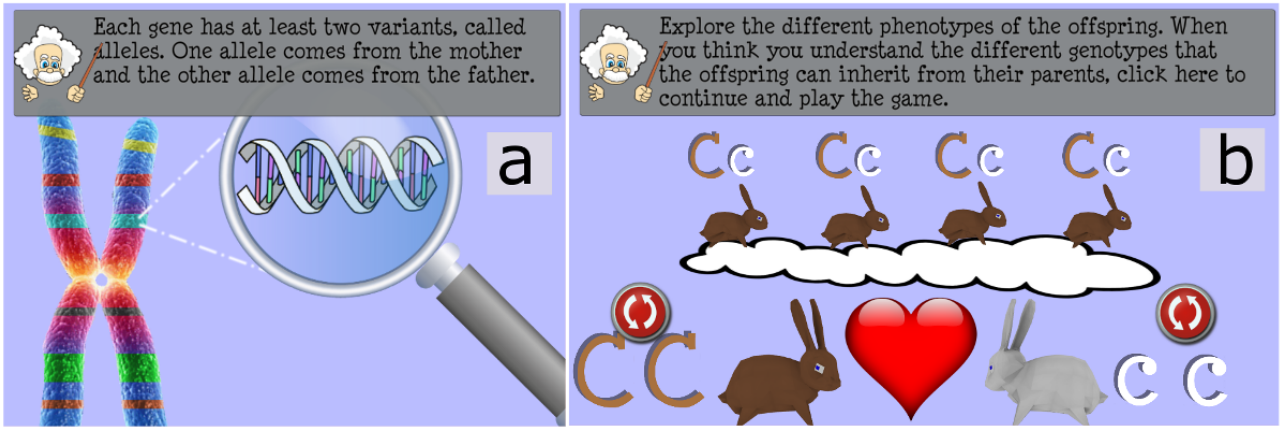
For the mini-games, we used two different approaches. The first approach was the creation of ad-hoc serious games: We implemented a two-dimensional jump-and-run game to convey Mendel's laws and incorporated genetic concepts into the game mechanics. The second approach was a modification of the mechanics of the arcade game Tetris to create a learning version of an existing game in order to represent genetic mutations. This approach may be familiar and appeal to most users, owing to the popularity of this arcade game [19,20].

The mini-games were designed exclusively to transmit basic genetic principles and improve general public literacy without revealing the genetic risk. These games are based on a simplified representation of mutations and Mendel's laws. For example, in the serious game Mutan-Tetris, the game field represents the events that could occur in a cell's life and their eventual consequences on the organism. In the serious game Heredi-Rabbit, the game challenges are established by the possible allelic combination following hereditary transmission.

For the adventure game, a narrative based on a dramatic curve was employed. The narrative can increase pleasure and provide background and motivation for the player to involve himself or herself in the game [21].

The adventure game was conceived to spread awareness about genetic risk. The player manages the genetic risk by identifying with an avatar and modifying his or her behavior according to his or her genetic predisposition.

Figure 1. (a) An overview of basic genetic concepts (gene, alleles, genotype, and phenotype) is provided to the player before the game session. (b) The player can practice with Mendel's laws.



All the developed games are currently available in Italian and English languages. They were developed mainly for mobile and Web platforms and will be available to the public on the official website of the Mind the Risk project (2019) during the last year of the project [23].

Heredi-Rabbit

The aim of this game is to explain concepts of heredity (the process through which genetic traits are passed from parents to their offspring), with dominant and recessive genetic variants (phenotype expression if the gene variant is present in at least one copy versus gene variant expression if the gene variant is present in both chromosomes; Mendel's laws).

To help people with no prior knowledge in the field of genetics, a short tutorial is available before the game session. In this tutorial, several basic concepts of cells, chromosomes, genes, phenotype, and dominant and recessive traits are explained by the virtual narrator using text and simple animated illustrations. A brief introduction to the fundamental aspects of genetics (Figure 1a) and an optional practice exercise for Mendel's law (Figure 1b) explains the core of the game to the player.

In this two-dimensional jump-and-run game, the player has to make a rabbit mate with other rabbits in order to birth an offspring with a specific genetic makeup (final goal of the game session). The rabbit hops around, grabs carrots to gain energy, avoids traps, and meets rabbits of the opposite sex (Figure 2a). The player can choose to mate the rabbit with the incoming rabbit based on their phenotypes, giving birth to an offspring (Figure 2b). In this phase of the game, the time allotted to the player to make a choice is limited (imposed pace), which maintains a high level of fun, engagement, and attention, since the player has to remember and apply the previously learned concepts quickly. As soon as the player makes a decision, the game is paused, the possible allelic combination and phenotype of the offspring are shown, and the player has time to reflect on Mendel's laws (self-paced). After a brief pause, the game resumes, and a new rabbit is randomly selected from the offspring. The new-born rabbit that inherits the genetic makeup as per Mendel's laws becomes the new runner rabbit (Figure 2c). The speed of the running rabbits can be regulated to optimize the time required to determine whether the incoming rabbit is appropriate for that game session goal. The game ends when the newborn running rabbit achieves the genotype goal specified at the beginning of every session.

Mutan-Tetris

The goal of this game is to explain the following aspects of mutations: definition of a mutation (an alteration of the nucleotide sequence in the DNA), factors that contribute to mutations (errors, mutagens, or environmental causes), fixable and unfixable mutations, hereditary mutations, and the increase in mutation rate with age.

In a simple introduction, the fundamental aspects of cell duplication (Figure 3a) and duplication errors (Figure 3b) are explained by the virtual narrator using text and simple animated and interactive illustrations.

Figure 2. (a) The player controls the rabbit with the aim to grab carrots to gain energy and avoid traps; (b) The player can choose to mate the running rabbit with other incoming rabbits based on their phenotypes, giving birth to an offspring; (c) The newborn rabbit inherits its genetic make-up according to Mendel's laws. When the targeted genetic make-up is achieved (goal), the game ends.

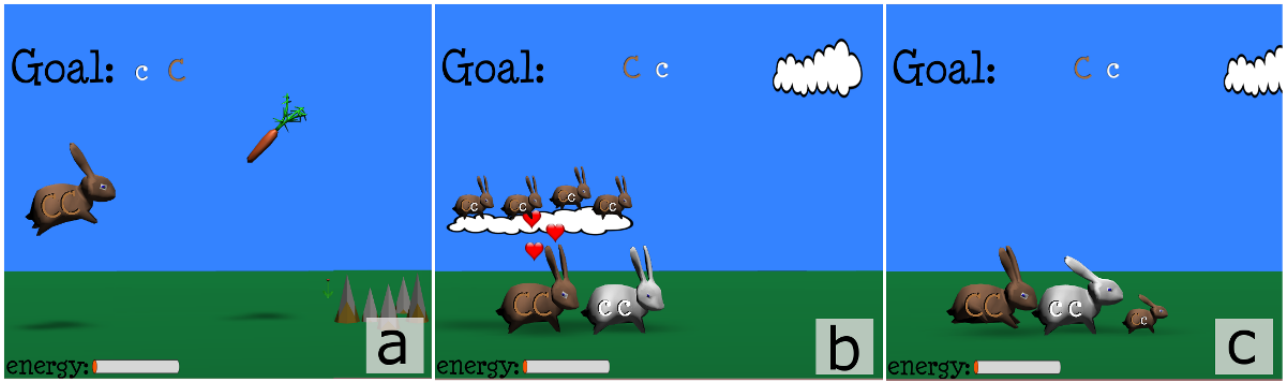
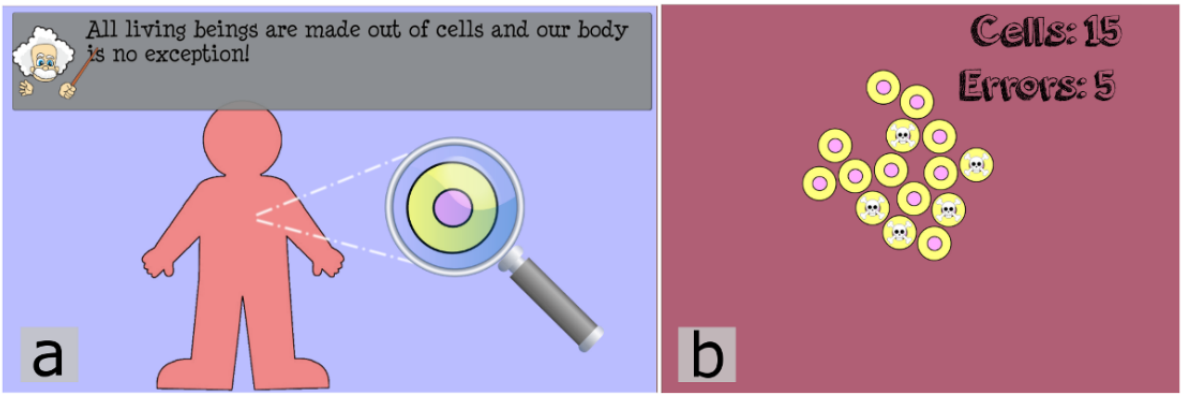


Figure 3. (a) The virtual narrator provides an introduction to the fundamental aspects of cell duplication and duplication errors using simple animated illustrations. (b) An interactive portion encourages the player to duplicate a predefined number of cells without duplicating cells containing errors.



In the tutorial, the player learns that some mutations are fundamental because they provide genetic variability, which is the basis for evolutionary changes over time. However, the game focuses on harmful mutations, both somatic (any cell of the organism except reproductive cells, not usually transmitted to descendants) and germline (can be passed to the offspring through reproductive cells), that may adversely affect the function of a cell (mutations occurring in coding DNA). We used a famous arcade game, Tetris, and modified its mechanics by adding bricks with new shapes (Figure 4). In the classical Tetris version, 7 different bricks exist, each with its own shape and color. Bricks fall from the top of the screen and the player has to rotate and shift them in the best way during the fall to form full lines at the bottom and prevent leaving empty spaces. The amount of time allotted to identify the best position and orientation of each brick is limited (imposed pace) in order to maintain the challenge and engagement. Every time a line fills up, it is erased, and the player gains points. In our version, the Tetris environment metaphorically represents a cell environment, bricks represent genetic material, and deleted rows represent correct DNA reading. Anyone who has played Tetris is familiar with the shape of the 7 bricks. In this game, we have introduced 3 new bricks that represent mutations, with different shapes, a blinking-eye icon in the middle, and dark colors. These bricks aim to warn the player of unexpected and unusual events. When such bricks appear, the game is paused (self-paced) and the narrator explains the origin of the "mutation" in detail. When the player has understood the brick, the game is resumed. Two of the new bricks are more difficult to use for deleting lines, but the player can still fit them in with other bricks and then delete rows: These bricks represent mutations that can be auto-fixed by our cells (Figure 4a and b). The third brick has a geometry that does not fit in the existing lines without leaving any space: The line cannot be completely deleted. Every time one of these bricks is introduced, one row of the Mutan-Tetris becomes indestructible, reinforcing the message that not all mutations can be fixed by our cells (Figure 4c). The game has been parameterized with several levels of difficulty, which modify the probability of appearance of the new "mutated" bricks and allow the player to explore all the serious game contents. If the player is unable to achieve the minimum score required to trigger the appearance of the mutated pieces, the player is informed that the level chosen is too difficult and is recommended to retry the game at an easier level, following which the game restarts. The game ends when no more lines can be filled or deleted and there is no space for new bricks in the playing field. The entire playing field filled with unfixed or damaging mutations represents an incoming condition that could affect "cell health."

Adventure Game

Gene Adventure, the World of Tomorrow, is an adventure game, wherein the player embodies a young adult named Eugene who lives his everyday life after undergoing DTC genetic testing (Figure 5a). The game takes place in a small city with several facilities (markets, restaurants, pubs, parks, etc). The dramatic curve of Eugene's story guides the player through several events

and answers the "why" of the game, stimulating involvement and motivation. During the game, Eugene learns about the presence of some gene variants and his risk of developing cardiovascular diseases (Figure 5b).

Unfortunately, he cannot manage this information. He is given several chances to obtain clarifications about the implications of the genetic result and its consequences on his health. The player must help Eugene find the best way to manage his cardiovascular risk by accomplishing several subtasks, making health-related decisions (Figure 6), modulating his lifestyle, and interacting with other characters.

The player is given three options for every choice throughout the game session, which are incorporated into the avatar's behaviors, and each option is assigned a score as follows: –1 for the unhealthy choice, 0 for the neutral choice, and +1 for the healthy choice. The chosen option is simultaneously translated into clear feedback as a modification of the color and expression of a "smile icon," which represent Eugene's health state and quality of life (Figure 7).

The three alternatives for each choice are formulated to reflect either recurring behaviors (habits) or occasional behaviors (occurrence) to show that some behaviors could be problematic if repeated over time, and other behaviors are problematic even they are occasional.

Figure 4. Mutant-Tetris. Classical Tetris is modified using several new mutated bricks. The bricks represent the genetic material, and elimination of a line represents correct DNA coding. (a, b) The two fixable mutated bricks increase the difficulty in deleting lines. (c) The mutated brick has a geometry that does not allow line deletion.

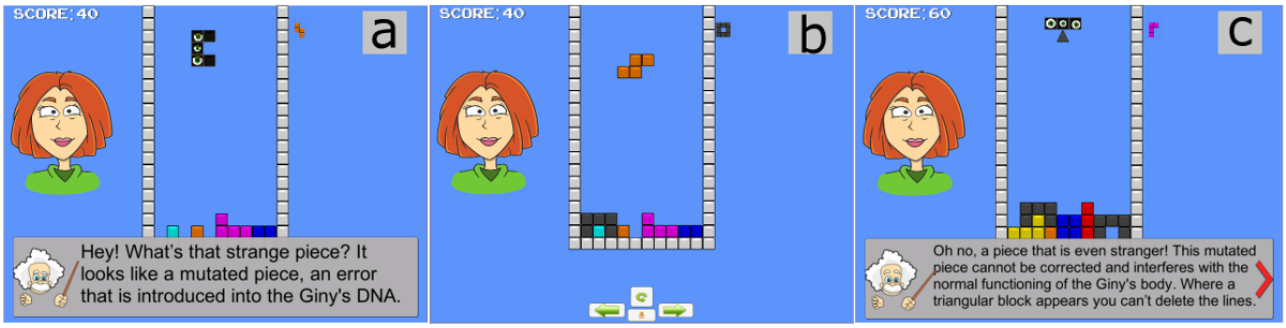


Figure 5. (a) Eugene is going to buy a direct-to-consumer genetic test online. (b) He receives the test results and discovers he is at high risk for cardiovascular disease.

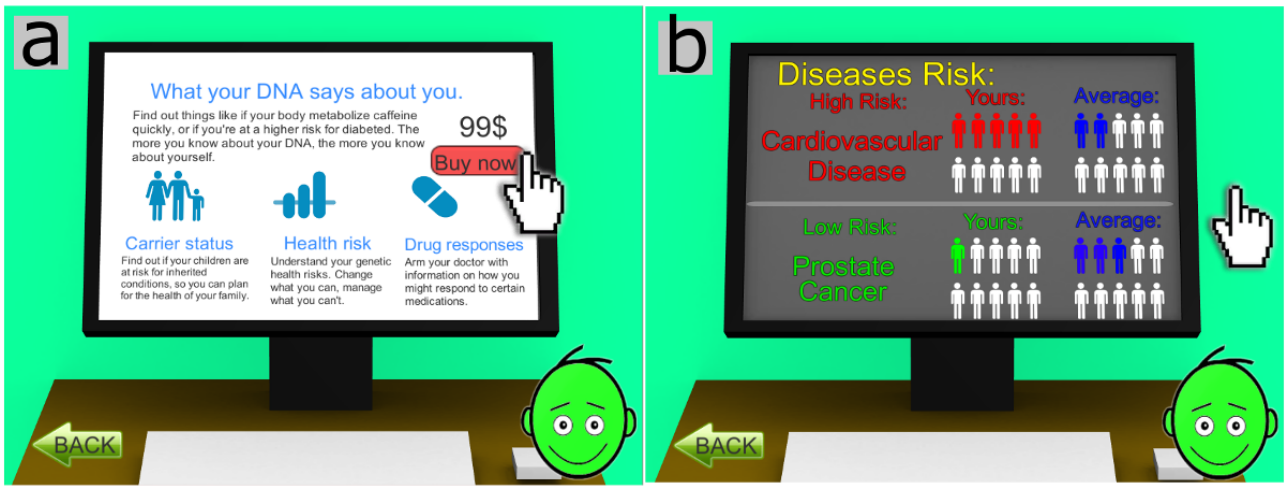


Figure 6. The player can decide whether Eugene has to talk to his doctor about his genetic risk for cardiovascular disease.

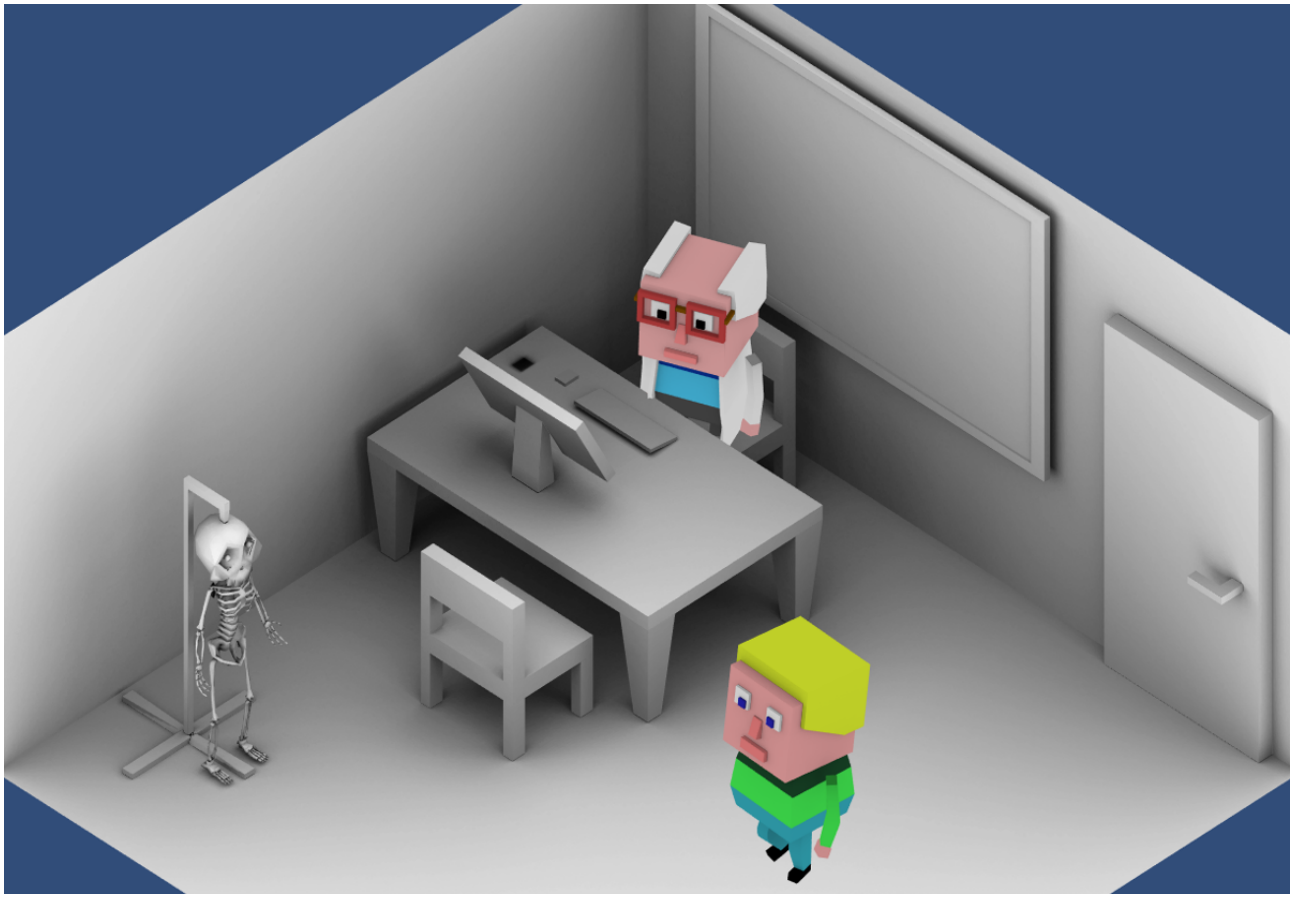
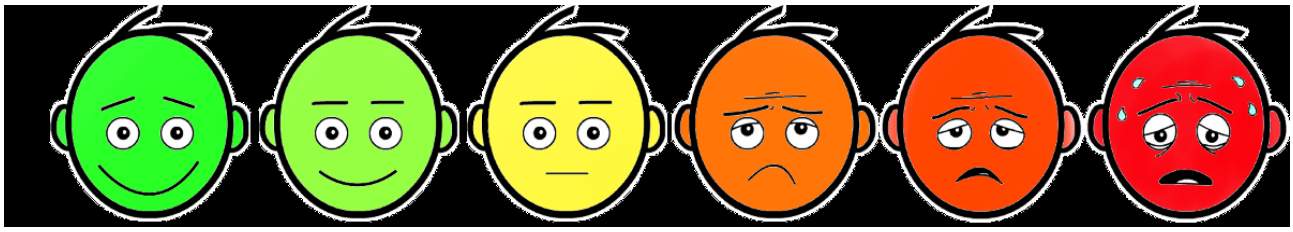


Figure 7. The colors and expressions of the "smile icon" represent Eugene's health status.



In-Game Assessment of Knowledge Transfer and Learning Progress

Play-based assessment is implemented through an algorithm that allows us to record changes in the player's decision-making ability and progress (how they accumulate points and experience and face new issues) during the adventure game session. The system tracks the players' choices, and the final score is converted into informative and evaluative feedback that is presented to the player at the end of the game session. Based on her or his performance, the player receives positive, intermediate, or negative feedback on 4 aspects: nutrition (Figure 8), physical activity (Figure 9), risk behaviors, and stress management and social interactions.

A composite description of the player's performance, its implications for health, and a final informative summary of genetic risk management constitute the end of the educational journey. Each game session for a first-time player should last for approximately 30 min.

Substudy 1

Game Evaluation: Serious Game Usability and Engagement

To assess the usability of the game, we defined usability as "the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use" [24]. According to the literature [25], usability testing is important for the serious game, particularly those designed for heterogeneous populations, including individuals that may not be accustomed to interacting with new technologies (ie, "nongamers").

Among all the procedures described in literature [26], two main approaches assess usability: an observational analysis, in which a user interacts with the system while the developers observe and note every significant player-game interaction or player's comment, and a survey-based analysis, in which the user fills out evaluation questionnaires after the game session [27-29]. Although several scales have been developed (eg, the System Usability Scale [30] and the Questionnaire for User Interaction

Satisfaction [31]), there are no validated scales to assess games usability thus far. Therefore, we decided to perform a mixed method combining observational analysis of participants and a self-report questionnaire—the Game Experience Questionnaire—to partially overcome the current limitations of both quantitative methods [32].

Figure 8. During the game, the player carefully chooses Eugene's diet to maintain correct nutrition habits.

Figure 9. During Gene Adventure, the player carefully manages Eugene's physical activity to maintain a good lifestyle.

The observational analysis will record participants' reactions during the game, with a particular focus on their comments and emotional reaction (laugh, groan, frustration, doubts on how to proceed, etc), to gain real-time information that may not be captured by posttest surveys [33]. The observational analysis will provide information on the overall engagement of the player: Deep engagement in serious games has been associated with learning and students' academic achievements [34,35].

Engagement refers to a holistic experience or mixture of involvement and enjoyment; it is a key factor for serious games and determines the effectiveness of learning. In previous studies, several measures such as scales of immersion and presence [36], flow [37], and engagement [38] have been applied for different aspects of engagement in serious games. The most-appropriate questionnaire for our serious game is the Game Experience Questionnaire [39] because it measures how players feel during the game session. This questionnaire comprises 33 items and assesses 7 core dimensions: immersion, flow, competence, positive effect, negative effect, tension, and challenge. For each item, participants state their personal experience on a 5-point Likert scale (from 0 indicating not at all to 5 indicating extremely).

Target Population and Recruitment

The pilot usability study will be conducted with a convenience sample of 30 participants. All participants will be recruited by e-mail through the students' institutional mailing list of the University of Milan (Italy; Master Course in Cognitive Science) and via authors' acquaintances. The e-mail invitation will entail a brief description of the tasks, the medium amount of time required, and the contact information of the experimenter. All the experimental sessions will be conducted in a quiet room at the University of Milan in the presence of an experimenter.

Considering the heterogeneity of potential users, we will enroll 10 participants and categorize them into 2 groups in each game: one group of 5 "young" participants, aged 16-30 years (major users, includes people who play games more frequently), and another group of 5 "middle-aged" participants, aged 31-65 years (minor users of video games). It is important to assess the usability of both age groups since the potential users of our serious game are individuals of all ages.

Method and Procedures

Participants will be assigned to one of the three games and will play the game individually. Before interacting with the game, they will complete an informed consent form. Participants will be briefly instructed about the game and prompted to play on their own without any further direction or instruction. In addition, they will be asked to speak loudly during the game in order to communicate their thoughts. At the end of the play session, participants will report any issue, negative or positive, that they encountered during the game and will be invited to complete the Game Experience Questionnaire. The programmers will dedicate time to address and fix the negative issues.

Data Analysis

All data on player usability collected from the observational analysis will be examined using text analysis for qualitative data, as reported previously [40]. The negative issues that could compromise the usability of the serious game will be classified on the basis of the usability heuristics developed by Bertini et al [41] (eg, consistency and mapping, ease of input, screen readability and glancability, flexibility, efficiency of use, and personalization) [42]. Nonparametric statistical analysis for quantitative data will be applied to the Game Experience Questionnaire, with group comparisons based on age and technological expertise (gamers vs nongamers; computer and mobile technology users vs nonusers). Statistical analysis will

be conducted using the SPSS Software (version 22; IBM Corp, Armonk, NY), with an alpha value of .05 set a priori for all analyses.

Substudy 2

Game Evaluation: Knowledge-Transfer Test

We will assess participants' learning outcomes to verify the effectiveness of serious games. Most studies evaluated the effectiveness of serious games through the use of pre- and posttest evaluations [43], whereas some studies used a control group of individuals who received the target information through other instructional techniques. We used both assessment methods.

Target Population and Recruitment

To test whether the learning goals were achieved, 60 teenagers and adults aged 16-65 years who volunteer to participate will be enrolled: 30 participants will be assigned to the experimental group and 30 participants, to the control group. Both groups will be age- and gender-matched. All participants will be recruited from the general population by using the author's e-mail and social media contacts, posters emailed to all University of Milan staff and students, and personal invitations and snowball sampling. The invitation will contain a brief description of the tasks, the median time required, and contact information. All the experimental sessions will be conducted in a quiet room at the University of Milan under the supervision of an experimenter.

Materials and Procedures

Before starting the game session, participants will complete a demographic questionnaire on age; gender; education level; previous experience with computer, mobile, or tablet devices; and habits of playing video games. Participants with no experience with technological devices will be excluded.

Participants enrolled (experimental and control groups) will complete the following steps: (1) knowledge-transfer pretest questionnaire, (2) self-efficacy pretest questionnaire, (3) serious game-playing session or paper-based information reading, (4) knowledge-transfer posttest, and (5) self-efficacy posttest.

First, an ad-hoc questionnaire will be used to assess genetic topic-specific knowledge, with questions on Mendel's laws, mutations, and genetic risk implications. The questionnaire comprises multiple-choice questions or true or false questions such as "From a pair of rabbits with Cc and cc genotype respectively, what is the proportion of their children's genotypes: (A) three CC rabbits and one Cc (B) three Cc rabbits and one (CC) two Cc rabbits and two cc (D) four rabbits cc" or "A healthy lifestyle can prevent or lessen the negative consequences of having genetic predispositions to some diseases (True/False)." Participants that correctly answer more than 80% of the questions in the pretest will be excluded from the study, due to the high base-rate literacy in genetics and genetic risk information. Data will be collected using the Lime Survey [44] in a supervised setting in a quiet room at the University of Milan under the supervision of an experimenter.

Second, a questionnaire will be used to assess perceived self-efficacy with regard to knowledge of genetics, defined as confidence in one's ability to use genetic information. The questionnaire comprises 8 items, 5 of which are taken from the Self-Efficacy Scale in Carrere et al [45] and include items such as "I am able to understand information about how genes can affect my health" and "I am able to explain to others how genes affect one's health." In addition, we added one item to assess the perceived knowledge on the interaction of lifestyle and genetic makeup: "I have a good idea about how my own behaviors might interact with my genetic makeup in affecting my health." These six items are to be answered on a 7-point Likert scale. Further, we added two items to assess the "task-specific" self-efficacy, that is, the self-efficacy participants experienced in answering the knowledge-transfer questionnaire. Self-efficacy is a precursor to the adoption of health-related behaviors [46]. We included its assessment in this protocol, because it is the only measurable parameter to verify the efficacy of serious games in promoting changes in behaviors in our study (we are unable to directly verify participants' changes in health-related behaviors and decision-making abilities in the light of the new knowledge). Due to the Dunning-Kruger effect [47] (a cognitive bias of illusory superiority), individuals with low literacy in genetics may mistakenly deem their confidence levels to be higher than their actual levels; however, we will be able to match each participant's expected and real performance, as we will assess their effective knowledge by using the knowledge-transfer questionnaire.

Third, participants will be allocated to the experimental group, where they will play the serious games, or the control group, where they will receive leaflets with the same information given to the experimental group (traditional paper-based approach for learning). Participants in the experimental group will play the two mini-games first (Heredi-Rabbit and Mutan-Tetris) to start from the basic concepts of genetics and proceed with Gene Adventure, which introduces concepts of genetic risk. The overall duration of the game session will be approximately 50 min. The control group will have approximately 50 min to read the genetic information in the leaflets, which is provided by the SCI in the games. Some examples of the content are as follows: "Each gene has at least two variants, called alleles. One allele comes from the mother and the other allele comes from the father" (Figure 1a) or "Some mutations have no effect; some could be auto-fixed by the organism; others could provoke illness, sometime serious (like cancer)." As the primary aim of our study is to investigate the efficacy of the serious games, we believe a media comparison is paramount to determine if knowledge transfer depends on the type of tool used.

Fourth, at the end of the game session, the experimental group and control group will be presented with the posttest questionnaire (with the same questions that were included in the pretest questionnaire) to assess genetic topic-specific knowledge. Significant differences between the test scores in both groups will indicate knowledge-transfer efficacy. Furthermore, the delta of pre- and posttests between the two groups will reveal differences in the efficacy of serious games versus traditional paper-based information.

First, participants from both groups will be asked to fill in the self-efficacy questionnaire again. The differences between pre- and posttest self-efficacy results will reflect the change in confidence of each participant's knowledge.

Data Analysis

For knowledge-transfer analysis, the Cohen *d* effect size will be calculated. Statistical analysis will be conducted using the SPSS Software (version 22; IBM Corp), with an alpha value of .05 set a priori for all analyses.

Results

In 2017, we collected evidence of game usability. Data have been submitted to the 6th International Conference on Serious Games and Applications for Health by the Institute of Electrical and Electronics Engineers 2018 [42] and used to improve game design. Knowledge-transfer testing will begin in 2018, and we expect to collect data on the learning outcomes of serious games in December 2018.

Discussion

Overview

Since the launch of the Human Genome project in 1990, there has been a need to improve genetic literacy among the general public [48]. Overall, genetic literacy refers to the understanding of basic biological mechanisms (eg, knowledge that DNA is an informative molecule and determines our variation and diversity); the personal and health implications of genetics; and the interaction and interdependence of genes, the individual, and the environment [49].

Unfortunately, even well-educated people lack an understanding of these concepts [50,51]. Due to the increasing impact of genetic testing [52] and the importance of decision making in disease prevention, it is crucial to educate people about genetics. Without such knowledge, individuals are more likely to make uninformed decisions or handover all decisions on genetic testing to their doctors.

Technological innovations such as serious games might become valid instruments to support public education and empowerment [50,53-55] and prepare citizens for informed personal and societal decision making in genetics.

Our main endpoint will demonstrate if the use of serious games increases people's knowledge about genetic mechanisms (eg, prototypes for heredity and mutation) and multiple genetic, behavioral, and environmental factors that contribute to the risk of onset of complex diseases such as heart disease (prototype first scenario in Gene Adventure).

We aim to develop an accessible and simple instrument by representing genetic concepts in an appealing narrative that respects the skills of the general population. With our prototype of Gene Adventure, people can experience, in a simulated life, the management of complex information such as genetic risk and develop a deeper understanding of genetics from experience. If this study proves the efficacy of serious games, the developed serious game could be used in combination with other traditional protocols for genetic counseling to spread awareness for decision making in medical genetics.

Limits and Future Proposal

This study is designed to test "learning" with reference to information acquisition. The pre- and the posttest questionnaires will measure the performance of correctly answering questions based on new information acquired through the serious game. Further, based on our protocol results, we will test another aspect of learning: the ability to apply newly acquired knowledge in unknown situations by, for example, creating a new scenario in which participants will be asked to make decisions about their own health based on the genetic (risk) issues.

Although there are several other interesting and related themes such as knowledge integration (the ability to integrate information on a given subject derived from different perspectives in a coherent mental representation) [56], this study is not designed to investigate them. At present, our experimental protocol is not sufficiently equipped to differentiate the contribution of each serious game in creating the final mental representation of genetic concepts. However, this study will provide some evidence for this issue through differences between the pre- and posttest performances, which will identify the concepts that participants have understood well, and their achievements during the Gene Adventure game, which will indicate how the users apply their knowledge to increase or decrease their character's health.

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Conflicts of Interest

None declared.

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Abbreviations

DTC: direct to consumer

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Protocol

A Tailored Advice Tool to Prevent Injuries Among Novice Runners: Protocol for a Randomized Controlled Trial

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Abstract

Background: Besides the beneficial health effects of being active, running is associated with a risk of sustaining injuries. Runners need to change their behavior to increase the use of effective measures and subsequently reduce the number of running-related injuries.

Objective: The RunFitCheck intervention was developed according to an evidence- and practice-based approach to stimulate injury-preventive behavior among novice runners. This paper describes the study design in detail.

Methods: A randomized controlled trial with a follow-up period of 5 months will be conducted. The participants will be novice runners. At enrollment, participants will be asked to report injury-preventive measures they usually take during their running activities. After completing the enrollment questionnaire, participants will be randomized to intervention and control groups. The intervention group will have access to the RunFitCheck intervention; the control group will perform their running activities as usual. Participants will be asked to report retrospectively in detail what they have done regarding injury prevention during their running activities at 1, 3, and 5 months after enrollment. Descriptive analyses will be conducted for different baseline variables in the intervention and control group. Relative risks and 95% CIs will be used to analyze behavioral changes according to the intention-to-treat principle.

Results: The project was funded in 2016 and enrollment was completed in 2017. Data analysis is currently under way and the results are expected to be submitted for publication in 2019.

Conclusions: To nullify the negative side effects of running, prevention of training errors is desirable. As the use of injury prevention measures is not compulsory in running, a behavioral change is necessary to increase the use of effective injury-preventive measures and to prevent running-related injuries.

Trial Registration: Netherlands Trial Register NTR6381; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6381 (Archived by WebCite at http://www.webcitation.org/736Xjm5jv)

International Registered Report Identifier (IRRID): RR1-10.2196/9708

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KEYWORDS

behavior; injury; prevention; running

Introduction

Running is one of the most popular ways to exercise in the Netherlands, with 2.1 million people running on a regular basis [1]. In addition to beneficial health effects of being active, running is associated with a high risk of musculoskeletal injuries. The incidence of running-related injuries (RRIs) is reported to range from 3-59 injuries per 1000 exposure hours [2-4], with most RRIs occurring in the knee, followed by the calf, Achilles tendon, and shin [5].

Risk factors for RRIs have been extensively investigated, but evidence remains contradictory and inconclusive. A history of injury in the past 12 months is reported to be the main risk factor for RRIs [6,7]. Especially, novice runners are at a high risk of sustaining an RRI, while according to running experts, half of the RRIs are related to training errors [3]. Consequently, these injuries could be prevented since modifying the training load should be easily realizable [8,9]. However, modifying one's training load and inherently preventing training errors might be easier said than done. A behavioral change among runners is necessary to increase injury-preventive behavior and, subsequently, the use of preventive measures. To our knowledge, 2 interventions aimed at runners to promote preventive behavior and reduce RRIs have been developed earlier [10,11]. Adriaensens et al [10] developed a tailored Web-based injury prevention intervention: a website with informational videos about the etiology and mechanisms of RRIs combined with injury-preventive advice and a Web-based questionnaire that allowed the website to provide tailored feedback based upon a series of predefined questions that created a personal risk profile of the user. Short-term (3 months) effects of the intervention (measured in recreational runners after a visit to the website of 30 minutes) were demonstrated on determinants and actual performance of sports injury behavior. Hespanhol et al [11] evaluated the effectiveness of adding Web-based tailored advice to general advice on the prevention of RRIs and determinants as well as actual preventive behavior in Dutch trail runners. Trail runners in the intervention group received specific advice tailored to their RRI status (no injury, no substantial RRI, or substantial RRI). In that study, no effect was observed on determinant and actual preventive behavior; however, RRIs were prevented [11]. Tailored Web-based intervention can thus be promising in promoting preventive behavior among runners and even prevent RRIs. The intervention developed by Adriaensens et al (Dutch Consumer Safety Institute) [10] was effective, but the Web-based questionnaire for tailored feedback was time-consuming. Therefore, the Dutch Consumer Safety Institute developed the RunFitCheck intervention to stimulate injury-preventive behavior among novice runners without the associated time burden. The next step is to evaluate its effect on injury-preventive behavior among novice runners. This paper describes the study design in detail.

Methods

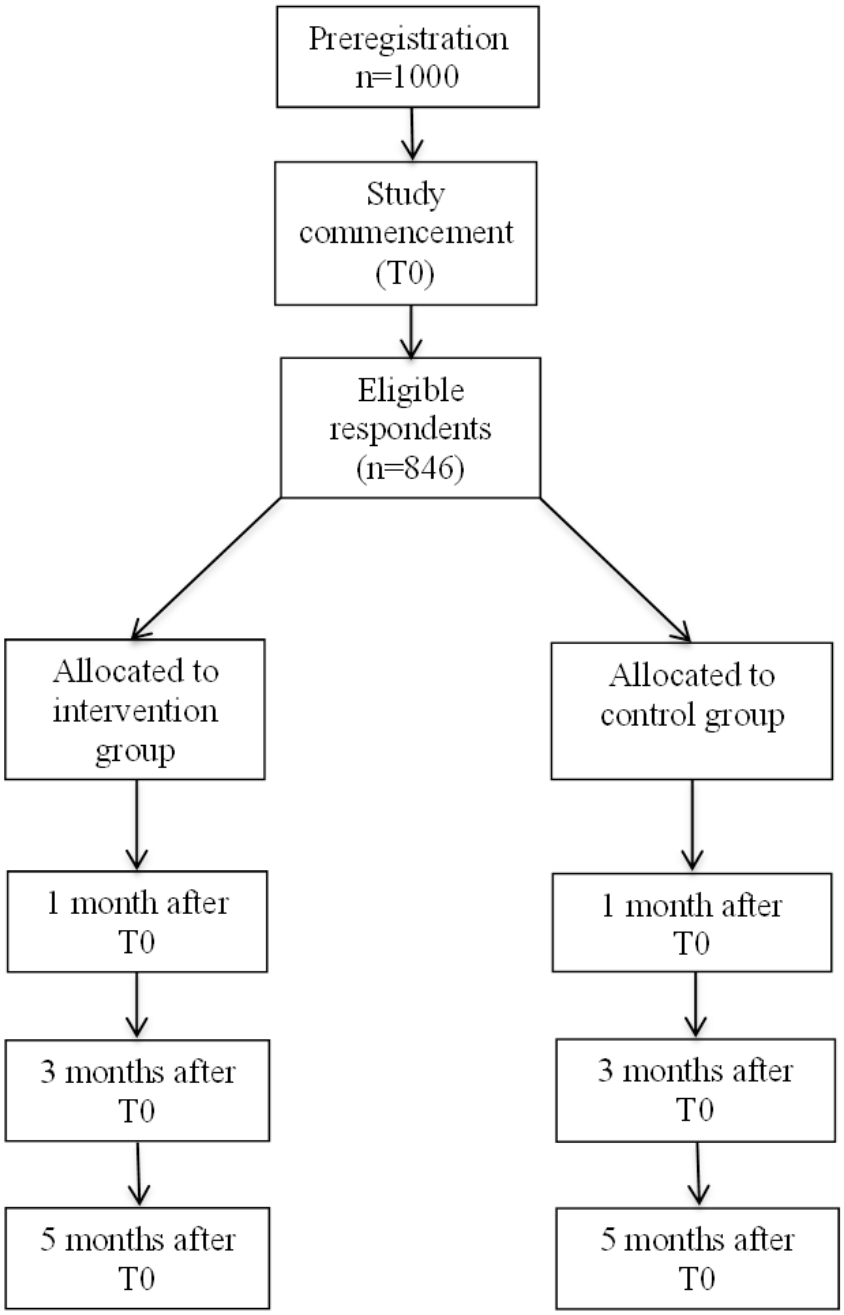
Objective and Hypothesis

The objective of the study is to evaluate the effectiveness of the developed RunFitCheck intervention (in Dutch) to promote injury-preventive behavior among novice runners. The hypothesis in this study is that the developed intervention will lead to 10% difference in favorable injury-preventive behavior in the intervention group compared with the control group.

Study Design

The Consolidated Standards of Reporting Trials statement was followed to describe the design of the study [8]. This statement is a checklist intended to improve the quality of reports of randomized controlled trials. A randomized controlled trial with a follow-up period of 5 months will be conducted (Figure 1). The study is registered in the Dutch Trial Registry (Netherlands Trial Register Number NTR6381).

Figure 1. Flowchart of participants of the randomized prospective controlled trial.



Ethics, Consent, and Permissions

The study protocol has been approved by the Medical Ethics Review Committee of the Academic Medical Center Amsterdam, the Netherlands (W16_335 # 16.417). Participants willing to participate in the study will give their informed consent prior to the start of the enrollment questionnaire. The start screen of the enrollment questionnaire will be used to obtain informed consent from the participants. This screen will contain information about the study, use of the data gathered, and rights of the participants in this study. If participants agree to participate in this study after they have read the information, they will have to tick a box to give their informed consent. When participants tick the informed consent box, they are able to continue to the first question of the enrollment questionnaire. The flowchart of the participants is presented in Figure 1.

Participants and Recruitment

The group of participants will consist of novice runners. The inclusion criteria are being aged 18 years and older, considering oneself as a beginner, a slightly experienced runner, or a rather experienced runner, and having less than one year of running experience when a runner considers oneself as an experienced or very experienced runner. Participants do not have to be a member of a running club. Participants will be recruited via social media networks (Facebook, websites, Twitter, LinkedIn, and newsletters) of the participating organizations (Dutch Consumer Safety Institute, Runner's World, and Royal Dutch Running Association [RDRA]) and will be able to preregister for the study in the 2 months prior to the start of the study.

Sample Size and Allocation

In this study, the aim is to increase injury-preventive behavior by 10% in the intervention group. In previous literature, 12.6% increase in injury-preventive behavior (in this case, the inclusion of a warm-up) was found during a 3-month intervention [10]. To achieve 80% power with a significance level of.05, the sample size calculation revealed that 384 participants per study group are needed in this study. Taking into account a response rate of 85% and a dropout rate of 10% over the 5-month follow-up period, a total of 1000 participants will be approached in this study. Eligible participants will be simultaneously allocated at random to the intervention or control group after study commencement, using a computerized random number generator (the Aselect function in Excel). No restrictions will be imposed for the allocation; simple randomization will be performed. All steps in the randomization process will be done by the principal researcher.

Intervention

The RunFitCheck intervention (in Dutch), is an intervention developed according to an evidence-based (intervention mapping) and practice-based (running experts) approach to stimulate injury-preventive behavior among novice runners (see Multimedia Appendices 1, 2, and 3). The development of the intervention was a collaboration with running experts and the target group and is described in detail in Kemler, Valkenberg, and Gouttebarge (in press).

A range of experts was consulted in the development of this intervention: a sports physician who is head of the medical commission of the RDRA and related to the RDRA as a sports physician since 1977; a sports physiotherapist specialized in running since 1992; 2 running coaches, of whom 1 is a fulltime running coach since 2002 and coach of both successful Dutch top athletes and recreational athletes, and a second coach who has over 40 years of running experience, was a top athlete himself, coaches recreational athletes, and has worked for the RDRA for 20 years; and a researcher specialized in sports injuries who performed the running-related literature review that laid the foundations for this study. These experts were consulted and their feedback combined with literature on the use of running apps (Romeyn, Kemler and Huisstede, in press). Through the consultation and research process, 2 main dimensions in the risk for RRIs, namely the physical load-taking capacity of runners and motivation of runners to achieve their running goals, were identified. Across these 2 domains, runners can be classified in 4 categories: (1) a low physical load-taking capacity and a low goal-orientation, (2) a low physical load-taking capacity and a high goal-orientation, (3) a high physical load-taking capacity and a low goal-orientation, and (4) a high physical load-taking capacity and a high goal-orientation. In order to classify runners within 1 of the 4 categories, they will answer 6 questions (Multimedia Appendix 4). Depending on their answers and related classification, runners will directly receive tailored advice on the website for achieving an optimal running practice. Examples of advice will be related to strength exercises, running technique improvement, and use of a training schedule. Advice about a warm-up will also be given. After receiving the tailored advice, runners can leave their email address on the website so that they will receive a tailored running schedule and a strength exercise schedule every week. The RunFitCheck intervention will be made available to the participants within the intervention group. Substantial efforts have been made to develop an intervention that provides practical injury prevention advice.

Running as Usual

The participants in the control group will perform their running activities as usual. The RunFitCheck website is not secured with a log-in code for the intervention group as the research team wants to avoid any additional barriers for participants to use the intervention. Participants in the control group will be able to visit and use the website alongside those in the intervention group; however, they will not be actively encouraged to do so during the study period. In order to determine whether control group participants accessed RunFitCheck, data from control group participants pertaining to websites they visit during the study period will be collected. Control group participants who have visited RunFitCheck will be excluded from the analyses.

Injury-Preventive Behavior

As the intervention developed by Adriaensens et al (Dutch Consumer Safety Institute) [10] was effective in promoting injury-preventive behavior but was time-consuming, the research team wanted to develop an intervention to stimulate injury-preventive behavior among novice runners without the associated time burden. In this study, injury-preventive behavior is defined as follows: (1) using a (personalized) training schedule: use of a training schedule that fits the physical condition of the athlete and represents a realistic running goal was proposed by running experts as an important factor in preventing running injuries; (2) performing strength and technique exercises [12] to improve the amount of force that can be exerted on the body while running; and (3) performing an active warm-up prior to running [13]. Each of these injury-preventive behaviors is divided into preparatory acts, such as searching for information about strength exercises and structural injury-preventive measures like performing strength exercises. All injury-preventive behaviors are assessed through single questions (yes, no, or not applicable).

Procedures

Upon enrollment, participants will be asked to report the injury-preventive measures they usually take before or during their running activities. Participants' demographic characteristics, including their contact email address, sex, age, running experience, running motivation, physical fitness, current injuries and physical complaints, and injury-preventive measures, will also be collected upon enrollment via a Web-based enrollment questionnaire (Table 1).

Table 1. Overview of research topics per questionnaire in this study.

Research topics	Enrollment questionnaire	At 1 month after enrollment	At 3 months after enrollment	At 5 months after enrollment
Age	Present	N/A[a]	N/A	N/A
Sex	Present	N/A	N/A	N/A
Sports participation other than running	Present	Absent	Absent	Absent
Running motivation	Present	Absent	Absent	Absent
Running experience (in months or years)	Present	Absent	Absent	Absent
Level of running (novice, seminovice, experienced, etc)	Present	Absent	Absent	Absent
Running frequency per week	Present	Present	Present	Present
Physical fitness	Present	Present	Present	Present
Risk perception	Present	Present	Present	Present
Injury-preventive behavior	Present	Present	Present	Present
Running-related injuries	Present	Present	Present	Present
Physical complaints	Present	Present	Present	Present

[a]N/A: not applicable.

All personal information and contact information from the participants will be handled by the principal researcher. This researcher will export the data from SurveyMonkey and store it in a password-protected drive. Participant names will be replaced with numbers and stored as reidentifiable data. The data with participant numbers will be utilized in the statistical analyses. Upon the conclusion of the data collection period, the questionnaire and associated responses will be deleted from SurveyMonkey.

Questionnaires will be administered at study commencement and at 1, 3, and 5 months post-commencement. In these follow-up questionnaires, participants will be asked to retrospectively report in detail what they have done in the past month(s) regarding injury prevention during their running activities and will be asked questions about their current injury-preventive behavior, running activities, and running injuries during running activities. The injury definition utilized in this study is “any physical complaint arising during a running activity that does not allow the participant to complete the activity or affects their ability to participate in future running activity” [14-17].

At 4 time points, a Web-based questionnaire will be sent by email to participants by the principal researcher, using the Web-based questionnaire system SurveyMonkey. When participants fail to complete a questionnaire, reminder notifications will be sent via email by the principal researcher using the Web-based questionnaire system SurveyMonkey 7 days after a questionnaire is due. A second reminder will be sent after 2 weeks.

The evaluation of the effectiveness of RunFitCheck will not take place in an experimental setting. Participants in the intervention group will be given access to the intervention, but no further conditions will be applied to the use of the intervention. In the questionnaires at 1, 3, and 5 months, the intervention group will be asked about their use of the intervention, attractiveness of the intervention, behavioral actions they take after being exposed to the intervention, their intention to use this intervention again, and how they would want to be informed about this intervention. If participants indicate they do not use the intervention, they will be asked to give detailed information about why they do not use the intervention.

Statistical Analysis

Descriptive analyses (mean [SD], frequency, and range) will be conducted for the different baseline variables in both study groups. To evaluate the success of the randomization, baseline variables will be analyzed for differences between the intervention and control group (chi-square test, independent *t* test, and Mann-Whitney test).

Relative risks (RRs) and a 95% CI will be used to analyze behavioral change according to the intention-to-treat analyses: (1) using a (personalized) training schedule, (2) performing strength and technique exercises, (3) performing a warm-up. Participants who do not execute a certain injury-preventive measure at study commencement will be selected for analysis, since among these participants, most behavioral change can be expected. If there are any differences in descriptive characteristics at baseline (eg, differences in sex, age, or running experience), subanalyses for sex, different age categories, etc will be performed.

Results

The project was funded in 2016 and enrollment was completed in 2017. Data analysis is currently under way and the results are expected to be submitted for publication in 2019.

Discussion

Principal Findings

This article describes the design of a randomized controlled trial evaluating the effectiveness of an intervention on injury-preventive behavior in novice runners. There are 3 major challenges in this study that can be acknowledged: (1) the recruitment of participants, (2) their adherence to this study, and (3) the measurement of injury-preventive behavior.

Recruitment of Participants

For the study results to be meaningful, 1000 novice runners need to be enrolled. To enhance enrollment and the possibility to preregister for the study, several strategies will be used, such as social media (Facebook, LinkedIn, and Twitter), newsletters from the RDRA (digital), and the magazine Runner's World (in print and digital). Preregistration will be possible by filling in a Web-based form on the website of the Dutch Consumer Safety Institute. Preregistration for the study will be advertised on Facebook and Twitter.

Social media has been previously utilized by the research team to recruit runners with close to 1000 participants recruited within 2 weeks. Respondents were recruited via social media, such as Facebook and Twitter, and they were invited to give their opinion on running, running injuries, and injury prevention. As the research team recruited nearly 1000 runners within 2 weeks, they are confident that they will achieve 1000 participants in this study with similar recruitment strategies.

Adherence to the Study

To provide an incentive to complete all components of the study, enrolled participants who complete all questionnaires will be entered into a draw to win a €200 gift voucher for running clothes. This strategy might enhance the respondents' adherence to the study. The gift voucher for running clothes will be a gift from RDRA. RDRA supports the RunFitCheck intervention but is not otherwise related to this study.

Injury-Preventive Behavior

As the intervention developed by Adriaensens et al (Dutch Consumer Safety Institute) [10] was effective in promoting injury-preventive behavior but time-consuming, the Dutch Consumer Safety Institute wants to develop an intervention to stimulate injury-preventive behavior among novice runners without the associated time burden. Therefore, injury-preventive behavior as a primary outcome in our study instead of the more traditional RRIs was chosen. It is well known that people find it difficult to change health-related behavior. Sustaining lasting change in health-related behavior is a detailed and lengthy process [18]. Our study assesses a small part of this process, focusing on a 10% change in injury-preventive behavior as an indication that the intervention is efficacious.

Acknowledgments

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Authors' Contributions

Both authors were responsible for the conceptualization of the idea and the preparation of the study proposal. EK was responsible for the preparation of the manuscript. VG was responsible for the critical review of the manuscript. Both authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Measuring goal-orientation of runners.

[PNG File, 674KB - resprot_v7i12e187_app1.png]

Multimedia Appendix 2

Classification of the physical load-taking capacity of runners and their motivation with regard to achieving their running goals.

[PNG File, 715KB - resprot_v7i12e187_app2.png]

Multimedia Appendix 3

Advice for strength exercises.

[PNG File, 689KB - resprot_v7i12e187_app3.png]

Multimedia Appendix 4

Short questionnaire to classify runners.

[PDF File (Adobe PDF File), 29KB - resprot_v7i12e187_app4.pdf]

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Abbreviations

RDRA: Royal Dutch Running Association
RR: relative risks
RRI: running-related injuries

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Protocol

A Web-Based Telemanagement System for Patients With Complex Inflammatory Bowel Disease: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: Telemedicine has been successfully used to provide inflammatory bowel disease (IBD) patients with health care services remotely via the implementation of information and communications technology, which uses safe and feasible apps that have been well accepted by patients in remission. However, the design of telemedicine apps in this setting involves difficulties that hinder the adherence of patients to the follow-up plans and the efficacy of these systems to improve disease activity and quality of life.

Objective: This study aimed to evaluate the development of a Web platform, Telemonitoring of Crohn Disease and Ulcerative Colitis (TECCU), for remote monitoring of patients with complex IBD and the design of a clinical trial involving IBD patients who received standard care (G_Control), nurse-assisted telephone care (G_NT), or care based on distance monitoring (G_TECCU).

Methods: We describe the development of a remote monitoring system and the difficulties encountered in designing the platform. A 3-arm randomized controlled trial was designed to evaluate the effectiveness of this Web platform in disease management compared with G_NT and G_Control.

Results: According to the schedules established for the medical treatment initiated (corticosteroids, immunosuppressants, or biological agents), a total of 63 patients (21 patients from each group) answered periodic questionnaires regarding disease activity, quality of life, therapeutic adherence, adverse effects, satisfaction, work productivity, and social activities. Blood and stool analyses (fecal calprotectin) were performed periodically. On the basis of the results of these tests in G_TECCU, alerts were generated in a Web platform with adapted action plans, including changes in medication and frequency of follow-up. The main issues found were the development of an easy-to-use Web platform, the selection of validated clinical scores and objective

biomarkers for remote monitoring, and the design of a clinical trial to compare the 3 main follow-up methods evaluated to date in IBD.

Conclusions: The development of a Web-based remote management program for safe and adequate control of IBD proved challenging. The results of this clinical trial will advance knowledge regarding the effectiveness of TECCU Web platform for improvement of disease activity, quality of life, and use of health care resources in complex IBD patients.

Trial Registration: ClinicalTrials.gov NCT02943538; https://clinicaltrials.gov/ct2/show/NCT02943538 (Archived by WebCite at http://www.webcitation.org/6y4DQdmt8)

International Registered Report Identifier (IRRID): RR1-10.2196/9639

(JMIR Res Protoc 2018;7(12):e190) doi:10.2196/resprot.9639

KEYWORDS

inflammatory bowel disease; Crohn disease; ulcerative colitis; information technology; eHealth; telemedicine

Introduction

Background

Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn disease (CD). The incidence of IBD is increasing gradually [1], and the prevalence of IBD in Spain is now 1 per 400 inhabitants [2]. Due to its chronic nature, IBD is associated with high levels of school and work disability, interference with social activities, and impairment of quality of life [3-6]. For these reasons, IBD generates a significant medical, social, and financial impact. Therefore, patients with IBD must undergo continuous and individualized monitoring to prevent structural damage and complications in the medium and long terms.

Changes in information and communications technology (ICT) over the last 10 years have affected the management of chronic diseases. Telemedicine is an ICT application that provides remote health care services, that is, without the need for direct contact with the patient. It has been associated with a high degree of satisfaction in patients with chronic diseases such as chronic obstructive pulmonary disease, diabetes mellitus, and congestive heart disease [7-9].

Telemedicine apps have been used to improve adherence to treatment and patient education in IBD (teletraining) [10]. Several studies have shown these apps to be feasible and acceptable for patients with IBD, and the level of satisfaction with them is at least comparable with that of patients who receive standard face-to-face care [11-14]. In addition to teletraining systems, Web-based apps have been developed to provide educational support to patients, thus potentially giving them increased independence for starting or maintaining treatment during a flare-up and for acquiring knowledge about the disease. However, these findings have not been consistent across different populations [15,16].

Current evidence suggests that the use of ICT is a safe way of monitoring patients with IBD, mainly UC in remission or with mild activity [14,16-18]. However, in some studies carried out to date, telemedicine apps require home installation and eventual repairs [14] with differences in reproducibility according to the population in which they are applied [16]. These hindrances interfere with the patients' adherence to follow-up plans and the efficacy of these systems to improve disease activity and quality of life. Moreover, it remains necessary to perform studies to confirm these findings in patients with more complex disease who require treatment with immunosuppressive or biologic drugs and to analyze the impact of telemedicine on the cost of care.

Study Objective

Therefore, this study addresses the main questions related with the use of a Web telemonitoring program in patients with complex IBD, a difficult context in which telemedicine has not been previously used and requires a closer follow-up. We describe the development of the remote monitoring platform *Telemonitorización de la Enfermedad de Crohn y Colitis Ulcerosa(Telemonitoring of Crohn Disease and Ulcerative Colitis,* TECCU) and the clinical trial protocol for evaluation of the intervention compared with nurse-assisted telephone care (G_NT) and standard care (G_Control). Moreover, we detail the selection of indices and questionnaires used to measure the study outcomes, the patient population, and the difficulties found in the design and implementation of the trial, with the aim of helping other investigators in the development of telemonitoring interventions in the setting of complex IBD.

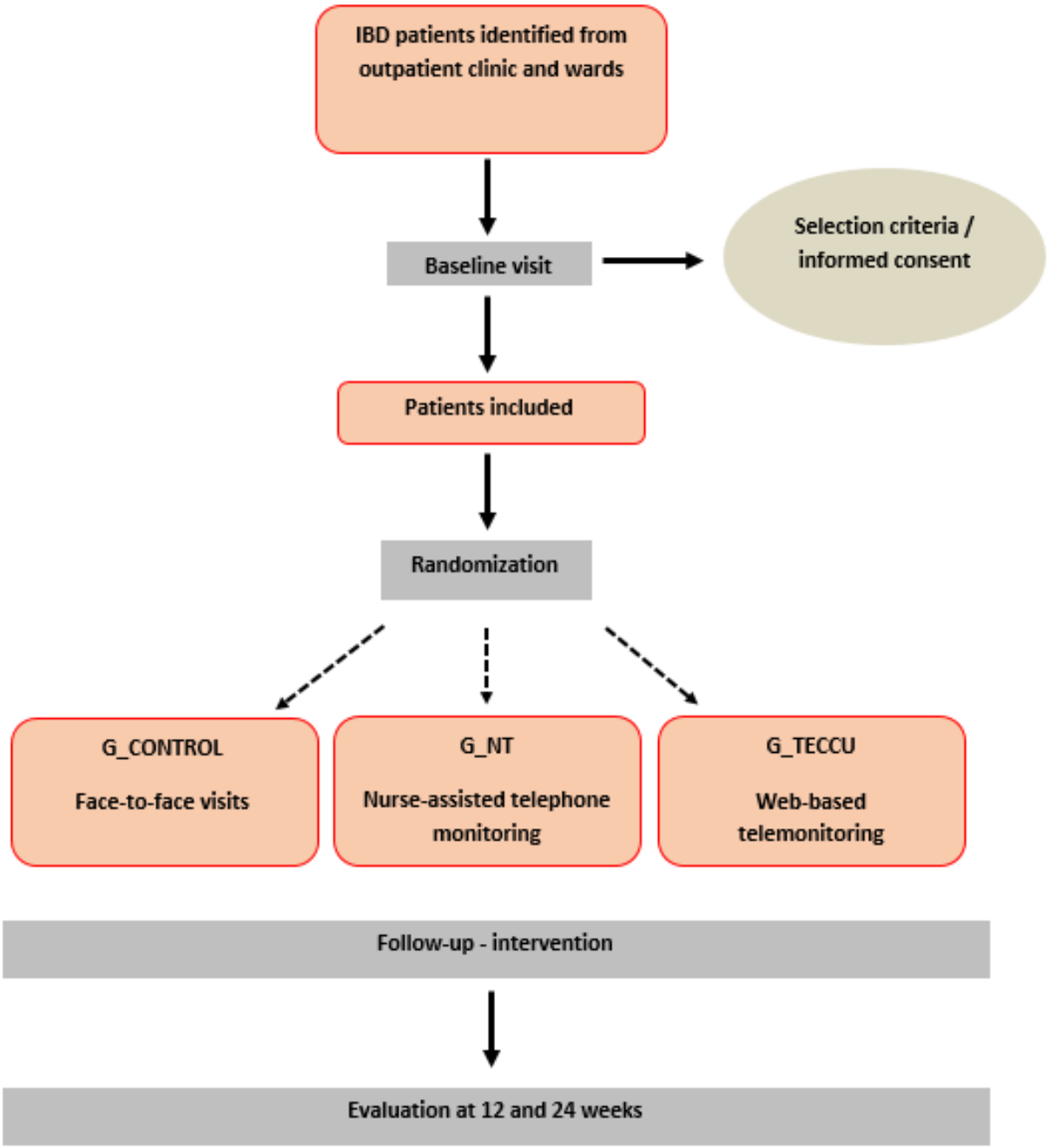
Methods

Study Design

We developed a Web-based telemanagement system—TECCU—for patients with complex IBD. To evaluate the effectiveness of the Web app for control of disease activity, we designed a randomized controlled clinical trial comparing follow-up of patients through the Web-based app (G_TECCU) with G_NT and G_Control. Eligible patients were randomized to 1 of the 3 groups in a 1:1:1 ratio using a Web-based tool to generate the random allocation sequence and ensure allocation concealment. All patients attended study visits at baseline and at 12 and 24 weeks, in addition to routine visits to the IBD clinic or telephone consultations based on group assignment at randomization (Figure 1). Disease activity, health-related quality of life (HRQOL), adverse effects, adherence, and use of health care resources were measured at baseline and during the 24-week follow-up. In CD patients, disease activity was measured with the Harvey-Bradshaw index (HBI), and in UC patients, it was measured with the simple clinical colitis activity

index (SCCAI, also known as the Walmsley index) for remote checkups and the 9-point Mayo score for face-to-face visits.

Figure 1. Flowchart of study participants. IBD: inflammatory bowel disease; G_Control: standard care; G_NT: nurse-assisted telephone care; G_TECCU: care based on distance monitoring.



Patient Selection

Patients were recruited from the IBD unit, La Fe University and Polytechnic Hospital (tertiary referral center), Valencia, Spain. The reference population was 320,000 inhabitants in 2016, although the IBD unit was available to patients from the whole Autonomous Community of Valencia. Thus, the potential population comprised 640,000 inhabitants. The hospital serves more than 1500 patients with IBD (over 400 of them treated with biological agents), has 2 specialist IBD nurses, and provides an email and telephone consultation structure for IBD patients to contact the hospital.

The study participants had been diagnosed with IBD at least 6 months previously according to internationally accepted criteria [19,20] and had to meet all the following inclusion criteria: age ≥18 years, CD or UC with moderate or severe activity/initiation of therapy with immunosuppressive or biological agents, and written informed consent to participate in the study. Patients were excluded if they met any of the following criteria: inability to speak or read Spanish; suspicion that monitoring will not be completed (outpatients); inability to manage a mobile phone/tablet or internet or not having a telephone line; uncontrolled medical or psychiatric disease, pregnancy, active perianal disease, presence of ileorectal or ileal pouch-anal

anastomosis; receipt of definitive ileostomy; and participation in another experimental study during patient enrollment.

To evaluate differences in the percentage of patients in remission and changes in the score of activity indices between the 3 groups, we calculated that a sample size of 60 patients (30 CD patients and 30 UC patients) was necessary. During the study period, patients were included consecutively from the outpatient clinic of the IBD unit or the gastroenterology department if they had been admitted for a flare-up. A total of 68 IBD patients who met selection criteria were invited to participate in the study. Of these, 4% (3/68) declined to participate owing to inaccessibility to the internet at home and 3% (2/68) did not meet the inclusion criteria. The remaining 63 eligible patients provided their informed consent and were randomly assigned to G_TECCU, G_NT, and G_control (21 patients in each group). All patients enrolled were included in a likelihood-based analysis.

Recruitment and Random Assignment

Patients were included consecutively from the outpatient clinic of the IBD unit or the gastroenterology department if they had been admitted for a flare-up of IBD. During the visit, the inclusion and exclusion criteria were verified and the patient was informed about the study through the patient information sheet. If the patient agreed to participate, he or she signed the informed consent document. Patients were assigned to the different groups using a secure and independent randomization tool. Once a number was assigned, it could not be reassigned.

Eligible patients were assigned to the groups through a computer platform that ensured that the researchers could not modify a patient's group. This process was performed using a block randomization method between the groups (1:1:1) with concealed allocation of participants. The blocks were numbered and ordered using a randomly generated sequence. Members of the research team who were in contact with patients did not have access to the randomization tables or lists.

Interventions

Types of Interventions

The trial had 3 arms with 3 different interventions (Figure 1):

1. G_control: Patients in the control group received the usual care provided in the IBD unit (outpatient clinic) to patients with moderately to highly complex IBD. We also provided on paper all educational material about IBD available for the remote monitoring patients as well as information on prevention and written action plans in case of flare-up to make the 3 groups more comparable. Moreover, the clinical status of patients was recorded weekly during the first 12 weeks and subsequently every 2 weeks until the end of the follow-up in a diary designed on paper. This care was complemented by ad hoc hospital care in the case of flare-ups or if patients' health deteriorated for any reason. Ad hoc intensive care was maintained until patients' condition stabilized, at which point he or she returned to follow-up based on standard care in the unit. The intervention was limited to recording of baseline variables, follow-up for identification of end points, and administration of activity indices and questionnaires on HRQOL, satisfaction, and work productivity.
2. G_NT: Patients in this group were asked about their health through a telephone call from nursing staff in the IBD unit, and we provided these patients with all educational elements and action plans available in the other 2 groups. Telephone assessment was performed periodically using structured interviews to evaluate clinical status with intensified schedules, in a similar manner to the G_control. The actions carried out depended on the results of the interview and the intervention protocol.
3. G_TECCU: Follow-up and monitoring in this group were performed telematically using the integrated platform for management of chronic patients NOMHADchronic, which was set up to meet the specific needs of IBD patients. Patients connected to the platform via the internet using a computer or an app on a mobile phone or tablet and had to complete questionnaires (both scheduled questionnaires and those requested by the patient at other time points) and introduce relevant follow-up data (eg, vital signs and analytical data). They also received advice, reminders, educational material about their disease, and information on prevention. Case managers received the information from each patient, which was filtered using an intelligent prioritization system and generation of alerts and push notifications according to an integrated intervention protocol. Physicians from the IBD unit were also able to access individual patients' data and received referrals about alerts and push notifications that had to be managed by medical staff.

NOMHADchronic Platform

The NOMHADchronic platform is an innovative technological system that was designed to boost the rollout of services for the management of chronically ill patients. The platform covers the needs of patients, professionals, and the organization managing the care process and coordinates the work of the professionals involved. This efficiency-based multiplatform system provides a flexible, integrated solution that can be adapted to provide various services. Artificial intelligence enables it to provide support for decision making. It was developed following the Health Level 7 (HL7) version 3 standard, thus enabling its easy integration with the electronic clinical history. It can be set up in such a way that plans and thresholds can be personalized according to each patient's profile. The system also makes it possible to create combined alerts using several variables, thus facilitating a holistic approach to the patient and not only to the specific diseases diagnosed.

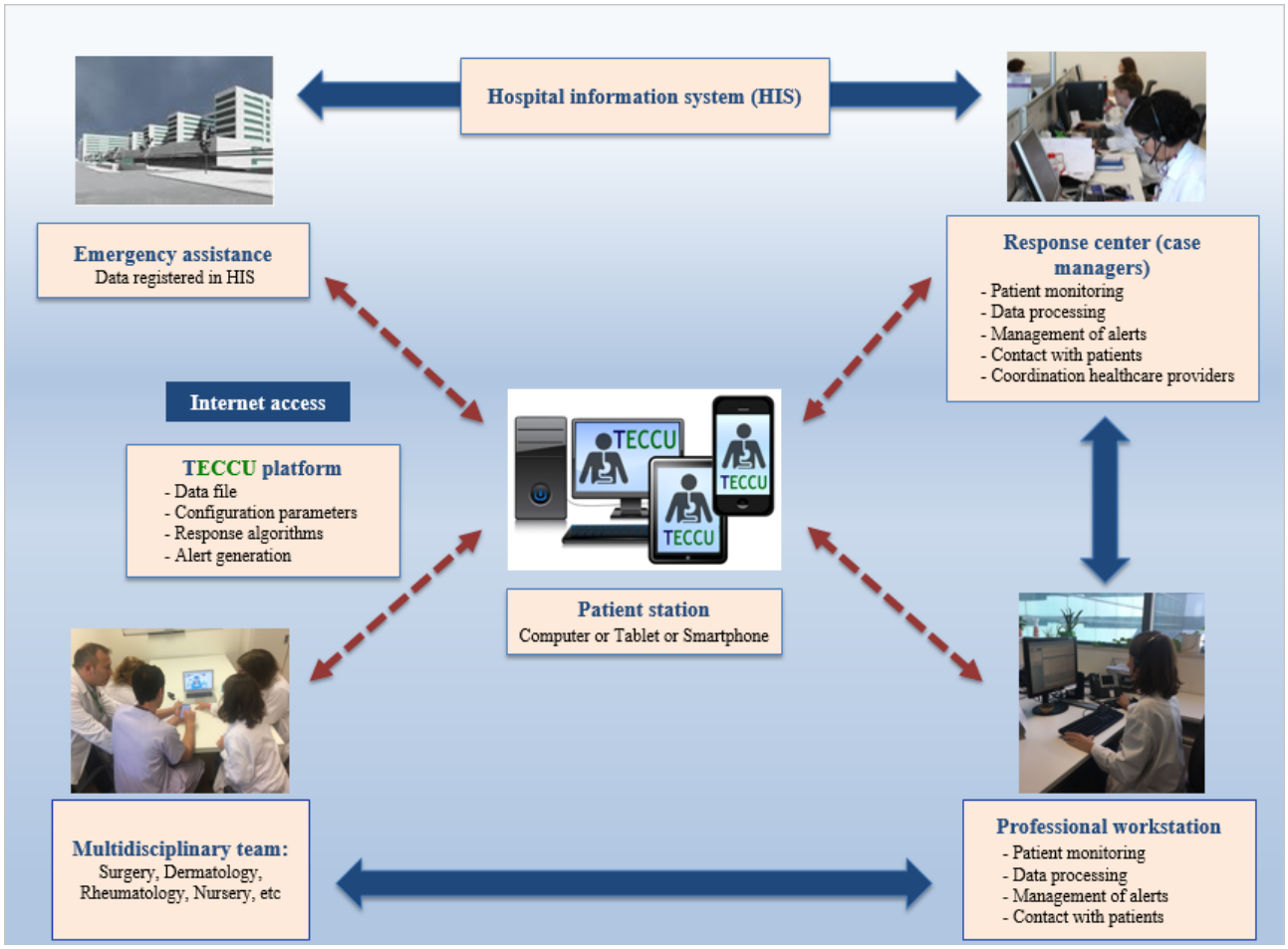
This program was initially designed to manage patients with other chronic diseases such as cardiovascular diseases or diabetes mellitus. The telemanagement care system was developed in collaboration with La Fe telemedicine unit, Tecnología Salud y Bienestar SA, and patients from our IBD unit. With the aim of adapting the platform to the particular needs of complex IBD patients, we performed consecutive meetings with patients and researchers to modify the original modules of NOMHADchronic. We changed the elements of the platform to monitor disease activity and other clinical outcomes with specific indices, the normal values, and parameters

recorded in the blood tests and fecal calprotectin as well as the follow-up schedule according to clinical guidelines in the management of IBD patients. Moreover, we incorporated educational elements to improve disease knowledge of patients and empowerment through interactive materials.

NOMHADchronic comprises NOMHADcore (the nucleus of the platform), the workstation (for health professionals), the response center (case managers), and the patient station (on the Web platform, tablet, or mobile phone). The solution involves various modules to cover all aspects of management of chronically ill patients: clinical information relative to patients' status, support for coordination of the different health care providers, logistics management, human resources management, and integration with monitoring devices and accessories (Figure 2). The tool concentrates on 4 main functional areas: innovative education, multimodal care communication, monitoring, and personal clinical history.

Researchers designed the follow-up protocol according to national and European guidelines [19-21] and set up the platform to include the components described in Textbox 1.

Figure 2. Telemonitoring system for patients with complex inflammatory bowel disease. TECCU: Telemonitoring of Crohn Disease and Ulcerative Colitis.

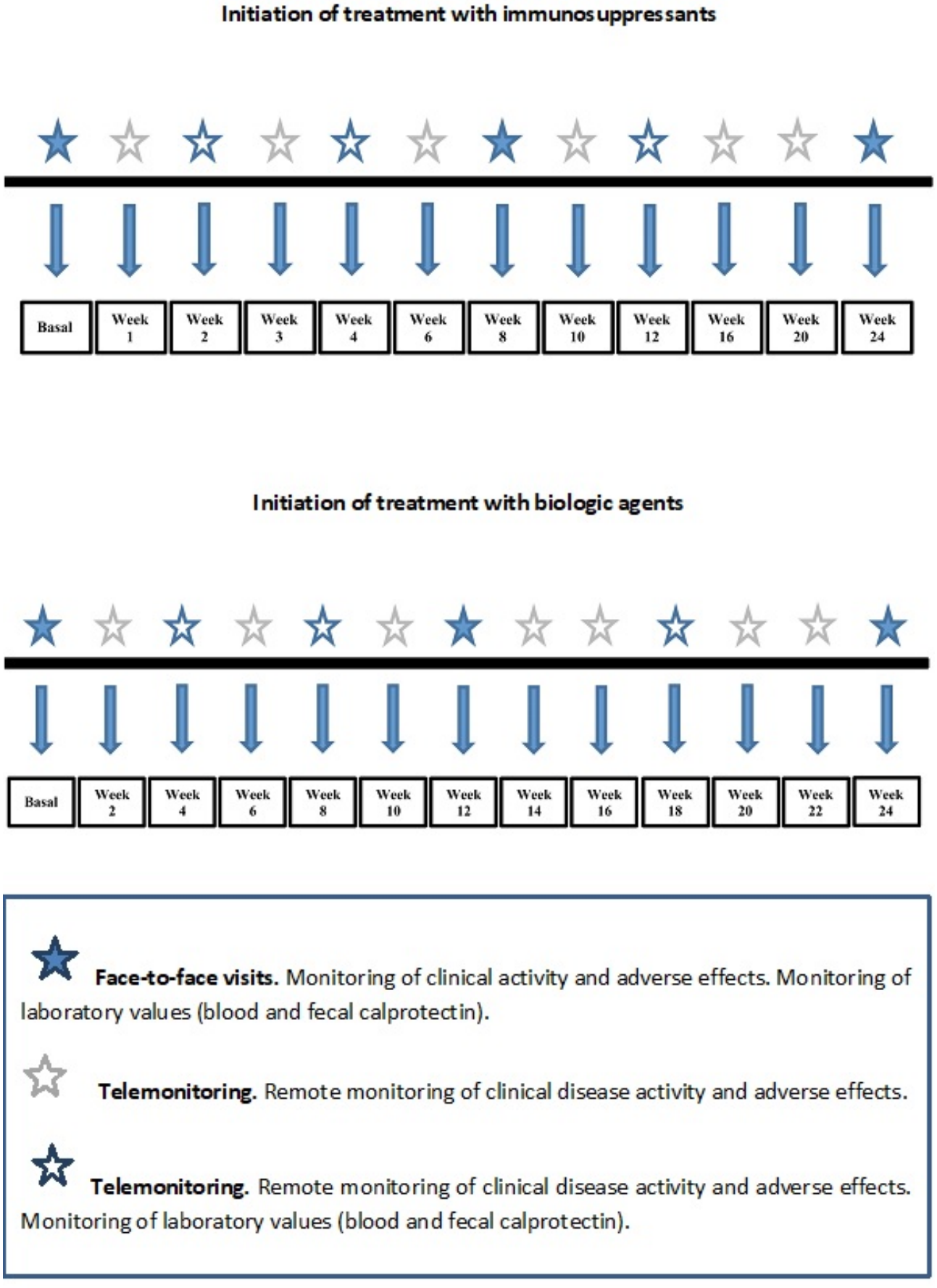


Textbox 1. Components of the development of the telemonitoring of Crohn disease and ulcerative colitis (TECCU) platform.

Components of the development of the telemonitoring of Crohn disease and ulcerative colitis (TECCU) platform:

- Detailed monitoring plan
- Definition of the main indicators and alarms
- Specific interventions for the patient
- Specific interventions for health professionals
- Configuration of the user environment in the health professional's app
- Configuration of the user environment in the patient's app

Figure 3. Follow-up timeline for G_TECCU receiving treatment with immunosuppressants or biologic agents.



Follow-Up Schedule

Irrespective of the study arm, the patients included followed a periodic monitoring program adapted to the type of medication they were taking (corticosteroids, immunosuppressantsor biologics). In the case of combined treatment with immunosuppressants and biologics, the follow-up program was similar to that of patients who were taking immunosuppressants alone. Furthermore, patients from the 3 arms who took the same type of drug underwent identical monitoring, which was performed along a time line for patients treated with immunosuppressive drugs and another for patients treated with biologics (Figure 3). The difference lay in the fact that patients from G_TECCU were monitored via the NOMHADchronic system, G_NT via a telephone line managed by nursing staff from the IBD unit, and G_control with the usual face-to-face visits. Irrespective of the group assigned and treatment prescribed, all patients had to visit the IBD unit at baseline, 12 weeks, and 24 weeks.

Telemonitoring of Crohn Disease and Ulcerative Colitis Self-Testing

Patients monitored via the Web-based system used NOMHADhome, which was installed from a page that was supplied to the patients and could be accessed via the internet. The resources of the NOMHADhome platform were also available on the NOMHADmobile app, which patients could download onto their mobile phone. After inclusion, these patients automatically received an email with a personal access code that enabled them to access the NOMHADhome platform. Each patient profile contained the following data: contact information (address, email, and phone number); active IBD medications; testing schedule (blood and stool tests); log of disease activity, medication use, body weight, vital signs, and quality of life; alerts and action plans; progress of inflammatory activity and vital signs in the form of graphs; electronic messaging to the study nurse coordinator and the health care provider; and educational tips (Figures 4 and 5).

Formative sessions of 30 to 60 min were performed with patients and investigators to improve practical utilization of the platform before starting follow-up. During telemonitoring, patients accessed via the internet the Web platform with their personal password and responded to different aspects of their disease. In all checkups, they introduced their vital signs, IBD symptoms to measure disease activity, medication adherence, and adverse effects to medication. In the main menu of the platform, patients accessed the questionnaires by clicking on the specific icons designed for this purpose and could then answer the multiple choice and yes or no questions needed to complete these items. When it was necessary to fulfill the results of blood tests or fecal calprotectin performed in their medical center, patients could introduce their results in different text boxes for each parameter similarly. Thus, the patient was able to self-complete all the clinical and analytical variables necessary to evaluate his or her disease status at each of the checkups programmed in their follow-up time line. In addition to these fixed monitoring points, the patient could complete the questionnaires voluntarily if his or her clinical status deteriorated.

To assess disease activity, CD patients calculated their modified HBI via text messaging. The HBI is a validated activity index that has been shown to correlate well with the criteria of the standard instrument for assessing disease activity for CD, the CD activity index [22]. The HBI includes 5 clinical variables that apply to the 24 hours since the previous evaluation on overall well-being, abdominal pain, number of liquid stools per day, presence of abdominal mass, and complications. For UC, patients completed the SCCAI via text messaging. The SCCAI has been shown to correlate well with other disease activity indices for UC and was recently validated for self-administration via a Web-based tool [23,24]. The SCCAI contains 6 questions on number of daytime and nocturnal bowel movements, urgency, blood in stool, general well-being, and extraintestinal manifestations of disease. In addition to disease activity, during clinical controls, patients answered a series of questions about medication adherence and adverse effects.

After completion of a scheduled or voluntary monitoring questionnaire, a personalized action plan was designed depending on the results obtained. On the basis of the responses to the different outcomes evaluated, the platform stratified patients in the professional workstation according to the severity of their health status in different levels of severity. Health care providers were then able to respond to patient needs according to each health status. The platform proposed a specific intervention according to preestablished algorithms and medical providers, in coordination with case managers, and finally implemented a customized action plan for each case as described in the following section.

Educational materials were also included in a specific section available in the main menu of the platform. At any time, patients could review the information adapted by our research group and they could answer different questions related to the information provided to check their IBD knowledge. Moreover, the platform allowed the interaction with health care providers through a messaging menu to contact case managers and medical providers as needed. Patients could ask questions related to their disease evolution or treatment by texting a message with the keyboard. These messages were frequently reviewed so that they were answered by our medical or nurse staff after 24 to 48 hours.

Description of Telemonitoring of Crohn Disease and Ulcerative Colitis Alerts and Action Plans

We established individualized alerts and action plans based on the answers to questions about the activity index, adverse effects, and results of blood and stool parameters. A scale of values was assigned for each alert depending on severity (green, yellow, orange, and red zone). For example, according to the activity index score (remission or mild, moderate, or severe disease), the patient is categorized in the green, yellow, orange, or red zone, and the health professional can select 1 or several actions to immediately begin self-testing (Tables 1 and 2). Each level of alert was associated with a preestablished intervention plan that involved closer monitoring, changes in drug dose, or even referral to the hospital emergency service or an outpatient clinic. These interventions were managed by nursing or medical staff depending on the degree of severity of the alert. Once the disease

was in remission again (green zone), the patient had to continue with the initially programmed follow-up. In some cases, the criteria for entering each zone could be modified by the researcher to adjust the specific clinical status of each patient.

Figure 4. Home page of the NOMHADhome platform, patient version. Translations for the screenshot: Mañana: Morning; Mediciones: Statistics; Cuestionarios: Questionnaires; Evolución de constants: Vital signs; Educación: Education; Buenos días paciente 0001: Good morning patient number 0001; Teclea tu PIN: Please type your PIN number; Otros: Other; Salir: Disconnect.

Figure 5. Home page of the NOMHADmobile platform and access to vital signs, patient version.

Table 1. Action plans according to Harvey-Bradshaw index activity index scores.

Harvey-Bradshaw index	Action plan
Score >16: Severe activity[a]	• Intervention 1: Send patient to hospital immediately[a]
Score 8-16: Moderate activity[b]	• Intervention 1: Request priority appointment in outpatient clinic[b] • Intervention 2: Adjust immunosuppressants and biologics[b]
Score 5-7: Mild activity[c]	• Intervention 1: Monitor 2-3 times per week[c] • Intervention 2: According to new score • Intervention 3: Adjust new medication or add new treatment
Score <5: Disease in remission[d]	• Continue with monitoring program[d]

[a]Red zone.
[b]Orange zone.
[c]Yellow zone.
[d]Green zone.

Table 2. Action plans according to Simple Clinical Colitis Activity Index (SCCAI) activity index scores.

Simple Clinical Colitis Activity Index (SCCAI)	Action plan
Score >5[a]	Contact the physician[a]
Score 3-5[b]	Follow-up with repeat of SCCAI in 5 days[b]
Score ≤2[c]	Continue with the same monitoring program[c]

[a]Red zone.
[b]Yellow zone.
[c]Green zone.

To ensure that patients in the G_TECCU arm adhered to the requirements of remote monitoring, 2 days before each monitoring date, they received a message via email if they were using the NOMHADhome app or a message via their mobile phone if they were using NOMHADmobile. Similarly, the patients were sent a reminder if they did not enter their data on the scheduled date.

Furthermore, all patients had access to tools that taught them about their disease. In G_TECCU, information was available on the NOMHADhome platform itself; in the G_Control and G_NT arms, the patients received written documents with the same information.

Health Data Security

TECCU Web platform protects the confidentiality of health data. The access to patient station and to workstation requires a personal password only known by the patient and health care providers, respectively. Moreover, health care providers register patients in the platform with a generic name and a code only identifiable by investigators. Finally, to avoid data correlation by a nonauthorized person, data included in the Web platform are not connected to other hospital information systems. Thus, only case managers and health professionals can see all the clinical history separately.

Notification of Adverse Effects

TECCU is a minimal risk system. The characteristics of the interventions in this study mean that patients are not expected to experience direct adverse effects. The interventions were proposed to control and achieve longer remission periods in patients with IBD. Therefore, they cannot cause lesions or damage the patients' health, since we did not test a new experimental drug; on the contrary, we used a Web-based telemonitoring system to give indications when flare-ups are detected or when these become more severe. With respect to the platform, a risk minimization study was performed to ensure the accomplishment of ethical norms and that the appropriate ethics committees approved the study. In any case, we recorded all adverse events occurring from the moment the patient gave his or her consent to participate in the study until 28 days after the study finished.

Statistical Analysis

Sample Size Calculation

It was decided that the most efficient means of determining differences between the 3 groups (G_control, G_NT, and G_TECCU) was by contrasting differences in activity indices for the diseases treated (CD and UC). Given that the scales differ, the analysis was stratified by performing a comparison for patients with UC and another comparison for patients with CD. The sample size was calculated by estimating that to detect a difference of 3 points in the HBI, taking into account an SD in the index of 4, a power of 80%, and an alpha significance level of .05, a total of 30 patients with CD (10 per arm) would be needed. Moreover, for a difference in the Mayo index of 2 points, taking into account an SD of 2.5, a power of 80%, and an alpha significance level of .05, a total of 30 patients with UC (10 per arm) would be needed. Therefore, the overall sample size was 60 patients (20 per arm).

We also stratified patients globally (CD and UC) by comparing those in remission or with inflammatory activity, irrespective of severity (mild, moderate, or severe).

Statistical Analysis Plan

First, we described the characteristics of patients in the test and control groups (by applying appropriate estimators according to the type of variables with their respective CIs for means or proportions) and evaluated possible differences between the groups using tests to assess differences in means or proportion. Second, we evaluated differences in the main outcome measure and in the secondary outcomes, again using tests to assess differences in means and proportions, as applicable. We then used linear regression models (or logistic regression models) to evaluate the significance and magnitude of the effect of the intervention while controlling for possible differences in the characteristics of patients from both groups. We generally used backward-forward models by initially constructing complete models and excluding nonsignificant variables one by one (*P* for removing variables=.10), although we tried to include the previously removed variables after each exclusion (*P* for including variables=.05). The yield of the models was evaluated using the coefficient of determination and, in the case of logistic regression, by evaluating its discriminative capacity (C-statistic) and calibration (Hosmer-Lemeshow test). The statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The analysis was performed on an intention-to-treat basis.

Costs were evaluated from a social perspective including direct health care costs. The unit cost was obtained by measuring the consumption of resources and applying the official price list of the Valencian Health Agency or other official bodies. When these were not available, they were estimated by evaluating the time and cost of the resources involved.

Ethical Considerations

The study was carried out in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects, as adopted by the General Assembly of the World Medical Association (1996). We followed the protocol, the principles of Good Clinical Practice, the guidelines of the International Conference on Harmonization, and the official regulations of the participating centers. The study protocol was reviewed and approved by the local independent ethics committee of La Fe University and Polytechnic Hospital, Valencia, Spain , the regional independent ethics committee (Comité Ético Autonómico de Estudios Clínicos de Medicamentos y Productos Sanitarios de la Comunitat Valenciana; CAEC), and the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios; AEMPS). The study was carried out by persons with the appropriate scientific and medical qualifications. The benefits of the study were proportional to the risks. The rights and well-being of the participants were respected at all times. According to the physicians involved in the study, the risks did not outweigh the potential benefits, and each participant provided his or her informed consent without coercion. The trial was registered at clinicaltrials.gov with the identifier NCT02943538. The results will be published according to the CONSORT guidelines.

Study Outcomes

Participants attended study visits at baseline, 12 weeks, and 24 weeks, in addition to routine visits scheduled for their clinical care. The variables measured at baseline were sociodemographic variables, disease activity, HRQOL, adverse events, adherence, and patient satisfaction. The results were recorded on a paper case report form designed ad hoc for the study. The same approach was used at 12 and 24 weeks. In addition, the hospital information system was consulted to collect data on mortality and variables associated with the consumption of hospital

resources (emergency and scheduled visits to the outpatient clinic, visits to the emergency department, emergency and scheduled hospital admissions during follow-up, and surgical procedures). This information was used in the cost-effectiveness study, which was based on direct health care costs.

Primary End Point

The primary objective of the study was to evaluate clinical remission at 24 weeks. In addition, clinical disease activity was evaluated at each of the checkups scheduled in the patients' time line. Remission was evaluated using the HBI for patients with CD [22]. In the case of patients with UC, we used the SCCAI [23] for remote checkups, together with the partial Mayo score for face-to-face visits.

Patients with CD and an HBI <5 were considered to be in clinical remission, whereas patients with scores of 5 to 7, 8 to 16, or >16 were classed, respectively, as having mild, moderate, or severe activity [22]. For remote checkups in patients with UC, clinical remission was defined as an SCCAI ≤2, whereas values of 3 to 5 or >5 points were classed as mild-to-moderate or severe activity, respectively [25]. In the face-to-face visits, clinical remission was defined as a partial Mayo score ≤2 and no individual Mayo subscore >1; scores of 2 to 5, 6 to 8, and 9 points were defined, respectively, as mild, moderate, and severe disease activity [26].

Laboratory parameters were measured at baseline and at each subsequent visit according to the individual patient's schedule and included complete blood analysis with nutritional profile and C-reactive protein (mg/L) and fecal calprotectin (µg/g) to assess inflammatory activity. The results obtained could lead to changes in the medication prescribed. The alert generated led to an intervention. Fecal calprotectin was assessed at baseline and 12 and 24 weeks after inclusion, although their values did not lead to a specific intervention.

Secondary End Points

Health-Related Quality of Life and Impact on Activities of Daily Living

The HRQOL of the patients at inclusion and at week 24 or at the end of the follow-up visits was evaluated using the following 2 tools: a specific questionnaire, the IBD Questionnaire 9 (IBDQ-9), and a generic questionnaire, EuroQol-5D (EQ-5D). IBDQ-9 has been validated for IBD and correlated extremely well with clinical activity [27]. The Spanish version of IBDQ-9 has been validated and correlated well with the IBDQ-36 questionnaire in Spanish [28]. EQ-5D is a generic questionnaire that has been used in patients with various chronic diseases, such as IBD, and has been validated in Spanish [29]. This instrument provides a global value for HRQOL and a visual analog scale (VAS). It is known that responses to EQ-5D items and the VAS score are better for patients in remission than for patients with active disease [30].

Furthermore, the impact of disease on work productivity and activities of daily living was evaluated using the Work Productivity and Activity Impairment questionnaire, which patients completed at baseline and at week 24. The questionnaire comprises 6 questions on the effect of the disease on work and activities of daily living during the previous 7 days. The greater the score on the questionnaire, the greater the effect is on work and daily activities. The Spanish version has been validated and has been shown to be reproducible in patients with CD [31].

Evaluation of Adherence and Adverse Effects

Adherence was evaluated using the Morisky-Green index [32], which has been used in clinical trials to evaluate adherence in patients with IBD [14]. We consider adherence to be adequate when the patient responds to all questions correctly and inadequate if any answer was associated with nonadherence.

Furthermore, patients responded to a series of questions related to the onset of specific adverse effects to the drugs they were taking at the time. These checkups reflect the adverse effects of immunosuppressive or biologic agents, as preestablished by the research team in the NOMHADchronic app.

Assessment of Utilization of Health Care Resources

We recorded information from each patient on the use of health care resources, specifically the number of unscheduled visits to the outpatient clinic, visits to the emergency department, and nonscheduled admissions to hospital. This information was recorded using the hospital information system, Orion Clinic, which has been certified by the Health Information and Management Systems Society and is used in daily clinical practice in La Fe University Hospital. We also recorded the following: the reason for the visit to the outpatient clinic, visit to the emergency department, or hospital admission; whether or not IBD-related surgery was necessary; and the total length of hospital stay. In addition, we recorded all deaths during the study (whether related to IBD or not).

Assessment of Satisfaction With Care

Patient satisfaction with the care received was evaluated at 24 weeks using an adapted version of the Client Satisfaction Questionnaire, which comprises 6 questions on the quality, usefulness, and viability of the care received as a result the intervention [33].

Results

This project was funded in 2012, and the platform was installed and configured from 2013 to 2014. Enrollment started in October 2014 and it finished in June 2016. At the time of this protocol's submission, data analysis was underway, and the first results are expected to be published in 2018.

Discussion

Importance of the Study Results and Principal Findings

Efforts, to date, have focused on telemonitoring systems in an attempt to positively influence adherence to treatment and knowledge of the disease in the follow-up of patients in remission or with mild-to-moderate disease [14,16]. This study is the first randomized controlled clinical trial to evaluate the efficacy of a remote Web-based management program for the follow-up of patients with IBD of moderate-to-high complexity. We compared standard face-to-face or nurse-assisted telephone

follow-up with remote monitoring based on a Web app (NOMHADchronic) for control of inflammatory activity, quality of life, adverse effects, adherence, and use of health care resources over a 24-week period. Patients with moderate-to-high disease complexity are considered to be those who start treatment with systemic corticosteroids, immunosuppressants, or biologics for control of inflammatory activity.

There is still little evidence on the role of telemedicine in monitoring health outcomes and reducing health care costs in the IBD setting. In 2001, Robinson et al [17] successfully implemented a self-care plan in patients with UC in remission. A total of 203 patients were randomized to G_Control or to self-management. During the 1-year study period, relapses in the self-management group were treated earlier and were shorter in duration, and utilization of health care resources decreased. Over a decade later, Cross et al [14] used a remote control system, Home Automated Telemanagement (HAT), to provide a secure patient portal to monitor symptoms, generate alerts, and inform patients about the disease in a randomized clinical trial. However, in this study, no significant differences were noted in disease activity and quality of life between patients followed with the HAT system and usual care, probably due to the small sample size and the design of the platform, which required home installation and repairs. To avoid these problems, the same group designed afterward a Web telemanagement program via mobile phone [34].

Web-based programs are a new and easy-to-use approach in telemanagement. The implementation of such programs reduces the costs of telemanagement because home installation is not required. Elkjaer et al [16] performed a pioneering study in Web-based management in which the concept of *constant care* was introduced for patients with UC. A randomized controlled trial comparing Web-based monitoring and standard follow-up was carried out with 333 patients with UC treated with 5-aminosalicylic acids (5-ASA) at hospitals in Denmark and Ireland. The remote care method was safe and feasible. The authors observed a trend toward higher adherence in patients managed using a Web-based system and that the duration of relapses was shorter than that in the G_control. These findings were associated with the ability of the Web-based program to empower patients to self-initiate 5-ASA in case of flare-ups. Moreover, in the experimental arm, patients made more phone calls and sent more emails but attended fewer face-to-face visits, and cost savings per patient-year were recorded.

Given that telemonitoring apps are well accepted by patients and seem to be a safe approach for follow-up of patients with less complex IBD (in remission or with mild activity), we designed a controlled, 3-arm clinical trial to compare the effectiveness of G_TECCU for the monitoring of inflammatory activity in patients with IBD of moderate-to-high complexity with G_control and G_NT. Our study enabled us to compare the main strategies applied to date in the follow-up of patients with IBD (standard or telephone support by a nurse) with remote monitoring. In particular, an easy-to-use Web-based program with a Web app (NOMHADchronic) would likely improve health outcomes and reduce costs more than other systems for remote management of the disease (eg, those that could require reparations at home) [35].

Another critical issue was the selection of activity index and biological tools for measuring disease activity and secondary outcomes remotely. We used clinical activity indices (HBI, SCCAI, and partial Mayo score) to evaluate the primary objective of the study. The SCCAI was previously used to evaluate the ability to control disease via telemonitoring systems [16] and was shown to correlate well with other, more complex activity indices that require endoscopy [36]. Similarly, the reduced 6- and 9-point versions of the Mayo index, which do not require endoscopy, have proven to be capable of detecting a clinical response to treatment, as is the case with the full Mayo score [26]. The partial Mayo score is only used at face-to-face visits because one of its items must be assessed by a physician. Nevertheless, as clinical indices may not reflect the true inflammatory activity of the disease, biological markers (C-reactive protein and fecal calprotectin) were used for the global evaluation and comparison of the 3 groups at the baseline and follow-up visits, which are sensitive enough to detect mucosal inflammation [37].

Strengths and Limitations

Regarding the development of the TECCU Web program, the main difficulties were related to the design of an easy-to-use system, which is compatible with a broad group of devices. We designed an interactive tool, which allows patients to register their evolution at each moment, through a simple and structured main menu containing all relevant aspects to control IBD activity. A practical problem with the use of TECCU was its incompatibility with Microsoft Internet Explorer Web browser, but patients and researchers were able to open the TECCU platform using Mozilla Firefox or Google Chrome, and there was a version available for Windows and Mac operating system computers and Android or iOS mobile phones. Another issue was the absence of videoconference, but the electronic messaging and the intelligent alert plans included in the platform allowed coordination of health care providers to provide response to medical problems after 24 to 48 hours. Our study is subject to a series of limitations. First, we included patients with IBD managed at a tertiary referral hospital, and the exclusion of patients with suspicion that monitoring will not be completed is subject to difficulties in determining the ability and willingness to use ICT in each case, which represent a potential source of bias. According to guidelines for management of IBD, patients evaluated at referral centers often have more complex disease, are often more difficult to treat, and need aggressive therapies. Patients treated in community hospitals, on the other hand, generally have milder disease and require less aggressive treatment. However, the NOMHADchronic program may also help community physicians to be more aware of the guidelines, and it could even be more effective in patients who can self-manage with less aggressive treatments, which may be easier to implement. Second, we did not perform colonoscopy in all patients because it would increase the costs of the clinical trial, and colonoscopy is not performed routinely in all patients in clinical practice. Nevertheless, we intend to analyze the subgroup of patients who underwent routine colonoscopy. Third, due to the kind of interventions assessed, neither the patients nor the researchers were blinded with respect to the intervention, but the results

were analyzed by an independent statistician who was blinded to group identification.

Conclusions

In conclusion, the development of a Web-based program for the management of patients with IBD proved challenging in terms of providing adequate remote monitoring of the disease and acceptance of the system, mainly as a result of including patients with moderate-to-severe disease. We describe the difficulties we faced during the design of a randomized clinical trial to compare Web-based monitoring of patients with standard face-to-face monitoring and telephone monitoring. We aimed to aid other investigators in the development of telemonitoring interventions and the selection of methods to measure health outcomes remotely as well as the groups of patients who benefit from this approach during the design of future studies in the IBD setting. The results of our trial will show the impact of the TECCU telemonitoring system on disease activity, quality of life, and health care costs through continuous care and patient empowerment. Future studies are necessary to validate the NOMHADchronic remote monitoring program in other, specific groups of patients, namely, those with noncomplex disease, those with limited access to medical care or social support, and patients who may not be able to attend a clinic with specialized IBD care.

Acknowledgments

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Conflicts of Interest

DD is the General Manager of Connected Health Services, the company that owns the intellectual property and commercial rights of the NOMHADchronic software platform, which was configured and used in the TECCU trial for the remote management of patients with CD and UC.

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Abbreviations

CD: Crohn disease
EQ-5D: EuroQol-5D
G_Control: standard care
G_NT: nurse-assisted telephone care
G_TECCU: care based on distance monitoring
HAT: Home Automated Telemanagement
HBI: Harvey-Bradshaw index
HRQOL: health-related quality of life
IBD: inflammatory bowel disease
IBDQ-9: IBD Questionnaire 9
ICT: information and communications technology
SCCAI: simple clinical colitis activity index
TECCU: Telemonitoring of Crohn Disease and Ulcerative Colitis
VAS: visual analog scale
5-ASA: 5-aminosalicylic acids
UC: ulcerative colitis

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Protocol

The Japanese Early-Stage Trial of High-Dose Methylcobalamin for Amyotrophic Lateral Sclerosis (JETALS): Protocol for a Randomized Controlled Trial

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects the upper and lower motor neurons. Currently, only riluzole and edaravone are approved as drugs to treat ALS and new agents with larger effect sizes are warranted. Exploratory analyses in our previous study (study ID #E0302-J081-761) have suggested that high-dose methylcobalamin (E0302) prolonged the overall survival of ALS patients and suppressed ALS progression in patients with a disease duration of less than 12 months.

Objective: This clinical trial aims to evaluate the efficacy and safety of E0302 for treatment of ALS patients within one year of onset.

Methods: The Japanese early-stage trial of high-dose methylcobalamin for ALS (JETALS) is a prospective, multicenter, placebo-controlled, double-blind, randomized phase III study conducted at 24 tertiary neurology centers and is funded by the Japan Agency for Medical Research and Development. A total of 128 ALS patients within one year of onset were randomized at a 1:1 ratio to receive intramuscular injection with E0302 50 mg or placebo twice a week for 16 weeks. The primary endpoint is changes in the ALS Functional Rating Scale-Revised (ALSFRS-R) total score at 16 weeks. If patients wish to receive E0302 50 mg after the double-blind administration period, E0302 will be provided to them until March 2020 during the continuous administration period.

Results: This study began in October 2017 and is being conducted at 24 participating institutions in Japan. The study is in progress and the patient enrollment period is scheduled to end in August 2019, with follow-up scheduled to end in March 2020.

Conclusions: This study is being performed to revalidate the efficacy and safety of E0302 in patients with early-stage ALS in the first year of symptom onset. If positive results are obtained, the aim is to apply for E0302 approval as a new drug for the treatment of ALS.

Trial Registration: ClinicalTrials.gov NCT03548311; https://clinicaltrials.gov/ct2/show/NCT03548311 (Archived by WebCite at http://www.webcitation.org/74Fw3rDzb)

International Registered Report Identifier (IRRID): PRR1-10.2196/12046

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KEYWORDS

amyotrophic lateral sclerosis; methylcobalamin; vitamin B12; JETALS; clinical trial

Introduction

Amyotrophic lateral sclerosis (ALS) is a disease of unknown etiology that affects upper and lower motor neurons and results in progressive systemic muscle weakness and atrophy. The median survival time—period from onset until the use of an invasive respiratory support device or death—is 20-48 months [1].

Many drugs have been evaluated in clinical trials for treating patients with ALS; however, apart from riluzole and edaravone, none have been approved by the US Food and Drug Administration. Riluzole has been shown to prolong survival by 2-3 months [2]. Edaravone has been shown to slow the advance of the ALS Functional Rating Scale-Revised (ALSFRS-R) score: the least-squares mean difference during 24 weeks between the edaravone group and the placebo group was 2.49 (SE 0.76, 95% CI 0.99-3.98; *P*=.001) in favor of edaravone [3].

Hence, the development of a drug that extends the survival time or ameliorates clinical symptoms of ALS is widely anticipated. High-dose methylcobalamin—an active form of vitamin B12—has been suggested to have a protective effect against neurodegeneration in vitro and in vivo [4-7]. Clinical research reports have suggested that administration of high-dose methylcobalamin to patients with ALS has yielded clinically beneficial results [8,9].

In one study, methylcobalamin (0.5 or 25 mg/day) was intramuscularly administered for 14 days to 24 patients with ALS [8]. As a result, the compound muscle action potential amplitude in the 25 mg methylcobalamin group was significantly increased after 4 weeks—2 weeks after administration was completed—compared with that before administration of methylcobalamin.

The aforementioned nonclinical and clinical research results showed that high-dose methylcobalamin may be an effective treatment option for ALS. Owing to the favorable safety and pharmacokinetic results in the phase I clinical study, the

subsequent phase II and III clinical studies targeting Japanese patients with ALS (study ID #E0302-J081-761) were conducted by Eisai Co, Ltd, hereinafter referred to as Eisai [9]. In that study, patients who were diagnosed with definite, probable, or probable-laboratory-supported ALS using revised El Escorial criteria within three years after symptom onset were enrolled and randomly assigned to receive placebo, E0302 (methylcobalamin) 25 mg, or E0302 50 mg intramuscularly twice weekly for 182 weeks. Primary endpoints were event-free survival (ie, time until death, invasive respiratory support device, or all-day noninvasive respiratory support device) and ALSFRS-R changes. In their study, 370 patients were analyzed—placebo (n=123), E0302 25 mg (n=124), and E0302 50 mg (n=123). Results showed that the E0302 25 mg and 50 mg groups had a tendency to surpass the placebo group with respect to ALSFRS-R total score as one of the primary endpoints, but did not go as far as indicating statistical significance.

In another study, 144 patients who were given a diagnosis of ALS within 12 months after symptom onset were analyzed—placebo (n=48), E0302 25 mg (n=54), and E0302 50 mg (n=42) [10]. The median event-free survival was 570 days, 1087 days, and 1197 days, respectively, which was prolonged in a dose-dependent manner (E0302 25 mg hazard ratio 0.64, 95% CI 0.38-1.09; E0302 50 mg hazard ratio 0.50, 95% CI 0.27-0.93; *P*=.01). In addition, ALSFRS-R changes were smaller in both E0302 groups (E0302 25 mg plus E0302 50 mg, *P*=.003; E0302 50 mg, *P*=.01) [10]. Although this observation was noted only in the results of the subpopulation analysis, the fact that high-dose methylcobalamin showed high efficacy in patients with ALS who were diagnosed early and registered in the study is considered clinically significant.

In this study, the incidence of adverse events was high, but the incidence of adverse reactions was limited. No obvious difference was observed between the placebo, the E0302 25 mg, and the E0302 50 mg groups in the occurrence of adverse events or reactions and there was no issue with the safety of intramuscular administration of E0302 25 mg or E0302 50 mg. One case of death by cardiac arrest was observed as a serious adverse reaction in the E0302 50 mg group, which was determined to be “possibly related” to the investigational product, since this association cannot be completely ruled out.

Based on the results of the phase II and III clinical studies conducted by Eisai, we planned to conduct an investigator-initiated trial to confirm the efficacy and safety of E0302 50 mg for treatment of ALS patients within one year after onset. In this trial, we adopted the updated Awaji criteria for the first time in the world, to our knowledge, which has displayed higher sensitivity compared to the El Escorial/revised Airlie House diagnostic criteria [11]. We adopted the updated Awaji criteria because we needed to increase the registration rate as much as possible, due to the enrollment of the early-stage patients. Our primary endpoint was the variation in the ALSFRS-R total score from allocation day to 16 weeks of treatment.

Methods

Trial Design Overview

This Japanese early-stage trial of high-dose methylcobalamin for ALS (JETALS) is a multicenter, randomized, placebo-controlled, double-blind, parallel-group comparative study. It comprises three study periods: observation, treatment, and continuing administration (see Figure 1). The eligibility of participants who registered for the observation period will be determined at the end of the 12-week observation period. Those confirmed as eligible will be registered in the treatment period and allocated to the placebo group or the E0302 50 mg group through dynamic allocation.

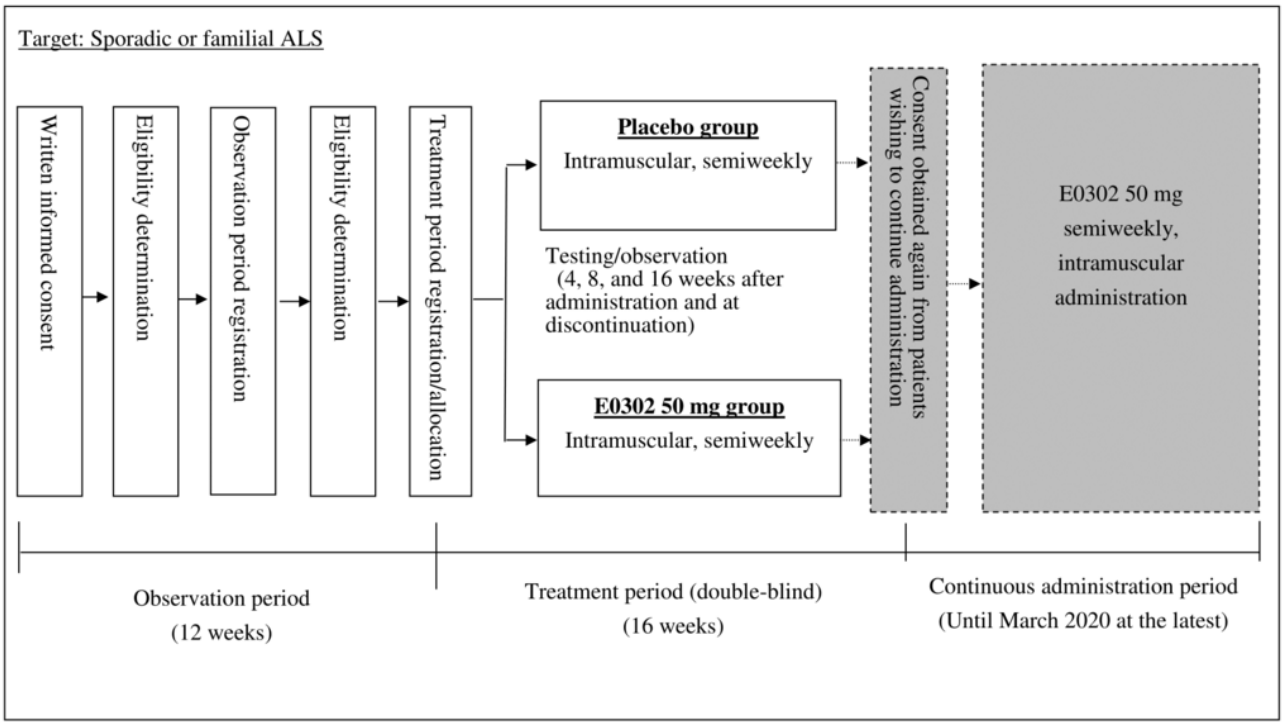
Randomization will be performed using a central registration system. Allocation will be done using a modification of the minimization method, which is a dynamic allocation method used to avoid selection bias in medical institutions. The investigational product will be allocated according to the patient registration sequence, taking into consideration the following characteristics: disease type (ie, bulbar onset, upper-limb onset, and lower-limb onset); ALS severity at the end of the observation period (ie, grade 1 or 2 according to Japan ALS severity classification, which ranges from grade 1 to 5, with grade 5 being the most severe); time from symptom onset to the start of the observation period (ie, ≤9 months or >9 months and ≤12 months); forced vital capacity (FVC) at the end of the observation period (ie, <90% or ≥ 90%), and edaravone administration history (ie, no or yes). These patient characteristics will be used as the allocation adjustment factors (ie, minimization factors) in consideration of the balance of groups within each facility and the overall balance.

E0302 50 mg or placebo will be intramuscularly administered twice weekly from the administration start date until the end of the 16-week treatment period. Investigational product administration and its efficacy, safety, and ALSFRS-R assessment will be conducted by various independent personnel to ensure as much blinding as possible during the treatment period. The efficacy, ALSFRS-R, and safety assessors will conduct necessary assessments at 4, 8, and 16 weeks after the start of investigational product administration, as well as at the time of event onset and at the time of discontinuation. All ALSFRS-R assessors underwent an ALSFRS-R training program, following the procedure manual made for this study.

The primary endpoint is a variation in the ALSFRS-R total score from allocation day until week 16 of treatment. Safety endpoints are adverse events, laboratory test results, electrocardiogram measurements, and vital sign measurements.

Subjects who wish to continue administration after week 16 of treatment will be transferred to the continuing administration period and they may continue treatment with E0302 50 mg until March 2020 at the latest. Independent assessment will not be necessary during the continuing administration period as investigators will conduct safety and efficacy assessments. The patients’ self-administration and the administration by their families and home-visit nurses at their homes will also be allowed in the continuing administration period.

Figure 1. Schematic depiction of the trial design. The study is composed of three periods: the observation period, treatment period, and continuous administration period. ALS: amyotrophic lateral sclerosis; E0302: methylcobalamin.



Eligibility Criteria

Target patients are those who were diagnosed with sporadic or familial ALS corresponding to the categories of definite, probable, or probable-laboratory-supported in the updated Awaji criteria (see Table 1) [11]. Inclusion and exclusion criteria are listed in Textbox 1; patients who satisfy all of the criteria will be included.

Patients will be considered as eligible participants according to the following: those who satisfied inclusion criteria 1-4, 6, and 7 when the observation period started; those who satisfied inclusion criteria 3 and 5-7 when the observation period was completed; those who did not meet any of the exclusion criteria when the observation period started; and those who did not meet exclusion criteria 1-4, 7-11, 13, and 14 when the observation period was completed.

Interventions

During the treatment period, the patients will be administered with E0302 50 mg/day, or a placebo intramuscularly twice weekly. During the continuous administration period, patients will be administered with E0302 50 mg/day, depending on each patient's request.

Outcomes

The primary endpoint is a variation in the ALSFRS-R total score from allocation day until week 16 of the treatment period. The secondary endpoints are the time from allocation day until the onset of an event (ie, 24-hour use of noninvasive respiratory support equipment, use of invasive respiratory support, or death) as well as variation in FVC, blood homocysteine concentration, the manual muscle test total score, grip strength (both left and right), the Norris scale total score, and the Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40) total score. The safety endpoints are adverse events, laboratory test results, electrocardiogram measurements, and vital sign measurements.

The endpoints during the continuing administration period are the time from allocation day until the onset of an adverse event (ie, 24-hour use of noninvasive respiratory support equipment, use of invasive respiratory support, or death) as well as variation in the ALSFRS-R total score, laboratory test results, electrocardiogram measurements, vital sign measurements, and adverse events.

Sample Size and Trial Duration

The target number of subjects is 128—placebo group (n=64) and E0302 50 mg group (n=64). In the previous study (ie, study ID #E0302-J081-761), the difference in the ALSFRS-R total score was estimated using data from a subpopulation of patients who were within one year of symptom onset when the observation period started and whose ALSFRS-R total score decreased by 1-2 points during the observation period (ie, 12 weeks) [10]. Based on the results of this subgroup analysis, we hypothesized that the E0302 50 mg group's score would exceed that of the placebo group by the difference in the ALSFRS-R total scores. The required number of subjects to set the type I error probability to ≤2.5% in the one-sided tests and to set the statistical power to ≥80% was a minimum of 60 patients per group, based on the subgroup population result. Considering that there will be discontinuations during the study, the target number of patients for this study was determined to be 64 patients per group.

The planned patient registration period is from October 2017 to September 2019; the planned study implementation period is from October 2017 to March 2020.

Table 1. Updated Awaji criteria.

Diagnosis grade	Criteria
Definite	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in the bulbar region and in at least two spinal regions or three spinal regions
Probable	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in at least two regions, with some upper motor neuron signs necessarily rostral (above) to lower motor neuron dysfunction
Probable-laboratory-supported	Clinical signs of upper and lower motor neuron dysfunction in one region together with neurophysiological evidence of lower motor neuron dysfunction in two regions
Possible	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in one region or upper motor neuron signs evident in two regions or lower motor neuron dysfunction evident rostral (above) to upper motor neuron signs

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria:

1. Patients from whom written consent to participate in this study was received

2. Patients who are ≥20 years of age at the time of providing informed consent

3. Patients diagnosed with sporadic or familial amyotrophic lateral sclerosis (ALS) corresponding to the categories of definite, probable, or probable-supported in the updated Awaji criteria

4. Patients who are within one year of symptom onset when the observation period started

5. Patients whose ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) total score has decreased by 12 points during the observation period (12 weeks)

6. Patients who are rated as 1 or 2 according to Japan ALS severity classification (grade 1-5, grade 5 most severe)

7. Patients seen on an outpatient basis

Exclusion criteria:

1. Patients who have undergone a tracheostomy

2. Patients who are using a noninvasive respiratory support device

3. Patients with ≤60% forced vital capacity

4. Patients with chronic obstructive pulmonary disorder

5. Patients with vitamin B12 deficiency-based neurological symptoms

6. Patients who have received edaravone within four weeks prior to observation period registration

7. Patients who have started riluzole, changed the dosage, or discontinued the medication after giving informed consent

8. Patients with cognitive impairment

9. Patients who are or may be pregnant

10. Patients with a serious respiratory disorder, cardiovascular disease, or liver or kidney disease

11. Patients with a malignant tumor

12. Patients who have participated in another trial within the 12 weeks prior to giving informed consent

13. Patients with current illness or those with a history of drug allergy or severe allergic disease (anaphylactic shock)

14. Patients who are determined to be unsuitable for this study by the investigator or subinvestigator

Statistical Considerations

The analysis sets for efficacy analysis are *full analysis set* and *per protocol set*. Full analysis set includes subjects who received the investigational product at least one time; this is the primary analysis set. Per protocol set is the secondary analysis set for confirming consistency of the results obtained from full analysis set from a sensitivity analysis standpoint. The *safety analysis set* refers to the set of subjects registered for the treatment period, excluding those who have no assessable safety data.

For the analysis of the primary endpoint, the difference in the ALSFRS-R scores from allocation day to each time point is the response variable; the administration groups, time points, minimization factors, and interaction between the administration groups and time points are the fixed effects. The ALSFRS-R total score on allocation day is the covariate and fits the linear model—Mixed-Model Repeated Measure analysis—with an unstructured covariance structure of the error variance. If the lower limit of the 95% confidence interval of the least mean square is over zero for the difference in the variation in the

ALSFRS-R total scores at week 16 when comparing the placebo and E0302 50 mg groups, then it will be determined to be statistically significant. The significance level of the efficacy endpoints is set at one-tailed 2.5%.

Ethics and Dissemination

The study protocol was approved by the Institutional Review Board at each site before the start of the trial. Substantial amendments of the study protocol must be approved by each Institutional Review Board. The trial was registered at ClinicalTrials.gov (NCT03548311) and the University Hospital Medical Information Network clinical trials registry (UMIN000029588). Written informed consent will be obtained directly from each patient.

Results

This study began in October 2017 and is being conducted at 24 participating institutions in Japan. The study is in progress and the patient enrollment period is scheduled to end in August 2019, with follow-up scheduled to end in March 2020.

Discussion

JETALS is a study that aims to verify the superiority of high-dose E0302 (methylcobalamin, 50 mg) intramuscular administration over placebo and to examine its safety in patients with ALS using the Japanese version of the ALSFRS-R as an indicator. Two revisions were made to the protocol of a previous study (study ID #E0302-J081-761), which was conducted as a preliminary study, targeting patients with ALS who were within one year of symptom onset.

The first revision changed the primary endpoint to a variation in the ALSFRS-R total score from allocation day to week 16 of treatment. The ALSFRS-R is a clinical assessment scale created to objectively and quantitatively assess the progress of patients with ALS. This scale can be used to clinically assess the motor function of the extremities, bulbar function, and respiratory function disorders. The ALSFRS-R score is frequently used as the primary endpoint in recent clinical studies targeting ALS. Because the ALSFRS-R is highly reliable for assessing ALS clinical symptoms using both the total score and item scores, and it can be used in clinical assessments, a variation in the ALSFRS-R total score was selected as the primary endpoint of this study [12]. Variations between different assessors may be minimized by having each assessor master the scale in advance through a training program. In our previous study (study ID #E0302-J081-761), the ALSFRS-R scores were evaluated at 4 and 16 weeks. For the patients who were given a diagnosis of ALS within 12 months after symptom onset, we predicted that after 16 weeks of treatment, it would be possible to detect a significant difference (data not shown). In addition, the ratio of ALSFRS-R scores between first symptom and first examination, during whole disease or within 100 days, correlates with survival time [13], hence the ALSFRS-R score at 16 weeks is thought to be a clinically important predictive factor of survival time. That is why we set the period of primary outcome evaluation at 16 weeks, from the points of view of effectiveness and ethics.

The second modification was changing the diagnostic criteria from the El Escorial/revised Airlie House diagnostic criteria to the updated Awaji criteria. The El Escorial/revised Airlie House diagnostic criteria are widely accepted, but their low diagnostic sensitivity has been considered an issue [14]. The reason for this low sensitivity can be attributed to the few cases in which widespread denervation is triggered in the early phase. In addition, another disadvantage of the El Escorial/revised Airlie House diagnostic criteria is that fasciculation potential, which is observed in the early phase of ALS, is not included in the electrodiagnostic criteria. The updated Awaji diagnostic criteria are advocated as an algorithm for combining the Awaji electrodiagnostic criteria and the El Escorial/revised Airlie House diagnostic criteria without variance [11]. In other words, the same framework as the El Escorial/revised Airlie House diagnostic criteria is maintained (ie, definite, probable, probable-laboratory-supported, and possible) and fasciculation potential is included as evidence of active denervation.

Geevasinga et al examined the testing sensitivity of each set of diagnostic criteria for 881 patients with ALS from 8 articles reported previously [11]. Data from 7 out of these 8 (88%) articles indicated that applying the updated Awaji diagnostic criteria over the El Escorial/revised Airlie House diagnostic criteria increased sensitivity, implying that the updated Awaji diagnostic criteria are definitely more advantageous.

This study targeted patients with ALS who were within one year of onset. Therefore, we used the updated Awaji diagnostic criteria, with its increased diagnostic sensitivity. Effects on efficacy assessment when using diagnostic criteria that differs from that used in the previous study needed to be confirmed. To this end, an analysis was conducted that narrowed down subpopulations corresponding to clinically definite, probable, and probable-laboratory-supported ALS based on the El Escorial/revised Airlie House diagnostic criteria. This was done when the observation period was completed and the effect of the criteria on the primary endpoint was examined.

Currently, only riluzole and edaravone have been approved as treatment drugs for ALS worldwide, but their effects are limited. As with the results of the subpopulation analysis, E0302 prolonged event-free survival more than 600 days and slowed the advance of the ALSFRS-R total score by 3.3 during 16 weeks; its safety and tolerability was well-established in the previous study [10]. Therefore, E0302 is highly anticipated as a new drug for treating ALS. E0302 can be used not only for monotherapy, but for multitherapy with riluzole and edaravone, which could change the strategy of ALS treatment.

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Conflicts of Interest

The investigational product is provided by Eisai Co, Ltd.

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Abbreviations

ALS: amyotrophic lateral sclerosis
ALSAQ-40: Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
E0302: methylcobalamin
FVC: forced vital capacity
JETALS: Japanese early-stage trial of high-dose methylcobalamin for ALS

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Protocol

Evaluating the Effectiveness and Safety of the Electroencephalogram-Based Brain-Machine Interface Rehabilitation System for Patients With Severe Hemiparetic Stroke: Protocol for a Randomized Controlled Trial (BEST-BRAIN Trial)

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Abstract

Background: We developed a brain-machine interface (BMI) system for poststroke patients with severe hemiplegia to detect event-related desynchronization (ERD) on scalp electroencephalogram (EEG) and to operate a motor-driven hand orthosis combined with neuromuscular electrical stimulation. ERD arises when the excitability of the ipsi-lesional sensorimotor cortex increases.

Objective: The aim of this study was to evaluate our hypothesis that motor training using this BMI system could improve severe hemiparesis that is resistant to improvement by conventional rehabilitation. We, therefore, planned and implemented a randomized controlled clinical trial (RCT) to evaluate the effectiveness and safety of intensive rehabilitation using the BMI system.

Methods: We conducted a single blind, multicenter RCT and recruited chronic poststroke patients with severe hemiparesis more than 90 days after onset (N=40). Participants were randomly allocated to the BMI group (n=20) or the control group (n=20). Patients in the BMI group repeated 10-second motor attempts to operate EEG-BMI 40 min every day followed by 40 min of conventional occupational therapy. The interventions were repeated 10 times in 2 weeks. Control participants performed a simple motor imagery without servo-action of the orthosis, and electrostimulation was given for 10 seconds for 40 min, similar to the BMI intervention. Overall, 40 min of conventional occupational therapy was also given every day after the control intervention, which was also repeated 10 times in 2 weeks. Motor functions and electrophysiological phenotypes of the paretic hands were characterized before (baseline), immediately after (post), and 4 weeks after (follow-up) the intervention. Improvement in the upper extremity score of the Fugl-Meyer assessment between baseline and follow-up was the main outcome of this study.

Results: Recruitment started in March 2017 and ended in July 2018. This trial is currently in the data correcting phase. This RCT is expected to be completed by October 31, 2018.

Conclusions: No widely accepted intervention has been established to improve finger function of chronic poststroke patients with severe hemiparesis. The results of this study will provide clinical data for regulatory approval and novel, important understanding of the role of sensory-motor feedback based on BMI to induce neural plasticity and motor recovery.

Trial Registration: UMIN Clinical Trials Registry UMIN000026372; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030299 (Archived by WebCite at http://www.webcitation.org/743zBJj3D)

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KEYWORDS

brain-computer interfaces; neurofeedback; neural plasticity; electroencephalography; hemiplegia; electric stimulation; robotics

Introduction

Background

Stroke is a common disorder and one of the main causes of disability worldwide [1]. Although about 60% of stroke survivors reacquire the ability to walk independently, only 15% to 20% of them can use their affected upper limb practically [2-4]. Therefore, restoring the function of the paretic upper extremity is a challenging goal of rehabilitation.

Recent advances in neuroscience have shown that the adult human brain has a larger degree of plasticity to recover from neural damage than previously thought [5,6]. Clinically relevant interventional approaches to improve the paretic limb itself have been developed. A systematic review based on a meta-analysis of the effectiveness of neurorehabilitation approaches reported that constraint-induced movement therapy (CIMT), electromyographic biofeedback, mental practice with motor imagery, and robotic interventions are all favorable for recovery of arm motor function [7].

Although recent improvements in rehabilitation have succeeded in promoting functional recovery from poststroke hemiplegia, no effective interventions have been established for finger motor function [7]. The standardized mean difference in motor outcomes in the above-mentioned interventions is all around zero without statistical significance. Therefore, an important clinical challenge is development of a rehabilitation method for recovery of finger function.

Brain-machine interface (BMI) is a type of technology that can detect increased sensorimotor cortex excitability induced by a motor attempt of paretic finger extension. The sensorimotor rhythm (8-13 Hz) in electroencephalograms (EEGs) over the affected primary sensorimotor cortex decreases in amplitude because of desynchronization of oscillatory-coupled neural membrane potentials, called event-related desynchronization (ERD), when cortical excitability is increased. Therefore, EEG-ERD associated with an attempt of volitional movement of the paretic finger guarantees recruitment of the remaining sensorimotor cortical neurons, which are required for functional motor recovery. Somatosensory stimulation of the paretic finger, given through motor-driven hand orthosis and neuromuscular electrical stimulation (NEMS), is contingent on the occurrence of EEG-ERD and may allow sensorimotor coactivation that is restricted to the target corticomuscular region. This should help selective reinforcement of the targeted finger movement. Studies with healthy volunteers showed that motor imagery with BMI modulates intracortical inhibition of the primary motor cortex [8] and excitability of spinal anterior horn cells [9]. These findings suggested that BMI affects not only the sensorimotor cortex but also the entire corticospinal pathway.

Shindo et al reported that finger motor function of chronic, severe hemiparetic patients improves after 12 to 20 sessions of motor exercise with a BMI system for 1 hour [10]. Other studies with functional magnetic resonance imaging revealed that cortical activity of the affected sensorimotor cortex during execution of paretic finger movement is enhanced after BMI rehabilitation, whereas that of other regions, such as the unaffected sensorimotor cortex, is reduced [11,12]. These studies suggest that motor exercise with BMI promotes volitional recruitment of surviving motor pathways and facilitates paretic muscle activity. Such BMI-derived functional recovery is enhanced by combination with anodal transcranial direct current stimulation (tDCS), a known agent of increased neural plasticity of the central nervous system [13], suggesting that central nervous system neuroplastic changes may play a role in the process of BMI-derived functional recovery.

Improvement in the Fugl-Meyer assessment upper extremity motor function (FMA-UE) score was larger than minimum clinically important differences (MCID) of FMA-UE (4.25) [14] in both patients trained with BMI alone and patients trained with BMI with tDCS [13]. In a recent clinical study of patients with severe hemiparesis, improvement in FMA-UE was an average of 3.4 points after robot training [15]. Thus, BMI training can improve upper extremity function in patients with severe hemiparesis to a clinically meaningful level.

Japanese guidelines for the management of stroke 2015 (JGMS 2015) [16] and the American Heart Association/American Stroke Association (AHA/ASA) guideline [17] recommend certain rehabilitation techniques. CIMT improves upper extremity function [18] and is recommended by both JGMS 2015 [16] and the AHA/ASA guideline [17]. However, voluntary movement of fingers and the wrist is essential to perform CIMT, and whether CIMT has any advantage over dose-matched conventional rehabilitation is unclear. CIMT requires a well-trained therapist and high-dose training, which is 3 to 6 hours per day for 2 weeks in its original form.

NEMS is also recommended by the guidelines [16,17]. Electromyogram (EMG)-triggered NEMS is effective for patients with moderate hemiparesis who can voluntarily move their upper extremity [19]. In addition, hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy is a

combination of hand splints and 8-hour daily use of assistive NEMS, referred to as the integrated volitional electrical stimulator (IVES) with a hand splint. [20-22]. HANDS therapy can improve hand function in patients with more severe hemiparesis than what is approved for CIMT. However, HANDS therapy requires finger extensor EMG that can be detected by the IVES device. On the other hand, BMI rehabilitation can be used in patients who are not able to activate their paretic finger extensor at all. HANDS therapy following BMI training induces additional improvement in paretic upper limb function in patients who obtain improvement in extensor muscle activities with BMI training [22].

The repetitive facilitative exercise (RFE) program is a new rehabilitation method that is a combination of high-frequency repetitive voluntary movements and neurofacilitation [23]. RFE improves the function of paretic upper extremities in subacute stroke patients. However, RFE can be used in patients with only mild to moderate hemiparesis, and special skills are required.

Noninvasive brain stimulation methods, such as repetitive transcranial magnetic stimulation and tDCS, are used in patients with mild to moderate hemiparesis, and the effectiveness of the combination of brain stimulation and intensive upper limb rehabilitation has been reported in several studies [24-26]. However, no methods have been established for use of brain stimulation of hemiplegic patients [25], and application of these methods in poststroke patients requires safety considerations [27,28].

Robotic therapy is recommended for consideration in patients with moderate to severe hemiparesis according to the AHA/ASA guideline [17]. A systematic review found that robotic therapy improves arm function [29]. However, whether robotic therapy is more effective than dose-matched conventional upper limb exercise therapies is uncertain [17].

Study Objectives

A systematic review and several guidelines [7,16,17] showed that some types of interventions (such as CIMT, EMG biofeedback, NEMS, mental practice, and robotics) can improve paretic arm function. However, no rehabilitation method has been verified to be effective for improving paretic hand function. Therefore, we planned a randomized controlled trial (RCT) to evaluate the effectiveness and safety of an intensive rehabilitation program using the EEG-based BMI rehabilitation system for patients with severe hemiparetic stroke.

Methods

Study Design

This is a single-blinded, multicenter RCT using a parallel arm design to evaluate the effectiveness and safety of 2-week BMI rehabilitation combined with intensive occupational therapy compared with motor imagery without any feedback and dose-matched occupational therapy. Overall, 4 hospitals in Japan participated in this trial. Patients were randomly assigned to either the BMI group or control group. The assessors were blinded, but patients were not. The primary outcome measure was change in upper extremity score of FMA between baseline and 4 weeks after the intervention.

Participants and Recruitment

The inclusion criteria were (1) time from stroke onset to be more than 90 days; (2) first ever stroke patients with upper extremity paresis; (3) no loss of proprioception in paretic fingers (patients able to detect a position change after maximum possible motion); (4) ability to raise the paretic hand to the height of the nipple; (5) passive range of motion greater than −10 degrees for metacarpophalangeal joint extension; (6) ability to flex the paretic fingers voluntarily but not to extend them; (7) ability to walk independently in daily life with or without assistance; (8) ability of the patient to understand and consent to the study protocol; and (9) aged 18 years or older at the time of agreement to participate in this study. The exclusion criteria were (1) serious medical conditions that would interfere with rehabilitation such as severe heart disease, uncontrolled hypertension, history of pulmonary embolism, acute pulmonary heart disease or severe pulmonary hypertension within 90 days before enrollment, severe hepatic or renal dysfunction, severe orthopedic impairment, severe cognitive or psychiatric disorder, and other serious medical conditions; (2) pacemaker or use of other implanted stimulators; (3) history of seizures within 90 days before enrollment; (4) participation in another clinical trial for regulatory approval within 90 days before enrollment; (5) receiving other special neurorehabilitation techniques for upper extremity paresis such as transcranial magnetic stimulation, therapeutic electrical stimulation, CIMT, and repetitive facilitative exercise within 90 days before enrollment; (6) injection of botulinum toxin or phenol for treatment of upper-limb spasticity within 90 days before enrollment; (7) impossible to record EEG because of skin status or skull deformity; or (8) other critical problems that would affect participation in the study.

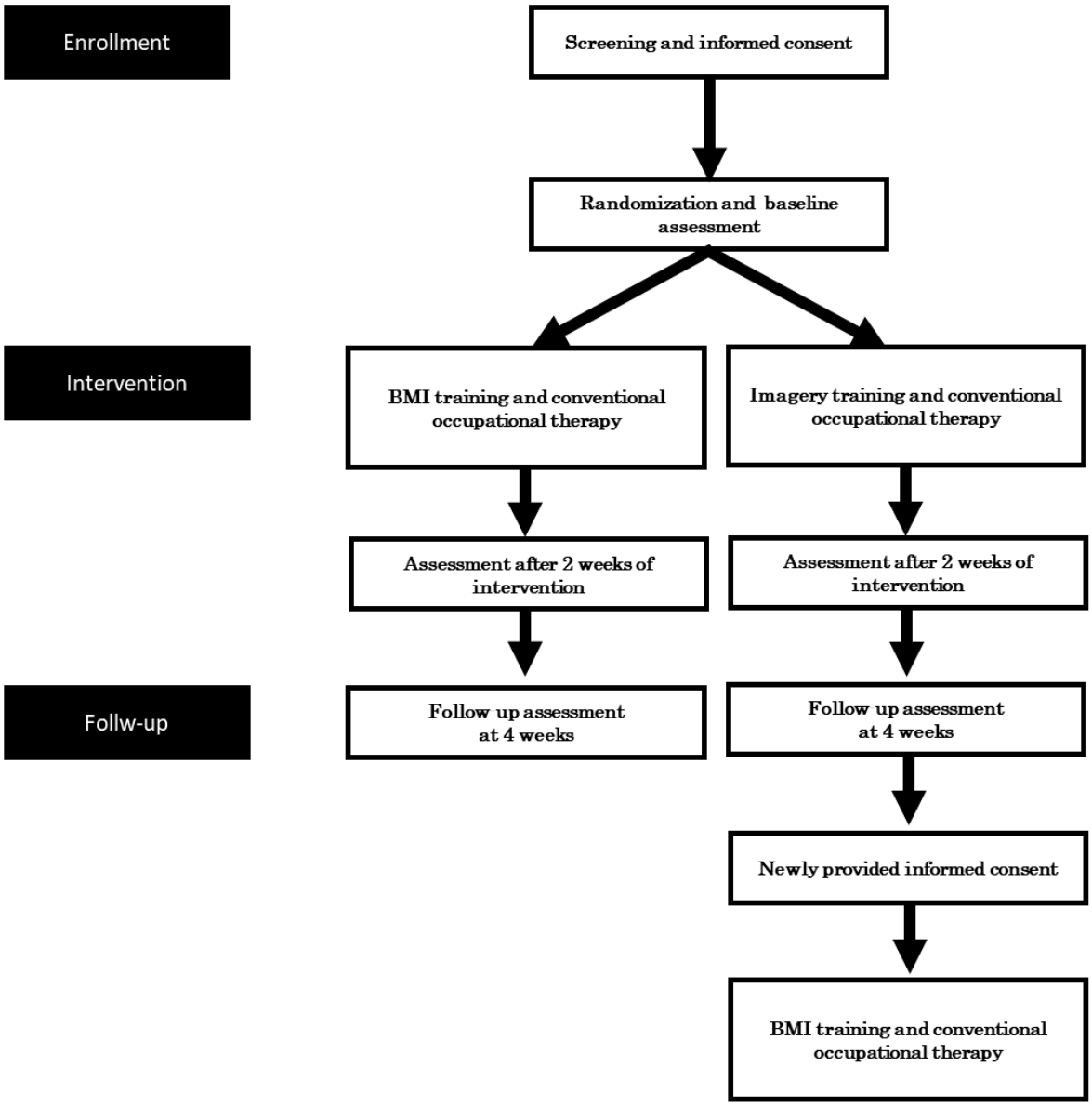
Prospective participants were recruited from outpatients of the rehabilitation department in Keio University Hospital, Saiseikai Kanagawa-ken Hospital, Tokyo Metropolitan Rehabilitation Hospital, and Tokyo Bay Rehabilitation Hospital. The recruiting physiatrists screened the participants for eligibility. We obtained written informed consent from patients who met all inclusion criteria and did not meet any exclusion criteria except exclusion criterion 7. The patients then tried the BMI system to check the skin status and rule out a skull deformity. If EEG could be recorded, the patient was registered as an eligible and consenting participant. Then they completed the baseline assessment. Treatment started within 28 days after registration.

Study Procedures

Study procedures are summarized in the Consolidated Standards of Reporting Trials diagram (Figure 1).

After follow-up assessment, participants allocated to control group received the same BMI training that would be conducted for participants allocated to BMI group if they wished and had newly provided informed consent. This BMI training started within 60 days after follow-up assessment.

Figure 1. Study design. BMI: brain-machine interface.



Randomization

Participants were randomly allocated to the BMI or the control group using a computerized block randomization scheme, including prestratification according to each participating hospital.

Blinding

The rater was blinded to treatment allocation, and the rater was not involved in the participants' treatment. The blinded rater assessed FMA [30-36]. Rater blinding was verified with a yes or no question: Did you rate the assessment score blindly? Participants were not blinded to their own treatment.

Intervention

Brain-Machine Interface Training

Electroencephalogram Recording

An Ag-AgCl electrode (ϕ=9 mm) for EEG measurement was placed over the ipsi-lesional sensorimotor cortex, namely, C3 (for the left hemisphere) or C4 (for the right hemisphere) according the international 10-20 system. An additional electrode was placed 20 mm lateral to C3 or C4. A ground electrode was placed on A1, and the reference electrode was placed on A2 (ipsilateral to the lesioned hemisphere). All electrodes were guided manually and fixed with a custom-made headset. The application-specific integrated circuit–based analog circuit and microprocessor were embedded inside the headset, and 2-channel EEGs were derived in a monopolar manner and processed with ×1200 amplification and 0.21- to 199-Hz filtering. The processed EEG signals were digitized at 200 Hz

with 12 bits (least significant bit 0.366 μV). Note that a notch filter of 50 Hz was used to minimize the power-line noise. EEGs were then transmitted to a laptop using a Bluetooth 3.0 wireless protocol and were subtracted from each other to derive a bipolar EEG. A 2 Hz to 50 Hz bandpass filter with a 50 Hz notch was again used to reduce noise contamination.

A 1-second time-sliding Hanning window was applied to this bipolar EEG signal with 87.5% overlap, and fast Fourier transform was applied to obtain the time-varying power spectrum of the signal. The two-dimensional (2D) feature vector with mean alpha frequency band power (7-13 Hz) and mean beta frequency band power (14-26 Hz) was constructed at each time segment and traced with time in the feature space. The discriminant line that determines EEG feature vectors as in either the *ERD* or *baseline* class was used for EEG labeling. The discriminant line was calibrated for each participant every day before the training session (see also Calibration section below).

Calibration

At the beginning of the BMI training, 10 trials of the cue-based motor task were conducted as a rehearsal, and the parameters in the linear discriminant analysis (LDA) for EEG-ERD detection in the BMI were calibrated using the obtained data. During the rehearsal, a 5-second resting period was first given and a text cue of either “attempt paretic finger extension” or “keep relaxing” was then displayed on the top of the computer screen. The participants performed the given cued task for the next 5 seconds. In total, 10 trials per class were given in a randomized order. A 2D feature vector with mean alpha frequency band power (7-13 Hz) and mean beta frequency band power (14-26 Hz) was obtained from a 1-second time-sliding Hanning window with 87.5% overlap. The feature vectors with annotations of either “attempt paretic finger extension” or “keep relaxing” were mapped onto the feature space, and the parameters in the LDA algorithm were optimized to separate the features into appropriate classes. Consequently, the LDA in the BMI training returned a value of *+1* (resting) or *−1* (finger extension) every 125 ms according to the EEGs.

Estimation of Sensorimotor Cortex Excitability From Electroencephalogram

Alpha and beta frequency band powers in EEG recorded over the sensorimotor cortex are analogs of sensorimotor cortex excitability [37]. EEG-ERD of these powers is also correlated with corticospinal tract excitability, disinhibition of gamma-aminobutyric acid-ergic intracortical inhibitory circuits [8], and spinal anterior horn cell excitability [9]. Extrapolation of these findings to poststroke patients with hemiplegia may be acceptable because ERD during paretic hand motor imagery is associated with ipsi-lesional corticospinal tract excitability in poststroke patients with hemiplegia [38]. Alpha frequency oscillation and its resonance among cortical and subcortical regions in poststroke patients with hemiplegia predicted motor outcome, suggesting that the alpha component is related to sensorimotor function. Recent clinical studies with BMI intervention also suggest that up-conditioning of EEG alpha and beta band frequency powers and their ERD during motor attempting of paretic finger opening through BMI training is associated with increased corticospinal tract excitability [10] and the blood oxygen level-dependent signal of magnetic resonance imaging in the ipsi-lesional sensorimotor cortex [11,12]. Repeated use of BMI that forces patients to increase alpha and beta frequency powers at rest and decrease their power during paretic hand motor attempting is, therefore, interpreted as neurorehabilitative training of the remaining corticomuscular pathway on the ipsi-lesional side.

Task-Specific Brain-Machine Interface Training

BMI training was conducted for approximately 40 min per session, 1 session per day, and 5 days per week, for 2 weeks.

The motor-driven orthosis was attached to the affected hand to achieve finger extension movement at the metacarpophalangeal and proximal interphalangeal joints. The orthosis was designed to remedy the finger position as the fingers arched with the thumb opposed, helping patients to hold or release objects. The thumb opposition position also helps maintain decreased flexor spasticity. The range of the angle in the orthosis action was adjusted by the examiner to avoid pain and spasticity. During the training, the motor-driven orthosis helped finger extension by a predetermined angle with 1659 Nmm at maximal torque. This setting allowed patients to perform task-specific training with BMI in a real-world setting.

A pair of disposable electrodes (25 × 45 mm) for electrical stimulation was placed over the belly of the paretic extensor digitorum communis muscle. Test stimulation (biphasic rectangular wave, pulse width of 1 ms, and frequency of 100 Hz) was then given, and the intensity was set at just above the motor threshold. Note here that this is a known intensity for recruiting Ia proprioceptive afferents of the stimulating muscle. Such NEMS of the target muscle of motor imagery contingent upon the occurrence of ERD may allow sensorimotor coactivation to be restricted to the target corticomuscular region and may foster plasticity and motor learning [39]. This should further help to selectively reinforce the sensorimotor representations.

The affected forearm was set on a balanced forearm orthosis. The participants sat in front of the desk, and 30 pegs were set on the desk peg board. Participants were asked to pick up a peg with the affected hand with the orthosis. After pinching a peg with the affected hand, participants pressed a button to start the preset BMI training sequence. As in the calibration session, 5 seconds of rest were first given, and a text cue of either “attempt paretic finger extension” or “keep relaxing” was then displayed on the top of the computer screen. The participants performed the given cued task for the next 5 seconds. The LDA-based EEG classifier returns either the value *+1* (EEG was at the resting condition) or *−1* (EEG-ERD) every 125 ms according to the EEGs and triggers the motor action of the orthosis and NEMS if a successive 1 second of the class *−1* is given in either cue of “attempt paretic finger extension” or “keep relaxing.” Note here that EEG-ERD-associated sensorimotor stimulation via the orthosis and electrical stimulation during attempting paretic finger extension function as positive reinforcers of the training. Patients tried to increase the probability of this condition through trial and error. The motor-driven orthosis and NEMS were not activated if EEG did not satisfy the criteria (even if participants

attempted finger opening). Repeated use of EEG-ERD-based BMI can, therefore, be interpreted as a reinforcer of the remaining corticomuscular pathway on the ipsi-lesional side.

Motor Imagery Training in the Control Group

Participants in the control group conducted the motor imagery training for approximately 40 min for 2 weeks, similar to the BMI training for participants in the BMI group. Participants wore the same headset as those in the BMI training, but they did not wear the hand orthosis. They were instructed to rest for 5 seconds and then to imagine extending their affected fingers for the next 5 seconds in the same manner, as those in the BMI training. At that time, the EEG was recorded in the same way as during the BMI training, but no feedback was given to the participants about the quality of the EEG. Neither passive movement or electrical stimulation was given during imagery.

Conventional Occupational Therapy

All participants received 40 min of standard occupational therapy per day, which consisted of gentle stretching exercises, active muscle re-education exercises, and introduction to bimanual activities in their daily lives.

Concomitant Care and Recommendation

During the 6-week period of intervention and follow-up, participants were asked not to undertake other specific intervention intending to improve hemiparesis (eg, CI therapy, NEMS, robotic rehabilitation, noninvasive brain stimulation) and botulinum toxin injection to hemiparetic upper limb. Moreover, they were asked not to change dose of antiepileptic agents, muscle relaxants, psychotropic agents, and anxiolytic agents. If participants were undertaking conventional occupational therapy before participating in this study, they were asked not to exceed the time and frequency of it during 30 days before intervention.

Intervention Fidelity and Monitoring of Adverse Events

Before beginning this study, treatment therapists were trained by a member of the research team with a high-level experience in BMI training for stroke patients. During the whole duration of the study, the members of the research team and research coordinator randomly visited training sessions, to ensure that scheduled intervention was being performed accurately and with high adherence to the protocol proposed. Any adverse unpredictable event was recorded in the registry of each patient and the electronic database of the study and managed according to the policies of the hospital, with referral appropriate medical follow-up.

Criteria for Withdrawal

Participants were withdrawn from the study in the event of any relevant deterioration in health likely to affect participation or if they withdrew their consent.

Outcome Measurement

Schedule of Assessment

The primary outcome measure was assessed by a blinded evaluator. Other functional measurements were assessed by evaluators who were trained by the organizer of this RCT. Most assessments were conducted at baseline, after intervention (post), and 4 weeks after intervention (follow-up). EEGs were recorded by the EEG-BMI rehabilitation system during each training session. The schedule of assessments is shown in Table 1.

Table 1. Schedule of assessments.

Time points and measure	Baseline	Intervention (10 sessions during 2 weeks)	Posttreatment	Follow-up (4 weeks after treatment)
Primary outcome measure				
Fugl-Meyer assessment	B[a]	—[b]	B	B
Secondary outcome measure				
Action Research Arm Test	E[c]	—	E	E
Motor Activity Log-14	E	—	E	E
Stroke Impairment Assessment Set	E	—	E	E
Modified Ashworth Scale	E	—	E	E
Barthel Index	E	—	—	E
Goal Attainment Scale	S[d]	—	—	S
Stroke-Specific Quality of Life Scale	S	—	—	S
Surface electromyography	EP[e]	—	EP	EP
Electroencephalography during brain-machine interface or imagery training	—	EP	—	—

[a]B: assessment of blinded evaluator.

[b]Dashes indicate "not applicable."

[c]E: assessment of well-trained evaluator.

[d]S: participant self-report.

[e]EP: electrophysiological data.

Primary Outcome Measure

Fugl-Meyer assessment Upper extremity motor function was assessed with the FMA (range 0-66 points, total score) [30,31]. FMA consisted of test A (shoulder/elbow/forearm: 36 points, A score), test B (wrist: 10 points, B score), test C (hand/finger: 14 points, C score), and test D (coordination: 6 points, D score). FMA was assessed according to the scoring manual [32], and the validity and reliability were previously confirmed [31,33].

The estimated clinically important difference of the FMA-UE scores ranged from 4.25 to 7.25 points in individuals with stable, mild to moderate upper extremity hemiparesis [34]. However, MCID for patients with severe hemiparesis remains to be shown. As a greater than 10% change in FMA motor scores may represent a clinically meaningful improvement based on clinical experience [35], MCID for severe hemiparesis may be lower than that for mild hemiparesis. A minimal detectable change of 3.2 points was reported in 31 patients with stroke [36].

Secondary Outcome Measures

Action Research Arm Test

Action Research Arm Test (ARAT) [40] is a frequently used, validated, and reliable measure of upper extremity function with 4 subsections: grip, grasp, pinch, and gross movement [41,42]. The maximum summed score is 57.

Motor Activity Log-14

Upper extremity disability in activities of daily living (ADL) was assessed with Motor Activity Log (MAL), which uses a structured interview [43]. MAL includes 14 items, scored on an 11-point amount of use scale (range 0-5) to rate how much the arm is used (MAL-amount of use) and an 11-point quality of movement scale (range 0-5) to rate how well the participants are using their affected upper extremity [43]. High construct validity and reliability have been reported in patients with chronic stroke [43,44].

Motor Scores of the Stroke Impairment Assessment Set

The Stroke Impairment Assessment Set (SIAS) is a comprehensive instrument for assessing stroke impairment with well-established psychometric properties [45,46]. SIAS assesses various aspects of impairment in stroke patients, including motor function, tone, sensory function, range of motion, pain, trunk function, visuospatial function, speech, and sound side function. Motor scores of the SIAS are composed of 5 items that assess arm, finger, hip, knee, and ankle functions and are rated from 0 (severely impaired) to 5 (normal).

Goal Attainment Scale

The Goal Attainment Scale (GAS) is a self-rating scale to evaluate subjective improvement following rehabilitation [47-50]. Patients rate the attainment level of the rehabilitation outcome for the goal that they set themselves. If the attainment is as expected, it is rated as 0. Improvement beyond expectation is rated +1 or +2 and that below expectation is rated −1 or −2.

Barthel Index

The Barthel Index (BI) is one of the most frequently used measures to evaluate ADL in stroke research [51,52]. BI measures independence in ADL; the maximum score is 100. The 10 assessed items of ADL are feeding, bathing, grooming, dressing, bowel control, bladder control, toilet use, transfers, mobility, and ascending and descending stairs.

Modified Ashworth Scale

Spasticity at the wrist and finger flexors of the affected upper extremity was assessed with the Modified Ashworth Scale (MAS), a 6-point rating scale used to measure passive muscle resistance [53].

Stroke-Specific Quality of Life Scale

The Stroke-Specific Quality of Life Scale (SS-QOL) was developed to assess health-related quality of life in stroke patients [54,55]. SS-QOL contains 49 items and covers 12 different areas of quality of life affected by stroke. The 12 areas of the SS-QOL are energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision, and work or productivity. Each area can be scored separately, but a total score is also available. The possible range of all scales is from 1 to 5, where a lower value indicates a lower health-related quality of life.

Surface Electromyography

The muscle activities of the paretic extensor digitorum communis and flexor digitorum superficialis muscles were recorded with Ag-AgCl surface electrodes with diameters of 9 mm (Nihon Kohden, Tokyo, Japan). The electrodes were applied with center-to-center spacing of 30 mm and were placed parallel to the muscle fibers and distal from the motor points of individual muscles. Before the electrodes were attached, the skin areas were rubbed with alcohol. Skin resistance was kept below 5 kΩ. An MEB-2300 EMG machine (Nihon Kohden) was used to record and analyze the EMG data. The bandpass filter was set at 20 Hz to 1 kHz. The patients were seated in a comfortable chair with their arms on an armrest and the angle of their elbows was kept at 70 to 90 degrees. They were instructed to rest for 5 seconds and then to extend their affected fingers for the next 5 seconds for 1 cycle. In total, 5 cycles of 5 seconds of rest and 5 seconds of extension were repeated.

Electroencephalogram During Brain-Machine Interface or Image Training

The EEGs during BMI or image training were recorded and stored in the EEG-BMI system. We compared the magnitude and duration of μERD between the BMI group and control group.

Statistical Analyses

The following 2 analysis populations are defined in this clinical trial. Statistical analyses were performed for each patient population.

The Full Analysis Set (FAS) essentially included all randomized patients, in accordance with the intention-to-treat principle, except for the following patients who violated major conditions in this study:

- Patients who did not meet major inclusion criteria in this trial
- Patients who did not receive any study treatment

- Patients who had no baseline measurements or no measurements after baseline
- Patients who withdrew informed consent after randomization and refused to generate any data in this trial

The Per Protocol Set (PPS) included patients who were compliant with the protocol and are defined in the patient-data handling document that will be finalized before the unblinding of this trial.

The primary analysis population in this trial is the FAS. The primary endpoint, a change from baseline in FMA at 28 days after study treatment, will also be analyzed for the PPS. The sensitivity of the primary analysis results will be examined via a comparison of results between the 2 analysis sets. All patients who received at least one study treatment are included in the safety analysis. The patient-data handling document, including the data handling rule for measurement at each time point, will be finalized before the unblinding. Methods to handle missing data will also be included in the statistical analysis plan (SAP) for this trial. Demographic factors and baseline characteristics are summarized by the treatment group.

Efficacy Analysis

Analysis of the Primary Endpoint

The primary endpoint of this trial is a change from baseline in the FMA at 28 days after study treatment. The superiority of the BMI group compared with the control group in terms of the primary endpoint will be demonstrated by means of an analysis of covariance model, which contains the baseline as a covariate and treatment group as a factor. Least squares means for the changes in treatment groups will be estimated and compared between the 2 groups. Missing data at 28 days after study treatment will be handled by multiple imputation, Rubin, which assumes missing at random as the missing data mechanism [56]. The details of the imputation model in the multiple imputation will be described in the SAP before the unblinding.

Analysis of Secondary Endpoints

For continuous endpoints, the same analysis model will be applied. For binary endpoints, 95% CIs for proportions by treatment groups will be estimated with the Clopper-Pearson method. The proportions of the 2 groups will be compared with Fisher exact test.

Safety Analysis

Adverse Events and Device-Related Problems

The safety primary endpoints in this study are proportions of adverse events and device-related problems. The number of events and the proportion will be calculated, and 95% CIs for the proportions will be estimated with the Clopper-Pearson method.

Sample Size Estimation

The total sample size in this trial was set at 40 patients (20 per group).

Rationale

The mean changes from baseline in the FMA at 28 days after study treatment are assumed to be 6.9 and 3.0 in the BMI and control groups, respectively, based on previous clinical studies [57,58]. The SD for the change is also assumed to be 4.0. Under these assumptions, 17 patients per group results in 80% power for testing the between-group difference in means with a two-sided 5% alpha. Taking into account 15% exclusions from the analysis, the target sample size in this trial was set at 20 patients per group (total of 40 patients).

Significance Level and Multiplicity

Significance levels for all tests in this trial are set at two-sided 5%, and confidence levels for all interval estimations are two-sided 95%. No multiplicity adjustment will be performed because this study has a single efficacy primary endpoint.

Interim Analysis

No interim analysis was conducted in this trial.

Change in Original Statistical Analysis Plan

All changes in the original SAP will be reported in the clinical study report for this trial.

Statistical Analysis Plan

The SAP for this study, which contains comprehensive details of data handling and statistical analysis methods, will be finalized before unblinding of this study.

Ethics and Dissemination

This study was conducted in accordance with Ministerial Ordinance on Good Clinical Practice for Medical Devices [59]. All participants provided voluntary written informed consent. Prospective participants were fully informed about what study participation involved and the potential benefits and risks. Ethics approvals had been obtained from the institutional review board of Keio University (protocol number: KCTR-D008, reference number: D16-03). In addition, for Saiseikai Kanagawa-ken Hospital, Tokyo Metropolitan Rehabilitation Hospital, and Tokyo Bay Rehabilitation Hospital, ethics approval had been obtained from the institutional review board of Saiseikai Kanagawa-ken Hospital (protocol number: KCTR-D008). Any protocol amendments will be submitted for ethical approval and communicated to the trial registry. The results of this study will be used to gain regulatory approval for the manufacture and sale of the medical device used in this study in Japan. After approval, the results will be presented at scientific meetings and published in journals.

Results

Recruitment started in March 2017 and ended in July 2018. This trial is currently in the data correcting phase. This RCT is expected to be completed by October 31, 2018.

Discussion

This multicenter RCT was designed to demonstrate the effect of EEG-BMI training compared with simple mental imagery on upper extremity function, including finger function, in poststroke patients with severe impairment of finger function. Although several neurorehabilitation approaches have shown clinically important improvements in arm function of poststroke,

hemiparetic patients, no intervention is widely accepted as effective treatment for improving finger function [7,16-18]. If this device is approved for manufacturing and sale by the Japanese government, it will be the first neurorehabilitation product targeting improvement of finger function. Clinically and scientifically, the results of this RCT will provide significant knowledge about the contribution of sensorimotor feedback to motor learning and recovery in poststroke patients compared with open-loop imagery.

Several studies have reported the effectiveness of rehabilitation using other BMI systems for chronic stroke patients with upper extremity paresis [58,60-63]. However, no device is approved as an official medical device. In addition, this trial will demonstrate that closed-loop sensory-motor feedback training with the EEG-BMI rehabilitation system can induce functional recovery and that this improvement will be maintained or will increase 4 weeks after the intervention, because the primary outcome is the change in FMA between baseline and follow-up 4 weeks after the end of the intervention. If rehabilitation induces plastic changes in the brain of chronic stroke patients, acquired recovery will be sustained or will increase in the several weeks following the intervention. On the other hand, the recovery will decrease if the effect of rehabilitation is transient. In this study, the control intervention is based on open-loop motor imagery training without any feedback. Therefore, the results of this RCT will provide several important suggestions about the mechanisms of the effect of closed-loop sensory-motor feedback training on neural plasticity in the damaged brain by comparing closed-loop feedback training using the EEG-BMI system with dose-matched, open-loop motor imagery training. This is a unique scientific point of view in this RCT compared with other studies of BMI rehabilitation.

In this RCT, we assess a sufficient number of functional measures of the upper extremity (such as ARAT, MAL, motor score of SIAS, and MAS), subjective satisfaction with the treatment (GAS), ADL (BI), and QOL (SS-QOL) to make the outcome of this RCT comparable with those of other trials. In addition, electrophysiological assessments (surface EMG and EEG during BMI training) will be adopted to elucidate the underlying mechanisms of improvement with BMI rehabilitation.

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Authors' Contributions

KM, TA, TO, KH, JU, MO, KO, TF, and ML contributed to the overall design of this study. KM, TA, MK, TO, KH, and JU wrote part of the draft. TA, in particular, contributed to planning of statistical analysis. JU, in particular, contributed to engendering of the EEG-BMI system. All authors revised the paper critically and approved the final version for publication.

Conflicts of Interest

ML and JU report a research agreement with Panasonic Corporation titled *Development and clinical application of advanced upper limb rehabilitation system based on EEG-BMI* during the conduct of the study. JU reports grants from the Japan Society for the Promotion of Science (16K01469; 15H05880; 23 · 01410) during the conduct of the study. ML and JU report grants from the Japan Agency for Medical Research and Development (13424858; 14528371) and grants from the Ministry of Education, Culture, Sports, Science and Technology (08001658; 09159054) during the conduct of the study. TF, JU, and ML report a grant from the Ministry of Health, Labor and Welfare (No. 12102976) during the conduct of the study.

In addition, JU has a patent (Japanese Patent No. 5283065) motor-related potential detection system, headset for its system, and system unit utilizing these components licensed to None; a patent (Japanese Patent No. 5813981) device aiming for electroencephalogram processing for rehabilitation and rehabilitation system licensed to None; a patent (Japanese Patent Pending No. P2015-205042A) rehabilitation device pending; a patent (PCT/JP2015/003271) control device for rehabilitation device and rehabilitation device pending; a patent (PCT/JP2015/003282; PCT/JP2015/003272) rehabilitation system and method for controlling rehabilitation system pending; biometric information processing method and program pending; a patent (Japanese Patent Pending No. 2017-204089) pseudo-electroencephalogram generation system and electroencephalogram recording system pending; a patent (Japanese Patent Pending No. 2017-204090) electroencephalogram classification system, its method, and programs pending; a patent (Japanese Patent Pending No. 2017-204091) evaluation system for electroencephalogram recording system, evaluation methods, and its programs pending; a patent (Japanese Patent Pending No. 2017-204092) inflammation evaluation system, evaluation method, and its programs pending; and a patent (Japanese Patent Pending No. 2017-204097) finger movement support device pending. JU, KO, and MO have a patent (Japanese Patent Pending No. 2017-204088) electroencephalogram recording system, its method, and programs pending, and a patent (Japanese Patent Pending No. 2017-204093) electroencephalogram recording system, its method and programs pending. KO and MO have a patent (Japanese Patent Pending No. 2017-204094) electroencephalograph and electroencephalogram recording system pending, a patent (Japanese Patent Pending No. 2017-204095)

finger movement support device pending, and a patent (Japanese Patent Pending No. 2017-204096) headset pending. JU, MO, KM, ML, and TF have a patent (PCT/JP2017/018216) biometric information processing device. ML, JU and MK are founding scientists of the startup company Connect Inc for the social implementation of university research results such as brain-computer interface and brain-machine interface, which were evaluated in this study.

Multimedia Appendix 1

Peer-review report from the Japan Agency for Medical Research and Development (Part 1).

[PDF File (Adobe PDF File), 293KB - resprot_v7i12e12339_app1.pdf]

Multimedia Appendix 2

Peer-review report from the Japan Agency for Medical Research and Development (Part 2).

[PDF File (Adobe PDF File), 33KB - resprot_v7i12e12339_app2.pdf]

Multimedia Appendix 3

Translation of the peer-review report from the Japan Agency for Medical Research and Development (Part 1).

[PDF File (Adobe PDF File), 77KB - resprot_v7i12e12339_app3.pdf]

Multimedia Appendix 4

Translation of the peer-review report from the Japan Agency for Medical Research and Development (Part 2).

[PDF File (Adobe PDF File), 10KB - resprot_v7i12e12339_app4.pdf]

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Abbreviations

ADL: activities of daily living
AHA: American Heart Association
AMED: Agency for Medical Research and Development
ARAT: Action Research Arm Test
ASA: American Stroke Association
BI: Barthel Index
BMI: brain-machine interface
CIMT: constraint-induced movement therapy
EEG: electroencephalogram
EMG: electromyography
ERD: event-related desynchronization
FAS: full analysis set
FMA: Fugl-Meyer assessment
GAS: Goal Attainment Scale
HANDS: hybrid assistive neuromuscular dynamic stimulation
IVES: integrated volitional electrical stimulator
JGM 2015: Japanese guidelines for the management of stroke 2015
LDA: linear discriminant analysis
MAL: Motor Activity Log-14
MAS: Modified Ashworth scale
MCID: minimal clinically important difference
NEMS: neuromuscular electrical stimulation
PPS: per protocol set
RCT: randomized controlled trial
RFE: repetitive facilitative exercise
SAP: Statistical analysis plan
SIAS: Stroke Impairment Assessment Set
SS-QOL: Stroke-Specific Quality of Life Scale
tDCS: Transcranial direct current stimulation
2D: two-dimensional
UE: upper extremity

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Protocol

Using the Social-Local-Mobile App for Smoking Cessation in the SmokeFreeBrain Project: Protocol for a Randomized Controlled Trial

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Abstract

Background: Smoking is considered the main cause of preventable illness and early deaths worldwide. The treatment usually prescribed to people who wish to quit smoking is a multidisciplinary intervention, combining both psychological advice and pharmacological therapy, since the application of both strategies significantly increases the chance of success in a quit attempt.

Objective: We present a study protocol of a 12-month randomized open-label parallel-group trial whose primary objective is to analyze the efficacy and efficiency of usual psychopharmacological therapy plus the Social-Local-Mobile app (intervention group) applied to the smoking cessation process compared with usual psychopharmacological therapy alone (control group).

Methods: The target population consists of adult smokers (both male and female) attending the Smoking Cessation Unit at Virgen del Rocío University Hospital, Seville, Spain. Social-Local-Mobile is an innovative intervention based on mobile technologies and their capacity to trigger behavioral changes. The app is a complement to pharmacological therapies to quit smoking by providing personalized motivational messages, physical activity monitoring, lifestyle advice, and distractions (minigames) to help overcome cravings. Usual pharmacological therapy consists of bupropion (Zyntabac 150 mg) or varenicline (Champix 0.5 mg or 1 mg). The main outcomes will be (1) the smoking abstinence rate at 1 year measured by means of exhaled carbon monoxide and urinary cotinine tests, and (2) the result of the cost-effectiveness analysis, which will be expressed in terms of an incremental cost-effectiveness ratio. Secondary outcome measures will be (1) analysis of the safety of pharmacological therapy, (2) analysis of the health-related quality of life of patients, and (3) monitoring of healthy lifestyle and physical exercise habits.

Results: Of 548 patients identified using the hospital's electronic records system, we excluded 308 patients: 188 declined to participate and 120 did not meet the inclusion criteria. A total of 240 patients were enrolled: the control group (n=120) will receive usual psychopharmacological therapy, while the intervention group (n=120) will receive usual psychopharmacological therapy

plus the So-Lo-Mo app. The project was approved for funding in June 2015. Enrollment started in October 2016 and was completed in October 2017. Data gathering was completed in November 2018, and data analysis is under way. The first results are expected to be submitted for publication in early 2019.

Conclusions: Social networks and mobile technologies influence our daily lives and, therefore, may influence our smoking habits as well. As part of the SmokeFreeBrain H2020 European Commission project, this study aims at elucidating the potential role of these technologies when used as an extra aid to quit smoking.

Trial Registration: ClinicalTrials.gov NCT03553173; https://clinicaltrials.gov/ct2/show/record/NCT03553173 (Archived by WebCite at http://www.webcitation.org/74DuHypOW).

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KEYWORDS

smoking cessation; mobile applications; randomized controlled trial; economic evaluation

Introduction

Background

Smoking is considered the main cause of preventable illness and early deaths worldwide [1]. Mathers and Loncar [2] estimated that about 100 million deaths were caused by tobacco addiction in the 20th century. Also, 5.4 million people worldwide die each year of tobacco-related diseases, and it is estimated that by 2030 smoking will cause 8 to 10 million deaths a year, over 80% of them in low- and middle-income countries [3]. According to the World Health Organization, in 2025, about 22% of the adult populations of Europe will be regular smokers [4]. Together with the Americas, Europe has the highest proportion of all deaths attributable to tobacco, estimated at 16% [1].

In Spain, in 2017, 22.08% of the population aged over 15 years smoked daily and 2.34% were occasional smokers. In Spain 25.58% of males and 18.76% of females are smokers; and 17.56% of young persons aged 15 to 24 years old have a tobacco habit, showing a relevant difference by sex (19.96% of males compared with 15.05% of females) [5].

In the Andalusian Health Service region, the largest public health problem is the smoking epidemic. To address this problem, a plan called “Comprehensive Tobacco Action Plan for Andalusia” has been defined and promoted [6] by the Andalusian Ministry of Health. This plan expects to reduce the incidence and prevalence of smoking in Andalusia, reducing complications and morbidity and mortality related to tobacco among the Andalusian population, and improving the quality of life of both smokers and nonsmokers. The plan hopes to create a smokefree future in a climate of social well-being and mutual respect, promoting healthy lifestyles, ensuring the right to health for all, and promoting public participation, with the final aim to guarantee smokers the best health care, based on scientific evidence, and ensuring continuity of care as an element of integral quality.

Smoking is usually considered to be exclusively a personal decision. This statement seems not to be true, since the clear majority of smokers claim that they wish to stop consuming tobacco when they are deeply aware of all the negative side effects to their health, yet they find it difficult to stop smoking due to the great addictiveness of nicotine. Fortunately, there are a variety of useful pharmaceutical products to help them quit. Among them, bupropion and varenicline are 2 drugs usually prescribed. At the Smoking Cessation Unit of the Virgen del Rocío University Hospital (VRUH) in Seville, Spain, patients willing to quit smoking are provided with a combination of both psychological advice and pharmacological treatment using any of the 2 previously mentioned drugs. This multidisciplinary strategy to quit has significantly improved the success rate [7].

Some research has been performed regarding the use of tailored mobile- and Web technology–based interventions and their impact on the smoking cessation process. Hébert et al [8] showed the utility of mobile phones for assessing the risk for smoking lapse in real time, and their findings endorsed the statement that tailored content may affect users’ urge to smoke, stress, and cigarette availability. Chakraborty et al [9] investigated the correlation between the personalization level of Web-based interventions and participants’ educational level when dealing with their smoking behavior, finding that highly individually tailored interventions were more effective for smokers with a low level of education. However, it is not clear what impact such interventions may have on smoking cessation efficacy in the long term. A recent observational study highlighted key insights related to participant engagement and cessation among adults who voluntarily subscribed to a 42-day mobile phone text message smoking cessation program [10], uncovering the need to improve program engagement. On the other hand, evidence showed a beneficial impact of mobile phone–based smoking cessation interventions on 6-month cessation outcomes, although caution should be taken in generalizing these results outside this type of intervention and context [11]. Nonetheless, there is still a need to demonstrate the added value that a tailored smoking cessation intervention based on mobile technologies has for the efficacy of long-term abstinence when added to psychopharmacological therapies.

Craving is a key component that has been shown to vary over time during a smoking cessation attempt and is highly related to treatment efficacy and cessation success [12]. In addition, it is documented that craving fades away during the first 2 weeks of abstinence [13]. However, cravings may return if former smokers’ coping strategies lose effectiveness over time, leaving smokers with less and less ability to resist the urge to smoke.

There is scarce evidence about the valuable support that physical activity and information and communication technologies (app gamification, short text sent as push notifications, and short message service [SMS] text messaging and Facebook) may provide to the smoking cessation process [14,15].

Objectives

As part of the SmokeFreeBrain H2020 European Commission project (Grant Agreement 681120) [16,17], this study aims at elucidating the potential role of the aforementioned technologies when used as an extra aid to quit. The Social-Local-Mobile (So-Lo-Mo) intervention focuses on providing health goals, including physical activity, with immediate feedback through the mobile app, reinforcing patients' ability to stay abstinent with motivational messages and offering patients tools to overcome cravings, such as playing specifically designed minigames.

The main objectives of this study are to analyze the efficacy and cost effectiveness of usual psychopharmacological therapy plus the So-Lo-Mo app (intervention group) compared with usual psychopharmacological therapy alone (control group) applied to the smoking cessation process.

Secondary objectives are the following: (1) to analyze the safety of pharmacological therapy, (2) to analyze patients' health-related quality of life (HRQoL), and (3) to monitor patients' healthy lifestyle and physical exercise habits.

Methods

Design and Setting

This is a 12-month randomized open-label parallel-group trial performed at the VRUH. It was retrospectively registered on June 12, 2018 (NCT03553173).

Participants and Recruitment Strategy

We calculated sample size during the study design phase according to the following parameters: (1) confidence level: 95%, (2) statistical power: 80%, (3) success rate in the control group: 35%, (4) success rate in the intervention group: 55%, and (5) expected dropout rate: 20%. This calculation yielded a sample size of N=236 participants. However, because this study was framed within a research project with tight deadlines for recruitment, we had only 12 months available for recruiting participants. Therefore, we calculated the sample size according to the average consultations performed by the Smoking Cessation Unit of VRUH during the last 5 years, which resulted in a slightly higher N=240.

Inclusion criteria are as follows: (1) the smoking population attending the Smoking Cessation Unit of VRUH, (2) age 18 years or older and the desire to give up smoking, (3) availability of an Android-based mobile phone, (4) ability to interact with the mobile phone (we will assess mobile phone literacy by asking patients if they commonly use other text exchange mobile phone apps such as Mail, SMS, or WhatsApp), and (5) willingness to sign an informed consent form.

We excluded patients who had some previous adverse effects related to the pharmacological treatment used in the study.

It should be noted that we will use the allocation to different pharmacological therapies as a reflection of usual care rather than a confounding factor for the analysis. We generated a list of 240 consecutive items by randomly assigning 1 of the study groups to each item. Participants were assigned to each of the study groups according to this list and following their order of enrollment.

We obtained written informed consent from all study participants.

Usual Psychopharmacological Therapy

Usual care consists of pharmacological therapy with bupropion (Zyntabac 150 mg; Glaxosmithkline SA, Tres Cantos, Spain) or varenicline (Champix 0.5 mg or 1 mg; Pfizer SL, San Sebastián de los Reyes, Spain) and behavioral therapy. In routine care, patients must pay for these treatments in the pharmacy. To facilitate patient recruitment and to avoid bias due to the treatment cost, the SmokeFreeBrain project is funding these costs, so participants receive the assigned treatment free of charge.

The psychological intervention process, which is performed individually, starts with an assessment of the smoker to complement his or her medical record. The first step is to assess the patient's smoking record (number of daily cigarettes, age at the start of regular smoking, previous quit attempts, and methods followed for quitting). The next step is to assess the patient's nicotine dependence level using the Fagerström Test for Nicotine Dependence [18] and motivation to quit smoking according to the Richmond test [19].

The psychological intervention starts once these assessments have been performed. This intervention includes providing information about smoking and the smoking cessation process, as well as supporting behavioral changes by providing new skills and strategies. Although there is a wide variety of psychological interventions to support the smoking cessation process, such as group behavior therapy programs and self-help materials [20], the most used methods delivered by the Smoking Cessation Unit of the VRUH are the motivational interview and cognitive behavioral therapy.

The motivational interview is performed in 2 stages—exploratory and decisive—and includes the following basic principles: (1) to express empathy, (2) to create discrepancy, (3) to overcome resistance, (4) to avoid arguing, and (5) to encourage self-efficacy.

The objective of cognitive behavioral therapy is to reconvert the smoker's thoughts, knowledge, and behavior related to smoking. To achieve this, the following are applied: (1) problem solving skills training, (2) social support (by phone and email), (3) self-analysis of reasons to quit, (4) cigarette consumption registry, (5) progressive reduction of cigarette consumption, and (6) relapse prevention strategies.

The Social-Local-Mobile Intervention

So-Lo-Mo is an innovative intervention based on mobile technologies and their capacity to trigger behavioral changes. In this sense, the app is a complement to pharmacological therapies to quit smoking providing, among other features,

personalized motivational messages sent by the system, peer-to-peer messaging, physical activity monitoring, lifestyle advice, and distractions (minigames) to help overcome cravings. The main objective of this app is to improve patients' adherence to the smoking cessation process by use of behavioral techniques in the form of motivational messages and SMS text messages. To this aim, the underlying algorithm is able to do the following:

- Send motivational messages as SMS text messages or in a notification-based format. High-priority messages—those related to specific dates such as New Year's Eve or holidays when people may relapse—are sent by SMS so that their delivery is guaranteed even when users do not have an internet connection on their mobile, while the rest of the messages are delivered via app push notification mechanisms, which uses an internet connection.
- Dynamically schedule message frequency according to the phase of the transtheoretical model of behavior change [21] that the individual is undergoing (preparation, action, or maintenance) and when the notifications should be delivered according to the individual's preferences.
- Dynamically determine the category (ie, content and type) of the message that is delivered to the individual according to the phase of the transtheoretical model of behavior change that the individual is undergoing, user health conditions, user feedback, and user filtering strategies. For this, we have defined the following motivational message categories: reduce tobacco consumption, increase risk perception, and increase benefit perception during the preparation phase; and general motivation, diet tips, exercise and active life recommendations, personal physical activity level, and positive facts of being a former smoker during the action and maintenance phases.

Figure 1 shows the 3 specific sections of the app that address how to resist cravings: (1) motivational messages that the user can request immediately from the system, (2) relaxation tools such as breathing exercises, and (3) minigames specifically designed to help the user overcome cravings. Hors-Fraile et al [22] provide further information on the methods and the underlying algorithm for delivering these text messages.

Study Outcomes

The main outcomes will be the efficacy and efficiency of the So-Lo-Mo intervention.

To assess efficacy, the main clinical outcome will be the smoking abstinence rate at 1 year measured by means of exhaled carbon monoxide and urine cotinine tests.

Figure 1. Sections of the app that address how to resist cravings.

Exhaled carbon monoxide is part of the smoke and can be measured by a carbon monoxide tester. The patient must perform a deep inspiration and hold the air for 15 seconds. Then, the patient must exhale the air inside the carbon monoxide tester (Micro+ Smokerlyzer; Bedfont Scientific Ltd, Maidstone, UK) in a slow, sustained, and complete fashion. The carbon monoxide tester then yields the exact amount of exhaled carbon monoxide in parts per million. Exhaled carbon monoxide levels are highest between 3 and 6 hours after smoking a cigarette. A person is considered to be smoker when his or her exhaled carbon monoxide is higher than 6 ppm [23].

The urine cotinine (SmokeScreen test; GFC Diagnostics Ltd, Chipping Warden, UK) is a colorimetric test that measures the main metabolites of nicotine, including cotinine. In Spain, patients with cotinine concentrations over 200 ng/mL are considered to be smokers [24].

To consider a participant to be a smoker, only 1 of the aforementioned conditions needs to be met.

To assess efficiency, we will carry out a cost-effectiveness analysis considering the recommendations of the proposed guidelines for economic evaluation of health technologies [25]. The analysis will adopt the perspective of the Spanish National Health System. We will express results of the cost-effectiveness analysis in terms of the incremental cost-effectiveness ratio, calculated by dividing the difference in total costs between the intervention group and the control group by the difference in quality-adjusted life-years (QALYs) between the 2 groups [26]. Cost analysis will include costs of the prescribed medication, time spent by the health professionals on the So-Lo-Mo intervention, health care resources utilization, and equipment and software costs related to the So-Lo-Mo intervention. We will calculate QALYs in order to assess the health benefit of the intervention regarding the cost-effectiveness analysis. QALY is a health outcome that includes both the quality and the quantity of life, and we will calculate it through 5-level EuroQol 5 dimensions questionnaire (EQ-5D-5L) scores [27], according to the Spanish validation [28].

The secondary outcomes will be safety, patients' HRQoL, and patients' healthy lifestyle and exercise habits.

We will measure safety as the number of adverse events related to pharmacological therapies. The following adverse events have been identified related to each pharmacological therapy: (1) for varenicline (Champix 0.5 mg or 1 mg): nausea (feeling sick), insomnia (difficulty sleeping), abnormal dreams, headache, and nasopharyngitis (inflammation of the nose and throat) [29]; and (2) for bupropion (Zyntabac 150 mg): insomnia, headache, dryness in the mouth (alteration of taste), skin reactions, convulsions, cardiovascular side effects, and severe skin reactions [30].

We will measure HRQoL through the EQ-5D-5L questionnaire [27] and the 36-item Short Form Health Survey [31].

We will monitor physical activity through the International Physical Activity Questionnaire [32] and healthy lifestyle in terms of the variation of body mass index during the follow-up consultations.

Moreover, information from all patients undergoing this study will include demographic data (age and sex) and socioeconomic data (profession and employment status); consumption history (eg, daily cigarettes, living with smokers, partner smokers, quit attempts); clinical information (eg, weight, size, blood pressure, comorbidities); and nicotine dependence measured through the Fagerström Test for Nicotine Dependence [18]. Multimedia Appendix 1 shows every variable of the evaluation framework and its use in each follow-up session.

Data Collection

We will record information subsets in the So-Lo-Mo clinical database according to the following schedule (Figure 2):

In session 1 (baseline), patients are assessed for the first time in the Smoking Cessation Unit as they are referred from either the Pneumology Unit or another clinical department. We will collect information regarding the following sections: general information, consumption history, smoking-related symptoms, clinical information, dependency, motivation, treatment assigned, HRQoL, physical exercise monitoring, and observations.

In session 2, 15 (±5) days after the baseline consultation, we will collect information regarding the following sections: consumption history, clinical information, motivation, symptoms related to abstinence, and observations. Relaxation techniques and risk-avoidance techniques will also be explained to the patient.

In session 3, 30 (±5) days after the baseline consultation, we will collect information regarding the following sections: consumption history, clinical information, motivation, symptoms related to abstinence, and observations. New relaxation techniques will be explained in case those previously explained proved to be useless. Patients will be coached for relapse prevention.

In session 4, 60 (±5) days after the baseline consultation, we will collect information regarding the following sections: motivation, symptoms related to abstinence, and observations. Risk-avoidance techniques will be reinforced.

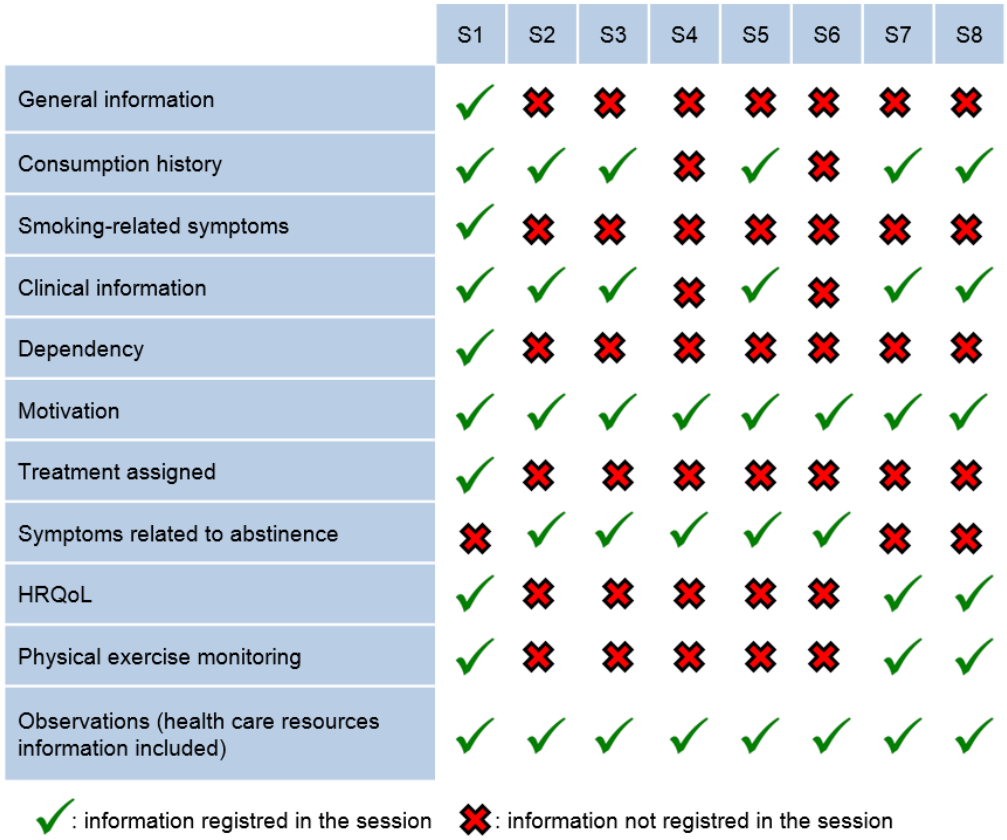
In session 5, 90 (±5) days after the baseline consultation, we will collect information regarding the following sections: consumption history, clinical information, motivation, symptoms related to abstinence, and observations. Patients will be coached for relapse prevention and confrontational techniques will be explained.

In session 6, 120 (±5) days after the baseline consultation, patients can be assessed by phone if they have completed the pharmacological treatment. In this session we will collect information regarding motivation, symptoms related to abstinence, and observations. Patients will be coached for relapse prevention and confrontational techniques will be explained.

In session 7, 180 (±5) days after the baseline consultation, we will collect information regarding the following sections: consumption history, clinical information, motivation, HRQoL, physical exercise monitoring, and observations (including

information on health care resources). Relaxation and confrontational techniques will be reinforced when needed.

Figure 2. Information subsets and follow-up schedule to record in the study clinical database. HRQoL: health-related quality of life; S1-S8: sessions 1-8.



In session 8, 365 (±5) days after the baseline consultation, we will collect information regarding the following sections: consumption history, clinical information, motivation, HRQoL, physical exercise monitoring, and observations (including information on health care resources).

We will develop a case report form built on the OpenClinica [33] tool to facilitate information management in the study. It is worth noting that OpenClinica is compliant with the Guideline for Good Clinical Practice, US Code of Federal Regulations, Title 21, Part 11, the US Health Insurance Portability and Accountability Act of 1996, and other regulations. This case report form is integrated with the VRUH's electronic health record system, so some data elements are automatically loaded into the case report form, thus avoiding double recording for clinicians.

Statistical Analysis

At the end of the study, we will carry out a descriptive analysis of patients' characteristics by absolute and relative frequencies for qualitative variables and mean (SD) for quantitative variables. We will perform a bivariate analysis of study groups for qualitative variables by chi-square test or Fisher exact test. Comparison of quantitative variables will differ depending on technical assumptions, such as parametric (Student *t* test or analysis of variance) or nonparametric (Mann-Whitney *U* or Kruskal-Wallis) tests.

To analyze the uncertainty of the incremental cost-effectiveness ratio results, we will provide a tornado diagram of the univariate sensitivity analysis, incorporating variations in the components of cost and QALY. The data analysis team will not be blinded to the allocation of participants.

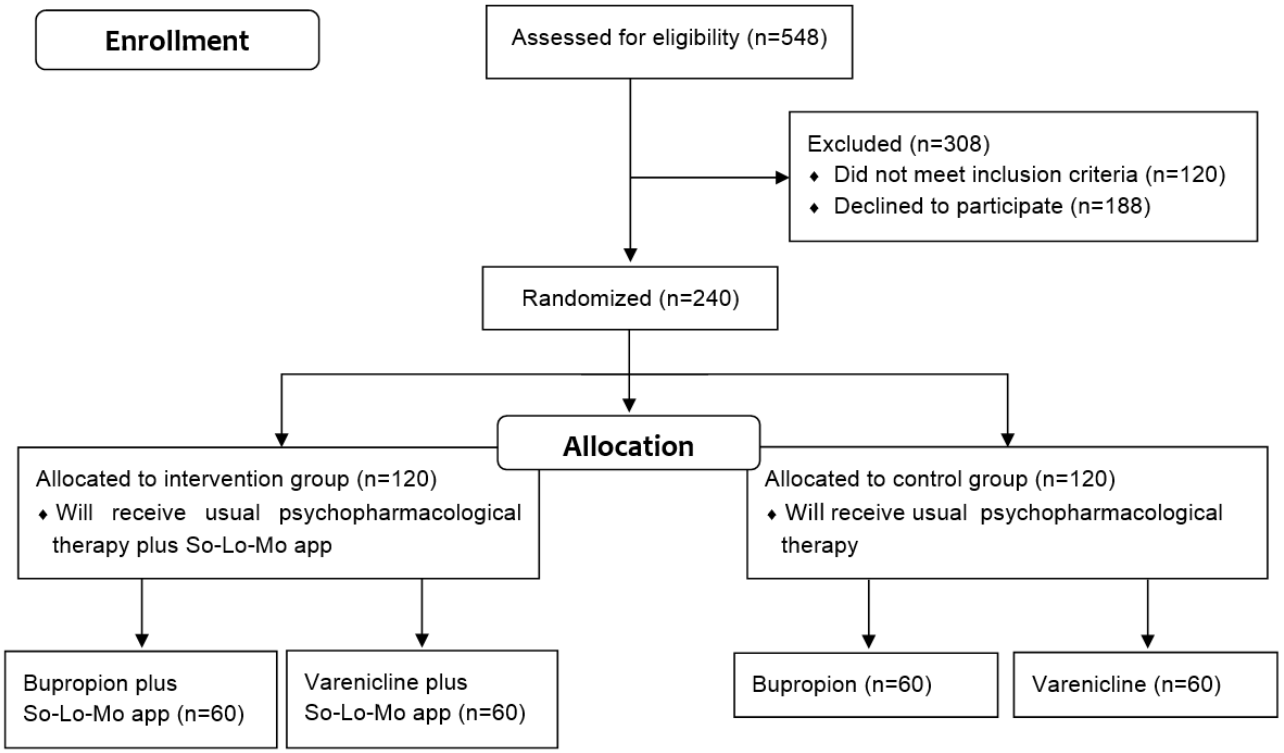
Results

We identified 548 patients using the hospital's electronic records system. From this initial selection, we excluded 308 patients: 188 declined to participate (149 did not show up for the baseline consultation, 27 refused the medication, 7 did not want to enroll in the study, and 5 did not want to quit smoking), while 120 did not meet the inclusion criteria (98 reported previous adverse effects related to the medication assigned, 15 were not smokers at baseline, and 7 did not have an Android-based smartphone available). A total of 240 patients were enrolled: the control group (n=120) will receive usual psychopharmacological therapy, while the intervention group (n=120) will receive usual psychopharmacological therapy plus the So-Lo-Mo app. Figure 3 shows the enrollment and allocation phases of the study.

The project was approved for funding in June 2015. Enrollment started in October 2016 and was completed in October 2017. Data gathering was completed in November 2018 and data analysis is under way. We expect to submit the first results for publication in early 2019.

Virgen Macarena–Virgen del Rocío University Hospitals Ethics Committee approved the study protocol in July 2016.

Figure 3. Flow diagram of the randomized open-label parallel-group trial of the Social-Local-Mobile (So-Lo-Mo) app.



Discussion

Nowadays, the treatment usually prescribed to patients who wish to give up smoking is a multidisciplinary intervention, combining both psychological advice and pharmacological therapy, since the application of both strategies significantly increases the chance of success in a quit attempt [34]. Psychological interventions can be performed at different levels depending on resource availability and the level of care, without a difference in efficacy between individual and group therapies. In this scenario, psychological treatments are based on confrontational techniques, including behavioral and cognitive behavioral therapies [35]. Behavioral therapies are designed to help smokers to recognize and avoid external stimuli temporarily associated with the consumption of tobacco, while cognitive behavioral therapies provide the tools to confront both physiological and cognitive stimuli with the urge to smoke. During the smoking cessation process, 1 in 3 smokers rely on the pharmacological treatment too [36]. There is a wide range of drugs that could support this process, and the physicians in the Smoking Cessation Unit at VRUH usually prescribe either varenicline or bupropion. Varenicline, bupropion, and nicotine replacement therapy reduce-to-quit interventions have all been found to be effective cessation interventions in smokers who would like to quit [37].

A recent systematic review of smartphone apps for smoking cessation highlighted that future studies should aim to develop and standardize an innovative and timely approach to evaluate apps for commitment to evidenced-based practice; to explore strategies to make scientifically supported apps easily searchable and more accessible to consumers, including indexing with plain language terminology; and to explore ways to inform the development of health apps to better align app content with evidence-based medicine [38].

In this sense, we will compare the efficacy of usual pharmacological treatment plus behavioral and cognitive behavioral therapies routinely delivered at VRUH when added to the So-Lo-Mo intervention. If adding the So-Lo-Mo intervention provides any meaningful increase in the smoking cessation treatment effectiveness rate, we can infer that this increment will also take place when added to nicotine replacement therapy, given that it is not as effective as varenicline or bupropion. Furthermore, we are conducting a parallel study to assess the perceived quality of the health recommender system and the level of engagement with the motivational messages. The analysis of these technical aspects will provide a more comprehensive understanding of the So-Lo-Mo intervention [39].

Cultural and material factors are also key elements that need to be further investigated to uncover their correlation with smoking habit in different geographical regions [40,41]. Recently, the Taipei Medical University joined the SmokeFreeBrain project and they are currently developing an intervention similar to So-Lo-Mo [42]. Their involvement reflects not only the capacity of this intervention to cross borders and go beyond the frame of a European project, but will also shed some light on the cultural grounding of the efficacy and effectiveness of the use of mobile technologies applied to the smoking cessation process.

Understanding the way social networks and mobile technologies can influence individual behavior and the decision of whether to smoke is essential to optimize their use as a means of

prevention and treatment in the future. A recent scoping review [43] showed how health recommender systems, like the one used in So-Lo-Mo, are being used in health care with many potential benefits for their users. However, most of the systems lacked any description of their design, follow-up of implementation, and behavioral change models they were based on. So-Lo-Mo is, thus, an innovative intervention based on mobile technologies and its capacity to trigger behavioral changes following the transtheoretical behavioral change model [21].

Although a large number of studies have assessed the effects of interventions intended to reduce the harm to health of continued tobacco use, it is important that more high-quality randomized controlled trials be conducted, and that these also measure the long-term health effects of treatments [44]. Another innovative contribution of our study is the focus on the cost-effectiveness analysis that will consider the economic impact on the Spanish National Health System and on patients' HRQoL.

Some limitations of our study should be acknowledged. First, the So-Lo-Mo app is developed for Android-based users only. However, in Spain the market share for Android-based devices in 2018 is 78.09% [45]. This means that only a small percentage of patients will be excluded from the study due to this criterion. Second, we did not calculate the sample size based on power calculations, as explained above, which will limit our ability to extract strong evidence about the efficacy and efficiency of the intervention applied to the smoking cessation process after completion of the study.

Acknowledgments

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Authors' Contributions

FJS, CLPC, and FOR designed the study protocol of the So-Lo-Mo intervention in the frame of the SmokeFreeBrain project. FJS, LCH, FJNB, CLPC, MAM, and FOR contributed to the study protocol refinement. FJS and FJNB drafted the manuscript. SHF, LFL, AC, and PB took part in the design of the So-Lo-Mo intervention. All authors edited and revised the manuscript draft. All authors reviewed and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Variables of the evaluation framework.

[XLSX File (Microsoft Excel File), 22KB - resprot_v7i12e12464_app1.xlsx]

Multimedia Appendix 2

Peer-reviewer report from the European Commission.

[PDF File (Adobe PDF File), 94KB - resprot_v7i12e12464_app2.pdf]

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Abbreviations

EQ-5D-5L: 5-level EuroQol 5 dimensions questionnaire
HRQoL: health-related quality of life
QALY: quality-adjusted life-year
SMS: short message service
So-Lo-Mo: Social-Local-Mobile
VRUH: Virgen del Rocío University Hospital

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Protocol

A Novel Just-in-Time Contextual Mobile App Intervention to Reduce Sodium Intake in Hypertension: Protocol and Rationale for a Randomized Controlled Trial (LowSalt4Life Trial)

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Abstract

Background: High sodium intake is a significant public health problem in the United States. Interventions that lower sodium intake can decrease blood pressure and improve cardiovascular outcomes. Restaurants and grocery stores are prime targets for intervention with about 77% of all sodium intake in the average US diet coming from processed and restaurant foods.

Objective: This study proposes that a mobile app intervention that promotes low-sodium alternatives at grocery stores and restaurants will reduce dietary intake of sodium and improve confidence following a low-sodium diet in hypertension.

Methods: In this single-center, prospective, open-label study, patients will be randomized to a mobile app or usual care for 8 weeks. We will randomize 50 patients (age>18 years) diagnosed with hypertension and on antihypertensive therapy for at least 3 months in a 1:1 manner stratified by gender. Study subjects will receive the mobile app, LowSalt4Life, or usual dietary advice for 8 weeks. LowSalt4Life provides a multifaceted intervention based on just-in-time contextual tailored messages at grocery stores and restaurants. The primary endpoint is the change in the estimated 24-hour urinary excretion of sodium from spot urine. Secondary outcomes include change in the sodium content of the food frequency questionnaire, confidence in following a low-sodium diet, urine chloride and creatinine dipsticks, and blood pressure.

Results: The project was funded in May 2016 until April 2018. This trial is currently enrolling patients. To date, 26 of the 50 patients needed have been enrolled. Results will be available in the Spring of 2019.

Conclusions: This randomized controlled trial will test the efficacy of just-in-time contextual tailored messages through a novel mobile app 8-week intervention on urinary sodium excretion in patients with hypertension. We will address a critical evidence gap in the care of patients with hypertension. If effective, this intervention could be scaled to assess effects on blood pressure and cardiovascular events in hypertension.

Trial Registration: ClinicalTrials.gov NCT03099343; https://clinicaltrials.gov/ct2/show/NCT03099343 (Archived by WebCite at http://www.webcitation.org/735HNzKlQ)

International Registered Report Identifier (IRRID): PRR1-10.2196/11282

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KEYWORDS

geofencing; hypertension; mobile phone; sodium intake

Introduction

Prevalence and Consequences of High Dietary Sodium Intake

High sodium intake is a significant public health problem in the United States. In a meta-analysis of 177,025 patients, higher sodium consumption was associated with higher risk of stroke (relative risk, RR, 1.23, 95% CI 1.06-1.43) and a trend toward higher cardiovascular risk (RR 1.14, 95% CI 0.99-1.32) [1]. Based on 2005 estimates, high dietary sodium is responsible for 102,000 deaths annually. The current federal guidelines advocate a daily sodium intake of <2300 mg with a further reduction to 1500 mg in persons aged ≥51 years and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease (CKD), while the average sodium intake for all Americans aged ≥2 years is approximately 3400 mg/day [2].

Effects of Interventions to Lower Sodium Intake

Interventions that lower sodium intake can decrease blood pressure and improve cardiovascular outcomes. The sodium-restricted Dietary Approach to Stop Hypertension eating plan reduced the systolic blood pressure (SBP) by 7.1 mm Hg in adults without hypertension and 11.5 mm Hg in adults with hypertension [3]. In an analysis of the Trials of Hypertension Prevention, participants randomized to low-sodium interventions had a 25% lower long-term risk of cardiovascular disease (RR 0.75, 95% CI 0.57-0.99) [4]. Following the 2003 introduction of a national salt reduction program in England, the 2011 national Health Survey estimated that the population's sodium intake decreased by ~550 mg/day [5]. During that same timeframe, the population's SBP declined by 3 (SD 0.3)/1.4 (SD 0.2) mm Hg, which was accompanied by a 42% decrease in stroke mortality (P<.001) and a 40% reduction in mortality due to ischemic heart disease (P<.001). After extensive adjustment for other potential factors, dietary sodium reduction was identified as the most likely contributor.

From a policy perspective in the United States, reducing sodium intake by 1200 mg/day is projected to prevent 60,000-120,000 coronary heart disease events, 32,000-66,000 strokes, 54,000-99,000 myocardial infarctions, and 44,000-99,000 deaths from any cause on an annual basis [6]. This reduction in sodium intake would also lead to US $10-24 billion savings in the health care system.

Patients Need Assistance at Grocery Stores and Restaurants

Over half of Americans consume 1-3 restaurant meals per week, and 23% consume ≥4 restaurant meals per week. In addition, the use of prepackaged foods in home meal preparation has increased substantially in recent years. Restaurants and grocery stores are prime targets for interventions, with about 77% of all sodium intake in the average US diet coming from processed and restaurant foods [7,8]. In a recent study on consumer knowledge of sodium intake and food labeling, only half of the over 400 grocery store shoppers could accurately use sodium label information to choose low-sodium food options [9]. The American Heart Association guideline for the dietary approach to prevent and treat hypertension states, "any meaningful strategy to reduce salt intake must involve efforts of food manufacturers and restaurants" [10].

A qualitative study using a focus group that included patients with heart failure proposed 3 primary themes for nonadherence to low-sodium diet as follows: lack of knowledge, interference with socialization, and lack of food selections [11]. Many participants in this study felt they needed more detailed information about a low-sodium diet. They also expressed frustration in eating out at restaurants stating eating out was an obstacle to adhering to their prescribed diet. Finally, patients stated there are limited choices and poor taste of foods with low-sodium content.

Advancements in Information Technology to Support Reduced Sodium Intake

We are currently witnessing broad social changes in the ways individuals expect to find and use information about their health. According to the Pew Research Center's Internet and American Life Project, nearly 90% of households now have at least basic internet access, and 70% of households have broadband service [12]. The use of mobile phones has nearly become ubiquitous (with 90% of individuals owning a mobile phone), with a growing majority of individuals (65%) using smartphones [13]. We believe that a mobile app that provides location-based, tailored messages can reduce the dietary sodium intake and increase participants' confidence in following a low-sodium diet.

The current state for self-monitoring of sodium intake in health information technology (IT) is to have users log all daily dietary intake, a process that requires substantial time and persistence. Patients or the mobile app then calculates dietary sodium intake and reviews it periodically, after the intake has already occurred. Our more proactive approach provides immediately available information on appropriate low-sodium options, as well as the ability to self-monitor the intake of specific high-sodium foods. This type of methodology could provide a significant change in thinking about self-monitoring for diets and nutrition.

From a health IT perspective, the use of contextual geofence-based push notifications is novel. This research will inform how users perceive these messages, which messages they understand most and ultimately if they act on the recommendations of the message. Furthermore, we will appreciate whether patients will accept that a mobile app follows their location to provide dietary recommendations. The research will inform the health IT community how to begin using location-based notifications in a way that does not turn users off to the idea of being tracked by someone.

Table 1. Conceptual model for health information technology intervention based on patients' beliefs.

Patient beliefs about a low-sodium diet and theoretical framework	Intervention
Lack of knowledge	
Attitude	Just-in-time messages based on geofencing technology when a patient enters a restaurant or grocery store provide the knowledge the patient needs to make an informed decision.
Value proposition in food choices	Associating hypertension and blood pressure to lower sodium intake.
Self-regulation	Patients will monitor the top 5 high-sodium foods.
Interference with socialization	
Normative belief	Nonobtrusive food options are presented as a push notification when the patient enters a restaurant or scans an item at the grocery store.
Lack of food selection	
Perceived control; Substitution and limitation as a food choice strategy	Several food options are presented that are usual food options at the restaurant and the ability to scan foods at the grocery store. This puts a patient in control of limiting sodium and substituting other low-sodium foods.

Theoretical Framework for the Health Information Technology Intervention

The Theory of Planned Behavior, self-regulation, and mindful decision making are the theories used in the intervention to illicit a behavioral change. The direct determinants of behavioral intention are attitude, normative belief, and perceived control. The Theory of Planned Behavior suggests that the determinant of persons' behavior is their behavioral intent [14]. Patients who hold strong beliefs that a positive outcome will result from a behavior will also have a positive attitude about that behavior. Normative beliefs are heavily dependent on the individuals' motivation to comply with those around them. Patients also have to perceive control of the situation, making the behavior decision easy to perform.

In our intervention, patients planning what they are going to order at a restaurant will receive a push notification from the mobile app informing them of the low-sodium options at that restaurant. In food selection, the choice has to be within an area individuals perceive as normal. Providing a food choice on a restaurant menu that others would also purchase gives patients a feeling like they are complying with social norms. In addition, patients have to perceive control of the situation, making the behavioral decision easy to perform. In the setting of a push message provided by the mobile app, we present patients with several options to give them control over which food to choose.

The theory of self-regulation suggests that individuals striving to achieve a behavioral goal learn from their successes and failures. This knowledge is then used to develop strategies that can lead to goal attainment. In this theory, self-monitoring refers to individuals' awareness of their engagement in a targeted behavior. An important factor in self-regulation is self-efficacy [15]. Self-efficacy refers to an individual's belief in his or her ability to perform a specific behavior [16]. Accurate self-monitoring, feedback, and self-efficacy are essential components of the self-regulation cycle and are critical for lowering sodium intake [15,17-19].

Behavioral change interventions that focus on self-regulation are particularly well suited for automation. Through the use of the intervention, we will assess patients' top 5 high sodium-containing food selections. These food selections will be embedded in the mobile app, and a daily push notification will prompt patients to document if they have reduced those foods from their diet.

Mindful decision making is key for patients to make positive food choices. Food choice decisions are complex and incorporate a variety of food behaviors [20]. Value negotiations are a component of food choice decisions. People negotiate competing values, prioritizing values to simplify food choice decisions. For example, patients with hypertension may value their health over other values like taste, cost, convenience, and relationships. Limitation and substitution are common strategies in food choice. Some may limit particular foods or ingredients to meet a goal, while others substitute one food for another to meet the same goal. Health IT can provide a behavioral change intervention for food choices. We provide just-in-time messages at a restaurant and the ability to scan items at a grocery store to promote limitation and substitution strategies. These strategies facilitate food choice decisions by making them automated, so values are not necessary for every situation.

Aim and Hypothesis

The LowSalt4Life Trial will study the effectiveness of a newly developed mobile app that provides mobile phone sensor-based contextual push messages related to following a low-sodium diet. We will randomize patients with hypertension to the mobile app or standard of care for 8 weeks. From baseline to 8-week follow-up, we will assess the impact of the mobile app on the dietary intake of sodium (measured by 24-hour dietary recall and 24-hour urinary sodium excretion) and confidence following a low-sodium diet, measured by the Self-Care Confidence in Following a Low-Sodium Diet Scale (SCFLDS). We hypothesize that the group randomized to the mobile app will demonstrate improvement in these measurements compared with the control group (Table 1).

Methods

Trial Registration and Funding

This trial is registered at ClinicalTrials.gov (NCT03099343, received March 28, 2017) and is funded by the Agency for Healthcare Research and Quality (R21 HS024567). The authors are solely responsible for the design and conduct of this study, all study analyses, drafting and editing of the manuscript, and its final contents.

General Design

This is a single-center, prospective, open-label designed clinical trial. Recruitment is being performed at the University of Michigan Health System through our patient recruitment platform and recruitment letters to patients that meet our study criteria. Enrolled patients will be randomized to the mobile app or usual care in a 1:1 fashion using the University of Michigan Consulting for Statistics, Computing and Analytics Research randomization tool. Patients randomized to the mobile app will receive a 30-minute training session about the mobile app and be instructed to use the mobile app for 8 weeks. To address the research bias in this unblinded trial, all primary outcomes measured are objective. Some outcomes are not objective and represent a limitation of this research. This study was approved by the University of Michigan Institutional Review Board.

Study Subjects

We will enroll 50 patients aged >18 years diagnosed with hypertension and on antihypertensive therapy for at least 3 months. Patients will be excluded if they have CKD, heart failure, SBP >180 mm Hg, diastolic blood pressure >110 mm Hg, insulin-requiring diabetes mellitus, or are taking a loop diuretic, corticosteroid, or nonsteroidal anti-inflammatory medication. CKD is defined as known kidney damage (structural or functional abnormalities) or estimated glomerular filtration rate of <60 mL/min/1.73 m^2 (CKD stage 3, 4, or 5). Initially consented participants will complete the Block Food Frequency Questionnaire (NutritionQuest) [21], and those with the estimated baseline sodium intake <2300 mg/day will be excluded before randomization.

Intervention

The intervention with the mobile app includes the following 2 parts: (1) just-in-time contextual tailored messages that promote behavioral changes when a patient enters a grocery store and restaurant and (2) the ability to easily scan and search for the foods at grocery stores and restaurants to find options containing lower sodium content.

Just-in-time contextual tailored messages are generated on the basis of a multifaceted system. Initially, participants complete the Block Sodium Screener (NutritionQuest) and survey to assess their confidence in following a low-sodium diet. Users then create alternatives to the top 5 high sodium-containing foods and map these items to locations. In order to properly target messages, we use artificial intelligence algorithms that analyze the changes in mobile phones sensors (including Wi-Fi, Bluetooth, accelerometer, gyroscope, magnetometer, global positioning system). This takes each user's past, recognizes his or her present context, and predicts future activity. These predictions then alert the mobile app that the user is entering a grocery store or restaurant. Once the mobile app knows the user's context, the user receives a tailored message based on the context (grocery store or restaurant), their individual top 5 high sodium-containing foods (from the Block Sodium Screener) and their confidence following a low-sodium diet. These messages are delivered by push notifications.

When a user taps on a just-in-time contextual tailored message, the app is opened to the appropriate section for their context, grocery store or restaurant. The grocery store section provides users with the ability to scan Universal Product Codes on food packaging or text search at the grocery store. The mobile app provides feedback on the sodium content of the food using a traffic light signal red (≥480 mg/serving), yellow (≥120 mg/serving to <480 mg/serving), and green (<120 mg/serving) to show consumers, at a glance, whether a product is high, medium, or low in sodium [22-24]. In addition, the app will list lower sodium options in the same food category (Figure 1). In restaurants, users are presented 3 low-sodium meals for that specific restaurant that were curated by the investigators and be able to search the restaurant's menu with items ordered by the sodium content, lowest to highest.

Outcomes

The Automated Self-Administered 24-Hour Dietary Recall (ASA24), developed by the National Cancer Institute for dietary research, will be used to estimate the dietary sodium intake during the trial. The ASA24 is an electronic 24-hour recall website that allows patients to self-administer the survey in a user-friendly manner. The ASA24 allows researchers to send the survey at defined intervals and automatically performs a dietary analysis by converting the dietary recall data into nutrient information based on the Food and Nutrient Database for Dietary Studies. In order to provide a detailed interview, the website includes a meal-based quick list, meal gap review, review of forgotten foods, a final review, and a question about whether the day's intake was usual or not. In this study, we will obtain the sodium content per day from the Food and Nutrient Database for Dietary Studies-based sodium content analysis completed by the ASA24 website. The ASA24 will be administered at week 0 and 8 of the study (see Figure 2 for details of outcomes).

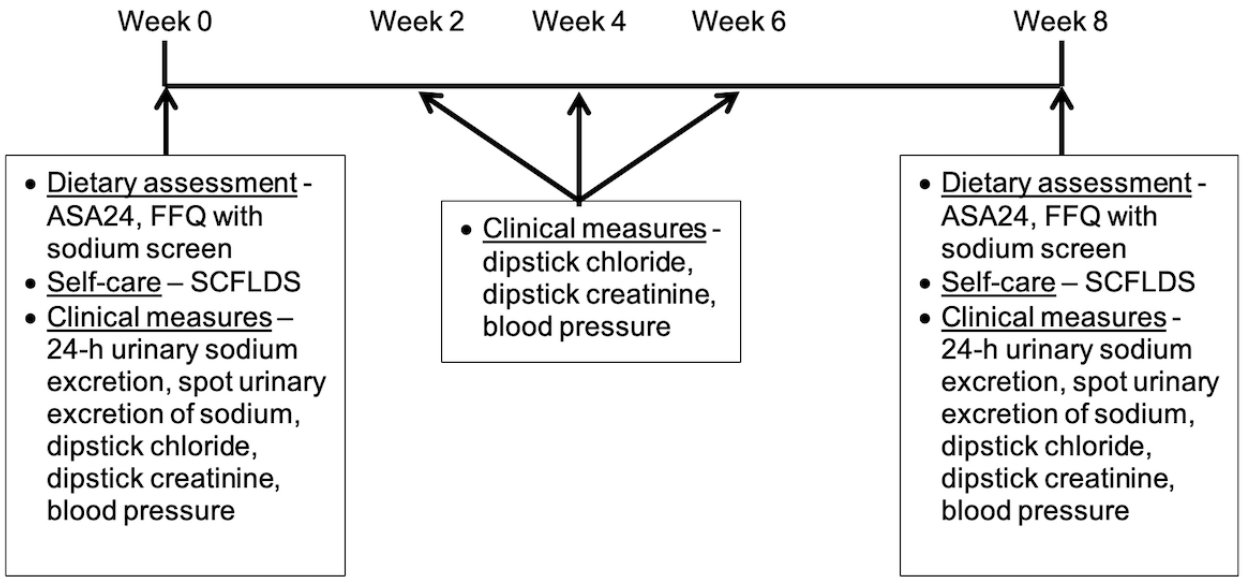
The most widely used method for monitoring the sodium intake is urinary sodium excretion measured by a 24-hour urine collection. Patients will be instructed to collect all urine voids for 24 hours and return them for analysis for sodium excretion. In addition, the 24-hour urine excretion will be collected at baseline and after 8 weeks. This method is not convenient (eg, difficult to perform collections at work), and some participants may have incomplete urine collections. Owing to these challenges, we will also explore other methods to estimate sodium excretion that would be more practical for use in larger trials.

In addition to the gold standard, the first method to estimate the 24-hour urinary sodium excretion is spot morning urine excretion of sodium. The Kawasaki formula will be used to estimate the 24-hour sodium urinary excretion from a fasting morning urine sample [25]. This approach has been proven to

provide a valid estimate of the sodium intake in several patient populations and in large-scale epidemiological studies [26]. Participants will be instructed to fast overnight, void in the morning, and provide us with a second morning urine sample on the day of the assessment. This measurement will be assessed at baseline and after 8 weeks of the study.

Figure 1. An example of the grocery store result screen for tomato soup using a traffic light signal.

Figure 2. Summary of outcomes in the trial. ASA24: Automated Self-administered 24-Hour Dietary Recall; FFQ: Food Frequency Questionnaire; SCFLDS: Self-Care Confidence in Following a Low-Sodium Diet Scale.



The second method for estimating the 24-hour urinary sodium excretion is with a spot urine sample using chloride and creatinine dipsticks. The dipstick method has been validated in patients with hypertension and correlates well with the 24-hour urinary sodium excretion (r=.86) [27]. The chloride dipstick is used as a surrogate for sodium excretion. The Quantab chloride dipstick (Hach, Loveland, CO, USA) is placed in a container filled less than halfway with urine. The chloride concentration is determined by observation of the change in color from brown to pale on the dipstick, which is the formation of silver chloride. The creatinine dipstick is similar to the chloride dipstick. The MultistixPro-10LS (Bayer, Elkhart, IN, USA) is a dipstick that includes a color pad for creatinine after it is placed in a container filled with urine. The color pad turns from yellow to green to indicate the creatinine concentration. The predicted 24-hour urinary sodium excretion is calculated on the basis of the 24-hour creatinine concentration calculated using sex, weight, race, and age. This model has been validated and correlates highly (r=.93) with 24-hour measurements of creatinine [28]. This measurement will be performed at baseline and after weeks 2, 4, 6, and 8.

The SCFLDS will be used to measure patients' confidence in following a low-sodium diet. It assesses patients' confidence in the ability to select and prepare low-sodium foods [29]. The tool consists of 7 items with 4 response options per item. The items ask patients to rate their level of confidence reading food labels, choosing low-sodium food during shopping, choosing low-sodium foods at restaurants, cooking low-sodium foods, choosing low-sodium foods at relatives or friends homes, estimating how much sodium they eat each day, and substituting low-sodium foods for high-sodium foods. The 4 response options are assigned a score of 1-4 (1=not confident; 2=somewhat confident; 3=very confident; 4=extremely confident) and then added for each question. Possible scores range from 7 to 28, and the higher score indicates greater confidence. The SCFLDS will be administered at baseline and after week 8 of the study.

Mobile device analytics will be collected to determine the extent to which the mobile app was used. This outcome will be key in determining the frequency and intensity of the intervention. After a participant receives a push notification on entry to a grocery store and restaurant, we will provide them with a push notification on exit asking them if they chose any of our alternative options. We will also collect any scanned items to understand better the specific foods that participants are seeking more information about. Blood pressure will be monitored on a weekly basis by patients, and the results will be entered into the mobile app and graphically represented.

Statistical Approach

The primary endpoint this study is powered for is the estimated 24-hour urinary excretion of sodium from spot urine. Based on the data in patients with hypertension, we conservatively expect the 24-hour urinary excretion of sodium to decrease from 3400 (SD 1200) mg/24 hours to 2400 (SD 1200) mg/24 hours (35% reduction in sodium intake) in the mobile app group and a decrease from 3400 (SD 1200) mg/24 hours to 3300 (SD 1200) mg/24 hours in the usual care group [30]. The total sample size of 24 patients (12 in each group) and 32 patients (16 in each group) will provide 80% and 90% power, respectively, for a 35% reduction in sodium intake. In order to account for patients dropping out or incomplete follow-up, we are enrolling a total sample of 50 patients (25 in each group). We will use a two-sided t test to compare the change in each outcome over time in the mobile app group versus the usual care group. Other quantitative measures of sodium intake will be 24-hour urinary excretion of sodium and estimated 24-hour urinary excretion of sodium from chloride and creatinine dipsticks, which will be analyzed using a two-sided t test and repeated measures analysis of variance, respectively.

Although not powered to determine the impact, other measures of the effectiveness of this intervention will be summarized and evaluated. The percent change in confidence following a low-sodium diet will be analyzed using a two-sided t test. The

change in blood pressure over time will be analyzed using repeated measures analysis of variance.

Data Safety and Monitoring

A Data Safety and Monitoring Plan has been developed for this small intervention trial. Adverse events will be recorded from the day of the first study-related contact and reported to the Institutional Review Board. All participants who experience an adverse event will be referred for treatment. No formal stopping rule for harm has been established for this pilot study, as it evaluates standard-of-care treatment in a low-risk population.

Results

The project was funded in 2016 and enrollment is expected to be complete in the Spring of 2019. The first results are expected to be submitted for publication in 2019.

Discussion

The purpose of this randomized controlled trial is to test the efficacy of just-in-time contextual tailored messages using a mobile app for 8 weeks in patients with hypertension. This is a novel, first of a kind patient-centered decision support tool using geofencing technologies. We hypothesize that this intervention will improve sodium intake compared with the control group. By testing this novel approach, we could be developing a highly scalable mobile health model to help patients optimize their dietary habits in grocery stores and restaurants. If effective, the broader implications to other cardiovascular diseases and clinical outcomes should be explored.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report from the Agency for Healthcare Research and Quality.

[PDF File (Adobe PDF File), 145KB - resprot_v7i11e11282_app1.pdf]

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Abbreviations

ASA24: Automated Self-administered 24-Hour Dietary Recall
CKD: chronic kidney disease
IT: information technology
RR: relative risk

SBP: systolic blood pressure
SCFLDS: Self-care Confidence in Following a Low-sodium Diet Scale

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Protocol

A Customized Intervention Program Aiming to Improve Healthy Eating and Physical Activity Among Preschool Children: Protocol for a Randomized Controlled Trial (Iran Healthy Start Study)

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Abstract

Background: Prevention of childhood obesity is a key approach to the primary prevention of noncommunicable diseases. Several models, based on the population health approach and aligned with ecological models, are used to design childhood obesity prevention programs around the world.

Objective: This study aims to introduce the design and evaluation plan of "Iran Healthy Start (IHS)/Aghazi Salem, Koodake Irani"—the customized Iranian version of Canadian Healthy Start/Départ Santé health promotion program—which is now being developed in Mashhad University of Medical Sciences (Mashhad, Iran) and focuses on improving physical activity and healthy eating among preschool children.

Methods: We will evaluate the intervention using a pilot randomized controlled design. The components of intervention include customized Decoda Web-based resources for children, an implementation guide for educators and managers, training and monitoring, communication and knowledge exchange, building partnership, and parent engagement. Outcomes include changes in anthropometry, physical activity level, nutritional risk status and dietary intake, and quality of life.

Results: The project is funded by Mashhad University of Medical Sciences. The intervention was completed by the end of March 2018, and the analysis is currently under way. The first results of the IHS intervention program are expected to be submitted for publication in December 2018.

Conclusions: The double burden of malnutrition in early years children is a major health concern in developing countries. This justifies the need for health promotion programs that are specifically designed to target both overnutrition and undernutrition prevention. If the efficacy approved, the IHS could potentially be a comprehensive health promotion program for young children whose lifestyle behaviors can be improved toward a healthy future life in a nutrition transition setting.

Trial Registration: International Clinical Trials Registry Platform IRCT2016041927475N1; https://en.irct.ir/trial/22497

International Registered Report Identifier (IRRID): RR1-10.2196/11329

(JMIR Res Protoc 2018;7(12):e11329) doi:10.2196/11329

KEYWORDS

childhood obesity; healthy eating; Healthy Start/Depart Sante; Iran; intervention; parent; physical activity

Introduction

At present, noncommunicable diseases (NCDs) and obesity—as the main predisposing factor of NCDs—are the most common cause of mortality and morbidity, with a higher prevalence in low-income and middle-income countries [1]. The World Health Organization (WHO) has introduced NCDs as the major challenge for development and emphasizes the need for urgent action to prevent and control NCDs [2]. Among the NCDs' risk factors, obesity needs particular attention, as metabolic syndrome and diabetes are directly associated with obesity [3,4]. Early childhood obesity is associated with a higher risk of developing NCDs at a younger age and premature death in adulthood [5,6], as adiposity tracks into adulthood [7]. Prevention of childhood obesity is a key approach to the primary prevention of NCDs [3]. Based on the WHO report, in 2016, an estimated 42 million children aged <5 years are overweight or obese, while around 70% of them live in Asia and Africa [8]. In Iran, according to the latest report of an Iranian national survey on May 2015, which was conducted in 30 provinces, the prevalence of overweight, obesity, and abdominal obesity among children and adolescents aged 6-18 years was 9.7%, 11.9%, and 19.1%, respectively [9].

After the announcement of the WHO on February 2015, regarding the urgency of ending childhood obesity around the world, societies and governments took urgent and meaningful action to address this issue. Childhood obesity is a complex and multidimensional health problem, and usually, single and narrow target interventions do not succeed. Evidence suggests that improving healthy eating and physical activity behaviors are the cornerstone for weight management strategies [10,11], along with decreasing sedentary activities [12,13] and maintaining healthy sleep patterns [14,15], Most recent intervention strategies have focused on modifying environment in a way that provides healthy options for children and increases opportunities for physical activity and healthy eating.

In developing countries, such as Iran, nutrition transition is occurring side-by-side with epidemiological transition. A history of low birth weight or stunting, which still exists in developing countries, is a risk factor for later overweight and obesity in children and consequent cardiovascular diseases or diabetes [16]. According to the data released from the WHO, United Nations International Children's Emergency Fund, and World Bank Group in 2016, Middle East and North Africa, which mainly include higher middle-income countries, have the highest prevalence of overweight and obesity (10.7%) after Eastern Europe and Central Asia (12.8%) among global regions, while the prevalence of coexisting stunting is 15.3% among Middle Eastern and North African countries [17]. The presence of both overweight and underweight in a population or even in families is recognized as "double burden of malnutrition" and highlights the importance of nutrition in early life and its close relation with later-life health conditions [8]. In such a situation, the question arises, "How can an obesity prevention program be conducted, where the problem of overweight and underweight simultaneously exists among children?"

Several childhood obesity prevention programs using different models based on the population health approach [18,19], and aligned with ecological models [20], have been designed and conducted around the world with different scientific rationale [21,22]. Interventions that adhere to principles of the population health approach are designed in accordance with the fact that in a comprehensive population health approach, all levels of impact, such as the intrapersonal (psychological and biological), interpersonal (psychological and social), institutional, community (resources and facilities), and governmental policy, should be included and stimulated to promote the achievements. Healthy Start/Départ Santé (HSDS) is a health promotion program, designed as a population health intervention aiming at promoting physical activity and healthy eating among both Anglophone and Francophone preschoolers in early daycare or preschools in Canada. HSDS is composed of the following 6 interlinked components: (1) evidence-based resource, "Literacy, Education, Activity, Play (LEAP)" from the Decoda literacy Web-based resources [23,24]; (2) HSDS implementation guide; (3) training and monitoring; (4) intersectoral partnership; (5) additional resources; and (6) communication, knowledge development, and exchange. In the evaluation of the HSDS intervention program, 230 children aged 2.5-4 years from very diverse sociocultural and economic backgrounds, from 10 childcare centers, were involved in the project. The results clearly represented groundbreaking and innovative work. Improvements were seen in healthy eating children, physical activity, and childcare environment. Healthy Start has been developed and initiated in the Saskatchewan province of Canada and is expected to expand to the whole country and other countries around the world. The first report of HSDS was released on November 2012 [25].

To address the challenge of childhood obesity and the double burden of malnutrition in a developing country, we decided to calibrate and customize HSDS as a health promotion initiative, which is now successfully running in 2 provinces in Canada [26]. "Iran Healthy Start (IHS)/Aghazi Salem, Koodake Irani" is the customized Iranian version of Canadian HSDS health promotion program, which is now being developed in Mashhad University of Medical Sciences (MUMS; Mashhad, Iran) and focuses on improving physical activity and healthy eating among preschool children. The principles of IHS are adapted from the original Canadian HSDS, considering unique conditions that exist in the Iranian culture, preschool education bylaws, curriculum, and environment.

Textbox 1. Study objectives.

1. To customize and implement the health promotion program (Iran Healthy Start), aligned with preschool bylaws in Iran
2. To determine whether Iran Healthy Start program can:
   - Increase physical activity level and attraction to physical activity among preschoolers
   - Reduce sedentary behaviors at home among preschoolers
   - Improve anthropometric parameters in preschoolers toward healthy weights
   - Improve quality of life in preschoolers
   - Improve eating habits and nutrition risk among preschoolers
3. To evaluate the feasibility, attrition rate, as well as facilitators and barriers for implementing this program in Iranian preschools
4. To calibrate measurement tools: validating the Persian translation of Nutrition Screening Tool for Every Preschooler and Children Attraction toward Physical Activity

From our point of view, some characteristics of HSDS make it more relevant to what we need. The key characteristic of HSDS is that it is based on evidence-based ecological framework [27] and adheres to the population health approach. Furthermore, it introduces strategies for all levels of influence. Another advantage of this program is its multicultural nature, which makes the program more relevant at the international stage and makes the customization easier, although it requires fundamental modifications to be feasible for Iranian preschool children. HSDS targets all children, regardless of their weight or risk of obesity, which is the primary prevention initiative (health promotion) in the public health approach. This level of prevention includes fundamental activities that are directed at reducing the risk of exposure to a risk factor in an individual or the population [28].

Textbox 1 shows the objectives of this study.

Methods

Study Description

This section is addressed on the basis of the Standard Protocol Items: Recommendations for Interventional Trials [29]. In a multisectoral approach, the key stakeholders, including Departments of Nutrition, Chancellor for Health and Chancellor for Research in MUMS, Provincial Education Department, and Nutrition Affairs Department of the Iranian Ministry of Health and Medical Education, are involved in the "IHS" program. The IHS is supported and funded by MUMS. A memorandum of understanding was signed between MUMS and HSDS lead organization (Saskatchewan Network for Health Services in French—Réseau de Santé en Français de la Saskatchewan) in Canada.

Providing the Intervention Material

Prior to the evaluation, we need to provide the material and equipment for children and educators, as well as materials for engaging parents. This step requires the active involvement of the expert panel for the development and customization of the educational content and assistants for providing the toolkit and supplementary materials for implementation.

Development of the Intervention Components, Materials, and Customization Process

Considering some basic differences between Iranian and Canadian education environment and principles, the following criteria were determined for the development and customization of the intervention components and content: (1) Iranian preschool education bylaws; (2) current nutrition and physical activity guidelines for preschoolers; (3) physical area or environment in most preschools in Iran; (4) Iranian common plays, lyrics or songs, and play tools among preschool children; (5) Iranian culture (menu, common foods, and eating culture); (6) known foods preferred by Iranian children of this age; and (7) commonly available foods and their cost. For this purpose, an expert panel, including a nutritionist, physical activity expert, epidemiologist, representative of Provincial Education Department, graphist, psychologist, and an expert in children plays and lyrics, gathered in eight, 2-hour meetings to reach a consensus. Accepted modifications for each component or material or activity unit were registered by the secretary.

The Intervention

The IHS program has 6 components (Table 1):

1. *Customized LEAP*: Comprises two illustrated handbooks.
   - Physical activity: containing 20 activity units along with a complementary chapter containing information for educators (ISBN: 2-25-7457-600-978).
   - Nutrition: containing 20 activity units along with a complementary chapter containing information for educators (ISBN: 9-26-7457-600-978).

   The activity units were translated and customized on the basis of the criteria discussed during the "customization" process. This handbook is accompanied with "Healthy-kid Toolkit," which contains utilities and materials for LEAP activity units.
2. *IHS Implementation Guide*: A handbook for managers and educators containing modified self-assessment tool, as well as principles of the program, action planning, policies and practices, details of implementation, log pages, and report pages for both educators and managers. It also contains a suggested healthy weekly menu for serving a snack or a hot meal for children at preschool.

3. *Training and Monitoring*: Comprises on-site training workshop followed by a supplementary booster session during the implementation (3-4 hours), as well as ongoing support through mobile and internet-based contacts (telegram) and weekly visits. The initial workshop introduces the program, objectives, customized LEAP activity units, IHS Toolkit, and resources. Educators and managers of intervention centers are invited to become a member of the IHS telegram channel, which is the most popular internet-based social network among Iranians. The implementation is monitored by weekly visits and daily logs and checking videos and photos while children do the activities every day.
4. *Building Partnership*: Attracting the participation of key stakeholders and policy makers:
    - Ministry of Health and Medical Education: Nutrition Affairs Department of the Ministry was informed about the details of the project from the inception of the project. The results of this pilot study will be reported to the aforementioned department for further steps toward the national implementation of the program.
    - Provincial broadcasting (radio and television): A television show and radio talks related to childhood obesity, physical activity in children, healthy nutrition, parenting, and many other related topics were recorded to introduce the program and report the future outcomes.
    - Provincial Education Department: Aiming at incorporating this program or any of its components into the current preschool education bylaws, several meetings were arranged with heads-in-charge.
5. *Parent Engagement*: This is the main distinction between HSDS and IHS and includes the following:
    - A scientific, user-friendly, and simple book entitled, "Knowledgeable Parents, Healthier Children," for parents aiming at improving their knowledge and practice regarding healthy eating for the whole family, especially their preschool child (ISBN: 5-24-7457-600-978).
    - Routine monthly meetings between parents and IHS team nutritionists.

    A 107-page book, which is written for parents, contains 5 main chapters as follows: (1) childhood obesity, the epidemic health problem; (2) the importance of healthy nutrition and physical activity for children; (3) the role of parents in children weight management; (4) parental challenges and worriment; and (5) specific nutrition and activity considerations for a preschool child. Parents are asked to read each chapter during one month. In monthly meetings, the content of each chapter is again explained and discussed for parents. These parent-nutritionist meetings are mutual, and parents are allowed to ask questions or share their comments or experiences regarding children's nutrition and activity issues. This book is written by 2 team members (MN and AM). Before releasing this resource, 3 collaborating mothers were selected to read the book and share their comments regarding the fluency, practicality, and usefulness of content, as well as suggestions for adding topics or other required data.
6. *Communication and Knowledge Exchange*: The purpose of this component is maintained by a comprehensive website [30] containing details of the program, pages for managers, educators, parents, and children, as well as social media tools and reports of the study findings for the stakeholders. This component is expected to improve knowledge, engagement, motivation, and level of cooperation in stakeholders, as well as knowledge translation and dissemination of the program and findings.

Tables 1 and 2 show a brief introduction of components of the Canadian HSDS and IHS programs. The Canadian HSDS program [26] consisted of children aged 2-5 years, and the duration of intervention was 11 months. The Iranian IHS program consisted of children aged 4-6 years, and the duration of intervention was 6 months.

Table 1. Brief introduction of the components of the Healthy Start/Départ Santé program.

Program components	Implementation items
Literacy, Education, Activity, Play	Illustrated handbook containing healthy opportunities for preschoolers and Food Flair
Healthy Start/Départ Santé Implementation Guide	Handbook for directors and educators
Training and monitoring	On-site training session, which includes the monitoring of Healthy Start/Départ Santé in the center, as well as a supplementary training session (1-2 hours)
Partnership	Partnerships and linkages with key stakeholders, decision, and policy makers
Additional resources	Supplementary resources from the government
Communication, knowledge development, and exchange	Hands-on material, website, social media tools, dissemination of evaluation findings, and communications through mainstream media releases

Table 2. Brief introduction of the components of the Iran Healthy Start program.

Program components	Implementation items
Customized Literacy, Education, Activity, Play	Illustrated handbook containing customized Literacy, Education, Activity, Play based on the Iranian preschool education bylaws, current nutrition, and physical activity guidelines for preschoolers, physical area, or environment in most preschools in Iran, Iranian common plays and lyrics or songs among preschool children, Iranian common playing tools and materials, Iranian culture (menu, common foods, and eating culture), known foods preferred by Iranian children of this age, and commonly available foods and their cost.
Iran Healthy Start implementation guide	Translated handbook for directors and educators
Training and monitoring	On-site training workshop and a supplementary booster session. The implementation is monitored by weekly visits and daily logs and sending videos and photos while children do the activities
Building partnership	Attracting the participation of the following: • Ministry of Health by reporting results of the pilot study and proposing the national governmental program • Iran broadcasting (radio and television) to introduce the program and report the outcomes • Provincial Education Department for incorporating the designed material into the preschool education bylaws
Parent engagement	A 107-page book provided for parents, containing 5 main chapters to be discussed in each gathering session of parents and IHS team nutritionist (routinely every month)
Communication and knowledge exchange	Website, social media tools, and reports of the study findings for the stakeholders

Development of the Evaluation Plan and Designing the Pilot Study

Obtaining Required Approval and Licenses

Conducting any educational interventions in preschools and schools in Iran needs a valid license from the Provincial Education Department. This license was obtained on October 8, 2016. MUMS and Chancellor for research provided the financial support. The study is approved by the Ethics Committee of MUMS (code: IR.MUMS.fm.REC.1395.208; September 25, 2016) and registered in Iranian Registry for Clinical Trials (ID: IRCT2016041927475N1; November 12, 2016) and is accessible through the WHO database of clinical trial registries. A comprehensive memorandum of understanding was entered between Chancellor for Health, MUMS and Saskatchewan Network for Health Services in French—Réseau de Santé en Français de la Saskatchewan (April 2017).

Development of the Evaluation Plan

Study Design

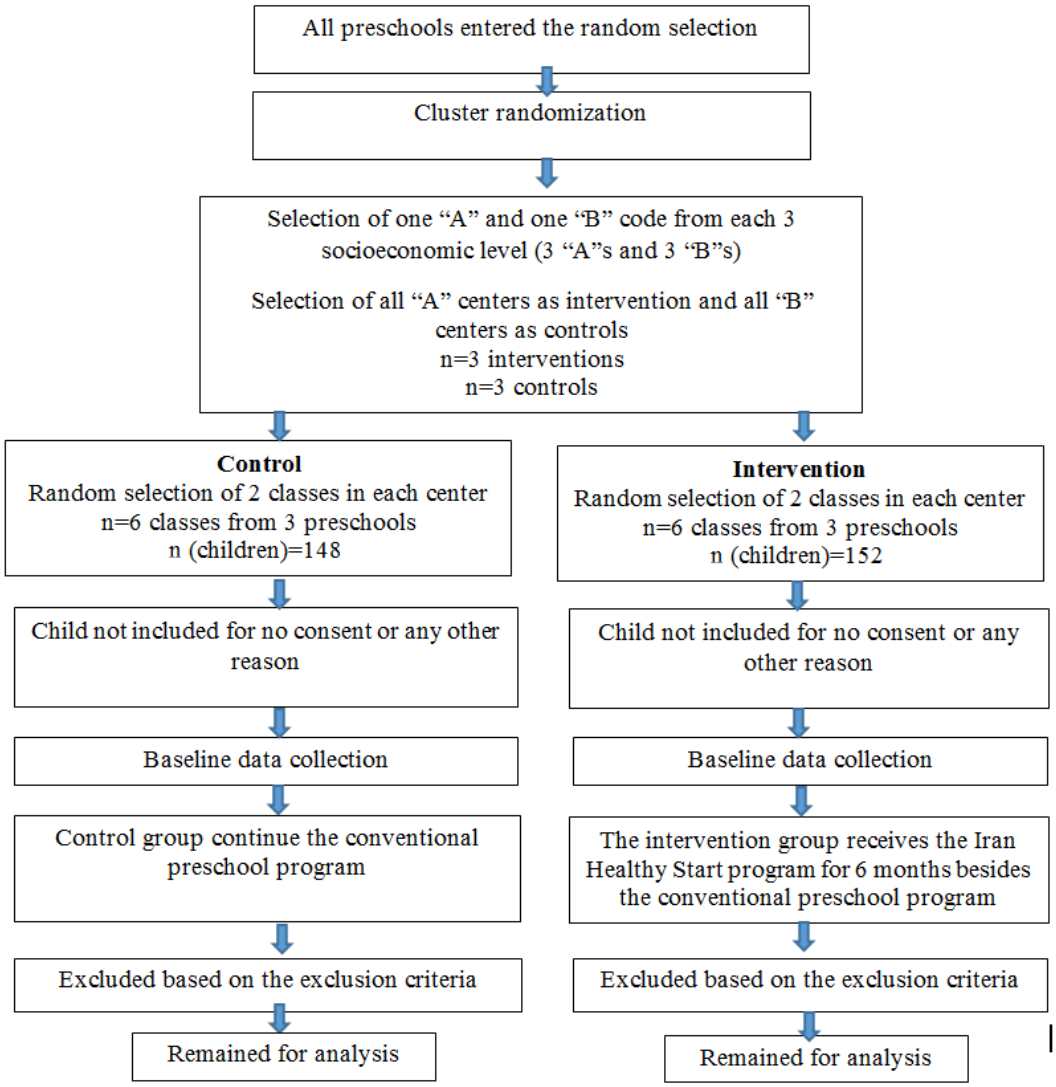
The evaluation of the IHS program is designed as a pilot randomized controlled trial. For recruitment, officially registered preschools in the Provincial Education Department database are stratified according to the socioeconomic status of people living in that area. The three levels of high, middle, and low socioeconomic areas are defined according to the categorization of the Provincial Education Department. Two preschools are randomly selected from each socioeconomic level (a total of 6 centers) and then allocated to the intervention and control groups (Figure 1). Overall, 3 centers in the intervention group (each center belongs to a different socioeconomic level) and 3 centers in the control group are defined. The selected centers are contacted in person and provided with comprehensive information. After confirmation of managers, 2 classes are randomly selected for enrollment (6 classes in the intervention group and 6 classes in the control group). Then, the parents of eligible children are invited in a meeting in preschool, and informed consent is obtained after a brief introduction on the whole program and the role of parents (for parents of the intervention group) and informing parents for data collection and cooperation in filling questionnaires (for parents of the control group). The components of the intervention program for managers, educators, children, and parents are conducted in intervention classes, and control classes receive the conventional preschool education program. Aiming to acknowledge the cooperation of control preschools, the wait-list approach is suggested to the managers to receive the intervention in the next educational year, as well as a comprehensive report for growth, nutrition, and physical activity status of each child, which is given after the intervention, is completed.

The intervention lasts for 6 months. The duration of an educational year in preschools in Iran is the same as elementary schools and lasts for 8 months (October-May). From March 21, there are around 2-week New Year (Norouz) holidays. The intervention will be completed before Norouz holidays. The required data are collected at baseline and after the completion of the intervention period.

Study Setting

Mashhad is a large city in the northeast of Iran and has 7 areas, based on the classification of the Provincial Education Department. Preschools in Mashhad are nonprofit and are under the supervision of the Provincial Education Department. Most of the preschools in Mashhad start at 7:30 am and close at 2:00 pm. This is the official time, but most children, even those whose parents are employed, come at 8:30-9:00 am and leave the preschool at 12:00-12:30 pm. In addition, preschool service taxis follow this time (8:30-12:30). Therefore, children spend around 4 hours at preschools.

Figure 1. Flow diagram of the recruitment process.



Participants and Data Collection

In the Iranian preschool bylaws, preschool is not a mandatory level, and all children aged 4-6 years can be registered either in preschool-1 (age, 4-5 years) or preschool-2 (age, 5-6 years). All children aged 4-6 years of the selected classes of each center are included in the study after a valid consent from their parents or legal guardian, while those with known chronic disease, such as cardiovascular, respiratory, endocrine, or musculoskeletal problems—after physician inquiry—as well as those who need to adhere to a specific diet, such as gluten-free or phenylalanine-free diets, are excluded.

Data reflecting the nutrition status, diet quality, physical activity and sedentary behaviors, quality of life, and anthropometry of children, as well as the general sociodemographic status of participants and their families are collected at baseline and after the intervention is completed (Table 3). Data collection is performed by a team of 4 nutritionists who are given comprehensive training to standardize the data collection. They learned how to consistently obtain anthropometric measurements, fill the required questionnaires, and train the use of pedometers and filling the parent-report questionnaires to parents. Data entry is done by one person for consistency (a PhD student). Each preschool takes about 7-10 days to collect all the required data. As parents' cooperation is very important in the data collection, aiming to acknowledge their cooperation, especially in control preschools, a gift for children and a free nutrition consultation for children and their parents, as well as a comprehensive report for child growth, nutrition, and activity status, are dedicated.

As this is a pilot study and we cannot estimate the attrition rate, there is no need to define the sample size, but sample characteristics represent the population of preschool children in Mashhad.

Table 3. Overview of the study process.

Group and action	Months
Intervention	
Introduction to managers	1
Training educators (workshop)	1
Introduction to parents	1
Baseline data collection	1
LEAP activity units every day	1-6
Providing ongoing support for educators	1-6
Booster session for educators at month 3	1-6
Resources and monthly sessions for parents	1-6
Filling daily logs, weekly reports and comments (increasing intervention efficacy)	1-6
Postintervention data collection	6
Feedback from staff and parents	6
Control	
Baseline data collection	1
Conventional programs in preschools	1-6
Final data collection	6

Table 4. A list of variables, tools, and data collection points.

Variable	Assessment tool	Timing
Sociodemographic data	Questionnaire	Baseline
Anthropometry (children)	Weight, height, waist and arm circumference, body mass index percentile, and body mass index *z*-scores for age	Baseline/End
Nutrition risk (children)	Nutrition Screening Tool for Every Preschooler	Baseline/End
Food intake and eating habits	24-hour recall×3	Baseline/End
Physical activity level (children)	• Children attitude toward physical activity • Physical activity level at home • Physical activity level by pedometers	
Quality of life (children)	Pediatric Quality of Life Inventory questionnaire	Baseline/End
Efficiency and adequacy of the parent material	Interview with parents	End
Feasibility of the program (weaknesses and strengths)	Interview with managers and educators	End

Variables of Interest

Several variables are considered to assess the defined objectives, which are specified earlier. Table 4 presents the main outcome measures that are administered among both intervention and control participants.

Sociodemographic Information

This questionnaire provides demographic data, such as parents' status, age, education level, job, family income, as well as some known childhood obesity associated variables such as parent-reported weight and height, duration of child exclusive and nonexclusive breastfeeding, age of solid food introduction, age of starting kindergarten, eating in front of screen, physical and sedentary behaviors, and some general parenting habits such as child force-feeding, use of food as reward or punishment, parents role model or the presence at meal time, and parental controlling approach.

Nutritional Assessment

Diet Quality

Children's food intake is assessed by the 24-hour recall for each child, which is filled for 3 days (2 regular days and 1 holiday) with a 14-day interval, at baseline and after the intervention. As parents provide children's midday snack themselves and educators are obligated to provide daily reports for parents about the amount of snack their child has eaten, parents are the best source for receiving the data of children's food intake. The Youth Healthy Eating Index (YHEI) was used for the analysis of the diet quality out of food recalls [31,32]. The YHEI focuses on the total fat, sodium, and saturated fat in children's diet by examining food choices rather than a direct calculation of the

nutrient intake. Furthermore, the YHEI focuses on trans-fatty acids, added sugar, and low fiber in children's diet, unlike the conventional Healthy Eating Index [31].

Nutrition Risk

The NutriSTEP [33,34] has been first designed and validated in Canada in different languages for assessing eating habits and nutrition problems in children aged 3-5 years. A license was obtained from the developers of NutriSTEP questionnaires. The Persian version of NutriSTEP was used after translation and cross-cultural adaptation [35]. The NutriSTEP scoring system categorizes children into low, medium, and high risk in terms of nutritional status. It covers 4 main domains related to children's food intake as follows: (1) food and fruit intake; (2) physical growth and development; (3) factors affecting the food intake and eating behavior; (4) physical activity and sedentary behavior.

Anthropometry

Weight, height, midarm circumference, and waist circumference are obtained from all participants, at baseline and after completion of the intervention, according to the standardized protocol [36]. Weight is measured using the Beurer BG13 Digital Scale, Germany, with a measuring rod of 0.1 kg and height using SECA 206 stadiometer, Germany, with a measuring rod of 0.1 cm. The waist and arm circumference are measured to the nearest 0.1 cm. Body mass index (BMI), BMI percentile, and BMI *z*-score are calculated using AnthroPlus software, version 1.0.4, Geneva, WHO, 2009 [37].

Physical Activity Assessment

The physical activity level is assessed using subjective and objective instruments.

Children Attitude Toward Physical Activity

This index is assessed through a 25-item, Likert scale validated questionnaire, which is answered by children with the assistance of an interviewer (educators) and scores children's attitude and degree of attraction toward physical activity [38,39]. The Children Attraction toward Physical Activity (CAPA) original questionnaire was translated into Persian and culturally adapted, based on the current guidelines for translation and cross-cultural adaptation of questionnaires [35]. The Persian version of the CAPA questionnaire has excellent internal consistency among Iranian preschool children after omitting 4 questions (Cronbach alpha=.93).

Physical Activity Level (Subjective)

The level of physical activity at home is assessed by a validated parent-reported questionnaire [40], after translation into Persian and cross-cultural adaptation [35].

Physical Activity Level (Objective)

Pedometers are used for this purpose. Cost, memory capacity, and use burden for children (weight, size, probability of child manipulation, and falling), as well as accuracy and validity, are considered for the selection of pedometers, based on McClain and Tudor-Locke's suggestion [41]. For this purpose, we use Omron HJ320 Triaxis pedometer at baseline and after the intervention. Further to its reasonable price, Omron HJ320 has several advantages to be used in children. It locates on child's waist, which is the body axis and gives a better estimation of the physical activity level. Furthermore, it has a 7-day memory and records the number of steps during 7 consecutive days. It is very light (45 g), easy to both set and use, and impossible for child's manipulation. All pedometers are set based on children's average length of steps.

Quality of Life

Quality of life measures are increasingly being used as an index of population health status after the constitution of the WHO on the definition of "Health" that is a state of complete physical, mental (including emotional and cognitive), and social well-being [42].

We use the Pediatric Quality of Life Inventory 4.0 questionnaire, for children (age 5-7 years) for this purpose [43,44], which has a previously validated Persian version [45] and contains 23 items encompassing 4 fields of children function—physical, emotional, social, and school—and is answered in a 5-point Likert scale.

Qualitative Interview With Parents, Educators, and Managers

We ask educators to write their comments about the feasibility, attraction, useful hints, and suggestions for increasing children's and parents' motivation to actively participate in the program, read the resource, and attend the training sessions during the intervention. After the intervention is completed, we have an in-person interview with managers, educators, and a number of parents to figure out some qualitative data regarding the feasibility of the program in Iran preschools education environment, as well as strengths and limitations of the program in components, materials, and implementation aspects. Parents in the intervention group are stratified to 4 strata, based on the portion of the book they were supposed to read during 6 months—(1) <25%; (2) 25%-50%; (3) 50%-75%; and (4) >75%. Then, 10 parents are randomly selected from each stratum and are contacted through a phone call, and qualitative data regarding the fluency, practicality, usefulness, comprehensiveness, and the potential barriers causing a lack of parental cooperation are collected.

Data Analysis

Descriptive analysis (frequency, percentage, mean, and SD) will be used to characterize and compare the basic characteristics of participants in the intervention and control groups. Outcomes related to nutrition and physical activity will be compared between the intervention and control groups to seek any possible improvements following the intervention. Considering the number of intervention (n=152) and control (n=148) participants, which anticipates a normal distribution, independent sample *t* test, and chi-square tests will be used for between-group comparisons, while paired sample *t* test and MacNemar tests will be used for analyzing within-group changes. Any possible covariates will be controlled with the analysis of covariance test. All tests are 2-tailed, and a significance level of <.05 will be considered statistically significant. Data analysis will be done by IBM SPSS Statistics for Windows, version 23.0 (IBM Corp).

Implementation

Training Educators

Aiming at empowering educators and integration of the implementation among intervention centers, a workshop at baseline and a booster session at the middle of the intervention period is conducted. Details of LEAP activities, activity demonstrations, role of educators, collaboration with parents, and other related implementation hints are presented and discussed.

Process Evaluation and Monitoring

The Reach, Effectiveness, Adoption, Implementation, and Maintenance framework is used to assess the implementation process [24]. Educators are asked to fill logs every day containing the code of activity unit, the time spent on each unit, and feedback of children learning. Photos or videos of LEAP activities are received by the implementation team every day through internet-based contacts (telegram channel). A team member has on-site weekly visits to ensure the standard implementation of the whole program and the activities.

Results

The project is funded by MUMS. The intervention was completed by the end of March 2018, and the analysis is currently under way. The validation papers of the Persian version of questionnaires (NutriSTEP and CAPA) are now completed and submitted for publication. The first results of the IHS intervention program are expected to be submitted for publication in December 2018.

Discussion

Developing societies need to have a health promotion program that can overcome the double burden of malnutrition. This requires both overnutrition and undernutrition prevention strategies to be combined and integrated into education and health systems. The IHS program has the potential of a comprehensive health promotion program for young children whose lifestyle behaviors can be modeled and improved toward a healthy future life. The IHS program is developed and customized considering several criteria. Looking at the preschool bylaws in Iran, there is not a systematic rule or program or guideline targeting optimal nutrition or structured physical activity for preschool children. Except for some preschools in the capital city (Tehran), almost all preschools are part-time and do not serve lunch for children. Breakfast and snack are routinely up to the parents, but in some preschools, especially in higher socioeconomic areas, a hot meal is served as breakfast or snack, but not lunch. Regarding the physical environment, usually there are 20-30 children in a preschool class, and the area of classes is usually around 12-15 m^2, with a small yard where around 10-15 children can safely play. Except for rural preschools, most urban centers do not have adequate space for children to even play or have moderate-to-vigorous physical activities. It is mandatory for preschool educators to teach training books in 2 volumes for preschool children during the educational year, which are developed by the Provincial Education Department and are aligned with the conventional educational objectives in the preschool bylaws, which are briefly titled as follows: (1) training physical and movement skills; (2) training emotional attitude and behaviors; (3) training intellectual skills; (4) training moral and social behaviors; (5) developing fondness for learning the Holly book (Quran); (6) training art and beauty; (7) increasing religious tendency; (8) training national identity; (9) training language skills; (10) promoting health and safety level; and (11) familiarity with the nature and conserving the environment. However, there are not any developed and designed activity units focusing on healthy nutrition and structured physical activity in the bylaws.

There are several main differences between the preschool education systems in Iran and Canada, which account for differences in the Healthy Start program components in the two countries. Instead of “Additional Resources” in HSDS, we included “Parent Engagement.” This component is the main difference and better to say the main strength of the IHS protocol. We engaged parents because based on the recent evidence, parents play a crucial role in children’s weight-control management. This role is comparable or even more important than children themselves [46,47]. Therefore, we organized the IHS program in 6 components as follows: (1) customized LEAP: illustrated handbook containing physical activity and nutrition cards accompanied with healthy-kid toolkit; (2) IHS implementation guide; (3) parent engagement; (4) training and monitoring; (5) communication and knowledge exchange; and (6) building partnership.

The results of this evaluation study might be a scientific foundation for future policies and plans. During the study, we will try to have a look at the feasibility and potential implementation problems and barriers in our country. The main obesity prevention program that is now being conducted in some provinces of Iran is “Ending Childhood Obesity (IRAN-ECHO).” This program is designed and implemented in the framework of the WHO-ECHO program [48]. IRAN-ECHO targets only overweight and obese children of school age. Thus, there is a lack of health promotion program in Iran that targets all children at a younger age where health-related behaviors are more modifiable.

This study has several strengths. First is the randomized controlled design of the study and the stratification, which is based on the socioeconomic level of families as an important independent variable influencing the risk of malnutrition among children. Another strength refers to strategies and plans that attract the active involvement of other stakeholders such as parents, preschool educators, and managers and policy makers.

Some limitations of this study need to be discussed as well. The first refers to a large number of students in each class and limited space; therefore, we had to modify physical activity units to those that can be done at class and do not need too much space. Another limitation is that it is not possible to give a menu for snacks or breakfast to families or preschool managers. The former relates to the fact that we have children from economically disadvantaged families who are unable to provide a healthy snack or breakfast menu every day, and the latter refers to the fact that serving breakfast and snack is not a routine daily

program of all preschools in Mashhad. Therefore, we decided to focus on that meal and advise the required modifications. Another limitation refers to the fact that we cannot include a follow-up period to evaluate the sustainability and long-term effects of the program because children of preschool level-2 usually leave the preschool at the end of the education year and it is not feasible to track them in other centers.

As a plan, this evaluation study will guide for the development and improvement of the IHS intervention to be qualified as a comprehensive health promotion program and conducted in the whole country, aiming at the prevention of overweight and obesity among preschool children.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review report 1 (in Farsi).

[PDF File (Adobe PDF File), 209KB - resprot_v7i12e11329_app1.pdf]

Multimedia Appendix 2

Peer review report 2 (in Farsi).

[PDF File (Adobe PDF File), 208KB - resprot_v7i11e11329_app2.pdf]

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Abbreviations

BMI: body mass index
CAPA: Children Attraction Toward Physical Activity
HSDS: Healthy Start/Départ Santé
IHS: Iran Healthy Start
LEAP: Literacy, Education, Activity, Play
MUMS: Mashhad University of Medical Sciences
NCDs: noncommunicable diseases
NutriSTEP: Nutrition Screening Tool for Every Preschooler
WHO: World Health Organization
YHEI: Youth Healthy Eating Index

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Protocol

Efficacy of an Education Session by Pharmacists for Patients With Asthma: Protocol and Design of a Randomized Controlled Trial

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Abstract

Background: Asthma is a chronic disease that requires indefinite long-term therapy. Many approaches have been developed to enable people with asthma to live as normally as possible. In medication therapy management, pharmacists could play important roles in supporting the everyday life of asthmatic patients, such as by providing education therapy management to ensure that patients achieve optimal therapeutic outcomes. A good collaboration between health care practitioners and patients will produce a better system in terms of therapeutic management, which will lead to health care cost savings related to emergency visits. Although the Government has made various efforts to manage asthma in Indonesia, without commitment and support from both patients and health care professionals, the expected outcomes cannot be achieved.

Objective: This study aims to evaluate the effectiveness of an educational intervention provided by pharmacists compared with that of usual care.

Methods: A randomized controlled trial comparing usual care with an education session by pharmacists is underway. The intervention comprises a one-on-one education session of 60 minutes with a pharmacist comprising information regarding (1) asthma medication that has been used; (2) how to use asthma medication devices correctly; (3) asthma symptoms and how to prevent exacerbation of asthma; and (4) how to manage asthma triggers and environmental control measures. The primary outcome measure is change in asthma control, as measured using the Asthma Control Questionnaire. Secondary outcomes include changes in Asthma Quality of Life Questionnaire score, lung function, asthma-related health visits, days off from work or study, and oral corticosteroid use. Research assistants who are masked to the group allocation will collect outcome data at the baseline and every month for a 3-month period. Informed consent will be sought at enrollment and intention-to-treat analysis will be performed.

Results: This study was funded in January 2017 and ethical approval was obtained in June 2017. The enrollment was started in August 2017, and about 72 participants have been enrolled. First results are expected to be submitted for publication in 2019.

Conclusions: This is the first study to evaluate the effectiveness of a pharmacist-guided asthma education session compared with that of usual care in Indonesia. If it is proven effective, this intervention program could improve asthma self-management by patients, which may reduce risks of poorly controlled asthma. This intervention could also be implemented in addition to the current usual care for patients with asthma.

Trial Registration: Thai Clinical Trials Registry TCTR20171219001; http://www.clinicaltrials.in.th/index.php? tp =regtrials&menu=trialsearch&smenu=fulltext&task=search&task2=view1&id=3068 (Archived by WebCite at http://www.webcitation.org/73Ci5eKtv)

International Registered Report Identifier (IRRID): DERR1-10.2196/10210

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KEYWORDS

asthma control; education session; pharmacist

Introduction

Asthma is a chronic disease that affects people of all ages worldwide. Uncontrolled asthma can restrict patients' daily activities and can place them at risk of death. According to the World Health Organization and Global Initiative for Asthma, as many as 300 million people worldwide, of different ages and races, are exposed to asthma; this number is predicted to increase to 400 million by 2025 [1]. Asthma is a health problem in both developed and developing countries [1-3]. Approximately 250,000 people die of asthma each year [3,4]. In 2007, asthma caused 3447 deaths in the United States—equivalent to approximately 9 people each day [5]. Death due to asthma is more common among adults than among children; it is also more common among women (2173) than among men (1274) [5]. In the United Kingdom, >10% of the adults exhibit asthma [6,7]. Although the proportion of population affected by asthma in Asian countries, including Indonesia, is lower than that in Europe or America, the proportion of elderly patients with asthma in Asian countries is quite high (1.3%-15.3%) [8]. Asthma can be controlled with appropriate therapeutic management. Patients with controlled asthma conditions can participate in normal activities and are not likely to experience fatal asthma symptoms [9].

Asthma is a chronic disease that requires indefinite long-term therapy. Various approaches are needed to optimize therapeutic treatments among asthma patients. Several studies in developed countries, such as the United States [10,11] and Australia [12-14], have showed that better health outcomes for asthma patients resulted from the following factors: adequate knowledge among asthma patients, regular monitoring of therapy, and high level of understanding among both health care professionals and patients regarding the disease management behavior. In Indonesia, asthma is one of the top 10 causes of morbidity and death, together with chronic bronchitis and emphysema [15]. In April 2007, observations in 5 provinces of Indonesia (North Sumatra, Central Java, East Java, West Kalimantan, and South Sulawesi) conducted by multiple chronic and degenerative disease subdivisions showed that, in general, asthma control efforts have not been effectively implemented; moreover, there is minimal availability of the equipment required for the diagnosis and management of asthma patients in health care facilities. In 1995, the prevalence of asthma in children was 12%; in 2008, results of the International Study of Asthma and Allergies in Childhood showed that asthma prevalence in 12-14-year-old children was 12.6% [16].

It is currently unknown how the implementation of pharmacist-guided education in asthma self-management might affect asthma self-management in Indonesia as there has been limited research regarding the understanding and behavior of patients for the management of asthma. Therefore, the proposed study has been designed to determine the effectiveness of pharmacist-guided education for asthma patients in Indonesia. Because medications play important roles in successful management of chronic diseases, including asthma, the role of pharmacists' expertise is essential in the implementation of medication therapy management. Studies have shown that improved asthma control can be achieved if patients are involved in self-management, including self-monitoring of asthma symptoms or lung function, as well as when patients follow written asthma action plans while maintaining regular contact with their health care professionals [17].

This study aims to evaluate the efficacy of pharmacist-guided education sessions provided to patients with asthma compared with that of usual care. We hypothesize that the intervention group will demonstrate superior asthma control, as measured by changes in the Asthma Control Questionnaire (ACQ) scores, after 3 months from the baseline.

Methods

Study Setting

Participant recruitment is ongoing at the outpatient Departments of Pulmonology at Universitas Airlangga Hospital. The study has been approved by the human research ethics committee of Universitas Airlangga Hospital. All participants provide written informed consent at the time of enrollment.

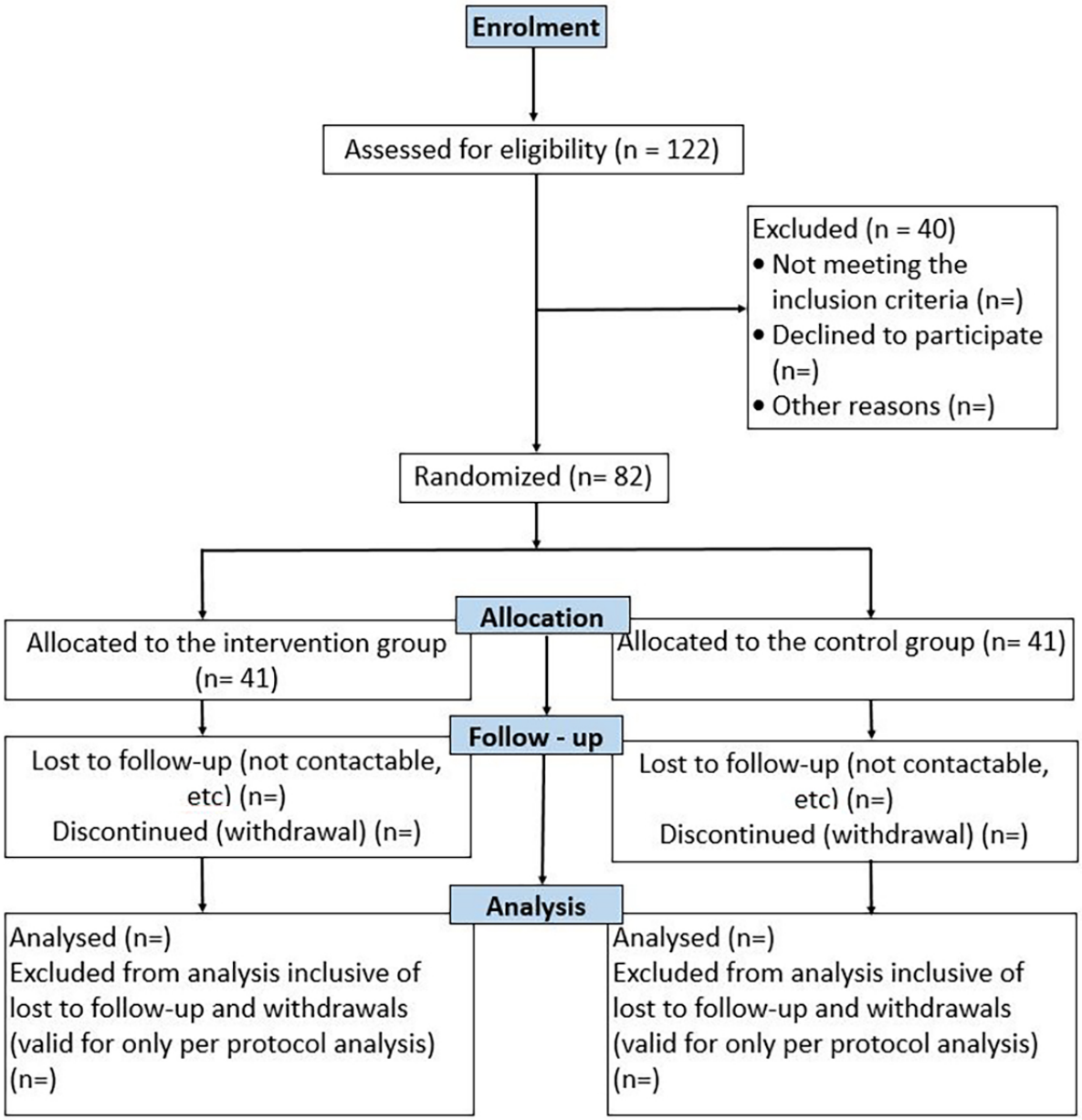
Study Design

This study is designed as a prospective, single-blinded, randomized controlled trial (Thai Clinical Trials Registry # TCTR20171219001); outcome assessors will be masked to group allocation at follow-up assessments. The flow of participants with the expected number is illustrated in Figure 1. The total duration of the study is 3-6 months, depending on the timing of the first visit and patient enrollment in the study. Both groups will be followed up for 3 months; the outcomes will be compared at 1, 2, and 3 months from the baseline to evaluate the efficacy of the intervention.

Inclusion and Exclusion Criteria

Eligibility for this trial includes patients with asthma who have used any regular medications for asthma within the previous 12 months, who are 18 years of age or older, and are able to communicate in Indonesian. Those who are unable or contraindicated to demonstrate the lung function with spirometer will be excluded.

Figure 1. Flowchart of study participants.



Trial Recruitment

The following methods of identification and recruitment of participants will be used in this study: First, the doctors will identify all patients with asthma visiting the outpatient Department of Pulmonology at Universitas Airlangga Hospital on the date of each patient's clinic visit. The research assistants will approach potential participants and perform screening on the basis of the inclusion and exclusion criteria that were described earlier in this protocol. Then, participant explanatory statements and expression of interest forms will also be provided at the outpatient Department of Pulmonology at Universitas Airlangga Hospital, which has access to the relevant information. Potential participants will be asked to leave their contact details to allow one of the research assistants to contact them. Finally, if a patient agrees to participate, written informed consent will be sought.

Group Allocation

Recruited participants will be allocated to intervention or control group on a 1:1 basis. Allocation will be concealed using the sealed opaque envelope technique. Random blocks of 4 and 6 will be chosen, and random numbers will be generated using a random allocation software program [18] by an external researcher not involved in the study. Only this researcher will know the allocation sequence. At the time of recruitment, the researchers coordinating this study will open the numbered envelope and allocate each participant to the control (usual care) group or the intervention (education) group. The outcome assessors will be masked to participant group allocation during follow-up assessments.

Control and Intervention Group

Control: Usual Care Group

Participants allocated to the control group will receive usual medical care provided by the Department of Pulmonology and its health care professionals. This includes regular monthly visits, depending on each patient's asthma severity or complications. If, during follow-up, it becomes apparent that asthma control has deteriorated since the prior assessment (eg, using the asthma reliever ≥3 times per week or requiring an increased preventer dose), the participant and corresponding health professionals will be notified with the participant's permission.

Intervention: Education Group

Before the delivery of educational sessions to patients, pharmacists in this study will undergo training provided by a certified asthma educator (EZ). The trial evaluates an intervention involving pharmacists to deliver a *one-on-one* education session regarding (1) asthma medication that has been used; (2) how to use asthma medication devices correctly; (3) asthma symptoms and how to prevent exacerbation of asthma; and (4) how to manage asthma triggers and environmental control measures. A video that explains how to properly use asthma medications with a variety of devices will be shown to the intervention group. The intervention group will also be provided with an asthma booklet that explains how to correctly use asthma medication and avoid asthma triggers. One of the researchers will contact participants' health care professionals if any medication changes or unscheduled asthma-related visits are needed.

A written asthma action plan, consistent with the Global Initiative for Asthma guidelines, has been translated into the Indonesian language and will be used to design a participant-specific treatment plan based on the information obtained at the baseline. The asthma action plan contains instructions regarding which medications to take when feeling well, how to recognize worsening asthma, what to do when symptoms are worsening, and what to do in the event of an acute attack, including a first aid plan. The flow of the study is described in Figure 2.

Outcome Measures

The primary outcome measure is change in asthma control, as measured by the Juniper ACQ [19]. Secondary outcomes include changes in Juniper's Asthma Quality of Life Questionnaire score [20], lung function, Adherence to Refills and Medications Scales scores, asthma-related health visits, days off from work or study related to asthma, and oral corticosteroid use.

Data Collection and Follow-Up

ACQ scores, Juniper's Asthma Quality of Life Questionnaire scores, Adherence to Refills and Medications Scale scores, asthma-related health visits, asthma-related days off from work or study, oral corticosteroid use, and preventer or reliever use data will be collected at the baseline and at 1, 2, and 3 months from the baseline to allow comparisons. Identical data collection forms will be used for both groups. The assessors responsible for collecting outcome data at 1, 2, and 3 months will be masked to participant group allocation.

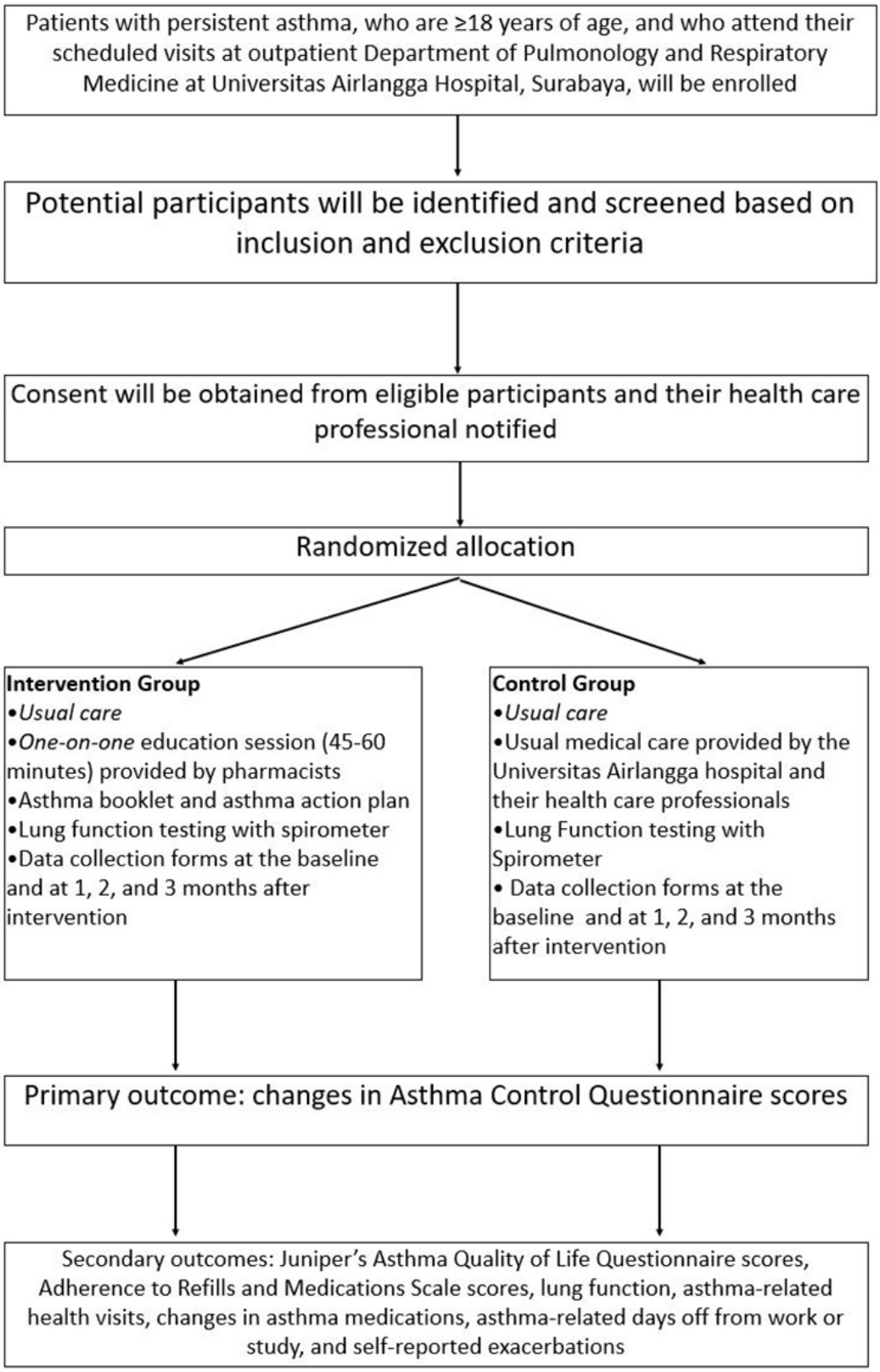
Sample Size

A sample size of 28 participants per arm using an estimated SD of 0.66 in ACQ scores will have 80% power (with 2-sided 5% significance level) to detect the minimal clinically important difference in the ACQ score of ≥0.5 between the groups [21,22]. To allow for 25% attrition, 41 participants will be recruited for each arm.

Data Analysis

The primary analysis will be performed in accordance with the intention-to-treat principle. The baseline characteristics of the 2 groups will be compared using Student's *t* test for normally distributed continuous variables, Mann-Whitney *U* test for nonnormally distributed continuous variables, and chi-square or Fisher's exact test (as appropriate) for categorical variables. Primary inferential analysis will be conducted using a mixed effects model for the intention-to-treat population. This model will include the treatment group and time as fixed effects, with an interaction between treatment and time to ascertain if the groups behave differently over time. Other demographic and clinical factors will be included as potential covariates in the mixed effects model. Comparisons will also be made of the following: the proportion of participants whose ACQ score improves >0.5 (minimal clinically important difference) over the study period, the proportion in whom asthma remains "not well controlled" (ACQ score ≥1.5), and those whose asthma is "well controlled" (ACQ score <1.5) at each time point [23]. Secondary outcomes will be summarized using descriptive statistics; analyses will be performed using the methods described above.

Figure 2. Flowchart of the study.



Results

This study was funded in January 2017 and ethical approval was obtained in June 2017. The enrollment was started in August 2017 and is currently ongoing; we plan to complete the enrollment by December 2018. About 72 participants have been enrolled in the trial. First results are expected to be submitted for publication in 2019.

Discussion

This is the first study to evaluate the effectiveness of a pharmacist-guided asthma educational session compared with that of usual care in Indonesia. If it is proven effective, this intervention program could improve asthma self-management by patients, which may thus reduce the risk of poorly controlled asthma. This intervention could also be implemented along with the current usual care for patients with asthma. This trial is designed to evaluate an educational program for patients with asthma in order to enable better self-management for the control of their asthma. The individualized written asthma action plan designed for each patient provides clear guidelines in terms of actions to be taken in case of worsening asthma.

The proposed intervention has the potential to improve asthma outcomes by facilitating better asthma self-management. This may translate to reduced health care costs in the form of fewer asthma-related unplanned medical and emergency department visits. If the intervention is efficacious, this could potentially influence clinical practice and health policy.

In order to improve health outcomes of asthmatic patients, solutions include regular monitoring as well as education regarding medication use and compliance. Most chronic diseases require patients to undergo therapy for an indefinite duration to meet therapeutic goals. Pharmacists have an important role in ensuring patients achieve optimal therapeutic outcomes. A pharmacist should be aware of this role, which involves providing adequate information to patients with chronic diseases. By building collaborations among health care professionals, a robust system of therapeutic management for patients with asthma will be established, enabling improvement of health outcomes and potentially reducing health care costs. Multiple efforts have been initiated by the government to manage asthma in Indonesia; however, without support and commitment from both health care professionals and community, the desired results cannot be achieved.

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Authors' Contributions

EZ conceived the project idea with input from GN, GNVA, and YN. EZ further developed the trial with input from all other authors: AB, MA, AS, GN, GNVA, and YN. EZ is managing the trial, while GN is organizing research assistant rosters. EZ wrote the first draft of this manuscript and refined it on the basis of comments and feedback from all other authors.

Conflicts of Interest

None declared.

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Abbreviations

ACQ: Asthma Control Questionnaire

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Original Paper

Acceptance and Resistance of New Digital Technologies in Medicine: Qualitative Study

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Abstract

Background: This study discusses the acceptance of new medical technologies in health care settings and resistance to these technologies from hospitals, doctors' surgical centers, electronic health (eHealth) centers, and related institutions. We suggest a novel method of identifying factors that influence the acceptance of, and resistance to, new technologies by medical staff and patients.

Objective: The objective of this study was to determine and evaluate the factors that influence acceptance and resistance to achieve a successful implementation of new technologies.

Methods: The target group was patients residing in Brandenburg and major stakeholders in the local health care structure, for instance, medical institutions and medical professionals. The process relies on 3 models: the technology acceptance model, the unified technology acceptance and use of technology model, and the theory of technical innovation diffusion. Qualitative methodology was employed in this study, and an exploratory design was adopted to gain new insights into a poorly understood phenomenon in the German context. This enabled the researcher to take a flexible approach toward exploring a wide range of secondary data and to choose a different approach when unexpected information emerged. Content analysis was used to identify and interpret the data, and the researcher assured that the meaning associated with the information has concurred with that of the original source.

Results: This study confirmed that adoption of new technologies in health care depended on individual opinions of the factors relating to them. Some medical professionals believed that technology would interfere with their ability to make independent diagnoses and their relationships with patients. Doctors also feared that technology was a means of management control. In contrast, other medical staff welcomed technology because it provided them with more opportunities to interact with patients and their carers. Generally, patients were more enthusiastic about technology than medical professionals and health care managers because it allowed them to have greater autonomy in selecting health care options. The need for all groups to be involved in the development of the new health care approach was an important outcome, otherwise resistance to it was likely to be greater. In other words, the strategy for change management was the indicator of success or failure. Therefore, following our analysis, a number of practical precepts emerged that could facilitate user acceptance of digital solutions and innovative medical technologies.

Conclusions: The acceptance of digital solutions and innovative medical technology by patients and professionals relies on understanding their anxieties and feelings of insecurity. The process will take time because individuals accept change at different rates. Hence, the development of an extensive user community to fully and successfully implement eHealth is less likely in the short term; however, this should not prevent the push for changes in health care technology.

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KEYWORDS

innovation diffusion; information and technology communication; telematics infrastructure; health care innovation

Introduction

The term electronic health (*eHealth*) encompasses all apps that integrate modern information and communication technologies (ICT) to treat and care for patients. Therefore, eHealth is considered to be a general term for a wide range of ICT-based applications, which process information electronically. This information can be exchanged to support patient treatment and care processes because medical data obtained from the eHealth card can be easily communicated. This information consists of emergency data, treatment plans, medications, and the electronic patient file or telemedicine applications. This health information is communicated via a telematics infrastructure [1], and eHealth is summarized as follows: "a new term used to describe the combined use of electronic communication and information technology in the health sector" [2].

Therefore, eHealth centers are institutions or workstations that are fully equipped with specific medical diagnostic equipment and information technologies (ITs). These features enable members to run diagnostic tests and communicate results to doctors in real time. Thus, eHealth centers demonstrate how modern health care can be delivered to underserved populations and can encourage healthier communities.

Health care innovations seek to achieve stability, security, sustainability, and high qualitative value through networked structures, technological solutions, and analog interaction spaces. Innovative medical technology and digital solutions are components of innovative patterns and models. However, the successful implementation of innovative medical technologies, in particular digital companions, depends on acceptance by medical staff, such as doctors and nurses. These individuals directly confront new technologies and their implementation, with patients positioned as customers. To determine if innovation benefits these groups, resistance must be identified and reduced by creating greater awareness of the technologies and convincing potential users of advantages associated with the use of these technologies. Therefore, in medical settings, the implementation of new medical technologies should also consider psychological indicators that indicate developing acceptance, thus supporting a win-win situation. Resistance to new technologies or procedures should be recognized by medical professionals and their customers. Once recognized, these forms of resistance can be overcome by carefully planned and appropriate interventions.

Therefore, we sought to identify drivers of and barriers to the adoption of new health care technologies by referencing existing studies and then generated recommendations for improving technology uptake and diffusion. The resultant recommendations will be tested in future research projects.

Acceptance is a perceptual phenomenon that involves evaluation of new experiences and arriving at a final decision with respect to the benefits and limitations of that experience. Acceptance outcomes are derived from attitudes or courses of action. The development of acceptance depends on the interaction of 3 elements: subjective acceptance, objective acceptance, and the context in which acceptance occurs. Acceptance is an unpredictable construct because modified perceptions or general conditions can lead to different levels of acceptance. The decision to accept or reject a certain technology depends on various influencing factors [3]. Psychological approaches focus on attitudes, positions, norms, and value system factors that influence acceptance. Emotions and sociodemographic factors, such as age, gender, and educational level, similarly influence acceptance. Objective acceptance relies on how relevant an individual evaluates an innovation's characteristics, acknowledging that identical characteristics may lead to different responses. This is because major influencing factors vary among individuals and may include financial impact, cost-benefit analysis, acquisition of necessary skills, or opportunities for work facilitation.

Technology acceptance also depends on perceived risks, such as whether the technology delivers secure care that is reliable and effective. Ease of use is of particular concern to users as new technology should facilitate more efficient execution of health-related tasks. The content factors related to acceptance are not directly related to users; rather, they externally influence users. One example of this could be jobs that are supported by new technologies and social processes in organizations, groups, or communities involved in implementing new technologies. Other contextual factors include organizational and social environments, including existing routines, political climates, participation cultures, the state of the economy, legal frameworks, and the processes by which innovation is introduced.

The technology acceptance model (TAM) is frequently used to explain acceptance [4] and provides insight into an individual's decision to use or reject technological innovations [5]. The TAM proposes that the use of technology depends on 2 variables: how useful the technology is perceived to be and how easily it can be employed. Perceived usefulness is defined as an individual's subjective evaluation of the new technology in relation to how much it will enhance their job performance. In contrast, perceived ease of use is the assessment of the effort required to learn and use technology. The balance of effort and usefulness underpins the development of user acceptance and influences user motivation. In general, an individual's motivation to use a technology is higher if that technology is easy to use. External factors, such as support measures, have a positive effect on the perception of usefulness and on understanding a technology. In general, individuals adjust to new procedures quickly.

The unified technology acceptance and use of technology (UTAUT) model is an extension of the TAM that bases the growth of acceptance on 4 factors: performance expectancy, effort expectancy, social influence, and facilitating conditions [6]. Performance expectancy is a person's perception of the extent to which a new technology brings about improvement and is the strongest predictor for the development of acceptance.

As with the TAM, effort expectancy in the UTAUT model is the perceived usefulness and complexity of the technology. Social influence describes an individual's perception of the extent to which others believe a new technology should be used and facilitating conditions under which individuals recognize interventions that support the use of the technology, for example, organizational or technical infrastructures. These models are used more than any other methods to explain acceptance, and some technology specialists suggest that studying their effectiveness has detracted from new research fields in technology acceptance. Their major shortcomings include the fact that research related to TAM was conducted under the assumption that a positive relationship exists between new technology use and user satisfaction, quality, and productivity; however, this was not proven [7].

The innovation diffusion theory examines technology uptake by individuals and organizations, focusing on the technological innovation development process from the invention stage to general acceptance or rejection. Five characteristics of innovation influence the diffusion of a new technology: relative advantage, compatibility, complexity, opportunity for a trial, and observability. Relative advantage is a technology's perceived superiority over current methodologies, whereas compatibility is a social factor related to how well the technology matches social norms and behaviors. The remaining 3 factors describe its practical usage, with complexity indicating how easy it is to learn, opportunity for a trial being the technology's amenability to evaluation and the chances of this occurring before adaptation is determined, and observability is associated with the capacity to observe the new technology's outputs and advantages over alternatives. Although all 5 factors affect the rate of technology diffusion and no single aspect is strong enough to predict acceptance, the rate of innovation diffusion is the most affected by low complexity, the opportunity to *try out* novel technologies, and observability [8]. Empirical studies have also found that relative advantage and compatibility have positive associations with technology adoption, whereas complexity is negatively related to adoption [9]. The limitations of the innovation diffusion theory include the interpretation of relative advantage, which is a subjective factor because a cost versus benefits comparison is most important to some individuals, whereas ease of use is more appreciated by others.

The indicators of the development of acceptance, characteristics of the actors, features of the technological innovation, planned interventions implemented for its introduction, and observable benefits for patients and practitioners (including social factors and diverse environmental characteristics) decide the likelihood of individual adoption and dissemination of innovations. The weaknesses associated with the 3 theories, however, represent a gap in the current literature. There is a need to verify whether the assumptions underlying TAM result in positive outcomes and whether the subjective nature of relative advantage affects the rate of technology uptake purported by the innovation diffusion theory.

As environmental factors do not change easily, they are considered to be exogenous. Endogenous components, such as the actors and innovation, are critical for the development of acceptance. These factors are explored in the proposed methodology.

Methods

Methodological Process

This study is the precursor to a future project; therefore, the methodology indicates how the entire study will proceed. This study gathers major findings from previous research on eHealth technology acceptance to make recommendations for enhancing uptake of technology diffusion, which will be later tested empirically.

Research Philosophy, Design, and Strategy

Social science research may adopt 2 diverse philosophies: objective and subjective stances. The objective stance seeks to determine objective cause-and-effect links between variables, whereas the subjective approach seeks to gather deep insight into how human beings interpret the same phenomenon differently. The objective approach is associated with a positivist research philosophy, which is similar to scientific approaches. It suggests that acceptable knowledge is generated from 1 source, that reality based on the phenomenon is independent of its context, and that the researcher has no effect on the outcomes of their research work; in other words, the research findings are value free. This stance is less important to resolving the research problem in this study, but its cause-and-effect links do form part of the solution. However, the subjective reasons as to why these links occur are of more practical value to health care providers and their patients; therefore, the emphasis of this study is on the subjective stance.

The subjective stance assumes that knowledge is derived from many sources because individuals observing the same phenomenon will tend to interpret it in diverse ways. These individualized interpretations exist as a consequence of each individual's diverse values, beliefs, and experiences. Hence, reality is socially constructed, and the researcher is a major part of the study; thus, research is value-laden. Traditionally, although research has been based on either an objective or a subjective stance, researchers have recently focused on a combination of both stances; however, these combinations can vary in their relative proportions. Therefore, the main research design for this study is exploratory, which means that the researcher takes a flexible approach toward obtaining in-depth insights into a new or poorly understood phenomenon, as is the case in this study. If the researcher discovers unexpected information, this information can be pursued and the direction of research altered. In contrast, an objective stance demands stringent adherence to a pre-established design, which can be of much less value for answering certain research questions. The study, which has 2 parts, intends to generate new findings, an inductive approach, while confirming known theory, which is referred to as deduction [10].

The research philosophy is, therefore, interpretative as the subjective and objective stances can be combined in 1 study [11]. The research strategy for this study is archival and documentary because secondary data are used to establish the current status of technology acceptance in eHealth. However,

moving forward, we will adopt a survey strategy using semistructured interviews to gain the opinions of medical staff and patients on the basis of the recommendations made by this initial study.

Methodology for Data Collection and Analysis

Qualitative research methodology, which is well established with the interpretivist research philosophy and with the theory-building inductive approach, was selected for the study. Therefore, qualitative data will be the main priority; however, some numerical quantitative data may also emerge.

In this study, secondary data will be collected from robust sources such as books, journal articles, specialist magazines, and reliable websites that are noncommercial. These archived data are freely available in electronic form and comprise specialist articles, quality newspaper reports, and interview transcripts, for instance [10]. The future study will employ semistructured interviews for the collection of empirical data suitable for identifying resistance from employees and patients in Brandenburg, Germany. In this case, feelings of fear and insecurity can be identified by means of standardized interviews as part of the development of acceptance because interview questions will be based on the findings of this study.

Sample

The sample for the second study is a purposive, nonprobability sample that uses the opinions of experts to answer the research question; the researcher selects the interviewees and invites them to participate. In-depth knowledge is more important than the generation of findings that are applicable to an entire population, particularly because populations in different communities are likely to hold diverse views [11]. The sample comprises a combination of the key stakeholders in the Brandenburg local health care structures and its patients, including doctors' practices, accident and emergency hospital departments, medical professionals, and other health care professionals. Local health care structures play a key role in technology adoption because they can serve as multipliers and act as partners for digital care solutions. The communication target groups, which are the focus of efforts to build new technology acceptance, include key medical opinion leaders: The Brandenburg Chamber of Physicians; The Brandenburg Association of Statutory Health Insurance Physicians; Associations of General Practitioners in Brandenburg; other relevant professional and trade groups; and representatives of the local, county, and state governments.

Data analysis for this study and the empirical study to test its findings will be conducted using content analysis. This means that the data collected and transcribed will be scrutinized to identify keywords and phrases that are associated with technology acceptance and how the development of acceptance might be enhanced and its diffusion rate accelerated. These words and phrases will be organized into major themes, which are interpreted for meaning by the originator or originators, and can then be discussed, summarized, and presented in tables and charts [12].

Ethics

All ethical standards associated with social science research are applied to this study. Although the first part is solely informed by secondary data, the researchers aim to interpret the data such that it reflects its original emphasis rather than the researchers' own preferences. In the future empirical study, the researchers will ensure that participants do not suffer any harm as a consequence of expressing their opinions, and strict confidentiality will be maintained; in other words, the report will not indicate the source of any view expressed within study interviews [11].

Results

The increased number of patients being treated is generally caused by the aging society, which incremented the complexity of health care systems. This is due to the number of terminal diseases experienced by these patients and the introduction of new technologies that enable medical professionals to diagnose illnesses more precisely. These technologies also give rise to surgical interventions that are more effective and less invasive. However, to benefit from new technology app, sustainable financial resources must be first organized in a cross-sectoral manner in primary care institutions, specialist clinics, and rehabilitation centers. However, the concept of a *boundary-less hospital*, although achievable, is hindered internally by insufficient, ineffective network design, silos resulting in poor communication, lack of an interdisciplinary approach, and inefficient processes. eHealth services have the potential to resolve the challenges of treating increasing numbers of patients, including those with chronic diseases, and creating efficient communication between departments. Many studies have demonstrated the benefits of telemonitoring, reducing hospital emissions, and controlling chronic conditions remotely for patients. However, despite these positive facts, uptake has been slow [13] because the potential cost-saving advantages of new technologies are not always evident to major stakeholders. In some cases, new technologies that comprise eHealth solutions are initially associated with higher costs and more time compared with traditional alternatives [14].

Major influencers in the adoption of eHealth are reported in empirical studies, for instance, the extent of trust that the patient has in a service provider, perceived user-friendliness of tools, health condition severity, and anonymity when using self-diagnosis tools. Medical professionals have concerns regarding the design of eHealth services and the technologies on which it will rely. Medical professionals also hold subjective opinions of the usefulness of new technology, its complexity, and/or how familiar technology is to end users. Hospital culture, location, and size have impacted the decision makers' consideration for the relevance of tools such as eHealth applications for radiology and patient scheduling. Hence, there are 3 groups of main stakeholders comprising important subgroups, and these subgroups affect both acceptance and the development of acceptance.

Empirical research on patient acceptance factors affirms the importance of age. Although older people tend to need health care services the most, this group is often averse to technology,

to the point where customized interventions are needed to support tool adoption. Despite widespread adoption of mobile technologies, such as smartphones, in Germany, with millions of people downloading apps, very few older adults use eHealth apps, preferring websites and email [15]. This suggests a lack of awareness of the benefits of these applications. In general, the study demonstrated that acceptance is a multistage process and that patients developed acceptance according to defined stages and at different speeds. Various organizations and medical professionals serve to raise awareness within the health care system; therefore, service providers should increase their marketing efforts. This might include highlighting benefits to patients through enhanced communication with medical professionals and greater access to support and 24/7 monitoring of known illnesses. Medical professionals could also leverage patient awareness of the potential for individualized service because they hold access to electronically organized patient information, which can be continuously updated.

Medical professionals and organizations could also inform patients of reliable medical websites, which provide information on the benefits and costs of eHealth. In addition, health service and medical professionals should elicit feedback from patients to support more effective use of eHealth tools and help improve the quality of these tools. In effect, patients need to be involved in the development of eHealth acceptance [13].

eHealth cards were introduced in Germany approximately 10 years ago upon their mandated use. An empirical study found that primary care doctors felt that eHealth could lead to fewer prescription errors and improve communication among various individuals and groups providing patient care. However, doctors also stated that their involvement in technology development and their ICT expertise were very low. The study also found that 46% of the variance in the perceived usefulness of eHealth cards was related to IT capability [16]. Health care professionals' motivation to use eHealth records depended on the quality of interaction with the patient; however, lack of time, workload volume, perception of technology as a major threat to medical professional autonomy, and potential use of technology as a management control tool were significant barriers, according to a systematic literature review of 52 studies [17]. The extent of IT support and training had a substantial impact on the acceptance and implementation of eHealth technology by medical professionals. If there was no standard process and procedure for the health care organizations at the local, national, and regional levels, doctors and managers were less motivated to use the system.

Patients tended to be more positive about eHealth technologies than the other 2 user groups, recognizing that they had autonomy in their health management. If managers simply imposed eHealth techniques and processes for health professionals and other staff, the failure rate was high. In contrast, when a planning and implementation process involved user groups and a bottom-up development system, enthusiasm and commitment were generated. Hence, the actual change management process was the driver of success or failure. This review also identified that the most frequent reasons for acceptance of eHealth records were design, technical concerns, privacy and security, capacity for fully integrated health information systems within and across organizational boundaries, ease of use, costs, familiarity, and productivity. A total of 4 health care user groups were the subject of 3 linked studies: doctors, other health care professionals, health information professionals, and managers [17]. The participants were asked to rate the importance of and potential for implementation of 10 factors. Here, participants agreed that importance and applicability were criteria for success. There was a high agreement among managers that interoperability and outcome expectancy were the most important factors, whereas high levels of consensus among health care and health information professionals focused on perceived usefulness, productivity, motivation, and participation of end users in implementation. In addition, although health care professionals agreed that patient and health professional interaction, time constraints, workload, and available resources were important, an additional area of high agreement among them was management. These findings illustrate the differing priorities of the user groups, who therefore have different roles to play in the implementation process.

The volume of data associated with eHealth necessitates greater cognitive effort and creates a higher administrative burden. Consequently, many key players perceive eHealth solutions as an additional time-consuming effort rather than as a source of useful applications. Moreover, 1 reason for this opinion is that these individuals were not invited to participate in the process of developing technical solutions, and therefore, their needs were not considered. Consequently, they failed to understand how innovation supports their daily tasks. In Germany, awareness of eHealth solutions is lower than that in other countries. Therefore, new medical technologies are not widespread, leading to an information deficit. Older adults are not sufficiently familiar with telemedicine supplies and products, and this lack of awareness is aggravated by the paucity of cross-functional interactions among various health care sectors. As no reliable and protected nationwide infrastructure exists, deficiencies in the quality of care and efficiency of administrative and delivery processes occur. Manual collection and transmission of data also generate administrative delays and can be a source of error, which results in the real potential of eHealth solutions being underappreciated. In most cases, low technology–related expectations act as a self-fulfilling prophecy because major stakeholders, such as doctors, imagine that their peers will not fully support eHealth solutions and will not exchange data consistently. Therefore, developing an extensive user community to fully and successfully implement eHealth is less likely to occur in the short term [18].

Discussion

Principal Findings

The discussion of the research findings focuses on the challenges to the effective development of acceptance, which were revealed by this study and compared with the theoretical framework presented in the Introduction. In health care, the decision to use or to avoid new technologies depends on various factors, as suggested in previous studies [3]. Although some factors are common to patients, medical professionals, and health care organizations and their managers, there exist substantial

differences in users' perceptions of the importance of each factor. This observation agrees with earlier research that posits that decision making regarding acceptance is a subjective process [4,5]. For example, some doctors expressed concerns that technology could affect professional autonomy while diagnosing or treating patients. Another concern was that the organizations might use eHealth tools as means of controlling doctors. These perceptions succeed in generating negative attitudes toward implementing change. Doctors perceived technology as a positive factor by potentially reducing errors when prescribing patient treatments and as a means of improving communication with other groups and individuals caring for patients. However, doctors stated that their involvement in the development of technology and their ICT expertise were very low. The study also found that 46% of the variance in the perceived usefulness of the eHealth card related to IT capability [19].

Importantly, there were different levels of agreement among user groups on the 10 criteria considered to be important for eHealth adoption. Outcome expectancy and interoperability were the most important to managers, whereas perceived usefulness, productivity, and motivation were important to health care professionals. However, there was a high consensus among medical professionals regarding the importance of patient-carer interactions, available time, workload, and available resources. Interestingly, they also emphasized the importance of end-user involvement in implementation. Managers and medical professionals considered that the lack of standardization and integration among health care systems was a huge demotivating factor for eHealth implementation; therefore, this was not a facilitating condition. Based from the UTAUT model, the social condition factor is the most important aspect as it is represented by the age of patients. This factor therefore measures the complexity of the technology when compared with traditional methods shown by the way change was introduced, which can either be imposed by a top-down process or ushered in by a bottom-up process [6]. Ease of use was a general factor that was reinforced by these findings and support measures such as IT training and support for medical professionals, as reflected by the TAM [4,5]. Doctors also suggested that their involvement in technology implementation was low and that ICT expertise was an issue for them (and for all stakeholders generally) because the capacity to use the electronic system had a 46% effect on how useful they felt the technology to be. These findings also align with the innovation diffusion theory [9] in terms of relative advantage, perceived complexity, time, and opportunity to evaluate the technologies while undergoing training, with the opportunity to observe its potential advantages indicating how easy it is to learn. The opportunity to evaluate technology before deciding whether to adopt it and the observability of technology-related advantages were also inferred in the training and support that health professionals felt were necessary for acceptance. This study also suggested that the patients were encouraged by the eHealth-related capacity for health self-management; however, trust in the care provider, system's ease of use, severity of the medical condition, and data security were additional concerns [6]. In addition, technology did not appear to be an issue for patients because they had already used it; rather, issues centered around lack of awareness of the usefulness of the technology.

Recommendations for the Planned Electronic Health Center

The findings of this study have generated a range of recommendations for the planned eHealth center, which are presented in this final section.

The major stakeholders, who will be the users of the telemedicine processes, must be involved in the design of the eHealth centers and associated technologies. All those who are involved should be active participants in each phase of the innovation process as part of responsible research and innovation. To make an informed contribution, all medical professionals need to be informed about the major features of the innovation and its major benefits, especially effective treatment of more patients, with lower effort per patient. A transparent, accurate, user-centered ICT strategy that acknowledges feelings of insecurity and ensures that the information provided meets the needs of the target group must be devised. Merely instructing users on how to use the technology is insufficient for gaining their interest and commitment. Transfer of knowledge and skills in terms of the practical impact that technology can have on health care outcomes must be an integral part of the learning process. The implementation strategy must also include interventions that build a positive attitude toward the technology among various target groups of patients and the general population. Hence, the implementation strategy must be integrated into the overall eHealth strategy with a prolonged rollout period. This will enable all stakeholder groups to adapt and acknowledge the fact that technology diffusion occurs at different rates. Involving all stakeholder groups appropriately in the development of the change interventions will reduce their resistance to change and enable introspection of the groups' perceived barriers to implementation. The advantages will become more observable to each group, and the realization that they each have different ideas about what those advantages are will be better appreciated. Individuals responsible for the implementation process must be regarded as trustworthy and proficient. This will encourage them to visibly demonstrate their support for the change and their role in accomplishing technology implementation.

With regard to the effective use of technology, professional learning and development personnel must introduce the various applications and explain their functionality to potential users, medical institution employees, and patients.

To address the perceived lack of cross-functionality, the communication among various key players must be improved and simplified. This could bring about a change in the traditional structures. The creation of a high level of acceptance through communication, participation, and support is an important condition for countrywide care delivery through eHealth solutions. Each innovation needs to be adapted to the wishes of the target group. Patient adherence is obtained after acceptance has been secured among employees of medical facilities, reinforcing the need for the acknowledgment of different rates of technology acceptance. Patients' acceptance of innovation depends on their perceived ability to both use and directly

benefit from it. Prejudices have a negative effect on patients' readiness to deal intensively with *digital companions*, for instance. However, patient acceptance can be enhanced if doctors, surgery staff, community nurses, and other patients convey a positive perception toward the respective innovations. Conversations regarding change should take place with patients to increase their awareness and provide an opportunity to identify their resistance factors and overcome them. As patients' positive perception depends on positive emotions and moods, their emotional participation must be encouraged, potentially through enjoyable elements that can be integrated into health care apps.

Patients' acceptance of innovation could also be improved by offering sessions in health or community centers where the technology could be tested. Trained individuals would be available to offer support as the patients test the technical innovation. These settings also offer the potential for observability as other patients discuss the usefulness of the devices. During this time, a trained individual should be available to answer patients' questions and explain the hardware and functions. A positive experience could be the first step toward patients developing a connection with the innovation because, in these settings, patients can be made to feel safe as their use is monitored. Users must interact with technologies and test their multipurpose options. Simulation environments can also be useful, including living labs. Technology users are important sources of information throughout all phases of product development. The simulation environment, with support from trained personnel, is important for developing acceptance, particularly among older adults residing in Brandenburg. Fortunately, these individuals are usually interested test users. The transdisciplinary experience data obtained from a living lab can subsequently be integrated into the structural concept of the eHealth center.

The demonstration of added value for patients and care providers is important, although some patients and medical staff react with skepticism to technical innovations and fear excessive external control. These feelings of insecurity among patients can be reduced by interactions with qualified and aware health care staff in living lab settings. Targeted health promotion through regional media, advertisements, or radio spots can create awareness of the advantages of eHealth centers. Related marketing objectives should include generating as much persuasion, memory value, and attention value as possible. Knowledge-imparting campaigns and information seminars that notify target stakeholder groups of relevant technology features are an additional option. As many patients view Web-based information before a consultation, there is danger that they could receive incorrect information or apply the information in the wrong context. The eHealth center gives patients quality-assured information and serves as an informational health platform; it can also recommend robust online sources.

As described in the Introduction, service providers view innovations in a positive way when the innovations have a positive effect on their daily activities. The acceptance of innovation among health professionals in Brandenburg will be achieved when the patient care goals are achieved more quickly and rendered at a higher quality through the use of new service delivery processes. This also applies to interface management and information flow. Employees will accept a technical innovation if resource use during service provision is lower and/or the revenue obtained by accessing new target groups is higher. Therefore, the eHealth center must help reduce professional burdens such as time pressure or the steadily rising mobility and documentation requirements in Brandenburg. Confident health professionals can convey their positive attitudes regarding innovation to their patients.

Conservative organizational forms, such as hospitals and their employees, often fail to easily adapt to technical innovations. Doctors, in particular, may hide their opposition to change. This could present a challenge for the planned eHealth center that is characterized by technological and procedural innovations. The benefits of innovation must be presented to hospitals in a very tactful manner; the reality of the need for economic efficiency exposes hospitals to challenges that relate to cost savings and competition. The eHealth center could help hospitals to stay competitive in the long run by facilitating the delivery of high-quality care while producing cost-effective services.

In view of the less-developed IT infrastructure in Brandenburg compared with other federal states, the creators of the eHealth center should lobby for internet access, broadband expansion, and rapid data transmission. Population groups with low digital affinity should be assisted in their efforts to acquire digital competence and suitable equipment through cooperation and coordination. Special attention should be given to data protection. Acceptance by the key players depends on the degree to which special encryption methods ensure the protection of personal data. However, patients with significant illnesses care less about the storage and protection of their data and more about their health care [20].

Further Questions or Research Issues

The research on acceptance involves understanding the feelings of insecurity, fear, and apprehension experienced by different stakeholders. These feelings can be identified through suitable data collection processes. Comparing stakeholder perceptions is important to this ongoing study: initially, a sample from the target group will be interviewed about their feelings of insecurity and subjective perceptions of how technological innovations are implemented. Subsequently, the participants will be asked to test the innovation within a simulation or other environment that facilitates innovation testing. After a designated period, the participants will be interviewed again to reassess their feelings and perceptions. This process is intended to provide valuable insights into how testing an innovation positively influences key players' perceptions.

Conclusions

This research into the psychological indicators of acceptance shows that acceptance is critically dependent on the subject, object, and the general conditions that surround acceptance. In the case of the construction of an eHealth center, the acceptance subjects include target groups of patients (or the general population of individuals interested in preventative medicine issues) and medical professionals. The acceptance object is the technical innovation. The technical and social conditions are

considered exogenous as they cannot be influenced easily or quickly. These general conditions are diverse. The first step toward securing the acceptance of digital solutions and innovative medical technology by patients and professionals is to understand their anxieties and feelings of insecurity on the basis of empirical study findings. This insight will create an opportunity to further categorize and evaluate the specific issues of the target group of disabled and elderly persons in the federal state of Brandenburg. The final step will be the generation of reliable recommendations for action for the eHealth center of the Federal State of Brandenburg. For both groups, acceptance can be generated only through a directed, transparent awareness campaign that provides users with sufficient information and the opportunity to test new technologies. Hence, users can directly experience the benefits of the technologies and acquire a positive attitude toward the new products.

Conflicts of Interest

None declared.

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Abbreviations

eHealth: electronic health

ICT: information and communication technologies
IT: information technology
TAM: technology acceptance model
UTAUT: unified technology acceptance and use of technology model

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Protocol

The Internet of Things in Health Care in Oxford: Protocol for Proof-of-Concept Projects

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Abstract

Background: Demands on health services across are increasing because of the combined challenges of an expanding and aging population, alongside complex comorbidities that transcend the classical boundaries of modern health care. Continuing to provide and coordinate care in the current manner is not a viable route to sustain the improvements in health outcomes observed in recent history. To ensure that there continues to be improvement in patient care, prevention of disease, and reduced burden on health systems, it is essential that we adapt our models of delivery. Providers of health and social care are evolving to face these pressures by changing the way they think about the care system and, importantly, how to involve patients in the planning and delivery of services.

Objective: The objective of this paper is to provide (1) an overview of the current state of Internet of Things (IoT) and key implementation considerations, (2) key use cases demonstrating technology capabilities, (3) an overview of the landscape for health care IoT use in Oxford, and (4) recommendations for promoting the IoT via collaborations between higher education institutions and industry proof-of-concept (PoC) projects.

Methods: This study describes the PoC projects that will be created to explore cost-effectiveness, clinical efficacy, and user adoption of Internet of Medical Things systems. The projects will focus on 3 areas: (1) bring your own device integration, (2) chronic disease management, and (3) personal health records.

Results: This study is funded by Research England's Connecting Capability Fund. The study started in March 2018, and results are expected by the end of 2019.

Conclusions: Embracing digital solutions to support the evolution and transformation of health services is essential. Importantly, this should not simply be undertaken by providers in isolation. It must embrace and exploit the advances being seen in the consumer devices, national rollout of high-speed broadband services, and the rapidly expanding medical device industry centered on mobile and wearable technologies. Oxford University Hospitals and its partner providers, patients, and stakeholders are building on their leading position as an exemplar site for digital maturity in the National Health Service to implement and evaluate technologies and solutions that will capitalize on the IoT. Although early in the application to health, the IoT and the potential it provides to make the patient a partner at the center of decisions about care represent an exciting opportunity. If achieved, a fully connected and interoperable health care environment will enable continuous acquisition and real-time analysis of patient data, offering

unprecedented ability to monitor patients, manage disease, and potentially deliver early diagnosis. The clinical benefit of this is clear, but additional patient benefit and value will be gained from being able to provide expert care at home or close to home.

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KEYWORDS

Internet; computer systems; computing methodologies; information systems; information storage and retrieval; dataset; patient care; health services; Internet of Things; Internet of Medical Things

Introduction

The Use of Internet Devices to Capture Health Data

The popularity of smart watches, wearable tech, and mobile phone technology have ushered an era of internet-enabled digitally connected devices. Daily, one can observe wide use of mobile phones and relatively low-cost devices and associated internet connectivity. Mobile phone user numbers are increasing worldwide; 95% of individuals in the United States and 94% of individuals in the United Kingdom own a mobile phone, with the majority of them having access to mobile phones [1,2]. Global spending on these devices is projected to be US $410 billion in 2022 [3]. In 2017, there were more connected devices (estimated 8.4 billion) than people (around 6 billion) in the world [4]. The number of devices is estimated to grow to 20.4 billion by 2020 [4]. These devices are used to track steps, heart rate, and various forms of activity and health data, demonstrating that consumers are becoming increasingly interested in their wellness and health [5] (also known as the *quantified self*-movement [6]).

Defining the Internet of Things

The Internet of Things (IoT) or Internet of Medical Things (IoMT) extends the Web through the deployment of ubiquitous devices with capabilities for embedded identification, sensing, and data exchange features [7]. These smart objects form the foundation of cyber-physical networks, which establish an extensible foundation for a networked data exchange [8]. IoT enables the capability to deploy, manage, and analyze interconnected devices, constructing a real-time extension to provide broad sensory analytic hardware and software for our physical world.

The Possibility of Internet of Things to Address Health Care Challenges

IoT has potential to collect and integrate possibly more precise, relevant, and high-quality data in real time to monitor processes and outcomes [9]. IoT can contribute to connecting patients, medical staff, wearables, information technology systems, and medical equipment and integrating them using on-demand internet connectivity [10]. The most promising benefits of IoT for health care might be in increasing workforce productivity, cost savings [11], operational efficiencies [12], improved patient experience and care, and human error reduction [13,14]. These benefits can be applied to address health care challenges and facilitate behavior change and promote well-being of patients by giving them ownership of their health (Textbox 1; the textbox is adapted from Table number 1 in Meinert et al's analysis [15]). Such ownership could enable proactive behavior changes, preventing onset of health issues, and better management of existing conditions.

IoT offers opportunities to take the model of health care from encounter-based care through connected continuous care. The rapid growth of consumer-centered health-orientated apps and wearables has created an exponential expansion of device data collection. This growth has encouraged the development of patient-centered focus in IoT. These widely used connected devices could enable improvements in patients' safety by integrating different sources of data.

Textbox 1. Key health care Internet of Things (IoT) use cases.

Improving patient safety and outcomes by

- Using insights from the integration of different types of data (eg, health and environment) collected by different sources (eg, mobile devices and electronic health record)
- Using data for improved prediction (eg, artificial intelligence)

Facilitate people's lives and reduce costs by

- Providing tools such as voice-assisted note taking and reminders
- Automating processes that do not need humans

Improving health care delivery by

- More actively involving people in their health care decisions
- Providing the right information at the right time
- Giving access to health care like other industries such as banking and retail industry do (eg, Amazon) by providing teleconsultation, ePrescribing, and delivery of medication

This can then be used for proactive identification of needs to enhance delivery by providers and optimizing value for payers by identifying gaps that can be closed. Moreover, patients could be more effectively engaged in taking care of their own health, which could facilitate prevention and monitoring of illnesses.

Current Trends in Industry and Research

To inform perspectives on the IoT, we have drafted a systematic review protocol to analyze the state of the literature of the technology and its applied use in health. This protocol and the review will be submitted for peer review in a medical journal. This section summarizes initial findings on current trends in the industry and research.

Internet of Things Properties

Having defined IoT as devices that create a framework for data exchange and sensory analysis of the physical world, we further refine their implementation characteristics of their use. IoT devices follow 7 physical properties in their design and implementation [16]:

1. Tracking: The capability to capture geophysical and dimensional properties in movement. This tracking enables awareness of location, movement, and trends and provides proximity to activity [16].
2. Identification and authentication: Correlation and authentication of devices to individuals is vital to ensure linkage of data to a specific individual. Such identification and authentication enable integrity and verification of source data [16].
3. Data collection (monitoring): The capability to store, retrieve, and send data for analysis [16].
4. Sensing: The capability to allow for awareness of physical presence [16].
5. Control: Ensure that the behavior of a person or machine is desired and allows to take corrective action [17,18].
6. Optimization: Using rules to enable complex decision making by the system or sensors to improve performance [17,18].
7. Automation: Combining control and optimization of data and control from IoT and other sources to allow making independent decisions [17,19].

The IoT provides broad app scenarios based on these core features as they create the ability for data collection, which can be structured via capabilities enabled in software design, using tracking and sensing to create proximity and awareness data. These IoT features can vary in their complexity from rudimentary and complicated to highly complex [17].

Internet of Things in Health and Care

The rapid growth of consumer-centered health-orientated apps and wearables has created a significant expansion in device data collection. This growth has encouraged the development of patient-centered focus in IoT. The equal challenge and opportunity in this application of IoT in health is to create a structured framework for both use and data transfer to allow data to be usable across social, clinical, and wider health care contexts to extend the reach of primary, secondary, and tertiary care.

Health Internet of Things Classification and Use Cases

Health IoT can be beneficial from the perspective of the patient because these devices create a means of directly connecting health services with the patient. Health IoT use cases can be broadly categorized in the following patient-centered contexts [7,9,14,20,21]:

1. Safety: real-time health data management enables health systems to enable individual and population markers to enable patient safety. Specific cases include:
   - Vital signs and patient monitoring,
   - Real-time health status and predictive information,
   - Public health policy and regulation decisions in pandemic scenarios,
   - Pharmacoepidemiology, and
   - Broad population health management.
2. Satisfaction: traditionally, interactions with health systems require physical visits to primary or secondary care for capture of health-related data. The use of IoT enables an extension of data and the ability to provide health system interaction outside of formal health care settings. The convenience of providing this type of care may influence patient satisfaction. Specific cases include:
   - Responsive feedback and
   - Telemedicine.
3. Engagement: building on a health record, the ability to coordinate decision making, create patient-specific education, and manage prescriptions, all enable an interactive virtual basis for information exchange between providers and patients. Specific cases include:
   - Care coordination,
   - Medicine adherence, and
   - Personalized health care and well-being planning.

Although it might be possible to examine health IoT from a classification context removed from the patient, a patient-centered view is essential in consideration of the way health IoT can enable an expansion of health systems beyond the physical parameters held in traditional implementation of care. By using such a view to place health IoT use cases, we can begin to envisage both the opportunities and the challenges in the deployment.

Key Implementation Challenges

Although the implementation of IoT devices has broad reach and capability, their use has identified key issues in their deployment [5]:

1. Computational limitations: Devices, due to a limited form factor are constrained in their on-board computational power.
2. Energy limitations: Another limitation of form factor is the amount of battery storage that can be stored to power devices. Limitations in battery storage means devices have to be recharged for ongoing data transmission, which can limit the utility of devices, especially in scenarios of intense data capture.
3. Scalability: Systems storing data must be able to increase capacity; as the number of connected devices increases,

this places increased demands on network infrastructure and computational infrastructure to process and manage inbound data.

4. Multiplicity of devices: With open frameworks, there creates a possibility to design an infinite number of devices, but the challenge with these devices is the need to validate the data they are providing and support their use. Device manufactures may also ignore standards and develop proprietary data structures inhibiting interpretation by third parties.
5. Dynamic network topology: Although the ability to create a dynamic network structure is an advantage of IoT systems, the permutations of the network design create a need to ensure there is ability to analyze each data point, which may be difficult.
6. Tamper-resistant packages: Because devices are implemented broadly and not within closed networks, the potential ease of access and ability to compromise these devices is a key security concern. To mitigate the risk of tamper, it is necessary to develop tamper-resistant form factors that cause compromise in system functionality and capability to achieve integrity of devices. In the event devices are compromised, the ability to detect this to report potentially compromised data is vital.
7. Dynamic security updates: Another key consideration of security is the need to ensure integrity of embedded systems; the expansive proliferation of IoT devices creates a possibility of exploiting systems for security penetration, and IoT can enable dynamic updates of devices.

Case Studies

In this section, we explore current implementation use cases of IoT technologies. These technologies were selected following review of technologies presented at Health Care Information and Management Systems Society (HIMSS) 2018 and, additionally, identified following review of exemplar technologies from initial data analysis in a forthcoming systematic review on IoT in medicine. Although this list is not comprehensive, it provides examples of implementation use cases impacting broad elements of care. As part of this study, further review of available technologies matched to areas of user need shall be identified. Key considerations within these technologies include technical aspects of solution implementation and their benefits from a patient perspective.

Medically Prescribed Internet of Medical Things Devices: Livongo

Challenge

Managing chronic conditions is challenging for patients because they require medication adherence and lifestyle modifications [22,23]. Increasingly, patients are also managing multiple chronic conditions, with about two-thirds of adults living with 2 or more chronic conditions and the prevalence increasing up to 70% among the adult population aged over 70 years [24].

Opportunity

Livongo provides a platform for management of chronic conditions, through use of a digitally connected software ecosystem for device interactivity and real-time care support through consumer health technology. By using artificial intelligence (AI) to learn patterns and create actionable insights, Livongo is able to store real-world data on patient history for analysis and action [22].

Use Case or Patient and User Perspective

Livongo's diabetes program enables an IoT glucose monitor to send data directly to its cloud infrastructure, allowing for real-time data analysis and support. This enables the capability for real-time patient feedback and support throughout the day. Simplifying means of data collection into accessible devices and tracking status via interactive dashboards enable better monitoring and feedback for patients and provide capabilities for better remote clinical feedback. The device is *prescribed* to appropriate patients by their health provider and feeds data back to the provider's electronic record system. This system has been selected as a preferred supplier for the Cerner Millennium (Kansas City, USA) electronic record system that is in use at Oxford University Hospitals (OUH) National Health Service (NHS) Foundation Trust [22].

Evidence and Outcomes

Livongo is collaborating with the company Lilly to identify trends in the impact of remote diabetes self-management education, detailing the drivers of healthy behaviors and helping our understanding of how people living with diabetes can stay more engaged in their health [22]. Analysis of real-world behavior studies will provide evidence on what impact use of this system has on disease management. In addition, a study found that individuals with diabetes had lower likelihood of having hypoglycemia and hyperglycemia when using Livongo with a *diabetes coaching team* [23].

Environmental Monitoring: CleanSpace

Challenge

Evidence suggests that air pollutants may cause serious health effects and specific population groups are especially sensitive to the impact of negative air quality [25,26]. Although tracking of air quality is done at a macro level, detailed hyper-local data are difficult to capture because of a lack of sensors collecting this information [27].

Opportunity

CleanSpace is an IoT sensor used to monitor air pollution. It uses machine learning to create hyper-local population data to enable users to understand in real-time quality of air. The sensor harvests radio-frequency energy from its environment to recharge its battery. At present, it only measures carbon monoxide (CO) but is claimed as a generic marker of other pollutants (particularly from traffic) [28]. CleanSpace is a product of Drayson Technologies who already have an academic and commercial relationship with the University of Oxford and OUH.

Use Case or Patient and User Perspective

The small form factor of CleanSpace enables them to be located in buildings or on mobile physical objects (eg, bicycles) to generate low-level data on air pollution. These data can be used by researchers, health care providers, and public health services

to analyze trends on possible correlation of air pollution and health conditions. Awareness of patient-level pollution can lead to individual action in seeking activities or events where there is better air quality, encouraging actions to promote better air quality within the individual's environment, and potential to instigate preventative treatment of respiratory disease.

Evidence and Outcomes

The Environment Research Group (King's College London) and National Physical Laboratory completed product performance validation measuring ambient concentrations of CO, comparing CO with other major urban pollutants.

Bring Your Own Device Integration: Validic

Challenge

There are huge challenges for access, integration, standardization, storage, and use of IoT device data. As increased number of devices are brought to market, a need to leverage these products within a common software framework will be necessary to leverage the opportunity to have continuous data linkage among devices. This is particularly true with the proliferation of personal health monitoring devices. These devices have the potential to contribute to a *bring your own device* (BYOD) IoMT infrastructure, but only if the data are appropriately curated.

Opportunity

When device connectivity and data access can be simplified, this can enable deriving and analyzing meaningful insights. Interactions between health care providers and their patients can be facilitated, which can improve patient adherence and engagement and can be used to more effectively manage multiple conditions and programs of care.

Use Case or Patient and User Perspective

Validic Mobile [29] is a set of libraries that enables health care organizations to easily integrate Bluetooth smart in-home health devices (eg, blood pressure monitors, thermometers, and heart rate monitors), Apple Healthkit [30], and VitalSnap technologies [31] into their existing iOS and Android mobile apps. The VitalSnap technology allows access to data from nonconnected devices using the camera on the mobile phone to capture and record data from the device's display screen, which is validated by the device user.

Validic Impact is a remote monitoring device-agnostic platform that operates between devices and software on mobile devices, laptops, and personal computers. Validic Impact involves device connectivity and data delivery, customizable rules engine and alerts, patient enrollment flows, patient onboarding and support tools, clinician ordering or monitoring dashboard, integration into the clinical record, remote care admin dashboard, and device management tools.

Validic has been selected as the BYOD partner of choice for the Cerner electronic health record (EHR) system that OUH uses.

Evidence and Outcomes

Validic enables real-world data, which can be used to validate app claims by creating a single-point connection to perform analytics on individual- and population-level use.

Voice-Enabled Devices: Orbita

Challenge

Amazon Alexa, Google Assistant, and multiple other chat bots provide capabilities to intuitively communicate with users via voice. Although they provide the capability for active user engagement, their base functionality requires regulation and customization to have functional use in health contexts.

Opportunity

Using application programming interfaces (APIs), voice-enabled systems can integrate with EHRs and combine data from connected devices. This data ecosystem can create surveys, capture results, manage common requests and questions, and use AI to provide automation of these interactions.

Use Case or Patient and User Perspective

Orbita voice [32] is working with care homes to provide the ability to give families the ability to interact with each other via voice, give clients the ability to be able to ask questions about medications, clarify postsurgery instructions, and develop other bespoke scenarios that mirror existing face-to-face interactions. Having the capability to increase communication and engagement on treatment and better data collection on issues impacting care delivery could lead to stronger patient engagement and treatment adherence through continuous communication channels.

Evidence and Outcomes

There is increasing data to indicate the rise in popularity of using voice-enabled response; however, the development of these technologies and their implementation use cases are nascent and require further examination.

Personal Health Records: Apple Health Records

Challenge

The vendor-specific nature of medical data capture and concerns for privacy and security make access to personal health data stored by providers challenging for patients [33]. Viewing this information is often complicated (requiring multiple log-ins or storage credentials). Recently *patient portals* have been developed, but these typically only provide Web-based access to individual provider systems [34].

Opportunity

Mobile devices have mass consumer appeal, the ability to create a user-friendly, secure, and integrated means to capture and integrate health data with a platform, which can be shared with clinical teams. As patients move from health systems to using consumer devices that record medical-related information, the ability to integrate these data in one place creates a scalable and transportable mechanism for storage of health data.

Use Case or Patient and User Perspective

Using the Fast Health Care Interoperability Resources (FHIR), standard for data sharing of electronic medical records [35], plus the Substitutable Medical Apps, Reusable Technology (SMART) infrastructure for secure access [36], a pilot group of medical centers in the United States is enabling patients to access their medical data via the Apple Health Records feature available in Apple iOS version 11 [37]. APIs to enable SMART on FHIR app use are being deployed at OUH in the third calendar quarter of 2018—the first UK site to do so.

Evidence and Outcomes

There is a growing body of studies examining the portability and use of Apple Healthkit for patient uptake and adoption [38]. However, these systems require Apple hardware accessibility, and this increases the challenge of vendor lock-in. Although the utility of a general health data management system independent from hospital EHRs is intuitive, its application for adoption requires further study.

Wayfinding: Kaleida Health

Challenge

Kaleida Health [39] serves 8 counties in New York with an average of 17,000 visitors per day and more than 1 million patients annually. Visitors are likely to ask an employee for directions if are not given direction every 30 feet while traveling through a building. This can increase anxiety of visitors, interrupt staff, and decrease productivity [40].

Opportunity

It is estimated that by 2019, 25% of health care organizations will use experimental wayfinding [41]. The goal of this study was to implement a wayfinding system that helps daily visitors confidently navigate Kaleida's campuses. The purpose of the wayfinding tools was to provide a convenient end-to-end experience. The potential benefits of implementing a wayfinding system include understanding where users are going, cutting wait times and improving on-time appointments, reducing staff interruptions, balancing demand and capacity, improving customer satisfaction and the patient experience, lowering stress, and differentiating from competitors.

Use Case or Patient and User Perspective

Kaleida implemented a number of wayfinding tools, including indoor Global Positioning System and mapping, Bluetooth Low Energy beacon technology, mapping apps (eg, Google Maps), location- and condition-sensing technologies and platforms, IoT aggregation platforms, contextual messaging, parking management systems, digital signage, and self-service kiosks. Training was provided to make visitors and staff aware of the wayfinding tools. The experience for visitors starts at home with appointment notifications on their mobile phone, driving directions to the parking lot closest to the location of their appointment, suggestions on when to leave home, and integration with the city's parking system and other parking garages. Inside the hospital, an internal geofence shows a 3D map of the destination to the visitor with a blue dot moving along the route to indicate the visitor's current location. Secure connections are provided that link back to the patient's electronic medical records.

Evidence and Outcomes

Key benefits of the wayfinding solution are improved efficiency, patient satisfaction, and engagement. The solution provided an integrated experience to visitors.

Patient and Public Involvement

As demonstrated by the case studies, IoT technologies herald promise for stronger data integration, means to encourage patient proactive health monitoring, data integration, and other benefits. To better understand these considerations, factors influencing user perspectives on the impact of these technologies, and needs associated with distributed device accessibility, we propose to hold focus groups with patients to further explore the impact these technologies could have on their experience of care.

An application to hold these focus groups has been submitted to the University of Oxford's Central University Research Ethics Committee. This study will be conducted with support from the Patient and Public Involvement, Engagement and Experience team at the Oxford Academic Health Science Network.

If the projects proposed earlier are chosen, it will also be possible to conduct a service evaluation of technology use at OUH, with the patients and professionals involved.

Implementing Internet of Things at Oxford

Background of Oxford's Digital Health Infrastructure

Oxford's health care is delivered by 3 core providers:

1. OUH, an approximately 1200-bed acute hospital over 4 sites in Oxford (John Radcliffe Hospital, Churchill Hospital, and Nuffield Orthopaedic Hospital) and Banbury (Horton General Hospital), which provides a full spectrum of emergency and elective physical health services for the city, a regional population of up to 3.5 million, and some national services (eg, Craniofacial surgery).
2. Oxford Health (OH) NHS Foundation Trust, which provides in- and out-patient mental health service across Oxfordshire and community health services across a wide geographical footprint, including the neighboring counties of Berkshire, Buckinghamshire, and Wiltshire.
3. Primary care services are delivered to the 740,000 patients of Oxfordshire by 70 general practices (GP).

The majority of primary and secondary care services are commissioned by the Oxfordshire Clinical Commissioning Group (CCG). In addition, the South Central Ambulance Service (SCAS) provides emergency response and transportation services and Oxford County Council (OCC) provides social care.

Oxfordshire has a relatively mature digital health care ecosystem. This has recently been acknowledged by the award of Global Digital Exemplar (GDE) status to OUH, OH, and SCAS. Collectively, this has injected £33.4 million of funding (including match) into developing services to reach a standard that is comparable with the best international health care institutions. At present, each of the provider institutions has a

different EHR provider: Cerner at OUH, Adastra and CareNotes at OH, Egton Medical Information Systems (EMIS) Health at all bar 2 GP practices, Liquid Logic at OCC, and 3 separate systems at SCAS covering out-of-hours, and 111 and 999 services.

Innovation

OUH and the Oxford Academic Health Science Network have received funding from the European Union's European Regional Development Fund to support the delivery of a digital health innovation program called TheHill. This funding is being matched by OUH and runs from April 2018 for 2 years. It will enable the employment of staff plus events and seed funding to support the development of needs, ideas, and businesses who are working on innovative digital health solutions. In addition, an innovation hub is being built on the John Radcliffe Hospital campus in partnership with the School of Architecture at Oxford Brookes University. Although the activities are funded and sited on the OUH site, TheHill will support ideas from across the Oxfordshire health ecosystem. It is intended that research, development, and evaluation activities will take place in partnership with all members of the Oxford Academic Health Science Centre (AHSC), including Oxford University.

Challenges

Local challenges in the implementation of new digital systems exist but are surmountable and outweighed by the opportunities that exist in the Oxford ecosystem:

- There is heterogeneity of clinical systems reflecting a current lack of digital connectivity among the providers, with regard to the electronic medical records that are used by frontline clinicians to treat patients. Some integration exists through the Oxfordshire Care Summary—a core subset of clinical information that is available to members of OUH, OH, GPs, and SCAS.
- The *patient-facing or self-management* work-stream of the OH GDE Strategy mentions the use of consumer wearable sensors. The OUH and SCAS GDE roadmaps do not explicitly refer to the use or integration of IoT data.
- At present, there is no clear guidance for health care workers on how to engage with IoT devices (eg, which ones to recommend to patients and how to use them).
- There are general concerns from health care staff about data security and privacy when using or accessing patient data. The European Union General Data Protection Regulation and UK-specific Caldicott guardian infrastructure provide frameworks but require experience and expertise to apply to new technologies and systems.
- Resources (staff, support, and capital expenditure) for the implementation of new digital systems in the NHS are limited, although the GDE programme provides a window of opportunity.

Population Health

Digital population health involves the integration of data across a patient's interactions with health and care services to create a longitudinal care record. This can enable better coordinated, more effective, and efficient care for both the individual and the population they are part of. It is often extended to include any aspect of the health record that extends engagement with patients, for example, through patient portals and personal health records.

The OUH GDE programme is funding the procurement of a set of digital population health solutions. The implementation of these solutions is being supported by the CCG through their technical support team at the South Central West Commissioning Support Unit. These products are the key conduits to enable IoT integration, and therefore, we will focus on how this might be achieved.

The products that Oxford is implementing are provided by Cerner Inc (Kansas City, USA). This means that integration to OUH's EHR is embedded but the solutions are vendor agnostic, so integration to the other providers in the network will be possible without the need for them to change their EHR systems.

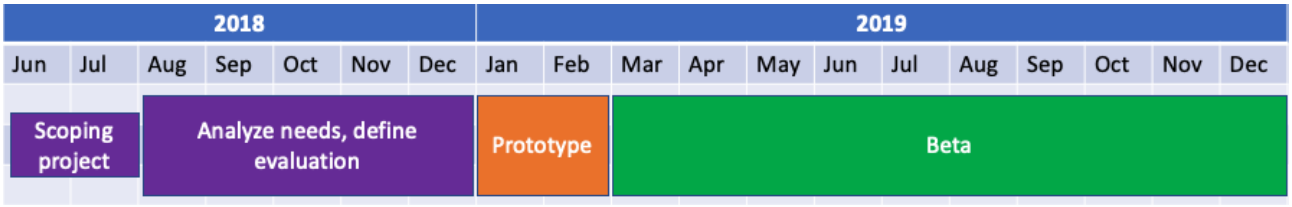
Three technical solutions will be implemented:

1. Health information exchange: This is the ability to view an aggregated summary of the data held in the EHR of all connected providers for an individual patient. It is planned to go live in October 2018. The information shown includes vital signs, and so, this will be a potential mechanism to surface personal connected device data to all health care providers regardless of the provider EHR through which it is ingested.
2. HealtheIntent: This is cloud-based, programmable data platform that receives and normalizes patient-level data from multiple health sources, such as an EHR, but can also include complementary data reflecting the social determinants of health (eg, environmental monitoring and economic factors). This will go live in February 2019. Once the data exist in the system, a variety of off-the-shelf (HealtheRegistries) and bespoke (HealtheAnylytics, HealtheDataLab, and HealtheCare) tools can be used to interrogate, analyze, and draw actionable insights from the data.
3. HealtheLife: This is the patient portal for OUH. It will go live in December 2018. It provides the functionality for patients to view aspects of their health record and is the potential mechanism through which consumer IoT data could be connected or prescribed IoT device data presented to patients. It only interacts with the OUH EHR (Cerner Millennium) and so does not show or interact with data held in HealtheIntent. Separate portals exist into each EMIS instance for users to see their primary care records and OH plans to open its own portal toward the end of 2019, although currently the functionality has not been confirmed.

Importantly, Oxford will be the only second UK site to go live with all these solutions.

A regional consortium will be applying for funding from NHS England's health data interoperability project, the Local Health and Care Records Exemplar. This offers additional opportunities for proof-of-concept (PoC) studies to be undertaken. The consortium may feature industry partners offering cloud-hosted solutions that integrate tools to apply machine learning to the population health data that are collated.

Figure 1. High-level project Gantt chart.



Additional Technical Platforms

Substitutable Medical Apps, Reusable Technology on FHIR: Fast Health care Interoperability Resources

SMART is an open, standards-based technology platform that enables innovators to create apps that seamlessly and securely run across the health care system. It uses the FHIR. It is rapidly becoming accepted across the digital health community as the default standard for developing apps that can run across different vendor platforms, without requiring the creation of point-to-point data exchange solutions for every implementation.

OUH will be the first UK site to implement Cerner's Ignite APIs that enable SMART apps to read and write data to the EHR. Once HealtheIntent is implemented, the Ignite APIs will provide similar access to this resource. These APIs will be live in Oxford from Q3 2018. SMART apps can be developed internally or procured from an increasing number of small and medium size enterprise vendors (mostly based in the United States) who are publishing them to an *app store*. New apps will require a combination of validation from Cerner plus at a local level. The processes to support this are evolving.

CareAware

CareAware is Cerner's platform for integration of IoMT data. It is cloud hosted, EHR agnostic, and vendor neutral. It is currently deployed in Oxford. It is enabled by a library of over 1000 of the most common medical devices. A validation program exists to onboard additional IoMT devices. However, 2 different routes exist to feed data into the system depending on whether they are prescribed to consumer, also known as BYOD; this is shown in Figure 1:

1. Prescribed devices are typically linked through a full service from the vendors. Two key partners have established relationships with Cerner to do this: IdealLife and Livongo. Within the US market, both can be drop shipped via an order placed in the Cerner Millennium EHR. Depending on the service contract, the provider will ship their devices, onboard users through proactive calls, and provide full ongoing technical service.
2. Cerner has partnered with Validic to ingest and normalize data from BYOD devices. This is initiated by patients through the HealtheLife portal, where the device can be selected and permissions granted to access the personal data stored by the device vendor.

New Device Research

Cerner's *Project Yukon* is an experimental research project aiming to create a *connected* medical examination room. This will feature voice, video, and movement trackers; integrated examination devices (such as stethoscopes); and point-care-testing (eg, blood and urine analysis). It has some similarities to the consumer shopping experience that Amazon has recently demonstrated.

The potential to on-board data from more advanced diagnostic devices, such as the Firefly otoscope (used to examine the ear canal), provides opportunities to use IoMT to perform more accurate remote diagnosis and management. This could complement existing voice and video telehealth systems to deliver more responsive care [42]. Needs exist where patients and professionals are geographically remote from each other. This may support care where patients are mobile or time constrained or where specialist expertise only exists in centralized locations (such as Oxford) serving patients across regions, countries, or internationally.

Methods

Proposed Proof-of-Concept Projects

On the basis of the industry research, case studies, and local environment, we propose a spectrum of PoC projects that will create the capability to explore both cost-effectiveness, clinical efficacy, and user adoption of IoMT systems.

These projects cover 3 areas:

1. Bring Your Own Device Integration (BYOD) Integration,
2. Chronic disease management, and
3. Personal health records.

Bring Your Own Device Integration

Bring your own device presents an opportunity for patients to use personal medical devices to capture health information. The purpose of this project will be to give patients the capability to use their own devices connected to the OUH EHR digital infrastructure for disease management.

Aims

The aims of this project will be as follows:

1. To enable EHR-integrated smart device interoperability,
2. To demonstrate accessibility to various devices across the same disease state, and
3. To compare use of personal devices with controlled medical devices and evaluate adoption and clinical data accuracy.

Technologies

The following technologies will be explored:

1. Cerner Care Aware activation and
2. Validic UK instance.

Chronic Disease Management

The purpose of this project will be to evaluate the effectiveness of a mobile Health solution designed to provide accurate data collection and to create resource efficiency by replacing staff with technology for data capture and reporting.

Aims

The aims of this project will be as follows:

1. To evaluate impact to clinical staffing and hospital visits and
2. To evaluate patient perspectives on technology use.

Technologies

The following technologies will be explored:

1. Drayson gestational diabetes monitoring and
2. Cerner Care Aware activation.

Adoption

The key considerations in the analysis of adoption are uptake and the sustained use of access to personal health records. This project will enable direct patient access of personal health records.

Aims

The aims of this project will be as follows:

1. To allow for access to patient record via disconnected device,
2. To create conduit for data exchange of recorded data via consumer device, and
3. To evaluate patient perspectives on technology use.

Technologies

The following technologies will be explored:

1. Cerner EHR and
2. Apple HealthKit.

Proof-of-Concept Next Steps

It is recommended to hold a workshop over summer 2018 (late September), where this report can be presented to the Promoting the Internet of Things via Collaborations between Higher Education Institutions & Industry (PITCH-In) partners and projects can be scoped and developed in more detail.

Each project will first gather user needs to link needs to the underlying technology and then use an iterative process to conceptualize the overall solution, which will be beta-tested across an extended trial. Ethical approval will be sought for the study and evaluation design and each project stage-managed by a controlled project management process (Figure 1).

Projects will be expected to deliver 7 key outcomes:

1. Scoping document: project initiation document,
2. Evaluation approach including
   - Technical benchmarking of management strategy, security, governance, quality, operations, architecture, and supporting process,
   - Evaluation benchmarking of factors impacting adoption, including analysis of how socioeconomic, education, ethnicity, age groups, and associated factors are considered in take-up of technologies,
3. Needs analysis with patients,
4. Alpha prototype demonstrating,
5. Beta system implementation,
6. Completed evaluation, and
7. Final report.

Results

This PoC projects will be funded by the Research England's CCF. The project started in 2018. During March 2018, the OUH Digital Innovation Lead and Cooksey Fellows from the University of Oxford Health Care Translation Group attended the HIMSS 2018 conference and attended a site visit at Cerner's Innovation campus. During this trip, the team investigated the potential for IoMT technologies and their applicability to the Oxford ecosystem. Results are expected to be available by the end of 2019.

Discussion

Internet Data Collection Enablement of Population Health Analysis

The rapidly developing Oxford digital health ecosystem offers tremendous opportunities for PoC studies to investigate and share understanding of the use of IoT in health care. During 2018 to 2019, several technical solutions will be deployed that will give Oxford a unique position within the United Kingdom (and only 1 of a small handful of international sites) to implement real-world health care IoT solutions. The combination of digital population health solutions to integrate data sources; patient portals to engage users; ingestion platforms for IoT devices; and open-source interoperability APIs can be leveraged to develop, test, and evaluate needs, ideas, and solutions with frontline staff, academics, and industry partners.

Conclusions

This report has been prepared to support the University of Oxford's input to the PITCH-In project, which is being led by the University of Sheffield in partnership with the universities of Oxford, Cambridge, and Newcastle and industrial and health sector partners. PITCH-In has been awarded £4.9 million by Research England's CCF to drive forward collaboration concerned with the IoT across multiple industries, including health care.

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Conflicts of Interest

None declared.

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Abbreviations

AHSC: Academic Health Science Centre
AI: artificial intelligence
API: application programming interface
BYOD: Bring your own device
CCF: Connecting Capability Fund

CCG: Clinical Commissioning Group
CO: carbon monoxide
EHR: electronic health record
FHIR: Fast Health Care Interoperability Resources
GDE: Global Digital Exemplar
GP: general practice
IoMT: Internet of Medical Things
IoT: Internet of Things
HIMSS: Health Care Information and Management Systems Society
NHS: National Health Service
OCC: Oxford County Council
OH: Oxford Health
OUH: Oxford University Hospitals
PITCH-In: Promoting the Internet of Things via Collaborations between Higher Education Institutions & Industry
PoC: proof-of-concept
SCAS: South Central Ambulance Service
SMART: Substitutable Medical Apps, Reusable Technology

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Protocol

Establishing Digital Biomarkers for Occupational Health Assessment in Commercial Salmon Fishermen: Protocol for a Mixed-Methods Study

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Abstract

Background: Commercial salmon fishing in Alaska is one of the most dangerous occupations in the United States. Between 1992 and 2008, the average annual industry mortality rate was 128 deaths per 100,000 workers, and despite an increase in industry regulations, there has not been a significant decrease in mortality rate since 2000. Unpredictable fishing openings and fierce competition for limited resources result in periods of intense sleep deprivation and physical strain during the short commercial salmon season in Alaska.

Objective: We hypothesize that the combined effect of sleep deprivation, intense physical workload, and significant short-term chronic stress may be deleterious to health in both the short- and long-term among commercial salmon drift gillnet fishermen in Alaska. The objective of this protocol is to determine the feasibility of the study design to test this hypothesis.

Methods: The study design uses mixed methods and includes biometric monitoring consisting of heart rate variability, respiration, and movement data collected via a personal, wearable biometric device. Additional methods include observational data on activity, including duration and quality of sleep, weather, catch, and financial gain, as well as the collection of salivary cortisol. As such, the study will provide a holistic assessment of individual stress on multiple simultaneous timescales: immediately and continuously through the personal wearable biometric device, on the minute-hour level through the multiple daily collections of salivary cortisol, and by the hour-day through the use of participant and environment observational data.

Results: Data collection was initiated in July 2017 and will extend through August 2019. Initial data collection has indicated that the methods outlined in this protocol are feasible and allow for effective collection of qualitative and quantitative data related to the psychological and physiological impact of Alaska commercial salmon fishing.

Conclusions: We anticipate that the use of a biometric device will be crucial in establishing measures of stress and physical activity within a population and environment uniquely challenged by physical isolation, strong weather patterns, and the potential for significant financial gain by fishermen. The potential exists for individuals engaged long-term in the fishing industry, through repeated and extended exposure to periods of intense sleep deprivation and chronic stress, to be at increased risk of cardiovascular disease.

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KEYWORDS

digital health; digital biomarkers; occupational health; health and safety; fishermen; physiological health; stress

Introduction

Background

Commercial salmon fishing in Alaska is one of the most dangerous occupations in the United States. Between 1992 and 2008, the average annual industry mortality rate was 128 deaths per 100,000 workers [1], and despite an increase in industry regulations, there has not been a significant decrease in mortality rate since 2000 [2]. Comparatively, the next most dangerous civilian occupations, as of 2016, are aircraft pilot, roofer, truck driver, and farmer, with rates of 55.5, 48.6, 24.7, and 23.1 fatalities per 100,000 workers, respectively [3]. Given the seasonal and often isolated nature of the work, reliable statistics on injuries are unavailable. The majority of recorded injuries and mortality result from vessel disasters, on-deck injuries, particularly those involving machinery, and falls overboard [2,4]. The industry is calling for injury prevention efforts such as increased use of personal flotation devices, but efforts to date have proven minimally successful.

Studies have demonstrated a significant, positive relationship between sleep deprivation and response time and vigilant attention [5]. Sleep deprivation has also been shown to decrease resilience to stress and have a detrimental impact on complex reasoning and decision making [6]. Unpredictable fishing openings and fierce competition for limited resources result in periods of intense sleep deprivation and physical strain during the short commercial salmon seasons in Alaska. For example, in the 24 hours from July 15-16, 2018, there were a total of 19 hours open for fishing in two 9.5-hour periods and only 5 hours during which fishing was not allowed (referred to in the industry as a closure), also in two 3-hour periods. Given the average 5-week season, most fishermen find it imperative to maximize fishing time. Sleep, therefore, most often occurs during short closures, which are typically also used to deliver fish, clean, and mend gear, resulting in sleep patterns which resemble naps rather than true sleep. The National Institutes of Health recommends that healthy adults receive between 7 and 8 hours of uninterrupted sleep per night [7]. For the purposes of this study, and in keeping with the American Academy of Sleep Medicine, sleep deprivation is defined as a pattern of sleep that results in excessive daytime sleepiness, mood changes, performance issues, and poor health outcomes [8].

The work of commercial gillnet salmon fishing is often highly physically demanding, requiring regular lifting and pulling of heavy items and repetitive movements associated with picking fish from nets, which is performed at high speeds and often for hours at a time. While the industry is currently focused on reducing acute morbidity and mortality, chronic stress, sleep deprivation, and the maintenance of high levels of physical exertion may also contribute to morbidity later in life through increased cardiometabolic risk [9]. We hypothesize that the combined effect of sleep deprivation, intense physical workload, and significant short-term chronic stress may be deleterious to health in both the short- and long-term among commercial salmon drift gillnet fisherman in Alaska.

In order to identify the physical and physiological impacts of commercial fishing on individuals, we intend to complete a mixed-methods study designed to elucidate the ways in which sleep deprivation, poor sleep quality, and chronic stress impact the short- and long-term health of industry participants. Advancements in biometrics of activity, movement, and physiology in combination with biomarkers of acute and chronic psychosocial stress can provide insight into how the lifestyle and occupational factors associated with commercial fishing may negatively impact both the physical and psychological health of fishermen, while observational data can provide context into the daily activities and environmental pressures inherent to the industry.

Biometric devices provide an objective method for quantifying physical activity. Measuring physical activity and sleep deprivation has proven historically challenging and traditionally has been performed using self-report via physical activity questionnaires. While cheap and relatively easy to administer [10,11], physical activity questionnaires are incapable of objectively quantifying physical activity and, due to self-report, are inherently unreliable. One study in 2011 found a 40% difference between participants who met recommended daily activity levels when daily activity levels were determined through self-reported questionnaire versus direct researcher observation [12]. Objective methods are necessary to quantify physical activity in order to assess its impacts on health.

Recent advancements in personal activity tracking devices promise a solution to the issue of subjectivity. The use of accelerometers and heart rate monitors to record energy expenditure and other measures of physical activity is not new, but improved technology, including media sharing, has rendered the products more reliable, reducing cost and increasing their popularity among consumers [13]. Modern personal tracking devices have been found to have a high level of accuracy and interdevice reliability [11,13-16] and provide an objective measure of physical activity [11,13-15]. While research-grade devices have been more thoroughly validated in laboratory settings, the recent advancements in commercially available biometric devices provides a novel and cost-effective approach for field research due to their ease of application. Further validation studies are needed to assess the reliability and accuracy of these devices in research settings. Studies have shown that only a short period of use is required in order to get an accurate assessment of an individual's activity due to natural daily fluctuations in exercise. A recent study found that wearing an accelerometer for only 3 days was sufficient to accurately reflect activity [17]. This reduces the potential inconvenience caused by wearing such a device for an extended period of time. Although personal wearable tracking devices have demonstrated advantages for collecting measures of physical activity in individuals, little research has been done on their utility within an environment as complex and dangerous as commercial fishing. We anticipate that the use of a biometric device will be crucial in establishing measures of stress and physical activity within a population and environment uniquely challenged by physical isolation, strong weather patterns, and the potential for significant financial gain by fisherman.

While the collection of biometric data would enable us to monitor the body's physical response to external stressors, the additional collection of the stress hormone cortisol allows for

the measurement of the body's chemical responses to the same stimuli. Cortisol, a hormone of the hypothalamic-pituitary-adrenal (HPA) axis, is produced by the adrenal glands in response to stress. Cortisol follows a circadian rhythm during which levels peak 30 to 45 minutes after waking and then decline throughout the remainder of the day [18-21]. In a normal state, the HPA axis responds to psychosocial stress through increasing cortisol production [22-27]. Cortisol plays an important role in maintaining cellular homeostasis through diverting metabolic operations toward systems at risk of dysregulation [22,24,25,27]. In healthy individuals, cortisol suppresses immune response and prevents increasing levels of proinflammatory cytokines [27-30]. Chronic stress causes a dysregulation of the HPA axis resulting in blunted cortisol reactivity [25,29,30]. A significant, negative correlation between the number or intensity of psychosocial stressors and cortisol levels has been shown in individuals with posttraumatic stress disorder, work-related stress, and traumatic events early in life [25,29]. The exact mechanism through which this dysregulation occurs is not well understood as it may be regulated through the reduction of cortisol production or the insensitivity of glucocorticoid receptors on target tissues [25,27]. Cortisol is a glucocorticoid hormone that activates the pathways responsible for preventing the release of proinflammatory cytokines in response to environmental, psychosocial, and physiological stress and is the most commonly used biomarker to assess levels of acute and chronic physiological stress [20,21,31-33]. Cortisol is a useful biomarker because it can be measured through saliva, allowing for noninvasive measurement of physiological stress response throughout the day.

While biomarker data is integral to understanding the human response to stress, observational data collected through participant observation provides an environmental context that is otherwise missing with the collection of biomarkers alone. Participant observation is a method of research used extensively within social science disciplines [34]. It involves the observation and recording of participant activities within their daily environment, instead of an artificial research environment, and has been found to be particularly useful in community health research [35-37]. Participant observation is often preferred to survey data collection due to improvements in reliability and recall and has the added benefit of allowing the observer to record external environmental conditions which may impact the participant's behavior [35]. Mixed-methods studies, which include the use of both quantitative and qualitative data, in this case biometric, observational, and biomarker, can provide a more holistic perspective of health.

Short-Term Health Impacts

Short-term health risks associated with sleep deprivation align most closely with industry safety concerns. Sleep deprivation, which results from an inadequate quantity or quality of sleep, has been shown to result in an increased risk of acute injury resulting from delayed response times. In addition, it has been shown to retard decision-making capabilities [38]. These incidences of injury and mortality result in the statistics which make the industry one of the most dangerous in the country.

Long-Term Health Impacts

The short-term poor health outcomes resulting from commercial fishing are likely to cause the greatest concern to industry leaders and occupational health providers due to the stark image the statistics present. The long-term health impacts of combined sleep deprivation and intense physical and psychological stress, however, may result in a myriad of chronic diseases that have the potential to significantly negatively impact later life fitness and quality of life and potentially contribute to premature mortality. Acute sleep deprivation has been shown to impact control of cardiovascular regulation while altering inflammatory regulatory response and endothelial function [39], and short sleep duration has been found to be associated with numerous poor health outcomes including cardiovascular disease [40]. While the impact of short sleep duration seems to increase with age, even healthy early adults demonstrated significant effects [41,42]. Studies of the long-term impacts of sleep deprivation are inconclusive due in large part to experimental differences in environment, timing, and study population. Elevated blood pressure and hypertension have long been associated with increased risk of morbidity and disability as well as mortality from causes such as cardiovascular disease and stroke [41,43]. The relationship between sleep processes and the cardiovascular system are likely bidirectional, as poor cardiovascular health can result in disturbed sleep from causes like obstructive sleep apnea [44].

As with sleep deprivation, experiencing chronic stress has long-term health implications including memory impairment, increased abdominal obesity, and elevated risk of cardiovascular disease. Chronically elevated cortisol levels have been significantly associated with memory impairment in healthy adults [45] and have been demonstrated to interfere with attention and working memory in several experimental studies [45-48]. Besides detrimental effects to memory, variation in cortisol levels is associated with increased risk for abdominal obesity and metabolic dysregulation through perturbations of the HPA axis [19]. Persistent dysregulation of the HPA axis can result in a blunted cortisol response to stimuli, which has been linked to imbalances between proinflammatory and anti-inflammatory activity in the body [49]. This results in heightened levels of inflammatory cytokines, such as c-reactive protein and interleukin-6, that influence the etiology of cardiovascular disease and are predictors of cardiac episodes [49]. A similar relationship to inflammation has been found with interrupted sleep [50-52]. Within the general adult population, coronary heart disease and stroke are two of the leading contributors to morbidity and mortality in the United States [53]. The most recent report from the American Heart Association estimates that one American dies every 40 seconds from complications related to cardiovascular disease [53]. In 2013, 1 in every 9 deaths was attributed to myocardial infarction [53]. The potential therefore exists for individuals engaged long-term in the fishing industry, through repeat and extended exposure to periods of intense sleep deprivation and chronic stress, to be at increased risk of cardiovascular disease.

Study Objective

The objective of this study is to determine the feasibility of using a wearable biometric device in combination with observational data and biomarkers of acute stress to assess the potential short- and long-term negative health impacts associated with Alaska commercial salmon gillnet fishing. The use of a personal wearable biometric device in tandem with salivary cortisol will allow us to collect continuous measures of physical exertion and stress in an infamously challenging environment and under austere conditions on 2 distinct time scales: biometric measures capture changes in the millisecond-to-second time scale while salivary cortisol records changes by the minute to hour. It also affords an accuracy that would not be possible with self-report surveys. The completion of this protocol will determine the feasibility of a mixed-methods study approach using a wearable biometric device, cortisol collection, and participant observation to answer crucial questions regarding safety and health impacts in a notoriously challenging population and occupation.

Methods

Study Design

This pilot study is intended to determine the feasibility of using a wearable biometric garment and salivary biomarkers (cortisol) coupled with qualitative data collection as measures of physiological and psychological occupational stress in commercial gillnet salmon fishermen in Alaska. A significant strength of this study design is that it will allow for a holistic assessment of individual stress on multiple simultaneous time scales: immediately and continuously through the personal wearable biometric device, on the minute-hour level through the multiple daily collections of salivary cortisol, and by the hour-day level through the use of observational data collection. We will use nonprobability convenience-based sampling to recruit 10 participants from the Bristol Bay, Alaska, commercial fishing fleet.

Recruitment

Fliers advertising the study will be posted in one of the main boat yards where Bristol Bay driftnet and setnet gillnet fishing vessels are stored and maintained, including the main office, bathrooms, and fishermen's lounge. Interested participants will be encouraged to contact the primary investigator via phone. Additional study information will be shared at this time, and if the potential participant retains interest in the study, an in-person meeting at a neutral location will be arranged. During the meeting, participant and study staff will discuss the study's goals, potential risks to participants, expectations for wearing the biometric measurement device, compensation structure, study schedule, and our inability to provide absolute confidentiality. We will stress that this is not a medical study. At this meeting, we will also demonstrate the use of the biometric measurement device procedures to the participant. The recruitment goal for this leg of the study will be capped at 10 participants in order to confirm feasibility of the protocol.

Selection Criteria

Recruitment will be limited to captains and crew members with a Bristol Bay, Alaska, commercial salmon drift gillnet license or crew license. At this phase of the feasibility study, recruitment will be limited to males between the ages of 18 and 50 years in order to maximize comparability of results from participants.

Ethics and Confidentiality

This study has been reviewed and approved by the University of North Carolina (UNC) Institutional Review Board.

Data Collection

Biometric Monitoring

Technological advances in wearable sensory devices have made it possible to gather extensive biometric data from subjects with minimal discomfort or researcher interference. Three key biometric measures are of particular interest when studying physiological stress response in ambulatory settings: accelerometry, heart rate variability (HRV), and respiratory analysis. HRV is calculated using variation in time between 2 heartbeats and provides a measure of the heart's ability to respond to regulatory impulses. It can therefore act as an indicator of changes in stress [54].

Biometric data will be collected using Hexoskin (Carre Technologies Inc) technology in order to measure and record physical activity, heart rate, respirations, and sleep quality. In laboratory settings, Hexoskin technology has been found to have low variability and good agreement and consistency [55], although results of field testing have been mixed [56]. We believe that the Hexoskin design, as a form-fitting and moisture-wicking shirt, will provide less interference in the required daily activities of active fishermen. The devices have previously been found to be effective at collecting biometric measures in other highly active participants, including hikers and elite cyclists [56,57]. Similar products have been used to study occupational stress in firefighters and policemen, but to our knowledge, there have been no studies which made use of similar technologies to study commercial fishermen. The combined measures of HRV, respiration, and movement present a proxy for physical and psychological stress, as the heart rate increases in response to stressors through the fight-or-flight reflex. We use Hexoskin, an electrocardiograph (ECG) device, in order to capture HRV through variation in the R–R interval. HRV has been identified as an important measure of physical stress and activity and is not captured by photoplethysmograph (PPG) devices. Due to the challenging field environment in which we propose this research taking place, we determined that use of the Hexoskin would be the most applicable due to its comfort of wear and ease of data extraction while in an off-the-grid field environment [56].

After training performed by the primary investigator, the participant will wear the biometric device for a total of 48 hours prior to the initiation of the fishing season, in order to determine baseline measures. Every 12 hours, the device will be removed in order for the data to be uploaded to a database and the device's battery to be recharged. Following the collection of baseline measures, the participant will wear the device for a

total of 48 hours during the peak of the commercial sockeye salmon fishing season. As during the baseline measurement period, the device will be removed every 12 hours so the data can be uploaded and the batteries can be charged.

Cortisol

Salivary cortisol will be collected 5 times per day over the course of 2 days prior to the initiation of the fishing season in order to create a diurnal baseline before the introduction of extreme stressors associated with the fishing season. Before the study begins, the participants will be trained on how to collect samples according to the procedures [58]. Participants will be asked to collect their samples upon waking, 30 minutes postwaking, before lunch, in the evening, and prior to sleep using the passive drool technique. The collection vials will all be labeled before collection begins to avoid any commingling or mislabeling of specimens. All samples will be frozen and packed in ice before they are brought back to the UNC Human Biology laboratory for analysis. Using the same procedures, the participant will collect salivary cortisol for 3 days during the peak of the commercial sockeye salmon fishing season. Due to the erratic and inconsistent sleep patterns during the fishing season, the participant will not be able to provide salivary samples at the same 5 times each day. Instead, the participant will collect their saliva samples at approximately every 5 hours, with flexibility in specimen collection time when needed to allow for sleep.

Observational Data

During periods of biometric data collection, the primary investigator will observe the participants and make note of key events in their day and the time at which they occurred, including but not limited to waking, sleeping, eating, opening times for fishing, fishing initiation, time spent setting the net, net collection, fish picking, and travel. The investigator will also note factors such as weather and the quantity and weight of catch. Quantity and weight of catch will be verified using industry catch tickets, provided to each captain as a receipt upon the delivery of each catch. Observational data will be recorded using time-demarcated spreadsheets and will ultimately be used to calculate total hours of sleep per day. Given the variability of commercial fishing openings, sleep patterns during the season are often sporadic, with fisherman typically sleeping in shifts and for short periods of time throughout the day (investigator observation). Data recorded by the Hexoskin device during periods identified as sleep will be used to determine sleep quality.

Data Analysis

The 3 data sources will be assimilated and synchronized in order to produce a filtered and preprocessed dataset for each participant suitable for statistical analysis. Fishing period data will be compared to baseline data as the control for analytical purposes.

Accelerometry

Accelerometry will be quantified using the physical activity index developed by Bai and colleagues [59]. This new metric uses the variance of oscillations along all 3 axes to calculate summary measures using predetermined epochs. ActivityIndex software (R Foundation for Statistical Computing) will be used to calculate the physical activity index from the raw accelerometry data collected from the Hexoskin.

Heart Rate Signal Processing and Variability

HRV refers to the variation in time between consecutive heartbeats over a specific amount of time. Changes in the time interval reflects periods of stress due to activation of the autonomic nervous system. While there remains ongoing research into the contributions of the sympathetic and parasympathetic nervous systems on HRV, its utility as a tool to detect changes in cardiac autonomic regulation is well established [60]. HRV is a popular measure in part due to noninvasive collection procedures and the plethora of computer-based analytical tools available [61]. HRV collection will be recorded for 3 phases—baseline, event, and postevent—according to recommended standards. This will allow the researchers to measure both the reactivity and recovery of HRV following both stressful and strenuous events that occur during the fishing season. Reactivity refers to the changes between the tonic baseline HRV and phasic stimulus-response HRV. Assessing the phasic HRV within the context of the activity is needed in order to determine whether the response is adaptive or not [54]. In this study, HRV will be filtered to reduce variations in signal by smoothing the HRV time series, and the ECG will be preprocessed in order to address noise interference by using a low-pass and high-pass filter and differentiator [62]. Participant average parameters will be calculated based on baseline data, and periods of stress will be identified by calculating mean and standard deviations within preset periods of time. HRV will be analyzed using the open source RHRV package (R Foundation for Statistical Computing).

Statistical Analysis of Heart Rate Variability

Before analyzing HRV, we will use ECG sensors to examine the electrical activity of study participants as the heart depolarizes. As the biometric monitoring device does not include all 10 electrodes required for a full ECG, this will constitute a semicomplete ECG. R-Project Statistical Software (R Foundation for Statistical Computing) will then be used for analysis.

Respiratory Analysis

Baseline average respiratory rate will be calculated from respirations measured during the control period prior to the initiation of fishing. Respiratory data collected during the peak of the season will be compared using VivoSense software version 3.0 (Vivonoetics) to determine periods when the participant's respiratory rate was significantly different from baseline.

Statistical Analysis of Observational Data

Observational data will be analyzed using Dedoose software version 8.0 (SocioCultural Research Consultants) to identify key periods of change. These periods are graphically represented according to the period of time during which they occurred and will be graphically overlaid on the HRV data, presenting a more complete picture of the environment in which rates of elevated and diminished stress response occurs.

Mixed-Model Trajectory Analysis

Mixed-model trajectory analysis will be used to quantify the participant's time series data. Maximum likelihood estimation and fit statistics tests will show which elements of the model improve fit to the observed data. This will help to control for biased estimates in a small sample size.

Feasibility Analysis

Feasibility of the study protocol will be analyzed by determining the number and type of missed or incompletely collected data points. If data points fall outside of the normal range as found for previously reported field collection of biometric, salivary, and observational data collection, necessary protocol amendments will be made. Participants will also be interviewed postseason, at the completion of data collection, in order to identify challenges they may have had with the study protocol or use of the biometric device or salivary collection itself.

Sample Size and Power

The implications of this study are limited by a small sample size of 10. However, given the study objective of determining the feasibility of using a personal wearable biometric device technology to study the physical and psychological occupational stress endured by commercial gillnet salmon fisherman in Bristol Bay, Alaska, the authors feel that the sample size does not present a limiting factor in achieving the study goal.

Results

Data collection was initiated in July 2017 and will extend through August 2019. Data analysis will take place in fall 2019, and results will be disseminated via peer-reviewed publications in winter 2019. We anticipate that, if successful, this protocol will produce findings that could contribute substantially to the existing knowledge base regarding occupational health within the commercial fishing industry. Such findings would provide a foundation from which to revisit industry safety standards and an evidence base for future occupational health interventions.

Discussion

We anticipate that the use of a biometric device will be crucial in establishing measures of stress and physical activity within a population and environment uniquely challenged by physical isolation, strong weather patterns, and the potential for significant financial gain by fishermen. This information can assist industry leaders in addressing sustained high rates of mortality within the industry and inform interventions to improve the health and well-being of fishermen. The primary limitation of the protocol is a small sample size, necessitated by the in-depth methods and physical isolation of study participants. We feel, however, that the high potential for knowledge to be gained justifies this limitation.

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Conflicts of Interest

None declared.

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Abbreviations

ECG: electrocardiograph
HPA: hypothalamic-pituitary-adrenal
HRV: heart rate variability
PPG: photoplethysmograph
UNC: University of North Carolina

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Protocol

Development and Validation of a Diabetic Retinopathy Screening Modality Using a Hand-Held Nonmydriatic Digital Retinal Camera by Physician Graders at a Tertiary-Level Medical Clinic: Protocol for a Validation Study

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Abstract

Background: Visual impairment and blindness from diabetic retinopathy (DR), which can be reduced by early screening and treatment, is an emerging public health concern in low-income and middle-income countries (LMICs) owing to the increasing prevalence of diabetes mellitus (DM). However, no systematic screening exists in most LMIC settings. The Western province of Sri Lanka has the highest prevalence of DM (18.6%) in the country. A situational analysis identified a marked gap in DR screening (DRS) and treatment services uptake in this region; only opportunistic screening is practiced currently.

Objective: The aim of this protocol is to describe the methods of development and validation of a DRS intervention using a hand-held nonmydriatic digital camera by physician graders in a non-ophthalmological setting at a tertiary-level medical clinic to propose a valid and feasible modality to improve uptake.

Methods: DRS modality was developed after assessing barriers and identifying the most appropriate personnel, methods, and location for screening services, following formative research work. The validation will be conducted in a public sector tertiary care center in the Western province of Sri Lanka. The selected physicians will be trained on capturing and grading images according to a valid locally adopted protocol. Two physicians rated high on training will screen a sample of 506 people with DM at a medical clinic. They will use nonmydriatic and mydriatic 2-field imaging strategy. The validity of the proposed screening procedure will be assessed and compared with the mydriatic indirect biomicroscopic examination by a senior retinologist.

Results: The validity of screening by physician graders will be analyzed and the sensitivity, specificity, and predictive values (with 95% CIs) calculated by the dilation status and for each grader. The diagnostic accuracy at each level of severity of DR will be assessed to define the most appropriate referable criteria. Data is currently being collected.

Conclusions: The outcome of this study will be useful for the detection of a defined level of DR at non-ophthalmological setting to filter the people with DM before referral to an eye clinic. This will be helpful to improve the uptake and identify risk groups

in advance to prevent sight-threatening DR. Furthermore, evidence from this study will be useful for the implementation of a DRS program in this region and in similar communities.

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KEYWORDS

diabetes; diabetic retinopathy; digital imaging; hand-held camera; mydriatic; nonmydriatic; physician grader; screening; Sri Lanka

Introduction

The prevalence of diabetes mellitus (DM) and the number of people affected by DM is increasing rapidly in all regions. The International Diabetes Federation estimated that 425 million people had diabetes in 2017, which will increase to 629 million in 2045 globally [1]. This increase is expected to be the highest in low-income and middle-income countries (LMICs) compared with high-income countries (HIC) [2]. Diabetic retinopathy (DR) is a common microvascular complication of DM, which can lead to visual impairment and blindness if not detected early and treated [3]. Many studies have reported that visual loss from DR can be largely prevented by early screening and appropriate treatment [4-6]. Diabetic retinopathy screening (DRS) can be done in 2 ways, systematic screening similar to national-level programs in HIC versus opportunistic screening and case detection, which is common in low-income settings. Most LMICs are unlikely to have full population-based screening program owing to resources constraints. The current method of DRS in most LMICs is direct ophthalmoscopy, which has a lower diagnostic accuracy and found to be ineffective even after training [7]. The mydriatic biomicroscopic examination by an ophthalmologist is practically not possible in these countries owing to a low number of ophthalmologists, and eye clinics are overburdened with highly prevalent blinding conditions such as cataract [8].

The reasons for the unavailability of DRS programs (DRSPs) in LMIC settings are mostly attributed to the lack of skilled human resources, financial resources, and evidence of what works in the local system [9-11]. Therefore, it would be important to understand the approaches for screening, especially in non-ophthalmological settings. Conventional digital cameras need a larger space, skilled photographers, and large image storage devices. In addition, systematic screening using sophisticated table-top imaging systems incur high capital investment though they are cost-effective [12]. Hand-held digital cameras are easy to move, require minimum space, minimum power consumption, and are user-friendly [13]. In addition, nonmydriatic hand-held cameras are less discomforting to participants and can be used while people with DM are waiting in front of a physician for consultation. The usage of a camera without pupil dilatation is comfortable to people with DM, as well as easy for providers. However, the latter depends on the quality of the image available for grading [14].

Various photographic studies have looked at the diagnostic test accuracy of DRS using digital imaging. Most of these studies used static table-top imaging systems and were conducted in HICs. These studies have shown a sensitivity of 68%-97% and a specificity of 71%-100% in nonmydriatic imaging using ophthalmic human resources as index graders [15-18]. Similarly, in mydriatic imaging, most of the studies have used table-top imaging systems, ophthalmic human resources as index test graders, and were conducted in HICs. These studies have shown a sensitivity of 77%-97% and a specificity of 76%-98% in mydriatic digital imaging [19-22]. There is a gap in evidence in digital retinal imaging in LMICs using non-ophthalmic human resources. In addition, the usage of context-specific imaging systems, such as hand-held digital retinal camera, in non-ophthalmic setting was not reported in the current literature.

Sri Lanka has achieved remarkable development in the health sector; however, there are public health concerns such as DR which have not been addressed to date [23]. The crude prevalence of DM in Sri Lanka was 12.6% (>20 years), being highest in the Western province (18.6%, 95% CI 15.8%-21.5%) [24]. In the Western province, there are approximately 750,000 (age>18 years) people with DM, 20% (150,000/750,000) of whom are likely to have nonproliferative DR (NPDR). A situational analysis conducted in this region has shown that the number of people undergoing opportunistic screening and free treatment in the public sector was far lower than the estimated need [25]. There is no systematic DRS in the Western province despite the high prevalence of DM [25]. In addition, there is no published data on this topic from Sri Lanka. The aim of this protocol is to describe the methods of validation of a DRS approach using digital imaging by physician graders in a tertiary-level public sector medical clinic. This study will demonstrate the functional and technical feasibility of using a hand-held digital camera in an LMIC non-ophthalmological setting and assess the diagnostic accuracy.

Methods

Ethics Approval

Ethics review committees of National Eye Hospital (Colombo, Sri Lanka) and London School of Hygiene & Tropical Medicine (United Kingdom) granted ethics approval.

Development of the Diabetic Retinopathy Screening Modality and Training

The initial formative research showed that nonmydriatic digital retinal imaging at medical clinics by general physicians was a potential option for the local setting. We selected 9 general physicians from a tertiary-level institution following informed consent, and they underwent a competency-based training by 2 retinologists from a tertiary center, which included the following: capturing retinal fields using a hand-held fundus camera, identification of signs of DR (including macular signs) using images, and DR grading according to an adapted

classification system (Table 1). DR signs are graded at 4 levels as follows: none=R0, mild NPDR=R1, moderate NPDR=R2, severe NPDR=R3, and proliferative DR and above=R4. Macular changes are graded as follows: none=M0 (maculopathy absent) and exudate(s) or blot hemorrhage(s) within 2-disc diameters from the center of the fovea=M1 (maculopathy present). Guidelines were used to standardize reporting of image quality, which included ungradable images based on the proportion of the retina visible for grading (Figure 1). After the training, physicians were tested using a set of standard images of DR, and the two physicians who reached the required level of agreement with the retinologists (κ=.8-.9) were selected as graders in the validation study.

Table 1. Adapted diabetic retinopathy classification for the validation study.

Signs	No DR[a] (R0)	Mild BDR[b] or NPDR[c] (R1)	Moderate BDR or NPDR (R2)	Severe NPDR (R3)	PDR[d] (R4)
Microaneurysms	No	Few	Multiple	Multiple	Present
Hard exudates[e]	No	Few	Multiple	Multiple	Present
Cotton wool spots	No	Occasional	Multiple	Multiple	Present
Intraretinal hemorrhage[e]	No	Few	>20 in 1-3 quadrants	>20 in 4 quadrants	Present
Venous beading	No	Occasional	Present in 1-2 quadrants	Present in >2 quadrants	Present
IRMA[f]	No	No	Present ~1 quadrant	Prominent >1 quadrant	Present
NVD[g]	No	No	No	No	Present
NVE[h]	No	No	No	No	Present
Vitreous or preretinal hemorrhage	No	No	No	No	Present—advanced PDR
Traction	No	No	No	No	Present—advanced PDR
Fibrosis	No	No	No	No	Present—advanced PDR

[a]DR: diabetic retinopathy.

[b]BDR: Background DR.

[c]NPDR: nonproliferative DR.

[d]PDR: proliferative DR.

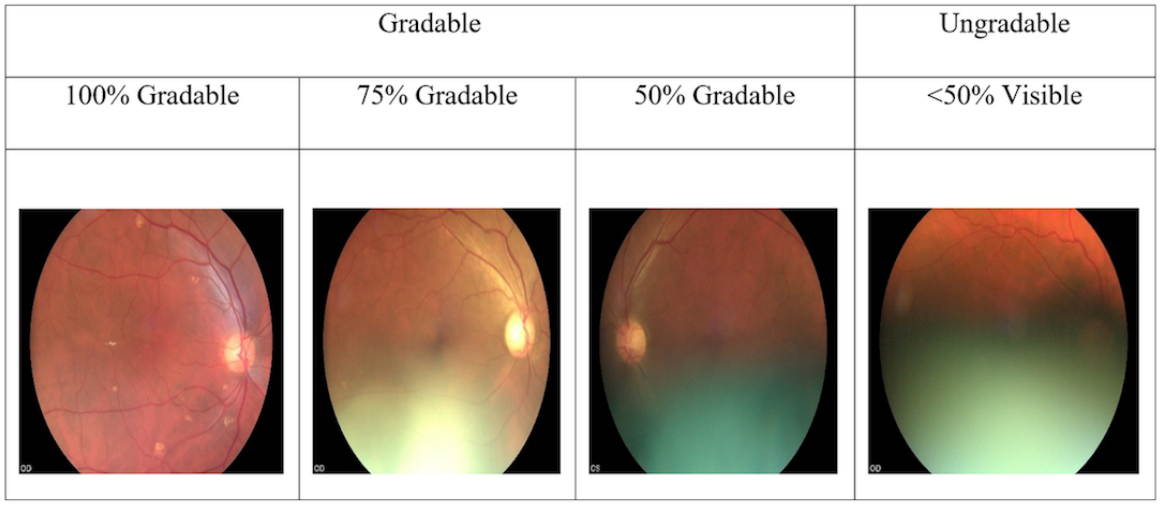
[e]Not within the definition of maculopathy.

[f] IRMA: Intraretinal microvascular abnormalities.

[g]NVD: Neovascularizations over the disc.

[h]NVE: Neovascularizations elsewhere.

Figure 1. Evaluation of image quality-levels of gradeability based on the proportion of the image that can be graded.



Sample Calculation and Recruitment

The sample size (n=405) was calculated on the basis of 95% CIs, 10% margin of error, expected sensitivity 70%, and the prevalence of moderate NPDR among people with DM of 20%. Then, we inflated the sample size by an additional 25% (n=101, total n=506) to take account of ungradable images. An interim analysis will be undertaken to ascertain the level of ungradable images (ie, <50% of the retina visible) and the sample size increased, if required.

This study is a prospective observational study by design. A consecutive sample of diagnosed people with DM (age >18 years) without previous DRS at an eye clinic will be eligible to participate, after giving written informed consent. Eligible participants will be recruited by trained research assistants when people with DM present for routine medical care at the main tertiary center in Colombo. People with DM with previous retinal screening, DR-related treatment (laser treatment, intravitreal injections, and pars plana vitrectomy), and those who were currently under any DRSP or treatment will be excluded from the study. Figure 2 shows the participants' flow diagram. Participants' characteristics will be documented in a questionnaire schedule by research assistants on recruitment.

Figure 2. Participants' flow diagram in the validation.

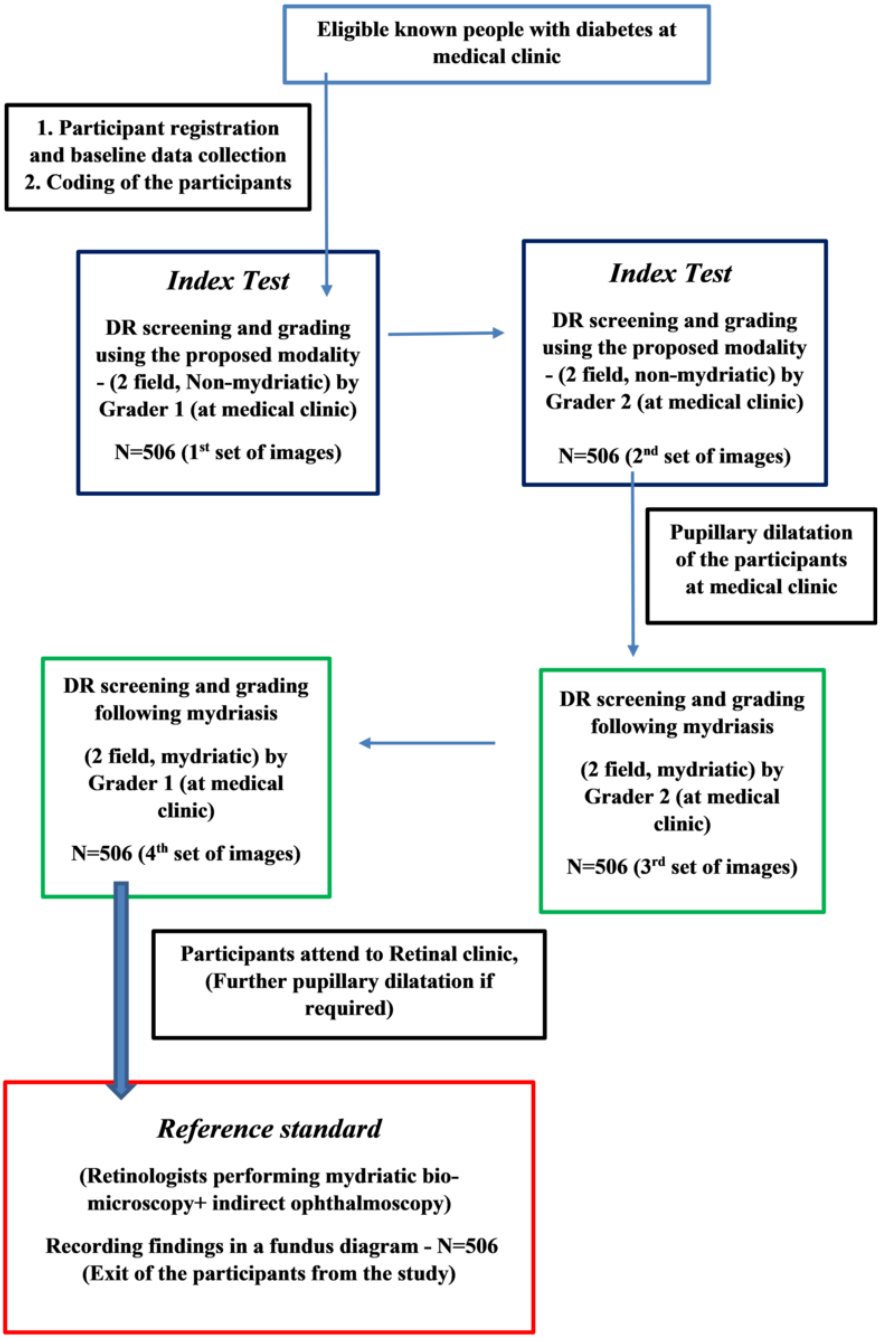
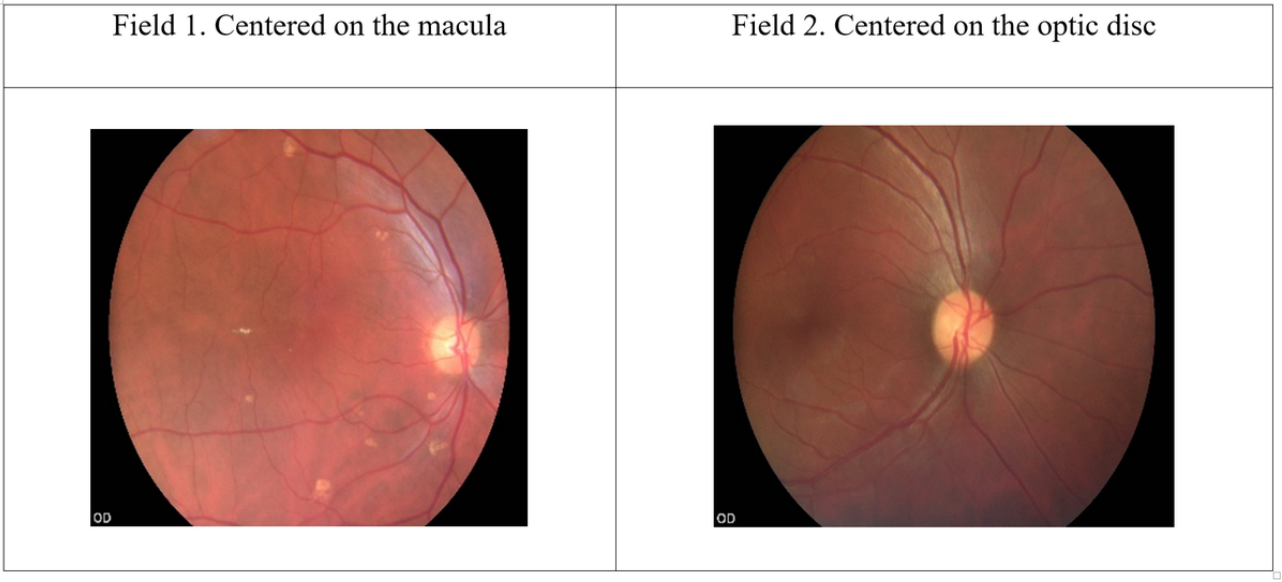


Figure 3. Two retinal fields captured.



Imaging System, Capturing Images, and Grading

Two-field nonmydriatic and mydriatic retinal images will be captured and stored (Figure 3). Participants will undergo digital retinal imaging (using VISUSCOUT100 hand-held nonmydriatic fundus camera-2017; Carl Zeiss, Germany) by the physician graders at the time of presentation. This imaging system has a 40° field-of-view with 5 megapixels (type of camera sensor: complementary metal-oxide semiconductor; resolution 800×480) and captures color and red-free images in a focus range of −20 D (diopters) to +20D. The minimum pupil size required is 3.5 mm, and 9 light-emitting diodes are available for internal fixation.

First, 2-field (first field-macula centered, second field-disc centered; Figure 3), 40° retinal images will be captured in each eye by each physician grader without pupillary dilatation. Subsequently, participants' pupils will be dilated using 2.5% phenylephrine, and the same fields will be captured, following adequate mydriasis (5-6 mm).

Each set of images will be coded and stored by research assistants after capturing. The coded image sets will be given back to the same physician graders for grading. During grading, nonmydriatic images will be graded first. The graders will be masked to the history and clinical examination findings. The retinopathy and macular signs will be identified and entered by physician graders into a hardcopy data table. Finally, it will be entered into a Microsoft Excel datasheet by research assistants. The grading data consistency checks and cleaning will be done by an independent statistician.

Reference Test

The reference test will entail a detailed, dilated fundus examination by an experienced retinologist using slit-lamp biomicroscopy with a 90D lens and indirect ophthalmoscopy using a 20D lens. After imaging, this examination will take place as early as possible. The retinologist will be masked to the clinical status and physician graders' findings. In addition, a detailed anterior segment examination (clarity of cornea and status of the lens) and media (vitreous) examination will be done by the reference test grader. The lens opacity will be graded according to the lens opacity classification system, version 111.

Quality Assurance and Agreement Analysis

For quality assurance, 15% of each nonmydriatic and mydriatic image sets will be evaluated by the retinologist for technique, ability to image the required field, and gradeability. Then, 15% of each hundred image sets will be given back to physician graders for double grading to assess the repeatability and intragrader agreement in the first and second attempts of grading images. A sample of the same image sets (n=200) will be graded by the retinologist to calculate the intergrader agreement.

Data Analysis

We will analyze the validity of screening by physician graders and calculate the sensitivity, specificity, and predictive values with 95% CIs for each method of screening and by the grader. The analysis will be conducted by including and excluding ungradable images and considering each eye as a unit of analysis and by a person considering the worst eye. Intragrader and intergrader agreement (kappa) for both mydriatic and nonmydriatic index tests will be calculated and compared with the findings by the retinologist. A subgroup analysis will be conducted for the identification of the presence or absence of DR (any DR), moderate NPDR, and above with or without macular signs to make recommendations for a referable criterion for the local context in DRS by physician graders.

Results

The physician graders have been trained, and currently, validation is being done in the Western province of Sri Lanka. The results of this study will be published in detail according to the Quality Assessment of Diagnostic Accuracy Study guidelines [26]. Data will be entered using a Microsoft Excel (2016) worksheet and transferred into STATA/IC-v14.2 analytical package following cleaning, consistency checks, and analysis. The sensitivity, specificity, and predictive values for

each strategy and each level of DR will be presented using the same variables of 2 physician graders (nonmydriatic and mydriatic separately) compared with the reference standard, along with 95% CIs.

Discussion

The level of skills acquired by physician graders is an important factor in the screening outcome. Different non-ophthalmologist graders have successfully conducted DRS in some settings [27-29]. We will describe the diagnostic accuracy of the detection of DR by physician graders. In addition, we will be able to study the effect of a range of population characteristics on the validity of detecting DR using imaging and understand the role of non-ophthalmic personnel to make recommendations for a systematic DRSP. In addition, we will describe the referral criterion applicable to this local context based on the validation study results. Defining a referable level DR at a non-ophthalmological setting, in a context where there is no systematic DRS, will filter out those not needing a referral and therefore reduce the workload at an ophthalmologist's clinic. The 7-field imaging strategy used in early treatment diabetic retinopathy study is considered as the gold standard in DRS [30]. However, this technique is practically not feasible in this context owing to resources constraints. Therefore, we proposed to use the locally accepted reference standard of retinologists' examination as the suitable reference standard. Digital retinal imaging has previously shown diagnostic accuracy levels that would comply with the accepted standards of established national-level screening programs [15,22,31].

A few studies (conducted in HICs) have used non-ophthalmologist human resources in DRS, with which we could compare our results. In Singapore, a nonmydriatic fundus camera showed a sensitivity of 69.8% (95% CI 61.3%-77.2%) and a specificity of 94.4% (95% CI 92.3%-96.1%) for nonphysician graders using a single field [32]. A study in the United Kingdom on DRS by general practitioners using 35-mm color images showed that detecting any level of DR increased from 62.6% (95% CI 55.9%-69.4%) with direct ophthalmoscopy to 79.2% (95% CI 73.6%-84.9%) using retinal photographs, and specificity remained unchanged (direct ophthalmoscopy 75.0% [95% CI 69.5%-80.5%] vs 73.5% [95% CI 68.0%-79.1%]) [33]. They concluded that retinal photography by trained general practitioners in primary care settings could attain an acceptable level of detection of sight-threatening DR (87%) [33]. In Thailand, the use of single-field digital nonmydriatic imaging showed a sensitivity of 80% and a specificity of 96% in a sample of people with DM, where 54.7% people with DM were aged 41-60 years and 45.3% people with DM had diabetes since 1-5 years [34].

Another important consideration in this study would be the gradeability of images. The image gradeability will depend on the lens opacity, media opacity, pupil size, and reflectivity of the fundus. We envisaged poor gradeability in nonmydriatic imaging considering the high prevalence of cataract in this local setting. Furthermore, iris color, age, and other population characteristics may affect the quality of images [14]. Scanlon et al showed that in the >80-years age group, the technical failure rates reduced from 41.6% to 16.9% following mydriasis. This study concluded that the odds of having one eye ungradable increases by 2.6% (95% CI 1.6%-3.7%) for each extra year since the diagnosis of DM and major cause of ungradability was having central cataract (57%) [35]. We will describe the factors affecting gradeability of images in addition to the diagnostic test accuracy results.

In this study, we will demonstrate the diagnostic accuracy of physician graders compared with the retinologist to make recommendations for developing an integrated DRSP in LMICs where there is no systematic DRS. The outcome of this study will be useful for the implementation of a systematic DRSP in this region and similar communities.

Acknowledgments

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Authors' Contributions

MMPNP conceived the project idea. MMPNP is coordinating and conducting this research project in the Western province as a fulfillment of a research degree. GVSM and JLYY supervised the student work. GVSM, CG, JLYY, TP, and DM made substantial contributions for the concept development, methodology, and study design. CF is the Principal Investigator of the project from collaborating institution and supervised the project work locally. AK will supervise the project-related work of DRS at the medical unit. MD and KB conducted the training of physician graders and KB will conduct the reference standard clinical examination of participants. MD and KB will involve in managing those study participants who require further investigations and treatment. LP and HD will conduct the validation of DRS intervention at present in the Western province.

Conflicts of Interest

None declared.

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Abbreviations

DM: diabetes mellitus
DR: diabetic retinopathy
DRS: diabetic retinopathy screening
DRSP: diabetic retinopathy screening program
HIC: high-income country
LMICs: low-income and middle-income countries
NPDR: nonproliferative diabetic retinopathy

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Protocol

Supported Web-Based Guided Self-Help for Insomnia for Young People Attending Child and Adolescent Mental Health Services: Protocol for a Feasibility Assessment

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Abstract

Background: Sleep disturbance in adolescents is common, with up to one-third reporting significant symptoms of insomnia. Research with adults has demonstrated that Web-based cognitive behavioral therapy for insomnia (CBTi) can improve both sleep and mental health. However, research with adolescents is lacking, and we know little about whether CBTi would have similar effects on this younger population.

Objective: This paper summarizes the protocol of a study to assess the feasibility of adding supported Web-based CBTi to the usual care of young people aged 14-17 years attending specialist Child and Adolescent Mental Health Services (CAMHS).

Methods: This is an open trial where we will recruit young people (N=50) aged 14-17 years attending specialist CAMHS with primary or comorbid symptoms of insomnia. In addition to their usual care, young people will be provided with Sleepio, a 6-session, Web-based CBTi self-help program for insomnia. Sleepio teaches a range of techniques including sleep hygiene, relaxation training, stimulus control, sleep restriction, and cognitive techniques that participants will be helped to apply through brief, weekly telephone support calls. Questionnaires and interviews will be completed at baseline and postintervention (8-10 weeks) and will assess sleep, symptoms of depression and anxiety, and acceptability of Sleepio and telephone support.

Results: Recruitment started in May 2018 and continued until the end of October 2018.

Conclusions: This study will provide preliminary evidence about whether supported Web-based CBTi is acceptable to young people with mental health problems and about the postintervention effects on sleep and symptoms of anxiety and depression. This information will determine whether a randomized trial to determine the effectiveness of Sleepio should be undertaken.

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KEYWORDS

adolescents; mental health; sleep; cognitive behavioral therapy; mobile phone

Introduction

Insomnia

Poor sleep during adolescence is common, with insomnia, defined as chronic dissatisfaction with sleep quantity or quality, being the most prevalent sleep disorder [1,2]. Insomnia symptoms are reported by one-third of adolescents and up to a quarter fulfill the diagnostic criteria for insomnia, depending on the definition and method of assessment [3,4]. Insomnia symptoms are persistent [2] and are associated with significant mental health problems including depression, anxiety, substance abuse, and suicidal ideation [3,5-7].

Association Between Insomnia and Mental Health

Research examining the nature of association between adolescent sleep disturbance and mental health is limited and the findings are inconsistent [8]. There is evidence of a bidirectional relationship, where symptoms of insomnia during adolescence both predict and are predicted by depression and depressive symptoms [9-11]. However, overall, there is more evidence to suggest that insomnia symptoms precede the development of anxiety and depression in adolescence more than the reverse [8,12-14]. This suggests that the provision of interventions that directly address insomnia could reduce the risk of developing mental health problems or reduce current symptomatology [12].

Cognitive Behavioral Therapy for Insomnia

With adults, there is well-established evidence that treating insomnia can improve mental health including depression [15], anxiety [16], and psychotic experiences [17]. Interventions are based on cognitive behavioral therapy for insomnia (CBTi) and typically include a range of techniques including stimulus control, relaxation training, sleep restriction, sleep hygiene, and cognitive techniques to manage worries and intrusive thoughts [18]. Insomnia interventions can be delivered via the internet, with systematic reviews concluding that Web-based CBTi is effective and improves both sleep and mental health [19-21].

Cognitive Behavioral Therapy for Insomnia for Adolescents

With adolescents, research examining the effect of CBTi on sleep and mental health is promising but very limited [18,22]. An open, uncontrolled pilot study assessing a 5-week CBTi intervention for depressed adolescents with insomnia found postintervention improvements in sleep and mood [23]. Similarly, augmenting depression treatment with CBTi in a randomized controlled trial involving 40 adolescents aged 12-20 years resulted in positive effects on sleep and depression [24]. In a community study, Bruin et al [25] found that CBTi delivered either face-to-face or over the internet to 12-19-year olds with insomnia was similarly effective and resulted in comparable improvements in sleep and psychopathology (anxiety and depression) compared with a waiting list control group. The authors concluded that improvements in psychopathology were attributable to a reduction of insomnia and recommended that further research should be undertaken within clinical settings.

Study Aim

The aim of this study is to assess the feasibility of adding supported Web-based CBTi to the usual care for young people aged 14-17 years attending specialist Child and Adolescent Mental Health Services (CAMHS).

Methods

Study Design

This is a pre-post uncontrolled mixed-methods feasibility study. The study was funded by the Wiltshire Child Mental Health Commissioning Group, and ethical approval was obtained from the South West-Central Bristol Research Ethics Committee (17/SW/0178).

Setting

The study will be undertaken in CAMHS within the Oxford Health National Health Services Foundation Trust. The Trust serves a wide geographical area that includes Bath and North East Somerset, Swindon, and Wiltshire.

Participants

Young people will be eligible to participate if they are aged 14-17 years, attending CAMHS with symptoms of insomnia (ie, time asleep/time in bed ≤85%) as either a primary issue or as a comorbidity, motivated to try and improve their sleep, and interested in using Sleepio.

Motivation is assessed by rating each of 3 questions on a 10-point Likert scale from 0 (strongly disagree) to 10 (strongly agree). The questions relate to problem severity (“At present, sleep is a big problem for me”), desire to change (“I want to change my sleep”), and self-efficacy (“I feel I can change my sleep”). For inclusion, each item must be rated ≥5.

Young people will be ineligible to participate if they are presenting with active suicidal ideation, they have been diagnosed with psychosis, there are current safeguarding concerns (ie, the young person has suffered abuse within the last 6 months or is the subject of a safeguarding investigation), or they have a significant developmental disorder (eg, autism) that prevents them from understanding the program.

As this is a feasibility study, any face-to-face intervention or medication that the young person is receiving through CAMHS will not be interrupted. This trial will, therefore, run alongside any treatment as usual.

Recruitment and Consent

Clinical staff working in CAMHS teams across Bath and North East Somerset, Swindon, and Wiltshire will identify eligible young people. Interested young people and their caregivers will be provided with a project information sheet, and their details will be passed to the research team. A research assistant will contact the young person to discuss the project, obtain written consent, and complete baseline measures. For those under the age of 16, parental consent will also be required. Meetings will take place at the individual’s home, at the University of Bath, via telephone, or at a community venue, depending on participants’ preference.

Intervention

Sleepio is an established, fully automated, Web-based, self-administered sleep intervention that has been evaluated with adults [17,26,27]. The intervention is free to study participants and consists of 6 sessions, each lasting approximately 20 minutes, which are released each week. The sessions are accessed via a Web browser on a tablet, desktop, or mobile phone. The program is highly interactional, and content is presented via an animated cartoon therapist (The Prof). Participants complete daily mobile app or Web-based sleep diaries throughout the program, with an algorithm personalizing the content to the individual’s needs. Sleepio is

based on CBTi and incorporates cognitive, behavioral, and educational components (Figures 1 and 2).

Figure 1. Sleepio's animated therapist, The Prof. Source: Big Health licensed under fair use.

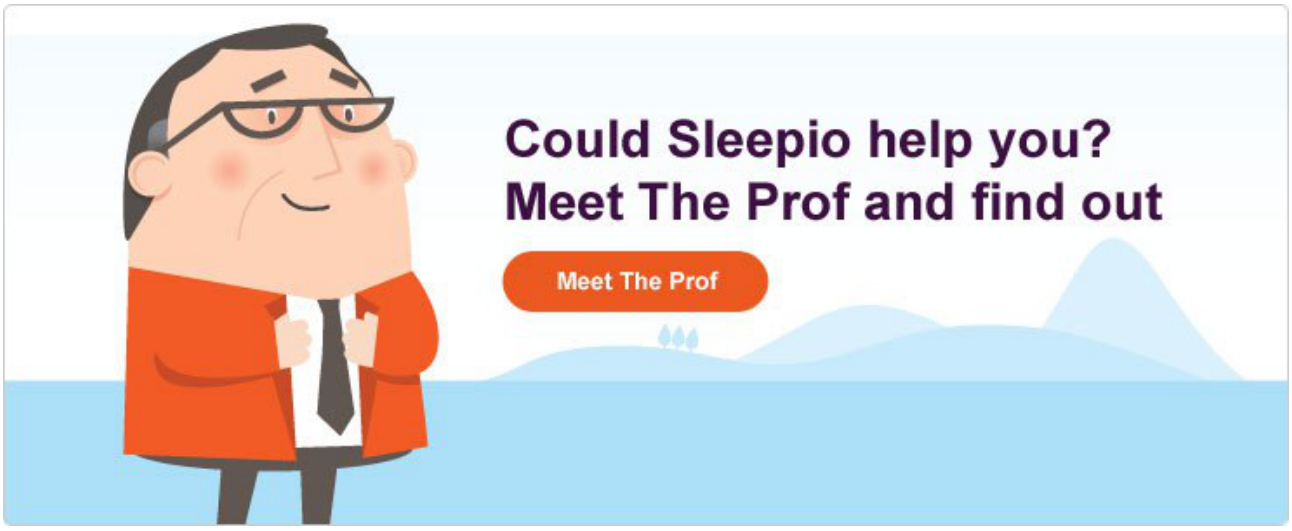


Figure 2. Part of a Sleepio session around debunking myths about sleep. Source: Big Health licensed under fair use.

Cognitive Component

Paradoxical Intention

Insomnia sufferers often pay too much attention to their sleep and the consequences of sleep loss. Their worries about not being able to fall asleep increase their anxiety and arousal, which has the effect of inhibiting the onset of sleep. Paradoxical intention attempts to disrupt this unhelpful process. The person is encouraged to deliberately stay awake for as long as he or she can, thereby reducing the anxiety associated with attempting to sleep and resulting in an easier onset of sleep.

Cognitive Restructuring

People with insomnia tend to have unrealistic expectations and beliefs about sleep and the consequences of not sleeping. They may overestimate how much sleep they need, underestimate how long they have slept, or catastrophize about the consequences of poor sleep. Cognitive restructuring involves challenging these negative and unhelpful sleep beliefs and developing more balanced and helpful ways of thinking.

Mindfulness

Before falling asleep, insomnia sufferers report being very aware of their negative and unhelpful thoughts. They may ruminate about the previous night where they failed to sleep or rehearse worries about the future and how bad the next day will be if

they do not sleep. Mindfulness techniques can help individuals to focus on the here and now and to acknowledge and accept their thoughts and feelings without engaging with them.

Positive Imagery

Sleep creates anxiety for insomnia sufferers, which contributes to their difficulty falling asleep. To counter this negative perception of sleep and the bedroom, individuals are encouraged to create positive images, thereby reducing anticipatory anxiety.

Putting the Day to Rest

Insomnia sufferers often complain of a racing mind, where they ruminate about their day and rehearse what they might need to do in the future. To counter this tendency, people are encouraged to make time before bed to reflect on the day and to plan for tomorrow so that they have emptied their minds before bed.

Behavioral Component

Sleep Restriction

If sleep is limited, there is a tendency to spend more time in bed in order to catch up. However, people with insomnia find it difficult to fall asleep, resulting in them spending more time in bed awake. Sleep restriction limits the amount of time in bed to maximize the proportion of time spent asleep. As sleep improves, the sleep restriction limit is increased.

Stimulus Control

This aims to strengthen the association between bed and sleep. Many insomnia sufferers spend a lot of nonsleep time in bed, tossing and turning, reading, watching TV, gaming, etc. Stimulus control involves establishing bed as a place for sleep. Using bed for nonsleep activities is discouraged, and if the person wakes or is unable to sleep after 15 minutes, he or she is encouraged to get up and do something else relaxing before trying again.

Relaxation

To help individuals feel more relaxed and ready for sleep, they are taught a range of relaxation exercises they can undertake. These are designed to relax their body by reducing the physiological sensations of stress, thereby preparing individuals for sleep.

Educational Component

Sleep Hygiene

This provides information about developing a calming nighttime routine and place to sleep. Information is provided about reducing caffeine, blue screen use, and daytime naps; increasing exercise; and making the bedroom warm, dark, quiet, and free from distractions.

The Process of Sleep

This helps discover some important information about the duration of normal sleep, the factors that affect both sleep quality and quantity, and the fact that sleep is an involuntary process.

There are four different areas of Sleepio: sleep diary, case file, library, and community. There is also a Sleepio app that can be used to augment the Web version. The app allows users to fill in their sleep diary, view their daily schedule, and access relaxation audio files.

Sleep Diary

Users are required to complete a daily Web-based sleep diary that feeds into the underlying algorithms that tailor the Sleepio program content to the individual.

Case File

At the very beginning of the program, users are asked to define the goals that they want to achieve with Sleepio. This progress is tracked throughout and can be viewed in individuals' case files. Here, they can also view their to-do list and daily schedule that The Prof helps them compile throughout the course. The case file also contains tools such as a recommended reading list, a thought checker, and a day planner, and users can download worksheets and audio files.

Library

The library contains articles about sleep, which augment the Sleepio sessions.

Community

There is a community section within Sleepio where users can post comments and interact with each other. As this section is not moderated and is intended for adults, young people will be instructed not to access this area of the website.

Brief Telephone Support

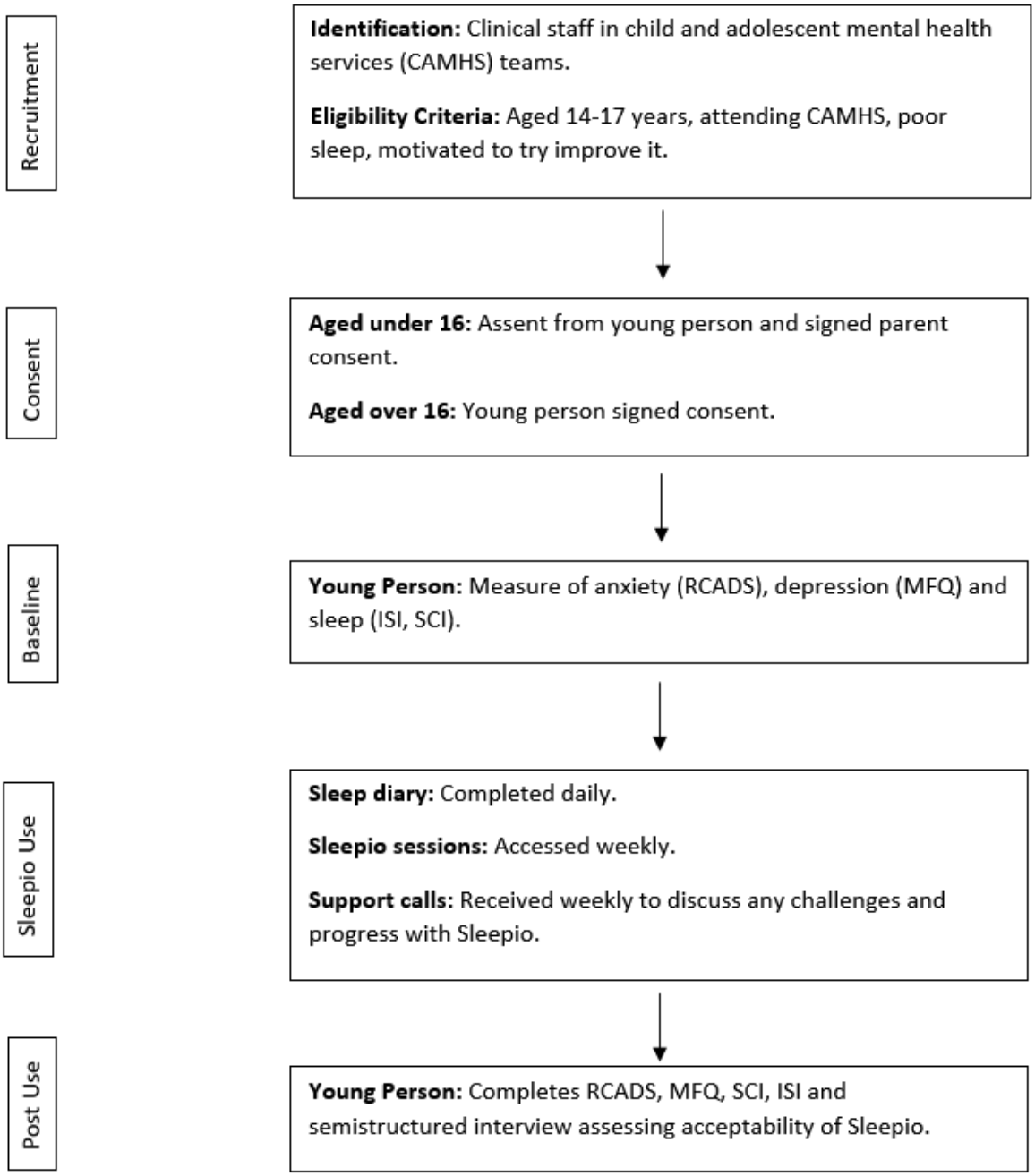
Engagement with Web-based self-help mental health programs is variable and is typically lower than that with guided interventions [18]. Although Sleepio is a self-administered program, maintaining engagement and program compliance with CBTi may be particularly challenging for adolescents [19]. As Sleepio has not previously been used with this age group, we will augment the programs with brief (15 minutes), weekly support telephone calls from a trained Sleepio Assistant. The assistants have an undergraduate university degree in psychology and previous experience of working with children or young people. They have completed the Sleepio program themselves before undertaking a half-day training focusing on how to facilitate the program with young people. The support calls are designed to maintain motivation and engagement and follow a similar process to that used by Luik et al [27]. The calls will be empathic and motivating and will help the young person reflect on how techniques can be applied to their situation. The call will start by reviewing the young person's sleep diary followed by a discussion about how any new strategies identified in previous Sleepio sessions have been applied. The discussion will then review the current Sleepio session and how and which new skills can be applied to his or her situation. Finally, the young person's progress toward achieving his or her goals will be discussed, any questions answered, and the time and date of the next call agreed. The telephone calls are specifically restricted to sleep and the Sleepio program, and no other problems will be discussed. The length of each support call will be recorded.

Study Procedures

The study procedures are summarized in Figure 3.

Once eligible young people have provided consent and completed baseline measures, they will be emailed an individual access code for Sleepio. A Sleepio Assistant will contact each young person to discuss the goals that they wish to achieve at the end of Sleepio and agree times for future support calls. Sessions are released each week.

Figure 3. Study procedure. CAMHS: Child and Adolescent Mental Health Services; RCADS: Revised Child Anxiety and Depression Scale; MFQ: Mood and Feelings Questionnaire; ISI: Insomnia Severity Index; SCI: Sleep Condition Indicator.



The Sleepio Assistants will monitor progress through the Sleepio dashboard, which summarizes when the young person has accessed each session. Reminder emails and telephone calls will be sent if young people are not engaging with their session. When the 6 sessions have been completed, a member of the research team will arrange to meet with the young person and conduct the postuse assessment.

Outcome Measures

The following standardized assessments will be completed pre- (baseline) and post-Sleepio completion (8-10 weeks). Although the program consists of 6 weekly sessions, previous research indicates that the majority of participants complete the course within 10 weeks [28]. Our primary outcome is changes in sleep, with secondary outcomes assessing symptoms of depression and anxiety.

Sleep

Insomnia Severity Index

The Insomnia Severity Index (ISI) is a 7-item self-report measure assessing symptoms of insomnia over a 2-week period on a 5-point scale. The ISI assesses the severity of sleep onset, sleep maintenance, and early morning awakening problems; sleep dissatisfaction; interference of sleep difficulties with daytime functioning; whether sleep problems are noticed by others; and distress caused by sleep difficulties [29].

Sleep Condition Indicator

The Sleep Condition indicator (SCI) is an 8-item self-report measure assessing sleep and its impact on daytime functioning over the previous month on a 4-point scale. The SCI is an internally consistent (alpha=.86) measure with a clinical cut-off <17 correctly identifying 89% of those with probable Diagnostic and Statistical Manual of Mental Disorders 5th edition insomnia disorder [26,30].

Mental Health

Anxiety: Revised Child Anxiety and Depression Scale

The Revised Child Anxiety and Depression Scale (RCADS) [31] is a 47-item questionnaire assessing Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria for social phobia, separation anxiety, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and major depressive disorder. Each item is rated on a 4-point Likert scale of frequency ranging from never (0) to always (3), and items are then summed to produce subscale and total anxiety scores. There are age- and gender-related norms for identifying clinically significant scores (total score ≥64-80).

Depression: The Mood and Feelings Questionnaire

The Mood and Feelings Questionnaire (MFQ) [32] consists of 33 items each rated as either true (scores 2), sometimes true (scores 1), or not true (scores 0). The MFQ has high criterion validity and correlates well with other measures of depression. A total score of ≥27 is associated with major depression, 17-26 with mild depression, and ≤16 with no mood disorder [32-34].

Experience of Sleepio

At the postuse assessment, a semistructured interview will be undertaken with young people to gather detailed feedback on their experience of Sleepio. The postuse interview collects both quantitative and qualitative data. Young people rate on a 4-point scale for ease of use, helpfulness, preference over face-to-face meetings, whether sessions were understandable, and if they would recommend Sleepio to a friend. Changes in sleep, mental health, and overall satisfaction are assessed on a 1-10 scale. Qualitative questions assess how, where, and how often Sleepio was accessed; which techniques and sessions were most useful; experience of telephone support; and how the program can be improved.

Usage

The number of Sleepio sessions completed by each individual will be recorded from the Sleepio dashboard along with his or her weekly sleep efficiency and quality ratings.

Sample Size

Formal power calculations were not deemed necessary due to this being an initial feasibility study. Recruiting 50 young people should provide sufficient information to determine whether Sleepio is perceived as acceptable and results in improved sleep and mental health in young people [35].

Statistical Analysis

We will present descriptive statistics summarizing the cohort in terms of age, gender, sleep, and anxiety and depressive symptomology. Descriptive statistics will also be used to summarize engagement with Sleepio in terms of the number of sessions completed versus the number of those who dropped out. *t* test analyses of mean scores will be conducted on the total scores for the pre- and postmeasures of sleep (ISI and SCI) and on the total and subscale scores for the pre- and postmeasures of mood (RCADS and MFQ). This will allow exploration of any changes in sleep or psychological functioning following Sleepio use. Postuse semistructured interviews will be analyzed to determine the acceptability of Sleepio among young people. The interviews will be audiorecorded and transcribed. A predefined framework will be derived from the interview schedule and adapted following participant responses for analysis.

Results

The study closed at the end of October 2018.

Discussion

Study Aims

This study aims to determine the feasibility of adding supported Web-based CBTi for young people aged 14-17 years attending specialist CAMHS. Our study is addressing an important problem and will provide preliminary evidence about whether supported Web-based CBTi is acceptable to young people with mental health problems and about the postintervention effects on sleep and symptoms of anxiety and depression. If found to have a positive effect on mental health, this low-intensity intervention delivered with minimal therapist support could readily increase the limited capacity of traditional CAMHS. However, the implementation, effectiveness, and sustainability of supported CBTi in child mental health services would need to be determined before its widespread adoption could be advocated.

Limitations

Although this is a feasibility study, limitations in the study design need to be acknowledged. First, we are relying on self-report measures of sleep and are not using objective actigraphy measures. Retrospective self-report may be prone to inaccuracies, but while wearable devices are able to prospectively monitor and track sleep, they are not always reliable or accurate [36]. Subjective reports do provide useful information, which we will supplement with prospectively completed sleep diaries as young people progress through Sleepio [8].

Second, this is an open trial, and we do not have any control or comparison groups. This will not allow comparative insights into whether any improvements are due to the Sleepio intervention, the young person's ongoing mental health intervention, or the passing of time. At this stage, our primary aim is to determine the acceptability and feasibility of using Sleepio with young adolescents, not to determine its efficacy. The inclusion of comparison group(s) to control for these variables will be considered in a subsequent trial.

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Authors' Contributions

PS is the grant holder and principal investigator for the project. PS conceptualized the study design and drafted the manuscript. MD and AC are providing telephone support, and BC is the researcher undertaking pre- and postassessments. All authors read, contributed to, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAMHS: Child and Adolescent Mental Health Services
CBTi: cognitive behavioral therapy for insomnia
ISI: Insomnia Severity Index
MFQ: Mood and Feelings Questionnaire
RCADS: Revised Child Anxiety and Depression Scale
SCI: Sleep Condition Indicator

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Protocol

Predicting Prediabetes Through Facebook Postings: Protocol for a Mixed-Methods Study

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Abstract

Background: The field of infodemiology uses health care trends found in public networks, such as social media, to track and quantify the spread of disease. Type 2 diabetes is on the rise worldwide, and social media may be useful in identifying prediabetes through behavior exhibited through social media platforms such as Facebook and thus in designing and administering early interventions and containing further progression of the disease.

Objective: This pilot study is designed to investigate the social media behavior of individuals with prediabetes, before and after diagnosis. Pre- and postdiagnosis Facebook content (posts) of such individuals will be used to create a taxonomy of prediabetes indicators and to identify themes and factors associated with an actual diagnosis of prediabetes.

Methods: This is a single-center exploratory retrospective study that examines 20 adults with prediabetes. The investigators will code Facebook posts 3 months before through 3 months after prediabetes diagnosis. Data will be analyzed using both qualitative content analysis methodology as well as quantitative methodology to characterize participants and compare their posts pre- and postdiagnosis.

Results: The project was funded for 2015-2018, and enrollment will be completed by the end of 2018. Data coding is currently under way and the first results are expected to be submitted for publication in 2019. Results will include both quantitative and qualitative data about participants and the similarities and differences between coded social media posts.

Conclusions: This pilot study is the first step in creating a taxonomy of social media indicators for prediabetes. Such a taxonomy would provide a tool for researchers and health care professionals to use social media postings for identifying those at greater risk of having prediabetes.

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KEYWORDS

diagnosis; Facebook; infodemiology; protocol; social media

Introduction

Background

There are 86 million adults with prediabetes, with numbers rising in epidemic proportions. The Centers for Disease Control and Prevention has emphasized the need to confront prediabetes through National Diabetes Prevention Programs. In 2014, the Centers for Disease Control and Prevention reported that of the 37% of US adults who had prediabetes, 29% were unaware they had it and were therefore unlikely to seek out treatment [1]. When prediabetes is not diagnosed and treated accordingly, it can increase an adult's risk of heart disease, stroke, and type 2 diabetes, all of which have their own economic and quality of life burdens. Enhanced epidemiologic approaches are needed to identify large populations who are unaware they have prediabetes to maximize the efficacy of diabetes prevention programs.

Around 7 in 10 American adults use social media [2]. Infodemiology, an epidemiologic approach that uses social media and other Web-based sources to examine the spread or incidence of disease [3,4], has been used to successfully predict important issues of public health such as depression and the likelihood of depression resulting in suicide among military service personnel [5-7], infectious diseases such as influenza [8,9], and the spread of interest in health issues such as Zika [10]. Using infodemiology for surveillance (ie, infoveillance) can be very effective in identifying many real-world health trends. However, this methodology has not yet been used to identify chronic conditions or precursors to chronic conditions, such as prediabetes. Infectious diseases often present with a sudden onset of symptoms while the development of chronic conditions is more subtle. Given the association between prediabetes and lifestyle and the fact that many individuals share their lifestyle on Facebook, this study uniquely examines the posts of those with prediabetes in the 3 months before and 3 months after their diagnosis. This innovative approach sets the stage to screen large populations for prediabetes who may have otherwise had a missed or delayed diagnosis.

Prediabetes

Prediabetes is the stage between normal glucose levels and diabetes. There are a number of prediabetes risk factors noted in Textbox 1. Without the identification of prediabetes risk factors, confirmatory blood tests such as HbA_{1c}, fasting plasma glucose, or a 2-hour glucose tolerance test [7] may not be ordered. Glucose levels can normalize if prediabetes is identified early and lifestyle changes are implemented. Therefore, timely diagnosis is imperative. Unfortunately, only 6% of primary care providers (PCPs) can accurately identify all prediabetes indicators [11], potentially resulting in missed or delayed diagnosis. Further, with the primary care shortage of 1 physician for every 2500 patients, lack of access to PCPs limits the capacity for the current health care system to make an appropriate and timely diagnosis [12]. Thus, a predictive model of prediabetes using social media postings will allow us to identify individuals in need of screening whom PCPs may have missed. Further, we will also be able to identify individuals who have not yet seen a health care provider but are at risk for prediabetes.

Social Media

The majority of American adults use social media, and the social media digital divide is closing, as more adoption is increasing in baby boomers and older adults [2,13]. Further, social media use extends across ethnic and racial groups [2,14] due to mobile phone access.

Social media provides an outlet for individuals to share information about their lifestyle and health behaviors. This includes diet quality, activity, and sleep quality, all of which are associated with prediabetes [15-17]. For example, someone might post excessively about the movies and television shows they are watching, suggesting high levels of screen time and, thus, inactivity. While someone might post about the food they are eating, others might acknowledge unhealthy habits by sharing websites related to unhealthy eating. With the high rates of prediabetes and social media use, there is a high probability of a significant population of individuals with diagnosed and undiagnosed prediabetes using social media.

Textbox 1. Prediabetes risk factors.

- Overweight, body mass index >25 kg/m^2
- Age ≥45 years
- Hypertension
- Dyslipidemia
- Heart disease
- Family history of type 2 diabetes in a first-degree relative
- Sedentary lifestyle
- Smoking
- History of gestational diabetes or giving birth to a baby >9 pounds
- Polycystic ovarian syndrome
- African American or Asian race
- Hispanic ethnicity

This study will examine Facebook users with prediabetes and investigate their health behavior through the examination of Facebook posts 3 months before and 3 months after a diagnosis of prediabetes. Since this is a pilot study and the first infodemiology study to examine social media content and prediabetes, we decided to focus on 1 social media platform. We chose Facebook, as 8 in 10 adults use it [13] with substantial numbers across all age groups including 26.5 million users aged 55-64 years and 21.1 million users 65 years or older [18]. It is also a social media platform used worldwide, and, thus, health research and interventions using Facebook have the potential to influence large numbers of people.

Proposed Research

The proposed study is rooted in populomics: the study of social interactions that either result in disease or protect health on a population level. This multidisciplinary field incorporates the study of population-level risk characterization (eg, prediabetes behaviors or indicators) through the use of information technology. This knowledge is then used to support public health interventions [19]. Using Facebook data, we will address the need for early diagnosis in prediabetes in order to prevent progression to diabetes.

We propose to address gaps in prediabetes infodemiology by examining indicators of prediabetes in the Facebook posts of individuals before and after a diagnosis of prediabetes. Our overall hypothesis is that individuals with prediabetes will have indicators of prediabetes on Facebook postings prior to diagnosis. Thus, the purpose of our study is 2-fold: (1) develop a taxonomy of prediabetes indicators and (2) explore if prediagnosis Facebook data among individuals already diagnosed with prediabetes can predict a trajectory toward prediabetes.

Methods

Design

This is an exploratory retrospective study that will examine Facebook posts among individuals with prediabetes. Comparisons of prediabetes indicators before and after prediabetes diagnosis will be analyzed.

Participants

The setting is a family medicine clinic and community health center that is located in Southeastern Idaho, USA. The sample will be 20 adults with prediabetes. This sample size was chosen as this is an exploratory pilot study and the first infodemiology study to examine prediabetes and Facebook usage. Additionally, in this study, we aim to identify prediabetes indicators in social media data that can be verified with future large-scale studies. Furthermore, this pilot study will provide important information for future research on the feasibility of conducting infodemiology research on a chronic condition.

To be included, participants must be between the ages of 18 and 89 years, be able to read and write English, and be Facebook users who have been using Facebook for at least 3 months prior to their prediabetes diagnosis. Participants will have a medical record of prediabetes (diagnosis or hemoglobin A_{1c} [HbA_{1c}] value of 5.7-6.4) at some point since 2015. Participants will be excluded if they have type 2 diabetes or any other major health condition (eg, cancer or pregnancy) or life situation (eg, incarceration) that could be a confounder or significantly alter the content of Facebook posts.

Procedures

The study has been approved by the institutional Human Subjects Committee, and the family medicine clinic provided a letter of support.

Participants will be recruited through Idaho State University's Clinical Research Center at a family medicine clinic. Electronic medical record queries will be utilized to identify potential participants who would qualify for the study. Per protocols of past studies conducted by the Clinical Research Center, potential participants will be mailed a recruitment letter (see Multimedia Appendix 1) providing them with a brief description of the study and a return response card (with instructions that the card be returned by a certain date). The letter will include a statement that the clinic study coordinator will call the potential participant if the card is not returned by the predetermined date indicating that they are not interested. The letter will include an explanation of the call and can be avoided by returning the card (selecting the response that they are not interested in participating) or calling the staff to decline participation. The study coordinator will call potential participants who return the response card indicating interest in the study or who do not return the response card by the requested date. Potential participants who express interest in the study will have the protocol of the study explained to them and will take part in a screening via a telephone call to determine eligibility. This screening (see Multimedia Appendix 2) will verify that participants are eligible for the study. Eligible participants will be scheduled for a clinic visit with the study coordinator.

During the clinic visit, participants will complete formal written informed consent and a set of questionnaires (see Measures below). These questionnaires will be programmed with Qualtrics, and participants will complete the questionnaires over the Web on one of the Clinical Research Center's computers. Since participants will need to be Facebook users to be eligible for this study, we do not foresee any issues with participants completing Web-based questionnaires; however, paper copies of these questionnaires will be kept ready in case any participant does not want to complete questionnaires over the Web or technical difficulties arise. Participants will be thanked for their participation and provided with a US $25 gift card.

There is an item on the questionnaires that asks participants to provide us with their social media profile name on Facebook. After their clinic visit, we will send each participant a friend request (from a skeletal Facebook account created for this study, with a generic name and no mention of prediabetes, the research center or institution, or other research-related topics). We will then code all Facebook posts made in the 3 months before through the 3 months after their prediabetes diagnosis. Each post will be considered a single data point that will be attributed to the participant. Posts will be coded as they relate to prediabetes predictors. Once all Facebook posts have been coded, we will unfriend the participant and mail them a second

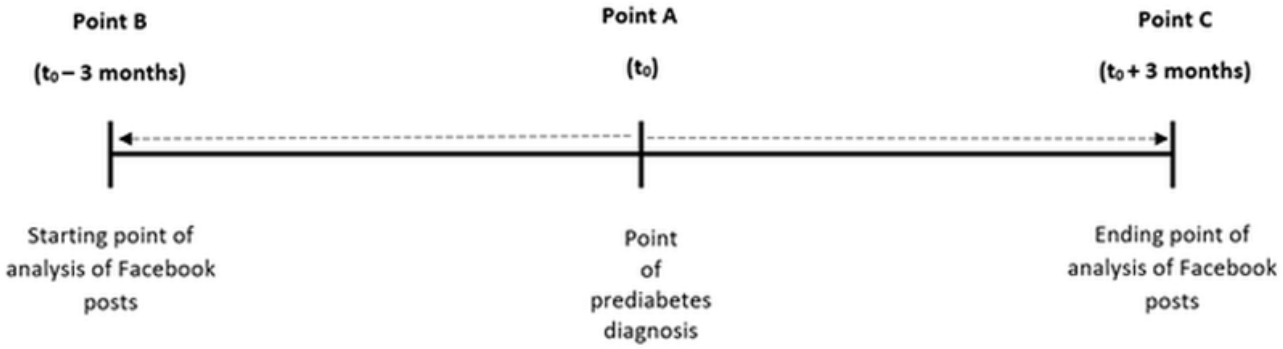
US $25 gift card. Figure 1 presents the timeline of data collection.

Measures

During the clinic visit, participants will complete a set of questionnaires. These include the Facebook Intensity Scale [20], which has been modified for other diabetes social media research [21]; the Diabetes Online Community Engagement Scale [21], modified to be about the Web-based community (as participants will have prediabetes); and the Computer-Mediated Social Support Scale [22]. Minor wording modifications were made to make the questionnaires appropriate for prediabetes (instead of diabetes) and social media. Additionally, we will ask participants about their use of health applications, as past research has shown that these can be helpful in the context of chronic health management [23,24]. Participants will also be asked to provide demographic and other information, including their profile name on Facebook.

For each participant, we will record their total number of Facebook friends, the number of family members on their Facebook profile, their posted relationship status (if any), and the date they joined Facebook or made their first Facebook post (if the joined date is not available). Each Facebook post from the 3 months before through the 3 months after prediabetes diagnosis will also be coded. This coding includes metadata on the post such as the time, date, and type of post (eg, text or video), the viral nature of the post (eg, the number of likes and if the post was shared from or to another page), and the nature of comments made about the post (eg, whether social support was provided and, if so, the type of social support). Additionally, the post's content will be coded so we can record mentions of symptoms (eg, hunger, fatigue, and negative mood), lifestyle factors (eg, exercise, eating, alcohol, smoking, and self-care), medical experiences (eg, treatment and interaction with health care providers), health tracking (eg, physical activity monitor and glucose), the health of others known to the participant, and additional content (eg, current affairs, religion, and games). Any photos posted by the participant will also be coded on a number of measures including social variables (eg, if the photo was of a group, if the participant was part of the group, or if the participant was tagged) and health variables (eg, if the photo was health-related, if the photo was of food, and the type and composition of the food).

Figure 1. Data collection timeline.



Results

Anticipated Timelines

The project was funded for 2015-2018, and enrollment will be completed by the end of 2018. To date, we have enrolled 18 out of the 20 anticipated participants and coded 9 participants' data.

We anticipate that all clinic visits will be complete by 2018, and all coding of Facebook posts and analyses of the data will be complete by 2019. The first results are expected to be submitted for publication in 2019.

Planned Data Analyses

A conventional content analysis approach will be used to directly code the Facebook text data [25]. An abstraction of the Facebook postings by several independent researchers will be completed to develop a category scheme to enhance the study reliability [26]. The research team will compare results and will work together to assure high intercoder reliability. This scheme will be used to facilitate the coding of the study data (text, photographs, images, and videos). A comprehensive codebook will be developed that will include the definitions for the categories used in the coding [27]. Major themes will be determined from the data based on a significant proportion of postings identifying the same issue [28]. A thematic approach will be used for the data analysis; the Facebook postings will be read and repeatedly reread for content. Exemplar quotations will be established for each category and theme [25]. Quotes that were common across the participants will be isolated and presented in the findings to show a connection with the data. The findings will be confirmed by sharing with the volunteer participants. Once the results are confirmed, a detailed presentation of the findings in a publishable format will be developed to share the results of the research.

Additionally, a quantitative analysis approach will be used to help characterize the participants and their data. Since this is a pilot study and the first step in attempting to determine an initial taxonomy of prediabetes indicators, we plan on generating a full snapshot of our participants and their Facebook postings by examining all their characteristics over the Web and their responses on self-report items (eg, demographics, means and SDs for scores on all questionnaires, means and SDs for the number of Facebook friends, etc). We will also conduct exploratory paired samples *t* tests to examine potential differences between the 3 months prediagnosis and the 3 months

postdiagnosis (eg, the number of posts, tags, comments, and type of post, etc).

Discussion

Principal Considerations

This pilot study aims to enroll 20 participants. Data from these participants and their 6 months of Facebook behavior should provide an adequate initial taxonomy of prediabetes indicators. These data will then support future studies with larger samples including testing the utility of the taxonomy on predicting prediabetes status.

Knowledge Translation

It is anticipated that this study will lead to future research in the field of infodemiology specific to furthering the examination of prediabetes as well as other health issues. Examining social media data may support precision health efforts. Precision medicine is more than "-omics" [29], and examination of big data such as social media postings, may support innovative interventions in which individualized care can be provided through identification of social health behaviors. Perhaps one day, the social behavior that people exhibit over the Web could be predictive of serious health issues, especially diseases that are preventable, such as type 2 diabetes. These identified people could then receive tailored messaging, which has shown to improve outcomes in those with chronic conditions [30] and could be used for primary and secondary prevention. Social media technologies that are commonly used by millions could be crucial in reversing the trends of prediabetes, obesity, and other health concerns in the United States and globally.

While our study attempts the novel approach of taking advantage of behavior that happens in a natural setting (individuals making Facebook posts) to predict prediabetes and, thus, has significant potential to public policy and health, there are also some potential limitations. First, it is possible that the findings may not necessarily generalize to users of all social media (eg, Twitter, Google+, and Instagram). More research would be needed to show that our findings apply across social media platforms. Second, our study is based on respondents in Southeast Idaho, and, thus, it is possible that the findings may not necessarily generalize to individuals elsewhere. Further research would help to test how well our findings hold in other settings. Third, there is also a potential for bias in that there could be a potential for self-selection bias; respondents who are tech-savvy, have high levels of computer self-efficacy, or those with low levels of privacy concern could possibly characterize those that opt to participate in this study. In qualitative research, there is always the potential for researcher bias and certainly in the interpretation of images and words. To control for this potential bias, our research team agreed to use bracketing, or suspense of our personal beliefs and bias, throughout both the data collection and analysis and also in the presentation of our findings. Individually, we also agreed to challenge one another if bias was perceived. To increase objectivity and data consistency, we also determined our coding protocol for the project prior to data collection.

Given the unique nature of our study, where the purpose is to understand whether one's posting could serve as an index to predict the onset of prediabetes, we think that the design we intend to employ is appropriate. Additional research with a more diverse population of respondents would help assess the validity of the findings.

Conclusions

The current project aims to develop an initial taxonomy for prediabetes indicators among Facebook users and to help us better understand the social media postings of those with prediabetes. These prediabetes indicators and initial taxonomy are crucial to supporting future larger-scale studies that can advance this programmatic line of research. The ultimate goal of this research will be to develop an automated method to identify social media users who are likely to have prediabetes. This would be especially helpful in the cases of those who have prediabetes but do not know of their health condition, as identification can lead to recommendations (eg, suggesting they be tested) and efforts that can prevent the progression of prediabetes to diabetes.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Deidentified recruitment letter.

[PDF File (Adobe PDF File), 26KB - resprot_v7i12e10720_app1.pdf]

Multimedia Appendix 2

Deidentified screening.

[PDF File (Adobe PDF File), 40KB - resprot_v7i12e10720_app2.pdf]

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Abbreviations

HbA_{1c}: hemoglobin A_{1c}
PCP: primary care provider

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Protocol

Developing, Implementing, and Evaluating a Multimedia Patient Decision Aid Program to Reform the Informed Consent Process of a Peripherally Inserted Central Venous Catheter Procedure: Protocol for Quality Improvement

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Abstract

Background: Informed consent has considerable clinical, ethical, and legal implications for patient safety and liability. Little information is available about the use of multimedia patient decision aids (PtDA) in the consent process for therapeutic invasive procedures such as the peripherally inserted central venous catheter (PICC). In addition, none of the available studies have designed their multimedia PtDAs based on the Agency for Healthcare Research and Quality's (AHRQ) comprehensive guide for informed consent.

Objective: This paper describes a patient-centered, systematic, multidisciplinary approach to develop, implement, and *alpha* test a multimedia PtDA to reform the informed consent process of a PICC for patients in 10 acute and intensive care units.

Methods: The development, implementation, and evaluation processes of the PtDA followed the phases in the Multimedia Production Framework: preproduction, production, and postproduction. Within this framework, we applied the criteria for judging the quality of PtDAs, the AHRQ's Health Literacy Universal Precautions Toolkit, and the AHRQ's Patient Education Materials Assessment Tool Guide. The methodology was guided by the Interprofessional Shared Decision-Making Model and the AHRQ's Making Informed Consent an Informed Choice guide. In the preproduction phase, we (1) reviewed the current consent form; (2) observed 18 consent processes; (3) surveyed the vascular access team (N=6 nurses) about their perception of the current process; (4) surveyed 30 patients for knowledge recall and retention, overall satisfaction, and attitude toward using a multimedia PtDA; and (5) wrote and reviewed the script for the multimedia program. The production phase focused on filming the PtDA in English and Spanish languages. The postproduction phase included integrating the multimedia programs into the care processes, developing a modified workflow for the consent process, and alpha testing of the English and Spanish PtDAs by (1) a group of 5 patients for clarity and understandability of the information; (2) nurses using the AHRQ's Patient Education Materials Assessment Tool Audio and Video; and (3) by the multidisciplinary change team.

Results: Based on the alpha testing, patients indicated that the content was easy to follow and read; nurses provided positive feedback, and their comments were mainly related to the changes in the workflow in the consent process of the PICC after using the PtDA; and the multidisciplinary change team suggested edits related to changing a few scenes. The final multimedia program consisted of 7 min and 37 s demonstrating detailed information about the PICC.

Conclusions: A systematic development of PtDAs for nonurgent invasive procedures may eliminate many limitations of the conventional consent process by ensuring comprehensive, standardized, and easy-to-comprehend information and providing sufficient time for the patients to reflect on the information. To be effective, PtDAs should follow a systematic, patient-centered, evidence-based, and rigorous approach in the development, implementation, and evaluation processes.

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KEYWORDS

multimedia; central venous catheters; decision support techniques; informed consent; intensive care units

Introduction

Overview

Informed consent has considerable clinical, ethical, and legal implications for patient safety, liability, treatment cost and outcomes, patient-centered care, Hospital Consumer Assessment of Healthcare Providers and Systems scores, and reimbursement [1,2]. Patients may sign the consent form without a complete understanding of the indications, benefits, and risks of treatment procedures. A culture of safety that embraces patient engagement in care is required for effective informed consent process. The lack of effective communication between the health care team and the patient is a root cause for informed consent–related sentinel events [2]. The Joint Commission (JC) and the Agency for Healthcare Research and Quality (AHRQ) urged hospitals to provide high-quality decision aids to support the informed consent process [1,2]. This paper describes a systematic approach to develop, implement, and *alpha* test an effective multimedia decision aid to reform the informed consent process of a peripherally inserted central venous catheter (PICC) procedure.

Background

Patient decision aids (PtDAs) are an integral component of a shared decision-making model. These evidence-based tools help people make informed decisions congruent with their personal values and preferences about their treatment options. Extensive work has been undertaken to test the effectiveness of PtDAs [3-10]. In a 2017 Cochrane review of 105 studies with 31,043 participants, the use of PtDAs helped patients feel clear about their personal values and improved the rate of patient engagement in the decision making by reducing the proportions of undecided patients and passive decision makers compared with usual care [4]. In addition, the use of more detailed PtDAs and those with expressed risk probabilities resulted in a significant knowledge improvement and accurate risk perception compared with basic PtDAs [4].

On the other hand, many of the available trials failed to provide sufficient details about the development process of their PtDAs [11]. Furthermore, little information is available about the process of integrating PtDAs into routine care. The availability of PtDAs in different formats, delivery modes, and information displays, and the varying levels of patient involvement in development and use introduce challenges in the development, delivery, and evaluation of such tools and require detailed description of their development, implementation, and evaluation processes. PtDAs should follow a systematic approach for development to judge the effectiveness of these tools and create reproducible products and replicable methodologies. PtDAs should also include the appropriate level of details about treatment procedures, taking into consideration health literacy principles to help patients make informed choices about their treatments. Standards for patient comprehension and effectiveness measures should also be in place [1,2].

Advances in multimedia technology have increased the utilization of multimedia PtDA programs to supplement the conventional informed consent process that is solely based on a face-to-face discussion. Multimedia is the “field concerned with the computer-controlled integration of text, graphics, drawings, still and moving images (video), animation, audio, and any other media where every type of information can be represented, stored, transmitted and processed digitally” [12]. The majority of the available studies used multimedia tools to support the informed consent process for surgeries and consistently found significant effects on reducing patient anxiety, improving patient understanding of the indications, risks and benefits of the surgery, and increasing satisfaction with the informed consent process [5,9,10,13-17]. Despite these promising results, little information is available about the use of multimedia PtDAs in the consent process of therapeutic invasive procedures such as the PICCs. In addition, none of the available studies have designed their multimedia tools based on the patients’ information needs and the AHRQ’s comprehensive guide for informed consent, *Making Informed Consent an Informed Choice* [1]. To respond to these gaps in the literature, our systematic process of developing, implementing, and evaluating the multimedia PtDA program to reform the informed consent process for the PICC procedure was based on the AHRQ’s guides for informed consent [1], health literacy [18], and patient educational materials [19]; the Interprofessional-Shared Decision-Making (IP-SDM) model [20]; the PtDAs’ quality criteria developed by the International Patient Decision Aid Standards (IPDAS) Collaboration [21]; and the Multimedia Production Framework [22].

Objective

This paper describes a systematic approach to develop, implement, and *alpha* test a multimedia decision aid to reform the informed consent process of a PICC procedure. PICC is one of the most commonly performed invasive procedures in intensive care units (ICUs) and acute care units (ACUs) and the only invasive procedure where nurses are the responsible clinicians to obtain the consent form. At our hospital, 220 to 250 PICCs are inserted monthly by nurses from the vascular access team—a team of certified nurses for PICC insertion,

safety, and care. These catheters are inserted when a prolonged intravenous medication, nutrition or fluids, or blood draw is required.

Our current PICC consent process lacks the use of any decision aids to improve patient engagement in the process [1,2]. In busy ICUs and ACUs, patient acuity and workload can hinder effective patient-health care team member communication and negatively affect providing *informed* consent, especially for the PICC as the most common invasive procedure in these units. The use of a PICC multimedia PtDA in ICUs and ACUs would optimize care outcomes and most importantly, engage patients in care processes by emphasizing the patient role in the safety of the PICC, an area that is often ignored in informed consents.

Methods

Overview

This quality improvement project was approved by the institutional review boards (IRBs) of the University Health System (setting of the study) and the University of Texas Health at San Antonio, Texas (the institution of the principal investigator) as non-regulated research. After the IRB approval, the multimedia PtDA program was developed for patients undergoing a PICC in the following 10 inpatient units: 2 medical surgical ACUs, 3 surgical ACUs, 1 hematology and oncology unit, 3 surgical ICUs, and 1 medical ICU. The PtDA was created for competent patients and family members or legal guardians of all patients, whether competent or incompetent patients. The development, implementation, and evaluation processes of the PtDA followed the phases described in the Multimedia Production Framework (see Figure 1): preproduction (planning), production (filming), and postproduction (testing and editing) [22]. This paper focuses on the development, implementation, and *alpha* testing processes of the PICC multimedia PtDA. Beta testing of the product (see Figure 1) will be presented elsewhere. Within the Multimedia Production Framework, we applied the Criteria for Judging the Quality of PtDAs developed by the IPDAS Collaboration [21], the AHRQ's Health Literacy Universal Precautions Toolkit Guide [18], and the AHRQ's Patient Education Materials Assessment Tool Guide for Audio and Video Materials [19]. The methodology to improve the consent process was guided by the IP-SDM model [20] and the AHRQ's Making Informed Consent an Informed Choice comprehensive guide for informed consent [1].

The IP-SDM model extends the decision-making process beyond the patient-provider dyad to include the interprofessional team. Patients in ACUs and ICUs usually face decision uncertainty or conflict related to the complexity of their medical conditions and the need for multiple therapeutic procedures. Within an organizational structure and social norms (macro system level), the IP-SDM model captures the complexity of the decision making in the daily organizational operations (meso system level, ie, informed consent process). The model focuses on the patient-family-interprofessional collaboration and places the *patient* at the center to emphasize a patient-centered approach of care [20]. Each individual in the model (ie, the patient, the family, and any member from the health care team) is a micro system [20]. The patient-centered process to make a decision outlined by the model includes the following: (1) understand the decision to be made and explore related options, (2) obtain and share information, (3) clarify one's own values and preferences, (4) evaluate the feasibility of the decision, (5) select the preferred choice, (6) implement the decision, and (7) assess the outcomes. It is important to note that these 7 activities are not only limited to the patient but also apply to all individuals involved in the shared decision-making process. In this study, the use of a multimedia PtDA for the PICC to supplement the consent process aims to help the patient-interprofessional-family interaction in the first 5 steps in the process.

Consistent with the IP-SDM model, the AHRQ's guide to reform the informed consent process creates a shared vision about what constitutes an effective informed consent at the macro, meso, and micro system levels and stresses the importance of engaging all stakeholders in the process. From that perspective, challenges to an informed decision might be at the macro (organization), meso (policies and procedures related to informed consent), and micro system levels (individuals in the patient-family-interprofessional team collaboration). For example, in the PICC consent process, challenges to an informed consent might result from lack of a culture of safety at the organization level (macro system), lack of clear policies and procedures for the informed consent, lack of decision support tools (meso level), ineffective patient-interprofessional interaction and communication, lack of family and social support, lack of knowledge about the available treatment options, mismatch between treatment options and the patient values and preference, and the complexity of the medical condition that hinders reaching a *preferred choice* (micro system level).

Phase 1: Preproduction Phase

Guided by the AHRQ's comprehensive guide for informed consent [1], this phase focused on identifying the consent process for the PICC as the opportunity for improvement, assembling an interdisciplinary change team with a change authority and a clear vision, agreeing on a plan for change, understanding the limitations of the current consent process, conducting comprehensive literature search, proposing a plan for implementation and evaluation, and writing and reviewing the script for the multimedia program.

Step 1: Formulate an Interdisciplinary Team and Articulate the Vision

A multidisciplinary change team was assembled to reform the consent process of the PICC procedure and develop the multimedia PtDA program to supplement the conventional process. The team included bedside nurses from the ACUs, a radiologist, a radiology nurse, nurse educators from the ACUs and ICUs, nurses from the vascular access team, the nursing director of the ACUs, the Vice President and Associate Chief Nursing Officer for Clinical Excellence and Ancillary Services, experts in marketing and communication from the Corporate Communications department, expert nurses from the Office of Patient Experience, experts in multimedia production, Information Technology (IT) department, and experts in health informatics. To sustain the change, the change team members were recruited from different organizational levels to include

micro (eg, bedside nurses from the unit), meso (eg, Corporate Communications, IT), and macro system (eg, nurse directors) and had a change lead role and authority to implement a change. Consistent with the hospital values to provide a Safe, Timely, Effective, Efficient, Equitable, and Patient-Centered (in short, STEEEP) care, the team had a shared vision to make the informed consent an informed choice.

Step 2: Assess Existing Informed Consent, Policies, and Practices

A review of the current informed consent document and policies was necessary to make sure the information is based on recent practice guidelines for central venous access and health literacy universal precautions and to maintain consistent information across the policies, the consent form, and the multimedia program. We found that our PICC consent form was created 10 years ago with no revision based on new evidence regarding risk factors of the PICC and expressed probabilities of its complications. The form also lacked the definition and details about the procedure. Therefore, a comprehensive literature search was conducted to locate and analyze best practice guidelines for central venous access and credible recent studies [23-33]. All guidelines and studies were summarized in terms of definition of a PICC; possible insertion sites; the need for anesthesia; the need for diagnostic equipment such as ultrasound or x-ray; indications; benefits; expected time period for having the catheter; common, less common, and rare risks and complications; health care team role in the care and safety of a PICC during hospitalization; patient role in the care and safety of a PICC during hospitalization; safety tips when a patient leaves the hospital with a PICC; and other possible treatment options. The research and change team agreed on the final document. Experts from the hospital Corporate Communications department reviewed the summary for fifth grade readability level and clarity based on the AHRQ's Health Literacy Universal Precautions Toolkit Guide [18], and necessary changes were made. On the basis of this summary, the definition of a PICC, details about the procedure, indications and risk factors, as well as expected complications with their probabilities were added to the consent form.

In addition to examining the consent form, 3 methods were used to understand the limitations of the conventional consent process of a PICC to develop an effective multimedia program. These methods include observing the current process and assessing the perceptions of nurses and patients about the current process. The research team reviewed and approved all tools, checklists, and surveys used for this purpose.

Observing the Consent Process

First, we observed 18 informed consent processes for the PICC procedure provided by the vascular access team nurses (N=6 nurses, 3 observations per each nurse). Two nurse educators independently conducted the observations using a standardized checklist to enhance objectivity. Observations included language of the discussion, time spent by the vascular access team nurse to provide patients information about the PICC procedure and sign the consent form, speed of discussing the information, level of distraction during the discussion, patient level of discomfort, type and adequacy of the content discussed by the vascular access team nurse, and questions asked by the patient during and after the discussion. The observers used the summary document created by the research and change team in Step 1 to guide their observations with regard to the content discussed. The 2 observers met after each observation session to review similarities and differences and reach consensus. Below is a summary of the observation results.

- Language: All consent processes were discussed in English language based on the patients' preferred language.
- Time: Nurses from the vascular access team spent on average 2 to 7 min discussing the procedure to the patient and obtaining the signature on the consent form, with a mean of 4.6 min (SD 1.4). Out of 18, 7 procedures took 2 to 3 min of discussion.
- Distraction: The observers reported 8 (out of 18) processes with distraction because the television was switched on, the patient's room door was open, or the patient received a phone call during the discussion.
- Patient comfort level: According to the observers, only 1 patient did not look comfortable (ie, had pain) during the discussion.
- Speed of the discussion: The observers reported *very fast* as the speed of discussing 4 (out of 18) observations. All other observations demonstrated appropriate speed.
- Information provided and adequacy of information: The 2 observers assigned *adequate* to all content, when discussed. Table 1 summarizes the number of episodes where nurses from the vascular access team did not discuss the content.

Questions asked by the patients during the discussion included:

1. Will I feel the needle going in? (1 patient)
2. Why you will have a mask? (2 patients)
3. Will I be covered up? (1 patient)
4. How long will the vein hurt? (1 patient)
5. Do I have to stop eating? (1 patient)
6. Will I get a CAT scan? (1 patient)
7. I am left-handed; do we have to go in on the left arm? (1 patient)
8. Are you going to take x-rays before or after? (1 patient)
9. Do I need to remove my necklace? (1 patient)

Questions asked by the patients after the discussion included:

1. Is this going home with me? (1 patient)
2. How to keep the line from coming out and after caught up on things? (1 patient)
3. What kind of line is this? What is this supposed to do? (2 patients)
4. Do I have to take antibiotic pills? (1 patient)
5. How long will I have this? (3 patients)
6. Will I have the same one throughout the chemotherapy? (1 patient)
7. What are the side effects of this procedure? (1 patient)
8. Who can remove it? (1 patient)
9. Why are my veins so small? Is it because I am on blood thinners? (1 patient)
10. So you'll check it with the x-ray after? (1 patient)

Figure 1. Process of producing, implementing, and evaluating the multimedia decision aid program for a peripherally inserted central catheter.

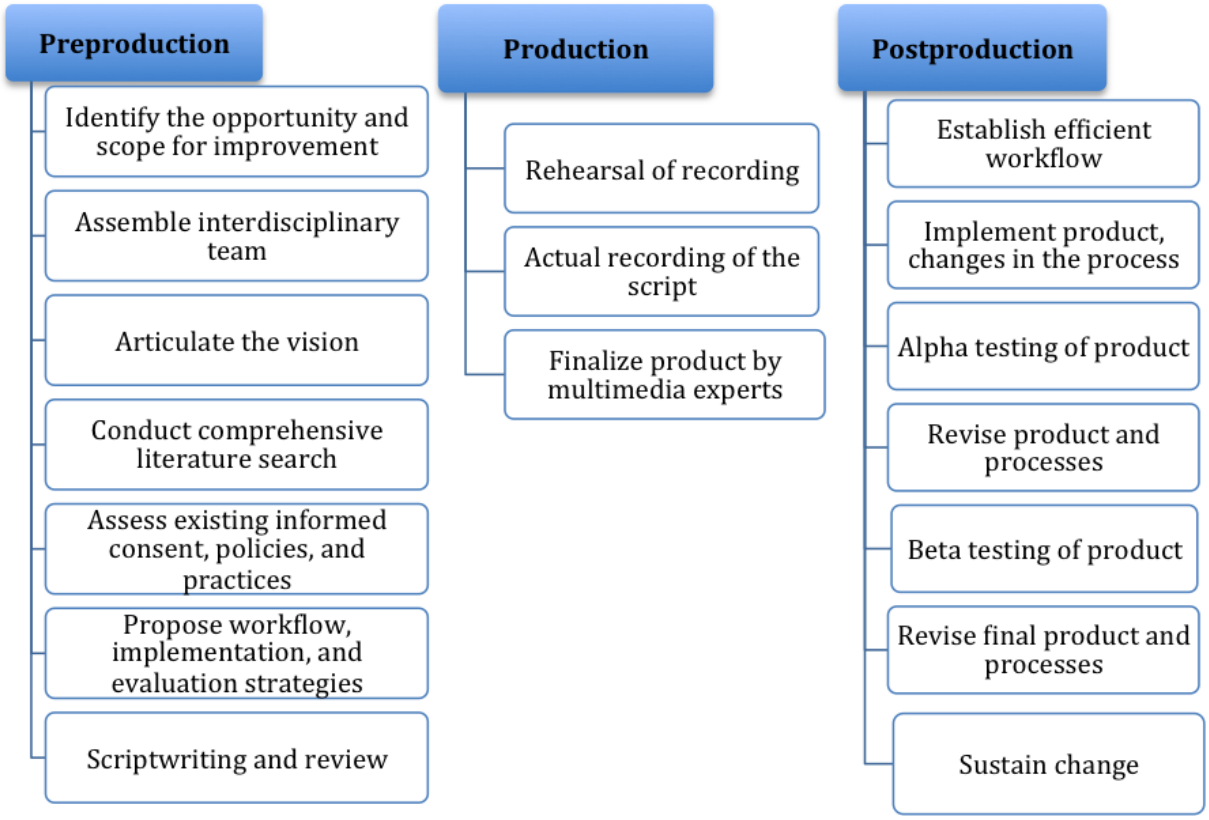


Table 1. Number of consent processes when the content was not discussed (N=18 observations).

Content	Number not discussed, n (%)
Definition of a PICC[a]	0 (0)
The need for anesthesia	0 (0)
Steps of the procedure itself (preparation, during, and after the procedure)	0 (0)
The need for diagnostic equipment such as ultrasound or x-ray	1 (5)
Indications or reasons	1 (5)
Benefits	1 (5)
Common or less common and rare risks and complications	1 (5)
Verification of patient and family members' understanding of the procedure	1 (5)
Possible insertion sites	2 (11)
Expected period for having the catheter	8 (44)
Health care team role in care and safety of a PICC[a] during hospitalization	16 (89)
Other treatment options	16 (89)
Patient role in care and safety of a PICC[a] during hospitalization	17 (94)
Safety issues when a patient leaves the hospital with a PICC[a]	18 (100)

[a]PICC: peripherally inserted central catheter.

The results of the observations identified the limitations of the conventional process. For example, spending 2 to 3 min in the discussion and obtaining the consent form does not reflect an effective informed consent process with a teach-back mechanism. Many of the consent processes also lacked discussing critical points (ie, patients and health care team role in the safety of a PICC). On the other hand, it is important to note that some of the questions asked by the patients after the discussion were already discussed by the vascular access team nurse during the consent process (ie, What kind of line is this? What is this supposed to do? What are the side effects of this procedure?). These results support the need for a reliable multimedia PtDA to supplement the conventional process to allow patients to view the content as many times as needed and

when they are ready to do so (ie, no distraction and no pain). The program should include necessary details about the procedure and be recorded with an appropriate speed of presenting the information.

Nurses' Perceptions About the Current Process

Second, we surveyed all nurses from the vascular access team (N=6) about the limitations of the current PICC consent process and suggestions for improvement. Nurses from the vascular access team are males with 3 to 17 years of experience in placing and maintaining PICC lines. All nurses have a bachelor's degree in nursing science and 1 nurse has an advanced degree as a nurse practitioner. Major issues nurses faced in providing informed consent for a PICC were related to time constraints. When asked about their opinion to use the multimedia to supplement the consent process, nurses responded very favorably emphasizing that the tool should be used to supplement rather than to replace the discussion between the patients and the health care team members.

Patients' Perceptions About the Current Process

Third, we surveyed 30 patients who received the consent process for the PICC procedure for knowledge recall and knowledge retention about the procedure, overall patient satisfaction with the consent process, and attitude toward using a multimedia PtDA to supplement the consent process. Corporate Communications reviewed and approved the final versions of all patients' surveys for clarity and readability. Moreover, 2 nurse educators administered the surveys. The medical record number was used to connect patients' responses on all questionnaires. Out of the 30 patients, 53% (16/30) reported their level of education as high school and the other 47% (14/30) reported college or graduate studies. The sample also included 10 (33%, 10/30) male patients and 20 (67%, 20/30) females. Ethnicity was almost equally distributed among non-Hispanic white (47%, 14/30) and Hispanic patients (40%, 12/30). Moreover, 4 patients (13%, 4/30) were black. Patients were selected from the 10 patient units where a PICC was inserted. A description of the questionnaires and the results are presented in Multimedia Appendix 1.

The questionnaire used for knowledge recall and knowledge retention was created based on recent guidelines for PICC [23-33] and included 3 *select one-answer* multiple-choice questions, 4 *select all that apply* multiple-choice questions, and 12 *true or false* questions. The knowledge recall questionnaire was administered within 4 to 8 hours after the discussion between the vascular access team nurse and the patient and obtaining the signed consent. The same questionnaire was administered to the same patients 24 to 48 hours after the consent process to measure knowledge retention. Multimedia Appendix 1 describes the percentages of correct answers selected by the patients. The correct responses are indicated for the multiple-choice questions and identified at the end of the question for true or false questions (see Multimedia Appendix 1, column 1). The mean score of knowledge recall was significantly lower than the knowledge retention (mean 12.6, SD 2.27, compared with mean 14.57, SD 1.9, respectively, paired sample *t* test=3.6, *P*<.001).

Out of the 19 knowledge questions, only 2 items were answered correctly by all patients in the knowledge recall and 3 in the knowledge retention questionnaires (see Multimedia Appendix 1). For ethical purposes, the data collectors corrected the wrong answers provided by the patients in the knowledge recall questionnaire after recording the original responses provided by the patients. This could explain the higher knowledge retention scores in comparison with knowledge recall. Items with the lowest knowledge recall and knowledge retention scores were related to common and rare risks of a PICC (Items 4 and 5), signs of infection from a PICC that a patient should report (Item 6), if the patient can move around freely (Item 8), and the frequency of inspecting the line site by the nurse (Item 9).

Patient satisfaction with the informed consent process consisted of 9 items with a 5-point Likert-type scale of agreement and was created based on the essential elements emphasized in the AHRQ's comprehensive guide for informed consent [1]. At the end of the survey, patients were asked to report their overall level of satisfaction with the informed consent process using a 5-point Likert-type scale that ranged from 5=very satisfied to 1=very unsatisfied, to write any additional comments about the information they received and to write other information they would like to know about the procedure to provide an informed consent. The survey was administered 4 to 8 hours after the consent process.

Table 2 shows the results of the patient satisfaction with the informed consent process. Patients' responses were coded as Agree for strongly agree and agree and as Disagree for strongly disagree and disagree. Neutral responses remained neutral in the analysis.

Out of the 30 patients, 27 (90%, 27/30) agreed that the information provided was comprehensive. Missing content reported by patients were other treatment options, provider role in care and safety of a PICC (10%, 3/30), and patient role in the care and safety of a PICC (7%, 2/30).

The mean patient satisfaction score with the PICC consent process using a 5-point satisfaction scale was 4.8 (SD 0.37). Patients added that they would like to know more about their role in the PICC (7%, 2/30) and to involve their families in the consent process (7%, 2/30).

In summary, all patients were satisfied with the consent process and felt that the timing of the discussion was convenient. Inconsistent with the knowledge recall scores, all patients reported that they completely understand the common complications of this procedure. Inconsistent with the observers' ratings of the process, all patients felt that the speed of discussing the information was reasonable. Only 2 (7%, 2/30) patients disagreed to the item "I understand my role as a patient in maintaining the safety of the PICC line."

In addition to patient satisfaction, patients' attitudes toward using a multimedia PtDA program to supplement the consent process survey was created based on the main benefits of using multimedia PtDAs identified in the literature [5,9,10,13-17]. The survey consisted of 6 items of a 5-point Likert-type agreement scale where 5=strongly agree and 1=strongly disagree. In this survey, we used the term *video* instead of

multimedia to enhance the readability and understandability of the items by the patients. The survey was administered at the same time of administering the patient satisfaction survey. Patients' responses were coded as Agree for strongly agree and agree and as Disagree for strongly disagree and disagree. Neutral responses remained neutral in the analysis. As shown in Table 3, patients reported a high positive attitude toward the use of multimedia as a supplement to the conventional process.

In addition to examining the current process, at this stage, a comprehensive literature search for the use of multimedia as a supplement to the conventional informed consent process was conducted. The research and change team also proposed the method for implementing and evaluating the multimedia PtDA and discussed the changes in the workflow of the PICC consent process. Details about the implementation and changes in the workflow are described in the postproduction phase.

Step 3: Scriptwriting

The principal investigator created the first draft of the script based on the PICC guidelines, the procedure content identified in Step 1, the limitations of the current process, the results of the patients' and nurses' perceptions about the current process, the first 5 activities of the patient-centered process to make a decision outlined by the IP-SDM model, the AHRQ's comprehensive guide for informed consent [1], the AHRQ's Health Literacy Universal Precautions Toolkit Guide [18], and the AHRQ's Patient Education Materials Assessment Tool Guide for Audio and Video Materials [19]. The script included introduction; purpose of the educational program; intended users of the program; disclaimer; background including a definition of the PICC and possible insertion sites; purpose of the line; other treatment options; common, less common, and rare risks and complications; education; procedure (before, during, and after, including the need for diagnostic equipment such as ultrasound or x-ray); expected time period for having the catheter; safety issues when a patient leaves the hospital with a PICC; and a conclusion. The introduction encouraged patients and family members to write down questions they might have about the procedure. The conclusion emphasized the need to ask all questions before signing the consent form. There was a great emphasis in the script on the health care team and patient roles in the care and safety of a PICC during hospitalization. The content stressed on clarifying the patient's values when considering the decision, that is, "Your provider discussed with you all other treatment alternatives of a PICC. Please let us know if you feel you need further information about these alternatives" and "Please make sure that you understand the risks, benefits and complications of the procedure before you sign the consent form."

The provider usually discusses other treatment options with the patient before ordering the PICC line, the details of these treatment options, and associated risks. Treatment options are individualized based on the patient condition and the reasons for the PICC and may include having another type of central line, for example, implanted port in the chest wall, whether an acceptable substitute for a PICC or changing the medication, and whether the intended infusion is a medication that has a potential to damage the peripheral veins. After explaining the intended treatment plan and all available options to the patient, they should be given the opportunity to agree or disagree with the plan of care before the provider places a PICC order in the electronic medical record (EMR). If the patient has questions about an alternative to the PICC placement, those questions are referred to the provider. Nurses from the vascular access team usually accompany the provider in this discussion. However, they are not qualified to discuss the risks and benefits of the alternative treatment options with the patient directly; they can explain the details of the PICC procedure.

Table 2. Patient satisfaction with the informed consent process (N=30).

Item	Agree, n (%)	Neutral, n (%)	Disagree, n (%)
The information provided was clear	30 (100)	0 (0)	0 (0)
The information provided was easy to understand	30 (100)	0 (0)	0 (0)
Timing of the discussion was convenient	30 (100)	0 (0)	0 (0)
Speed of information provided was reasonable	30 (100)	0 (0)	0 (0)
Provider attitude was positive during the discussion session	30 (100)	0 (0)	0 (0)
I completely understand the common complications of this procedure and know when to report them	30 (100)	0 (0)	0 (0)
Disruption during the discussion was minimal	29 (97)	1 (3)	0 (0)
I understand my role as a patient in maintaining the safety of the PICC[a]	28 (93)	0 (0)	2 (7)
The information provided was comprehensive to include: definition of the PICC; reasons for the PICC; steps of the procedure; common side effects; other treatment options; patient role in care and safety of the PICC; provider role in care and safety of the PICC; if the provided information was not comprehensive, please circle the missing content from the contents above	27 (90)	1 (3)	2 (7)

[a]PICC: peripherally inserted central catheter.

Table 3. Patient attitude toward using a multimedia program to supplement the consent process (N=30 patients).

Item	Agree, n (%)	Neutral, n (%)	Disagree, n (%)
I think the use of a recorded video about the procedure would be beneficial	29 (97)	1 (3)	0 (0)
The use of the video will allow patients to listen to the information as much as they need	29 (97)	1 (3)	0 (0)
The video will allow a patient to listen to the information about the procedure when he or she is ready to do so	29 (97)	1 (3)	0 (0)
The use of the video will better help a patient recall the information about this procedure	29 (97)	1 (3)	0 (0)
The video will decrease the patient level of anxiety	29 (97)	1 (3)	0 (0)
I highly recommend the use of the video as a supplement to the consent process	26 (87)	3 (10)	1 (3)

The script went through a review process by all members of the multidisciplinary change team. This process proved to be the most time consuming. Multiple versions of the draft were revised to lower the reading level. Some considerations in scripting included:

- deciding on the narrator and persons in the scenes
- determining the types of the scenes including the background of shooting, recording setting, the equipment, and pictures to be shown such as, the vascular access team picture, hospital logo, and the anatomy of the vascular system connecting to the heart where the PICC line will be inserted and the catheter tip location
- developing bullet points for the worded graphic slides to help patients understand the important concepts
- determining the sequences of the scenes (ie, sequence between the narrator, the worded graphic slides, the pictures, the patient room, etc).

After validating the final version of the script by the research team, 10 patients reviewed the script for clarity and readability. Among the 10 patients, 5 were male, 6 were Hispanic, and 7 indicated their educational level as high school, whereas 3 reported college degree. Patients' comments were related to clarifying the terminologies in the complications section of a PICC, such as *blood stream infection* and *deep tissues* and *embolism* in the following statement:

> *If there is damage to the catheter and the surrounding deep body tissues, a blood clot could travel into the blood to the lungs and cause pulmonary embolism.*

The statements were clarified and sent back to the same patients who indicated that the statements look much easier to understand after the modifications.

A certified company (MasterWord Services) translated the English script into Spanish for our Spanish-speaking patient population to ensure medically accurate translation of the script. Moreover, 2 expert nurses from the vascular access team were approached to voluntarily serve as the narrators. English was the mother tongue of the nurse who volunteered to record the English version of the program, and Spanish was the mother tongue of the nurse who volunteered to record the Spanish version of the program. The change team also asked a nurse to play a patient role during the recording of the vascular access team-patient encounter to maintain patient privacy.

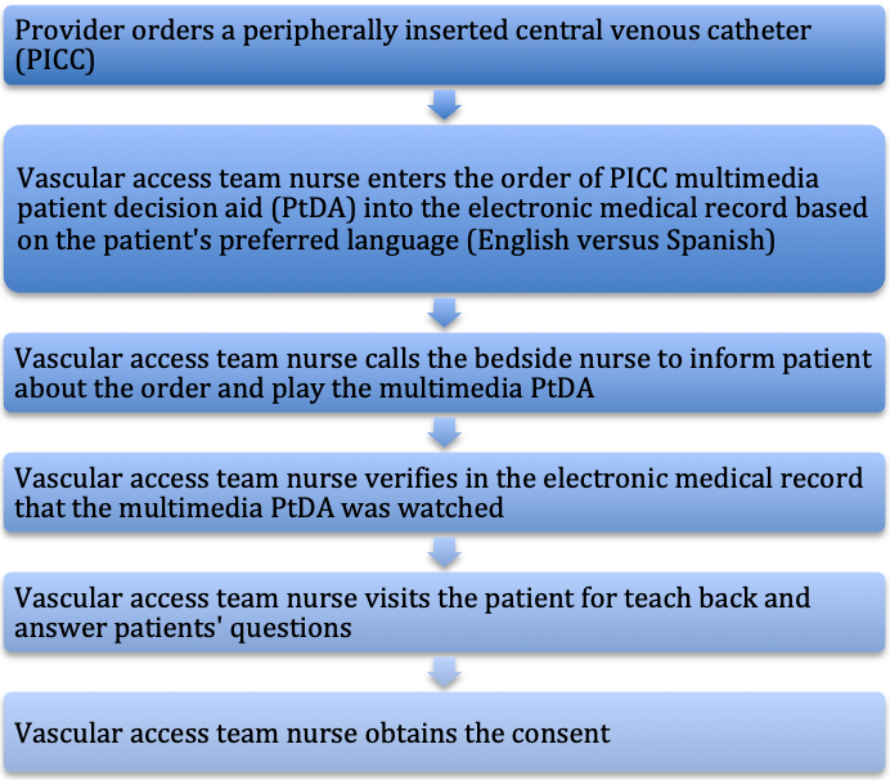
Phase 2: Production Phase

The hospital contracts with a local videographer and photographer to produce videos and photography projects. The team created still photography and developed multiple worded graphic slides to emphasize specific messages that we wanted the patients to remember to improve patient retention of material. These slides allow points where patients can pause the video and better understand warning or complication signs, their role in care processes, and other treatment options.

The actual production started with a rehearsal of the recording by the narrators and the multimedia experts. Different team members were present to provide feedback. Multimedia experts recorded the video in a variety of daylong shoots over several months using a Blackmagic 2.5K cinema camera. The recording took place in our hospital system video and photography studio and in a patient room where a bedside nurse played the role of a patient. Experts used professional lighting to help decrease the glare from the typical room lighting and made use of a green screen backdrop that allowed the research team to drop in neutral background images during the narration scenes.

The video shooting required multiple angle shots to provide us with options to tell the story of a PICC line insertion. Multiple video B-roll shots gave us alternatives to best display the nurse and patient interaction as well as close-up shots of the insertion, washing hands, sterile gowning, and an example of the PICC line insertion. A Shutterstock graphic showed veins and the heart to allow patients to see on a line-drawn image exactly where the PICC line would enter the vein and how it would approach the heart. A close-up photo of the PICC line not only allowed our video editing team to cover a cut between camera angles but also gave an opportunity to show the patient exactly what the line will look like. We also showed the consent form interaction exactly as it should happen, with the patient signing on the tablet.

Figure 2. A modified workflow of the peripherally inserted central venous catheter (PICC) informed consent process.



Phase 3: Postproduction Phase

The postproduction phase included integrating the multimedia PtDA program into the care processes, approval of the modified workflow of the PICC consent process, and alpha testing of the product. The IT department integrated the multimedia program into the Interactive Patient Care solution GetWell Inpatient. This solution is a personalized patient education and entrainment system that includes many videos and multimedia programs and is connected to the EMR for the purpose to engage patients and their families in their care. Patients may also use the system to provide feedback through various surveys, request housekeeping services, or to share their experience with patient relations. In addition, patients have access to a variety of television channels and recently released box office movies. All health education videos and multimedia programs within this system that are assigned through an order and watched by the patients are recorded in the EMR along with the time and frequency of watching.

The PICC multimedia program was added to the GetWell Inpatient Health Education Library with an ancillary code that was also built in the EMR on the patient education order. Health level 7 (HL7) admission, transfer, and discharge messages were sent to GetWell Inpatient through the Cloverleaf Interface Engine. The patient unit, room, and bed location in the admission, transfer, and discharge message were stored in the Interactive GetWell Inpatient system. The PICC PtDA multimedia program was embedded into the PICC order set within the EMR. When a PICC is ordered, the PICC education is ordered automatically and sent via HL7 order result message to the GetWell Inpatient system in the patient's room. This will lead to a notification display on the room television notifying the patient that an educational item has been ordered. When the education video has been viewed, an HL7 observation result message is sent back to the EMR with the time viewed and closes the education order. The EMR medical logic module writes all education results to the patient education log as well as to the results section of the EMR. After the integration of the multimedia program into the GetWell Inpatient, the change team approved the new workflow of informed consent as a result of using the PtDA program (see Figure 2).

In addition to the multimedia program, the research team also created an information sheet that includes the same information presented in the program about the PICC. The information sheet provided another resource for competent patients and family members.

The English and Spanish multimedia programs integrated into the EMR went through 3 alpha testing or validation phases. First, each program was tested by a group of 5 patients for ease and clarity of the language, understandability of the information related to the procedure, readability of the font when slides were displayed within the video, and clarity of the critical points. Test patients were selected from different educational levels and genders. Second, the programs were reviewed by all nurses from the vascular access team and 7 bedside nurses for logical sequence of the discussion, quality of the scenes, and adequacy of the information. Nurses used the AHRQ's Patient Education Materials Assessment Tool Audio and Video to rate the program [19]. The tool consists of 17 items—13 for understandability and 4 for actionability [19]. Third, the multidisciplinary change team reviewed the final product and for the second time applied the Criteria for Judging the Quality of PtDAs developed by the IPDAS Collaboration [21].

Results

Based on the alpha test, (1) the test patients indicated that the content of the programs was easy to follow and understand, and the font was readable; (2) all nurses provided positive feedback and their comments were mainly related to the changes in the workflow in the consent process of the PICC after using the PtDA; and (3) the suggested edits by the change team were related to changing few scenes (ie, a scene related to a nurse who played a family member role touching the PICC line). The final multimedia program consisted of 7 min and 37 s demonstrating detailed information about the PICC.

After the alpha test, the research and change teams created a plan to train all nurses from the vascular access team and bedside nurses on the new workflow to standardize the informed consent process. Two nurse champions were selected from each of the 10 ACUs and the ICUs to facilitate the training.

Discussion

Summary of Protocol Findings

This paper described a multidisciplinary, patient-centered, systematic process to develop, implement, and alpha test a multimedia PtDA program to reform the consent process of the PICC procedure. Our development, implementation, and evaluation processes were based on the IP-SDM model [20], the AHRQ's national guides for informed consent and health literacy [1,18], PtDAs' quality criteria developed by the IPDAS Collaboration [21], and the Multimedia Production Framework [22]. We are currently in the process of beta testing the program and will publish the results in the near future. The beta testing will focus on implementing the program and the effect of the PICC PtDA program on patient knowledge recall, knowledge retention, satisfaction with the multimedia program, and satisfaction with the informed consent process.

The preproduction assessment phase of this study identified the limitations of the conventional PICC informed consent process and supported the need for a PtDA to supplement the consent process [10]. Main limitations were related to the use of an outdated consent form that also did not include necessary information about the procedure definition, steps of the procedure, complications, and patient role in the safety of a PICC. Observing the current informed consent process revealed spending a short period in the process; availability of distraction during the discussion; not considering the patient comfort level, which may affect patient readiness to engage in a discussion; and inadequacy of the information discussed with the patients. Almost 90% to 95% of the observed processes missed discussing the health care team role and the patient role in the care and safety of a PICC during hospitalization. During the observations, we also found that patients ask questions about content that was already discussed by the vascular access team during the consent process. This may (1) reflect the shortcomings of the current process (ie, workload-related factors such as not spending enough time to discuss the procedure with the patient, or patient-related factors that affect comprehension such as pain and discomfort), (2) support the need for a self-paced resource such as multimedia PtDA available to patients when needed, or (3) suggest that the medical conditions of some patients in the ICUs and ACUs might be a barrier for patient engagement in the consent process [34], which advocates for the need to engage a proxy in the informed consent process [35].

Although patients were satisfied with the current consent process and believed they have sufficient knowledge about the procedure, associated risks and their role in the safety of the procedure and risks and complications about the procedure were the items with the lowest scores in the knowledge recall questionnaire. These results further support the need for a self-paced tool to better inform patients about the procedure.

Multimedia PtDA tools can be delivered to patients using DVDs, iPads, or directing the patient to an authenticated or unauthenticated website or patient portal where the information is stored on the health care setting internet or intranet [36]. In this study, we delivered the program using the Interactive Patient Care solution GetWell Inpatient. The system is integrated into our workflow since 2014 and is used to push many educational videos and multimedia programs to patients in addition to other purposes. The main benefits of using GetWell Inpatient are the ability of the patients to review the information at the point of care, when needed, as many times as needed, and to engage their families in the process, and the ability of the EMR to track the use of educational videos and multimedia programs by the patients.

Multimedia PtDAs are effective tools to engage patients in care processes and treatment options. Cost is one of the factors that may limit the production and utilization of multimedia PtDAs [3]. The costs associated with producing a multimedia PtDA vary with some contributing factors to include availability of expertise, video length, recording location (hospital environment versus studio), number of still images, and additional graphic enhancements. The filming time of our PICC PtDA (setting up, lighting, shooting, breaking down, etc) for both the English and Spanish versions to include B-roll was a total of 14.5 hours. Pre- and filming time periods were approximately 30 to 40 hours. The total cost associated with filming the PICC PtDA was approximately US $7800. The entire project took 15 months to complete, from January 2017, to March 2018.

Implications

The methodology we used to reform the consent process of the PICC includes essential steps that can be used to reform the informed consent process for any therapeutic procedure in other health care settings. These steps include:

- assembling a multidisciplinary change team with a change in authority
- articulating a clear vision
- conducting a comprehensive literature search about the procedure and multimedia apps
- rigorous assessment of the limitations of the current informed consent process, policies, and practices
- writing a script that is based on national guides, limitations of current process, and recent literature
- engaging patients in the evaluation of the current process and proposed change

- engaging all clinicians responsible for obtaining the consent for the procedure
- using credible guides and frameworks to guide the process
- using credible tools (ie, AHRQ's Patient Education Materials Assessment Tool Audio and Video) for assessment
- maintaining consistency across the informed consent document, multimedia app, and policies.

The evaluation process we used was robust and comprehensive to include observing the current process, assessing the perceptions of the vascular access team members about the limitations of the current process, assessing patients' satisfaction with the current process and their attitude toward the use of multimedia programs, and evaluating patients' level of knowledge recall and retention about the procedure. The group of patients who was engaged in the evaluation process was from different genders, educational levels, and race or ethnic groups.

Many factors may support the success of the beta testing of our program in the future. First, the improvement opportunity to make the informed consent an informed choice was a priority that was supported by the organization leadership. Second, all stakeholders (leaders, clinicians, and patients) were engaged in the change process. Third, the hospital has sufficient infrastructure for multimedia production. Fourth, GetWell Inpatient allowed seamless integration of the program and tracking of its use. Finally, our PtDA empowered patients by highlighting patients' role in the safety and care of a PICC line.

The JC requires informed consent to be clear, comprehensive, and engaging. Time pressure is a major challenge to provide an informed consent. Well-designed PtDAs empower patients to make informed decision about treatment options; reduce variation in practice; standardize the amount, quality, and clarity of the information provided; and provide critically ill patients the choice to review the information at times convenient to them, taking into consideration their readiness to learn.

Limitations

Although we followed a rigorous method to assess the need to reform the PICC consent process and to create and alpha test the PICC PtDA, there are some limitations that need to be considered. First, our patient sample used in the preproduction phase was limited to 30. Engaging more patients might provide additional insight into the limitations of the current PICC consent process that need to be considered when reforming the process. Second, although ethnicity was almost equally distributed among non-Hispanic and Hispanic patients for all patients who participated in the preproduction assessment and those who reviewed the script, the patients who reviewed the script indicated English as their preferred language and therefore reviewed the English version of the program. The beta testing may reveal additional insight for the Spanish version of the program. Third, the IP-SDM model emphasizes the role of family in the decision-making process; however, only few family members were engaged in the initial assessment of this process because many were not available. Some of our findings suggest engaging proxy or family members to help patients in the decision-making process in ICUs and ACUs.

Conclusions

PtDAs are recommended tools to supplement the informed consent process for treatment procedures. A systematic development of PtDAs for nonurgent invasive procedures can eliminate many limitations in the conventional consent process by ensuring comprehensive, standardized, and easy-to-comprehend information about the procedure and treatment options and by providing sufficient time for the patients to reflect on the information. To be effective, multimedia PtDAs should follow a systematic, evidence-based, and rigorous approach in the development, implementation, and evaluation processes. Including key stakeholders such as leaders, clinicians, and patients is fundamental for the success of these tools.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Number of patients who correctly answered questions in the knowledge recall and knowledge retention questionnaires (N=30 patients).

[PDF File (Adobe PDF File), 64KB - resprot_v7i12e10709_app1.pdf]

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Abbreviations

ACUs: acute care units
AHRQ: Agency for Healthcare Research and Quality
EMR: electronic medical record
HL7: health level 7
ICUs: intensive care units
IPDAS: International Patient Decision Aid Standards
IP-SDM: Interprofessional-Shared Decision-Making
IRB: institutional review board
IT: information technology
JC: Joint Commission
PICC: peripherally inserted central venous catheter
PtDA: patient decision aids

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Protocol

Prescription and Integration of Accredited Mobile Apps in Catalan Health and Social Care: Protocol for the AppSalut Site Design

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Abstract

Background: The use of new mobile technologies in the health and social welfare sectors is already a reality. The ICT Social Health Foundation, in accordance with the technology strategy of the Catalan government's Ministry of Health and its Ministry of Labour, Social Affairs and Families, is leading an initiative to create a public library of apps for its AppSalut Site.

Objective: The objective of this paper is to present an account of the design of the project, with a global perspective, applied to the Catalan ecosystem, which can be divided into 3 areas: the framework governing the recommendation and prescription of apps, the subset of interoperability for mobile environments, and the data storage infrastructure.

Methods: The security and credibility of the apps included in the catalog is ensured by submitting them to an accreditation process in the public domain that provides users with the guarantee that they are fit for purpose and trustworthy for the management and care of their health, while providing health care professionals with the possibility of recommending the apps in the doctor's surgery, as well as adding the information generated by the users' mobile devices to the information systems of the various organizations concerned.

Results: An examination of the abovementioned areas suggests possibilities for improvements in the future. The experience obtained from the development of this element has shown the heterogeneity of the vocabularies used, as expected, due to the lack of awareness on the part of the developers regarding the need to standardize the information generated by the app, requiring the foundation to take on the role of consultant.

Conclusions: The project has evolved in keeping with changes in the technological and social paradigm and responds very satisfactorily to the needs posed to it. It can be seen as a landmark experience in mobile strategies in the fields of health and welfare of any public health system. The experience has shown itself to be feasible in organizational terms, necessary in any attempt to integrate mobile technologies into public health practice, and a global pioneer in the field.

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KEYWORDS

mHealth; information integration; telemedicine; telemonitoring; mobile phone

Introduction

Background

An increase in the use of new mobile technologies in the field of health care has been thoroughly documented. *The Green paper on mobile Health* [1] describes mobile health (mHealth) as "an emerging and rapidly developing field which has the potential to play a part in the transformation of health care and increase its quality and efficiency." More recently, the *mHealth App Economics* report [2] predicted that in 2021, health apps would be recommended by health care professionals by means of specialized portals as part of routine visits to a doctor. The 2017 edition of the report [3] estimates that 325,000 mHealth apps are available to download from official stores (AppStore, Google Play, etc). The *A Connected Digital Single Market* [4] report points to the increasing ability of patients to upload their medical records to their electronic medical history and to interact with health care providers.

Despite a wealth of evidence regarding the degree of implementation of mHealth and its potential, few public initiatives are promoting specific strategies in the field of health app libraries; at the national level, the United Kingdom's National Health Service has its Digital Apps Library, which is still at the design stage, while at the regional level, the Andalusian Health Service maintains its *catalog of mobile health apps*, also standing for an accreditation process [5]. Catalonia, a pioneer in the adoption of mHealth policies, recently approved its Strategic Mobility Plan [6], urging the institutions involved in the sector to bring health care and social welfare services to the public via mobile technologies and to facilitate the transformation of the various social and health care processes to achieve integrated attention, which more effectively meets patients' needs. In response to this objective, the ICT Social Health Foundation created an apps library for the health and social care sectors called AppSalut. The foundation certifies that the apps featured in its library are suited for facilitating and improving the monitoring of patients' health. This guarantee is achieved by submitting all the apps to an accreditation process created by the foundation , which is in the public domain; the apps are subsequently made available to doctors who can recommend them during a consultation in order that the information generated can be added to the institutional information systems as an aid to making decisions. Furthermore, the AppSalut Site was created to help empower patients, making them aware of and responsible for their own health, while ensuring that information moves in both directions, between patients and their health care team.

This paper outlines the comprehensive, forward-looking solution developed by the ICT Social Health Foundation. It details the design of the project and the 3 elements on which it is based: the framework governing the recommendation and prescription of apps, the subset of interoperability for mobile environments, and the data storage infrastructure. This paper concludes with how the project will develop and possible changes in the future.

Objectives

The aforementioned speed with which mobile technologies have been adopted in the fields of health and social welfare implies a series of needs that the AppSalut Site has defined in terms of challenges, which are shown in Table 1.

Table 1. Needs and challenges in relation to the AppSalut Site.

Needs	Challenges
The app stores feature an enormous number of apps that are highly heterogeneous in terms of quality and type. A trusted framework is required to ensure that both doctors and patients use apps that meet certain minimum requirements.	Certify the app's relevance and added value by means of an accreditation process.
The apps also capture and record data by means of associated devices (glucometers being the most frequent).	Standardize the devices linked to mobile apps.
Every device uses its own platform, meaning that doctors who wish to access the data generated by their patients must enter the same number of platforms as devices used by their users.	Design a single platform for viewing all the collected data and adding it to the health system's information system.
The aforementioned apps and devices collect data without necessarily adhering to international standards.	Standardize the data from the apps through the use of an interoperability framework.
The collected data cover very different themes (related to lifestyle, physical activity, etc, both actively and passively) and its veracity must be proven.	Upload data solely at the doctor's discretion and distinguish it visually from the rest of the patient's medical history.
From the start, developers should become aware of the desirability and potential added value of incorporating information from the app with public information systems and that they take this into account during the app's technical design.	Support developers in the design of apps that are likely to be added to the library.
The prescription of mobile apps in the health environment is currently carried out on an informal basis: the doctors prescribe those they know or have been recommended to them by other professionals.	Create an institutional prescription process and integrate the recommendation of apps into clinical information systems.
Apps can serve to empower citizens in taking care of their health, and they can generate quality doctor-patient communication, giving a much more holistic vision of health, oriented toward promotion and prevention.	Organize the process around the Personal Health Folder.

In relation to the aforementioned challenges, and for the purpose of simplifying this account, 3 basic lines of action have been established, in the form of objectives: (1) the creation of a Web interface that outlines the process of accreditation and the prescription of apps, which serves as a point of contact with the app developers; (2) the creation of a framework of mHealth standards and interoperability; and (3) the implementation of a structured data repository that can be consulted both by patients and doctors and services that allow the stored information to be exploited. These objectives are specifically addressed through the structural elements that collectively make up a new health care process, which is made available to patients, known as the AppSalut Site.

Methods

The Framework for Interaction With Developers, Professionals, and Users

The first 2 processes that need to be systematized require an element of interaction between the team in charge of the project, the apps' developers, and the professionals who need to use them. In the first instance, the accreditation of the apps (the certification of their suitability for use) involves a process in which they must meet a series of conditions (not solely of a technological nature). In the second instance, a process needs to be designed through which professionals can recommend (or "prescribe") these certified apps to their patients (detailed below).

Accreditation Process

The design of the accreditation process must be based on a consensus between professionals in the sector: experts in the field of technology, health professionals (doctors, nurses, psychologists, and social workers), health communication professionals, expert patients, institutional representatives, and members of the public. This multidisciplinary approach ought to be shaped by working groups and meetings, with two major objectives: reaching a consensus on the stages of the accreditation process and the creation of a list of evaluation criteria. With reference to the first question, 5 different stages are to be taken into consideration:

1. *New apps*: consideration of a new app for approval by means of a preliminary form, filled out by the developer, containing certain basic information
2. *Initial validation*: meeting of certain preliminary requirements (eg, if the app is operational and whether it works correctly)
3. *Classification*: categorization according to the app's complexity (which may determine the type of evaluation that needs to be carried out)
4. *Evaluation*: a request is made to a committee of experts for them to apply a series of criteria, corresponding to different areas, by which they can evaluate the app
5. *Result*: if the procedure is satisfactory, the corresponding certificate of accreditation is generated and published in the app library

At the end of the process, the app is awarded a numerical score that is published in the AppSalut Site. The accreditation remains valid as long as the app is active or until changes are made to its content and functionality; consequently, those responsible for the app will have to commit to reviewing the process if such changes occur.

Recommendation Process

With regard to the recommendation process, 2 considerations must be met. First, it must be remembered that the prescription of the app must be properly integrated, both occurring as part of the currently existing patient clinical pathway and forming part of the information system used by clinicians. Second, it must be emphasized that mHealth technologies have largely focused on the management of chronic diseases, where continuity becomes a fundamental aspect [7]. It seems reasonable, therefore, that the starting point for these apps is during a consultation with the primary health care physician, where there is greater potential for the attributes of telemonitoring and the observation of chronic patients.

Data Interoperability

Interoperability is the ability to share information between components (such as systems or devices) without its meaning being lost. This communication must ensure the coherent exchange of data among departments, organizations, health care levels, or regions. Its main objective is to provide doctors with relevant information regarding their patients to ensure that the decision-making process takes place in a safe, efficient, and effective manner. Interoperability guarantees access to information regardless of where it was recorded, thus, favoring its reuse, minimizing blind spots, and ensuring the continuity in health care. Standard health interoperability is widely used and studied [8], although it is still emerging in the mHealth field. This is the second of the 3 elements that need to be developed in the framework of the AppSalut Site.

The chapter devoted to mHealth in the study entitled *From Innovation to Implementation, eHealth in the WHO European Region* [9] shows that more than half of the health centers that were surveyed promote the use of standards and interoperability in mobility, demonstrating that they form part of the health systems' agenda. A global pioneer, the Catalan model of interoperability in mHealth [10,11], focuses mainly on layers of syntactic interoperability (relative to the structure and format of the information to be exchanged) and semantics (which guarantees that the information maintains its integrity at the receiving component). With regard to the first of these levels, in traditional models of information exchange, Health Level 7 (HL7) messaging is commonly used for the notification of information and occasional events, such as in *Clinical Document Architecture-Release 2* documents for the sharing of clinical reports. Both standards are based on the exchange of XML files, and although they are specific to the health sector, they are not suitable for mobile apps. In contrast, the Fast Healthcare Interoperability Resources (FHIR) standard, also by HL7, was created to respond to new information-sharing needs, allowing the use of Representational State Transfer (REST) Web services in *JavaScript Object Notation* format. This standard allows the sending of only the relevant and/or necessary information, simplifying the exchange of health information and adapting the methods of transmission to the mHealth environment.

In terms of semantic interoperability, apart from sharing information between the apps and the central data repository, it is also essential that the data exchanged can be compared and exploited globally. As a result, it is imperative that if two apps register the same data, such as weight, they do so based on the standardized criteria that define the code, the type of data involved, and what units of measurement it represents. Based on a current state review of all the available controlled vocabularies, Systematized Nomenclature of Medicine–Clinical Terms (SNOMED-CT) has been chosen as a reference terminology due to its flexibility and enormous scope.

Data Repository

The data repository, as the third and final element that should make up this new care process, must store information from mobile devices for later use, either by doctors as part of health and social care systems and/or by patients themselves. Therefore, this requires a platform that can address the 3 Vs common to solutions based on Big Data: volume (a large number of mobile apps, users, and data are generated), velocity (data are captured in real time), and variety (every device structures information in a unique, heterogeneous manner, so the way in which it is stored must adapt to this diversity of origins).

To the aforementioned "Vs," we need to add two specific ones that are of great relevance in the health and social welfare sectors: veracity (it is necessary to ensure that the stored data come from a reliable source of information) and value. The information stored on the platform must allow the following uses: (1) for doctors, to personalize the treatment for patients, with the use of information originating from personal devices; (2) for patients, to visualize the information from mobile apps they have installed in a standard manner; (3) for the current information systems, to add the necessary information to patients' clinical history; and (4) for the remaining agents in the sector, the exploitation of the data, creation of alerts, prevention, and prediction.

Results

The AppSalut Site

In terms of the structure outlined in the previous section, the following is the outcome proposed by the ICT Social Health Foundation, in accordance with the specific characteristics of the Catalan public system. The process of defining the project has transformed the 3 identified needs into 3 corresponding products designed for the Catalan context and adaptable to other health systems.

In relation to the framework for interaction with developers, doctors, and users, the AppSalut Site [12] was created; it is a Web interface acting as an *mHealth Hub* for clinicians; app developers; patients; and the sector, where guidelines, rules of use, and news are published. The AppSalut Site backstage is, simultaneously, the ICT Social Health Foundation's management tool. Below is a summary of how the accreditation and recommendation processes are organized around this Web portal.

App Accreditation

The expert consensus on the app accreditation consists of 2 processes: first, a task force is dedicated to specifying the means of classifying the apps, based on the foundation's participation in the *CNECT mHealth Expert* groups and the mHealth subgroup of the European Commission's *eHealth Network*. Three parameters have been defined for evaluation, namely, the impact of use (in terms of the volume of users potentially susceptible to using the app in the Catalan context), the type of health recommendation that the app performs for users (more or less specific according to the use of the data supplied by users), and the type of sensitive information that is registered (a critical aspect to take into account because certain apps do not transmit data). These 3 indicators determine the requirements of the accreditation process, establishing which of the recommended or desirable criteria are obligatory, according to the 3 levels, whereby the obligatory criteria are essential for the app to pass the accreditation process (more detailed information on this aspect is provided in the Multimedia Appendix 1).

Second, a total of 5 working sessions with the expert groups and the advice of a specialized technology consultancy have resulted in the publication of 120 evaluation criteria that are grouped into 4 areas. First, functionality: the evaluation of the quality and utility of the app's contents. These are made up of 25 criteria and are given priority over the following 3 areas. Second, usability and design: accessibility, user experience, and visual aesthetics. Third, technology: technological reliability and adaptability of the app in general. Last, security: guarantee of data security and adherence to data management policies. The experience to date indicates that the technology and security areas usually work well, while functionality and usability are more critical (specifically, the latter shows that most of the analyzed apps had shortcomings in terms of accessibility for users with functional diversity). In light of these criteria, the evaluations are conducted by two committees, whose structure is summarized in Table 2.

In addition, those responsible for the evaluations are charged with developing proposals for modifying or improving the criteria. It is desirable that developers consider them in early stages of the design of apps, as far as possible, as their usability may be affected by being adapted to meet the requirements (eg, including a specific log-in process). With the publication of the criteria, guides, recommendations, and seminars aimed at providing support for developers, and help from all the relevant entities involved in the sector, the foundation has opted for an open, transparent accreditation process, which prioritizes the gaining of trust from patients and doctors.

Table 2. Constitution of the app accreditation committees.

Committee	Members
Functional (in charge of the functional criteria)	• Official College of Doctors of Barcelona • Official College of Nurses of Barcelona • Catalan Society of Clinical Psychologists • Association of Family and Community Nursing • Catalan Society of Family and Community Medicine • Official Association of Graduates in Physical Education and Physical Activity and Sports Sciences of Catalonia
Technical (in charge of the usability and design, technology, and security criteria)	• Currently managed by a specialized consulting company

Recommendation

The recommendation process is the route by which doctors can prescribe apps to users. As mentioned above, primary health care has been identified as the most appropriate process for monitoring the information recorded, with the general practitioner being identified as the principal agent responsible for the prescription process. In addition, it is the most technologically feasible option, given the needs of the specific case in question, as >90% of Catalan Primary Care Teams use the same clinical management software (named *eCAP*). The prescription process involves the stages identified in Textbox 1.

The Digital Health Platform

The Digital Health Platform (DHP) has been designed and implemented as a data repository that allows doctors to access all the information generated by the apps at any time and check it, if applicable, before it is included in the information system. It is primarily based on solving the stated objectives in a modular, interoperable way. The following are the main areas: (1) data storage, which includes the apps that have been recommended to patients, the catalog of variables, and the data originating from the mobile apps; (2) services for interacting with the data storage; and (3) the corresponding identification services. The following sections concern the sequence of tools presented in Table 3.

With regard to the access to information stored in the DHP, the system's architecture provides the possibility of allowing third parties to access the DHP's information system to upload data to their own repositories, but this has yet to be implemented.

The Software Development Kit and the Mobile Subset for Interconnecting With a Common Vocabulary

Based on the identified information exchange needs, the following interoperability devices have been developed. First, a Software Development Kit that will evolve into an FHIR implementation (this standard will be gradually phased in). Initially, a much simplified first version was created to send variables of the "identifying-value" kind. Its technical aspect was tested at a hackathon specifically intended for this purpose, allowing developers to assess the feasibility of uploading data from 14 different apps to the DHP, in a controlled environment [13].

The second defined interoperability device focuses on the semantic layer and consists of a subset of mHealth and mSocial mobility variables. The three main challenges presented by mobile technology are the great diversity data types, the rapid responsiveness required, and the app developers' lack of familiarity with the controlled vocabularies. As a result, the methodology used to standardize the controlled vocabularies also needs to be modified; to add an app to the AppSalut Site, its variables are analyzed and standardized in a specific way, assigning it a set of codes relating to the data types and the corresponding units of measurement. To help developers identify and standardize which variables to send, a notification template of variables has been created and information sessions have been held to emphasize the importance of applying the standards. As a result of these efforts, a subset of mHealth and mSocial mobility variables of SNOMED-CT has been defined, which has >50 concepts originating from 6 apps. This subgroup ensures that data exchanged between the apps and the DHP can be compared and exploited globally. Other vocabularies such as Logical Observation Identifiers Names and Codes, International Classification of Diseases-release 10, and Anatomical Therapeutic Chemical Classification are also taken into account, but these are mapped to SNOMED-CT to have a common base of reference terminology. The subset should, therefore, be seen as a dynamic tool that requires a versatile standard (FHIR).

The experience obtained from the development of this element has shown the heterogeneity of the vocabularies used, as expected, due to the lack of awareness on the part of the developers regarding the need to standardize the information generated by the app, requiring the foundation to take on the role of consultant.

Textbox 1. The prescription stages in the AppSalut design.

Recommendation

During the first visit, the health professional recommends a mobile app to a patient. To do so, the doctor accesses eCAP and once logged on, prescribes an app available on the AppSalut Site without the need to log on a second time. The patient then receives a short message service (SMS) text message on his or her mobile phone containing a registration code, allowing him or her to identify himself or herself when sending data.

Download

The user can download the app directly from official app stores (Google Play or AppStore) or through his or her Personal Health Record "My Health" account, where the prescription will have been registered.

Registration

Once the app is installed on patients' mobile device, they need to enter the code they were sent via SMS text message and accept the conditions of the service, thus, agreeing to have their data stored on a public network.

Setup

Depending on which app has been recommended, patients can activate a series of alerts on their device to warn them, if necessary, when they need to enter their information. The specifics of this stage depend on the app in question.

Uploading data

Apps automatically upload the information on a continual basis. Both patients and doctors can access their respective viewers in the AppSalut Site, which displays information relating to all the apps linked to AppSalut in the form of graphs and allows them to apply filters (date, time, etc).

Evaluation of the results

Doctors can visualize the information collected while patients have been using the app and select the data to be included in their clinical history.

Table 3. Tools and needs of the Digital Health Platform.

Tools	Needs
Nonstructured Query Language-type database	To store large volumes of unstructured data without having to predefine its structure
Representational State Transfer (REST) services	To allow mobile apps to upload data to the database
Credential validation services	To request the identification services to confirm the identity of a patient or a doctor
Simple Object Access Protocol and REST services	To allow users to interact with the stored data, either checking it or consulting it
Encryption and decryption service based on a public or private asymmetrical key	To ensure the veracity of the origin of the data
Software Development Kit	To allow app developers to access all of the platform's features concerning the inclusion of their data
A message in a custom format based on Health Level 7	To allow data from the apps to be added to the repository. The current message always has the "Variable-Value" structure where the variable name is its code in the corresponding catalog (Systematized Nomenclature of Medicine–Clinical Terms; the International Classification of Diseases, Ninth Revision, etc). The Software Development Kit sends the date and time of when the specific value of the variable has been registered
An identity server	To facilitate the creation and configuration of all of these services, both in the validation of credentials or tokens, as well as in the delegation and federation of the credentials

Discussion

This experience illustrates that an accreditation model is a key structural element of the prescription and data integration process. It must be conceived in a highly dynamic fashion, open to feedback from the agents concerned and adaptable to technological changes, plus the concerns of both app developers and patients. The multiplicity of actors related to social and health care assistance and the recent increase in devices connected to apps highlight the need for the process described to be dynamic and modular, in spite of its complexity. The certification of glucometers, for example, has become an important practice that has led to new challenges. In the same way, due to the interoperability framework, the proposed solution is an excellent starting point for a path that is gradually becoming defined; it is necessary to both expand the commonly controlled vocabulary in mobile technology (allowing developers to code according to international standards) and guarantee a communication protocol for mobile technologies regulated by an official body to face the contradiction of building local interoperability solutions to global products. The project's feasibility was recently confirmed in a pilot study lasting 5 months, conducted with 4 Primary Care Teams belonging to the Catalan public health system [14]. Further investigation needs to be addressed to record these first-stage experiences in the mHealth public prescription field.

The results obtained demonstrate the success of the AppSalut Site; the project has evolved in keeping with changes in the technological and social paradigm and responds very

satisfactorily to the needs posed by the analysis undertaken by the Catalan government's Ministry of Health and its Ministry of Labour, Social Affairs and Families in their Strategic Mobility Plan. It can be seen as a landmark experience in mobile strategies in the fields of health and welfare of any public health system. The experience has shown itself to be feasible in organizational terms, necessary in any attempt to integrate mobile technologies into public health practice, and a global pioneer in the field.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

App classification, by level.

[PDF File (Adobe PDF File), 22KB - resprot_v7i12e11414_app1.pdf]

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Abbreviations

DHP: Digital Health Platform
FHIR: Fast Healthcare Interoperability Resources

HL7: Health Level 7
mHealth: mobile health
REST: Representational State Transfer
SMS: short message service
SNOMED-CT: Systematized Nomenclature of Medicine–Clinical Terms

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Protocol

Benefits of Elective Para-Aortic Radiotherapy for pN1 Prostate Cancer Using Arc Therapy (Intensity-Modulated or Volumetric Modulated Arc Therapy): Protocol for a Nonrandomized Phase II Trial

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Abstract

Background: In patients with prostate cancer (PCa) with histopathologically proven pelvic lymph node (LN) metastasis (pN1) after extended pelvic lymph node dissection (ePLND), multimodality treatment consisting of treatment of the primary tumor and whole pelvic radiotherapy (WPRT) combined with androgen deprivation therapy (ADT) offers promising results, leading to better cause-specific survival rates compared with ADT alone. However, in case more than one pelvic LN is invaded by the tumor, approximately 40% of the patients relapse biochemically and clinically. Clinical relapse is present in the para-aortic LNs (M1a disease) in up to 77% of the relapsing cases.

Objective: We hypothesize that, based on the evidence that positive LNs represent the door to hematogenous dissemination, elective para-aortic irradiation will reduce the development of both retroperitoneal nodal (M1a) and distant metastasis (M1b or M1c disease), postpone the need for palliative ADT, and prolong the time to castration-refractory disease.

Methods: To test this hypothesis, we will conduct a prospective, nonrandomized phase II trial to study the efficacy of additional elective para-aortic radiotherapy (PART) in pN1 patients compared with those who were historically treated with adjuvant WPRT alone. We aim to include 137 patients with PCa and presence of pN1 disease after ePLND. With this number of patients, an improvement of 15% in the 5-year clinical relapse-free survival can be detected with a power of 80%.

Results: Recruitment of patients for this trial started in 2017 and will be completed approximately by March 2020.

Conclusions: This is the first phase II trial to investigate the benefits of an elective PART in patients with PCa. The results of this trial will potentially serve as a sound base for a later randomized phase III trial. All participants are given a PART information sheet and required to give written informed consent. Results are expected to be published in a peer-reviewed journal.

Trial Registration: ClinicalTrials.gov NCT03079323; https://clinicaltrials.gov/ct2/show/NCT03079323 (Archived by WebCite at http://www.webcitation.org/73ELimv1d)

International Registered Report Identifier (IRRID): PRR1-10.2196/11256

(JMIR Res Protoc 2018;7(12):e11256) doi:10.2196/11256

KEYWORDS

elective para-aortic radiotherapy; external beam radiotherapy; PART trial; prostate cancer

Introduction

Prostate cancer (PCa) is the most common nonskin malignancy and an important cause of cancer-related mortality in men in industrialized countries worldwide [1,2]. Mortality is highest in patients with high-risk PCa, defined by the guidelines of the European Association of Urology (EAU) as T-stage ≥cT2c or Gleason score ≥8 or prostate-specific antigen (PSA) >20 ng/mL. These patients benefit from aggressive local treatment (surgery with or without adjuvant radiotherapy or primary radiotherapy). To assess the risk of disease spread to pelvic nodes, predictive nomograms are used [3-5], although the EAU guidelines consider an extended pelvic lymph node dissection (ePLND) as a necessity in high-risk patients [6]. Indeed, ePLND has proven to be the most accurate nodal staging procedure and, therefore, remains the gold standard [7] with even a positive effect on PCa mortality, certainly in case of limited nodal disease [8] and negative nodes [9].

Historically, patients with positive pelvic lymph nodes (LNs; N1) were considered metastatic and treated with lifelong palliative androgen deprivation therapy (ADT) only [10]. However, in the 21st century, an important paradigm shift occurred. First, local treatment with curative intent is gaining interest in patients with N1 disease [11]. Hereby, also the extent of ePLND plays a crucial role in predicting cause-specific survival (CSS) as demonstrated by Abdollah et al [12]. Second, large retrospective series demonstrated an improvement in prostate cancer-specific survival (PCSS) when postoperative radiotherapy was added to ADT in pathologically node-positive (pN1) patients [13-15].

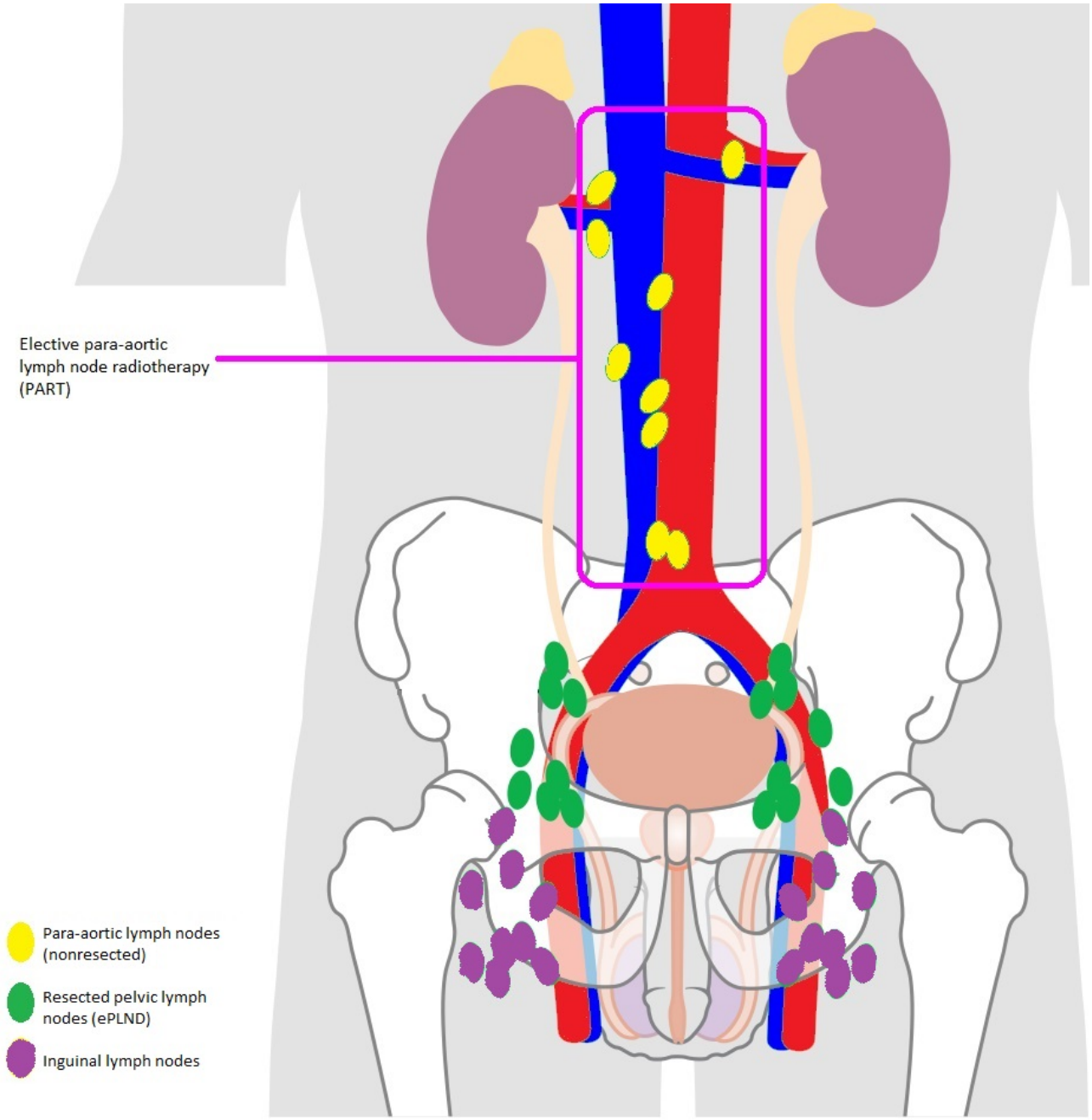
In the multidisciplinary approach for pN1 patients, multimodality treatment consisting of treatment of the primary tumor, long-term ADT, and whole pelvic radiotherapy (WPRT) has become the standard of care at the Leuven University Hospitals (LUH; Leuven, Belgium) and at the Ghent University Hospital (GUH; Ghent, Belgium). WPRT is delivered using intensity-modulated or volumetric modulated arc therapy (IMAT/VMAT) [16,17]. Clinical results demonstrated that this multimodality treatment is well tolerated and results in 5-year PCSS of >90%, with the best results observed in patients having a low number of positive LNs. Indeed, patients presenting with 1 or 2 positive LNs had a 5-year PCSS comparable to that of pN0 patients [18-20].

The number of pathologically metastatic LNs is a determinant for patient outcome. In case >2 LNs are pathologically invaded by the tumor, 30%-40% of the patients relapse biochemically and clinically [21,22]. Furthermore, some data suggest that extracapsular extension of pelvic nodal metastases is an important negative prognostic factor in pN1 patients [23].

Reportedly, clinical relapse (cR) is present in the para-aortic LNs (PALN, M1a disease) in up to 77% of the cases [24,25]. Rischke et al demonstrated the retroperitoneum to be the most frequent site of relapse after pelvic salvage treatment [26]. In the TNM classification, patients with positive PALN are denominated M1a disease and considered as a separate entity [27]. We hypothesize that these positive PALNs will lead to further hematogenous spread (M1b-M1c disease [27]) and that elective para-aortic irradiation will decrease the rate of further metastatic spread, postpone the need for palliative ADT, and prolong the time to castration-refractory disease. To test this hypothesis, we designed a prospective, nonrandomized phase II trial to evaluate the efficacy of elective para-aortic radiotherapy (PART) in pN1 patients compared with those who were historically treated with adjuvant WPRT alone (Figure 1).

This trial is novel and unique as it is the first to investigate the irradiation of the PALN region in pN1 patients with PCa to prevent further metastasis. This strategy has already been evaluated in advanced cervical cancer, but to the best of our knowledge, never in patients with PCa.

Figure 1. Graphic presentation of the study hypothesis.



Methods

Study Design

The PART trial is a nonrandomized phase II trial that was approved by the Medical Ethical Committee of the LUH (EC number: B 3222 0163 0604) and is written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines. Patients are recruited during the multidisciplinary consultation Urology-Radiation Oncology and at the Department of Radiation Oncology of the LUH, GUH, and other participating centers. After giving informed consent, they are included in the trial.

Inclusion and Exclusion Criteria

Men aged >18 years with histologically proven adenocarcinoma of the prostate at biopsy (cT1-4) who are referred for primary high-dose radiotherapy or patients after radical prostatectomy (RP; pT2-4) with presence of pN1 disease after ePLND are eligible for the study. pN1 disease is defined as the presence of regional LN metastasis in the true pelvis. These regions include the common iliac nodes, presacral nodes, external and internal iliac nodes, and obturator nodes [27]. In all participating centers, performing an ePLND is the standard of care in high-intermediate and high-risk patients, independent of whether the primary treatment is RP or high-dose radiotherapy [7,28]. If pN1 disease is present, patients are eligible if one of the following criteria is fulfilled:

1. Two or more positive LNs

2. Positive LNs/removed LNs >7%
3. Presence of extracapsular metastatic extension at the level of any LN

ePLND is defined as the removal of LNs around the external and internal iliac vessels and in the obturator fossa. Removal of additional LNs in the presacral area or around the common iliac vessels is at the discretion of the treating physician (but strongly advised if present on preoperative imaging). The minimum harvest of removed LNs that is considered representative is set at 14. Textbox 1 summarizes the inclusion and exclusion criteria.

After amending, patients with pN1 disease in the salvage setting will be allowed in the PART trial and will be prospectively followed with the same treatment protocol and study design to obtain data about acute and late toxicity. These data will be analyzed separately and will not interfere with the initial set-up of statistics.

Radiotherapy: Structure Delineation, Planning and Delivery

Structure Delineation

Details on delineation of the clinical target volume (CTV) of the pelvic nodal areas are provided elsewhere [29]. Briefly, the elective LN areas consisted of the obturator, internal and external iliac, presacral, and common iliac nodes [16]. Concerning the prostate bed (postoperative setting) and the prostate (primary setting), both T2-weighted magnetic resonance imaging (MRI) and computed tomography (CT) images are used to optimize delineation, as detailed elsewhere [30-32].

Delineation of the PALN starts caudally at the level where the abdominal aorta splits into both common iliac branches and stops cranially at the level of the renal artery and vein. The CTV of the PALN is created by adding a 7-mm 3-dimensional expansion to the abdominal aorta and inferior caval vein, excluding intestinal loops and vertebral bodies. Unless kidney function is impaired, CT imaging is done using intravenous contrast to optimize the visualization of the vessels and improve discrimination with the intestinal loops. The use of oral contrast to better visualize these intestinal loops is left at the discretion of the treating physician. Details concerning protocols on bladder filling and rectal preparation are provided elsewhere [33]. The planned target volume (PTV) of the LNs is created by expanding the CTV with an isotropic margin of 7 mm.

Concerning the organs at risk (OARs), the following structures are delineated: bladder, anal canal, rectum, sigmoid colon, small intestine, large bowel, femoral heads, spinal cord, cauda equine, bone marrow, and kidneys. Figure 2 depicts the delineation of the OARs.

Radiotherapy Planning

The applied planning technology is IMAT/VMAT/RapidArc (Varian Medical Systems, Palo Alto, CA, USA; Elekta, Stockholm, Sweden; Figure 3) [17]. The technology and feasibility to treat the PALN have been published [34].

Textbox 1. Para-aortic radiotherapy (PART) trial: inclusion and exclusion criteria.

Inclusion criteria

- Signed informed consent and willingness to comply with the treatment and follow-up
- Diagnosis of histopathologically confirmed prostate cancer
- No former treatment for prostate cancer, except radical prostatectomy and extended pelvic lymph node dissection (ePLND)
- Presence of pathologically node-positive (pN1) disease after ePLND (criteria of pN1 disease defined in the protocol)
- Age >18 years
- Karnofsky Performance score >70
- Ability to understand the informed consent (Helsinki Declaration)

Exclusion criteria

- Recurrent disease status defined as rising prostate-specific antigen after nadir postoperatively
- Presence of cM1a, cM1b, or cM1c disease [27]; patients with cN1 disease at radiotherapy imaging for planning are excluded
- Former radiotherapy, making whole pelvic radiotherapy (WPRT) or PART impossible
- Prior malignancy, not disease-free >5 years, except basocellular skin epithelioma
- Severe or active comorbidity likely to impact the feasibility of WPRT or PART (eg, ulcerative colitis)
- Disorder precluding the understanding of trial information

Figure 2. Graphic presentation of the delineation: clinical target volume (CTV)-para-aortic lymph node (LN)+CTV pelvic LN: purple; CTV prostate bed: red; bladder: yellow; sigmoid colon, small intestine, and large bowel: green; femoral heads: brown; bone marrow: light blue; kidneys: turquoise; spinal cord and cauda equina: marine blue.

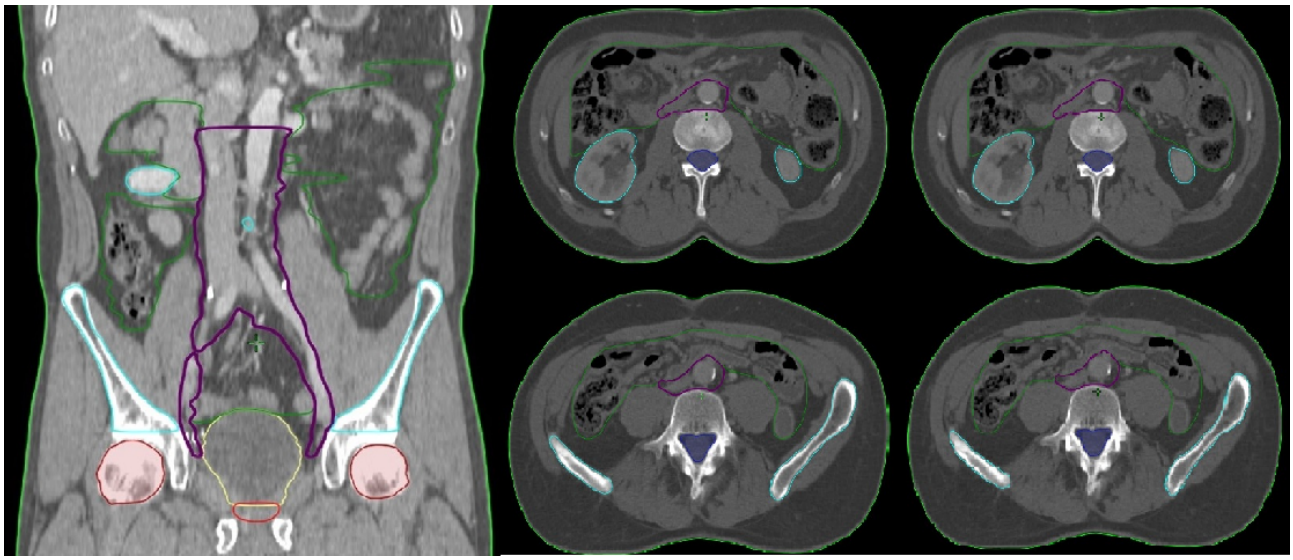
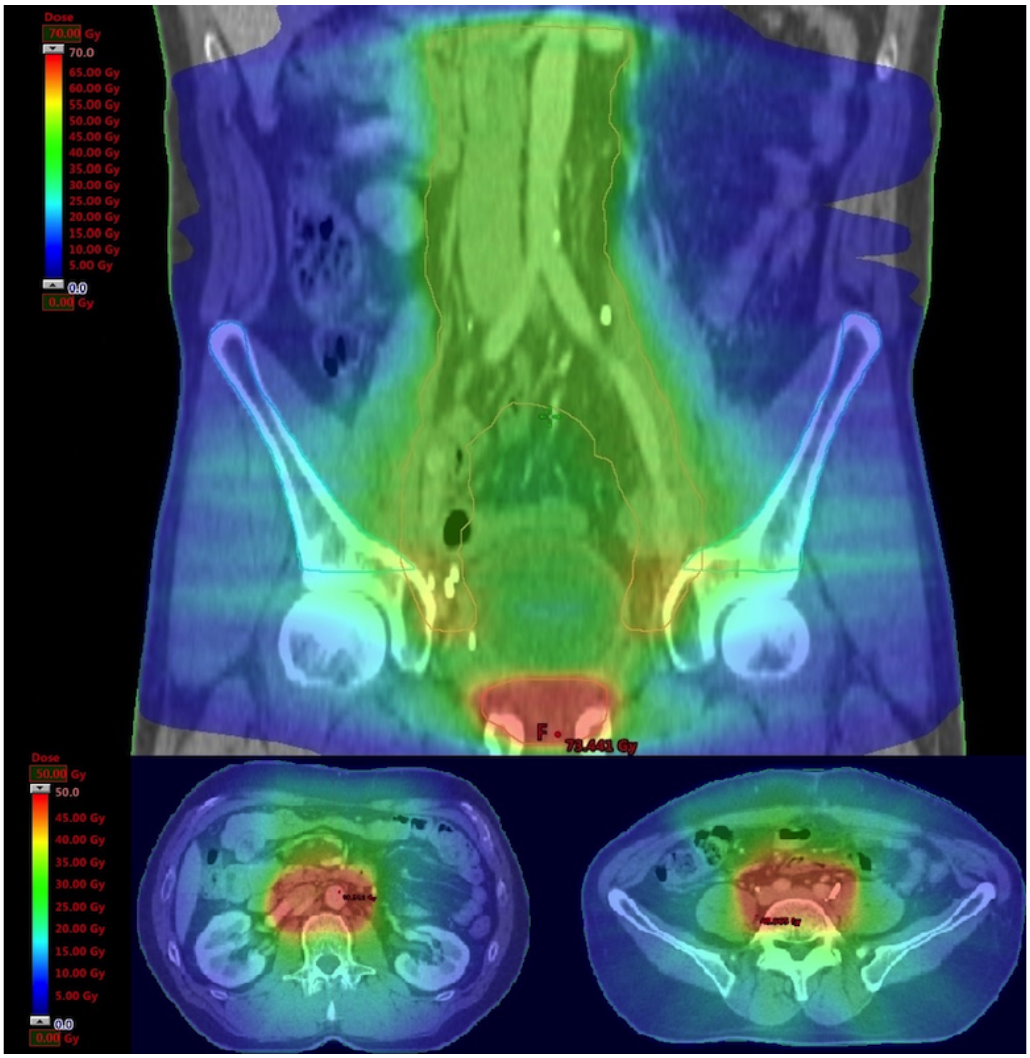


Figure 3. Dose distribution in para-aortic radiotherapy trial. Top: coronal dose distribution (dose range: 0-70 Gy); bottom: transverse dose distribution clinical target volume-para-aortic lymph node (dose range, 0-50 Gy).



Dose Prescription and Treatment Delivery

Dose will be prescribed as D_{98} (ie, the dose received by 98% of the volume and a surrogate for minimal dose) to the PTV of the pelvic LN and PALN. This D_{98} is 45 Gy, to be delivered in 25 fractions of 1.8 Gy. In case of the postprostatectomy situation, the PTV of the prostate and seminal vesicle bed will be treated with a median dose of 70 Gy in 35 fractions. In case of primary radiotherapy to the prostate, the median PTV dose will be 65 Gy in 25 fractions (moderate hypofractionation). Details on dose prescription and constraints for OARs are provided elsewhere [16]. Treatment will be delivered using 6 to 10-MV photons from a linear accelerator (both Elekta and Varian Systems are used). Image-guided radiotherapy is obligatory and will be performed using daily cone-beam CT [35].

Hormonal Treatment

ADT will be started 2-4 weeks before the start of radiotherapy to overcome the androgen receptor-induced radioresistance [36]. The duration of ADT is 24 months (long term) as all patients belong to a very high-risk population and long-term ADT is the standard of care in these patients [37,38]. Of note, both the use of an luteinizing hormone-releasing hormone-analogue and an antagonist is allowed.

Primary Endpoint

The primary endpoint is 5-year clinical relapse-free survival (cRFS), defined as the absence of any cR that would be visible at top of the line imaging (see below). Any detected clinical recurrences (r) would be anatomically mapped and categorized as local (rL), pelvic nodal (rN1), retroperitoneal nodal (rM1a), bone (axial, perpendicular, or both, rM1b), or soft-tissue (rM1c). Combinations of different relapse sites are of course possible and will be reported accordingly. Apart from the anatomical site of relapse, the number of relapses, size per relapse, and the subsequent treatment will be recorded.

PSA measurements are performed during follow-up according to a fixed schedule (Table 1). If PSA is undetectable, patients are considered free of cR. In case of biochemical relapse, defined as PSA >0.2 µg/L in the postprostatectomy setting and PSA >nadir+2 µg/L in the primary setting [39,40]. In addition, positron emission tomography-CT (PET-CT) imaging using prostate-specific membrane antigen ligand or $^{18}F/^{11}C$-choline-based PET-CT imaging is acquired. Additional imaging tools include multiparametric MRI and MRI of the axial and perpendicular bones. The decision to perform additional imaging will be taken after multidisciplinary consensus in all cases.

Table 1. Standard Protocol Items: Recommendations for Interventional Trials 2013 diagram: Para-Aortic Radiotherapy (PART)-trial.

Timepoint	Study period					
	Enrollment: Screen visit & pre-PART ($-t_1$)	Postallocation				
		During PART		Follow-up		
		Weekly	Last day	Month 1, 3, 6, 9, 12	Month 18, 24, 30, 36, 42, 48, 54, 60	Year 6 up to year 10, yearly
Enrollment						
Eligibility screen	X					
Informed consent	X					
Interventions: Elective PART		__[a]				
Assessments						
Clinical examination	X		X	X	X	X
Laboratory analysis[b]	X		X	X	X	X
Registration of pretreatment gastrointestinal and genitourinary morbidities[b]	X					
Registration quality of life using validated questionnaires	X		X	X	X	X
Registration of PART-induced toxicity (Common Toxicity Criteria for adverse events)[b]		X	X	X	X	X
Imaging (after discussion at an interdisciplinary tumor board)	X			X[c]	X[c]	X[c]

[a]Elective PART occurs during the whole period—daily instead of weekly, including the last day.

[b]Standard examinations; laboratory analysis is described in the protocol.

[c]In case of prostate-specific antigen relapse or symptoms.

Secondary Endpoints

Secondary endpoints are quality of life (QoL), treatment-related acute and late toxicity, time to palliative ADT, time to castration-refractory prostate cancer (CRPC), CSS, and in-field pelvic and para-aortic disease control.

The QoL is measured using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire [41]. In addition, the EORTC prostate cancer module [42], the EuroQol 5 dimensions questionnaire [43], the International Consultation on Incontinence Short Form score [44], and the International Index of Erectile Function scoring system [45] are used to assess urinary, bowel, and sexual functioning and symptoms and evaluate the side effects of hormonal treatment associated with radiotherapy. QoL questionnaires are handed over to patients before treatment (baseline score) and at well-defined time points (end of treatment; 1 month, 3 months, 6 months, and 9 months after treatment; every 6 months until 5 years after treatment; and every 12 months until 10 years after treatment). QoL results will be presented in accordance with guidelines for reporting health-related QoL outcomes in cancer clinical trials published by the EORTC [46].

Treatment-related toxicity is assessed using the Common Toxicity Criteria for adverse events version 4.0 (CTCAE v4.0) [47]. Abdominal pain, diarrhea, enterocolitis, fecal incontinence, flatulence, hemorrhoids, proctitis, rectal fistula, rectal hemorrhage, rectal pain, noninfectious cystitis, hematuria, urinary frequency, urinary incontinence, urinary retention, urinary tract pain, erectile dysfunction, and fatigue are scored as adverse events according to CTCAE v4.0. Symptoms are scored before treatment. In addition, PART-induced acute toxicity (CTCAE v4.0) is scored weekly during radiation treatment and 1 month and 3 months after treatment. Furthermore, treatment-induced late toxicity (CTCAE v4.0) is scored at 6, 9, and 12 months after treatment; every 6 months until 5 years after treatment; and every 12 months until 10 years after treatment.

Time to palliative ADT is defined as the secondary endpoint of this trial. Indications to initiate palliative ADT are based on the EAU guidelines [39,40] and include the following: PSA>50 µg/L or PSA doubling time <6 months or symptoms due to progressive disease. In case of oligometastatic recurrence (1-3 synchronous metastases), metastasis-directed therapy is the preferential treatment option [48]. Time to CRPC is defined according to the criteria defined in the EAU guidelines [39,40]. CSS is defined as the interval from the date of diagnosis to the date of death from PCa or to the last follow-up date for censoring purposes, if the patient is alive and is still being followed at the time of data cut-off.

Laboratory Analysis

All laboratory tests are considered standard and include PSA measurement, peripheral blood cell count with formula, kidney function tests, liver function tests, and testosterone measurement. These laboratory tests are done during every follow-up visit.

Time Schedule

The aim is to recruit the necessary number of patients within a timeframe of 48 months. Follow-up of these patients will be lifelong to correctly estimate the primary and secondary endpoints. Reports on acute PART-induced toxicity and QoL will be expected within 6 months of the closure of the trial. Furthermore, the primary endpoint will be calculated after a median follow-up of 60 months.

Safety

This project has been funded by “Kom op tegen Kanker” (study number: S59533). The investigators shall report all serious adverse events (grade 3 or higher) immediately to the sponsor. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers. For reported deaths of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested. Patients will be withdrawn from PART if they develop grade 4 toxicity. Based on former experience in cervical cancer, there is negligible chance for occurrence of grade 4 toxicity when PART is delivered [49].

The investigator shall ensure that all relevant information about suspected unexpected serious adverse reactions that are fatal or life threatening is recorded and reported as soon as possible to the minister, and to the competent ethics committee, and in any case, no later than 7 days after knowledge by the investigator of such a case.

All other suspected unexpected serious adverse reactions shall be reported to the minister and the ethics committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the investigator. Furthermore, the principal investigator shall inform other investigators.

Sample Size and Statistics

We aim to improve 5-year cRFS by 15% (primary endpoint). This would result in a 5-year cRFS of 75% compared with the control group with WPRT only that reaches a 5-year cRFS of 60% [18,20]. For a log-rank test comparing two survival curves with a one-sided significance level of .1, assuming uniform accrual with an accrual time of 48 months and a follow-up time of 12 months, a sample size of 137 is required to obtain a power of at least 80%. Taking into account a dropout of 10%, we aim to include 151 patients. The control group consists of pN1 patients treated with adjuvant ADT and WPRT alone from whom the data have been published before [20]. The incidence of acute and late toxicity will be recorded. In addition, actuarial risk estimates for developing acute and late toxicity will be calculated using Kaplan-Meier analysis. Time to palliative ADT, time to CRPC, CSS, and in-field pelvic and para-aortic disease control will be calculated using Kaplan-Meier actuarial analysis. cRFS, time to CRPC, CSS, and in-field pelvic and para-aortic disease control times are defined from the date of LN dissection until an event or last follow-up. Statistical analysis will be performed using the latest version of SPSS (IBM Corp, Armonk, NY, USA).

Results

Ethical approval to conduct this study (version 2.0 from December 1, 2016) was granted by the Medical Ethics Committee University Hospitals/Catholic University Leuven (14/12/2016). Written informed consent of patients is mandatory before recruitment. Recruitment of patients started in 2017 and is expected to be completed by March 2020.

As a result of the PART trial, we will publish the 5-year cRFS, defined as the absence of any cR that would be visible at top of the line imaging, our primary endpoint. Furthermore, we will compare these results with the 5-year cRFS of a historical control group of patients who underwent WPRT; the results of this historical control group have already been published by Poelaert et al [20]. This control group includes patients with PCa who underwent PLND and pelvic radiotherapy between January 2000 and January 2016 at a tertiary center (GUH). Those patients were rigorously treated by several authors of this manuscript (GDM, VF, KDC, and NL). A total of 154 pN1 patients with PCa who received WPRT were included. As described in the "Sample size and Statistics" section, survival curves of both groups will be compared using log-rank test. Besides, acute toxicity and QoL results will be published after short-term follow-up, whereas treatment-related late toxicity and QoL results, time to palliative ADT, time to CRPC, CSS, and in-field pelvic and para-aortic disease control will be published after a longer follow-up period.

Discussion

Currently, management of pN1 PCa is shifting toward a multimodal approach aiming at cure. Several recent studies have shown an improved CSS when adjuvant radiotherapy was added to ADT [13,20,49-51]. Unfortunately, recurrences are still observed. Data suggest relapse at the site of the PALN due to ascending PCa lymphatic spread from the pelvis up to the retroperitoneum in about 75% cases of LN-only recurrence [24,25]. New strategies to further enhance locoregional control while maintaining an acceptable level of toxicity are a possible tool to improve cure rates as locoregional relapse is linked to metastatic progression [52,53]. The use of extended-field IMRT to the PALN plus concurrent cisplatin in cervical cancer improved the outcome for patients with LN-positive stage IB2-IIIB cervical cancer [54]. Based on the evidence that positive LNs are observed before hematogenous spread occurs, we hypothesize that elective para-aortic irradiation will reduce the development of distant metastasis, postpone the need for palliative ADT, and prolong the time to castration-refractory disease.

This protocol describes the design of a nonrandomized phase II trial to evaluate the clinical effectiveness of elective PART using arc therapy for reducing disease recurrence in pN1 patients with PCa. To the best of our knowledge, this is the first phase II trial investigating the benefit of an elective PART in patients with PCa. The results of this study will hopefully provide a sound basis for a prospective randomized phase III study randomizing patients between WPRT only and WPRT with PALN irradiation.

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Authors' Contributions

CD participated in the data collection. GDM is the principle investigator. GDM and CD completed the ethics application and revisions. GDM, SJ, and VF have been involved in all stages of study design together with LD, NL, WE, PD, LVDB, WC, HV, LVW, KD, PO, PB, KH, and CB.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Funding approval (Kom Op Tegen Kanker / Foundation Against Cancer) based on peer review process (Dutch).

[PDF File (Adobe PDF File), 2MB - resprot_v7i12e11256_app1.pdf]

Multimedia Appendix 2

Funding approval (Kom Op Tegen Kanker / Foundation against Cancer) based on peer review process (English translation).

[PDF File (Adobe PDF File), 33KB - resprot_v7i12e11256_app2.pdf]

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Abbreviations

ADT: androgen deprivation therapy
cR: clinical relapse
cRFS: clinical relapse-free survival
CRPC: castration-refractory prostate cancer
CSS: cause-specific survival
CT: computed tomography
CTCAE: Common Toxicity Criteria for Adverse Events
CTV: clinical target volume
EAU: European Association of Urology
EORTC: European Organization for Research and Treatment of Cancer

ePLND: extended pelvic lymph node dissection
GUH: Ghent University Hospital
IMAT: intensity-modulated arc therapy
LN: lymph node
LUH: Leuven University Hospitals
MRI: magnetic resonance imaging
OARs: organs at risk
PALN: para-aortic lymph node
PART: para-aortic radiotherapy
PCa: prostate cancer
PCSS: prostate cancer-specific survival
PSA: prostate-specific antigen
PTV: planned target volume
QoL: quality of life
RP: radical prostatectomy
VMAT: volume-modulated arc therapy
WPRT: whole pelvic radiotherapy

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Protocol

Investigating Nutrition-Related Complications and Quality of Life in Patients With Gastroenteropancreatic Neuroendocrine Tumors: Protocol for a Mixed-Methods Prospective Study

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Abstract

Background: Gastroenteropancreatic neuroendocrine tumors (GEP NETs) are a heterogeneous group of tumors with distinct effects on the body due to their potential to secrete hormones and peptides. The incidence and prevalence of GEP NETs in Australia are rising. During 2000-2006, the annual incidence was approximately 3.3 per 100,000 population. To date, there has been development of clinical practice and consensus guidelines for NETs covering best practice for diagnosis, treatment, and medical management; however, the supportive care needs and optimal nutritional management of patients affected by NETs remains underresearched, and evidence to guide clinical practice is lacking. While there is emerging research describing the extent of morbidity in different types of GEP NET patients, little is known about the experience of people affected by these tumors and how nutritional status is impacted by either diagnosis or treatment.

Objective: The objective of this study was to explore nutrition-related complications and quality of life of patients diagnosed with a GEP NET and to generate evidence to inform future research and development of nutrition screening and management practices.

Methods: Patients diagnosed with a GEP NET at two metropolitan recruitment sites will be invited to participate in a 6-month, mixed-methods longitudinal study. Participants recruited to the study will receive usual care and participate in data collection for the study at 4 time points (at recruitment and 2, 4, and 6 months postrecruitment). Study data will include nutritional status, body weight, fat-free mass, and patient-reported outcome measures (dietitian contact, disease-related symptom presence and severity, dietary habits, health-related quality of life, psychological morbidity, and financial impact). At recruitment and 6 months postrecruitment, complete nutrient testing, including relevant plasma vitamin levels, will also be undertaken. A purposive sample of participants will be invited to take part in semistructured interviews to explore the experience of living with a GEP NET and associated nutrition complications.

Results: Ethics approval has been obtained, and study recruitment and data collection are underway.

Conclusions: This study will provide the first in-depth, comprehensive description of nutritional issues in patients with GEP NETs. Results will advance the knowledge of nutritional issues faced by patients with GEP NETs and help inform the development of screening tools and clinical practice guidelines.

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KEYWORDS

neuroendocrine tumor; diet, food, and nutrition; malnutrition; diet; vitamins; signs and symptoms; niacin; patient experience

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors most commonly located in the gastrointestinal (GI) tract, lung, and pancreas and are characterized by their propensity to secrete hormones and peptides. Gastroenteropancreatic (GEP) NETs arise in the neuroendocrine cells of the GI tract, most commonly the gastric mucosa, small or large intestine, and pancreas [1]. GEP NETs account for around 60% of all diagnosed cases and are considered a rare and complex disease that requires high-level multidisciplinary consultation and care [2]. GEP NETs have increased in incidence and prevalence over the past two decades. During 2000-2006, the annual incidence of GEP NETs in Australia was estimated to be 3.3 per 100,000 population [3]. In the United States alone, GEP NETs affect approximately 170,000 people, and their prevalence is greater than gastric, pancreatic, esophageal, or hepatobiliary adenocarcinomas [2,4].

Patients with GEP NETs can experience numerous and complex symptoms relating to the tumor mass effect (from the primary site or metastases), generalized symptoms of malignancy, side effects of hormonal hypersecretion, or treatment-related side effects [2,5]. Up to 30% of GEP NET patients, particularly those with tumors located in the small bowel, have carcinoid syndrome whereby their tumors secrete endogenous amine hormones, which can give rise to symptoms including flushing, fatigue, severe diarrhea, food intolerance, restlessness, fluctuations in mood, and pain [1,5]. GEP NET-related symptoms may persist for long periods (median 9.2 years) prior to diagnosis and, thus, have potential to substantially impact an individual's quality of life and health care service utilization [6-9]. The potential side effects of the disease and its treatment have been well documented [6,10]. Nevertheless, there is very limited published information on the nutritional impact of this disease and its treatment on patients.

Some studies have demonstrated decreased health-related quality of life (HRQoL) in patients with NETs compared with that in a healthy population [6,11-14]. However, there is a paucity of Australian data and limited information on the relationship between dietary changes, nutritional issues, and HRQoL. In the first global survey that examined the effects of an NET diagnosis on 1928 NET participants, most patients (71%) reported that an NET diagnosis had a substantially negative impact on their personal life, including reduced energy levels and reduced ability to perform household chores. Over half (58%) reported making dietary changes as a result of their NET [8]. To date, only 2 small studies have explored the presence of dietary change in patients diagnosed with an NET, and details on the extent of dietary change among NET patients are yet to be explored [15,16].

There is limited published information on the nutritional impact of GEP NETs. The severity and number of symptoms and side effects arising from carcinoid syndrome and its treatments are likely to have a major impact on a patient's ability to consume an adequate diet and have the potential to lead to inadequate nutrient intake, weight loss, and malnutrition. Malnutrition rates for GI cancers overall are well documented; however, there are limited data or published rates of malnutrition among patients with GEP NETs. There are 2 recent studies that have indicated that as many as 1 in 4 NET patients are malnourished, as assessed using the Malnutrition Universal Screening Tool and Subjective Global Assessment (SGA) tool [17,18]. Malnutrition has substantial negative consequences for cancer patients including increased mortality, poorer quality of life, increased health care costs, and reduced ability to cope with the demands of treatment [19,20].

Research is now emerging on the impact of serotonin-producing NETs, or treatment of NETs with somatostatin analogues, on niacin (vitamin B3) deficiency and risk of pellagra [21,22]. Pellagra is a nutritional deficiency characterized by dermatitis, diarrhea, and mental disturbance, which can lead to death in severe cases if untreated [21,23]. Evidence has indicated that the prevalence of biochemical or subclinical niacin deficiency may be as high as 30%-45%, but only 2 studies so far have reported on this [21,22]. More research is required to understand the relationship between NET tumors and niacin deficiency in order to inform screening practices and potential treatment options. There has also been some indication in the literature that up to 80% of patients with NETs are at risk for fat-soluble vitamin deficiency due to functional symptoms and resulting fat-malabsorption [15,24]; however, these studies were small and limited to cross-sectional data. The relationship between fat-soluble vitamin deficiency, NET diagnosis, and treatment needs further exploration to determine the extent of this risk and whether it needs to be addressed.

Although guidelines have been developed regarding the management of GEP NETs, they focus on the diagnostics and aspects of medical management of the disease but lack evidence-based information regarding nutritional management [1,25]. There is strong evidence to support early and intensive nutrition intervention in other GI cancers [19,26]; however, nutrition research to date has not focused on NETs. This reflects their rarity, heterogeneous nature, and the complex specialist care they require.

This study aims to provide detailed information on the nutritional impact of NETs on people affected by these complex tumors. Study findings will generate evidence to inform future research focused on the development of a nutrition screening and intervention program. The main objective of this study is to describe issues related to nutrition and HRQoL during diagnosis and treatment of a GEP NET including the following: (1) the prevalence of objectively assessed malnutrition and vitamin deficiencies and (2) the prevalence and severity of patient-reported physical symptoms, anxiety and depressive

symptomatology, financial burden, and patient-reported dietary habits.

Methods

Methodology

This mixed-methods, prospective longitudinal study will be performed at 2 metropolitan sites in Melbourne, Australia. The study will be conducted by staff at Peter MacCallum Cancer Centre and the University of Melbourne, Australia. Ethics approval has been obtained from the Peter MacCallum Cancer Centre Human Research Ethics Committee (EC00235) on April 20, 2017; the study will be conducted according to the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research 2007 (and updates) and the World Medical Association Declaration of Helsinki 2013. The study is being undertaken in part-fulfillment of a PhD at the University of Melbourne.

Study Population

Patients attending their initial appointment at upper GI and NET clinics at participating sites will be approached to participate in the study. Eligible patients will be identified through screening of clinic lists and discussion with the NET multidisciplinary team at recruitment sites. Eligible participants will be those with a confirmed diagnosis of GEP NET, aged ≥18 years, receiving treatment or medical care at the recruitment site, able to communicate in English independently or having an interpreter present, and medically fit to participate (as per self or clinician report). Patients will be eligible for recruitment if they are within 6 weeks of their initial clinic visit because decisions regarding diagnosis and treatment that impact their eligibility are often made within that period. Patients will be ineligible if their NET is under observation only and they are, therefore, not required to attend regular appointments or if their care is transferred to another hospital not involved in the study. Both recruitment and data collection will occur in the outpatient setting when participants are attending for usual care. As this study is being undertaken as part of a PhD, the same researcher (PhD candidate) will perform recruitment and data collection at both participating sites.

Participation will involve a 6-month data collection period from the time of recruitment, and data will be collected at 4 time points: recruitment or baseline (T0), 2 months postrecruitment (T2), 4 months postrecruitment (T4), and 6 months postrecruitment (T6; Multimedia Appendix 1 and Figure 1). If participants are admitted to an inpatient ward during their participation in the study, they will remain in the study unless deemed too unwell to do so by the coordinating principal investigator and their treating medical practitioner.

Patient and Treatment Characteristics

Participant demographics will be collected from the medical records at baseline including age (in years), sex, ethnicity, date of diagnosis, tumor site, tumor grade and classification, treatment received (currently or previously received), and comorbidities present. Participants will be classified into categories based on demographic, disease, and treatment measures collected from the medical history (Textbox 1). Further patient-reported information will be collected at baseline using a customized self-report questionnaire including marital status, education level, employment status, and length of time experiencing symptoms prior to baseline. In this questionnaire, information on any previous nutrition- or diet-related diagnosis (eg, irritable bowel syndrome, food intolerance or allergy, diabetes, and inflammatory disease) will also be collected as presence of these conditions has the potential to confound results.

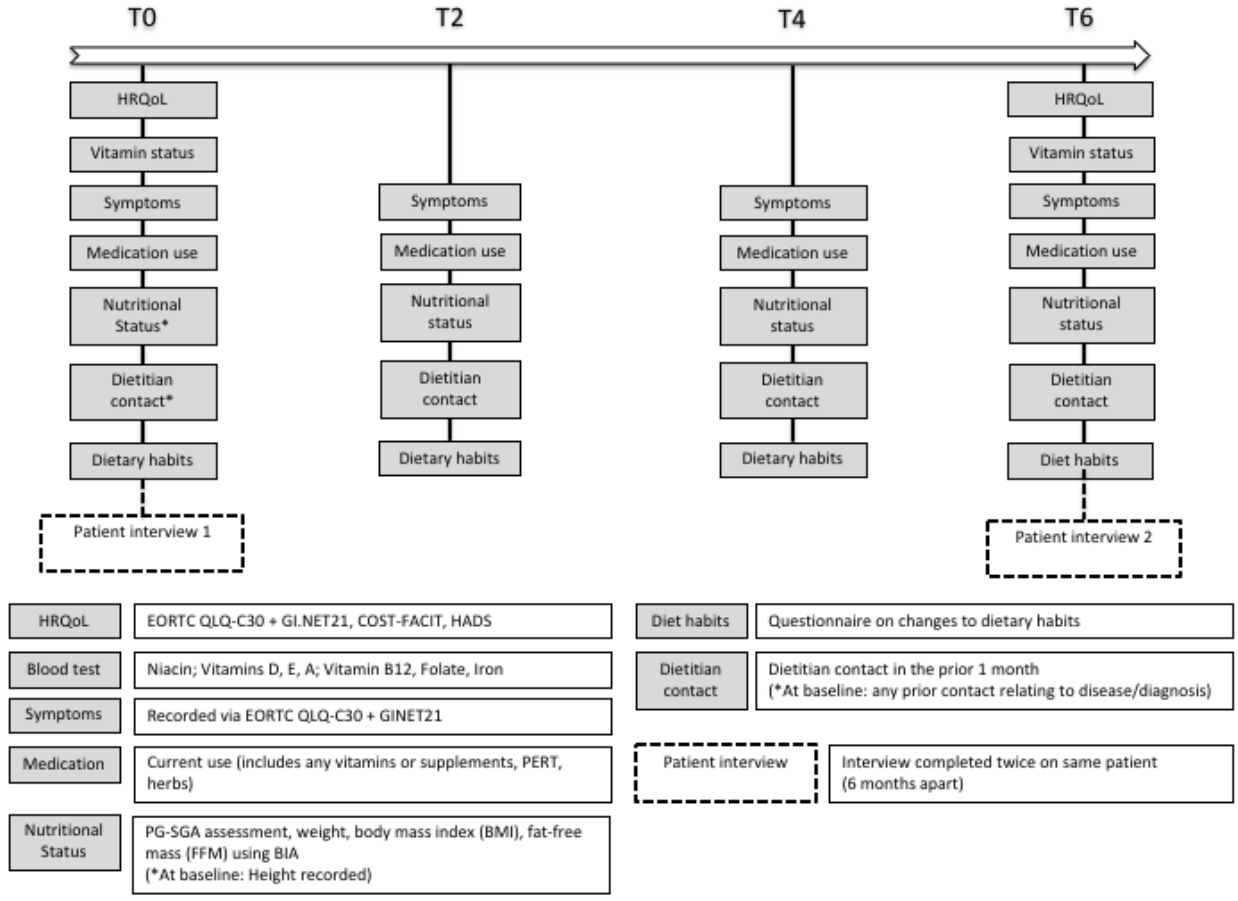
Assessments and Data Collection

Health-Related Quality of Life and Symptoms

Participants will complete the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and the NET-specific EORTC QLQ module GI.NET21 at all time points (T0, T2, T4, and T6) to determine HRQoL symptom prevalence and severity. The EORTC QLQ-C30 is a 30-item questionnaire composed of multi-item scales and single items, including 5 functional scales, 3 symptom scales, and 1 global health and quality of life scale [27]. The EORTC QLQ module GI.NET21 is designed to supplement completion of the QLQ-C30 and contains a total of 21-items, including a combination of single-item assessments and scales. The combined tools contain 51 items, the majority of which have a response format regarding the past week [27]. The combined EORTC QLQ-C30 and QLQ module GI.NET21 has been validated to assess quality of life and symptoms in patients with NETs [27]. Symptom severity is measured using a 4-point Likert scale (not at all, a little, quite a bit, and very much). Symptom prevalence and severity will be calculated using scores from the 3 symptom scales of the EORTC QLQ-C30 and 3 of the symptom scales (endocrine function, GI symptoms, and treatment-related symptoms) in the GI.NET21.

At T0 and T6, participants will also complete the Comprehensive Score for Financial Toxicity - Functional Assessment of Chronic Illness Therapy (COST-FACIT) to measure financial burden and the Hospital and Anxiety Depression Scale (HADS) to measure the presence of anxiety and depression. The COST-FACIT (version 1) contains 11-items and is one of the only available patient-reported outcome measures that describe the financial burden experienced by patients [28]. The HADS is a valid and reliable 14-item questionnaire with a self-rating 4-point Likert scale that assesses symptom severity and caseness of anxiety disorders and depression and is validated for use with adult cancer patients [29,30]. Scores from the HADS are divided into 2 subscales: depression (HADS-D) and anxiety (HADS-A), which are calculated by summation, with increasing scores indicating an increasing burden of depression and anxiety [29]. If at any stage, a participant reports elevated levels of distress or reports a score of 13 or above on the anxiety and depression subscales of the HADS, with their permission, this information will be shared with the treating team, and a referral to psychology services will be considered.

Figure 1. Data collection map. HRQoL: health-related quality of life; EORTC QLQ-C30+GI.NET21: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30+module GI.NET21; COST-FACIT: Comprehensive Score for Financial Toxicity - Functional Assessment of Chronic Illness Therapy; HADS: Hospital and Anxiety Depression Scale; PG-SGA: Patient-Generated Subjective Global Assessment; BIA: bioelectrical impedance analysis; PERT: pancreatic enzyme replacement therapy.



Textbox 1. Disease characteristics.

Tumor site

- Small intestine
- Colon
- Pancreas
- Other

Tumor grading (World Health Organization Classification 2010)

- Neuroendocrine tumor G1
- Neuroendocrine tumor G2
- Neuroendocrine carcinoma G3

Tumor classification

- Serotonin-producing gastrinoma
- Insulinoma
- Glucagonoma
- Vasoactive intestinal peptide tumor
- Pancreatic polypeptide tumor
- Somatostatinoma
- Calcitoninoma
- Growth hormone-releasing hormone tumor
- Neurotensinoma
- Adrenocorticotropin hormone-secreting tumor
- Growth hormone-releasing factor tumor
- Parathyroid hormone-related peptide tumor
- Unknown

Nutrient Testing

Participants recruited from the lead study site will be screened twice for nutrient deficiencies, using blood (serum) and urine samples, at T0 and T6. Only the lead study site will participate in nutrient testing due to funding restrictions and the increased cost of transferring samples from multiple sites. Serum samples will be collected from participants at the lead study site pathology department and analyzed for the following: vitamin B12, folate, iron studies, vitamin D, vitamin A, and vitamin E. Vitamin K, a fat-soluble vitamin, was excluded from analysis due to the requirement for analysis at an additional interstate pathology site, which was beyond the scope and budget of this study. Participants will be asked to complete a 24-hour urine sample collection for analysis of niacin status.

Nutritional Status and Anthropometric Measures

Nutritional status will be measured at all time points (T0, T2, T4, and T6) to enable measurement of change over time. Measures of nutritional status will include the following: height (at T0 only), body weight, body mass index (BMI), fat-free mass (FFM; see below) using bioelectrical impedance analysis (BIA) scales, and validated Patient-Generated SGA (PG-SGA) nutrition assessment tool (see below). Means and percent change relative to baseline (T0) will be calculated for each time point.

Fat-Free Mass

FFM will be measured using foot-to-foot BIA, which is a safe measure of body composition and useful to complement weight and BMI data. The heels of the foot are placed on 2 plates and the toes placed on the other 2 plates while the electrical current is carried via the anterior plate, and the voltage drop is measured over the posterior electrode [31,32]. The foot-to-foot technique has been demonstrated to be safe and effective in estimating FFM in cancer patients [31,33]. BIA will be measured on a commercially available device (Tanita Inc, Tokyo, Japan; model TI SC 330S). For each participant, total FFM (kg) will be calculated at each time point, and then, the change in FFM between time points will be calculated. A clinically significant difference in FFM between time points will be defined as 0.5-1.0 kg, which is based on previous studies of cancer patients [34,35].

Patient-Generated Subjective Global Assessment

Nutritional status and the presence of malnutrition will be measured using the nutritional assessment tool, the scored PG-SGA [36,37]. The PG-SGA has been evaluated as suitable for use as an outcome measure in clinical nutrition studies and validated for use in oncology patients [38]. The PG-SGA demonstrates a high degree of interrater reproducibility

(alpha=.64) as well as high sensitivity (98%) and specificity (82%) compared with other validated tools [38].

The scored PG-SGA consists of 2 sections: a history section completed by the patient and a clinician-completed section. Each component of the PG-SGA is assigned a score depending on the impact on nutritional status and a global assessment rating (SGA category). Change in PG-SGA score is more sensitive to subtle changes in nutritional status than in SGA category. The possible global assessment ratings in the PG-SGA are as follows: SGA A (well-nourished), SGA B (suspected or moderate malnutrition), or SGA C (severe malnutrition). Global PG-SGA score will be calculated to enable description of the prevalence of malnutrition. Therefore, participants will be classified into 1 of 2 categories: well-nourished (SGA score A) or malnourished (SGA score B or C).

Dietitian Contact

The contact received from a dietitian will be assessed at T0, T2, T4, and T6. Dietetic interventions received by participants during the study period will be collected from medical records where available. In addition, participants will also complete a 5-item purpose-designed questionnaire regarding contact they have had with a dietitian in the previous month. This questionnaire was created specifically for this study because a validated tool does not exist for these purposes.

Dietary Habits

Dietary habits of participants will be assessed at T0, T2, T4, and T6 to determine whether people diagnosed with an NET make any changes to dietary habits as a result of their disease or treatment. This 5-item questionnaire was developed specifically for the purpose of this study, as to our knowledge, a brief validated tool assessing changes in dietary habits and behaviors of cancer patients does not currently exist.

Medication Use

All medication usage, either prescription or nonprescription, including vitamin supplements and herbal medication will be recorded at T0, T2, T4, and T6.

Patient Interviews

Patient interviews will be carried out at 2 time points (T0 and T6) to gather information from patients about their experience of living with and undergoing treatment for an NET, with a focus on experience regarding nutrition-related complications and dietary change. The interviews will be semistructured. A purposively selected sample of participants who consented to take part in the study will be invited to participate in an interview. A purposive sampling method will be used to ensure a diverse representation of participant experiences as part of the interview data. Where possible, diversity will be achieved with regard to participant demographics, diagnosis, and treatment type. A maximum of 15 interviews will be completed based on evidence that data saturation (where no new themes emerge from interviews) commonly occurs after 10-12 interviews [39]. Data from participant interviews will be audiorecorded and transcribed verbatim. A thematic content analysis approach will be used to analyze interview data, which will be coded by the coordinating principal investigator and a cross-section of interviews cross-coded by supervisors to check the interrater reliability of themes identified.

Sample Size

The sample size will be pragmatic and determined by the combined number of patients attending the upper GI and NET clinics at the 2 participating sites. A minimum recruitment target of 80 patients, over 12 months, is based on an average minimum of 110 patients diagnosed with NETs across both participating sites. Recruitment estimates were based on the recruitment activity of a research project, with similar inclusion criteria, currently running at the lead participating site.

Using the approach described by Barlett et al [40], the margin of error for estimates of means based on EORTC QLQ-C30 and GI.NET21 data range from 2.2% to 8.8% of the scale or item ranges. These calculations assumed a sample of 80 patients, an alpha level of .05, a possible range of 100 points for each scale or item, and population SDs ranging from 10 to 40 [41,42]. For binary outcomes like PG-SGA classifications (ie, well-nourished vs malnourished), 80 subjects will yield a 5% margin of error of no greater than 11%.

Statistical Analysis

Descriptive statistics (counts and percentages, means and SDs, or medians and interquartile ranges, as appropriate) will be used to summarize patient demographic and clinical characteristics, including nutritional outcomes (nutritional status and vitamin deficiencies), and responses to patient-reported outcome measures (EORTC QLQ-C30, EORTC QLQ-GI.NET21, COST-FACIT, and HADS) at baseline and follow-up assessments. Descriptive statistics will also be used to summarize medication use and patients' responses to customized items on surveys covering dietitian contact and dietary habits. Descriptive statistics will be used to summarize the characteristics of patients who take part in the semistructured interviews.

Patient-reported outcome measures and customized items will be compared between subgroups of patients defined by nutritional outcomes (eg, malnutrition status as determined by the PG-SGA) and disease- and treatment-related characteristics (eg, disease type and stage) at recruitment and at 6 months postrecruitment using *t* tests or analysis of variance with post hoc testing as required. Evidence-based guidelines for the interpretation of between-groups differences in EORTC QLQ-C30 scores [43] will be used to characterize the size of observed differences on functional scales, symptom scales, and single items. In the absence of evidence-based guidelines for the EORTC QLQ-GI.NET21, the Cohen *d* effect size will be calculated and used to characterize the size of observed differences and interpreted using existing conventions [44]. Specifically, effect sizes will be interpreted as follows: 0.2, small-sized difference; 0.5, medium-sized difference; and 0.8, large-sized difference. Note that in the case of 3 or more subgroups, we will select a reference group, and all effect sizes will be calculated with respect to the reference group. If a nonparametric method is required to compare patient-reported outcomes between subgroups of patients, the bootstrap percentile method will be used to examine the difference of medians [45].

The confidence level of the intervals will be set at 0.95, and the number of bootstrap replications will be set at 10,000. In the case of 3 or more subgroups, we will select a reference group and compare all other subgroups to that reference group. All data will be entered into SPSS Version 23 or higher (Chicago IL, USA), and SPSS will be used for scoring, descriptive analysis, and parametric tests.

Results

Approval from the Peter MacCallum Cancer Centre Human Research Ethics Committee was obtained in April 2017. Study recruitment and data collection are underway.

Discussion

Clinical practice guidelines and consensus guidelines for GEP NETs with regards to best practice for diagnosis, treatment, and medical management are available, but the supportive care needs and optimal nutritional management of patients affected by these unique tumors remain underresearched, and evidence to guide clinical practice is lacking. The pathophysiology of the disease and its treatment can cause distressing symptoms that can have significant effects on vitamin synthesis and absorption, dietary habits, weight change, and appetite; however, evidence of the nature and impact of these complications is scant. Vitamin deficiency (niacin and fat-soluble vitamins) and malnutrition may be prevalent among patients with GEP NET, but there are limited data available to guide tailored screening and intervention programs.

This study will aim to provide the first in-depth, comprehensive description of nutritional issues in patients with GEP NETs and the first Australian data on nutritional complications in patients with GEP NETs. This study is deliberately targeting patients with all types of GEP NETs to enable evaluation and comparison of various disease and treatment types. Results of this study will inform further research approaches targeting specific nutritional complications and at-risk groups, later informing the development of evidence-based nutrition screening, intervention, and management practices in this patient group.

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Authors' Contributions

EL is the coordinating principal investigator and PhD student of this study. MK, NK, and MM are the study supervisors, and MM is a principal investigator on the study. EL drafted the study protocol and manuscript with assistance from MK, NK, MM, and KG. All authors read and revised the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Schedule of data collection.

[PDF File (Adobe PDF File), 44KB - resprot_v7i12e11228_app1.pdf]

Multimedia Appendix 2

Peer-review evidence.

[PDF File (Adobe PDF File), 63KB - resprot_v7i12e11228_app2.pdf]

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Abbreviations

BIA: bioelectrical impedance analysis
BMI: body mass index
COST-FACIT: Comprehensive Score for Financial Toxicity - Functional Assessment of Chronic Illness Therapy
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-GI.NET21: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire module GI.NET21
FFM: fat-free mass
GEP NET: gastroenteropancreatic neuroendocrine tumor
GI: gastrointestinal
HADS: Hospital Anxiety and Depression Scale

HRQoL: health-related quality of life
PG-SGA: Patient-Generated Subjective Global Assessment
SGA: Subjective Global Assessment

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Original Paper

Facilitating Web-Based Collaboration in Evidence Synthesis (TaskExchange): Development and Analysis

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Abstract

Background: The conduct and publication of scientific research are increasingly open and collaborative. There is growing interest in Web-based platforms that can effectively enable global, multidisciplinary scientific teams and foster networks of scientists in areas of shared research interest. Designed to facilitate Web-based collaboration in research evidence synthesis, TaskExchange highlights the potential of these kinds of platforms.

Objective: This paper describes the development, growth, and future of TaskExchange, a Web-based platform facilitating collaboration in research evidence synthesis.

Methods: The original purpose of TaskExchange was to create a platform that connected people who needed help with their Cochrane systematic reviews (rigorous syntheses of health research) with people who had the time and expertise to help. The scope of TaskExchange has now been expanded to include other evidence synthesis tasks, including guideline development. The development of TaskExchange was initially undertaken in 5 agile development phases with substantial user engagement. In each phase, software was iteratively deployed as it was developed and tested, enabling close cycles of development and refinement.

Results: TaskExchange enables users to browse and search tasks and members by keyword or nested filters, post and respond to tasks, sign up to notification emails, and acknowledge the work of TaskExchange members. The pilot platform has been open access since August 2016, has over 2300 members, and has hosted more than 630 tasks, covering a wide range of research synthesis-related tasks. Response rates are consistently over 75%, and user feedback has been positive.

Conclusions: TaskExchange demonstrates the potential for new technologies to support Web-based collaboration in health research. Development of a relatively simple platform for peer-to-peer exchange has provided opportunities for systematic reviewers to get their reviews completed more quickly and provides an effective pathway for people to join the global health evidence community.

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KEYWORDS

review, systematic; intersectoral collaboration; software; internet

Introduction

Background

Peer-to-peer Web-based marketplaces are designed to simply, quickly, and reliably connect people who need a service or product with people who can provide it. Services like Etsy, Airbnb, and Airtasker are already familiar to many people, and others are constantly being developed to cater to different sectors or groups in society [1].

In parallel with these developments, the conduct and publication of scientific research is becoming increasingly open, international, and collaborative [2-4]. For example, in the decade between 1990 and 2000, the proportion of scientific papers that were published by international collaborations doubled to almost 16% [4]. In the same period and subsequently, there have also been substantial developments in Web-based collaboration technologies. As a result, there is growing interest in Web-based platforms that can enable global, multidisciplinary networks of scientists in areas of shared research interest [5]. Platforms like ResearchGate, Academia, and LinkedIn provide professional networking opportunities across and beyond science. Other platforms like Benchling (molecular biology), Kaggle (data science), and nanoHub (nanotechnology) provide access to a range of tools, networks, and resources relevant to specific scientific fields.

TaskExchange [6] is an example of a Web-based collaborative platform in biomedical science. The aim of TaskExchange is to bring together people who need help with their systematic reviews and other forms of research synthesis (task posters) with people who have the time and skills to help (task responders), thereby facilitating efficient production of high-quality, relevant, up-to-date evidence syntheses to inform health policy and practice. From the outset, task posters were envisaged as being leaders and project managers of health evidence projects, while task responders would be altruistic individuals, such as retirees, or people seeking health evidence skills, such as medical students. Task posters are able to offer task responders authorship or acknowledgment in project outputs as well as a monetary reward, as deemed appropriate. This paper describes the rationale for TaskExchange and the processes involved in developing and running the platform. Data are presented to describe the use and effectiveness of the platform to date.

Systematic Reviews and Cochrane

Systematic reviews collate and synthesize evidence from research to support the best possible health care decisions and are a key step in the translation of the results of research into improved health care practice [7,8]. Producing high-quality, relevant systematic reviews and keeping them up to date requires substantial resources, skill, and time [9,10].

Cochrane has been producing systematic reviews for more than 20 years and is a leading producer of systematic reviews of health care research. The Cochrane Database of Systematic Reviews includes more than 7000 systematic reviews, and another 2500 reviews are in development [11]. Cochrane reviews are prepared by author teams who work with 1 of 52 Cochrane review groups responsible for a specific area of health care or policy. Author teams are often international in composition and can include clinicians, consumers, and researchers with a range of experience and skills working together.

Cochrane reviews and other research syntheses increasingly require input from contributors with specialist skills outside the immediate author team. Examples include translation (as Cochrane reviews include research published in multiple languages), specialist methodological input from expert statisticians, and input from health care consumers to ensure the relevance and usefulness of the reviews. Cochrane is committed to enabling diverse and inclusive input into the formulation, production, and dissemination of Cochrane reviews, seeking to ensure they meet global needs for high-quality evidence synthesis.

The increasing recognition of the importance of diverse contributions to the work of Cochrane, combined with growing interest from people to get involved in systematic reviews, led to the development of TaskExchange, a Web-based collaboration platform, to support the conduct and uptake of systematic reviews of health research evidence.

Methods

Platform Goals

The original aim of the development of TaskExchange was to create a platform that connected people who needed help with their Cochrane reviews with people who had the time and expertise to help. The initial concept included three major components:

1. Creation of a directory of experts in elements of the systematic review process.
2. The ability for members to post tasks that described a need they had for help.
3. The ability for members to respond to tasks that were in areas of their interest and skill.

Software Development

The development of TaskExchange consisted of 5 development phases using an agile approach, which included iterative development with frequent releases of new software and close collaboration between the development team and the project team [12]. Each development phase involved a sequential process, as shown in Figure 1. Software was iteratively deployed (made available live to users) as it was developed and tested, enabling close cycles of development and refinement. The platform was built by a software development company (Cogent) using Ruby (a programming language) and Ruby on Rails (a server-side Web application framework written in Ruby) and JavaScript (a programming language) on a server hosted by Heroku (a container-based cloud Platform as a Service). We built simple mechanisms for tracking user numbers, numbers of tasks posted, and response rates to posted tasks using data clips to display the results of structured query language queries on a Heroku database.

Development of TaskExchange

As described above, the development of TaskExchange was undertaken in 5 phases over 2 years. Table 1 describes each phase of development.

Figure 1. Development process.

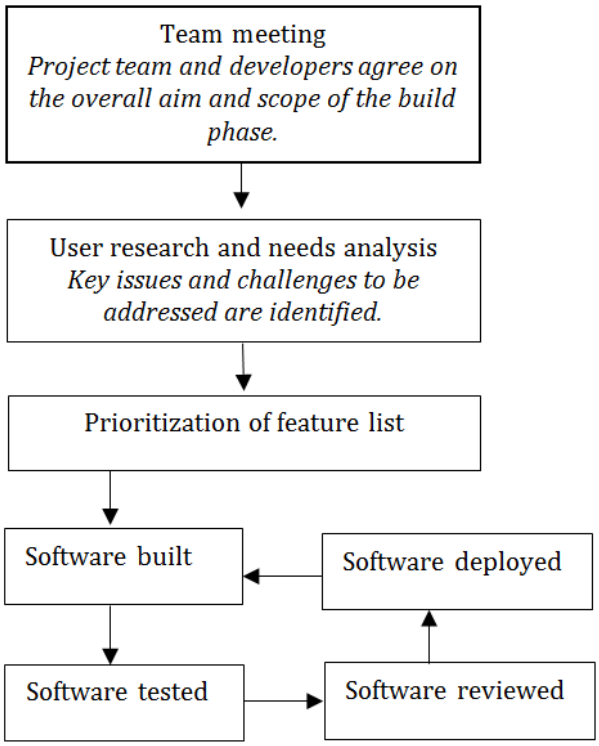

Table 1. Description of TaskExchange development phases.

Phase	Start date	Release date	Purpose	Summary of functions added
1	July 2015	October 2015	Test whether a simple, well-designed Web-based platform could help enable collaboration within the Cochrane community by connecting people who needed help with their review with others who had the time and skills to help.	Minimal functionality, allowed users to create a profile and post and respond to simple tasks.
2	December 2015	February 2016	Refine initial designs and develop a more fully featured prototype.	Improved task classification and addressed issues that had arisen in user testing.
3	April 2016	August 2016	Develop a more user-friendly, open-access platform.	Improved the matching of translation tasks by enabling users to specify required language skills. Improvements made to the way user profiles were created and displayed. TaskExchange opened to the public (it had previously been restricted to people with Cochrane accounts).
4	December 2016	June 2017	Add key features and broaden the scope of TaskExchange.	This phase focused on building features that enable users to endorse people for their skills and acknowledge their work. It also broadened the scope of the tasks within TaskExchange to include those relevant to the development of clinical practice guidelines.
5	January 2018	April 2018	Streamline the use of the platform for users.	This phase focused on creating a new dashboard within the platform for all users, called “My Tasks.” Users can manage all tasks they have posted and respond to within the MyTask tab.

Support and Community Engagement

After the release of the open-access platform (Phase 3 in Table 1), a part-time community engagement and partnerships manager (CEPM) was employed to oversee, implement, evaluate, and refine the Web-based community engagement strategy for the TaskExchange platform. The role aimed to increase user numbers, tasks posted, and tasks matched. We initially focused on building engagement with key brokers within the Cochrane community, including Managing Editors, and also areas where existing informal networks for finding help with systematic reviews were weakest (eg, translation and consumer networks). For each stakeholder group within Cochrane, the CEPM worked

with key champions to design a purposive engagement strategy including tactics such as webinars, articles in newsletters, and blogs and articles for group webpages.

The CEPM also aimed to engage people beyond those already working with Cochrane. Other organizations that focused on producing systematic reviews were engaged using similar tactics as those used with the Cochrane stakeholders. Additionally, social media, in particular, Twitter, was used to engage a broader audience, with strategic use of hashtags and identification of relevant Twitter champions who could help spread the message of TaskExchange. For TaskExchange members, the CEPM provided a point of contact and user support, capturing issues and opportunities for further platform development.

Results

Current Functionality of TaskExchange

The current version of TaskExchange is available on the Web [6]. The site is still in active testing and development. Multimedia Appendix 1 shows key webpages from the TaskExchange platform. Table 2 shows key features of the platform and dates when features were released.

TaskExchange also has administrative functions, including the ability for administrators to edit tasks and view usage data.

Growth of TaskExchange

Between November 2015 and May 2018, TaskExchange hosted 634 tasks and gained 2313 members. Figure 2 shows the monthly growth of tasks and members. Currently, around 40 tasks and 30 users are added per month (data are averages from the 3-month period of March-May 2018). Approximately 50% of TaskExchange members did not have an existing connection to Cochrane before joining TaskExchange.

TaskExchange Users

Table 3 describes TaskExchange users by global distribution, user type (poster vs responder), and skills. As shown in the table, 24.25% (561/2313) of the users are from Europe and a little over 10% (282/2313, 12.19%) are located in Asia. The geographical location of 41.98% (971/2313) of users is unknown, with these users opting not to share that information when signing up to TaskExchange. Only 34.37% (795/2313) of users have actively engaged on TaskExchange: 9.77% (226/2313) as posters, 22.96% (531/2313) as responders, and 1.64% (38/2313) as both posters and responders.

TaskExchange members have a broad array of skills. Members can nominate one or more skills from a predefined list that was compiled following consultation with the intended user community in early platform development. As seen in Table 3, the most common member skills are data extraction (426/2313, 18.42%) and literature screening (366/2313, 15.82%).

Types of Tasks Posted

Table 4 shows the number and types of tasks that have been posted on TaskExchange up to May 2018. Translation accounts for 49.8% (316/634) of all tasks, followed by data extraction (145/634, 22.9%) and application of inclusion or exclusion criteria (122/634, 19.2%).

Table 2. TaskExchange features and release dates.

Feature	Release date
Sign in (by creating a TaskExchange account)	February 2016
Sign in (by creating a Cochrane account)	January 2018
Create a personal profile describing member skills and experience	February 2016
Browse and search tasks using keywords or nested filters	February 2016, subsequently improved
Browse members using keywords or nested filters	February 2016, subsequently improved
Respond to tasks that interest members by sending a message from within TaskExchange	February 2016
Post tasks describing the nature and timelines of the task, the skills required, and reward offered	February 2016
Choose a responder appropriate for the task	February 2016
Unpublish tasks for which a responder has been found	February 2016
Report whether a task responder was found via TaskExchange	February 2016
Sign up to weekly task notification emails	February 2016
Endorse and acknowledge the work of TaskExchange members	June 2017
Manage all tasks posted and responded to from a central place (My Tasks)	April 2018
Report when a task has been completed	April 2018

Figure 2. Number of TaskExchange members and tasks, November 2015-May 2018.

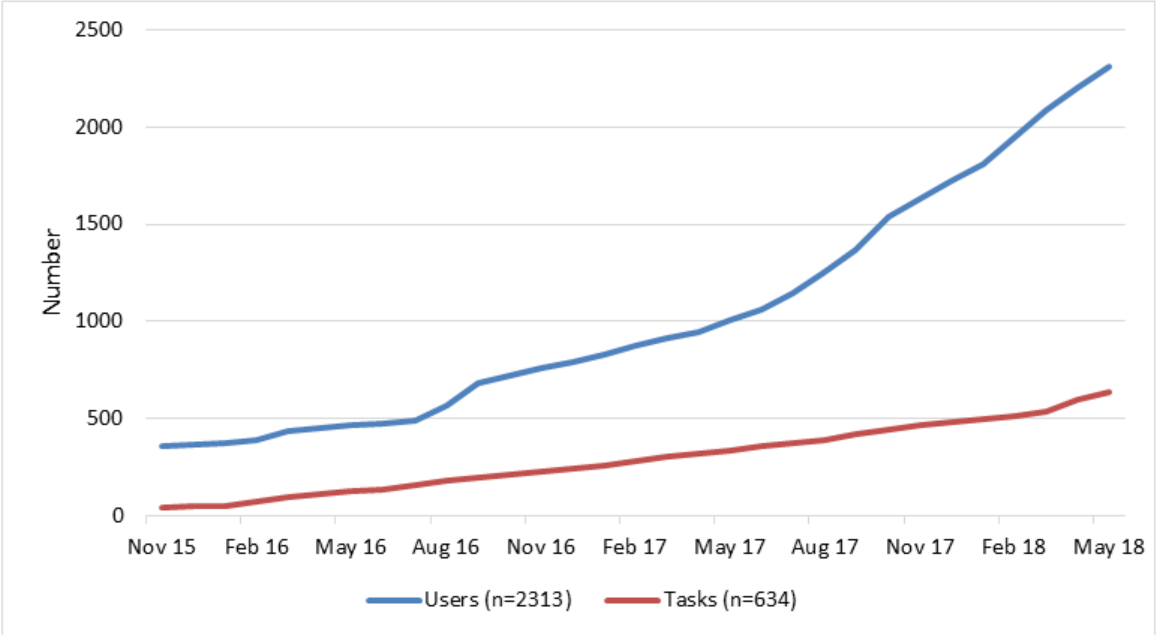

Table 3. Description of TaskExchange users (N=2313).

Descriptive variable	Value, n (%)
Global distribution of users	
Africa	62 (2.68)
Antarctica	0 (0)
Asia	282 (12.19)
Australiana	119 (5.14)
Europe	561 (24.25)
North America	196 (8.47)
South America	122 (5.27)
Unknown	971 (41.98)
User type	
Poster	226 (9.77)
Responder	531 (22.96)
Both	38 (1.64)
Neither	1518 (65.63)
User skills[a]	
Translation	296 (12.80)
Consumer input	72 (3.11)
Data extraction	426 (18.42)
Clinical input	180 (7.78)
Protocol development	258 (11.15)
Qualitative analysis	159 (6.87)
Question formulation	181 (7.83)
Report writing	309 (13.36)
Review	
Clinical content	189 (8.17)
Consumer	56 (2.42)
Knowledge translation	114 (4.93)
Copyedit	174 (7.52)
Methods	204 (8.82)
Prioritization	34 (1.47)
Risk of bias assessment	269 (11.63)
Screening	366 (15.82)
Searching	315 (13.62)
Statistical analysis	217 (9.38)
Summary of findings table	204 (8.82)
Other	10 (0.43)

[a]Users can nominate more than one skill.

Table 4. Type of task posted on TaskExchange and response rate per task type.

Type of task[a]	Total tasks[b], n (%)	Response rate per task type (%)
Translation	316 (49.8)	71
Consumer input	101 (15.9)	49
Data extraction	145 (22.9)	69
Clinical input	36 (5.7)	50
Inclusion or exclusion criteria	122 (19.2)	67
Protocol development	43 (6.8)	77
Qualitative analysis	16 (2.5)	81
Question formulation	26 (4.1)	81
Report writing	30 (4.7)	90
Review		
Clinical content	36 (5.7)	69
Consumer	66 (10.4)	38
Knowledge translation	18 (2.8)	83
Copyedit	17 (2.7)	53
Methods	32 (5.0)	91
Prioritization	1 (0.2)	100
Risk of bias assessment	57 (9.0)	56
Screening	47 (7.4)	70
Searching	41 (6.5)	80
Statistical analysis	30 (4.7)	70
Summary of findings table	25 (3.9)	76
Other	1 (0.2)	100

[a]Tasks can be categorized according to one or more of these categories.

[b]Total number of tasks, N=634.

Table 5. Rewards offered to responders and response rate per reward type.

Type of reward	Total tasks[a], n (%)	Response rate per reward type (%)
Payment	23 (3.6)	65
Authorship	86 (13.6)	72
Acknowledgment	481 (75.9)	63
No reward	79 (12.5)	68

[a]Total number of tasks, N=634.

Table 5 shows the distribution of rewards offered to task responders. Task posters can allocate one or more rewards per task from a set list that includes payment, authorship, and acknowledgment. They may also elect not to offer a reward. Table 5 shows that 75.9% (481/634) of tasks offer acknowledgment to the responder and only 3.6% (23/634) of tasks offer payment to the responder.

Task Responses

The response rate for tasks posted between the middle of August 2016 (when the site became openly accessible) and May 2018 was 78.1% (495/634), that is, 78.1% of tasks posted within that period received at least one response.

Table 4 shows the response rates per task type. Rates vary considerably across type, ranging from 38% (25/66) for consumer review to 100% for review prioritization, although only 1 task of the latter type has been posted. Table 5 shows that response rates vary little with the type of reward offered; 63.0% (303/481) for acknowledgment, 72% (62/86) for authorship, and 68% (54/79) when no reward is offered.

Task Matching and Completion

As with other peer-to-peer marketplaces, collecting accurate data on matching and completion is challenging and relies to some extent on task posters marking tasks as matched or completed. Also, data are difficult to interpret because of

variability in the nature and duration of tasks. For example, some tasks require more than one appropriate responder, and tasks vary in time to complete from as little as 5 minutes to tasks with no natural endpoint (eg, authorship on a Cochrane review that requires an ongoing commitment). We have recently (April 2018) improved the platform's functionality in tracking task matching and completion and look forward to monitoring these metrics going forward.

User Feedback

All development of the platform has been in response to issues or opportunities identified by users, sometimes through formal user research and sometimes through informal feedback.

Most members report successfully posting tasks and getting rapid, useful responses.

> *We used TaskExchange late last year and had a quick and positive response. Four articles were translated within a week for one of our Cochrane Reviews on breast reconstruction. TaskExchange is a great platform to speed up what could otherwise be a laborious process of finding people to help on a review.* [Melina Willson, Managing Editor, Cochrane Breast Cancer Review Group located at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Australia]

Similarly, TaskExchange members, particularly those seeking to build their experience with evidence synthesis, have been very positive about their experiences, often noting that initial small tasks led to more substantive roles.

> *I had started to work on reviews, and I noticed TaskExchange somewhere on the Cochrane webpage when browsing. I saw that an author team wanted help translating a Polish trial article, so I volunteered to do that, and was acknowledged in the publication which was a bonus for my CV. The authors have offered me more translation work, which is fantastic. I'd like to gain more skills in other aspects of reviewing, and I'm planning to seek opportunities through TaskExchange to meet my learning goals. TaskExchange has made it easy to get involved with more SRs and I'd recommend it to anyone wanting more experience.* [Jan Witowski, 4th year medical student from Poland]

Discussion

Principal Findings

This project demonstrates the potential of a Web-based marketplace platform to facilitate collaboration in health evidence synthesis. TaskExchange has been open access since August 2016, has over 2300 members, and has hosted more than 630 tasks covering a wide range of evidence synthesis activities. The task response rate since August 2016 has been 78%. Our focus is now on further building the TaskExchange community.

Connections to Other Work

The development of TaskExchange has occurred at a time when commercial Web-based marketplaces, such as Airtasker, 99designs, and Freelancer, are becoming more common in professional environments. However, while there are some exceptions (eg, Open Science Framework and Science Exchange), the uptake of Web-based marketplace approaches to connect health research professionals has been relatively slow, and studies of their impact are rare [5]. As a result, while there has been a rapid increase in the use of social networks for health research (eg, for participant recruitment or dissemination of health promotion messages) and research about the effectiveness of these approaches [13,14], we know little about how to use peer-to-peer approaches to support and connect researchers themselves.

There is a clear potential benefit in creating an integrated health evidence ecosystem in which health care decision makers, researchers, knowledge brokers, consumers, and others function as part of one closed-loop system [15]. Evidence suggests that involvement in research by clinicians can improve health care delivery and outcomes [16,17]. Platforms like TaskExchange are a useful first step in this direction, providing an easy entry into the research world for people interested in contributing to health research and also a useful portal for health researchers to reach out to other contributors in the broader health research and health care system. This potential to bring the research and nonresearch worlds closer is reflected in the large number of tasks on TaskExchange seeking contributors from consumers.

Limitations

As noted, we have limited data on the use and utility of TaskExchange. The focus on building user features and limited administrative or management features has made sense while we have been operating in a prototyping, "can-it-work?" mode. As we focus more on refining, expanding, and sustaining TaskExchange, we will further build these elements of the system to help us better respond to user needs and understand how the platform can be further developed and improved.

Next Steps

Building on our partnership with the Guidelines International Network, we are also exploring opportunities to expand the use of TaskExchange to other organizations working in health evidence synthesis. Given the similarity of tasks undertaken and the overlap in communities, it seems natural that guideline developers, health technology assessment organizations, and others in similar fields would benefit from TaskExchange. Acknowledging this, TaskExchange has recently been customized and broadened to meet the needs of guideline developers, and further changes are possible in the future.

TaskExchange is also a key element of Cochrane's work to provide pathways for new contributors to join Cochrane. As part of this work, we are looking to build connections between TaskExchange and Cochrane Crowd. Cochrane Crowd is Cochrane's citizen science platform, a global community of volunteers who are helping to curate the research needed to support informed decision-making about health care by, for example, identifying randomized controlled trials for inclusion

in systematic reviews. Cochrane Crowd currently has almost 7000 members who receive training in simple systematic review-related tasks that underpin Cochrane reviews.

TaskExchange provides a natural next step for Crowd participants who wish to further develop their skills and experience. We have recently released a feature that helps new users identify beginner-level tasks within TaskExchange, and we hope in the future to enable Crowd participants to carry their profile over into TaskExchange so that they can demonstrate their track record and experience.

Conclusions

The development of TaskExchange demonstrates the potential for Web-based collaboration to improve the efficiency of and facilitate broader involvement in health research. Through a relatively simple platform, TaskExchange provides opportunities for systematic reviewers and guideline developers to get their work completed more quickly and provides an effective pathway for people to join the health evidence synthesis community.

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Authors' Contributions

TT is a coleader of TaskExchange and is the Project Manager for the platform. TT wrote the first draft of this paper and oversaw paper revisions. ES is the Community Engagement and Partnerships Manager for TaskExchange. ES conducted descriptive analyses and led revisions of this paper. CM and JE are coleaders of TaskExchange and have been involved in the development of the platform since its inception; they contributed crucial feedback to the first and subsequent drafts of this paper. The Project Transform Team is the broader administrative group under which the TaskExchange project has been undertaken. Members of this group are as follows: Project Executive: Julian Elliott (colead), James Thomas (colead), Sally Green, Chris Mavergames, Steve McDonald, Anna Noel-Storr, David Tovey, and Tari Turner. Research Committee: Mike Clarke, Julian Elliott, Paul Glasziou, Sally Green, Chris Mavergames, Steve McDonald, Anna Noel-Storr, James Thomas, David Tovey, and Tari Turner. Project Team: Clive Adams, Lorne Becker, Linn Brandt, Rachel Churchill, Agustin Ciapponi, Gordon Dooley, Ruth Foxlee, Demian Glujovsky, Toby Lasserson, Geraldine Macdonald, Sue Marcus, Rupert McShane, Melissa Murano, Charlotte Pestridge, Daniel Perez Rada, Gabriel Rada, Jacob Riis, Ian Shemilt, Emily Steele, Anneliese Synnot, Chris Watts, Karla Soares-Weiser, and IT Services developers.

Conflicts of Interest

All authors are either employed by, receive funding from, or are associated with Cochrane. However, the results of this research will not benefit the investigators financially or personally. None of the authors have other interests to declare.

Multimedia Appendix 1

Key webpages on the TaskExchange platform.

[PDF File (Adobe PDF File), 128KB - resprot_v7i12e188_app1.pdf]

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Abbreviations

CEPM: community engagement and partnerships manager
NHMRC: National Health and Medical Research Council

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Original Paper

Development of an Internet-Based Cognitive Behavioral Therapy Self-Help Program for Arabic-Speaking Immigrants: Mixed-Methods Study

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Abstract

Background: Recent years have seen an increase in Arabic-speaking immigrants in Sweden and other European countries, with research showing this group to suffer from elevated levels of various forms of psychological disorders. There is a lack of treatment options for immigrants with mild to moderate mental health problems, with barriers including lack of accessible services and concerns that problems will not be understood by health care providers.

Objective: This study aims to describe the process of developing a transdiagnostic internet-based cognitive behavioral therapy self-help program in Arabic for mild to moderate symptoms of common psychological problems such as anxiety, depression, and insomnia.

Methods: The iterative development process, including feedback from 105 pilot users as well as 2 focus groups, is described.

Results: Overall, the modules were rated as acceptable by the pilot users, with overall ratings ranging from 3 to 4 points on average for the respective modules on a 5-point Likert scale. Feedback from the 2 focus groups was overall positive with regard to the content and structure of the program but also included suggestions for improving the Arabic translation as well as the usability of the material.

Conclusions: An internet-based self-help program that is deemed acceptable by an Arabic-speaking audience can be successfully developed, thus providing increased access to psychological help for an at-risk population. However, further research regarding the efficacy of this type of intervention is warranted.

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KEYWORDS

internet; cognitive behavioral therapy; Arabs; focus groups

Introduction

Background

Recent years have seen a sharp increase in Arabic-speaking immigrants in Sweden, with a majority of these arriving from either Syria or Iraq [1]. Research has found that this group suffers from elevated levels of various forms of psychological disorders [2-4], most likely because of both pre- and postmigration factors, such as exposure to armed conflict and trauma in their country of origin, as well as the stress and uncertainty inherent in the asylum-seeking process [5]. Although research on the mental health of Arabic-speaking immigrants in Sweden specifically is scarce, existing studies indicate an increased risk for depression, anxiety, and psychosis compared with the majority population [2].

There is a lack of treatment options for immigrants with mild to moderate mental health problems in Sweden, partly because of an overall low availability of psychotherapy in Swedish

primary care [6], and especially given the fact that many recently arrived immigrants naturally lack proficiency in the Swedish language, restricting access even further [7]. Moreover, previous research has established that immigrant populations tend to underutilize mental health services in relation to the majority population [8], with common barriers including lack of services in their respective language (eg, Arabic), concerns that problems will not be understood by health care professionals because of cultural differences, as well as stigma associated with mental health issues [9]. This was also true in a Swedish study, which found that refugees received more psychiatric inpatient care than the Swedish native population but similar levels of outpatient care, leading the authors to speculate that there were barriers to accessing care for milder forms of psychiatric problems [10].

Internet-delivered cognitive behavioral therapy (ICBT) could be one way to approach some of the issues mentioned above, as internet-delivered treatment can be translated into different languages and has the potential to reach more people than conventionally delivered psychotherapy, requiring less therapist resources [11]. Moreover, it has been hypothesized that internet-delivered treatment could increase treatment seeking for groups with higher mental health stigma by offering increased anonymity and accessibility [12].

Importantly, any treatment is more likely to be effective if it is *culturally adapted* to fit the target audience [13], with cultural adaptation referring to the process of adapting or substituting one or more aspects of a treatment to make it more aligned with the target population's norms and values [14]. Chu and Leino [14] outlined a data-driven framework for the adaptation of psychological interventions, providing common concepts and a taxonomic structure for adapted treatment components. They distinguished between adaptations of peripheral treatment components, referring to engagement and treatment delivery, and core treatment components, referring to adaptations of the actual treatment components themselves [14].

At least two randomized controlled trials have tested culturally adapted ICBT, one targeting depression among Chinese Australians [15] and the other targeting posttraumatic stress disorder among Arabs living in the Middle East [16]. Both trials showed moderate-to-large between-group effects on primary outcome measures. However, both studies tested forms of *therapist-guided* ICBT, that is, ICBT where the patient has access to a therapist that provides weekly support and also answers questions about the treatment material, treatment techniques, as well as the application of those techniques. Therapist-guided ICBT has been shown to be more effective than *self-guided* ICBT, which refers to treatments where there is no therapist contact [17]. However, a recent meta-analysis by Karyotaki et al [18], analyzing data from 3876 participants in trials of self-guided ICBT for depression, revealed a significant between-group effect compared with the control conditions with a between-group effect size of Hedge g=0.27, a small but significant effect, leading the authors to conclude that self-guided ICBT can be considered an evidence-based first-step approach in treating symptoms of depression [18].

Objectives

On the basis of these previous findings, an ICBT self-help program in Arabic aimed at Arabic-speaking refugees and immigrants living in Sweden with mild to moderate mental health problems was developed. This study reports on the process of developing this program.

Methods

Point of Departure

The development of the self-help program was initiated in collaboration with the Swedish Association of Local Authorities and Regions. The core development team involved 4 clinical and research psychologists, a webmaster, and a translator. The Iterapi platform [19] was used to deliver the program. The program was made available in 3 languages: Swedish, English, and Arabic. The focus here will be on the development of the Arabic version of the program. For an overview of the developmental process, see Figure 1.

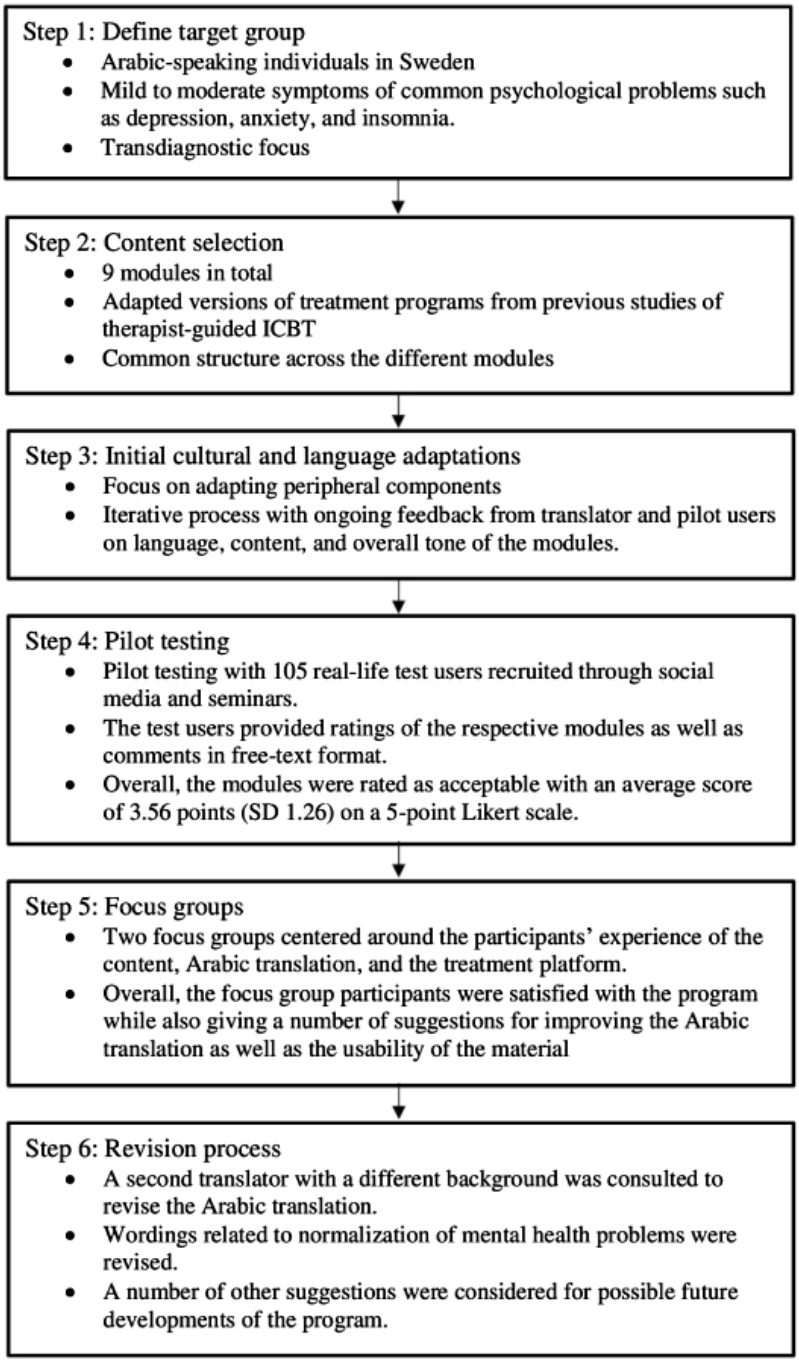
Target Group, Aims, and General Considerations

The target group was Arabic-speaking individuals living in Sweden with mild to moderate symptoms of common psychological problems such as anxiety, depression, stress, and insomnia. The aim was to develop a first-step approach to treating these symptoms in a cost-effective way that would allow for wide dissemination. Hence, a decision was made to develop a self-guided rather than therapist-guided program. In addition, we made the program transdiagnostic, with modules targeting a variety of different expressions of psychological problems, rather than just focusing on a specific disorder. This decision was motivated by previous research indicating that transdiagnostic ICBT programs are equally effective in treating anxiety as disorder-specific programs and possibly more effective in treating depression as well as improving quality of life [20].

Content Selection

It was decided that the program should consist of 9 modules in total: (1) Introduction, (2) Do you feel depressed? (3) Do you have problems with anxiety? (4) Do you have trouble sleeping? (5) Do you feel stressed out? (6) Do you have problems with worrying and rumination? (7) Do you have difficulty managing your emotions? (8) Do you suffer from painful memories? and (9) Final chapter and summary. The first chapter included a general introduction to basic cognitive behavioral therapy (CBT) principles and the last chapter a general summary and strategies for maintaining and continuing positive changes. The contents of the remaining 7 chapters were largely adapted versions of treatment programs from previous studies by our research group (see eg, [21,22]) that were abbreviated and adapted to fit the self-help format, for example, by removing some of the more interactive elements that were deemed to require ongoing therapist support. The basic structure of the modules was similar across the different problem areas, starting with psychoeducation about the problem area, a CBT conceptualization exemplified with a case example, and finally a number of exercises or strategies for handling maladaptive thoughts and behaviors viewed as causing and maintaining the problems.

Figure 1. Flowchart of the steps involved in the developmental process. ICBT: internet-delivered cognitive behavioral therapy.



Cultural and Language Adaptation

The culture and language adaptation consisted of an iterative process, with ongoing feedback from the translator as well as number of pilot users of mixed Arabic origin commenting on the language, content, as well as the overall tone of the modules. The next step involved a total of 105 real-life test users evaluating 133 modules in Arabic through a built-in evaluation function at the end of each module. The users were asked to rate the respective modules on a 5-point Likert scale with regard to whether they found the content understandable, whether it was helpful, and whether they intend to make use of the information and advice in the future. They were also asked to provide an overall rating of the module using the same 5-point Likert scale. It was also possible to provide comments in a free-text format. In addition, 2 focus groups were held, with the aim to provide detailed feedback with regard to how the modules are experienced by the target audience.

The focus groups centered around three main questions:

- How did the participants experience the content and structure of the modules?
- How did the participants experience the Arabic translation?
- How did the participants experience the treatment platform?

The focus group data were analyzed using qualitative content analysis [23], focusing on identifying key themes in the participants' experience of the treatment program.

Importantly, with regard to cultural adaptation, the initial versions of the program focused mainly on the adaptation of peripheral treatment components including language, semantics, as well as the treatment format itself, which was hypothesized to enhance treatment seeking and engagement by increasing anonymity, given that mental health is still highly stigmatized in Arabic culture [24]. With regard to adaptation of core treatment components, the initial versions of the modules contained no adaptations of this kind other than trying to normalize psychological problems in the context of having recently gone through stressful changes and upheavals (such as fleeing one's country of origin) as well as modifying case examples to make them more appropriate for the target audience. One reason for this is the fact that Arabic culture is very diverse across the Arab world [25], making it difficult to adapt the treatment in a way that would be suitable for Arabs originating from different regions of the Arab world. In addition, Hassan et al [26] reported a changing discourse regarding mental health among Syrian refugees more compatible with a Western viewpoint, illustrating the fact that culture is a dynamic phenomenon [27] and thus making it impossible to a priori know to what extent Western psychological treatment models need to be adapted for Arabic immigrants in Sweden, hence the need for a more iterative adaptation process. Along this line, a study by Beshai et al [28] failed to find any differences between depressed Canadians and Egyptians with regard to negative and positive automatic thoughts and dysfunctional attitudes, lending support to the applicability of the cognitive model of depression in an Arab population.

Participants

Test Users

The test users evaluating the Arabic versions of the modules were recruited through advertising through social media platforms and Web search engines. In addition, a number of Web-based seminars aimed at professionals working with recently arrived immigrants were held, aiming to disseminate information about the project. Interested individuals visited the program website where they had to register using an email address and provide a personal password. Once registered, the participants had free access to all the material and were asked to provide ratings as described above at the end of each module. No information was collected about the participants, except for their ratings of the respective modules. The reason for not collecting additional information about the test users was to guarantee their anonymity, as we hypothesized that this would make it significantly easier to recruit test users, given the aforementioned mental health stigma in Arabic culture.

Focus Groups

The participants in the first focus group consisted of, to our knowledge, the only Arabic-speaking clinical psychologist and the only 2 Arabic-speaking psychology students living in the county of Östergötland where the project took place. All 3 participants were female and were aged between 20 and 40 years. All 3 participants were born in Arabic-speaking countries and had immigrated to Sweden as children together with their families. The participants in the second focus group were recruited at the local branch of the Swedish Red Cross language group for recently arrived immigrants. The 6 participants comprised 5 recently arrived Arabic-speaking immigrants from 4 different countries (Sudan, Eritrea, Afghanistan, and Somalia) with varying professional backgrounds as well as 1 librarian with experience of working with Arab immigrants volunteering for the Swedish Red Cross. All 5 immigrants were male, whereas the librarian was female, with the participants aged between 20 and 60 years.

Results

User Evaluations

The results from the 105 real-life test users are summarized in Table 1. Overall, these users rated the modules as acceptable. However, because of the small number of users evaluating some of the modules, it is difficult to evaluate the relative acceptability of the individual modules. With regard to comments by test users in the free-text format, only 21 of the users made use of this function. Of these, 5 users commented on the helpfulness of the program, stating that it was easy to understand or that they preferred this treatment format compared with visiting the doctor. One of these users also asked about the possibility to translate the material into additional languages. Furthermore, 5 other users were more ambiguous or negative in their comments, with 1 user questioning the usefulness of this type of text-based approach. Two others expressed difficulties in applying the material, whereas 1 of the 2 simultaneously expressed gratefulness for an increased theoretical understanding gained from reading the texts. Another user explicitly stated that he or she wanted a quick solution and that the program failed to provide this. The remaining users used the free-text comment section either to ask a specific question regarding their psychological or medical problems or to make more general statements (eg, about mental health), and thus, they did not provide specific feedback on the material per se.

Focus Groups

Overall, three main themes emerged from the analysis of the first focus group, which were as follows: *Word choices in the Arabic translation*, *Computer literacy in target population*, and *Satisfaction with content and structure.* With regard to the first theme, all participants agreed that some parts of the Arabic translation needed revision, as some words were overly academic and therefore might be difficult to understand for nonacademics. They also agreed on other words being primarily used in North African countries and therefore making some paragraphs confusing to Arabs originating from countries in the Middle East. In addition, the participants also pointed out a number of spelling and grammatical errors in need of correction.

Table 1. Mean rating and SD for treatment modules in Arabic.

Module	Did you find content understandable?, mean (SD)	Did you find the material helpful?, mean (SD)	To what degree will you make use of this information?, mean (SD)	Overall rating, mean (SD)	Recommend to a friend, n (%)
Introduction (n=52)	3.67 (1.42)	3.44 (1.42)	3.58 (1.46)	3.5 (1.2)	45 (87)
Do you feel depressed? (n=38)	4 (1.41)	3.61 (1.5)	3.3 (1.56)	3.55 (1.35)	32 (84)
Do you have problems with anxiety? (n=4)	3.5 (1.73)	2.5 (1.73)	2.5 (1.91)	3.25 (1.71)	2 (50)
Do you have trouble sleeping? (n=9)	3.89 (0.92)	4.11 (1.05)	4.33 (0.71)	3.44 (1.51)	7 (78)
Do you feel stressed out? (n=4)	4.5 (0.58)	4.5 (0.58)	4.5 (1)	4 (1.41)	4 (100)
Do you have problems with worrying and rumination? (n=14)	4 (1.3)	3.71 (1.44)	3.64 (1.45)	3.93 (1.27)	12 (86)
Do you have difficulty managing your emotions? (n=5)	3.8 (1.01)	2.8 (1.3)	3.6 (0.89)	3.2 (1.48)	4 (80)
Do you suffer from painful memories? (n=4)	4.75 (0.5)	3.75 (0.5)	3.75 (0.5)	4 (0)	3 (75)
Final chapter and summary (n=2)	4 (1)	2.5 (0.5)	4 (1)	3 (0)	2 (100)
Overall (n=132)	3.88 (1.33)	3.54 (1.4)	3.57 (1.43)	3.56 (1.26)	111 (84.1)

The second theme pertained to whether or not Arabs living in Sweden had sufficient computer literacy skills to make use of the program. This was primarily brought up as a concern by 1 participant who gave the suggestion to have a short video clip on the start page, introducing the user to the Web page and material to make the program more user-friendly. With regard to the third theme, all participants agreed that they were satisfied with the content and structure of the material and saw little need for improvements or revisions.

The analysis of the second focus group resulted in four main themes, which were as follows: *Overall satisfaction with program*, *Enhancing usability*, *Stigmatization of mental health*, and *Additional content*. With regard to the first theme, all participants in the second focus group agreed that the overall structure and content were satisfactory, although they said that the program could be enhanced by making the material more interactive, for example, by adding free-text fields, which users could use to reflect on their own progress with the exercises. The second theme had to do with several suggestions put forward by the participants on how to improve the usability of the program. Similar to the first focus group, they too pointed out several spelling and grammar errors in need of correction to make the texts easier to understand. One participant also recommended having shorter versions of the material for users with less reading experience, whereas another participant suggested that it would be good to have the possibility to have the text read out loud by the program for users with reading or concentration difficulties. The third theme focused on stigmatization of mental health problems in Arabic culture and ways to address and work around this to get more users to actually make use of the program. Relating to this, 1 participant suggested putting more emphasis on biological explanatory models for mental illness as this might be viewed as less stigmatizing than psychological explanations. Another participant suggested putting even more emphasis on normalizing psychological problems and help seeking to reduce stigmatization. A third suggestion from another participant was to have a person with authority in an Arab population, such as a psychiatrist or psychologist with an Arabic background, introduce the material in a short video clip at the opening page, dispelling common myths and misunderstandings about mental health. Overall, there was a concern among the participants that mental health stigmatization would constitute a barrier for many users accessing the program. Finally, the fourth theme had to do with some participants seeing a need for additional content in the program to meet the needs of Arab immigrants in Sweden. One participant suggested we address problems with concentration, perhaps in a separate module. An additional suggestion concerned having more information with regard to good habits when living in Sweden, such as eating vitamin D supplements and the importance of going outside despite the cold weather. Finally, 1 participant also saw a need among many immigrants to address issues relating to shame and guilt concerning culture-specific practices (eg, culture-specific sexual practices and child-rearing practices) that come about when viewing these practices from the lens of Swedish culture.

Revision Process

In response to the feedback received, it was decided that a second translator would be consulted to further review the Arabic translation as this was a theme that was brought up in both focus groups. This translator was herself an immigrant from Syria with an academic background from Damascus, whereas the first translator was born in Sweden and had acquired Arabic as a second language and was currently living in Egypt. With regard to suggestions to increase usability by shortening the material even more, this was decided against, given the potential risk to dilute the content, especially given that the material already consisted of distilled versions of well-researched programs. However, other suggestions relating to this theme, such as having a function that reads the text out loud, were deemed interesting but outside the scope of the current revision process. With regard to the issue of stigmatization as a barrier to accessing the material that was brought forward by the second focus group, we decided to look

over the wordings of the program in relation to normalization of mental health problems. However, in most cases, we decided to stick with the original wording as we did not want to blur the important distinction between clinically significant suffering and normal functioning. Moreover, we also decided not to change the emphasis more to biological explanatory models as we felt that this might risk making the CBT conceptualization less conceptually clear and stringent. Regarding some of the other themes that were brought up in the focus groups, such as adding new content, addressing other problem areas, or using video to introduce the material to make it more user-friendly and possibly reduce stigmatization, we felt that these were interesting ideas for future developments of the program, given their more encompassing nature.

The Final Internet-Based Self-Help Program

The final version of the program was equally accessible on computers and mobile devices such as mobile phones and tablets. To make use of the material, the user had to register using an email address and provide a personal password. No personal information was collected about the user except their ratings of the various modules. The program is currently freely available through the Iterapi platform at Linköping University, as described above, and the plan as of now is to continue to host the program through this platform.

Discussion

Summary of Findings

Overall, it seems that an acceptable internet-based self-help program in Arabic can be successfully developed, based on the results from the focus groups and test user evaluations. With regard to the cultural adaptation of the program, it seems that the relatively modest adaptations made to the material were sufficient to make the program acceptable for the target audience. This might reflect a changing discourse regarding mental health, both in the Middle East and among Arab immigrants, moving from more traditional, religious, or supernatural explanatory models to biological and psychological models more in line with a contemporary Western perspective [26].

Discussion of Results

The 105 test users gave acceptable ratings for the modules, although the sample size was too small to examine the relative acceptability of the different modules. With regard to the comments left by the users in the free-text section, they can be seen as indicative of the fact that this type of intervention will likely be helpful for some but not all individuals, as reflected by the small effect sizes found in previous research [18]. Other individuals will likely need more extensive treatment approaches where more help is provided, for example, with regard to the application of treatment principles.

With regard to the 2 focus groups, although they both agreed on the overall acceptability of this program, they also had a number of suggestions for improving the program. In the end, we chose to mainly focus on one of these suggestions, namely, consulting a second translator to review the wording of Arabic translation, removing or changing words that were overly academic or that are only used in North African countries. However, the participants in the second focus group also came with a number of interesting suggestions on how to further develop the program, which we have considered below under Future Directions.

Limitations

In retrospect, it would have been a good idea to conduct focus groups earlier in the developmental process before deciding on which problem areas to focus on in the different modules. Had we done this, we might have included additional material aimed at concentration difficulties, as suggested in the second focus group. In line with this, it might also have been beneficial to conduct the focus groups and revise the program before testing the program with a group of test users. The reason that we chose the procedure that we did was to first get a sense of the overall acceptability of the program and then, if the program overall was deemed acceptable, get more specific feedback through the focus groups. However, reversing the order would have enabled us to have the test users try out the final version of the program, which would likely have yielded different feedback and also somewhat higher ratings of acceptability.

An additional limitation concerns the lack of information regarding sociodemographic characteristics of the test users. This limits the generalizability of the findings, given that we cannot know for sure whether the test users are representative of the target population. On the other hand, as there was no monetary compensation or other compensation for the test users, it is likely that the individuals who signed up for the program did so because they had some degree of mental health problems that they wanted help with. Furthermore, given that the program will continue to be freely accessible in the same way as during the test period, it is reasonable to assume that the test users are representative of those who might use the program in the future.

A final limitation concerns the fact that online programs such as this one necessarily are limited to those individuals with access to the internet, which is probably not always the case for newly arrived immigrants or refugees. However, it is important to underscore that internet-based self-help programs merely constitute 1 potential pathway for accessing psychological help and should not be used as an excuse to not develop other types of services or treatment formats.

Future Directions

Future directions include working to disseminate the program further, making it widely known to both service providers and potential users so that it is actually put to use. Other possible future directions include going forward with some of the suggestions put forward by the 2 focus groups, such as having voice recordings of the material, integrating the use of video more in the material, and addressing problems with concentration, as mentioned above. Another interesting possibility would be to test the material in a more formalized way in a randomized controlled trial, to evaluate the efficacy of the program in treating mental health problems among the target population.

Conclusions

In conclusion, an acceptable internet-based self-help program in Arabic for mild to moderate symptoms of psychological problems can be successfully developed. However, further research is warranted regarding the efficacy of the program. Future developments of the program should consider making the program more user-friendly by, for example, adding voice recordings of the material as well as adding additional content addressing specific concerns of the target population.

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
ICBT: internet-delivered cognitive behavioral therapy

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Original Paper

App-Based Intervention Combining Evidence-Based Behavior Change Techniques With a Model-Based Reasoning System to Promote Physical Activity Among Young Adults (Active2Gether): Descriptive Study of the Development and Content

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Abstract

Background: The Active2Gether intervention is an app-based intervention designed to help and encourage young adults to become and remain physically active by means of personalized, real-time activity tracking and context-specific feedback.

Objective: The objective of our study was to describe the development and content of the Active2Gether intervention for physical activity promotion.

Methods: A systematic and stepwise approach was used to develop the Active2Gether intervention. This included formulating objectives and a theoretical framework, selecting behavior change techniques, specifying the tailoring, pilot testing, and describing an evaluation protocol.

Results: The development of the Active2Gether intervention comprised seven steps: analyzing the (health) problem, developing a program framework, writing (tailored) messages, developing tailoring assessments, developing the Active2Gether intervention, pilot testing, and testing and evaluating the intervention. The primary objective of the intervention was to increase the total time spent in moderate-vigorous physical activity for those who do not meet the Dutch guideline, maintain physical activity levels of those who meet the guideline, or further increase physical activity levels if they so indicated. The theoretical framework is informed by the social cognitive theory, and insights from other theories and evidence were added for specific topics. Development of the intervention content and communication channel resulted in the development of an app that provides highly tailored coaching messages that are framed in an autonomy-supportive style. These coaching messages include behavior change techniques aiming to address relevant behavioral determinants (eg, self-efficacy and outcome expectations) and are partly context specific. A model-based reasoning engine has been developed to tailor the intervention with respect to the type of support provided by the app, send relevant and context-specific messages to the user, and tailor the graphs displayed in the app. For the input of the tailoring, different instruments and sensors are used, such as an activity monitor (Fitbit One), Web-based and mobile questionnaires, and the location services on the user's mobile phone.

Conclusions: The systematic and stepwise approach resulted in an intervention that is based on theory and input from end users. The use of a model-based reasoning system to provide context-specific coaching messages goes beyond many existing eHealth and mHealth interventions.

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KEYWORDS

physical activity; mHealth; moderate-vigorous physical activity; mobile phones

Introduction

Insufficient physical activity (PA) is a risk factor for avoidable burden of disease [1,2]. About 25% of the adult population worldwide [2] and around 50% in many western countries such as the US and the Netherlands [3] do not meet the recommended guidelines for PA. Moreover, engagement in moderate-vigorous PA (MVPA) decreases with age, in particular when transitioning from adolescence into (young) adulthood [4,5].

In general, health promotion interventions informed by established health behavior theory have been found to be associated with higher effect sizes than interventions not based on theory [6-8]. Research examining the determinants of PA mainly focuses on social cognitive and social ecological factors [9-15]. Social cognitive theories and models, such as the health belief model [16], the theory of planned behavior [17], and the social cognitive model [13], have been developed to explain health behaviors and guide health behavior research and behavior change [18,19]. Although these models mainly focus on intrapersonal and interpersonal factors, social ecological models more explicitly recognize that behavior may also be strongly influenced by contextual factors, such as the sociocultural and physical environments people live in [19-21]; for example, Sallis et al [20] proposed a framework recognizing that individuals are physically active within different domains (eg, recreation, transport, household, and occupation), where different factors on multiple levels influence their overall PA behavior. Thus, interventions that aim to increase levels of PA should not only target intra- and interpersonal factors but also take their physical and social environments into account.

Besides interventions being informed by theory, interventions are more likely to be effective when established behavior change techniques (BCTs) are incorporated [6,8,22]. More specifically, interventions that included a self-monitoring feature in combination with features such as prompting intention formation, specific goal setting, providing feedback on performance, or reviewing behavioral goals were significantly more effective at promoting PA and healthy eating than interventions that did not include these BCTs [8].

Systematic reviews further showed that Information and communications technology (ICT)-supported, individually tailored interventions are superior to generic interventions in promoting PA and user engagement and appreciation [6,23-25]. Moreover, Krebs et al [23] demonstrated that dynamic tailoring (ie, iteratively assessing and providing feedback) was associated with larger effect sizes than static tailoring (ie, all feedback is based on one baseline assessment) [23]. Additionally, Rabbi et al [26] reported promising results when using machine-learning techniques to automatically create contextualized and personalized feedback to increase levels of PA. Modern technology, such as smartphones, smartphone apps, and activity trackers, offer new possibilities in health promotion, especially in young adults, of whom the majority owns a smartphone [27,28]. Furthermore, the rapid growth of the popularity and variety of health and fitness apps and activity trackers suggest that young adults will appreciate and adopt an app-based PA intervention.

Several content analyses have been conducted to identify if and how constructs of behavior change theories and BCTs are incorporated in PA promotion apps. Generally, the apps analyzed were lacking applications of behavior change theories and the use of evidence-based BCTs [29-33]. Moreover, apps mostly provide generic advice or tips about PA; gamification, punishment, and context-aware feedback are rare among PA apps [34]. Only a few apps incorporate some form of adaption to the user [34]. Lastly, existing apps fail to meet the guidelines for PA [35,36]. Despite the fact that health and fitness apps are popular among smartphone users [37,38], recent research indicates that most presently available apps lack the necessary empirical basis to make a meaningful difference in PA promotion [7]. Thus, those apps are less likely to be effective, and room for improvement exists when using an app to promote physical activity. A recently published systematic review examined studies that used apps in interventions to influence health behavior, including PA [39]. The majority of those studies that targeted adults reported significant short-term intervention effects on levels of PA [39]. Furthermore, the majority of the interventions that reported significant changes in behaviors and health-related outcomes included BCTs, such as goal setting, self-monitoring, and feedback on the performance [39].

In summary, innovative ICT-supported mobile technology-based approaches that are evidence based and include dynamic tailoring using intelligent data interpretation techniques may help to effectively support achievement and maintenance of behavior change in the PA domain. However, both the empirical basis and dynamic tailoring are lacking in current apps. Thus, PA apps that incorporate constructs of behavior change theories and BCTs and provide dynamically tailored feedback are needed. Therefore, we developed the Active2Gether intervention that combines mobile (app-based) technology with dynamically tailored feedback and aims to go beyond existing (mobile) PA interventions. The Active2Gether intervention is an app-based intervention designed to help and encourage young adults to become and remain physically active by focusing on the domains of active transport, stair climbing, and sports participation. To do so, participants of the Active2Gether intervention will be categorized into one of the 3 awareness categories (education, coaching, and feedback). Participants in the education category will receive educational messages on the benefits of PA, whereas participants in the feedback category will receive motivational messages to maintain their active lifestyle. Participants who are in the coaching category will be coached on sports participation, taking the stairs, or active transport. Every week, the participants will be asked to choose their coaching domain and to set a weekly goal. Participants will receive a message with a suggestion for a coaching domain and a weekly goal based on their previous behavior, but the final decision will be up to the user. The participants will receive a Fitbit One activity tracker that can be synced to the Active2Gether app and will allow the

participants to monitor their PA behavior through the Active2Gether app. Additionally, participants will receive (daily) coaching messages addressing relevant behavioral determinants. The content of the messages will be tailored to the user's behavioral determinants, occupational status, and weather. Lastly, the intervention offers the opportunity to monitor and compare the behaviors with those of other Active2Gether participants because the app will display the activity data of the participant, including a graph displaying the activity data of 6 other participants, preferably friends. The graph with the activity data of others will rank the participants based on their step activity and the user preferences for social comparison (ie, upward or downward comparison). Taking this preference into account does influence the effectiveness of social comparison as a behavior change technique [40]. The aim of this paper was to describe the systematic development and content of this Active2Gether PA-promotion intervention. The methods section provides a brief overview of the stepwise approach that was used to develop the intervention and a brief description of the target population and the methodology used to develop the intervention. The results section will provide more detailed information on the results of the systematic development and content of the intervention.

Methods

Target Population

The Active2Gether intervention focuses on healthy and highly educated young adults aged 18-30 years who have a suitable smartphone running on Android version 4.0 or higher.

Intervention Development

We used a 7-step systematic approach to develop and evaluate the intervention (Table 1). To ensure that the app was informed by relevant health behavior and health behavior change theory and evidence, the development was guided by the program-planning model developed by Kreuter et al [41]. Some steps were adapted because it felt more logical to the research team, and the order of some steps were changed; for example, creating tailoring algorithms, automating the tailoring process, and developing the communication channel are described in the same step. The 7 steps are further described in the Results sections.

Table 1. Description of the stepwise process for the development of Active2Gether.

Steps	Step description
Step 1: Analyzing the (health) problem	• Describing a theoretical framework on how to promote MVPA[a] • Selecting behavior change techniques based on theory and evidence to address determinants of behavior, based on existing studies and reviews [42,43]; Assessing existing apps (what is available?) [30]; Exploring preferences of end users [44,45]
Step 2: Developing a Program Framework	• Identifying relevant physical activity behaviors to increase MVPA. Defining the main and subobjectives of the intervention • Describing framework components
Step 3: Writing (tailored) messages (the order of this step was changed: Step 5)[b]	• Writing tailored messages
Step 4: Developing tailoring assessments (the order of this step was changed: Step 3)[b]	• Selecting and developing measurements to assess levels of physical activity, behavioral determinants, locations, and connected friends
Step 5: Developing the Active2Gether intervention (steps were merged)[c]	• Designing tailoring algorithms for the reasoning system • Channel of communication: building a Web-based app and system to combine and interpret data and send messages
Step 6: Pilot testing	• Pilot-testing the intervention to detect errors and impracticalities in order to improve the intervention prior to its implementation
Step 7: Testing and evaluating the intervention	• The intervention will be used by a larger group of participants and then analyzed and evaluated with respect to effect, process, and impact

[a]MVPA: moderate-vigorous physical activity.

[b]According to the program-planning model by Kreuter et al [41], the tailored messages should be written in step 5, whereas the tailoring assessments should be developed in step 3.

[c]Creating tailoring algorithms, automating the tailoring process, and developing the communication channel are described in the same step, whereas according to the program-planning model, these are steps 6 and 7, respectively.

Step 1: Analyzing the (Health) Problem

Identifying Determinants of Change and Reviewing Applicable Theories and Models

Because theory-based interventions are associated with higher effect sizes than interventions not based on theory [6,46], defining the theoretical framework for the intervention is necessary. To do so, prominent health behavior theories and scientific literature were reviewed.

Social cognitive theory (SCT) was adopted as a basis for the theoretical framework as it is one of the most prominent behavior change theories used to inform interventions targeting health behavior change [10,47,48], and a recent meta-analysis reported that SCT concepts may explain 31% of variance in PA [10]. SCT addresses both individual and social factors and recognizes the reciprocal relation between individuals and their context or environment. For these reasons, SCT thus guided and informed the intervention's theoretical framework; insights from other theories and evidences were added for specific topics. Figure 1 shows the structural pathways of Bandura's SCT [49], and Figure 2 shows the specific theoretical framework [49] that is used for the Active2Gether intervention. In Figure 2, the bold lines and boxes represent the elements that are based on the Social Cognitive Theory, and the dotted lines and oval boxes represent behavioral determinants added to the theoretical framework.

Selection of Behavior Change Techniques

We first identified evidence-based and relevant BCTs and linked these with the behavioral determinants of the theoretical framework by means of a review of the relevant literature, based on an existing taxonomy of BCTs [42,43]; see Multimedia Appendix 1 [9,22,42,43,50-53]. To explore which BCTs were used in already existing PA promotion apps, a systematic content analysis of such apps available in iTunes and Google Play was conducted [30]. Additionally, focus group discussions with the target population were conducted. The methods and results of these focus groups have been published in more detail elsewhere [45]. Finally, a Web-based cross-sectional survey was conducted among 179 young adults to assess their ratings with respect to the importance of specific BCTs applied in apps and their preferences for personalized tailoring [44].

Figure 1. The structural pathways of Bandura's social cognitive theory.

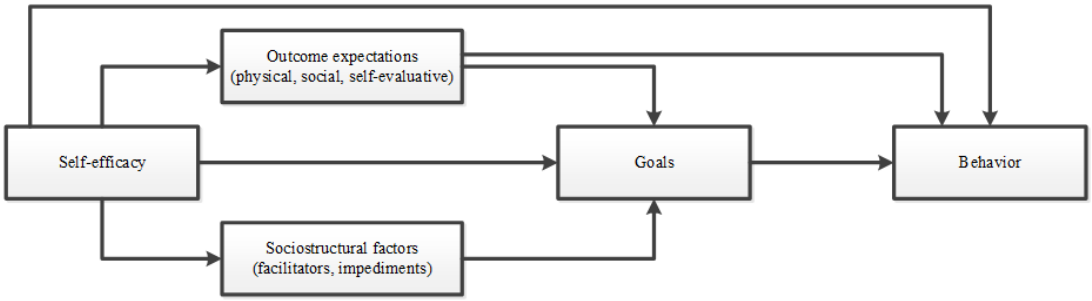
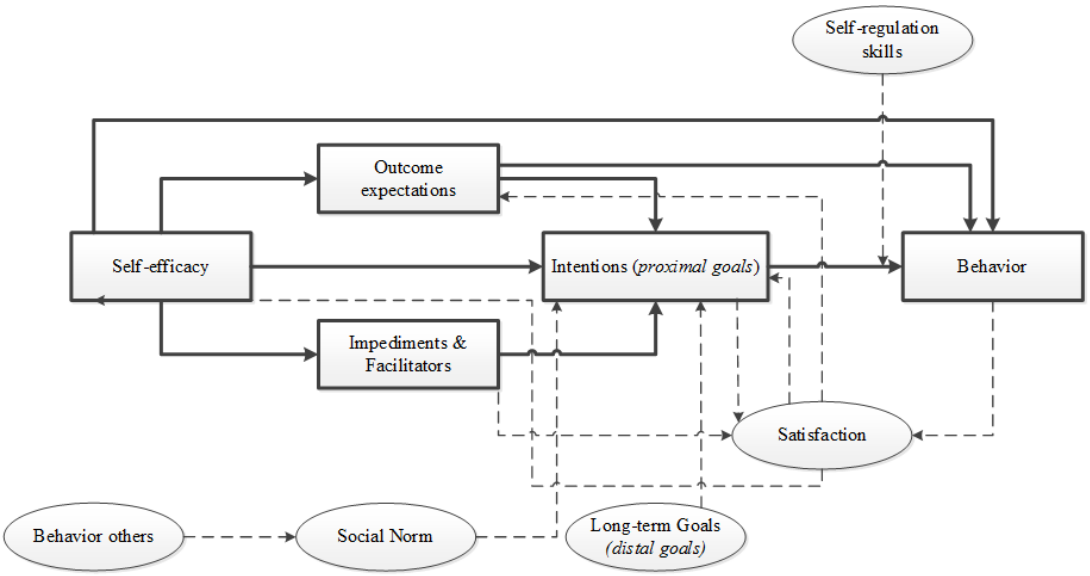


Figure 2. The specific theoretical framework that is used for the Active2Gether intervention.



Step 2: Developing a Program Framework

Defining the Intervention's Primary and Secondary Objectives

The foundation of the intervention is the definition of the program's outcomes and objectives [54,55]. Therefore, specifying who and what will change as a result of the intervention is necessary [54,55]. Intervention objectives were based on the Dutch guidelines for physical activity for adults, which included the following: 30 minutes of moderate PA for at least 5 days a week or 20 minutes of vigorous PA for 3 days a week [56].

Describing Framework Components

Based on steps 1 and 2 and the research team's expertise, a general framework was developed. The aim was to develop a highly tailored intervention that contains a self-monitoring tool, goal setting, social comparison, and motivational and context-specific messages.

Tailoring and personalization of the intervention content is realized in the following 6 ways: determining the personally appropriate type of support (ie, education, coaching, or feedback), selecting the personally relevant and preferred domain of PA for user coaching (ie, sports participation, stair use, or active transport), suggesting a weekly goal, selecting the personally appropriate behavioral determinants for coaching, sending only relevant coaching messages and filtering out nonrelevant messages, and tailoring and personalization of the app content.

Step 3: Writing (Tailored) Messages

Next, we translated the BCTs into actual tailored feedback messages and advice. For each BCT per behavioral determinant (Multimedia Appendix 1), a set of messages was created that was tailored to the three coaching domains (ie, sports participation, active transport, and stair climbing). Consequently, a message library was created that contained feedback and advice messages tailored to all possible levels of the relevant behavioral determinants, as recognized in the underlying theoretical framework.

Creating the message library was an iterative process of brainstorming, writing a set of messages (AM), and providing feedback and suggestions (JM and StV). To test whether the tone of voice and content appealed to the target population, a subset of messages was pilot-tested among 7 people of the target population.

Step 4: Developing Tailoring Assessments

To tailor the messages to the individual users, assessment methods were selected.

Assessment of Activity

First, after considering functionalities, validity, and costs of a range of available activity trackers, the user's activity was monitored using Fitbit One, which includes monitoring of steps and stairs climbed. Fitbit One was chosen because of its functionalities and small size [57]. The activity monitor communicates with the Fitbit app and website that display the collected data for example by showing a color-coded chart indicating the proximity to the step goal, which is set to a default of 10,000 steps per day.

Fitbit allows developers and researchers to access Fitbit data and thus integrate the Fitbit data into health behavior interventions such as Active2Gether. To access Fitbit data, Fitbit offers an application programming interface (API). Fitbit One was validated using smaller time intervals (ie, minutes, hours, and days) relevant for real-time feedback and instant behavioral insights to its users. Healthy young adults (N=34) wore the ActiGraph GT3x+ and a Fitbit One for one week. Detailed information on the methodology can be found elsewhere [58].

Assessment of Behavioral Determinants

Literature was reviewed for relevant, existing, and validated questionnaires to assess behavioral determinants. Behavioral determinants are assessed by means of a questionnaire with both its long and short versions, which were selected based on validations of such questionnaires. The long version is part of an "intake" questionnaire before the actual intervention and as a point of departure for the tailored intervention, whereas the short version is used repeatedly throughout the intervention period to dynamically tailor the intervention content to the user.

Assessment of Location Data

A questionnaire was designed for the purpose of assessing information on significant places. In addition, the Active2Gether app was built in a way that enabled the collection of the user's location data.

Assessment of Connected Friends

To increase the users' engagement, we assessed whether users' friends were also participating in the Active2Gether intervention. Because Facebook is very popular among Dutch young adults—93% of Dutch adults aged 18-24 use Facebook [59]—Facebook was used to find connected friends that were also participating in the study.

Step 5: Developing the Active2Gether Intervention

Creating Tailored Algorithms

To realize such tailored coaching, we developed a system that combines detailed behavior monitoring with intelligent data interpretation and model-based predictions. Thus, by combining data from the different sources, the system enables personalization of the coaching strategies to try to achieve the most positive effect on behavior change. Detailed information on the system and the development of the system can be found elsewhere and is not described in the Results section [60].

Designing and Developing the Communication Channel

We decided that the communication channel of the Active2Gether intervention should be a smartphone app. The app shows the website in a format that is viewable on smaller screens. Thus, the intervention content was accessible through the app or the website. The research team developed the design template of the smartphone app. Information on the development of the app can be found elsewhere [60].

Step 6: Pilot Testing

To detect possible bugs in the system and to assess user friendliness and appreciation, the app was pilot-tested in two steps. First, the Active2Gether team (AM, JSM, Adnan Manzoor Rajper, SJtV, and MCAK) used the initial version of the Active2Gether app. Bugs, nuisances, etc, were monitored, listed, and fixed accordingly when and where possible. Second, 7 people from the target population (5 women, 21-28 years old, all highly educated, or studying at the bachelor's or master's level) were recruited to use the adjusted version of the app, monitor bugs and nuisances, provide feedback in person, and answer a questionnaire regarding use, user friendliness, and appreciation. The app was further adjusted based on that information.

Step 7: Testing and Evaluating the Intervention

The intervention, the Active2Gether app, will be evaluated for its efficacy to change weekly levels of MVPA in young adults and for the usability of the app.

Results

Step 1: Analyzing the (Health) Problem

Identifying Determinants of Change and Reviewing Applicable Theories and Models

As a result of Step 1, a theoretical framework was built based on the relevant scientific literature (please see further details below). The theoretical framework was subsequently used to develop the content of the intervention and predict the PA behavior of the users so that the intervention content could be tailored to each individual user.

Self-efficacy, a key construct within SCT (and in other health behavior theories) [18,49], was adopted as a key construct in Active2Gether. Self-efficacy is defined as someone's beliefs in his or her own capabilities to perform certain actions needed to achieve a desired outcome. Self-efficacy affects PA both directly and indirectly, as seen in Figures 1 and 2. Self-efficacy may influence outcome expectations—one's beliefs about the positive and negative consequences of one's behavior, such as participating in physical activities [18,49]. In other words, people who are more efficacious about being physically active will also be more likely to expect the favorable outcomes of participating in physical activities. [49] Moreover, self-efficacy may also influence how people perceive potential obstacles and impediments [49] and may also influence intentions to engage in PA behaviors [61]. Goal setting was adopted as a second important basis for change, where goals can be either proximal (ie, shorter-term intentions to act) or distal (ie, longer-term goals to achieve something) [49,62]. Distal goals are goals set for the longer term and they set the course for personal change [62]. According to Bandura [49], distal or long-term goals can initiate behavior change but are not sufficient to change behavior directly, as seen in Figure 1. Goal setting is dependent on the levels of self-efficacy and perceived barriers and opportunities. In line with this notion, a meta-analysis inspired by the action-control framework indicated that 48% of the participants who intended to be physically active failed to do so. Therefore, forming intentions is often not sufficient to realize behavior change; self-regulatory and action-control techniques are needed to support behavioral enactment [63]. A further meta-analysis on effective techniques in healthy eating and PA interventions concluded that interventions that offered self-monitoring and addressed self-regulation were more successful in increasing PA than interventions not including those techniques [8]. SCT posits that when individuals adapt and revise their behavior, they may adjust their beliefs and goals regarding this behavior [49]. In our theoretical framework, we therefore included "satisfaction," which is defined as an evaluation of the PA behavior.

In line with SCT, we also recognized that the social environment influences behavior through social norms and that performing certain behaviors can evoke social reactions, both positive and negative [49]. In the Active2Gether intervention, we address not only intrapersonal (eg, lack of motivation and tiredness) and social barriers (eg, lack of support) but also contextual impediments (eg, lack of time, weather and travel distance), as seen in Figure 2. Lastly, it was decided that users will be categorized based on their awareness of their personal PA levels before they will be coached; people who are overly optimistic about their PA levels (ie, who believe they engage in adequate amounts of PA while their data show insufficient levels) will be much less likely to be motivated to increase their PA levels [64].

Selection of Behavior Change Techniques

Content analysis showed that the apps available to date generally lack sufficient incorporation of evidence-based BCTs [30]. BCTs that were applied most often were providing feedback on performance, prompting self-monitoring of behavior, prompting specific goal setting, and planning social support or social change [30]. Additionally, focus group discussions with the target population indicated that participants preferred self-monitoring, goal setting, and a ranking feature but were not willing to share their accomplishments on social media for social comparison and initiating social support [45]. The focus groups further suggested that the Active2Gether app should be highly personalized, have an easy-to-use design and format, include a coaching feature that provides tailored feedback to self-set goals, enable competition with friends by ranking or earning rewards, and include the option to personally customize the application [45]. Finally, a Web-based cross-sectional survey among 179 young adults to assess their ratings with respect to the importance of specific BCTs applied in apps and their preferences for personalized tailoring confirmed the need for a personal coaching feature and showed that BCTs addressing goal setting, goal reviewing, feedback, and self-monitoring were rated as important to be incorporated in an app, whereas social support and social comparison were considered less important [44]. The combined results of the literature review, focus group discussions, and survey guided the selection of BCTs to be included in Active2Gether (Multimedia Appendix 1).

Step 2: Developing a Program Framework

Defining the Intervention's Primary and Secondary Objectives

Step 2 resulted in the decision to make the following the primary objective of the Active2Gether intervention: increase total time spent in MVPA for those who do not meet the Dutch guideline, maintain PA levels of those who meet the guideline, or further increase PA levels if they so indicated. The secondary aims were defined as follows: to increase the underlying specific categories of MVPA (ie, minutes of weekly sports participation, weekly numbers of stairs climbed, and weekly minutes of active transport) and to enhance the underlying determinants of the PA behaviors.

Describing Framework Components

The framework contained information on the levels of tailoring and an outline of the steps taken to deliver tailored messages. Detailed information on the framework components can be found in Multimedia Appendix 2.

Step 3: Writing (Tailored) Messages

In line with Self-Determination Theory [65], the messages were written in an autonomy-supportive style. Messages were also written in a way that supports relatedness and individualization (eg, by addressing the users personally by their names). By respecting their autonomy and making them feel related to the Active2Gether intervention, we aimed to increase the user's willingness to follow up on the coaching messages. Moreover, the messages were written in a positive gain-framed style, that is, a style that describes the potential gains (eg, in health, fitness, and relaxation) when participating in PA rather than focusing on loss (ie, ill health, lack of fitness, and stress) when not engaging in PA [66]. The majority of the messages were tailored to determinants in the theoretical framework, the weather, and occupational status.

A pilot test of a subset of messages among 7 female bachelor's and master's students indicated that the messages were friendly, motivational, and empathic; some were perceived as autocratic, whereas some were not. Some minor changes were made to the messages.

Step 4: Developing Tailoring Assessments

Further decisions were made on how to measure the characteristics for tailoring messages.

Assessment of Physical Activity

Our test of the validity of the Fitbit One indicated that Fitbit can be considered a valid device to assess step activity for real-time minute-by-minute self-monitoring, although an overestimation of 677 steps per day by Fitbit was seen compared with the ActiGraph [58]. However, the validation study indicated that Fitbit is less suitable for providing instant real-time feedback and daily feedback on PA intensity levels (ie, minutes of moderate, vigorous, or MVPA) because it substantially and systematically overestimates the time spent per intensity level per hour [58]. For that reason, Fitbit is only used to assess step activity.

Participants need to give permission once for the application to access their activity data. These then can be collected regularly, and a summarized version of the data is stored in the Active2Gether database. These data are utilized in the following several ways: for presenting the activity level (ie, number of steps and number of stairs climbed) to the user, for determining the type of coaching, and for tailoring coaching messages.

Assessment of Behavioral Determinants

We decided to assess behavioral determinants by means of a questionnaire with both its long and short versions, which were selected based on the validations of such questionnaires. The long version is based on existing questionnaires that have previously been validated (ie, Neighborhood Quality of Life Survey and Self-efficacy scales) or questions used in previous studies and were translated and adapted where necessary [20,21,67]. In the short questionnaire, we decided to use single item questions to assess each of the behavioral determinants that are part of the framework and the system. In the short version of the questionnaire, all determinants are specified for each coaching domain (ie, sports participation, stairs use, and active transport). These items were not pretested as such but were based on the long questionnaire. Multimedia Appendix 3 [12,68,69] provides an overview of the questions asked in the long and short versions of the questionnaire, including the answer options.

Assessment of Location Data

We also included questions about the participants' significant places (eg, home address, parental home, sports location, university, work location) in the intake questionnaire. These questions focus on travel options from their home to significant locations, thus information about the active and nonactive transportation options. Additionally, information about the number of stairs available at each location and the maximum number of stairs the participant is willing to climb in one go is assessed as well.

The user's location (GPS coordinates) is collected using Google's location services that can be linked with the Active2Gether app. The location data are used to determine whether the user visited his or her significant locations (eg, home, study or work place, and sports club) and to derive information about transport and travels that have been made. In addition, information about the characteristics of locations is used for personalized coaching messages to the user. For instance, if a person is being coached on using the stairs more often at their place of work or study, it is only useful to suggest this when the option to climb the stairs is indeed present at the worksite or university.

Assessment of Connected Friends

Information regarding the participants' friends is collected using the Facebook API. Users are asked to provide access to their Facebook ID and their connections by logging into Facebook once and giving permission for this. It is important to note that Facebook does not provide personal information about someone's Facebook connections but only a list of Facebook IDs of their connections. This information can be used to see whether any Active2Gether users are connected on Facebook.

If two participants of the current intervention are connected on Facebook, they see a ranking within the app that shows achievements of both users. In this way, the users only share their achievements with a closed group and not with "everybody," according to the preferences stated in the focus group discussions.

Step 5: Developing the Active2Gether Intervention

Designing and Developing the Communication Channel

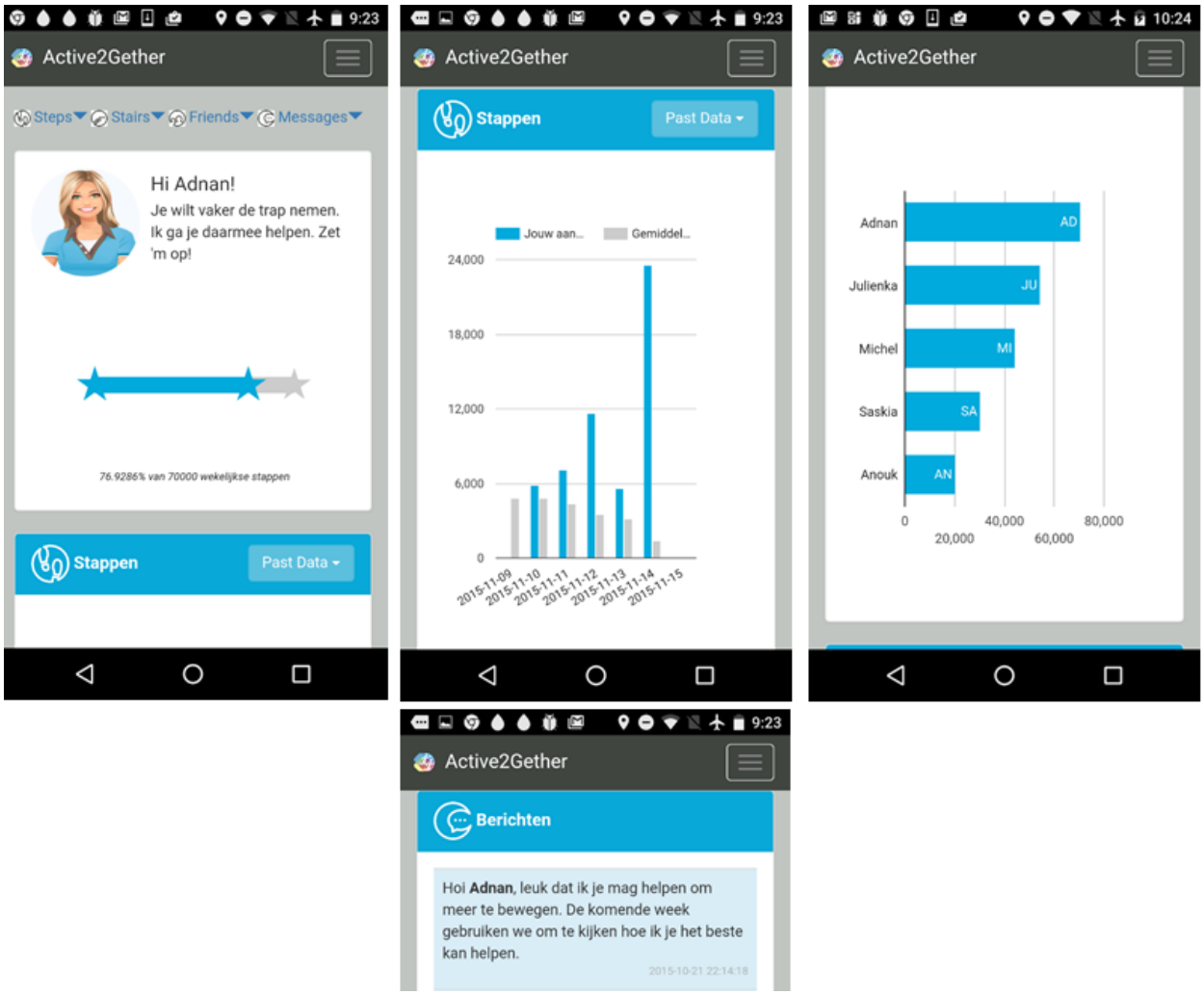
The Active2Gether app shows a nonpersonalized, generic avatar with a welcome message that mentions the user's current weekly goal. The app displays the current number of daily steps and stairs climbed. In addition, the app shows the following 4 graphs: a bar chart with the step progress toward 70,000 steps per week, a ranking with 6 other Active2Gether users—where possible Facebook friends—based on the step activity over the last seven days, the activity data for each weekday for the current coaching domain (ie, minutes of sport activity, numbers of stair climbed, or minutes of active transport), and the step activity for each weekday. The third and fourth graphs display the user's own data and the average data assessed within Active2Gether. Moreover, these graphs can be adjusted according to the user's preferences, that is, they can show data for the last week, last month, or from the first use.

Tailored messages and short questions are sent via push messages through the app. After the user reads the messages, they are displayed at the bottom of the app. Only the 5 messages sent most recently are displayed in the app. Figure 3 shows a screenshot of the app.

Step 6: Pilot Testing

The app was adjusted based on the feedback of the 7 participants who pilot-tested the app; for example, the timing of the different steps in the tailoring process (ie, determining the type of feedback, the coaching domain, the weekly goal, and the most promising behavioral determinants) did not originally account for exceptional cases in which a user takes very long to complete a step, causing the next step to be skipped. In the adjusted version, multiple checks and safety mechanisms were implemented to make sure that the tailoring process could still be finished correctly in such conditions. Also, automated messages to remind users to charge their Fitbit and to synchronize their data were added to the system because of the observation that participants in the pilot study sometimes did not notice when it was necessary to do so.

Figure 3. Screenshot of the Active2Gether app.



Step 7: Testing and Evaluating the Intervention

After developing the intervention, an evaluation study was conducted for which data have been collected between March 2016 and September 2016 and data cleaning and initial analyses are now being conducted. A three-arm quasi-experimental trial—with two active control groups—with a baseline and two follow-up assessments at 6 and 12 weeks was conducted to examine the effectiveness of the Active2Gether intervention. This trial is registered in the Dutch trial registry, No. NTR5630. A detailed description of the study protocol can be found in Multimedia Appendix 4 [12,68,69].

Discussion

This study describes the development and content of Active2Gether, an app-based intervention, which was developed using a systematic and stepwise approach. The aim of the Active2Gether intervention is to empower young adults to become and remain physically active by providing them with app-based tailored coaching and feedback. Active2Gether makes use of an activity tracker and personalized, context-specific feedback. It focuses on 3 PA domains, builds on established behavior theory, and applies evidence-based BCTs and a model-based reasoning system to provide individually tailored coaching messages based on current scores on the behavioral determinants.

The development and content creation of Active2Gether was a stepwise process. The program-planning model proposed by Kreuter et al [41] was mainly used to guide the development and content of the Active2Gether intervention. It states that the health problem needs to be analyzed before developing an intervention, the intervention needs to be based on theory and scientific evidence, and the developmental process is a loop of development, evaluation, and adjustment of the intervention. Program-planning models provide detailed guidance to develop an intervention, which also takes time. Because the possibilities of modern technology in interventions are rapidly evolving, possibilities and preferences that were assessed at the beginning of a lengthy development process may be outdated at the time of implementation or evaluation. The development and content of Active2Gether were guided by relevant health behavior theories and scientific evidence, aiming to develop an intervention that provides a highly tailored feedback. Consequently, less attention was paid to app design and aesthetics that might have resulted in a less appealing app compared with commercial apps. Furthermore, the app is only available for Android devices running on version 4.0 or higher and is therefore not available for older Android devices and smartphones running on other operating systems. Active2Gether incorporates a number of conditions to secure high levels of engagement. First, our approach, integrating a model-based reasoning system, allows us to provide the user with a dynamically tailored intervention that adjusts to the changes in the user. Second, by applying multiple levels of tailoring in the app and the content of the messages (ie, type of support, coaching domain, coaching messages, and weekly goals), the app is likely to be regarded as personally relevant and increase feelings of relatedness. Third, by comparing the PA of the user with that of other Active2Gether users (if possible with their Facebook friends), we expect to further increase personal relevance and relatedness. Lastly, by giving the user the option to select from 3 PA domains and set their own goals with guidance and suggestions based on their own input, we expect higher levels of autonomy, resulting in higher motivation to follow up on the coaching messages. However, to implement these different levels of tailoring, detailed user information is needed repeatedly; thus, frequent user input is needed, which increases user burden.

To date, mobile phones and personal digital assistants have been used to monitor PA with either smartphone apps or external devices, deliver feedback, provide information, and offer a support system to the participants [7]. Active2Gether makes use of an external device, Fitbit One, to monitor PA and provide feedback through the app based on the user's behavior. However, Active2Gether goes beyond existing interventions by combining data from multiple sources to send context-specific messages. Furthermore, the majority of the published interventions focuses on step activity [70,71], whereas Active2Gether focuses on sports activity, stair walking, and active transport as well. Therefore, the app may be more appealing to participants who do not like to participate in sports, especially because the user can adapt to his or her coaching domain every week. However, Active2Gether does not yet incorporate geofencing (ie, sending location-triggered messages), which would further improve the possibilities for context specificity and real-time feedback and advice by, for example, sending a reminder to climb the stairs at work when users are close to their work location.

So far, the majority of the app-based interventions to promote PA showed positive short-term effects [39]. In line with other app-based PA interventions, Active2Gether makes use of self-monitoring, goal setting, and providing feedback. However, Active2Gether provides dynamically tailored feedback using artificial intelligence-based techniques and including conditional factors (ie, weather), whereas other interventions use logic statements and decision rules to specify which messages should be sent to the user; for example, Active2Gether uniquely assesses behavioral determinants every week to provide tailored advice and feedback on the current behavior, whereas most studies mostly provide feedback on the current behavior only [72-76]. Current app-based interventions to promote PA focus on step activity or overall MVPA [72-77], whereas Active2Gether focuses on sports activities, active transport, and stair walking as well. The majority of papers on app-based interventions reported significant effects [39], and a study that combined machine learning techniques to send personalized messages that were contextualized to the user's environment and previous behavior showed promising results with regard to the efficacy of the intervention [26]. Because the Active2Gether intervention went beyond the majority of those apps and included BCTs proven to be effective, we expected to find significant intervention effects compared with the 2 (active) control groups.

Active2Gether is ambitious and innovative and incorporates certain risks, for example, the intervention highly relies on input from the activity monitor and location sensor and thus on the

user to turn on and synchronize the tracker with the server. Furthermore, it relies on responses from the users on repeated questionnaires. If they do not provide input at all or if they do not provide true and honest answers, the coaching messages that are informed by this information may become irrelevant and nontailored. Moreover, if a participant is not a Facebook user or has no appropriate contacts, the personalization could be limited. Finally, if technical problems are encountered, this may result in errors in synchronization and sending messages late or not at all. To limit the burden for the participants and minimize their input to reduce potential technical problems, future research could make use of smartphone sensors to assess the participant's behavior.

The overall effectiveness of Active2Gether thus needs to be, and is being, evaluated in a quasi-experimental trial with a 12-week follow-up. However, because app-based interventions offer the possibility to deliver just-in-time interventions that are relevant for the user's situation for that particular moment, a study is needed to examine the possible effectiveness of specific real-time feedback and advice moments [78]. An ecological momentary assessment [79] in such a quasi-experimental trial setting may help to assess potential specific effects throughout the intervention period. An evaluation of the efficacy of the intervention and the usability can help to further adapt and improve the intervention for future research. Furthermore, data collected during the trial can provide insights on how to further personalize content to the users. The quasi-experimental trial also includes monitoring of app use and a process evaluation of app use and appreciation that will provide information on larger scale dissemination, implementation, and changes required to improve conditions for wider use of the app.

Because the intervention has been developed with an early consideration for the preferences of the target population, it is more likely to meet the expectations of the target population. Consequently, the intervention is more likely to be adopted by the target population. However, the intervention might be prone to technical errors, and a significant input from the user is needed to provide tailored feedback. This might be a burden for the participants, leading to a lower adoption rate. We conducted a small pilot study to test the Active2Gether app and to detect bugs and technical errors; ideally, the pilot study would have been conducted with a larger sample. The current version of the Active2Gether intervention has been developed for young adults with higher education owning a smartphone running on Android version 4.0 or higher. The content needs to be adjusted before offering the intervention to other target populations.

This paper describes the systematic development of an intervention that is based on theory and input from end users. The use of a model-based reasoning system to provide context-specific coaching messages goes beyond many existing eHealth and mHealth interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Overview of the behavior change techniques (BCTs) that were selected to target the behavioral determinants of the theoreticalframework and how they were applied within the intervention.

[PDF File (Adobe PDF File), 288KB - resprot_v7i12e185_app1.pdf]

Multimedia Appendix 2

Components and flow chart of the tailored intervention.

[PNG File, 285KB - resprot_v7i12e185_app2.png]

Multimedia Appendix 3

Overview of the questions used for the short and long version of the questionnaire.

[PDF File (Adobe PDF File), 215KB - resprot_v7i12e185_app3.pdf]

Multimedia Appendix 4

Study protocol.

[PDF File (Adobe PDF File), 313KB - resprot_v7i12e185_app4.pdf]

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Abbreviations

API: application programming interface
BCT: behavior change technique
ICT: Information and communications technology
MVPA: moderate-vigorous physical activity
PA: physical activity
SCT: social cognitive theory

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Protocol

Endotracheal Intubation Among the Critically Ill: Protocol for a Multicenter, Observational, Prospective Study

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Abstract

Background: Endotracheal intubation can occur in up to 60% of critically ill patients. Despite the frequency with which endotracheal intubation occurs, the current practice is largely unknown. This is relevant, as advances in airway equipment (ie, video laryngoscopes) have become more prevalent, leading to possible improvement of care delivered during this process. In addition to new devices, a greater emphasis on airway plans and choices in sedation have evolved, although the influence on patient morbidity and mortality is largely unknown.

Objective: This study aims to derive and validate prediction models for immediate airway and hemodynamic complications of intensive care unit intubations.

Methods: A multicenter, observational, prospective study of adult critically ill patients admitted to both medical and surgical intensive care units (ICUs) was conducted. Participating ICU sites were located throughout eight health and human services regions of the United States for which endotracheal intubation was needed. A steering committee composed of both anesthesia and pulmonary critical care physicians proposed a core set of data variables. These variables were incorporated into a data collection form to be used within the multiple, participating ICUs across the United States during the time of intubation. The data collection form consisted of two basic components, focusing on airway management and hemodynamic management. The form was generated using RedCap and distributed to the participating centers. Quality checks on the dataset were performed several times with each center, such that they arrived at less than 10% missing values for each data variable; the checks were subsequently entered into a database.

Results: The study is currently undergoing data analysis. Results are expected in November 2018 with publication to follow thereafter. The study protocol has not yet undergone peer review by a funding body.

Conclusions: The overall goal of this multicenter prospective study is to develop a scoring system for peri-intubation, hemodynamic, and airway-related complications so we can stratify those patients at greatest risk for decompensation as a result of these complications. This will allow critical care physicians to be better prepared in addressing these occurrences and will allow them to improve the quality of care delivered to the critically ill.

Trial Registration: ClinicalTrials.gov NCT02508948; https://clinicaltrials.gov/ct2/show/NCT02508948 (Archived by WebCite at http://www.webcitation.org/73Oj6cTFu)

International Registered Report Identifier (IRRID): RR1-10.2196/11101

(JMIR Res Protoc 2018;7(12):e11101) doi:10.2196/11101

KEYWORDS

airway; endotracheal intubation; hemodynamics; intensive care unit; multi-center; prospective study

Introduction

Significance

When compared to other settings, such as the operating room, endotracheal intubation in the intensive care unit (ICU) carries with it a higher morbidity and mortality, likely due to many factors, including a lack of physiologic reserve [1-3]. For example, the incidence of a difficult airway in the ICU may be as high as 23% [2]. Unwanted effects associated with endotracheal intubations performed in the ICU include, but are not limited to, arterial desaturation, cardiovascular decompensation, esophageal intubation, regurgitation of gastric contents, and cardiac arrest [3-5]. Additionally, as intubation attempts increase, the rate of complications also increases [6]. In recognition of the above, institutions across the country have developed intubation bundles to reduce these unwanted effects. Moreover, the use of a systematic approach to, or protocol for, endotracheal intubation may reduce intubation complications [7-9]. This was recently demonstrated in a trial utilizing an intubation protocol, whereby immediate life-threatening complications surrounding ICU intubations were reduced [10].

Challenges in Endotracheal Intubation

Recently, there have been a variety of new devices emerging that are designed to assist with a difficult airway, such as video laryngoscopes. These devices have been reported to reduce unwanted effects of endotracheal intubation (ie, a failed airway). In addition to new devices, intubation checklists and sedative choices have undergone changes with uncertain effects on patient morbidity and mortality. Currently, many clinicians use the newer devices, such as video laryngoscopes, as evidence indicates that these devices result in better laryngeal view and improved intubation difficulty score with lower risk of a failed airway as compared to conventional techniques (ie, direct laryngoscopy) [11-15]. Moreover, these newer devices are user friendly even in unfamiliar hands [16]. A recent meta-analysis comparing video laryngoscopy with direct laryngoscopy reported similar findings, where video laryngoscopy reduced the risk of difficult airway, Cormack 3/4 grades, and esophageal intubation, but increased the first-attempt success rate. Additional outcomes, such as severe hypoxemia, severe cardiovascular collapse, or airway injury, were not different between the two techniques [17]. Moreover, video laryngoscopy maintains its effectiveness when used during an emergency [18]. Despite the evidence of positive outcomes for the newer devices, not all providers utilize these modalities, possibly due to inexperience with the newer techniques or evidence suggesting no benefit [19,20]. As an example, a recent study surveying Canadian resuscitation physicians demonstrated that most use direct laryngoscopy as their go-to technique for emergent endotracheal intubations [21]. Similarly, ICU physicians in Israel, when surveyed, seem to prefer fiber-optic intubation for routine airway management [22].

Medications and Procedural Advances in the Field

Along the same line as airway equipment, sedatives used during endotracheal intubation have evolved over time. Over the years, evidence has suggested that the use of etomidate in the critically ill, especially in sepsis, may be associated with increased morbidity and mortality [23-25]. However, other studies find no associations with etomidate and patient outcomes [26,27]. Etomidate traditionally has been the preferred induction drug because of its favorable hemodynamic profile. However, with mounting evidence for adrenal suppression and possible associations with mortality in septic patients, the clinician now struggles with the ideal sedative for endotracheal intubation [28-30]. Other agents and/or admixtures have shown promise [31,32]. Not only has the choice of induction medication changed in recent years, but current evidence suggests that the use of paralytics may help facilitate endotracheal intubation [33,34]. In addition, paralytics are now recommended in the setting of acute respiratory failure, with evidence demonstrating improved outcomes [35]. Thus, using paralytics in a patient with suspected lung injury who needs intubation for acute respiratory failure may be of benefit. However, certain situations may preclude their use [36].

Importance of This Study

As outlined above, temporal changes in airway and sedation management in recent years have occurred with mixed study results and the importance of short-term outcomes (ie, postintubation hypotension, hypoxemia, and difficult airway) on patient morbidity and mortality has been demonstrated. Therefore, characterization of current intubation practice among the critically ill is warranted. With this characterization, scoring systems may be developed that aid the clinician in providing optimal outcomes for patients. This information in turn may allow the clinician to provide a tailored plan, in terms of both airway and hemodynamic management of the critically ill who are in need of intubation.

Approach

In order to examine the current endotracheal intubation practice among the critically ill, a multicenter, observational, prospective study of adult, critically ill patients was conducted from July 2015 to January 2017 involving 20 ICUs.

Study Objectives

Our first objective is to derive and validate a prediction model for airway difficulty among the critically ill as defined by three or more attempts at laryngoscopy and/or the need for another operator [37].

Our second objective is to derive and validate a prediction model for hemodynamic compromise (ie, postintubation hypotension, defined as a decrease at any point in mean arterial pressure of <65 mmHg; systolic blood pressure of <80 mmHg and/or a decrease in systolic blood pressure of 40% from previous; or the introduction, or increase in infusion rate, of any vasoactive agent during the 30-minute window following endotracheal intubation) [38,39].

Our third objective is to derive and validate a predication model for hypoxemia defined as a decrease in SpO_2 of <88% during the procedure.

Methods

Study Approval and Trial Registration

The Institutional Review Board at the Mayo Clinic in Rochester, Minnesota, approved this study protocol (Institutional Review Board #15-002328). This study was under waiver of informed consent and authorization given the observational nature of the study with the use of deidentified data. The trial was registered at ClinicalTrials.gov (#NCT02508948).

Design and Setting

This is a multicenter, observational, prospective study of adult critically ill patients admitted to both medical and surgical ICUs at the listed participating sites within the United States (see Multimedia Appendix 1), who meet the criteria designated below for which endotracheal intubation was needed.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for the study are listed in Textbox 1.

Study Enrollment Procedures

All adult endotracheal intubations across all ICUs were eligible for this study. Given that this procedure is an unpredictable event, the patients were not able to consent, nor was a health care power of attorney readily available. The sites were to initiate immediate data collection; therefore, obtaining informed consent was impractical. In addition, the observational study design did not impact the procedures performed, devices used, or medications given to patients.

Study Protocol

A steering committee oversaw the administration of the protocol and was comprised of both anesthesia and pulmonary critical care physicians. A data collection form was created that focused on two periprocedural aspects of the intubation process, including airway and hemodynamic management, and was used at all participating sites (see Multimedia Appendix 2). Regarding airway management, rapid sequence intubation was defined a priori according to Sellick [40]. Although the participating sites obtained formal training in the use of the data collection form prior to study initiation, online content in the form of a web link was established to answer frequently asked questions, as well as to establish a forum among the investigators with all questions related to the study discussed (see Multimedia Appendix 3). Moreover, monthly HEModynamic and AIRway (HEMAIR) investigator meetings were conducted to further provide a platform for questions and discuss future collaborations, with a newsletter sent afterward to participating sites (see Multimedia Appendix 3). The data collection form was uploaded into RedCap during data entry. Data were obtained by the proceduralist or site study coordinator and verified by the primary investigative team. The sampling method utilized in this study was convenience sampling.

Data Management

Each clinical site was responsible for patient enrollment and data collection. Each site also provided a research investigator who was responsible for capturing and entering the study data into the study database during the collection time period. The study database was housed and managed at the Mayo Clinic in Rochester, Minnesota, including running periodic, basic data-quality-monitoring queries. Data collection on outcome measures was done weekly by trained study coordinators at each site.

Statistical Analysis

For descriptive summaries, continuous measurements will be represented as mean (SD) for parametric distributions and median (interquartile range, IQR) for nonparametric distributions. Dichotomous variables will be represented as counts and percentages. For descriptive studies, all procedures will be included for patients who require endotracheal intubation more than once during the same ICU stay. For hypothesis testing, we will consider two-tailed tests of $P<.05$ to be statistically significant and will report point estimates and 95% confidence intervals. The first endotracheal intubation in the ICU will be used in analyses to assess for associations between predictors and an adverse outcome. Model building will be performed using lasso regression with 10-fold cross-validation. In all cases, distributional assumptions will be assessed, with appropriate transformations used as necessary. SAS version 9.4 (SAS Institute Inc) and R statistical software version 3.4.1 (R Foundation for Statistical Computing) will be used for all analyses.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Adult patients (≥18 years of age)
- Admission to medical or surgical intensive care unit
- Endotracheal intubation performed between July 2015 and January 2017

Exclusion criteria:

- Pediatric patients (<18 years of age)
- Endotracheal intubations occurring in nonintensive care unit locations

Sample Size

We based our sample size on the occurrence of intubation complications. Since we are most concerned with the occurrence of airway-related complications (ie, difficult intubation), and hemodynamic complications (ie, hypotension), our sample size is powered for the occurrence of these two complications. Difficult intubation and hypotension were defined in our study with an expected incidence of 12% and 11%, respectively, during the peri-intubation period [37,41]. Thus, we determined that an effective sample of 804 was sufficient to provide statistical power to detect an incidence of 12% with precision and margin of error of 1%. However, we included over 1000 patients from all sites to answer any subsequent secondary and tertiary hypotheses.

Results

The study is currently undergoing data analysis. Results are expected in November 2018 with publication to follow thereafter. The study protocol has not yet undergone peer review by a funding body.

Discussion

The HEMAIR study did not alter the care that patients received. Additionally, sharing deidentified data protected the privacy of the patients. With these procedures and requirements in place, the physical rights and welfare of patients were not adversely affected by study participation or by the waiver of consent and authorization. This multicenter, prospective trial will be among the first to include a large, diverse patient population from across the United States with a large sample size. The potential benefits would include deriving and validating prediction models for immediate severe complications regarding airway and hemodynamic management surrounding intubations among the critically ill. With this information, it is our hope that clinicians will have a tool to predict which patients will become unstable during this procedure so they may adjust treatment plans, allowing for improved quality of care delivered during this procedure. This prospective observational trial is even more important, as postintubation hypotension and hemodynamic derangement is noted by some to occur at a fairly high rate, possibly leading to increased risk of mortality [42].

Authors' Contributions

NS is the principal investigator of the HEMAIR study and conceived the study design. RK is the lead study coordinator and coprincipal investigator and participated in data collection. DS is the chief statistician and performed statistical analysis for the study. MS and DD are trial coinvestigators and participated in data collection. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

HEModynamic and AIRway (HEMAIR) site investigators.

[PDF File (Adobe PDF File), 27KB - resprot_v7i12e11101_app1.pdf]

Multimedia Appendix 2

HEModynamic and AIRway (HEMAIR) data collection form.

[PDF File (Adobe PDF File), 30KB - resprot_v7i12e11101_app2.pdf]

Multimedia Appendix 3

HEModynamic and AIRway (HEMAIR) newsletter.

[PDF File (Adobe PDF File), 440KB - resprot_v7i12e11101_app3.pdf]

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Abbreviations

HEMAIR: HEModynamic and AIRway
ICU: intensive care unit
IQR: interquartile range

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Protocol

Voluntary Stopping of Eating and Drinking in Switzerland From Different Points of View: Protocol for a Mixed-Methods Study

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Abstract

Background: “To die with dignity” has reached the significance of a core value in democratic societies. Based on this unconditional value, people require autonomy and care. "Voluntary stopping of eating and drinking" (VSED) represents an alternative to assisted suicide because no one else is involved in the action of death fastening, even though from outside, it might be considered as an extreme form of passive euthanasia. However, there are no data available about the prevalence and frequency of either explicit VSED or the implicit reduction of food and liquid in Switzerland. The responsible and independent ethics committee of the Greater Region of Eastern Switzerland (EKOS 17/083) approved this study.

Objective: The objectives of the study were to research the prevalence and frequency of different types (implicit and explicit) of VSED in Switzerland; to explore the experiences, attitudes, handling and recommendations made by palliative care experts; to develop a practical recommendation about VSED, which will be validated by experts in Delphi rounds.

Methods: This protocol describes a convergent mixed-method design to answer the research questions. In the first step, a cross-sectional trilingual survey (in German, French, and Italian) will be carried out to obtain a comprehensive representative picture of VSED in Switzerland. In the second step, qualitative research will be carried out by focus group interviews with palliative care experts. The interviews will be recorded, transcribed, and analyzed using generic coding, and embedded in an explorative descriptive qualitative approach. Based on the results of the first two steps, a practical recommendation will be developed. Experts will validate the practical recommendation in Delphi rounds.

Results: The enrolment was completed in summer of 2018. Data analysis is currently underway and the first results are expected to be submitted for publication in the end of 2019.

Conclusions: The results of this study will provide important information about the prevalence and frequency of VSED as well as the interpretation of palliative care experts about handling VSED in daily work. Furthermore, the practice recommendation will help professionals and institutions to improve the quality of care in patients and their relatives who made the decision to fasten death by VSED.

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KEYWORDS

voluntary stopping of eating and drinking; project protocol; questionnaire; cross-sectional study; focus group interviews; explorative descriptive qualitative research; practical recommendation; palliative care

Introduction

Background

"To die with dignity" is a metaphor for finding a good end to one's own life. When asked about a "good death," studies have shown that people name the following factors: consciously experienced death at home, without pain, in good mental condition, at the end of a long, fulfilled life, and after having arranged "last things". For many people, "death with dignity" includes autonomy, control, and self-determination [1-4].

Even under comprehensive, high-quality palliative care, suffering during the process of dying is not always avoidable [5]. Facing unbearable pain despite palliative and therapeutic possibilities results in the wish to prematurely end one's life. Particularly at the end of life, many aspects of suffering cannot be addressed effectively by means of symptom control or modern medical treatment [6]. Various reasons result to wishing for a premature death, for example, low quality of life, senseless suffering, fear of losing one´s independence and dignity, or the wish to control the conditions of death while maintaining self-determination [7]. Mental and spiritual suffering, symptom clusters, bleeding, open wounds, altered body image, social isolation, and loss of the meaning of life are further forms of suffering, reaching far beyond pure symptom control [6,8].

The wish to prematurely end one´s life seems to be difficult to understand for persons who have not been confronted with unbearable suffering. To induce premature death, persons turn to organizations offering assisted suicide, which is possible in Switzerland for people with terminal diseases whose end of life is imminent [9]. However, taking barbiturates is not a viable option for everyone. Similar to that in the Netherlands [10,11], people are looking for other options, including the decision to engage in "voluntary stopping of eating and drinking" (VSED). VSED is the clearly stated desire of a person to abstain from eating and drinking to deliberately end his life prematurely. It takes 7 to 21 days until the process of dying is initiated. It is only interrupted when the person has second thoughts and starts eating again. VSED seems to be an ethical way to end unbearable suffering in a self-determined way [12-14]. This does not seem to be very common for several reasons [15]. Nevertheless, owing to lacking popularity of VSED or complete rejection of prematurely inflicted death, moral conflicts can arise on the part of medical and nursing professionals [16-18]. Food intake is associated with high social value and symbolizes social participation [19]. For this reason, family members may interpret VSED as refusal or deficit of professional care [12]. However, patients, particularly those in advanced stages of an oncological condition, explicitly express their wish for premature or assisted death to doctors and nurses [20]. Furthermore, there is an unverified assumption that VSED leads to intensified, additional suffering for patients [12]. Even in the scientific community, VSED is rarely taken into account as an option. These aspects can be regarded as possible reasons for rare scientific research on VSED.

Next to the phenomenon of VSED as a clearly expressed desire of a person to prematurely end her or his life, there are other forms. If a person refuses to eat and drink but is unable to explain or does not want to talk about it, this is called implicit or unspoken (V)SED [21], which is not uncommon [22]. This poses a major challenge for professionals and relatives to first recognize the refusal of eating and drinking and to explore the reasons behind it.

Aims and Research Questions

This study aims to investigate the prevalence and frequency of VSED in Switzerland. In detail, the occurrence of implicit (V)SED and explicit VSED as well as the experiences, attitudes, handlings, and recommendations made by palliative care experts deserve study. Based on these results and in addition to previous and updated work, a practice recommendation shall be developed for professionals in specialized palliative care. The practice recommendation will be specified and evaluated by experts in Delphi rounds. For this study, the following research questions are essential.

Part I

- How frequent and prevalent is the implicit (V)SED and explicit VSED in palliative care throughout Switzerland?
- What kinds of experiences, attitudes, handlings, and recommendations regarding VSED exist when comparing palliative care experts?

Part II

- What is the perception and interpretation of the implicit (V)SED and explicit VSED in Switzerland for experts in palliative care in their daily work?
- What interpretations do the experts in palliative care drag from the experiences, attitudes handlings, and recommendations in their daily work?

Part III

- What information in the form of a practice recommendation based on the findings in Parts I and II and available international research literature can be gathered regarding VSED?

Methods

Background

The theoretical framework is based on the SENS-model of Eychmüller [23]. This approach structures palliative care problems at the end of life with the aims of palliative care: self-efficacy, self-determination, security, and support. These aims including the World Health Organization definition is the basis of the SENS-model, which is clustered into 4 main areas: symptom management, decision making, network, and support [23]. To answer the research questions, a convergent mixed-methods design [24] will be used to pursue the research questions in Parts I and II. Quantitative data will be collected through a cross-sectional trilingual survey (in German, French, and Italian). This will be used to obtain a comprehensive representative picture of the prevalence and frequency, meaning, handling, and recommendations of VSED in Switzerland [25]. Qualitative data will be collected using focus group interviews to obtain palliative care experts' meaning and interpretation of experiences, attitudes, handlings, and recommendation in their

daily work. After completion of Part I and Part II, quantitative and qualitative data are going to be integrated and discussed.

The reason for choosing this mixed-methods design is based on the integrity of the data, which influence each other. Both instruments are going to be developed at the same time. With this approach, quantitative data can be compared and integrated with qualitative data and vice versa. This brings the advantage that possible inaccuracies are reduced by different viewpoints.

Subsequently, a practice recommendation will be developed based on the survey results (Part I) and focus group interviews (Part II) as well as the current literature. Furthermore, it will be subsequently validated in expert discussion rounds based on the Delphi method [26].

Part I: Survey

Instrument

A standardized evidence-based questionnaire is going to be developed, tested, and translated into French, Italian, and additionally into English for reasons of publication. The development of the questionnaire [27-31] is planned to be based on a literature update of the review of Ivanović, Büche [10]. The questionnaire will be tested by 10-20 experts in a standard pretest [29,32-34] and validated by 15-30 experts through the content validity index of Polit, Beck [35]. The forward and backward translation will be carried out for each language by 2 independent translators, subsequently aiming for a consensus through a consultant based on the Standard Linguistic Validation Process of Mapi-Institute [36].

Recruitment and Sampling

A representative sample of palliative care experts, employees in ambulatory care service, Long-Term Care, and general practitioners will be sought for in each case. Access to palliative care experts is first sought through professional association.

- Outpatient care: The employees are informed about the questionnaire via Associations Spitex priveé Suisse [37] and Spitex, a nonprofit professional association for outpatient care [38] via email and invited to participate.
- The employees in Long-Term Care should be contacted through CURAVIVA—Association Homes and Institutions Switzerland [39] via email for answering the questionnaire.
- The physicians should be reached through Foederatio Medicorum Helveticorum, Association of Swiss doctors [40].

Two reminders are scheduled for 3-4 weeks, which are either sent again by the respective professional association or directly by the first author. Members' mails are obtained through the professional associations' website. The survey can be started in February and depends on the correspondence and the possible resulting requirements (eg, the introduction of specific questions at the end of the survey) of the professional associations. The recruitment of all professional associations was planned until June 2018. The survey lasted until the end of August. We expect a return rate of 20% per group. This will be as follows: Associations Spitex priveé Suisse 35 of 175 members; Spitex 85 of 426 members; CURAVIVA 260 of 1302 members; and Foederatio Medicorum Helveticorum 282 of 1411 members.

Data Collection and Analysis

Questback will be used for the survey of the target groups. This is a state-of-the-art software and has a high standard for Web-based surveys [25,34]. Two reminders scheduled for 3 weeks are planned to get as many answers as possible. Data analysis is conducted using SPSS Version 24 and will be supported by a statistician. The descriptive statistics will be reported in absolute and relative values with indications of mean (SD) or mode. Ordinal variables will be calculated using the Mann-Whitney U test or Kruskal-Wallis test by ranks and Spearman rho. Nominal variables will be calculated using chi-square (Fisher's exact test) and Mann-Whitney U test or Student *t* test and metric variables using analysis of variance.

In addition to descriptive statistical analyses, methods of inferential statistics will be used [41,42]. The following hypotheses underlie the research:

- There is a difference between the 3 target groups, Outpatient Care, Inpatient Long-Term Care, and Family Physicians, and their gender in terms of occurrence, stands, and attitude [43,44].
- There are differences between younger (<50 years) and older (50 years) participants in terms of occurrence, stands, and attitude [45].
- There is a difference between participants in terms of levels of competence in palliative care in terms of occurrence, stands, and attitude [45].
- There is a difference between participants with short (<20 years) and long (≥20 years) work experience in terms of occurrence, stands, and attitude [45].
- There is a difference between attendees with and without personal experience accompanying a person with the VSED in terms of stands and attitudes [44].

Part II: Focus Group Interviews

Qualitative data will be collected by interviewing experts of palliative care in focus group settings. Because the VSED phenomenon can lead to controversial discussions both inter- and intraprofessionally, utilizing focus groups is particularly suitable for showing the different attitudes. We hope that the participants' possible different views will allow us to gain deeper insight into understanding their attitude. Therefore, an explorative descriptive qualitative approach [46,47] was selected, following the coding methodology of Saldaña [48]. The focus group interviews will gather information about the meaning and interpretation of experts in the prevalence and frequency of VSED as well as the experiences, attitudes handlings, and recommendations about implicit (V)SED and explicit VSED in their daily work.

Recruitment and Sampling

The participants of palliative care congresses and network meetings have been sought out for this purpose. These congresses are well suited to nurses and medical professionals who are often confronted with end-of-life decisions and are expected to include participants with and without experience in caring for a person during VSED. Accordingly, 5-6 groups with up to 10 participants are covered. Each group will discuss 1 of the following topics for about 50 minutes: caring for the

person concerned, support of relatives, accompaniment of professionals, how to deal with implicit (V)SED, and the appropriate use of recommendations and communication about VSED.

Data Collection and Analysis

A moderator will perform semistructured interviews that will be digitally recorded [49,50]. According to the pragmatic rules of transcript by the approach of Flick [51], it will be carried out using MAXQDA 12. Data will be analyzed following the constant comparative method described by Glaser [52]. Codes will be built through an inductive analyzing procedure using generic coding (first and second cycles), as described by Saldaña [48]. Each new incident, which can be assigned to an already existing code, is compared with the incidents it contains. With this approach, the properties and dimensions can be developed and the code becomes a category that can be related to other categories. In the second step, possible characteristics of the participants are drawn to their statements. If, for example, the data show that participants with palliative care education tend to have a different response as participants without further training, these are specifically compared with each other in the categories. By describing the categories considering the relationship with each other, a theory is developed.

Data Integration of Part I and Part II

In this step, the results of Part I and Part II will be integrated and discussed. If possible, quantitative data will be qualified and qualitative data will be quantified. Owing to the very different sample sizes from the survey and focus groups, it is likely that data integration will take an explanatory approach. This means that comparable statements from the quantitative and qualitative studies are listed side by side in a table and will be related to each other; for example, factors (described by the focus groups) can be identified and describe why an item (from the survey) was answered that way [24].

Part III: Practice Recommendation

Instrument Development

Based on the findings from Part I and Part II and especially the findings of the data integration section of Part I and Part II, a development of a practice recommendation is being considered. The aim is to set strategies for professionals to deal with implicit (V)SED and explicit VSED with patients, relatives, and interdisciplinary team members. As basis for development, international publicized articles will be updated. The developed practice recommendation will then be refined in the project team and in cooperation with the project partners.

Delphi and Consensus Procedures

Approximately 20-30 experts and scholars from various disciplines (nursing, medicine, geriatrics, palliative experts, ethicists, and sociologists) will then validate the final practice recommendation in a minimum of 2 and if needed, several Delphi rounds until a consensus is reached. The experts are assigned the task of checking the practice recommendation for intelligibility, comprehensibility, and completeness. The experts will be acquired via the existing network of VSED. The Delphi rounds will be carried out with the survey tool QuestBack and will be conducted in English. The consensus procedure will be carried out personally to ensure the quality of the responses.

Ethics Approval and Consent to Participate

This investigation is neither a clinical trial nor an observational study with vulnerable groups. Thus, no personal data will be collected. Participation in the study is voluntary, and the participants will be assured irreversible anonymity. Nonparticipation does not entail any disadvantages. With an accompanying letter (via email, cover letter, and information letter on the webpage), the participants will be informed in detail and made aware of the aim and purpose of the study as well as the utilization of the generated data and their personal rights. The participants of the focus group interviews will be informed about the project in advance and asked when the interview starts. The ethical approach is based on the principles of the "Declaration of Helsinki" and "informed consent." Anonymity and respect for human dignity is guaranteed at all times during the research process. Drawing any conclusions about the respondents will not be possible at any time [53]. The responsible institutional review board of the Greater Region of Eastern Switzerland (EKOS 17/083) approved this study.

Results

After approval of the Ethics Committee (EKOS 17/083), the Swiss Academy of Medical Sciences provided the first partial funding. As soon as the first results are available and the study phase Part III begins, the second partial funding will be planned. The funding from Ebnet-Foundation and palliacura have each paid their share. The development of the questionnaire (Phase I) started in 2016 and was completed in the spring of 2017. Contacts to the professional associations were successfully established, and the recruitment was completed by the end of August. The focus group interviews have since been completed, and the transcription of the audio files are in progress. The results are forthcoming.

Discussion

Strengths

In Switzerland, there is a very high willingness to become a member of professional associations. Through the participation and support of the professional associations, we are able to guarantee a Switzerland-wide survey.

Limitations

We recognize that that a trilingual survey, despite the translation process, carries the risk that participants' statements may be interpreted and answered differently. In addition, the results will subsequently be published in English, which translates the statements further. The participants of the study will be given the summarized results in 3 languages via the professional associations and sent via a newsletter. To ensure that the participants in the study receive the results, the participating professional associations receive the summarized results in 3 languages and make them available for internal use.

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Authors' Contributions

SS and AF were responsible for the conception and design of the study and were also major contributors in the writing of the manuscript. MM was responsible for the ethical analysis of explicit and implicit value statements in the data. MM, DB, and WS critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

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Abbreviations

VSED: voluntary stopping of eating and drinking

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Protocol

A Novel Smartphone App to Support Learning and Maintaining Competency With Bier Blocks for Pediatric Forearm Fracture Reductions: Protocol for a Mixed-Methods Study

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Abstract

Background: Distal forearm fractures are among the most common injuries presenting to the pediatric emergency department (PED). Bier block (BB), or intravenous regional anesthesia, is a safe and effective alternative to procedural sedation for closed reduction of forearm fractures; it is associated with fewer adverse events, a shorter length of stay, and reduced costs. BB has long remained relatively underutilized; however, with an increasing emphasis on efficient resource use and patient-centered care, there is renewed interest in this technique.

Objective: Our tertiary PED recently became the first in Canada to successfully implement an active BB program. Subsequently, we developed a mobile BB smartphone app designed to support the sustained departmental use of BB. The app can be used for training and maintenance of competency and incorporates instructional material, as well as our institutional BB protocol, printable medication order sheets, and monitoring forms. The present report describes the development and functionality of the BB smartphone app.

Methods: We have described app development and content. App dissemination metrics will be tracked, and user feedback will be analyzed using a self-administered electronic survey. Additionally, app utilization in our PED will be compared with real-world clinical use of BB for fracture reductions.

Results: The first iteration of the BB app was launched in 2015, with the most recent update in September 2018. App metric tracking is planned for January 2020 until December 2021.

Conclusions: We have highlighted how the BB app serves as a paradigm of an educational tool designed not only for individual users but also for supporting the department-wide implementation and dissemination of a new technique. App dissemination and use metrics will be tracked and correlated with clinical use of BB in the PED.

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KEYWORDS

intravenous regional anesthesia; lidocaine; procedural sedation; mobile phone

Introduction

Background

Bier block (BB), or intravenous regional anesthesia, is a safe and effective alternative to procedural sedation for forearm fracture reduction [1-3]. Using a pneumatic tourniquet, the isolated injured extremity is injected with local anesthetic to provide complete limb analgesia below the tourniquet cuff for painless fracture reduction. The patient remains conscious throughout the procedure, for which, therefore, no preprocedural fasting is required, postprocedure observation period is minimal,

and potential risks of procedural sedation are avoided. Intravenous access is required only on the affected limb and only briefly during infusion of local anesthetic. Consequently, this technique is associated with reduced length of stay and resource utilization [4] and can be used for children as young as 2-4 years [1,2,4].

Despite BB's apparent benefits, it remains infrequently employed for forearm fracture reductions. A survey of 44 North American pediatric emergency departments (PEDs) reported that the most common reason cited for not using local anesthesia techniques was the efficacy of procedural sedation. The authors further suggested that limited physician comfort and perceived longer preparation time were important barriers to BB use [5]. These factors, coupled with sporadic clinical opportunity, departmental logistics, and personnel turnover, are all important challenges to the successful implementation of a sustained BB program.

Recently, our center became the first Canadian PED to successfully introduce a BB program for forearm fracture reductions. PED personnel were trained at the time of BB implementation using a multimodal training course. We observed a sustained increase in BB utilization following training, reaching nearly 40% of all forearm fracture reductions at 2 years. However, course participants reported a modest but significant decrease in comfort with BB at 6 months, and the majority of participants expressed interest in refresher training [6].

Objectives

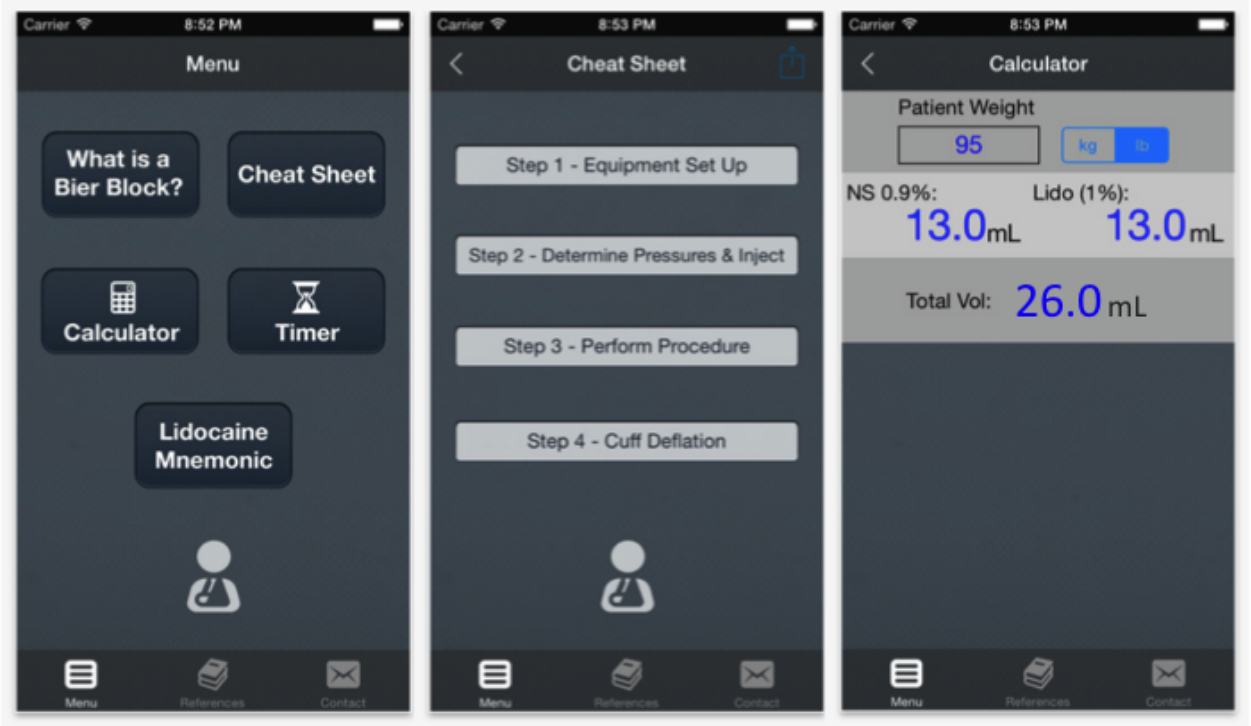
Smartphones are widely used and medical smartphone apps have been shown to support the acquisition of technical skills [7]. We have developed a novel point-of-care smartphone app designed to facilitate learning and maintenance of BB competency. Here we report on the app development process and functionality, with an emphasis on both its utility for individuals interested in using BB and its function as a model for the development of an educational tool to support the implementation of any new technique in the emergency department (ED). App dissemination metrics will be tracked, and its utilization at our center will be compared with real-world clinical use of BB for fracture reductions.

Methods

Mobile App Content and Functionality

The app functions as a self-contained tool to support the utilization of BB by both physicians and nurses and may be used by either novice or experienced users. Additionally, the app contains supporting resources necessary to facilitate the establishment of a departmental BB program. The BB app (Figure 1) contains a brief description of BB and a demonstration video. From the main screen, users can find complete step-by-step instructions. A dose calculator determines weight-based lidocaine dosing, in metric or imperial units with maximal dosages, and a timer directly integrates a stopwatch function. A user-friendly memory aid is provided for the signs, symptoms, and management of lidocaine toxicity. A tab from the main menu links to evidence-based BB references including our institutional protocols for BB and local anesthetic toxicity management, a medication order sheet with integrated dosage calculator, and a safety monitoring record. All reference materials can be saved, printed, or emailed from within the app directly. All content was adapted from our evidence-based institutional BB training course [6].

Figure 1. Main menu and selected screenshots of the BB smartphone app. (Source: Apple App Store Store, MUHC Bier Block App; Developer: Silverbirch Ventures, Toronto, ON).



Feedback was collected from departmental stakeholders following BB training to determine preferences for app content and features. The app was piloted for technical ease of use and clarity, and ongoing quality feedback was incorporated into subsequent app updates. All content and protocols received institutional approval for release from the McGill University Health Centre.

Technical Requirements and Associated Costs

Beta testing was performed using Apple's proprietary TestfFight software (Apple Inc). Total app storage requirement is 30 MB, and once installed on a mobile device, all content is available without internet connection. The current version is compatible with Apple iOS devices and is available for free through the Apple App Store. Development costs were under Can $1250 in addition to a mandatory fixed recurring cost of Can $100 per year to maintain an Apple developer account.

App Evaluation

App dissemination will be tracked using the analytics provided by the app builder and the Apple App Store Analytics software, as described elsewhere [8]. Metrics tracked will include Web-based app views, referrals, user engagement (number of sessions and active devices), total downloads, and retention. Users will be invited via the app to participate in a self-administered electronic survey to assess self-reported perceptions of the BB app. User-perspective surveys will be developed and reported according to published guidelines [9]. Specific data on app utilization and timing of use will be tracked among users in our PED in parallel to real-world clinical use of BB for pediatric fracture reductions [6]. Tracking of app usage in our PED will make use of the external tester function of Apple TestFlight software.

Results

The BB mobile app was launched in January 2015, with updates incorporating user feedback until 2016, and underwent a final content update in September 2018. After receiving approval by the McGill University Health Centre Research Ethics Board, app analytics and clinical correlation metrics will be evaluated between January 2020 and December 2021.

Discussion

The BB app was developed to improve and maintain comfort of individuals performing BB and to enhance the sustainable functioning of a departmental BB program. The app was designed for interdisciplinary use by both nurses and physicians. This point-of-care tool supports maintenance of competency that is often limited by sporadic clinical opportunities when used alone as a quick reference, in combination with other models' procedural learning such as simulation, or as a cognitive aid during both simulation and real-world use. To our knowledge, this is the only app for BB, and it is unique in its range of functionality.

Despite the rapid proliferation of medical smartphone apps, there is a paucity of literature on the use of apps to learn or support ED procedures, and such apps are very few. The majority of currently available medical apps contain basic demonstration videos, instructional texts, clinical decision rules, or calculators. More recently, apps with greater functionality and sophistication have been described for point-of-care use in acute care settings [10]. Hawkes et al have described an app for neonatal intubation that increased physician knowledge and improved procedural performance [7].

The BB app is also exemplary of how a smartphone tool can complement and augment the introduction of a new technique throughout a department or institution. Procedure preparation time is shortened by convenient access to printable medical order sheets, monitoring forms, and dose calculators. The use of such an app may reduce the time and resources required for frequent departmental refresher training and can help bridge the gap between courses for infrequent users or new personnel. Moreover, full evidence-based protocols within the app facilitate knowledge translation to other departments and institutions wishing to implement a similar program.

Our BB app does not provide details regarding pneumatic cuff inflation and safety checks, which vary by make and model of the automatic tourniquet system. Importantly, the BB app itself has not undergone peer review; however, this is not unusual or unique to our app [11], but could someday become necessary in a changing regulatory environment [12]. Moreover, we have not quantified the effect of the app to prevent the attrition of comfort among BB users and how the app compares to refresher courses. Understanding how to best integrate this and other apps into current educational models of procedural learning remains to be studied, but is beyond the scope of this report.

In summary, BB is safe and effective for pediatric forearm fracture reductions but remains underutilized. We have developed a novel BB smartphone app to overcome the barriers to more widespread use of this technique. The app is not only a resource for individual BB users but also provides a case study for how an institution can develop an educational tool to support a new program and enhance knowledge translation with other centers.

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Conflicts of Interest

None declared.

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Abbreviations

BB: Bier block
ED: emergency department
PED: pediatric emergency department

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Protocol

An Electronic Clinical Decision Support System for the Assessment and Management of Suicidality in Primary Care: Protocol for a Mixed-Methods Study

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Abstract

Background: Suicide is a global public health concern, but it is preventable. Increased contact with primary care before the suicide or attempted suicide raises opportunities for intervention and prevention. However, suicide assessment and management are areas that many general practitioners (GPs) find particularly challenging. Previous research has indicated significant variability in how GPs understand, operationalize, and assess suicide risk, which subsequently has an impact on clinical decision making. Clinical decision support systems (CDSS) have been widely implemented across different health care settings, including primary care to support practitioners in clinical decision making. A CDSS may reduce inconsistencies in the identification, assessment, and management of suicide risk by GPs by guiding them through the consultation and generating a risk assessment plan that can be shared with a service user or with specialized mental health services.

Objective: Our aim is to co-develop and test with end users (eg, GPs, primary care attendees, mental health professionals) an electronic clinical decision support system (e-CDSS) to support GPs in the identification, assessment, and management of suicidality in primary care.

Methods: Ours is an ongoing embedded mixed-methods study with four phases: (1) qualitative interviews with GPs to explore their views on the content, format, and use of the e-CDSS, as well as consultation with two service-user advisory groups (people aged ≤25 and people aged ≥25) to inform the content of the e-CDSS including phrasing of items and clarity; (2) participatory co-production workshops with GPs, service users, and clinical experts in suicidality to determine the content and format of the e-CDDS; gain consensus of the relevance of items; establish content validity and identify pathways to implementation, using the Consolidated Framework for Implementation Research; (3) building the e-CDSS so that it guides the GP through a consultation; and (4) usability testing of the e-CDSS with GPs and service users in one primary care practice involving a nonlive and a live stage.

Results: The study was funded for four years, to take place between 2015 and 2019, and is currently completing phase 4 data collection. The first results are expected to be submitted for publication in June 2019. The findings will enable us to evaluate the feasibility, acceptability, and usability of a suicide-specific, electronic, guided decision support system in primary care.

Conclusions: This study will be the first to explore the feasibility, acceptability, and usability of an electronic, guided decision support system for use in primary care consultations for the improved assessment and management of suicidality.

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KEYWORDS

suicide; primary care; general practitioner; clinical decision support system

Introduction

Suicide is a global public health concern costing the lives of over 800,000 people per year [1]. It is among the three leading causes of death in those aged 15-44 and the second leading cause of death among children and young people aged 15-29 [1]. Among the strongest risk factors for suicide are history of suicide attempts, mental illness, and self-harm [2]. The likelihood of suicide may be reduced where health professionals and service users openly and compassionately identify and collaboratively address suicide risk. Research shows increased contact with health professionals and in particular, general practitioners (GPs), in the months prior to a suicide or an attempted suicide [3-5]. Contact rates range from 60%-83% in the 12-month period before suicide [4-6], and 45% of those who die by suicide are likely to have had contact with a primary care provider within 4 weeks of suicide [3]. Primary care is often both the first and last health care contact for those who take their life [7]. These high rates of pre-suicide contact suggest that primary care services are well placed to identify early, assess, and mitigate risk of suicide. Primary care is, therefore, considered an appropriate context to develop suicide prevention initiatives [8].

Suicide risk assessment and management, however, is an area that most GPs find particularly challenging, despite being a common feature of their work. In a typical morning or afternoon primary care surgery in the United Kingdom, at least one new case of depression out of 20 patients requires suicide risk assessment [9]. Organizational barriers including time constraints and a heavy workload coupled with a lack of specialist clinical skills and insufficient mental health training have been identified by GPs as significant barriers to the assessment and management of suicidal presentations [10-12]. A recent study by Michail et al [11] has identified significant variability in how GPs understand and operationalize risk, which subsequently has an impact on clinical decision making. GPs may be more likely to inquire about suicide risk following recognition of clinical features associated with depression, psychosis, or long-term physical health problems [13], yet evidence shows that depression is not systematically detected and managed by GPs [14,15]. This variability in clinical decision-making processes may be because practitioners tend to develop “mindlines” or heuristics linking certain risk factors with eventual outcomes [16,17]. Such cognitive devices may be developed by practitioners to aid information gathering and clinical decision making in time-pressured contexts. Heuristic-based decision making enables a rapid problem-solving approach to fast track a diagnosis or clinical decision; this is sometimes referred to as a “pattern matching” approach to clinical reasoning [18]. However, these cognitive shortcuts employed by practitioners could prove to be problematic. If allowed to become automatic and unconscious, they could lead to misdiagnosis and poor patient experience [19]. Heuristics and “gut-hunches” may play an important role in determining when clinicians inquire about suicide risk and influencing situations where practitioners fail to identify suicide potential [20].

Clinical decision support systems (CDSS) are “any electronic system designed to aid directly in clinical decision making, in which characteristics of individual patients are used to generate patient specific assessments or recommendations that are then presented to clinicians for consideration” [21]. A recent systematic review identified three categories of CDSS used across different health care settings, including primary care [22]. These include decision prompts, information retrieval systems, and bibliographic databases. All three types of CDSS have been shown to be positively associated with improved health care delivery including enhanced clinical decision making, supporting accurate diagnosis, and improving standards of chronic disease management and preventative care [22]. One of the added benefits of CDSS software is the “cognitive forcing function,” which may temporarily prompt the GP to switch from heuristic based to analytical decision making [23].

A suicide-specific electronic CDSS (e-CDSS) could address some of the aforementioned barriers to suicide assessment and management in primary care [11] by guiding GPs through the clinical risk assessment at the time of the consultation. Although there are several evidence-based suicide prevention training programs, for example, Applied Suicide Intervention Skills Training, and Skills-Based Training On Risk Management (STORM) for suicide prevention demonstrating sustained improvements in knowledge, skills, and attitudes [23-26], these do not address the challenges to assessment and management of suicidality in primary care, such as lack of guidance during the consultation and support in clinical decision making [11]. Suicide prevention training programs for GPs specifically have produced ambiguous results as many of these are provided to health professionals at population levels, rather than targeting GPs at their work place in primary care [27].

On the contrary, a suicide-specific e-CDSS could provide a standardized method of recording risk history and flagging ongoing social circumstances or risk factors [11], thus, facilitating appropriate management options. Most importantly, it could save the GP work and time by generating a risk assessment and management plan that can be shared with a service user and carer(s) or with specialized mental health services. Emerging evidence suggests that technology-based suicide prevention developments can assist clinicians with the identification and management of suicide risk, by providing clinical decision support [28]. However, this is still an underexplored area.

The aim of this study is to co-develop and test with end users (eg, GPs, primary care attendees, mental health professionals) an e-CDSS to support GPs in the identification, assessment, and management of suicidality in primary care.

Methods

Design

This is an embedded mixed-methods study incorporating a quantitative strand within a broader qualitative design (Figure 1). This design allows for bringing together insights from the different stages of the study to give a comprehensive approach to content development and initial evaluation of the e-CDSS in practices. The study will take place in the East Midlands, United Kingdom, between September 2017 and February 2019. The study received ethics approval by East Midlands - Nottingham 1 Research Ethics Committee (17/EM/0317).

Sample and Recruitment

Phase 1

Qualitative Interviews With General Practitioners

GPs working in National Health Services (NHS) primary care practices across the East Midlands will be invited to take part in an individual face-to-face qualitative, semistructured, audiotaped interview with one researcher (MH) to explore their experiences of assessing suicide risk in primary care as well as their clinical reasoning and decision making about risk management. The interviews will also explore GPs' views on the content, format, and use of the e-CDSS during consultation with at-risk individuals.

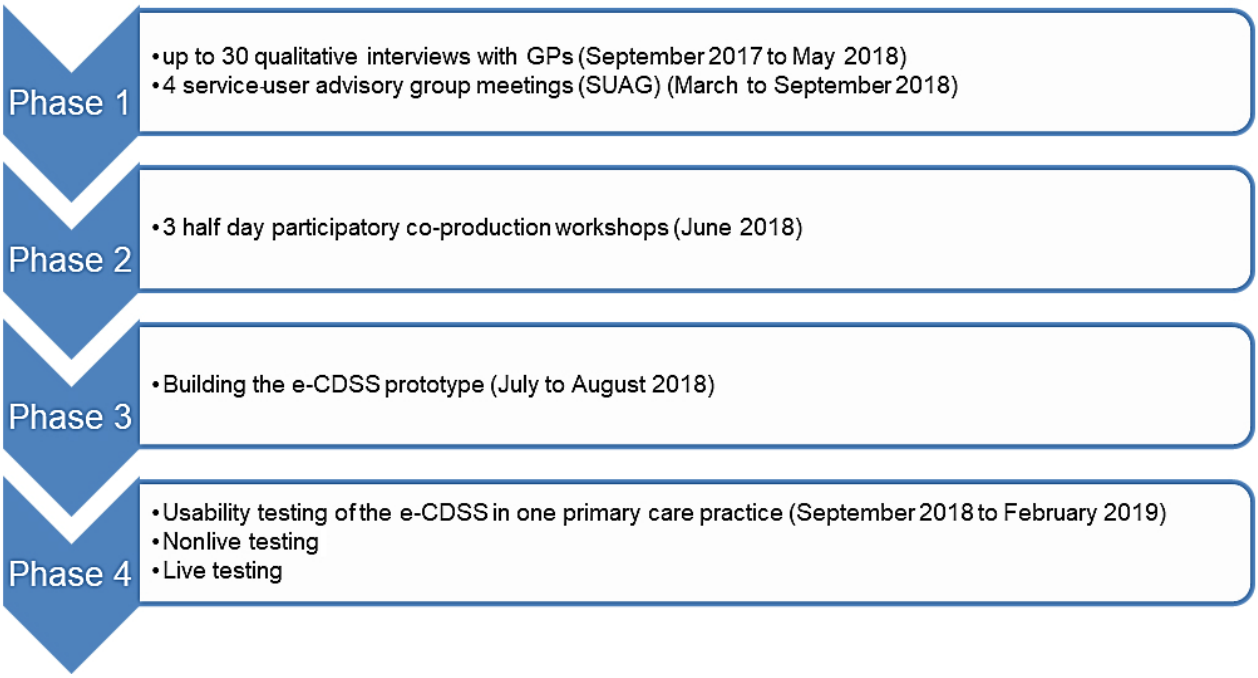
For Phase 1, up to 30 GPs will be recruited from primary care practices across the East Midlands region. The GP cluster leads, the mental health lead, GPs, or mental health commissioners across the various clinical commissioning groups in East Midlands will be initially approached to discuss the study and recruitment procedure. An invitation letter will be cascaded by email to all GPs by either the mental health lead GPs/commissioners or cluster leads, to inform potential participants about the study and encourage them to participate. Interviews with GPs will take place at times and locations convenient to them. For Phase 2, a purposive sample of GPs (ie, age, gender, ethnicity, and years of experience) will be drawn from Phase 1 and invited to attend the co-production workshops.

Service-User Advisory Group

To inform the development and design of the e-CDSS, two service-user advisory groups (SUAG) (people aged ≤25 and people aged ≥25) will be convened and meet (separately) four times between March 2018 and September 2018. The aim of this consultation would be to discuss potential items for inclusion in the e-CDSS, including phrasing and clarity, and to gauge the advisory groups' view of whether proposed items might facilitate further disclosure or hinder concealment of suicide-related information.

For Phase 1, up to 10 participants aged 14-65 registered with a GP in Nottingham City or Nottinghamshire County will be recruited from various sources. These include primary care practices, third sector organizations, charities, self-help groups, existing public and patient involvement networks (eg, Collaboration for Leadership in Applied Health Research and Care [East Midlands] Patient and Public Involvement work stream), and social media. Participants would have to have a history of being through a GP consultation where suicidal thoughts, feelings, or behaviors had been discussed. For young people under the age of 16, participation is conditional on parental/guardian consent. For Phase 2, a purposive sample of service users (eg, age, gender, ethnicity) will be drawn from Phase 1 and invited to attend the co-production workshops.

Figure 1. Study research design. e-CDSS: electronic clinical decision support; GP: general practitioner.



Phase 2

Co-Production Workshops

A group of experts and health care professionals including GPs and service users from Phase 1 (drawn based on age, gender, and ethnicity) as well as clinical experts in suicidality will be invited to attend three half-day participatory co-production workshops. In the first co-production workshop, the research team will present the expert group with a list of questions and prompts extracted from (1) previously published assessment scales for suicide and self-harm, and (2) GP data during Phase 1, for inclusion in the e-CDSS. Using a modified Delphi approach, the expert group will individually rank these items according to their perceived relevance for assessment of self-harm and suicidality using a 4-point Likert scale (1=not relevant, 2=somewhat relevant, 3=quite relevant, 4=highly relevant). A prespecified consensus margin (≥65%-70%) used by previous similar studies [29] will be used to determine inclusion of items in the e-CDSS. In the second co-production workshop, the research team will redistribute those items within the prespecified consensus margin and ask participants to rank these items again according to their perceived relevance for assessment of self-harm and suicidality using the same 4-point Likert scale. After finalizing the items for inclusion in the e-CDSS, participants will be asked to complete the Content Validity Index (CVI) questionnaire to establish content validity (>0.80) [30]. This will then be followed by group discussion to reaffirm the face and content validity of the final items and to gain endorsement of items for inclusion in the prototype e-CDSS. This reconciliation of the data-driven methodological approach with the situated knowledge and perspective of GPs, people with lived experience, and suicide prevention experts is important to ensure goodness of fit of the prototype with end users and within the primary care context. The aim of the third co-production workshop would be to identify pathways to implementation as well as barriers and facilitators of adopting the e-CDSS in routine practice, using the Consolidated Framework for Implementation Research [31]. The aim would be to create a "change map," that is, a graphical depiction of the pathway to long-term implementation of the e-CDSS.

Phase 3

Building the e-CDSS

Findings from Phase 1 and 2 will inform the most appropriate solution for an e-CDSS. The tool will be built by PRIMIS, a business unit of the University of Nottingham that specializes in building software to interface with and interrogate primary care information systems [32]. The tool will use clinical and informatics expertise alongside stakeholder requirements to present an option appraisal for a solution. Where possible, solutions will be based on existing Clinical Terms and Read Codes (ie, mandatory clinical coding systems for GP information technology systems). PRIMIS will account for current GP recording practices and the results of previous literature reviews in the field. A prototype of the tool will be developed in either The Phoenix Partnership (TPP) SystmOne or Egton Medical Information System (EMIS Web). The tool will take the form of a clinical system "protocol" (decision support algorithm) that will be response driven, that is, entries to the protocol will guide the user to the next appropriate stage.

Phase 4

Usability Testing of e-CDSS

An iterative evaluation of the e-CDSS prototype over a 6-month period will be conducted using an established theoretical and methodological framework [33] to refine the content of the final prototype, assess its usability, and provide the basis for initial evaluation of the e-CDSS in practice. The usability testing will be carried out in one primary care practice, and all GPs within this practice will be invited to participate. Usability testing will involve a nonlive and a live stage. Nonlive testing will involve GPs entering data into the e-CDSS in relation to simulated suicidal consultations based on clinical vignettes and completing a think-aloud exercise ("cognitive walk-through") in which they will be asked to describe possible next questions and lines of inquiry following on from prompts and items within the e-CDSS. GPs will be asked to complete a brief evaluation questionnaire (System Usability Scale [SUS]) [34] relating to the usability and function of the e-CDSS. Following "go-live" of the system, GPs will be asked to use the prototype e-CDSS during live patient consultations if and when appropriate (eg, during scheduled mental health clinics). Following the use of the e-CDSS, GPs will be asked to complete the SUS as well as a short survey questionnaire about the overall relevance of the e-CDSS to suicidal consultations, its impact on clinical decision and management, its impact on workflow, as well as adoption and acceptability.

Usability testing will take place in one practice (Nottingham City or Nottinghamshire County), and all GPs employed within the practice will be eligible to participate. The recruitment of the practice will be based on convenience sampling based on accessibility and expressions of interest.

At this stage, the study will not be seeking feedback from primary care service users who have been in a consultation where the prototype e-CDSS is used, since the aim of the current study is to design the content for and to build an e-CDSS to support GPs in the identification, assessment, and management of suicidality in primary care. The current study will seek to investigate the compatibility of the e-CDSS with GPs' consultation styles, the impact and integration into GP workflow, and its acceptability and feasibility to GPs. Further research is planned to formally investigate service user satisfaction within consultations in which the tool is used.

Feasibility, Usability, and Acceptability Criteria for Success for the e-CDSS

A set of predetermined criteria, in line with previous studies [35,36], will be used to assess feasibility, usability, and acceptability of the e-CDSS (Table 1). These criteria will be measured using data from co-production workshops (Phase 2), as well as the SUS and the survey questionnaire data GPs provide during usability testing (Phase 4). If the e-CDSS prototype does not reach the criteria for success, it will be refined according to the users' needs and retested by GPs until it is fully adapted to their requirements.

Table 1. Electronic clinical decision support (e-CDSS) feasibility, usability, and acceptability criteria for success.

Measure	Criteria	Study phase
Content validity	>0.80 on the Content Validity Inventory	Phase 2: Co-production workshops
Usability	≥70 on the System Usability Scale	Phase 4: Usability testing (nonlive and live stage)
Adoption/Acceptance	Frequency of use—evidence that the e-CDSS is used by general practitioners at least once in a surgery with any new patient with depression, or new or severe mental health problems	Phase 4: Survey questionnaire (free-text response plus Likert Scales)
Feasibility and relevance in practice	GP reports and feedback on satisfaction with the e-CDSS; perceived barriers; ideas for improvement; ideas for further utilization; impact on workflow; impact on content of consultation; and impact of management (eg, referral rates, prescription rates)	Phase 4: Survey questionnaire (free-text response plus Likert Scales)

Measures

Content Validity Index

The Content Validity Index (CVI) [30] is a widely used method of quantifying content validity for questionnaires with multiple items [30]. The CVI captures interrater agreement, through a standardized approach to computing agreement for each proposed item for inclusion in the questionnaire (or in this case the e-CDSS), as well as for the overall questionnaire. Participants are asked to rate each proposed item on an ordinal scale from 1=not relevant to 4=highly relevant. For each item, the number of ratings assigning 3 or 4 is then divided by the number of respondents to provide the proportion agreeing on the relevance of the item. The average score across each item of the e-CDSS will then also be calculated to generate a global content validity score. Scores of 0.80 are often considered the lower acceptable limits [30]. Application of the CVI will allow quantification of interrater agreement and be followed by group discussion to finalize the items for inclusion in the e-CDSS.

System Usability Scale

The SUS [34] will be administered to GPs during Phase 4 to measure the usability of the e-CDSS. This has been used extensively to assess the usability of a wide range of products and services including hardware and software, mobile devices, websites, and apps [37]. The SUS comprises 10 statements rated on a 5-point Likert scale (strongly agree to strongly disagree), recording respondents' views of the usability of the e-CDSS. Total scores for the SUS range from 0-100. Published guidance [37] suggests that products with adequate usability will score above ≥70.

Survey Questionnaire

A short survey questionnaire for completion by GPs at Phase 4 will be developed based on data from GP interviews and SUAG meetings (Phase 1) as well as relevant literature [11] to assess the overall relevance of the e-CDSS to consultations in relation to suicide presentations, its impact on workflow, adoption, and acceptance as well as its impact on the content of the consultation and clinical outcomes (eg, referral and prescription rates). The survey questionnaire will use a combination of Likert scales and free-text response. Quantitative items will be calculated to provide total scores, mean scores, and variance scores for each item across participants to provide an indication of acceptability of the e-CDSS to GPs in relation to clinical appropriateness, contextual appropriateness, and quality of actionable decision support. High variance might be seen for some items where practices vary a lot in context and less so on other items.

Data Analysis

Phase 1

GP qualitative interviews will be audio recorded and fully transcribed removing any identifiable data to preserve participant anonymity. Data will be analyzed using thematic [38] and content analysis [39]. Thematic analysis will allow the examination and recording of themes (patterns) within the GP data in relation to challenges in assessing and managing suicide risk in primary care, barriers and drivers for the use of the e-CDSS, and potential items and prompts for inclusion in the e-CDSS. Content analysis will be used to provide frequencies of coded themes including frequencies of those items and prompts mentioned by GPs during the interviews. NVivo 11 software [40] will be used to facilitate data analysis. Field notes kept during the SUAG group meetings will be presented in narrative form [41].

Phase 2

Statistical analysis will be descriptive (IBM SPSS 24.0). Consensus agreement will be calculated using counts (n) and proportions (%) for a median relevance rating of ≥3.25. Regarding the CVI, for each item the number of ratings assigning 3 or 4 will be divided by the number of respondents to provide the proportion agreeing with the relevance of the item. The average score across each item of the e-CDSS will then be calculated to generate a global content validity score. Scores of >0.80 are considered acceptable [30].

Phase 4

Consent, recruitment, and retention rates of GPs participating in the usability testing will be calculated. SUS item scores will be summed to obtain total scores. Total scores of ≥70 indicate adequate usability [37]. For the survey questionnaire assessing adoption, acceptability, relevance, and impact on management and workflow, we will present the mean, variance or standard deviations, and 95% confidence intervals for normally distributed variables, the median and interquartile range for skewed variables, and the frequency and proportion for categorical variables.

Results

The study was funded for 4 years, to take place between 2015 and 2019, and is currently completing phase 4 data collection. Enrollment to Phase 1 (GP interviews) was completed in May 2018, with 30 GPs interviewed, and 6 people with lived experience taking part in SUAGs. Phase 2 (co-production workshops) was completed in June 2018, with a total of 24 participants taking part (ie, GPs, service users, commissioners, mental health clinicians, and subject matter experts in suicide prevention). Phase 3 (building the e-CDSS is currently underway) and Phase 4 (usability testing of the e-CDSS) is scheduled to take place between autumn 2018 and early 2019. Data analysis will be ongoing throughout Phase 4, with the first results expected to be submitted for publication in June 2019.

Discussion

Principal Considerations

Suicide is a major public health issue, but it is preventable. As the majority of pre-suicide contact takes place in primary care, GPs have an increasingly important role in the early identification, assessment, and management of suicide risk. This research will lead to the development of an evidence-based, electronic, guided decision support tool for use in primary care for the improved assessment and management of suicidality. The end product will be the output of collaboration and co-production between the research team, health informatics experts, and key stakeholders including primary care practitioners and service users. This collaborative approach will facilitate the implementation and uptake of the tool, which is a potential gain of this research. In addition, this research is expected to raise awareness, improve education of GPs about suicide, and promote best practice in assessing and managing risk. If the feasibility, acceptability, and usability of the e-CDSS are established in this study, then further research would be needed to establish its effectiveness and efficiency in routine primary care consultations. A pilot, cluster (practice level) randomized controlled trial of e-CDSS versus usual care would examine whether the use of e-CDSS leads to improved skills and capacity of GPs to manage suicidal behavior. The primary outcome would be assessed using the Suicide Intervention Response Inventory-2 [42] at baseline, postintervention, and 6 months follow-up. Secondary outcomes would include self-reported preparedness measures [43]; GPs' attitudes (Attitudes Towards Suicide [44]) and confidence (using the 5-item STORM confidence in the assessment and management of suicidal people scale) [24]; service user satisfaction using qualitative interviews; and cost-effectiveness. If the effectiveness and cost-effectiveness of the e-CDSS is established, then this research could lead to improved assessment and management of suicidality in primary care and better patient experience of primary care mental health services.

Conclusions

This study will be the first to explore the feasibility, acceptability, and usability of an electronic, guided decision support system for use in primary care consultations for the improved assessment and management of suicidality. A CDSS may reduce inconsistencies in the identification, assessment, and management of suicide risk by GPs by guiding them through the consultation and generating a risk assessment plan that can be shared with a service user or with specialized mental health services.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the CLAHRC-EM scientific committee.

[PDF File (Adobe PDF File), 153KB - resprot_v7i11e11135_app1.pdf]

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Abbreviations

CVI: Content Validity Index
e-CDSS: electronic clinical decision support
GP: general practitioner
NHS: National Health Services
STORM: Skills-Based Training On Risk Management
SUAG: service-user advisory group
SUS: System Usability Scale

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Protocol

Development of an Electronic Data Collection System to Support a Large-Scale HIV Behavioral Intervention Trial: Protocol for an Electronic Data Collection System

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Abstract

Background: Advancing technology has increased functionality and permitted more complex study designs for behavioral interventions. Investigators need to keep pace with these technological advances for electronic data capture (EDC) systems to be appropriately executed and utilized at full capacity in research settings. Mobile technology allows EDC systems to collect near real-time data from study participants, deliver intervention directly to participants' mobile devices, monitor staff activity, and facilitate near real-time decision making during study implementation.

Objective: This paper presents the infrastructure of an EDC system designed to support a multisite HIV biobehavioral intervention trial in Los Angeles and New Orleans: the Adolescent Medicine Trials Network "Comprehensive Adolescent Research & Engagement Studies" (ATN CARES). We provide an overview of how multiple EDC functions can be integrated into a single EDC system to support large-scale intervention trials.

Methods: The CARES EDC system is designed to monitor and document multiple study functions, including, screening, recruitment, retention, intervention delivery, and outcome assessment. Text messaging (short message service, SMS) and nearly all data collection are supported by the EDC system. The system functions on mobile phones, tablets, and Web browsers.

Results: ATN CARES is enrolling study participants and collecting baseline and follow-up data through the EDC system. Besides data collection, the EDC system is being used to generate multiple reports that inform recruitment planning, budgeting, intervention quality, and field staff supervision. The system is supporting both incoming and outgoing text messages (SMS) and offers high-level data security. Intervention design details are also influenced by EDC system platform capabilities and constraints. Challenges of using EDC systems are addressed through programming updates and training on how to improve data quality.

Conclusions: There are three key considerations in the development of an EDC system for an intervention trial. First, it needs to be decided whether the flexibility provided by the development of a study-specific, in-house EDC system is needed relative to the utilization of an existing commercial platform that requires less in-house programming expertise. Second, a single EDC system may not provide all functionality. ATN CARES is using a main EDC system for data collection, text messaging (SMS) interventions, and case management and a separate Web-based platform to support an online peer support intervention. Decisions need to be made regarding the functionality that is crucial for the EDC system to handle and what functionality can be handled

by other systems. Third, data security is a priority but needs to be balanced with the need for flexible intervention delivery. For example, ATN CARES is delivering text messages (SMS) to study participants' mobile phones. EDC data security protocols should be developed under guidance from security experts and with formative consulting with the target study population as to their perceptions and needs.

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KEYWORDS

electronic data capture; ecological momentary intervention; HIV prevention and treatment; mHealth; mobile phone; text messaging

Introduction

Background

Data collection systems are integral to the design of behavioral intervention trials and have rapidly evolved from systems that are limited by rudimentary data collection tools, such as pen-and-paper assessments, to electronic data capture (EDC) systems that incorporate mobile phones and other mobile data collection devices. Advancing technology has increased functionality and permitted more complex study designs. To date, papers on mobile EDC systems have focused on improving health care delivery, disease surveillance, and epidemiological surveys in resource-poor settings [1-6]. Few publications describe the use of mobile EDC systems to support multiple study interventions, study management, as well as outcome assessments [4,7]. This paper fills in gaps in the literature by describing the EDC system from an ongoing HIV biobehavioral intervention trial, Adolescent Medicine Trials Network "Comprehensive Adolescent Research & Engagement Studies" (ATN CARES), and highlights the benefits and limitations of what current EDC systems can provide. We begin with an overview of EDC system functionality and highlight salient features for behavioral intervention trials.

As a basic role, EDC systems support data collection and increase the capacity to collect and store different types of data, compared with non-EDC systems. The ability of EDC systems to link to different mobile devices offers flexibility in capturing information over different time intervals and locations and from different sources. Our prior work has used EDC systems to store biological, anthropometric, social network, and self-reported measures that were collected over several time points as part of large-scale behavioral intervention trials in South Africa [8,9], India [10], and the United States [11]. In addition, EDC systems provide access to data in near real time, often through a Web portal. Easy data access throughout the study implementation period facilitates improved decision making and monitoring by research staff supervising the study progress. Staff activity monitoring in the literature has been presented for resource-poor settings, as in the monitoring of community health workers in Africa [12,13].

The ability to link EDC systems to study participants' mobile devices provides additional opportunities for intervention delivery, referred to as ecological momentary interventions [14]. EDC systems have been used to deliver automated short message service (SMS) text messages to participants' mobile phones to provide health education, medication, and clinic visit appointment reminders [15,16]. Frequent reporting through ecological momentary assessment (EMA) [17-19] is a mechanism for self-reflection and self-management that can lead to behavior change on its own, referred to as "reactivity" [17,18,20]. Lastly, EMA data collection and the ability to view EDC system data in near real time provides opportunities to intervene in EMA responses in a timely manner relative to less frequent reporting that occurs during in-person follow-up visits.

The EDC system for ATN CARES incorporates multiple functions summarized above: data collection, mobile phone-based intervention delivery, and real-time data access for timely data quality monitoring and decision making that pertains to participant care. Most mobile EDC systems utilized in the past did not have multiple functions [21]. The ATN CARES population also provides opportunities to highlight the benefits and limitations of current mobile EDC systems.

Study participants are youth living with HIV (YLH) and HIV-negative high-risk youth (HRY). By focusing on YLH and HRY, we highlight the benefits of what an EDC system can provide for a tech-savvy study population that already uses mobile phones to a high degree in its daily routines [22]. In addition, a focus on YLH and HRY underscores considerations of cultural sensitivity, privacy, and participant protection that remain and need to be addressed, regardless of the level of sophistication in an EDC system.

Objectives

The objective of our paper is to present the design of an EDC system for the CARES trials and show how multiple EDC functions introduced above can be integrated into a single EDC system to support a large-scale behavioral intervention trial.

Methods

Adolescent Medicine Trials Network "Comprehensive Adolescent Research & Engagement Studies" Overview

A suite of interventions, "CARES," is being conducted through the HIV ATN. Three separate studies share an overarching aim to address the increasing HIV epidemic among youth aged 12-24 years. Toward this goal, interventions were developed for YLH and HRY. Recruitment began in May 2017. Participants are being recruited through social service agencies, homeless shelters, HIV care clinics, and clinic referral in Los Angeles (LA) and New Orleans (NO). During recruitment, interested youth are screened, which seeds a case in the EDC. Eligible youth are consented and enrolled into one of three studies based on HIV test results and responses to screening questions.

Enrolled youth are then administered a baseline assessment and are repeatedly assessed at 4-month intervals over a 2-year period. YLH are administered blood tests for HIV viral loads, and HRY are tested for HIV seropositivity. Both cohorts are tested for the presence of sexually transmitted infections (STI) and administered drug screenings and assessments to self-report on HIV-transmission risk behaviors.

Assignment to one of the following three studies occurs at enrollment.

- *Study 1 (ATN 147)* is an observational study and is enrolling YLH who are acutely infected with HIV or youth who are YLH but untreated with antiretroviral therapies (ART) or treatment naïve for comparison. ATN 147 participants are aggressively treated with highly potent ART, as soon as possible after infection to examine variation in viral reservoirs over time. Participants receive an Automated Messaging and Monitoring Intervention (AMMI). AMMI has two components. Participants receive daily SMS text messages on their mobile phones that are tailored to their specific health needs such as medication reminders and health messages that are appropriate for YLH. The second component administers a weekly SMS text message survey for self-management and to keep YLH engaged in the study; survey nonresponse prompts follow-up from study staff. In addition, participants receive peer support, through a Web-based platform, and coaching support. Coaching by trained paraprofessionals is provided to make treatment referrals and provide brief interventions.
- *Study 2 (ATN 148)* is a randomized controlled trial (RCT) and is enrolling YLH with an established and unsuppressed HIV infection. At enrollment, YLH are randomized to one of the two study arms—A Standard Care arm that provides the AMMI or a Stepped Care arm. In the Stepped Care arm, increasingly intense interventions are delivered if a participant's viral load is detectable at follow-up visits. Steps of increasing care include the following: (1) the Standard Care AMMI; (2) standard care plus peer support; or (3) standard care plus peer support and coaching support.
- *Study 3 (ATN 149)* is an RCT and is enrolling HRY. Eligibility is based on being HIV negative and being at risk for acquiring HIV based on a number of risk factors. The HRY are randomized to one of four study arms in a factorial design—AMMI only as standard care (across arms), AMMI and online peer support, AMMI and coaching, or AMMI and online peer support with a coach. Similar to ATN 147 and 148, the weekly SMS text message survey provides an opportunity for self-management and engagement. In addition, the survey queries HRY on symptoms of HIV infection. Study staff follow-up with HRY indicating symptoms of acute HIV-related flu and referred for immediate HIV testing.

The EDC system was developed through the *CommCare* system, an open-source mobile data collection platform that is developed and hosted by *Dimagi, Inc*. In a typical research setting, a separate EDC system would have been developed for each study; we could have done so for ATN CARES using the *CommCare* system. A single recruitment strategy and assessment schedule across all three studies and in both cities facilitates the use of a single EDC system for most data collection and technology-based intervention activities. There is one exception to a single recruitment strategy that is being implemented across cities. We discuss the exception to highlight the flexibility of the EDC system to allow the study flow and data entry forms to differ by study and city if needed. Recruitment venues in NO include bars and other public venues that do not provide private spaces in which to administer the full screener. Instead, a (mini) prescreener is administered in public venues. Interested YLH or HRY who are eligible based on the prescreener are invited to be screened and enrolled, if eligible, in a more private setting (eg, a clinic). *CommCare* data collection includes screening, study assignment and randomization, enrollment, contact information, 4-month self-report assessments, laboratory test results (ie, HIV and STI tests, and drug screenings), and weekly SMS text message surveys. In addition, the CommCare system pushes automated SMS text messages to participants' phones for intervention activities. After enrollment, participants receive an SMS text message on their mobile phone to welcome them to the study and inform them of their study arm assignment if they are enrolled in ATN 148 and 149. Furthermore, participants receive daily SMS text messages as part of the AMMI unless they opt out. All study procedures were approved by the institutional review boards at participating universities. Further details on each of the three studies may be found in the corresponding study protocol papers [23-25].

Electronic Data Capture System Development for Adolescent Medicine Trials Network "Comprehensive Adolescent Research & Engagement Studies"

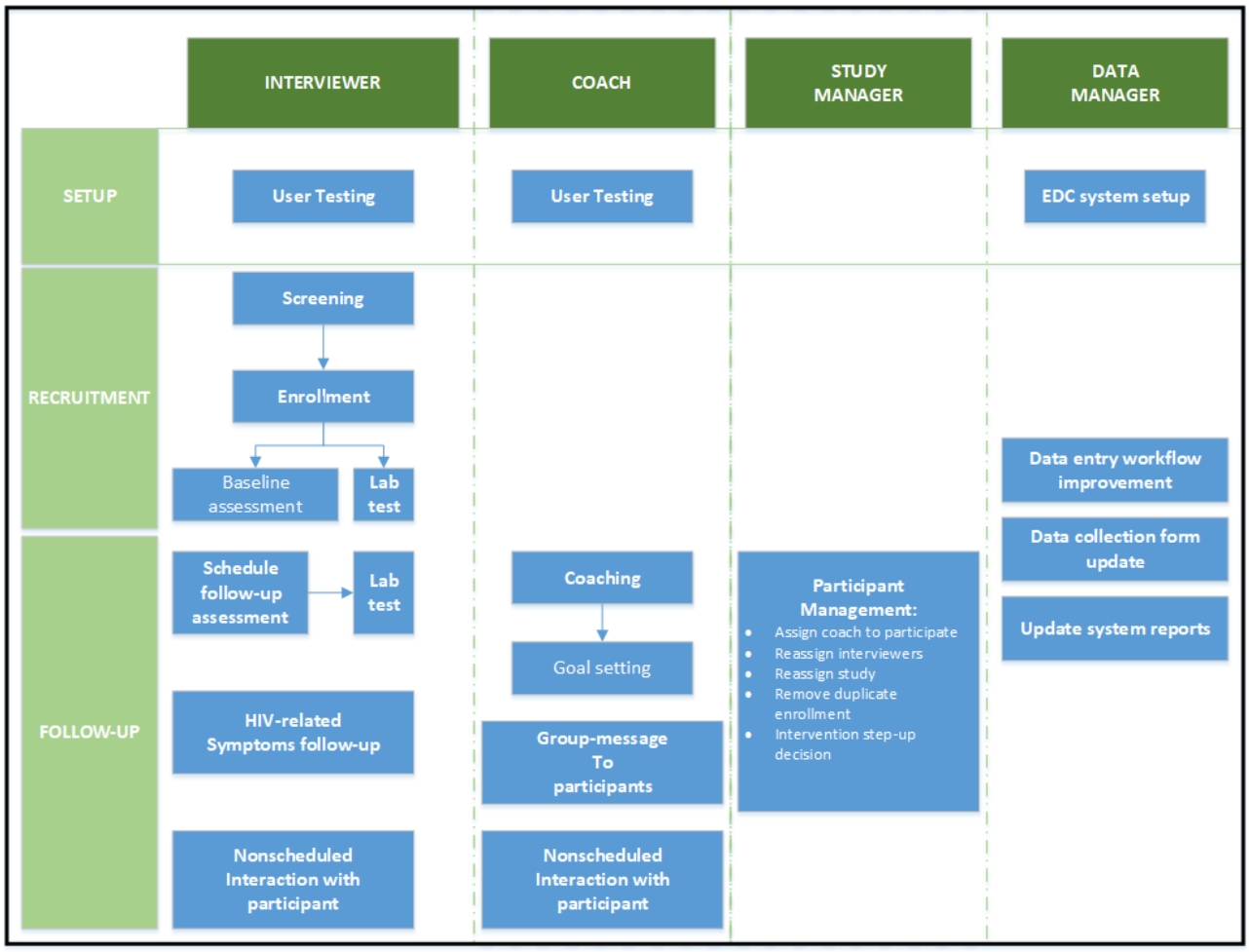
The development of the EDC system began with meetings between the ATN CARES research team and *Dimagi* technicians. Workflows were developed for all three studies described above and focused on major decision points regarding participant screening, enrollment, randomization, and retention. Determination of research staff roles in accessing the EDC system was carried out in parallel to the development of the workflow and is summarized in Table 1. Four roles were identified for the research staff who act as interviewers, coaches, study managers, or data managers.

Figure 1 provides an overview of the study workflow by role. In the figure, boxes without arrows connecting them to other boxes indicate processes that can occur at any time during setup, recruitment, or follow-up study phases. The EDC system was designed to allow data to be entered on the following study aspects: recruitment and retention, study intervention, study management, and outcome assessment. The EDC system offers flexibility in authorizing different levels of access to the study data depending on the role. Interviewers and coaches access the EDC system the most to enter and view study participant information across all three studies.

Table 1. Roles, purpose for accessing electronic data capture (EDC) system, and level of access granted for research staff who use the EDC system.

Role name	Access
Interviewer	Enter assessment, laboratory testing, and locator data via *CommCare* app. View participant data.
Coach	Enter semistructured coaching log via apps. Have access to reports and messaging utility, including sending out a group message to participants. View participant data.
Study manager	Complete research-related actions by submitting data such as rerandomization, reassigning a life coach for participants, or making stepped care decision. View reports and submitted data. Edit submitted data.
Data manager	Create and edit *CommCare* app. Create and edit reports and submitted data. Manage *CommCare* user access.

Figure 1. Schematic for roles of 4 types of research staff who access the electronic data capture (EDC) system and the study flow that pertains to each role during the study period.



Both roles enable one to view the following key information for each participant: basic demographics, participant tracking information (eg, preferred methods of contact and contact information), session calendars that contain scheduled interviewer assessment dates or coaching session dates depending on the role, study participants' progress in terms of completed assessments, and field notes that are entered by interviewers and coaches. Coaches have access to all notes, while interviewers have access only to interviewer notes.

Study managers utilize the EDC system to act upon a participant's study status directly, such as investigator actively withdrawing a participant from the study, assigning a specific coach to a participant, or rerandomizing a participant if the HIV serum status changes. Study managers, coaches, and interviewers only have access to data collected in their city of residence (LA or NO). Restricted access not only adds a layer of protection for participant data but also streamlines research staff workflows. For example, coaches can more quickly locate, access, and browse participant notes than if they had to filter information from participants across both cities. The data manager has access to data across both cities. The data manager troubleshoots day-to-day data entry issues and can update any aspect of the EDC systems to reflect new study needs, including a change in assessment questionnaires and updating system reports or data entry workflow. In addition, the data manager can assist study managers in editing submitted data when data entry errors occur. Furthermore, the data manager creates reports for quality and progress monitoring of study teams.

Design of Electronic Data Collection Forms

Once the study flow was established, the research team worked with *Dimagi* technicians to design forms that supported data entry for each of the study tasks. Some forms were fairly standard based on prior HIV intervention trials that we had conducted and included assessment forms for in-person 4-month visits and weekly SMS surveys, laboratory forms to record laboratory testing results, and locator forms to enter participant contact and tracking information. A less standard form provided a place for coaches and interviewers to document nonscheduled visits with study participants, hereafter referred to as an *interaction log*.

Forms were initially developed outside of the EDC system for easy sharing and viewing by research team members, including members who would not be accessing the EDC system but gave input on its design. For example, the baseline and follow-up assessments were developed in Microsoft Word. Once finalized, forms were then built in the EDC system using one of the following three methods: (1) built directly within the EDC system by *Dimagi* technicians or the data manager; (2) built in Excel, converted to an XML file, and then uploaded into the EDC system as a readable XML file using a free Web-based service [26] (); or (3) built in Excel as a reference table (eg, SMS text message banks) and imported into the EDC system.

Electronic Data Capture System Testing

Prior to study initiation, study workflow was tested by conducting screening, enrollment, and baseline assessment procedures with mock study participants. This gave us a chance to ensure that the research staff understood how to use the EDC system, that questions and prompts on each form were properly specified, and that the EDC system was assigning participants to appropriate studies and randomizing when required. Mock interviews with study participants were supplemented by scenarios that were generated by the data manager to ensure that all possible scenarios were tested, even scenarios that were not anticipated to occur very often. For example, a scenario was generated for a YLH who was initially enrolled into ATN 149 but then tested HIV positive at a later date, requiring study reassignment and rerandomization if the youth was assigned to ATN 148. Testing was conducted in an iterative fashion where the data manager made corrections and enhancements to the EDC system specifications after each round of testing.

Goal and Requirements of the Electronic Data Capture System

Several general system requirements were considered throughout the development phase for daily tasks across all three studies. The EDC system was designed to (1) integrate data entry tasks into a single EDC system across all three studies and both cities where the study is taking place (LA and NO); (2) be intuitive for user navigation so that minimum training for study staff would be required; (3) be easy to modify so that EDC system changes can be programmed in a timely manner by a trained data manager or other research staff member; (4) support and maintain both incoming and outgoing SMS text messages; and (5) offer high-level data security during data collection in the field and for data storage. More details on each system requirement are provided below.

An Integrated System

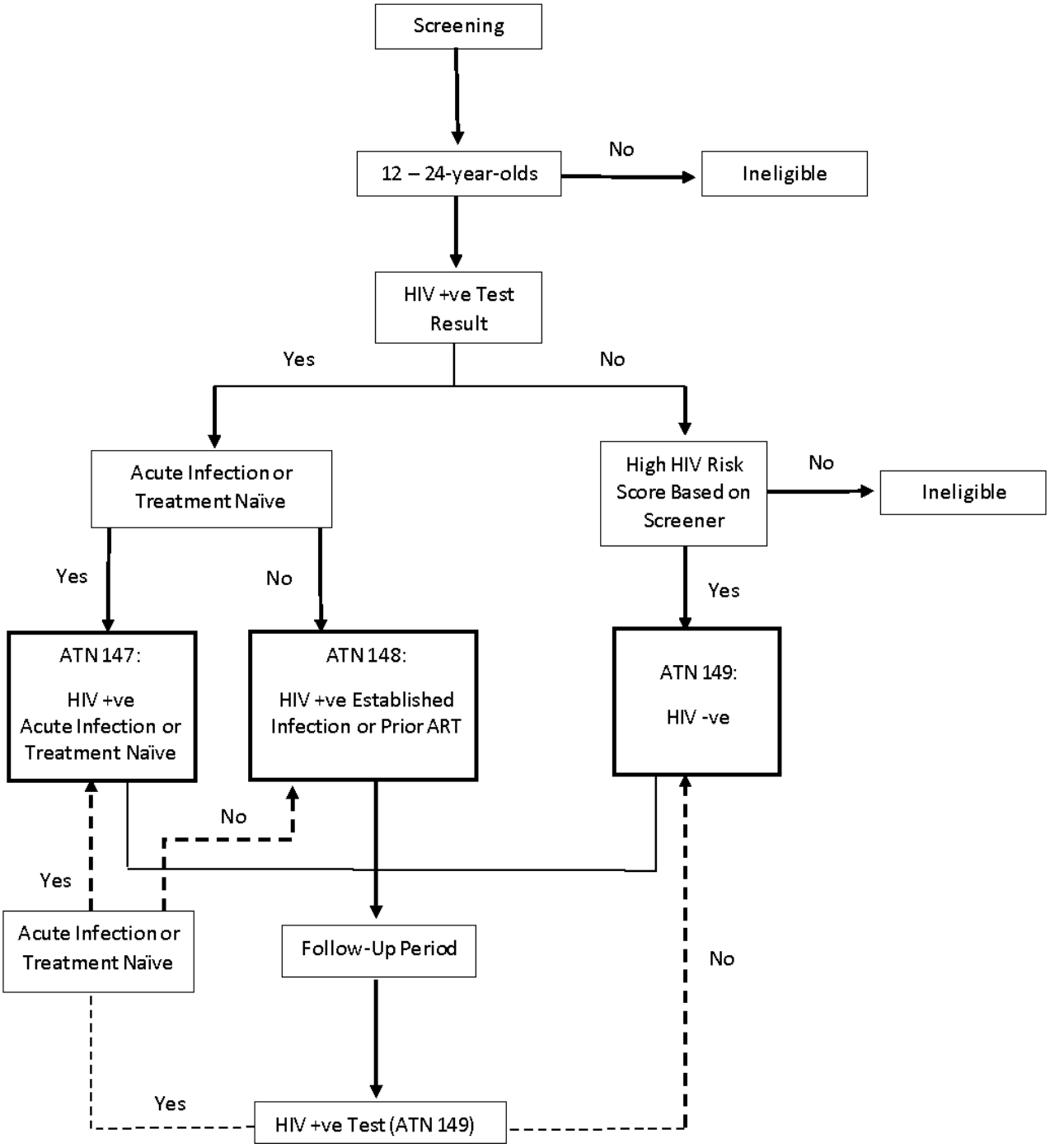
Data across all three studies in LA and NO are entered and accessed through 2 points of access: a *CommCare* mobile app on an Android device, either a smartphone or computerized tablet, or a *CommCare* Web portal on a desktop computer. The primary goal in the development of the EDC system was to streamline study activities so that additional study data that needed to be captured outside of the EDC system were minimized, especially data on paper. An integrated and paperless system minimizes errors in transferring data between separate databases and allows real-time data synchronization and utilization.

Integration required the assignment of a unique participant identifier for each study participant in the EDC system across various data sources, such as survey, study management, and lab sample collection and storage. A participant is opened as a "case" within the EDC system and assigned a unique participant ID when they express interest in study participation, complete the screener, and are determined to be eligible based on the screening data. The same participant ID is then used for tracking lab specimen data and weekly survey responses. Integration was made possible by carefully planning all the decision points and data sources at the outset so that they could be captured in a single EDC system; EDC systems typically only collect study outcome data. The following paragraphs provide examples of study tasks and decision points that are often conducted outside of EDC systems but managed by the CARES EDC system.

Eligibility, Study Assignment, and Randomization

Eligibility, study assignment, and randomization are all conducted within the EDC system. Figure 2 shows the decision processes. The first decision point for determining eligibility and study assignment is based on a rapid HIV testing information that is entered into the EDC laboratory form. A positive HIV diagnosis assigns participants to ATN 147 or 148. ATN 147 is recruiting acutely infected YLH and treatment-naïve YLH with established infections as a control sample. If a participant is treatment naïve, he or she will be preliminarily assigned to ATN 147. The ATN 147 laboratory team will then confirm through data entry the stage of infection based on various HIV RNA viral load blood tests. YLH with unsuppressed and established infections are recruited for randomization within ATN 148. A subsequent decision point occurs for interested youth who do not test HIV positive. They are eligible to participate in ATN 149 for HRY if the summation of responses to screening questions is above a certain threshold. For example, transgender youth and ethnic minority gay and bisexual youth automatically become eligible. Youth who identify as heterosexual but report multiple HIV risk factors such as homelessness, substance use, mental health problems, and past incarceration are classified as HRY and are eligible. Once participants are assigned to ATN 148 or 149, they are then randomized to a study arm.

Figure 2. Study assignment schematic showing assignment to one of three studies (Adolescent Medicine Trials Network, ATN, 147-149) through the electronic data capture (EDC) system after screening; ATN 149 participants who test positive for HIV during the follow-up period are reassigned to ATN 147 or 148. ART: antiretroviral therapy.



Randomizations

ATN 148 and 149 are RCTs and require participants to be randomized after study enrollment is completed by entering rapid diagnostic test results. Study participants are automatically randomized to ATN 148 and 149 study arms within the EDC system. An exception occurs if study participants change studies and need to be randomized again. For example, it is possible for an HRY in ATN 149 to become HIV positive during the study (Figure 2). The participant would then be offered enrollment in ATN 147 or ATN 148 depending on the stage of infection and prior ART utilization. In this instance, interviewers update study assignment and data managers conduct the subsequent study arm (re)randomization.

Several randomization challenges were addressed so that randomization schemes could be programmed within the EDC system for ATN 148 and 149. RCT randomization schemes are typically stratified on one or more sociodemographic participant characteristics and site such as clinics. Randomization within the EDC system required careful consideration of how best to capture key variables and keep the scheme simple so that it could be programmed within the system. It was determined that the EDC system would feasibly accommodate 2 levels of stratification. Interviewer comprises the first stratification level

and is a proxy for the site. An interviewer was used instead of site because the *CommCare* app is designed to function offline in the event of interrupted internet connectivity. This also means that randomization needs to occur through interviewers' mobile phones without a connection to the EDC system. In general, interviewers are assigned to sites and serve as suitable site proxies. Self-reported sexual orientation identity (based on screening questions) was determined to be another important stratification variable and is being used as the second stratification variable for randomization.

Interaction Log

The interaction log records all nonscheduled interactions that any study staff have with participants, including content areas such as simple relationship building, participants updating contact information, rescheduling of participants' appointments, confirmation of participants' STI treatment, and so forth. For each interaction, we collect parameters that include date of the interaction and methods via which the interaction was completed (eg, phone, in-person, SMS text message, email, or social media). Specifically, we also require the study staff to report any failed interaction attempt to track staff effort required for each participant. This information is used for supervision and problem solving to maximize study retention.

Coach Monitoring Log

In addition to the interaction log, coaches record coaching activities through a separate log. This log records semistructured coaching activities, including coaching content areas and skills utilized, date of coaching, and the method of contact. The EDC systems record the length of each coaching session so that we can track coaching effort required for each participant assigned with a coach. Logged coaching information helps coaching supervisors to monitor and support coaching performance and better assign coaching workload. In addition, coaches are aided as they can refer to prior information through the mobile app to inform current interactions with participants. These data can also be used for analyses on engagement or utilization and dose-response effects.

Data Collected Outside of the Electronic Data Capture System

Despite efforts to capture data through a single EDC system, there are 3 instances where data are collected outside of the EDC system. First, participants were initially administered weekly surveys through SMS text messages. Response rates were low. Based on participant feedback, greater flexibility was provided to participants in filling out weekly surveys through SMS text message or an email prompt. Participants who receive email prompts are linked to a Web-based survey that is conducted through Research Electronic Data Capture. Second, participants who are randomized to receive peer support as an intervention component are asked to participate in a private social media discussion forum that is hosted through *Muut* [27], a JavaScript app. Conversation content data are collected through the *Muut* platform. Third, cost-effectiveness analyses will be conducted and require an estimation of staff time. Coaching logs and other intervention information are being entered into the EDC system, but they do not provide information regarding the amount of time spent performing study tasks. Staff activity information that is captured by the EDC system is being supplemented by *Time It*, a mobile app that allows individuals to record time spent carrying out different tasks.

Intuitive Use

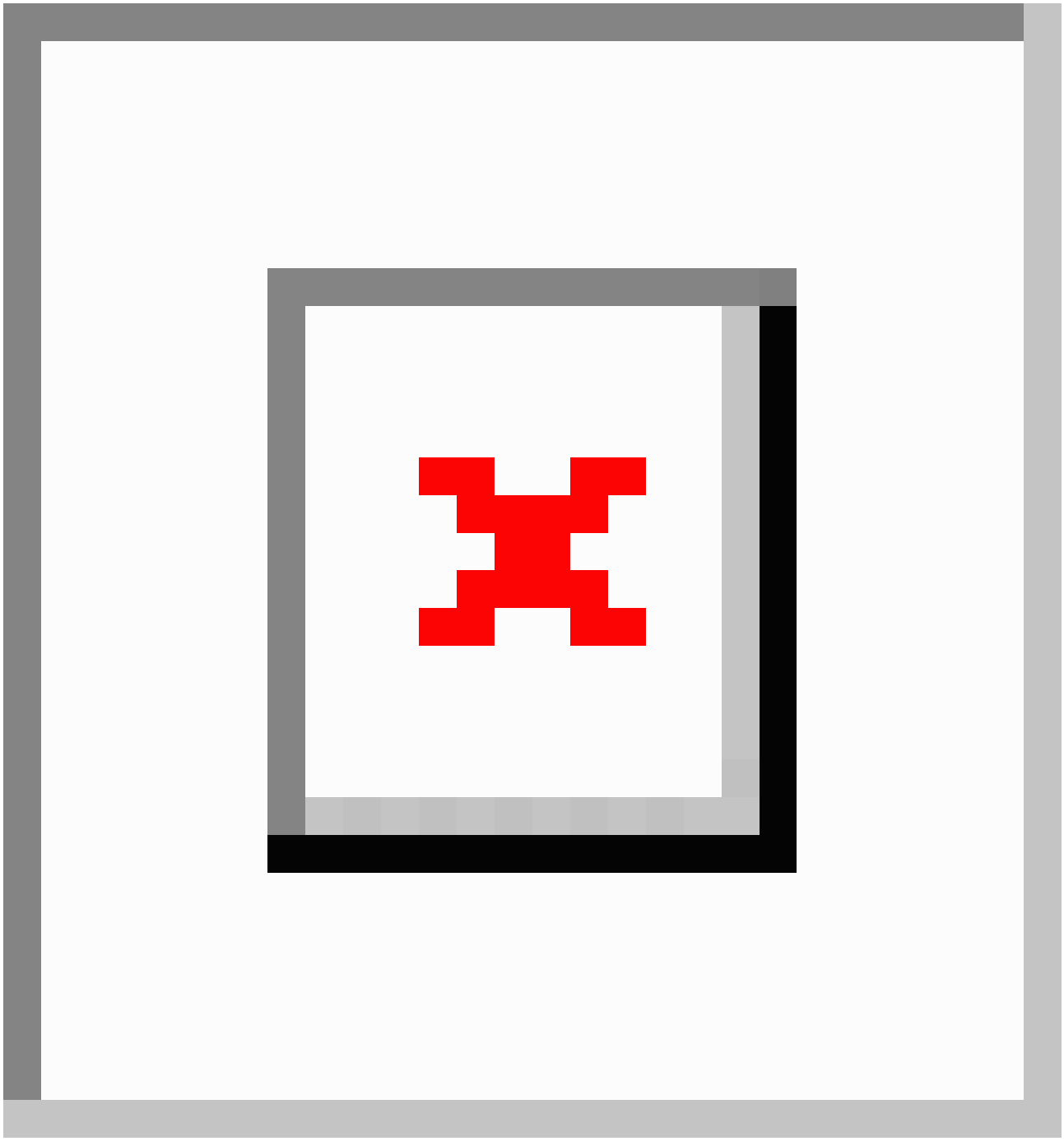
The EDC system was developed to be intuitive to use to reduce user burden, minimize data entry error, and, in turn, reduce data cleaning. For data entry purposes, all EDC system users (shown in Table 1) access the system through a *CommCare* mobile app on an Android phone or tablet or through a Web portal on a computer. Figure 3 shows screenshots of the CommCare app that are seen by interviewers. The left-hand screenshot shows a menu with study tasks in a logical workflow that begins with "Screener" and ends with "Retention Status." The right-hand screenshot shows the enrollment progress of a participant under the "Manage Enrollment" workflow indicated in the left-hand screenshot, with forms checked off once they are completed. The app was designed with an appealing dashboard that includes icons to guide users through their designated research tasks. The EDC system is set up to guide interviewers to complete the necessary steps for enrollment, including obtaining consent, collecting locator information, conducting a baseline assessment survey, as well as entering lab test data. Participants who complete the enrollment will then graduate to follow-up workflow, where (1) participants are randomized and may be opened up for life coaching interventions; (2) participants receive AMMI and surveys on their phone; and (3) follow-up assessments instead of baseline survey assessments will be available for those participants.

Intuitive use is also aided by built-in logic checks and data point validations. Users cannot enter information into subsequent fields within forms that clash with prior information that was entered into the system. For example, a warning will show up if an interviewer tries to enter an HIV viral load result for a seronegative participant. Information is also shared between forms; this means that information such as gender at birth and age that was collected during screening does not need to be asked again in the baseline assessment. Many participant characteristic variables such as HIV status and birth sex are used to set up appropriate skip patterns including for follow-up assessments. For example, questions regarding pregnancy at the baseline interview are only asked among female participants. HIV stigma questions are only asked among participants who had been positive for more than 4 months at the time of recruitment, that is, the baseline interview.

Easy Modification

The EDC system is set up so that changes to any of the study forms can be programmed in a timely manner without any special programming abilities by a trained research staff member, mainly the data manager. Figure 4 illustrates the ability to easily modify forms. A screenshot is shown for one of the sociodemographic multiple-choice questions from the baseline assessment that queries place of birth. Fields such as "Display Text" are selected by mouse clicks and modified by keystrokes.

Figure 3. Screenshots of CommCare mobile app that links to the electronic data capture system.



Short Message Service Text Messaging

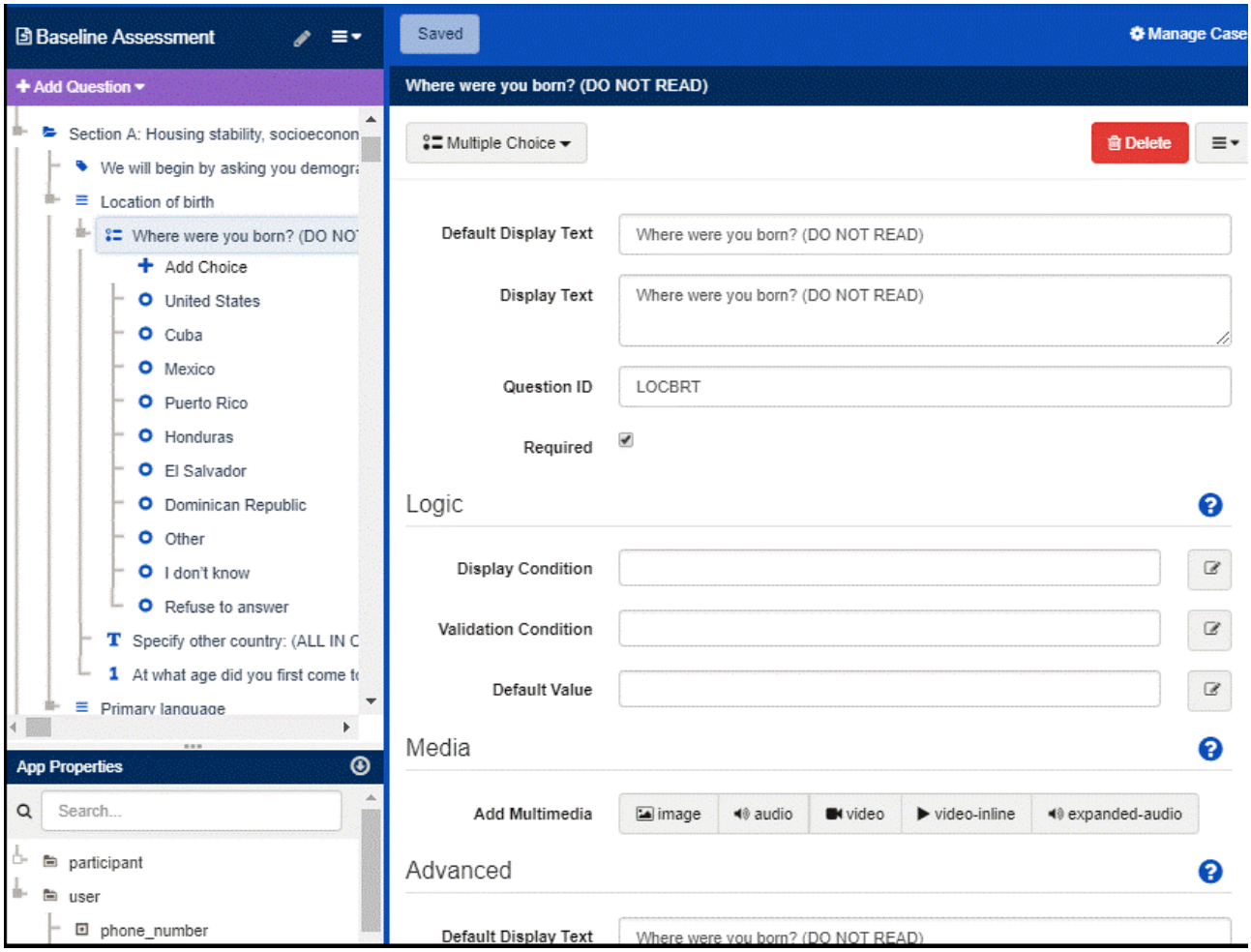
The EDC system was set up to manage all SMS text messaging with study participants. This occurs in 3 instances. Shortly after study enrollment, participants receive a welcome SMS text message that also contains information on intervention arm assignment, if participants are assigned to ATN 148 or 149. For example, if a participant is assigned to have a coach, both the participant and the coach receive an immediate SMS text message informing them of the initiation of their coaching relationship. Participants who are randomized to receive peer support are sent an SMS text message invitation to join a peer support group with a weblink to the registration page. All participants receive weekly SMS text message surveys and daily health promotion messages that span 5 domains as follows: general health, mental health, sexual health, substance abuse, and medication adherence. The specific messages that are sent to participants are based on one of four risk profiles that they are assigned to within the EDC system: gay, bisexual, and transgender youth (GBTY) living with HIV, non-GBTY who are living with HIV, high-risk GBTY, and high-risk non-GBTY.

Data Security

The EDC system is set up to meet Web standards for compliance with the Health Insurance Portability and Accountability Act. The EDC system incorporates redundant safeguards to protect participant data. For example, mobile devices used for data entry are password-protected, saved form data are encrypted on

the device and during transmission, and form submissions are transmitted and removed from devices as soon as internet connectivity is established.

Figure 4. Screenshot of the electronic data capture system interface that is used by the data manager to create and edit assessment questions.



Results

Experiences in Developing the Electronic Data Capture System

By using *CommCare* as the major EDC system, we were able to meet most of the requirements set during the study design. In particular, real-time data download allows generation of multiple reports that can inform recruitment planning, budgeting, life coaching quality, interviewer supervision, as well as data collection quality itself. In addition, the EDC specification that aims to minimize the need for participant tracking documents that reside outside of the EDC system improves their overall interaction experience with participants and increases field worker efficiency. For example, within the EDC system interviewer role, we can easily identify participants that require immediate follow-up efforts and, then, initiate contact with participants per their preference, such as their preferred way of contact and preferred pronoun that is used to address them in person or through an SMS text message. Finally, the EDC system is a nonprogrammer-friendly platform and allows nonprogramming data managers to update the EDC system for each study needs in a timely fashion. For example, as the field staff discover new types of interactions that they have with study participants, the data management team can easily expand and redefine the list of interactions available for selection within the interaction log to accommodate this unforeseen task in near real time.

Electronic Data Capture System Implementation

At the time of writing, CARES studies have been in the field for approximately 10 months from May 2017 to early July 2018; recruitment is ongoing. We present sample sizes to summarize information that has been catalogued and managed through the EDC system and, in turn, to underscore the performance of the EDC system across studies 1-3. Of 1053 youth who have been screened (576 in LA and 477 in NO), 812 have been recruited and enrolled (408 in LA and 404 in NO). Study 1 enrolled 26 YLH, study 2 enrolled 70 YLH, and study 3 enrolled 716 HRY. Four-month assessments (ie, assessments at the first follow-up) have been conducted on 608 participants. In addition, the EDC system is being used to facilitate intervention delivery as discussed above. For example, a total of 16,994 daily SMS text messages have been sent to 627 participants' phones, and 432 participants have filled out at least one weekly SMS text message survey as part of the AMMI. Among YLH in study 2 who have been randomized to the Stepped Care arm, 3 have stepped up from the AMMI to the next level of support.

Electronic Data Capture System Challenges

We experienced several challenges after the implementation of the EDC system. Most of these challenges were resolved by modifying the system. We discovered multiple discrepancies between real-world field worker (ie, coach and interviewer) needs and workflow scenarios that the research team was able to envision and test before the EDC system was launched in the field. For example, the initial HIV clinical visit would be the ideal setting for the research staff to collect all baseline information for acute-infected YLH. However, the impact of learning of an HIV diagnosis during the first clinical visit is potentially overwhelming for YLH. It was decided that alternative study protocols should be set up so that research staff do not need to go through all the risk behavior questions listed in the screening form or any other required forms with newly diagnosed YLH during enrollment. As a result, we built additional features within the EDC system that allow interviewers to circumvent data entry into some of the enrollment forms that typically require data entry if an HIV-positive test result is also entered into the EDC system. A participant ID is still generated for lab specimen tracking. This alternative workflow allows interviewers to focus on the consent and blood draw with participants during their first clinical visit.

Despite the EDC system training for field workers prior to study implementation, the major challenges around the EDC system lie in data quality control among field workers. In particular, accurately logging ad-hoc participant interactions proved to be especially challenging for field workers. First, we found that field workers tend to prefer to enter information into the open-ended running notes as opposed to the prespecified types of interactions that are captured by form fields. Second, open-ended note documentation styles vary greatly among field workers, making a quick review of the notes across field workers harder. To address this, we first expanded the capabilities of the interaction log to capture additional data regarding field workers' interactions with participants that we could not anticipate. Field workers were then required to memorize what information could be collected within the interaction log. Furthermore, the data management team put together additional data entry training sessions to standardize the use of open notes after consulting with the intervention team.

Another issue came up regarding daily SMS text messages and weekly surveys that the EDC system sends to participants' phones. Participants can discontinue the receipt of SMS text messages and surveys during the study. Our original plan was that participants would have to contact the study staff to discontinue the receipt of daily messages and weekly surveys. We found that the SMS text message server is legally required by Federal Trade Commission regulations to allow a participant to opt out of all SMS text message services by replying to the daily message or weekly service with a "STOP" command. Obviously, those who opt out of the SMS text message intervention component will not receive the full intervention, essentially creating an additional ad-hoc intervention arm. Fortunately, the EDC system allows study managers to track the list of participants who opt out, and subsequently, field workers can reach out to study participants to attempt to re-engage them. In the least, the study team can track participants who self-select the ad-hoc intervention arm.

Discussion

This paper describes an EDC system that is currently being used to support the implementation of a large-scale HIV intervention trial across multiple sites. Several key considerations underpinned the EDC system infrastructure development, and they should also be considered in the design of other EDC systems, regardless of study-specific requirements.

First, research teams need to decide whether EDC systems will be developed in-house or through a third-party vendor. The ATN CARES team chose the latter option to move away from the "pilotitis" paradigm, where a lot of money is spent on developing mHealth apps from the ground up that are not sustainable [28,29]. Instead, we are agnostic to specific technology with a focus on study procedures and intervention functions over specific technology platforms. For example, we focused on the development of the SMS text message content with the notion that multiple platforms can execute the messaging function of the intervention.

In the end, we decided to use the *CommCare* platform through Dimagi that used many "off-the-shelf" system components such that programming from the ground up would not be required. In addition, the *CommCare* system satisfies most of the requirements as described above and offers flexibility in determining costs on a fixed grant budget. We selected the *CommCare* PRO plan because it provides a basic level of technical support and training for the research team while also allowing us to reduce costs by having a trained research staff member to complete the majority of EDC system programming in-house, which saves cost in the long run. We selected *Dimagi* as our EDC system vendor based on prior lessons while working with numerous EDC system vendors. While cost and the ability to provide basic system requirements are important considerations, we strongly advise selecting vendors based on prior experience collaborating on research projects. Basic system requirements that are intrinsic to research, such as randomization and the need to protect patient data, are not as likely to be obvious to vendors without prior research collaborations and are likely to result in more system development iterations than what would be required by working with a research-oriented vendor. Additional time and effort can easily offset what seemed to be initial cost savings.

Second, the needs of the target population and the protection of electronic data collected on the target population were the top priorities in the development of the EDC system. A number of electronic safeguards were put in place to ensure a high degree of security as described in the Methods section. In addition to electronic safeguards, there is no substitute for the formative work that precedes the implementation of any behavioral intervention trial. In an iterative fashion, the CARES research team discussed all study procedures and presented study protocols to community advisory boards that comprised the target population, prior to the development of the EDC system. The SMS text message content, for example, was highly vetted and pilot-tested by the CARES research staff prior to the

implementation of the study. A priority was placed on developing the SMS text message content that is culturally sensitive and would not contain any specific references to HIV; medication reminders were generic to encourage general medication adherence.

A limitation of the EDC system is that it does not support all data entry tasks and technology functions that the intervention requires. For example, the EDC system does not support online peer support groups; a separate system was set up through *Muut* for that purpose as discussed earlier. We posit that the inability to rely on any single EDC system to meet all study requirements is likely to be the case for a large-scale intervention trial. In addition, we note that the use of different technology solutions that support EDC, Web-based discussions, email, and other functions mirrors how we use different social media tools to meet different needs in our daily routines. These different options add to the richness of possibilities for the development of future behavioral intervention trials.

The EDC system that was developed for the ATN CARES trial presents as an example of how a commercially available and integrated data capturing system can meet all system requirements and support almost all needs of a large-scale research trial. While most EDC challenges can be resolved through programming updates, there are important considerations prior to the database implementation, such as identifying an appropriate EDC vendor with research experience and consulting with the target study population in developing participant-friendly study content.

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Authors' Contributions

The following individuals contributed to the study: Mary J Rotheram-Borus, Sue E Abdalian, Maria Isabel Fernandez, Jeffrey D Klausner, Sung-Jae Lee, Maryann Koussa, Leslie Kozina, Manuel Ocasio, Robert E Weiss, Ronald Brookmeyer, Karin Nielsen, Yvonne Bryson, Tara Kerin, Chelsea Shannon, Ruth Cortado, Kate Mitchell, Elizabeth M Arnold, Norweeta Milburn, Cathy Reback, Marguerita Lightfoot, Danielle Harris, and Jasmine Fournier.

Conflicts of Interest

JW and AC work for Dimagi Inc, the company that developed the open source mobile data collection platform used in this study. Other authors have nothing to declare.

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Abbreviations

AMMI: Automated Messaging and Monitoring Intervention
ART: antiretroviral therapies
ATN: Adolescent Medicine Trials Network
CARES: Comprehensive Adolescent Research & Engagement Studies
EDC: electronic data capture
EMA: ecological momentary assessment
GBTY: gay, bisexual, and transgender youth
HRY: high-risk youth
LA: Los Angeles
NO: New Orleans
RCT: randomized controlled trial
SMS: short message service
STI: sexually transmitted infections
YLH: youth living with HIV

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Protocol

Testing the Efficacy of a Social Networking Gamification App to Improve Pre-Exposure Prophylaxis Adherence (P3: Prepared, Protected, emPowered): Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV prevalence is high among young men who have sex with men (YMSM) and young transgender women who have sex with men (YTWSM), particularly among minorities. Despite its proven efficacy and safety, the uptake of and adherence to pre-exposure prophylaxis (PrEP) among YMSM and YTWSM is currently limited. To date, evidence-based interventions to promote and sustain PrEP adherence have been limited and not shown to be highly efficacious. Given the widespread adoption of smartphones, mobile apps can be utilized to increase PrEP adherence for many YMSM and YTWSM.

Objective: The study consists of a formative research phase to develop an app-based intervention, P3 (Prepared, Protected, emPowered), to increase PrEP adherence, and a randomized controlled trial (RCT) to test its efficacy. P3 is a mobile app built on an established health platform, which includes social networking and game-based components to encourage PrEP adherence among YMSM and YTWSM. P3+ includes all P3 features plus adherence counseling delivered via two-way text messaging (short message service, SMS) through the app.

Methods: The formative research phase includes usability testing to assess users' comprehension of P3's educational content, understanding and use of intervention features, and overall impressions of app functionality, followed by app refinements. A subsequent field trial will identify and resolve any remaining technical challenges. A three-arm RCT (P3, P3+, and standard of care) will then be conducted at 6 iTech subject recruitment venues to assess intervention efficacy and to conduct a comparison of costs to deliver the 2 intervention arms.

Results: This is an ongoing research project with initial results from the formative work expected in 2020 and those from the RCT in 2021.

Conclusions: P3 aims to provide an engaging, interactive experience that is highly appealing for the target population, leveraging technology already heavily integrated into the lives of young people, and thus meeting users' needs in a familiar, stimulating way. If efficacious, P3 could be a sustainable, easily disseminated, lower-cost PrEP intervention for YMSM and YTWSM. Further,

the research aims to determine the processes that are essential to developing and implementing future health-related gamification interventions.

Trial Registration: ClinicalTrials.gov NCT03320512; https://clinicaltrials.gov/ct2/show/NCT03320512 (Archived by WebCite at http://www.webcitation.org/74OVZkICl)

International Registered Report Identifier (IRRID): DERR1-10.2196/10448

(JMIR Res Protoc 2018;7(12):e10448) doi:10.2196/10448

KEYWORDS

HIV; men who have sex with men; mobile phone; mobile apps; pre-exposure prophylaxis; transgender women; youth

Introduction

Background

Between 2002 and 2011, rates of new HIV infections declined by >30% overall in the United States but increased by 132% among young men who have sex with men (YMSM) aged 13-24 years [1]. Regional studies suggest that HIV prevalence among transgender women (TW) are among the highest of all risk groups, especially TW of color and African-American TW in particular [2-4]. There is overwhelming scientific evidence of the efficacy and safety of pre-exposure prophylaxis (PrEP) to prevent HIV infection in YMSM and young transgender women who have sex with men (YTWSM) [5-7]. However, efficacy in all PrEP studies has been strongly correlated with drug levels, and drug monitoring indicates that adherence has been suboptimal in a substantial proportion of participants [5-7]. Adherence to medications, including PrEP, is known to be a significant challenge for adolescents and young adults [8-14]. In a recent study of PrEP use among 200 YMSM (mean age 20.2 years; 54.5% black, 26.5% Latino), at week 4, 56% had protective levels of intracellular tenofovir-diphosphate (TFV-DP) (ie, consistent with >4 pills per week). This decreased to 48% at week 24 and 34% at week 48. PrEP adherence rates were lower among black YMSM and below the protective threshold at all time points measured [14]. To date, there are no proven interventions for YMSM and YTWSM to promote consistent and persistent PrEP adherence. Interventions that improve PrEP adherence are urgently needed to maximize HIV prevention benefits for YMSM and YTWSM.

The use of smartphones to deliver HIV prevention and care interventions has grown substantially in recent years due to: (1) wide-scale adoption of smartphone technology among high-risk groups, (2) the ability to deliver interventions in real time within risk contexts, and (3) low implementation costs [15-19]. Multiple formative studies conducted with HIV-positive men who have sex with men (MSM), including YMSM, demonstrate the feasibility and acceptability of smartphone apps to support antiretroviral therapy adherence [20-23] and inform the development of an app to address adherence to PrEP. Preferences for intervention features include connections to peers and providers, provision of discreet and personalized medication reminders, and ensuring that the apps take a more holistic approach in terms of content [20-22,24].

A smartphone-delivered PrEP adherence intervention is well suited for YMSM and YTWSM, given that they have a high uptake and utilization of smartphone technology [25-27]. P3 (Prepared, Protected, emPowered) is a smartphone app for HIV-uninfected YMSM and YTWSM that utilizes social networking and game-based mechanics to improve PrEP adherence. Built on a successful, evidence-based platform designed by our collaborating technology partner, Ayogo, and informed by work to improve antiretroviral therapy adherence among HIV-positive YMSM [28], P3 is tailored to the unique needs and motivations of at-risk YMSM and is flexible and responsive to changes in technology and emerging PrEP practice standards and guidelines.

Social engagement and provision of support are powerful tools for behavior change, both of which can be achieved with smartphone technologies. Social networking sites often provide venues for health-related activities including searching for information and connecting with peers by sharing information, posting questions, and joining special-interest groups [29]. While some Web-based interventions have provided HIV prevention information through existing social networking sites [30,31], to our knowledge, no app-based interventions have been designed to capitalize on social involvement as a means through which HIV-uninfected YMSM and YTWSM can receive information and social support, experience more positive social norms and reflective appraisals, and feel a sense of connectedness to peers [32,33]. P3 provides anonymity so that YMSM and YTWSM on PrEP can feel comfortable sharing their thoughts or experiences related to PrEP within the safety of a respectful, affirming environment.

Although smartphone apps can deliver individualized, tailored content through complex algorithms, added individual adherence counseling delivered by trained counselors might provide a degree of personalization that could improve outcomes. The available literature suggests that some tools, including technology-based tools, may be more beneficial to patient adherence when combined with education or counseling [34-36]. Text-based counseling offers a convenient, confidential, and user-controlled experience, providing support to YMSM and YTWSM who otherwise may not be willing or able to access services in person. Interacting with the adherence counselor in the P3+ arm may heighten participants' sense of accountability, enhance motivation, and allow participants to have their unique adherence and related needs addressed dynamically.

Theoretical Framework for Intervention

P3 development is guided by evidence-based interventions and health behavior change theories including social cognitive theory (SCT), narrative communication (eg, storytelling), and the principles of persuasive technology [37-42]. P3 addresses key

principles of SCT including: (1) observational learning by doing daily activities; (2) modeling and vicarious experiences (observing and participating in daily discussions, exploration of narrative "choose-your-own adventure" stories); (3) self-efficacy and verbal persuasion from expert sources (multimedia knowledge center, tailored messages); and (4) reinforcements (rewards and achievements delivered through the app) [37,38]. The Fogg Behavioral Model of persuasive technology informed the development of Ayogo's Empower platform, the operating system on which P3 was developed [39]. According to the Fogg Behavioral Model, the principal factors to promote behavior change using technology include *triggers*, *ability*, and *motivation*. App notifications are *triggers* for healthy behaviors while app content also helps participants identify their own daily triggers. Regular self-report prompts act as additional triggers and help participants establish healthy habits. *Ability* is increased through knowledge and by identifying small steps toward target behavioral goals (eg, understanding side effects, knowing how to fill a prescription). Participants also get tips from others who are dealing with similar issues and through narrative stories that reinforce the consequences of healthy and unhealthy behaviors. App *motivators* include social support, rewards, goal setting, and achievement.

Aims and Objectives

The aims of this project are to conduct formative research that includes usability testing to assess users' comprehension of P3's educational content, understanding and use of intervention features, and overall impressions of app functionality followed by app refinements. A subsequent field trial will identify and resolve any remaining technical challenges with the app and allow for the finalization of study procedures, including biologic specimen collection. A three-arm randomized control trial (RCT) including P3, P3+, and standard of care (SOC) will then be conducted at 6 iTech subject recruitment venues (SRVs) to assess intervention efficacy and to conduct a comparison of costs to deliver the 2 intervention arms.

Methods

Trial Registration, Ethics, Consent, and Institutional Board Approval

The research and ethics presented in this study have been reviewed and approved by the Institutional Review Board of the University of North Carolina at Chapel Hill, USA (17-9551). A Certificate of Confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent will be obtained for participants who are 15-17 years old. The study is also registered on ClinicalTrials.gov (NCT03320512).

Phase 1: Formative Research—App Development and Testing

Intervention Description

Building off of the Empower platform developed by our technology partner, Ayogo, we created a prototype for P3 (Textbox 1 and Figures 1-3) that incorporates best practices for app development [23,25], theoretical constructs [23,25], and results from our formative data [24,28,43]. Ayogo specializes in mobile-enabled, play-based apps that improve chronic illness self-management. P3 is a user-centered, multicomponent care support app that accommodates the different developmental challenges, motivations, and needs of diverse YMSM and YTWSM by including content in multiple formats. These formats include text, videos, quizzes, and a social discussion board that facilitates peer-to-peer sharing of challenges and successes. Tailored medication strategies and reminders, personalized messages, and game-based elements [24,44], such as health-related quests, in-app rewards, social connectivity, and "unlocking" character-driven narratives, encourage behavior change. To further maximize app engagement, P3 also employs a financial incentive system to encourage daily use [45]. Using the principles of present-biased preferences [46], loss aversion [47,48], and past or future reward motivation [49], we will award small monetary incentives (US $0.50) for each day of app use (not daily adherence) and deduct US $1 for each day of nonuse.

P3+ will include all features of the P3 app but also includes adherence counseling, via two-way text messaging (short message service, SMS) sessions with trained counselors based on the Next Step Counseling (NSC) adherence counseling curriculum [51,52].

NSC is an interactive, client-centered motivational intervention that was developed and implemented during the Pre-exposure Prophylaxis Initiative (iPrEx) trial and was found to be highly acceptable among men who have sex with men [52]. The intervention is based on the information-motivation-behavioral skills model and provides flexible, individualized counseling with the goal of supporting adherence and the accurate reporting of adherence. The key components of NSC include the review of participant experiences with adherence, exploration of adherence facilitators and barriers, identification of adherence needs, identification of strategies to meet needs, and development of an adherence action plan [51,52].

Study Sites

To ensure diverse representation of youth, we will test P3 in 6 US cities with iTech SRVs (Boston, MA; Philadelphia, PA; Chicago, IL; New York City, NY; Houston, TX; Atlanta, GA) [50]. All SRVs are located in areas with a high adolescent prevalence of HIV. Each participating SRV has extensive experience engaging, enrolling, and retaining youth in prevention studies.

Formative Research Aims

Usability testing will be conducted to assess user comprehension of the educational content, understanding and use of intervention features, and overall impressions of the app functionality. Subsequently, field testing will be conducted to identify and resolve any remaining app technical challenges and allow for the finalization of study procedures, including biologic specimen collection.

Usability Testing

Usability testing will be conducted at 2 iTech SRVs (Chicago, Illinois; Boston, Massachusetts) with 8-12 YMSM and YTWSM who are on PrEP, have used PrEP in the past, or are considering

initiating PrEP. Participants will be English speaking, HIV-uninfected YMSM and YTWSM between the ages of 16 and 24 years, who are familiar with Android or iOS smartphones. In-person and Web-based methods will be used to recruit participants.

Usability testing will be conducted by members of the research team in accordance with the National Institutes of Health usability guidelines [53]. Pre- and postusability surveys will be completed using Web-based computer-assisted self-interviewing (CASI) to determine app usability and acceptability. Participants will be compensated for their participation. A usability report will be compiled and reviewed by the full investigating team, the technology partner, and the iTech Analytic Core (AC). The report will include a list of common issues, such as navigation problems, and recommended design improvements. These findings will be used to guide app modifications.

Field Testing

Field testing of P3 and P3+ will be done at 3 iTech SRVs (Philadelphia, Pennsylvania; Houston, Texas; Bronx, New York), with 15-24 YMSM and YTWSM who are starting PrEP or are nonadherent to PrEP. Eligible participants will be those who (1) are aged 16-24 years; (2) were assigned male sex at birth; (3) report sex with or intentions to have sex with men or TW; (4) have reliable daily access to an Android or iOS smartphone with a data plan; (5) are able to speak and read English; (6) are HIV-uninfected (confirmed by self-report at enrollment visit); and (7) initiated PrEP within the last 60 days and have an active PrEP prescription (prescription confirmed by study staff) OR are on PrEP >60 days but self-report adherence on average <6 pills per week over the past month and have an active PrEP prescription (prescription confirmed by study staff). Individuals who cannot be consented due to active substance use or psychological condition will be considered ineligible.

Textbox 1. P3 core components and content.

Profile Page

- Privacy features: These include avatars, pseudonyms, confidential personal identification number to open the app, and app time-out after 5 minutes of inactivity.
- App progression meter: Visual display of current app "level," virtual bank account funds, and in-game currency, which is visible to other participants. Participants level up and earn in-game currency based on app use. Participants redeem currency to unlock narratives and other app features.

Daily Discussion

- Social prompts: Daily discussions foster community and peer sharing, model successful behaviors, and provide reinforcement (eg, how do you remember your meds?). Notifications are sent when someone has commented or "liked" a particular post.

Medication Tracking and Adherence Support

- Medication reminder system: Personalized, discreet reminders and habit-building solutions promote pre-exposure prophylaxis (PrEP) adherence.
- Tailored adherence strategies: The app uses information provided during the initial set up (eg, time of day PrEP is taken) to suggest adherence strategies (eg, take when I brush my teeth). Tailored feedback on new strategies is provided when adherence falters.
- Refill reminders: Participants can create personalized reminders for PrEP refills.
- Adherence dashboard (portal): Provides the study team with an easily interpretable, real-time overview of each user's PrEP tracking and app use. Automated "canned" and tailored messages can be delivered to provide support and encouragement. A message library will be developed with input from Youth Advisory Boards at the participating iTech subject recruitment venues. All 6 of the recruitment sites have active Youth Advisory Boards that meet monthly to discuss and provide input on planned and ongoing studies [50]. Provides ability to deliver Next Step Counseling to P3+ participants.
- Adherence Counseling: Next Step Counseling conducted in-app through text-messaging. Key features include reviewing participant adherence experiences, exploring adherence facilitators and barriers, identifying adherence needs and strategies to meet needs, and developing an adherence action plan [51,52].

Brain Builders

- Daily Quests: Actionable routine tasks help users set goals and build knowledge and skills.
- Brain games: Quizzes and interactive exercises help users check knowledge and skills.

Knowledge Center

- Multimedia library: Includes PrEP-related information and information about safer sex, relationships, and general health and wellness. Users are prompted with a reflection question after each article to apply the material to their lives. A visual shows progress toward completing each section.

Character-Based Narratives

- "Choose-your-own adventure" narratives feature young men who have sex with men or young transwomen who have sex with men navigating common situations that impact PrEP care and adherence (eg, substance use, stigma). Playing through story paths allows users to face hard choices that impact health and practice problem solving.

Figure 1. Screenshot of the home screen.

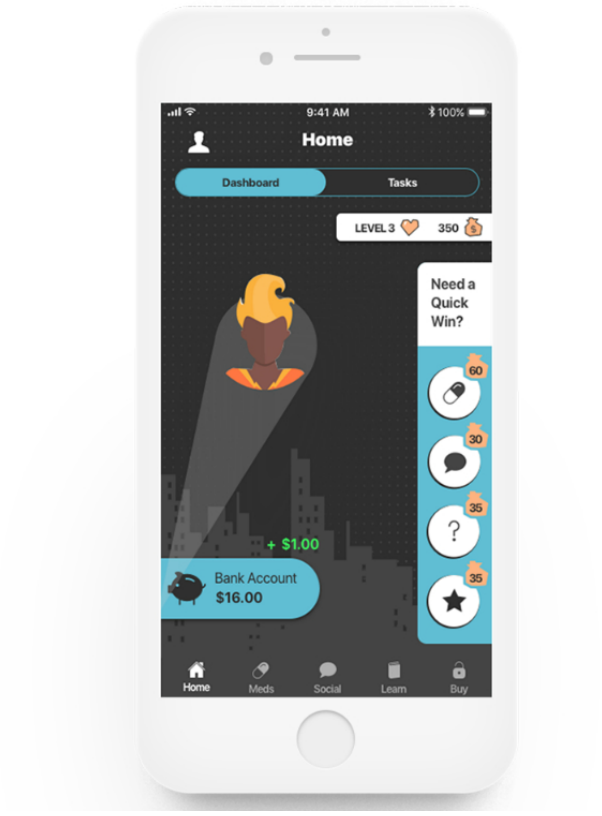


Figure 2. Screenshot of the home screen: daily tasks.

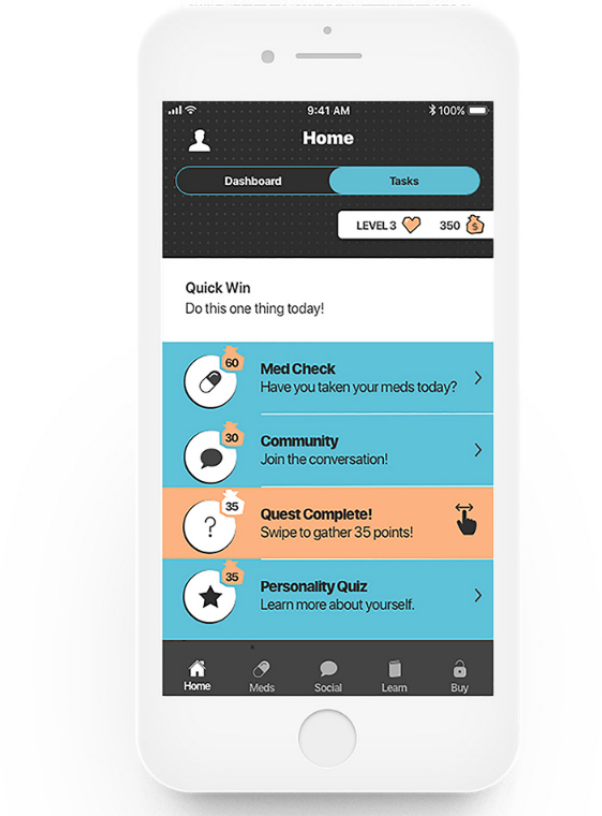
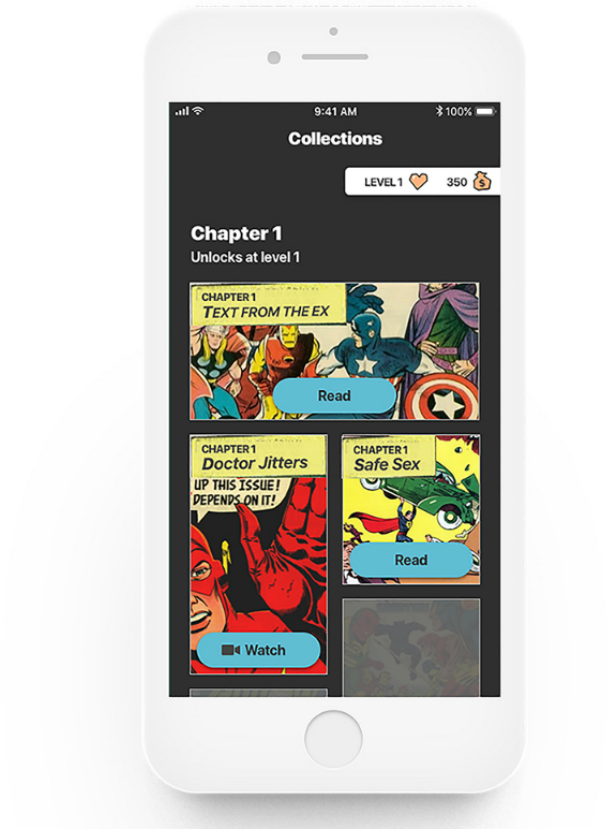


Figure 3. Screenshot of unlocking the narrative collections.



Recruitment methods will be the same as those used for usability testing. Youth who meet initial eligibility criteria (1-5 above) and indicate that they meet the HIV-uninfected and PrEP prescription criteria (6-7 above) will be scheduled for an in-person enrollment visit. To confirm they meet the study eligibility criteria, they will be asked to report on their HIV status and provide evidence of an active PrEP prescription. Participants who report that they are HIV-positive will be linked to care at one of the clinical care sites and will not be enrolled. Youth confirmed as eligible will complete the informed consent process, provide baseline dried blood spots (DBS) to test for TFV-DP or emtricitabine-triphosphate (FTC-TP) levels, provide hair samples to test for FTC levels [54], and complete a computer-assisted self-interviewing (CASI) survey.

Study staff will help participants download the app on to their phones and provide a tour of the app to highlight features. The adherence counselor will also make initial contact with them during the enrollment visit to ensure that the features of P3+ are also understood. Participants will be compensated for their time at the end of the visit.

During the 1-month study, participants will be asked to use the P3 app daily. They will be asked to schedule and have at least 2 counseling "chat" check-ins with the adherence counselor and will be asked to engage in two-way texting with the adherence counselor to ensure the full technological functioning of the texting portal. Individuals will be instructed to contact study staff immediately to report difficulties with any app components or to report any problems with their phone or phone service.

At the end of the 1-month field trial, participants will return to the site to complete posttrial procedures. These procedures include DBS and hair collection and a posttrial CASI survey that assesses app, DBS, and hair collection feasibility and acceptability. A semistructured qualitative exit interview conducted using Health Insurance Portability and Accountability Act of 1996 (HIPAA)–compliant videoconferencing software will focus on how participants used the app over the 1-month field trial, any technical challenges they may have encountered, and whether and how they thought that use of the intervention could translate into behavior change. Participants will be compensated for participation at visit completion. A field-testing report will be compiled and reviewed by the investigator team and the technology partner. The report will include: (1) list of app functionality issues, including any issues with the texting portal; (2) recommended design improvements that will be used in the final iterative stages of app adaptation; and (3) recommended changes to DBS and hair collection procedures.

Phase 2: Randomized Control Trial

Design

The second phase of the trial will consist of a three-arm RCT to test intervention efficacy among YMSM and YTWSM who are starting PrEP or are nonadherent to PrEP (Figure 4). The study arms will be P3, P3+, and SOC. Participants will be recruited from 6 iTech SRVs (Bronx, New York; Chicago, Illinois; Atlanta, Georgia; Houston, Texas; Boston, Massachusetts; Philadelphia, Pennsylvania). We will enroll up to 240 participants and randomize them 1:1:1 to receive P3,

P3+, or SOC. Assessments will be completed at months 0, 3, and 6.

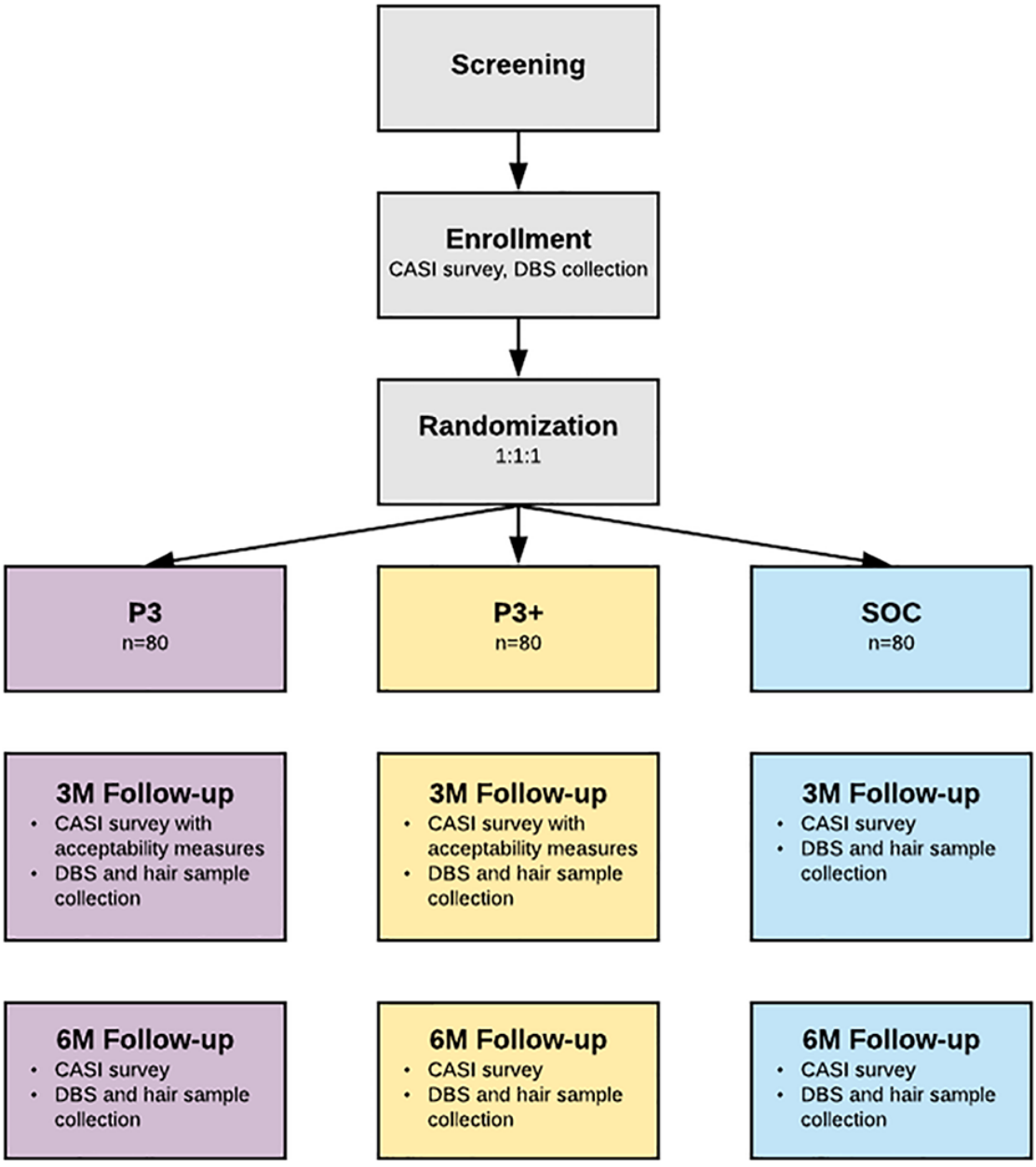
Participants

We will enroll up to 240 participants. Eligible participants will be those who: (1) are aged 16-24 years; (2) were assigned male sex at birth; (3) report sex with or intentions to have sex with men or TW; (4) have reliable daily access to an Android or iOS smartphone with a data plan; (5) are able to speak and read English; (6) are HIV-uninfected (confirmed by self-report at enrollment visit); and (7) are not currently on PrEP but plan to initiate in the next 7 days and have an active PrEP prescription (prescription confirmed by study staff) OR initiated PrEP within the last 30 days and have an active PrEP prescription (prescription confirmed by study staff) OR are on PrEP >30 days but self-report adherence on average <6 pills per week over the past month and have an active PrEP prescription (prescription confirmed by study staff). Individuals who participated in the field trial will not be eligible for participation in the RCT.

Recruitment and Retention

We will utilize 6 iTech SRVs to enroll YMSM and YTWSM. Multiple methods will be used for recruitment including in-person, venue-based (including recruitment from local PrEP clinics or providers), and Web-based recruitment mechanisms. For those initially eligible, contact information will be acquired, and an in-person enrollment visit will be scheduled. Youth who are confirmed as eligible for the study will be guided through an informed consent or assent process by research staff.

Figure 4. Randomized controlled trial study design. CASI: computer-assisted self-interviewing; DBS: dried blood spots; 3M: 3 month; 6M: 6 month; SOC: standard of care.



Retention procedures include sending emails, text reminders, and calendar invites to participants for follow-up survey and visit completion.

Randomization

Those providing consent will also provide a baseline DBS sample and complete a baseline CASI survey. Participants will then be randomized in a 1:1:1 ratio into the SOC, P3, or P3+ condition based on a randomization sequence developed by the Analytic Core lead statistician and loaded into a HIPAA-compliant Web-based CASI platform form. The randomization sequence will be stratified by SRV.

Participants randomized to the P3 or P3+ arms will be guided by study staff through the app download process and given an app site tour to highlight features. Those in the P3+ arm will be provided with additional information about the adherence counseling portal.

Randomized Controlled Trial Procedures

P3 Intervention Condition

Participants (n=80) will receive the P3 app on their Android or iOS smartphone device. P3 includes gamification features built into a technology platform that helps users to build self-efficacy and habituate positive health habits. The app includes social features, a PrEP-specific knowledge center, game elements, loss aversion mechanics, and a daily habit-building interface. They will have access to the app over a 6-month period but will only receive financial incentives for the first 3 months.

P3+ Intervention Condition

Participants (n=80) will receive the P3+ app on their Android or iOS smartphone device. This version of the app will include all features of the P3 app as well as two-way text messaging sessions with trained counselors based on the NSC adherence counseling curriculum [51,52]. P3+ participants will have access to the app over a 6-month period but will only receive financial incentives and have access to the adherence counselor for the first 3 months.

Standard of Care

SRV staff will inform participants (n=80) of SOC services that should be available to them at their prescribing PrEP provider's practice and will provide them with written materials regarding PrEP adherence. According to Centers for Disease Control and Prevention guidelines [55], medication adherence counseling is a key part of PrEP SOC, should occur at PrEP initiation and at 3-month intervals, and should include education about PrEP (ie, medication dosage and schedule, management of common side effects), adherence support, and monitoring of medication adherence (ie, identify factors interfering with adherence and develop a plan to address them, reinforce success, and normalize occasional missed doses). Medication adherence counseling should be conducted at each PrEP follow-up visit.

Follow-Up Visits

At app intervention completion (month 3), participants will complete an in-person visit and will provide a DBS sample for TFV-DP and FTC-TP testing, hair samples for FTC testing, and complete a follow-up CASI survey. The assessment should occur as soon after the 3-month enrollment period as possible. At month 3, those participants in either the P3 or P3+ arm will be allowed to continue using the app but will not be provided incentives for usage nor have access to the adherence counselor (P3+ arm only). The 6-month assessments will include DBS and hair collection, and a follow-up CASI survey. These assessments should occur as soon after the 6-month enrollment period as possible.

Qualitative Exit Interview

A sample of 20 users (10 in the P3 and 10 in the P3+ arm) including both high and low users will complete a qualitative exit interview, conducted using HIPAA-compliant videoconferencing software, which will allow for an in-depth and nuanced understanding of the usage of P3 or P3+ over the 3-month intervention trial. High users of the P3 arm are defined as those who use the app on average >4 days during the intervention period; moderate to low users are those who use the app on average <3 days. High users of the P3+ arm include those who use the app >4 days on average and participate in >3 adherence counseling sessions; moderate to low users are those who use the app <3 days and participate in <2 counseling sessions. The Web-based interview will last 45-60 minutes, and audio only will be recorded using the software platform and transcribed by secure transcription service. Participants can opt to include video chat, but no video will be recorded. Interviews will be semistructured and focus on how participants used or did not use P3 or P3+ over the 3-month trial and what additional components (either technology-based on in-person) might be useful to further impact behavior change.

Incentives

Participants will be compensated with US $50 upon completion of their enrollment visit, and US $50 each at the 3- and 6-month visits (US $150 total). Participants randomized to the P3 or P3+ arms have the possibility of earning an additional US $135 for app usage over the 3-month app intervention period. Compensation can be provided in person or mailed to subjects, depending on what is allowed at the specific SRV.

Data Collection

Baseline assessments will be conducted at the enrollment visit, with follow-up assessments conducted at 3 and 6 months.

Primary Outcome Measures

The primary outcome is PrEP adherence, measured by the levels of TFV-DP and FTC-TP in DBS plasma, consistent with >4 doses per week at the 3- and 6-month follow-ups.

Secondary Outcome Measures

Secondary outcomes include self-reported retention in PrEP clinical care, PrEP persistence, sexual risk behaviors, sexually transmitted infection incidence, and SCT constructs including self-efficacy, outcome expectations, and self-regulation.

Cost Outcomes and Cost Effectiveness

To compare costs between the intervention arms, we will collect information on (1) time spent by study staff for training and supervision of adherence counselor(s); (2) time participants spend in the adherence counseling sessions; and (3) costs

associated with the delivery of both P3 and P3+, including the costs of providing financial incentives. The procedures we will use to quantify the resources required to deliver the interventions will be organized in standard expenditure categories: personnel, supplies, equipment, services, space, and overhead.

Statistical Analyses

Primary Clinical Outcomes

The primary analyses will assess the efficacy of the P3 or P3+ intervention at 3- and 6-month follow-ups. Efficacy is defined as the difference in the proportion of patients with protective levels of TFV-DP or FTC-TP when comparing the intervention arms to the SOC. The primary test of the efficacy of the intervention (P3 or P3+) will be of the null hypothesis that there is no difference in the proportion of patients with protective levels of TFV-DP and FTC-TP at either the 3- or 6-month visit against the 2-sided alternative of some difference in proportion. These tests will be conducted at the 0.05 level of significance, and we will present corresponding 95% CIs for the treatment effects.

For this analysis, we will use longitudinal targeted minimum loss-based estimation (TMLE) [56] to estimate the proportion of participants with protective levels of TFV-DP and FTC-TP at each time and in each intervention group. TMLE is a methodology for constructing efficient and robust estimates of treatment effects and utilizes time-varying patient characteristics to account for bias due to informative participant drop out. If patient characteristics predict adherence, TMLE may also lead to greater power of tests about estimated treatment effects [57]. Patient characteristics that will be included in the estimation include demographic characteristics, social support, app usage and engagement, app acceptability, substance use, anxiety, and depression. We will use influence function-based covariance matrix estimators of the 3- and 6-month treatment effects to conduct a 2-degree-of-freedom Wald-style test of the null hypothesis. This test will be inverted to construct a 95% CI about the estimated treatment effects.

A detailed description and figure describing the power calculation are included in Multimedia Appendix 1. Based on the power calculation, we conclude that the study has >80% power to detect a 6-month treatment effect of 20% (difference in percentage adherence) even if there is no 3-month effect, or, conversely, a 3-month treatment effect of 20% even if there is no 6-month effect. In the more realistic scenario, where there is a treatment effect at both time points, we have >80% power to detect effects if the 3- and 6-month treatment effects are >14%.

Secondary Clinical Outcomes

We will conduct an analysis parallel to the primary analysis exactly as above but with the 2 P3 intervention arms separated (ie, P3 vs SOC, P3+ vs SOC). For each of the above analyses, we will additionally study the efficacy of the P3 or P3+ arms as measured by continuous levels of TFV-DP or FTC-TP in order to assess subclinical differences in adherence. Specifically, we will estimate the ratio of geometric mean levels in the intervention and SOC groups using longitudinal TMLE. We will also assess intervention efficacy on a panel of self-reported outcomes including retention in PrEP care, PrEP persistence, sexual risk, incident sexually transmitted infection, and SCT model constructs. For binary outcomes, we define intervention efficacy as a difference in proportions, while for continuous outcomes, we define efficacy as a difference in means.

Cost Outcomes and Cost Effectiveness

Incremental cost effectiveness ratio between the 2 intervention arms will be defined as $\Delta C/\Delta E$, where ΔC denotes the estimated difference in mean costs of the intervention and ΔE reflects the estimated difference in mean effectiveness between the interventions. ΔC and ΔE will be estimated using longitudinal TMLE as with the primary analysis, and closed-form influence function-based Wald-style 95% CIs will be constructed for these estimates.

Results

Usability testing will begin in winter 2017. Following app revisions based on usability test results, field testing will begin (anticipated start: spring 2018). Field testing and final app refinements will be completed over the course of 6 months. We anticipate completion of Phases 1 and 2 and app refinement by fall 2018. The RCT is anticipated to begin in winter 2018 and will be completed over the course of 2 years (completed in winter 2020), and it is anticipated that analyses and results will be ready for dissemination by May 2021.

Discussion

P3 is a novel smartphone app intervention designed to improve adherence among YMSM and YTWSM initiating or nonadherent to PrEP. Phase 1 of the study (usability testing and field testing) will guide app development and refinement. In Phase 2, in addition to testing the efficacy of P3 alone, this study will test the efficacy of P3+ (medication adherence counseling delivered through the app). If successful, our interventions will improve PrEP adherence, retention in PrEP clinical care, and PrEP persistence in our subject population. Given the significant health sequelae associated with HIV infection and the paucity of scalable intervention programs for this population of young adults, the knowledge to be gained from this research is significant.

Sustainable, integrated HIV prevention interventions are critically needed to improve health outcomes and reduce HIV incidence, particularly among communities of YMSM and YTWSM. Interventions that take advantage of technology-based platforms have great potential to encourage health promotion behaviors [23-25,58-60]. However, there is currently a lack of evidence-based interventions targeting adherence to PrEP [59].

P3 is the first intervention to include gamification to increase PrEP adherence among YMSM and YTWSM. Gamification uses game design components and principles of psychology outside of gaming contexts, thus providing opportunities for sophisticated engagement of participants in Web-based behavioral interventions [60,61]. Game components can be used to educate, entertain, and motivate participants. Health behavior interventions can utilize gamification to deliver highly engaging content, enhancing the degree and depth of participant

interaction and increasing behavior-change learning opportunities [59-61].

The measurement of plasma for intracellular drug concentration will be the primary outcome of this study. This approach is considered the gold standard for determining if and how often an antiretroviral has been taken. However, there are limitations to this method. Namely, the collection of plasma is invasive, requires substantial processing to enable intracellular measurements, and has long turn-around times. Furthermore, the results represent only a short-term measure of drug-taking behavior. Given the rapid processing time of the proposed hair sampling procedure (matrix-assisted laser desorption electrospray ionization) which requires minimal sample processing, and the sample can be analyzed within 1 hour [54]), this technique could be used to provide real-time adherence monitoring in future studies.

Anticipated limitations of this study include the use of self-reported secondary outcomes, which may be subject to social desirability bias. However, this is metered by using DBS to determine protective levels of TFV-DP and FTC-TP as a primary outcome. Contamination may also be an issue, as participants at each of the 6 SRVs can be randomized to any of the 3 arms, and participants from P3 or P3+ could show the program to those in the SOC arm. The possibility that providing financial incentives for app use may not be sustainable or impact behavior is a consideration. While economic approaches have shown mixed effects for changing behaviors, it is clear that some populations respond to financial incentives [45,62,63]. Further, employing behavioral economics principles will maximize engagement and study retention (eg, accumulated money can only be collected after participants complete their required follow-up activities), overcoming significant barriers for mobile health interventions [64-66]. Tying the incentive to intervention use rather than reported adherence reduces ethical concerns around coercion and minimizes the impact of the incentive on intrinsic motivation for adherence [67].

We anticipate that due to the developmentally and age-appropriate content featured in the P3 app, these interventions will improve PrEP adherence. Based on the results of this study, particularly the differences between the P3 and P3+ arms, modifications to the intervention can be made, and the most appropriate intervention components can be deployed on a larger scale.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Power calculation.

[PDF File (Adobe PDF File), 329KB - resprot_v7i12e10448_app1.pdf]

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Abbreviations

CASI: computer-assisted self-interviewing
DBS: dried blood spots
FTC-TP: emtricitabine-triphosphate
HIPAA: Health Insurance Portability and Accountability Act of 1996
NSC: Next Step Counseling
P3: Prepared, Protected, emPowered
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SCT: social cognitive theory

SOC: standard of care
SRV: subject recruitment venue
SMS: short message service
TFV-DP: tenofovir-diphosphate
TMLE: targeted minimum loss-based estimation
TW: transgender women
YMSM: young men who have sex with men
YTWSM: young transgender women who have sex with men

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Protocol

Adaptive Antiretroviral Therapy Adherence Interventions for Youth Living With HIV Through Text Message and Cell Phone Support With and Without Incentives: Protocol for a Sequential Multiple Assignment Randomized Trial (SMART)

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Abstract

Background: Youth living with HIV (YLH) aged 13 to 24 years made up over a fifth (21%) of new HIV diagnoses in 2016, yet only 27% of YLH are virally suppressed. YLH have been shown to be poorly adherent to antiretroviral therapy (ART); however, there has been limited research investigating how to increase adherence in YLH. Mobile health (mHealth) interventions may be one promising way to do this.

Objective: This study (ATN [Adolescent Trials Network] 144 SMART) aimed to compare adaptive interventions that could increase ART adherence in YLH aged 15 to 24 years. This includes mHealth initiatives, the tapering of interventions, and the use of incentives. Cost-effectiveness of sequencing the interventions without incentives before providing incentives and the savings on societal costs due to suppressed viral loads will be determined. This protocol is part of the ATN Scale It Up program described in this issue by Naar et al.

Methods: This study uses a Sequential Multiple Assignment Randomized Trial design. Approximately 190 participants are being recruited, enrolled, and randomized to either cell phone support or text message support. Both intervention groups receive 3 months of intervention, followed by a second randomization based on response to the intervention. Responders test tapering their intervention, and nonresponders test receiving incentives.

Results: Data collection for this study is projected to begin in August 2018 and last until June 2020.

Conclusions: This is an innovative study, particularly in terms of population, intervention types, focus on cost-effectiveness, and recruitment. This study could be particularly effective in improving adherence in YLH while reducing long-term individual and societal costs.

Trial Registration: ClinicalTrials.gov NCT03535337; https://clinicaltrials.gov/ct2/show/NCT03535337 (Archived by WebCite at http://www.webcitation.org/74alXb92z)

International Registered Report Identifier (IRRID): PRR1-10.2196/11183

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KEYWORDS

adaptive clinical trial; antiretroviral therapy; medical adherence; cell phone; HIV; mHealth; text messaging; adolescent

Introduction

Adherence to Antiretroviral Therapy in Youth Living With HIV

Adherence to antiretroviral therapy (ART) is a critical factor contributing to low rates of viral suppression among youth living with HIV. At the end of 2015, there were approximately 60,300 youth living with HIV (YLH) aged 13 to 24 years in the United States [1], and this number continues to increase. In 2016, YLH made up 21% of new HIV diagnoses—the equivalent of 8451 new cases in that year alone [2]. National treatment guidelines recommend initiating treatment with ART as soon as an individual is ready [3]. Even with simpler, more potent, and better-tolerated medications, viral suppression is difficult to achieve in youth. Only 41% of YLH in 2014 received HIV-related care, 31% were retained in care, and 27% were virally suppressed, the lowest percentage of any age group [1].

Adherence to ART is critical to sustain health, reduce transmission [4], and minimize the development of ART resistance [5]. Nonadherence has both public health implications and personal health risks. High viral load (VL) increases the likelihood of viral transmission [6], and nonadherent individuals may be more likely to transmit drug-resistant strains of the virus [7]. Conversely, treatment adherence decreases the pool of infectious individuals when condom use is poor, even among youth aware of their HIV status [8].

The Centers for Disease Control and Prevention (CDC) released a statement in 2017 that further underscored the importance of ART adherence and VL suppression. The CDC's statement acknowledged that individuals living with HIV who have an undetectable VL are not able to transmit the HIV virus [9]. This is commonly known by the slogan launched by the Prevention Access Campaign: Undetectable=Untransmittable, or U=U [10], and has ushered in a new era of treatment as prevention for HIV as well as contributed to reduced stigma for those living with HIV [11].

Youth, in particular, are frequently shown to be poorly adherent to ART [12-15]. In a study with ethnic and racial minority YLH, 39% reported suboptimal adherence [15]. In a recent review, only 51% of youth on ART achieved viral suppression of less than 400 copies/mL [16]. Data from the largest cross-sectional study to date found that only 37% of perinatally infected and 27.1% of behaviorally infected youth were virologically suppressed [17]. Of the YLH in the study, 30.5% reported engaging in unprotected sex in the last 90 days and 74.4% had detectable viremia. In addition, young men who have sex with men who have detectable VLs have been found to have higher rates of serodiscordant, condomless anal sex than those with undetectable VLs [18]. Finding effective adherence interventions for YLH to reduce HIV transmission is a public health imperative, and improved ART adherence is a particularly promising avenue.

A growing body of research has explored predictors of adherence to ART in YLH. Depression and anxiety have been consistently associated with poor adherence to ART. Adherence should be considered within the broader contextual issues present in the lives of youth, such as HIV stigma and disclosure, peer relations, and mental health and substance use [13,19,20]. Ethnic or racial minority status [15,21,22], lack of social support [15,22,23], and low self-efficacy [15,24] have also been associated with poor medication adherence in youth living with HIV. Poor medication adherence has been linked to financial and structural challenges such as housing instability [25] and lower level of education [26]. MacDonell et al [15] explored social cognitive predictors of ART adherence in a large, multisite sample of racial and ethnic minority YLH. Results indicated that social support, self-efficacy, psychological symptoms, and substance use were predictors of adherence. Taken together, this body of literature suggests that adherence interventions offering social support and promoting self-efficacy, while aiding with problem-solving of contextual barriers, may be beneficial.

Interventions for Increasing Antiretroviral Therapy Adherence

Although it has been abundantly clear for over two decades that adherence to ART is a critical problem, the field has identified only a limited number of modestly successful interventions for YLH, including motivational interviewing [27,28], directly observed therapy [29], multisystemic therapy [30], and cell phone reminder calls [31,32]. These failed to demonstrate lasting impact on VL beyond the intervention. All the interventions, except the cell phone reminder pilot studies [31,32], require in-person sessions, which may be difficult for nonadherent youth to complete. Interventions that reach youth more frequently, using modern and youth-friendly means of intervention delivery such as cell phones, may hold promise for improving both short- and long-term adherence.

Cell phones may be a powerful tool for HIV prevention and treatment intervention [33]. Interventions delivered via cell phone may offer an advantage over traditional, in-person interventions in cost, flexibility, and ease of adapting the intervention to the participant. Our pilot study found that daily phone call reminders, with incentives for 80% intervention adherence, were both acceptable and feasible for nonadherent youth [32]. Cell phone intervention delivery allows for tapering of the frequency of calls or texts in response to the needs of each participant, which could help sustain the impact of the intervention over a longer period of time for a lower cost. However, few interventions utilizing cell phones as a stand-alone mode of intervention (vs as part of a larger intervention) have been tested, and even fewer have targeted YLH.

Electronic reminders, particularly text messages, have been found in the short term to impact health behavior, including medication adherence of adults with a range of chronic conditions [34,35]. Text message adherence reminders have demonstrated some success in adults with HIV in Africa [36,37].

Recent studies have demonstrated the efficacy of text messages for adherence support and retention in care among US adolescents and young adults living with HIV, although the majority of studies were pilot studies [38,39]. An uncontrolled pilot study of 25 moderately nonadherent youth aged 14 to 29 years (baseline adherence=75%) using personalized, interactive, daily text messages demonstrated significant improvements in self-reported adherence in a 24-week intervention but lacked the power to detect VL changes [40]. Building on this pilot work, a randomized, controlled crossover study [41] utilizing personalized text messages in moderately nonadherent (missed 1+ dose in the last week or 4+ in the last month) youth aged 16 to 29 years found significant improvement in those reporting >90% adherence at 6 months compared with controls (60.5% vs 51%); improved adherence was maintained at 12 months [41].

Although interventions using text messaging to improve adherence in YLH show promise, cell phone–delivered interventions are not limited to text messages. Cell phone–delivered interventions that use voice calling may offer some of the advantages of text messaging (eg, youth-friendly delivery and modern applicability) but retain more of the important elements of human interaction (eg, social support and alliance). A recent qualitative study supports the use of cell phones as a strategy to maintain adherence to antiretroviral refill appointments at a public HIV clinic in Nigeria [42]. A pilot of cell phone support with incentives (CPS-I) in a cohort of highly nonadherent youth demonstrated significant improvements in adherence and VL during the 24-week intervention and 24-week postintervention [43]. Although promising, this study was small, and 7 of the 19 intervention subjects were unable to adhere to the strict intervention requirements [43].

Design Base

This study utilizes a Sequential Multiple Assignment Randomized Trial (SMART) design. SMART designs have numerous advantages over traditional trial designs. These are among the newest generation of improved clinical trial designs and methods and are used to inform the development of adaptive treatments or interventions [44,45]. This design is a cost-effective and methodologically rigorous way to maximize clinical utility and real-world implementation in the resulting adaptive intervention. Adaptive interventions are interventions in which the type or dosage of the intervention (eg, number of texts sent) is adjusted based on participant characteristics or response (eg, VL). Thus, an adaptive intervention allows treatment to be tailored to the specific needs of each participant. A SMART design involves multiple intervention stages, with each stage corresponding to one of the critical decisions involved in the adaptive intervention.

Theoretical Base

The intervention is guided by the conceptual model of supportive accountability [46]. This model was developed to guide research into human support components of mobile health (mHealth) interventions. The model is based on the premise that human support increases adherence through accountability to a coach (in the intervention, an adherence facilitator or AF) who is perceived as trustworthy, knowledgeable, and benevolent. Accountability should involve clear, process-oriented expectations that the patient is involved in determining (eg, reporting adherence, problem-solving). The effect of accountability may be moderated by patient motivation so that patients with higher intrinsic motivation may actually require less support.

The process of support is also mediated by the mode of communication (eg, phone, text messages, and computer), with different advantages and disadvantages for each mode. There is evidence that "lean media," or those modes of communication with less face-to-face contact and fewer visual social cues, may be associated with more positive, even idealized, attributions of communication partners. This is because people tend to form stronger impressions based on more limited social and interpersonal cues [47]. Interactions via lean media, including CPS and text messages, have the potential to foster social accountability toward improved adherence.

Multiple studies have demonstrated that social support is a strong predictor of good adherence to ART [43,48-50], and retention to HIV care is predicted by clients' perceptions of providers as engaging and validating [51]. Although overall social support was predictive in these studies, specific aspects such as instrumental support (ie, practical assistance) and informational support (advice or problem-solving) were found to be predictive of adherence in adults with HIV [50]. The content of conversations in the CPS study [43] is designed to validate the importance of adherence, prompt problem-solving (through informational support), and provide instrumental assistance (through referrals) to address barriers as they emerge. This intervention utilizes social support constructs to provide tailored conversations to improve both short- and long-term adherence. Social support theory also suggests that an ongoing alliance could be protective against depression, substance use, and general stress [52-55].

Cost-Effectiveness

It is increasingly important in the face of competing demands for health care resources to establish not just the efficacy of interventions but also their relative economic value. The National Institutes of Health (NIH) established cost-effectiveness analysis as a key priority in 2015 [56]. By integrating cost-effectiveness analysis into a SMART trial, we can simultaneously determine not only the most effective sequences but also whether the added costs of potentially more effective sequences are worthwhile. Within an implementation science framework, costs include those associated with executing implementation strategies as well as those associated with service delivery as uptake changes [57]. Understanding the potential barriers and facilitators to intervention sequences for widespread implementation can provide additional critical information about treatment sequences. Many have argued that the science-practice gap is inflated by the bias toward step-wise progression of research from development, to efficacy, to effectiveness, to implementation, and that hybrid designs can maximize clinical implementation earlier in this developmental process [58]. Thus, we can greatly enhance the potential for intervention scale-up by comparing interventions in real-world settings and identifying effective sequences of treatments and

their cost-effectiveness ratio while simultaneously studying the context of implementation in a Hybrid 1 Effectiveness-Implementation trial [58,59].

In addition, helping people living with HIV maintain an undetectable VL is in itself a way to reduce sexual transmission of HIV, as highlighted by U=U. Therefore, not only is this intervention a potentially cost-effective way to achieve VL suppression in YLH, but it may also prevent future cases of HIV transmission to those who are HIV negative. This potentially saves the health care system hundreds of thousands of dollars per person. A recent study found that the medical cost saved from preventing a single HIV infection is US $229,800 [60]. This rises to US $338,400 if those living with HIV entered into the care cascade early on and stayed in care [60]. This figure grows higher when taking into account secondary infections avoided and societal costs saved (eg, social services and housing, patient and family time, productivity, physical tolls, and emotional distress) [60]. It is clear that VL suppression is a key part of saving medical costs related to HIV care, both for the patient themselves and for the public.

Aims

The aim of this study is to test an adaptive adherence intervention, which utilizes 2 mHealth intervention designs, in an effort to promote adherence to ART and maintain VL suppression in YLH from across the United States. Both interventions are delivered remotely, utilizing a central research center. In addition, this study aims to increase understanding of the context for wide-scale implementation of this type of intervention as well as to understand the benefit of incentives for nonresponders and tapering of interventions for responders.

The primary hypotheses are as follows:

1. Youth randomized to CPS will have significantly greater VL suppression (primary outcome) and self-reported medication adherence (secondary outcome) at 24 weeks than those in the SMS text message support group.
2. Nonresponders randomized to CPS with incentives will have significantly greater VL suppression (primary outcome) and self-reported adherence (secondary outcome) than those randomized to SMS with incentives.

Secondary aims include assessing the following concepts, all central to the *Scale It Up* program described in this issue [61], within the different intervention sequences within the SMART design: (1) cost-effectiveness; (2) the 5 components of the Self-Management Model over time (see ATN: Scale It Up overview paper in this issue); and (3) the barriers and facilitation throughout Exploration, Preparation, Implementation, and Sustainment (EPIS) Model phases (identified in ATN 153 EPIS protocol paper in this issue).

Methods

Overview of Content and Delivery

This study is part of the Scale It Up program as described in the overview paper in this issue [61] and employs a SMART design with repeated measures (NCT03535337). Approximately 190 YLH participants are being recruited, consented, enrolled, and randomized to either CPS or SMS (short message service). CPS is provided on all weekdays except holidays. Weekend and holiday adherence are assessed at the first CPS contact with the participant following the weekend and/or holiday. SMS is provided every day, including weekends and holidays. Both intervention groups receive 3 months of intervention, followed by a second randomization, which is be based upon response to the intervention.

Participants who respond to the intervention, that is, those with a suppressed VL (<200 copies/mL) in either group, are randomized to receive either 9 months of follow-up without intervention (standard care) or 3 months of tapered intervention (CPS-T or SMS-T twice a week) based on their previous intervention modality, followed by 6 months of follow-up without intervention (standard care; see Figure 1).

Participants who do not respond to the intervention, that is, those with a VL ≥200 copies/mL at the 3-month study visit, are rerandomized to CPS or SMS; however, an incentive is added to both arms. This incentivized CPS or SMS (CPS-I or SMS-I) provides the opportunity to explore the role of incentives with each intervention modality. After 3 months of CPS-I or SMS-I, participants receive 3 months of tapered intervention (CPS-T or SMS-T twice a week) based on their most recent intervention modality followed by 3 months of follow-up without intervention (standard care). Those who are unable to provide a documented VL result at the 3-month time point are considered nonresponsive to the intervention and are rerandomized to an incentive arm.

All participants complete a Web-based, computerized survey, which measures self-reported adherence, substance use, depression, and other mediators and moderators of adherence at baseline and every 3 months thereafter until study completion (12 months for both responders and nonresponders). In addition, a VL result is obtained from participants or their care provider, or they can provide a blood sample for a study-sponsored VL assay.

Participants are compensated US $40 after completing the baseline and each follow-up assessment for a total of US $200 for all study assessments. Participants in the CPS-I or SMS-I arms who reach 75% monthly adherence to calls or text responses receive an additional US $50 for up to 3 months (up to US $150). As all activities are conducted remotely, compensation is provided via electronic gift cards (eg, Amazon, Target, Walmart).

Recruitment and Eligibility

Eligibility Criteria

To be considered eligible for enrollment, an individual must meet the following criteria: (1) a youth living with HIV (aged between 15 years and 0 days and 24 years and 364 days, inclusive, at the time of signed informed consent or assent), (2) willing to provide proof of VL ≥200 copies/mL or blood specimens for HIV VL measurement within 6 months before baseline enrollment, (3) prescribed an ART medication regimen for a minimum of 3 months before eligibility VL, (4) the sole owner of a device capable of sending and receiving calls and text messages, and (5) able to provide consent for the research

team to communicate with the participant's HIV care provider team.

Exclusion criteria include the following: (1) participants whose mental, physical, or emotional capacity does not permit them to complete the protocol as written; (2) inability to understand written or spoken English; or (3) concurrent participant in any behavioral research intervention designed to impact medication or care adherence, as indicated in the screener.

Recruitment Methods

A number of recruitment strategies previously utilized by the Center for HIV/Educational Studies and Training (CHEST) are being implemented [62-64] by the *Scale It Up* Recruitment and Enrollment Center (REC). To ensure the desired sample of 190 participants is reached, both site referrals and national media campaigns are being used. The following are methods through which recruitment takes place: (1) referrals from *Scale It Up* clinical subject recruitment venues (Table 1), (2) social media ad campaigns, (3) geosocial networking data application ads, (4) nationwide flyers and recruitment material distribution (Figures 2 and 3), and (5) indirect recruitment through CHEST Online Master Screener. To date, a nationwide recruitment strategy has not been used for an HIV ART adherence clinical trial.

Determining Final Eligibility

After potential participants are recruited, participants may complete the study-specific screener online or over the phone (Figure 4). The study screener screens for the inclusion and exclusion criteria for the study. Upon completion of the study screener, interested individuals are informed whether they are preliminarily eligible to participate in the study.

If a participant is preliminarily eligible and interested in participating in the study, the REC staff member discusses several options for submitting proof of VL test results and ART prescription. The staff member explores a number of methods with potential participants, in response to the need to be flexible for the population. The options for submitting proof of an unsuppressed VL (≥200 copies/mL) within 6 months before baseline and of ART prescription within 3 months before the submitted VL test are as follows: (1) self-submission through an online, secure Qualtrics form (eg, uploading a picture of their medication bottle or recent VL results); (2) submission directly by the participant's health care provider via a release of information; and (3) through study-provided testing at a local Quest site.

Figure 1. The SMART (Sequential Multiple Assignment Randomized Trial) study design. CPS: cell phone support; CPS-I: incentivized cell phone support; CPS-T: tapered cell phone support; MFU: month follow-up; NRsp: nonresponders; Rsp: responders; SC: standard care; SMS: text messaging support; SMS-I: incentivized text messaging support; SMS-T: tapered cell phone support; VL: viral load.

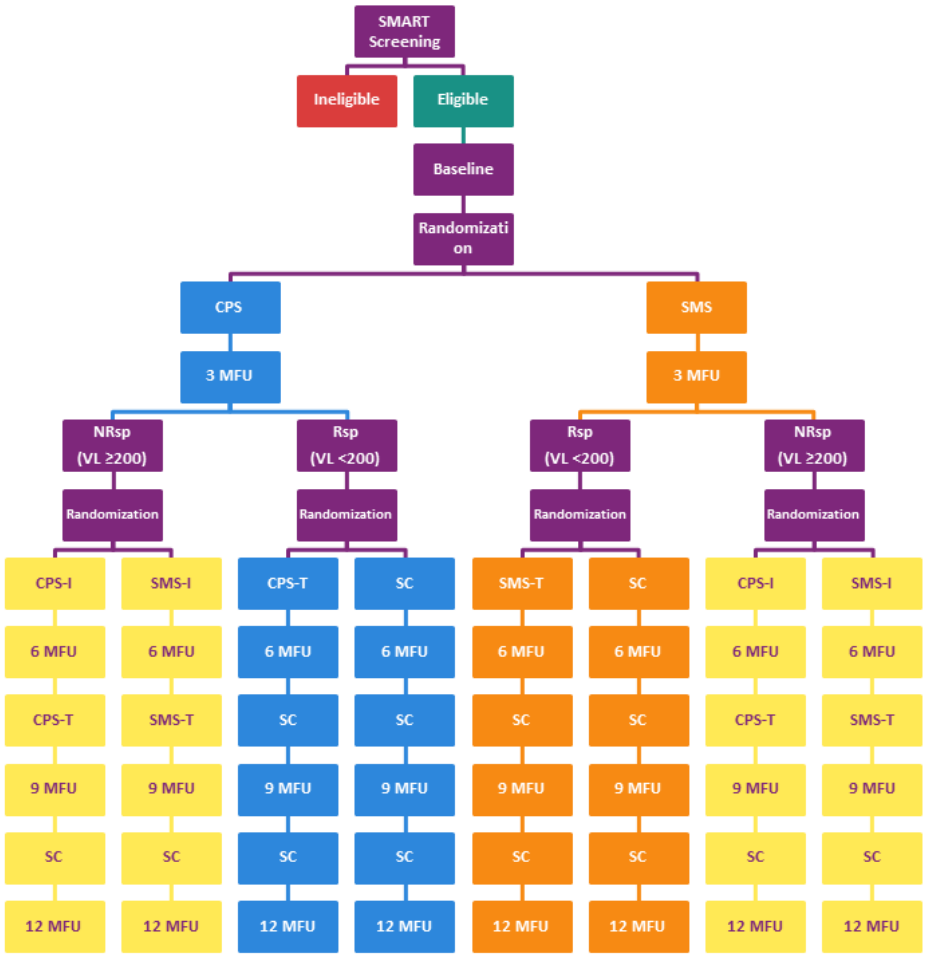
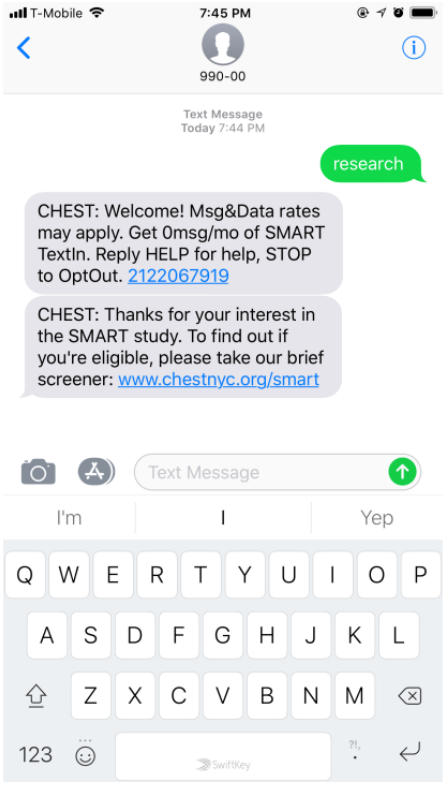


Table 1. Scale It Up clinical subject recruitment venues.

Site name	Location
Johns Hopkins University	Baltimore, MD
The University of Alabama at Birmingham	Birmingham, AL
SUNY Downstate Medical Center	Brooklyn, NY
Children's Hospital Los Angeles	Los Angeles, CA
St. Jude Children's Research Hospital	Memphis, TN
University of Miami	Miami, FL
Children's Hospital of Philadelphia	Philadelphia, PA
University of California San Diego	San Diego, CA
University of South Florida	Tampa, FL
Children's National Medical Center	Washington, D.C.

Figure 2. The SMART (Sequential Multiple Assignment Randomized Trial) recruitment card.

Figure 3. SMART (Sequential Multiple Assignment Randomized Trial) text-in recruitment.



It is emphasized to the participants that although the AF can help triage any medical or psychosocial needs that come up during their conversation with the participant, these interactions and access to the AF is not a substitute to continuing to use their main resource for care. For example, if the participant has an acute medical or psychosocial problem or needs an appointment scheduled, they should not call the AF, but instead, use their care site's working hours or after-hour telephone numbers (as they apply) to get their needs addressed.

A study staff member reviews the potential participant's VL and ART documentation to determine that they meet the enrollment criteria. A study staff member sends the potential participant the SMART enrollment link, which contains the study consent/assent form, Health Insurance Portability and Accountability Act (HIPAA) Authorization form, and the baseline computerized survey. Upon completion of all portions of the enrollment link, participants are considered enrolled in SMART and are randomized and stratified into their respective intervention arms for the first period of the study.

Intervention Design

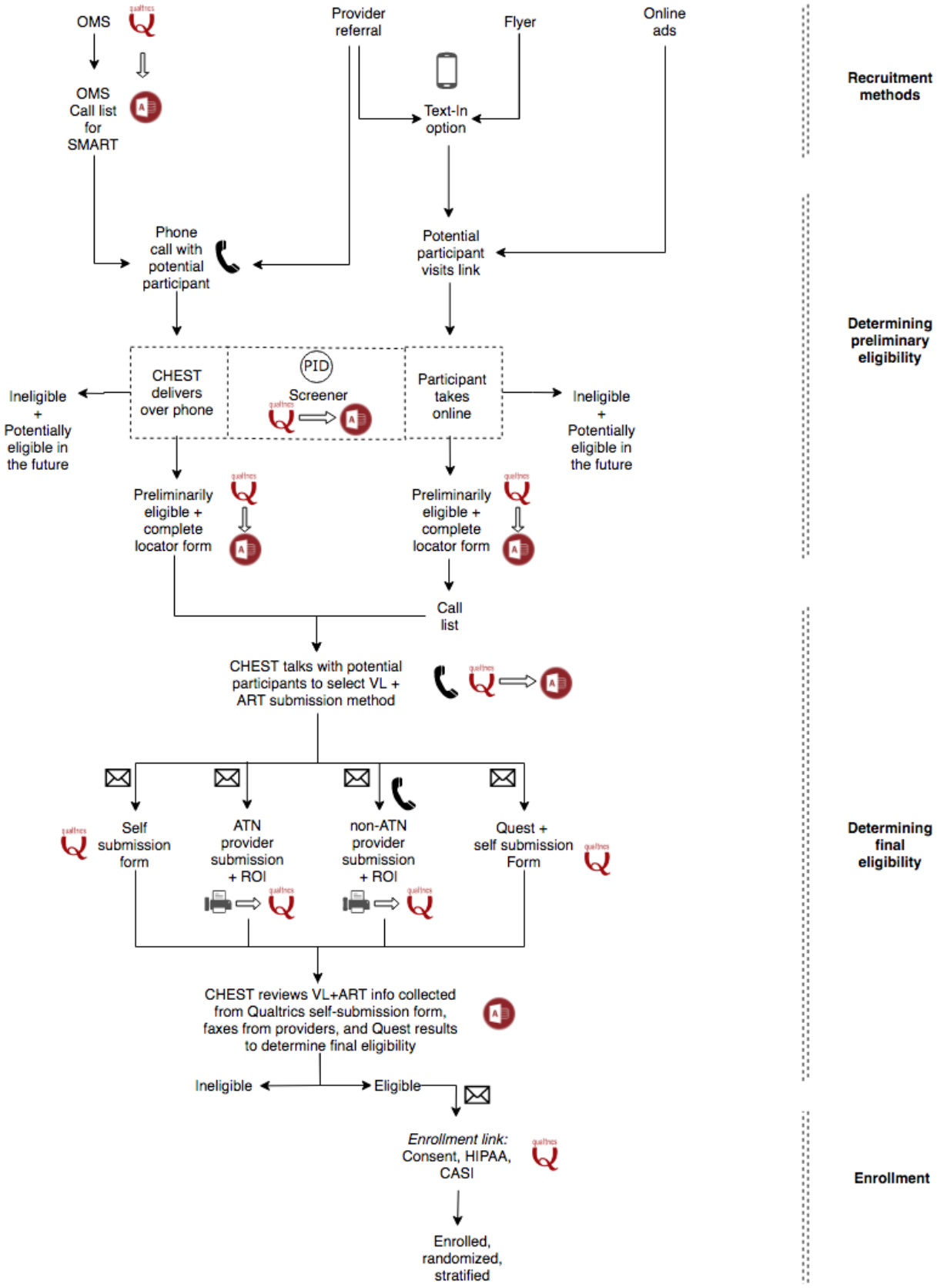
Cell Phone Support

Each participant randomized to CPS is assigned a lead and back-up AF. At the time of study entry, the AF and the participant choose a start date and arrange a call time that is after their daily ART dosage time and within office hours. For those participants taking their medication after dinner/before bed, the AF calls in the morning to confirm they took their ART the night before. Although the study allows flexibility in planning for the timing of taking the medication and the phone call that follows is based on the participant's schedule, the call time is mutually agreeable to the AF and the participant. All calls must take place during the agreed upon time range.

Preferably, calls begin the next Monday following the baseline visit and/or within 2 weeks of study entry. Calls from the AF occur from Monday to Friday, once a day and continue for 3 months, except for major holidays. Although the initial call lasts 10 to 15 min, it is expected that most calls last less than 5 min. AFs take an additional 5 min to document the content of the call. To protect the confidentiality of the participant, the AF confirms that the person who answers the cell phone is the participant enrolled in the study. Voice recognition can be used as the primary confirmation; however, participants are also offered the use of a code word for identification purposes to further protect their privacy. AFs use study cell phones to conduct the daily calls, send/receive texts, and receive voice messages.

If a participant does not answer a prearranged call, the AF leaves a reminder message requesting that the participant calls back within the next 30 min. If a return call is not received within 30 min, the AF repeats the call once at the end of the 30 min. If the participant returns the phone call after more than 30 min have elapsed, the AF conducts the call; however, the delayed call counts as nonadherent to the intervention. If the participant answers but is unavailable to talk, this is counted as nonadherent. If the call is missed due to an issue with the AF, it does not count as nonadherent to the intervention.

Figure 4. The SMART (Sequential Multiple Assignment Randomized Trial) recruitment flowchart. ART: antiretroviral therapy; ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions; CASI; computer-assisted self-interview; PID: participant ID; OMS: online master screener; ROI: release of information; VL:viral load.



On each call, the AF assesses if the participant has taken their medication for that day and if medication was taken during days when calls to the participant were not completed (ie, weekends and holidays). If the participant has not yet taken their ART, the AF waits for the participant to retrieve and take their medication, if available. If the participant usually takes their

ART the night before, then the AF does not request that the participant take their medication during the call. If the participant is nonadherent, the AF assesses reasons for nonadherence and engages the participant in brief problem-solving around identified barriers. The AF also discusses any new or ongoing problems in the participant's life (eg, related to housing, transportation, or food) and provides support in problem-solving to address the issues. In addition, the AF reinforces prioritizing medications, reminds participants about scheduled appointments, and suggests scheduling any relevant referrals (eg, case management, mental health services, and substance use counseling) with their health care providers. Participants needing more intensive assistance are referred to their care team using the information provided on the participant's locator form, and with the youth's permission, the AF contacts the care team to share the concerns.

Following the call, the AF completes a checklist about the call. The checklist includes the following: length of the call; time required to reach the participant for intervention purposes; comprehensive record of queries regarding barriers to medication adherence that have arisen during the time between calls; and a place for brief field notes that capture the specifics of medication barriers, advice given, referrals given, and the successful or unsuccessful resolution of barriers when such occurrences arise. The AF also triages any questions or concerns that come up during the course of the call and provides them to the HIV health care provider with the participant's permission. Any adverse events reported by the participant to the AF are triaged by the REC clinical team and appropriate procedures are followed.

Text Message Support

Participants enrolled in the SMS intervention receive daily personalized SMS adherence reminders for 3 months. Participants are able to choose the timing and the wording of the text message to protect confidentiality (eg, have you taken your vitamin today, have you flossed your teeth today). Participants are asked to text back if they did or did not take their ART medications. The texts are sent through Trumpia, a robust, customizable technology to deliver text messages to participants and track their responses. Trumpia is compliant with HIPAA laws as all personal identifiable data are encrypted.

Incentives and Tapering

After 3 months of either the CPS or SMS intervention, participants are sorted into new intervention arms depending on their VL. Participants submit proof of VL and complete a computerized survey. Participants whose VL is <200 copies/mL are categorized as "responders," because they were able to successfully reduce their VL by adhering to their ART medication during the past 3 months. Participants whose VL is ≥200 copies/mL are categorized as "nonresponders."

All responders are randomized into the tapered intervention arm or into standard care, where no interventions (calls or texts) are made. Those originally in the CPS group receive the CPS tapered (CPS-T) intervention or standard care; likewise, those in the SMS group receive the SMS tapered (SMS-T) intervention or standard care. In the tapered interventions, calls and texts are reduced to 2 days per week. CPS-T and SMS-T last for 3 months until the 6-month follow-up, after which participants transition into standard care. At this point, all responders are in standard care, which continues throughout the 9- and 12-month follow-ups.

Participants who were nonresponders after the first 3 months are randomized to CPS or SMS, but with the addition of an incentive. They receive incentives for text messaging or cell phone support participation. Those participants who answer the cell phone support call or respond to the text messages 75% of the time or more each month receive an additional US $50 during the incentive phase. This is implemented for 3 months until the 6-month follow-up, after which the intervention is tapered to 2 times per week. Those in CPS-I enter CPS-T, and those in SMS-I enter SMS-T. After the 9-month follow-up, participants enter standard care until completion of the study at the 12-month follow-up.

The 3-, 6-, 9-, and 12-month follow-up assessments for all participants include a VL and a computerized survey.

Training of Interventionists

The AFs are staff members who are not licensed professionals or graduate students who have completed clinical externship training. AFs should (1) be able to interact and engage with youth; (2) be knowledgeable about HIV infection and its treatments, including side effects and their management; (3) be skilled in interpersonal communication and be able to display empathy for the participant; (4) trained in motivational interviewing; (5) maintain a professional relationship and not invade the personal boundaries of the participant; and (6) be trained in providing a link between the participant and their main resource for care, as a means of providing referral services for necessities and counseling, if needed.

All AFs attend a 2-hour webinar designed to familiarize AFs with the purpose of the study, definition of adherence, role of the AF, HIV basics, cultural humility, building rapport and effective communication, legal issues, and protocol review. Following the training, AFs participate in a minimum of 2 telephone role plays during which they practice an initial phone call with a participant and a daily phone call. These training calls last about 30 min, including the role play and feedback. AFs are also encouraged to practice role plays with each other to obtain not only more time in practice but also to experience the role of being the participant during the cell phone support call.

Fidelity Monitoring

A fidelity evaluation is conducted to assess whether the AF is collecting the correct information and providing an appropriate level of support. This is to ensure fidelity to intervention delivery and to detect areas of the AF training that need to be improved. A clinical coordinator conducts this fidelity evaluation.

All intervention phone calls between the AF and participant in this study are digitally recorded utilizing an amplifier and recorder, and all digital recordings are saved on a secure network for review. The clinical coordinator reviews 20% of all audio files for each AF during the initial 3 months. The audio files

are randomly selected from all audio files saved by the AFs. If 90% of reviewed files are found to be adherent to the requirements listed above, the clinical coordinator only reviews 10% of all audio files after the initial 3 months. The recordings are assessed for adherence to the phone call script, advice, referrals, centering of participants in discussion, order of content discussed, and appropriate length of call.

Results

This study began recruitment in August 2018, and all participant components are projected to end in June 2020.

The primary analysis will be a comparison of the VL suppression rate (primary outcome) between the CPS and the SMS groups at the first stage of randomization (see Study Design). This will be performed using a chi-square test. We will also compare the drop in VL (measured in logarithmic scale with base 10) between the 2 groups. As this is a continuous measure, we will use a 2-sample *t* test to conduct this analysis. We will also compare medication adherence rate (secondary outcome) between the 2 groups using a chi-square test. All the primary analyses will be based on initial assignment to groups, using the intention-to-treat principle. Each of the primary hypotheses will be tested using linear mixed-effects (LMEs) regression analyses [65]. All LMEs will be tested for goodness-of-fit using Wald-type test, which shows satisfactory performance for models with fewer (<5) covariates [66]. For testing primary hypothesis 1, the model will include up to 4 repeated assessments of VL suppression (months 0, 3, 6, and 12) as the dependent variable. For primary hypothesis 2, we will only focus on nonresponders (for both CPS and SMS at stage 1) and compare the VL suppression as dependent variable using a repeated measure LME (months 0, 3, 6, 12). Each LME model will include a random intercept and slope and fixed effects for adherence intervention group, time, and the stratification variables: clinical site, age, and gender. A likelihood ratio test will examine the incremental contribution of the group by time interaction, which represents the interaction of interest for primary hypothesis 1 and primary hypothesis 2, testing for a differential adherence intervention effect over time. The decision rule for each primary hypothesis calls for rejection of null hypothesis if this interaction is statistically significant using the Hochberg step-up alpha adjustment [67]. A site by group interaction will be also examined and included in each model (above) if significant at the .05 level. In addition, likelihood ratio tests will be used to compare the model fit with that having a first-order autoregressive (AR1) covariance structure, as described by Hedeker and Gibbons [65].

We will also conduct similar models as mentioned above, however, predicting adherence to ART (secondary outcome), which is measured at every time point. Each model will be a 2-level model in which time points (level 1) are nested within participants (level 2). This approach accounts for the nonindependence of repeated measurements within individuals. The purpose of the LME-based [68] analysis for the primary aim is to determine which of the first-stage intervention, CPS or SMS, is associated with the most improvement in VL and adherence, regardless of which second-stage treatment participants received. As noted in SMART design, we compare combinations of subgroups (as in 2 specific aims) but not individual subgroups. The study is designed and powered to test the 2 primary hypotheses with 1 primary outcome. As it is customary, secondary and exploratory aims are not powered [69]. However, we expect that data based on SMART design will yield valuable information for hypotheses generation, involving high-quality embedded interventions, which can guide the design of subsequent confirmatory studies.

The first of the secondary aim is to compare the effect of tapering with termination at the second randomization among those who received CPS and those who received SMS and achieved VL <200. We will compare viral suppression rates among the 2 groups (tapering vs termination), followed by a more refined analysis using LME modeling. We will first perform a chi-square test between the 2 viral suppression rates, followed by mixed-effects modeling. The purpose of the second secondary aim is to determine which of the adaptive intervention arms lead to the greatest improvement in VL and adherence over the entire study period. To perform this, we will estimate the viral suppression and adherence rates following each of the 8 embedded interventions and conduct a chi-square test. As both responders and nonresponders are rerandomized, there is no need to use inverse-probability weighting [70]. However, to account for the correlation induced by subjects shared between any 2 embedded interventions, we will use robust (sandwich) SE as in the generalized estimating equations approach [71].

In addition, we will study the moderators of treatment effect. This is a potentially impactful goal, given the gradual but assured paradigm shift in behavioral interventions from “one-size-fits-all” approach to the modern personalized medicine. Potential moderators in the current context are self-reported adherence, substance use, and depression—these can be incorporated in the analysis of the SMART data to deeply personalize the adaptive intervention for future patients. Due to the 2-stage nature of the adaptive interventions, a straightforward regression analysis including potential moderators in the model as interaction terms is not suitable due to the possibility of unmeasured confounding induced by selection bias (also known as “collider-stratification bias”) that can be present in time-varying settings, even in presence of randomization [72]. To avoid this bias, one needs to employ 2 separate regressions corresponding to the 2 stages of SMART and carefully move backward through the stages; such a state-of-the-art approach is known as Qlearning [73]. Each regression will contain interaction terms between the stage-specific treatments and the appropriate stage-specific moderators. If any interactions come out significant, then patient characteristics can be used to deeply tailor the interventions for future patients. This will be performed using the R software package qLearn [74]. As customary, secondary aims are not powered and exploratory in nature.

Discussion

Key Innovations

This study is highly innovative in that it focuses on a critical area for intervention—adherence to ART in YLH—and goes

beyond what has been done previously in several key ways: (1) it directly compares 2 successful, potentially sustainable, and youth-friendly modes of mHealth youth adherence intervention delivery; (2) the project uses a SMART design to explore a number of key issues surrounding sequencing mHealth interventions in a cost-effective manner that would be practical in clinical settings; (3) the CPS intervention uniquely addresses multiple barriers to ART adherence in real time using a social support framework; and (4) the study explores the clinical and public health costs of sequencing of interventions based on viral suppression and sexual transmission risk.

Technology-based interventions offer tremendous advantages for delivery of brief interventions in terms of reach, ease of replication, anonymity, and cost. They also have an advantage in functionality or how quickly and easily they can be modified for a specific population. mHealth assessments and interventions have been shown to be powerful tools through which brief, targeted interventions can be delivered to people with HIV or at risk of acquiring HIV [75-77]. Texting and cell phone voice calls, in particular, have been linked to improved adherence to ART [41,43,78,79]. However, no study to date has directly compared the use of SMS with CPS for intervention delivery and efficacy. There are currently *no* specific evidenced-based CDC-supported ART adherence interventions for youth. Cell phones are a convenient and culturally relevant mechanism for intervention delivery, and socioeconomically disadvantaged youth and ethnic and racial minority youth report high rates of access and use [43,80-82].

This innovative SMART design [83] not only compares the efficacy of the proposed CPS and SMS interventions but also explores other key issues such as the role of incentives in participant engagement, the impact of tapering intervention frequency, and the potential cost-effectiveness of sequencing the interventions without incentives before providing incentives. This design allows us to explore potential benefits of sequencing our interventions in a way that mimics what would likely happen in a clinical setting (eg, start with the less intensive, less costly interventions, and if that fails, move to the more intensive and costly intervention with incentives). Finally, the design allows us to test an additional secondary aim, whether tapering the interventions and removing incentives will maintain improved adherence in those that reach a suppressed VL (in both arms). All youth adherence intervention studies to date have found that adherence declines once the intervention is over, and tapering an adherence intervention in youth has not yet been done. This will offer clinical sites a less intensive, low-cost option that could be employed indefinitely in highly nonadherent youth.

Another key intervention is the way the study overcomes the numerous barriers to ART adherence (eg, forgetting, not feeling like taking ART, medication reminds me of HIV) [84]. Effective adherence interventions need to address forgetting, but also promote motivation, reinforce positive reasons to take ART as prescribed, and offer solutions to barriers as they arise or change over time [85]. The CPS intervention is based on the model of social accountability, so that cell phones are used to provide instrumental and informational support, foster patient accountability to their AF, and promote real-time problem-focused coping.

A further key innovation is the use of a centralized model for recruitment and for providing the mobile intervention. The centralized model provides a single location in which multiple activities can occur. This can provide cost savings as staff members can be cross-trained to screen, recruit, and provide adherence support. This may be of benefit when case managers in individual clinics may be overloaded with providing direct care to their clients. In addition, nationwide recruitment through social media combined with the distribution of recruitment materials to HIV care providers such as Ryan White-funded clinics may also provide a cost-effective manner to recruit participants when it is getting more difficult to identify and recruit youth with an unsuppressed VL.

Finally, in the clinical setting, cost-effectiveness becomes critical to understanding how to implement sequences and tapering. Each of these adaptive intervention sequences has differing costs, and we will be able to help determine which intervention might be best for which groups (eg, behavioral acquisition vs perinatal acquisition, substance abuse, depression). From a broader public health perspective, it is clear that youth nonadherent to ART are frequently the same patients engaging in other risky behaviors such as condomless anal sex [18]. Thus, a successful intervention such as this one has the potential to lower the risk of HIV transmission. The assessment of sexual risk and viremia will allow us to estimate the cost benefits from reduced HIV transmission for each sequence.

Limitations

There are some limitations to this study. Participants are not required to verify that they have been on ART for at least 3 months for study enrollment. Although participants must submit proof of an ART medication bottle or prescription, this does not necessarily have to be from at least 3 months ago. It is possible but unlikely that a subject would have inadequate time to suppress VL under 200 copies/mL if use has been less than 3 months.

This study also relies on mHealth intervention methods, specifically through phone calls and text messages, as a way to improve adherence. The requirement to be the sole owner of a device capable of sending and receiving calls and text messages, although necessary for confidentiality, may pose a barrier to some study participants. As a result, this study may not be accessible to all YLH, particularly those who are low income and do not have a mobile device or who may share a mobile device.

Finally, participants are required to be able to communicate in English. This means that YLH who are not yet fluent in English, such as those who have recently immigrated or who live in areas that are primarily non-English speaking, would not be eligible for this study. However, these are populations which could also benefit from ART adherence interventions if they were made to be accessible, and it is plausible that cultural differences in implementation may be missed.

Overall, this dynamic and adaptive study shows great promise. It offers a highly innovative SMART design to assess the efficacy of 2 mHealth interventions to promote adherence to ART.

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Conflicts of Interest

None declared.

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Abbreviations

AF: adherence facilitator
ART: antiretroviral therapy
CDC: Centers for Disease Control and Prevention
CPS: cell phone support
CPS-I: cell phone support + incentives
CPS-T: cell phone support tapered
EPIS: Exploration, Preparation, Implementation, Sustainment Model
HIPAA: Health Insurance Portability and Accountability Act
LME: linear mixed-effects
mHealth: mobile health
NIH: National Institutes of Health
REC: Recruitment and Enrollment Center
SMART: Sequential Multiple Assignment Randomized Trial
SMS: short message service (text message support)
SMS-I: text message support + incentives
SMS-T: text message support tapered
VL: viral load
YLH: youth living with HIV

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Original Paper

Adolescent Medicine Trials Network for HIV/AIDS Interventions Data Harmonization: Rationale and Development of Guidelines

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Abstract

Background: The Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) research program aims to defeat the rising HIV epidemic among adolescents and young adults in the United States.

Objective: This study aims to optimize cross-study analyses and comparisons of standardized measures (variables) collected in the ATN.

Methods: Guidelines were developed for harmonizing measures to be collected across ATN studies.

Results: Eight domains were identified for harmonization—Demographics and Socioeconomic Characteristics, Sexual Behavior and Risk, Substance Use and Abuse, HIV-Positive Cascade, HIV-Negative Cascade, Mental Health, Social Support and Isolation, and Pre-exposure Prophylaxis Cascade.

Conclusions: The collection of selected key measures in a uniform manner across studies facilitates the characterization of participant populations, comparisons between studies, and pooled analysis of data from multiple studies.

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KEYWORDS

adolescent; Adolescent Medicine Trials Network for HIV/AIDS Interventions; data harmonization; HIV

Introduction

The Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) research program aims to defeat the rising HIV epidemic among adolescents and young adults in the United States by increasing awareness of the HIV status and access to health care for those diagnosed with HIV. The ATN develops and conducts behavioral, community-based, translational, therapeutic, microbicide, and vaccine trials in HIV-at-risk and HIV-infected youth aged 12-24 years, with a focus on the inclusion of minors. The ATN research is conducted through collaborations within the network and with researchers in other institutions across the United States. The ATN website [1] provides additional information about the network.

The ATN currently includes 3 research program projects (or U19s) and a Coordinating Center with >20 currently active study protocols across the network. Without standardization, data collected across these different studies may be difficult or impossible to combine. In turn, this could potentially hamper efforts to compare data across studies or describe the US adolescent and youth populations choosing to participate in the ATN research.

Therefore, the ATN Analytic Committee (AC) developed guidelines for harmonizing (ie, standardizing) measures (variables) to be collected across ATN studies to optimize cross-study analyses and comparisons. This set of harmonized measures facilitates pooled analysis of data and allows the characterization and comparison of participants across ATN studies conducted among diverse populations in the United States.

Methods

Adolescent Medicine Trials Network for HIV/AIDS Interventions Data Harmonization Process

The AC developed a set of harmonized measures to be collected across the diverse set of projects in the ATN. Eight domains were identified for harmonization: 5 "standard" domains for which characteristics (measures, variables) will be collected in all ATN studies unless a strong operational or scientific rationale exists otherwise; and 3 "additional" domains for studies planning to collect data in these domains (Figure 1). The data harmonization guidelines focus primarily on survey questions and measures and include recommendations for the order in which the measures should be collected, as well as the ordering of levels for particular measures.

The 5 standard domains were developed by reviewing common measures collected by previous and current ATN studies and identifying key areas of interest among ATN studies; these domains included "Demographics and Socioeconomic Characteristics," "Sexual Behavior and Risk," "Substance Use and Abuse," "HIV-Negative Cascade," and "HIV-Positive Cascade." The 3 additional measure domains that were identified for harmonization across ATN studies included "Mental Health," "Social Support and Isolation," and the "Motivational Pre-exposure Prophylaxis (PrEP) Cascade." These additional measures are not required but recommended for studies that plan to collect related information. The ATN data harmonization guidelines were reviewed and received the final approval by the ATN Executive Committee (EC). The following paragraphs describe the process undertaken by the ATN AC for identifying and selecting measures to include within each domain before submission to the ATN EC for approval.

Standard Domains

The "Demographics and Socioeconomic Characteristics" domain was developed by the collective AC by compiling common survey questions and measures collected in current and previous ATN studies. A draft of the demographic and socioeconomic measures was then distributed to AC members for discussion. The AC members provided their feedback and measures were discussed during biweekly calls. The AC removed measures from the standard domains that could not obtain AC and EC consensus, but these measures remain available for optional use by future ATN studies.

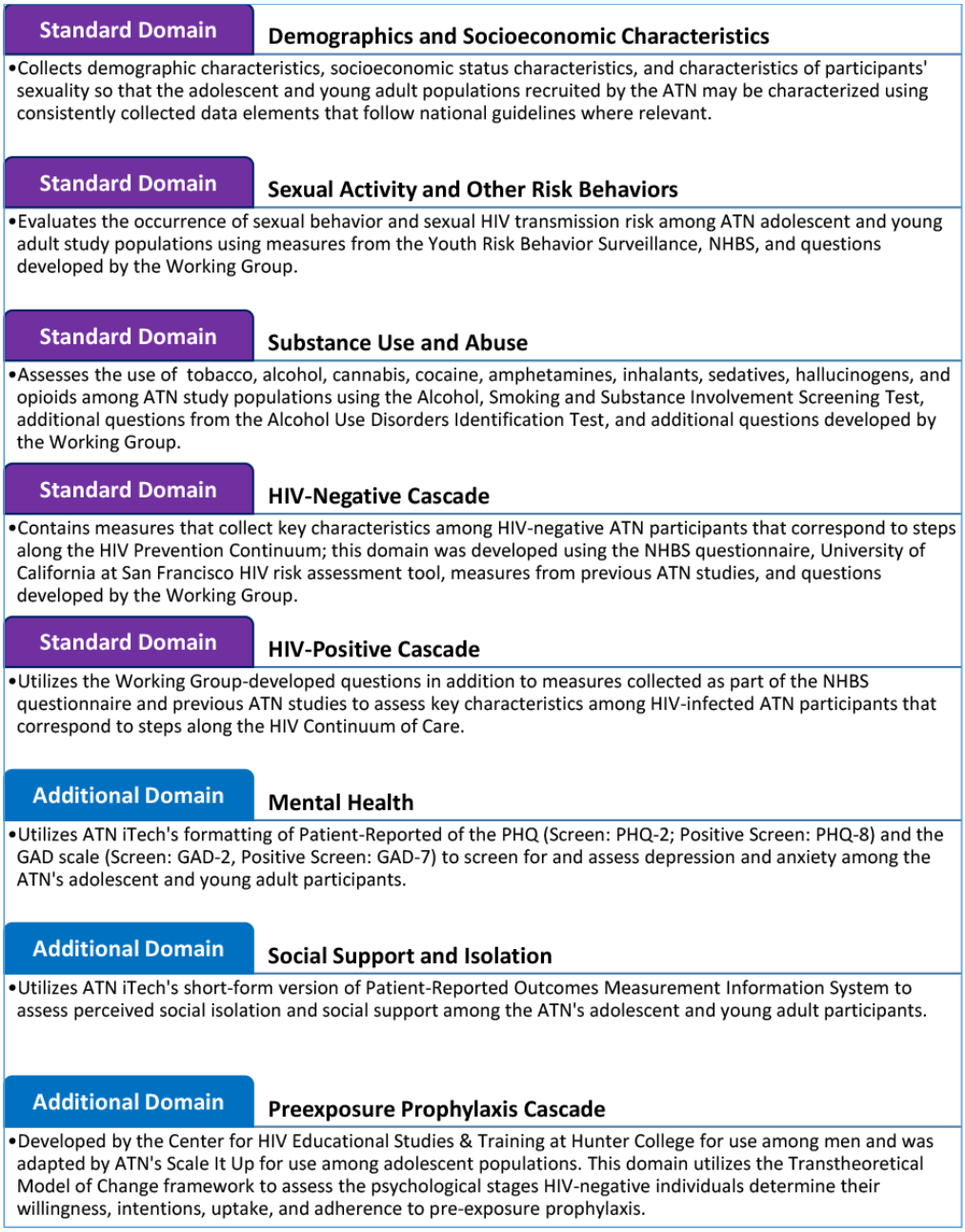
The AC identified "Substance Use and Abuse," "Sexual Behavior and Risk," "HIV-Negative Cascade," and "HIV-Positive Cascade" as critical domains to be developed by smaller working groups. To facilitate the creation of working groups for each of these 4 domains, U19 team members indicated their willingness to participate in or lead any of the 4 working groups. These working groups were charged with 3 objectives as follows: (1) review currently planned and previously conducted ATN studies to gain a broad understanding of data points within the domain that might be collected in future ATN research studies; (2) evaluate potential data items for the utility and feasibility of collection in a standardized manner in upcoming ATN research studies; and (3) recommend a core set of data items for collection in upcoming ATN studies and provide additional recommendations that might be used in some but not all studies, if appropriate. The working groups held calls as needed to review the existing measures and literature and develop a list of proposed questions and measures to include in their assigned domain. The recommended questions and measures were then presented to the larger AC for feedback and approval.

The Sexual Activity and Other Risk Behaviors Working Group sought to determine a minimum number of data points with broad relevance by utilizing data measures from the Youth Risk Behavior Surveillance (YRBS) [2,3].

Prior to the formation of the working groups, the AC agreed that using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) would be a good starting place for the "Substance Use and Abuse" domain [4]; this decision was largely based on the use of the ASSIST instrument in previous ATN studies. The Substance Use and Abuse Working Group then identified additional variables that are often included in ATN studies' data collection instruments but are not already collected in the ASSIST.

The "HIV-Negative Cascade" and "HIV-Positive Cascade" domains are critical components to the data harmonization guidelines because the ATN research agenda is focused on the prevention and treatment care continua. Regarding the HIV prevention cascade, the ATN seeks to develop and examine the feasibility and potential impact of the delivery of novel services, delivery of services in novel settings, and the use of novel engagement strategies for reaching high-risk youth and promoting the uptake of essential services such as HIV testing, sexually transmitted infections (STI) testing, risk screening, condom distribution, PrEP, and postexposure prophylaxis (PEP).

Figure 1. A summary of the domains included in the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) data harmonization guidelines. GAD: Generalized Anxiety Disorder; NHBS: National HIV Behavioral Surveillance System; PHQ: Patient Health Questionnaire.



For the HIV treatment and care cascade, the ATN seeks to determine the most effective strategy or set of strategies for linking positive youth to care, promoting retention in care (including antiretroviral uptake and adherence), and obtaining and sustaining viral suppression. These research goals motivated the selection of many of the measures included in the "HIV-Negative Cascade" and "HIV-Positive Cascade" domains, as well as in other standard domains. The HIV-Negative Cascade and HIV-Positive Cascade Working Groups used measures from existing surveys, like the National HIV Behavioral Surveillance (NHBS) survey [5], and some additional customized data items used in previous ATN studies to define a minimum set of harmonized measures that would capture information along the continua.

Additional Domains

For the 3 additional domains for harmonization (Mental Health, Social Support and Isolation, and Motivational PrEP Cascade), the process was streamlined. U19 representatives proposed sets of measures that were already harmonized within their U19. The Patient Health Questionnaire and the Generalized Anxiety Disorder Scale (GAD) were proposed to measure mental health [6-10], while the Patient-Reported Outcomes Measurement Information System (PROMIS) measures were proposed to measure social support and social isolation [11]. The Motivational PrEP Cascade measures were adapted for use with adolescents from measures developed by the Center for HIV Educational Studies & Training at Hunter College for use in HIV-negative men who have sex with men (MSM) [12]. The AC reviewed and approved the compiled measures before receiving the final approval from the ATN EC.

Results

Adolescent Medicine Trials Network for HIV/AIDS Interventions Data Harmonization Guidelines

The ATN data harmonization guidelines describe general guidelines in addition to domain-specific harmonizing measures or variables to be collected across ongoing and upcoming ATN studies (Multimedia Appendix 1). These guidelines provide specific formatting and skip pattern information for standardization across the ATN. Standardized data fields and datasets are critical to enabling comparisons across studies and analyses that combine data from multiple network studies.

The general data harmonization guidelines are as follows:

1. For the 5 standard domains, all characteristics (measures, variables) should be collected in all ATN studies, except when there is a strong operational or scientific rationale to exclude them. Measures for the 3 additional domains (Mental Health, Social Support and Isolation, and the Motivational PrEP Cascade) are recommended for studies planning to collect data in these domains.
2. Conventions for nonresponse will be handled on a per study basis. Thus, where relevant, the set of acceptable values (levels or responses) for a given variable may be augmented with additional values such as “Don’t know” or “Unsure.” Individual study teams are encouraged to develop data collection strategies that minimize nonresponse or missing data.
3. In general, the order of characteristics does not reflect any suggested ordering for data collection, unless indicated otherwise. For example, the current National Institute of Health (NIH) and Food and Drug Administration guideline recommends a 2-question format for requesting race and ethnicity information, with the ethnicity question preceding the question about race.
4. For a particular characteristic, the following is recommended regarding the ordering of the levels (possible responses). First, following Clinical Data Acquisition Standards Harmonization recommendations, a consistent order of responses should be used from question to question; exceptions to this would be cases where a validated instrument (eg, a standardized assessment questionnaire) is used. If there is a logical sequential order (ie, ordinal variables), as in the current educational level, order the levels accordingly. For nonordinal variables, order according to the anticipated likelihood of response level or alphabetically.
5. Possible response values can be separated further, if finer details are desired. However, more detailed possible response values should be designed in a way that they can be aggregated to match the values listed for each of the harmonized data items in Multimedia Appendix 1.
6. Skip patterns are highlighted in blue within the data harmonization tables provided in Multimedia Appendix 1.

Standard Domains

Demographic and Socioeconomic Characteristics

The initial data domain selected for ATN-wide harmonization included demographic characteristics, socioeconomic status characteristics, and characteristics of participant sexuality (Table 1 in Multimedia Appendix 1). These characteristics were identified to be of primary importance owing to their relevance to virtually all ATN studies and the desire of the ATN to be able to characterize the adolescent populations recruited by the ATN using consistently collected data elements. Race and ethnicity data were collected in accordance with the current Food and Drug Administration guidelines and NIH policy [13,14]; in accordance with that policy, ethnicity data were solicited first, and the race was collected in a check-all-that-apply format. The ZIP code for the location at which each participant primarily lives was collected to allow linkage to census track data. In addition, data on each participant’s current gender identity, sex assigned at birth, and sexual identity were collected. The possible responses to these questions were designed to be consistent with the National Coalition for Sexual Health guidelines for health care providers and customized for adolescent populations served by the ATN [15]. Owing to the significant footprint of the ATN in the Lesbian, Gay, Bisexual, Transgender, Queer adolescent community, we collected several data elements regarding the degree to which immediate family members and peers are aware of participants’ sexual identity. A supportive family environment has been shown to be highly influential regarding a Lesbian, Gay, Bisexual, Transgender, Queer adolescent’s mental and physical health and risk-taking behavior [16-18]. Furthermore, data elements related to whether a participant is currently in school or working, their level of education, and their health insurance coverage were collected to characterize the socioeconomic status.

Sexual Behavior and Risk

The Sexual Behavior and Risk domain aims to evaluate the occurrence of sexual behavior and sexual HIV transmission risk among the general ATN study populations. The content selection was informed by data from the YRBS, which identified low rates of condom use, a high number of sexual partners, and concurrent substance use during sex among the challenges to HIV prevention among youth [2]. To maximize comparability to existing national datasets on sexual behavior among youth, the working group included members who were familiar with the implementation of sexual behavior measures utilized in the YRBS. Wherever possible, ATN-harmonized questions were designed to be comparable to YRBS. It is recommended that the characteristics listed be collected in the order presented in Table 2 of Multimedia Appendix 1.

To reduce participant demand, the working group opted to collect count-data on the number of sexual partners (lifetime and past 3 months) but not on the number of sexual events. Because questions on the biomedical prevention uptake were developed as part of the HIV-Negative Cascade, this domain focused on the assessment of condom use during sex. Again, to minimize the participants’ burden, the decision was made to prioritize identifying the mere occurrence of recent (past 3

month) condomless sex rather than quantifying the amount of risk (eg, the number of condomless sex events). To do this, a series of "yes" or "no" questions asking about condomless sex with partners whose HIV status was known (either HIV-negative or HIV-positive) or unknown were included in the harmonized measures. In lieu of collecting data on the number of condomless sex acts, a visual analog scale was utilized to query the percentage of time participants utilized condoms while having sex in the past 3 months. Finally, the working group incorporated a single item inquiring about the lifetime occurrence of either alcohol or drug use during vaginal or anal sex.

The working group acknowledges that the harmonized sexual behavior and risk measures are limited in their nature. Studies within the ATN vary in their emphasis on sex; thus, nuanced data on sexual behavior would represent an unnecessary burden on participants in some studies. In contrast, studies aimed at achieving reductions in the sexual HIV transmission risk may need substantially more detail in their data collection. For these studies, the working group recommended the AIDS Behavior Risk Assessment, the YRBS, or the NHBS questionnaire as additional resources [2,5,19-21].

Substance Use and Abuse

Many adolescents experiment with the use of alcohol or other illicit substances [22,23]. The use of such substances has been shown to be associated with an increase in risky sexual behavior and, therefore, a greater risk for HIV transmission [24-26]. The ATN adapted several standardized instruments to assess alcohol and nonprescription drug use for use in studies of adolescents (Table 3 in Multimedia Appendix 1). The ATN data collection instrument was primarily derived from the ASSIST [4,27,28], which has been used in previous ATN studies (eg, ATN 071). As its name suggests, the ASSIST is a screening tool for substance use to be used in a clinical setting. For the ATN, it was adapted for computer-assisted self-interview as a means of quantifying the degree of substance use for adolescent participants and to collect basic information on the impact of substance abuse on their daily lives. In ATN studies where site staff will administer the ASSIST, the Substance Use and Abuse Working Group recommended using the traditional, interviewer-administered ASSIST format, which is designed for that type of implementation [23].

Substance use was assessed for the following classes of substances: tobacco, alcohol, cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, and opioids. For most substances, ≥5 examples were given using terminology appropriate for the adolescent populations studied by the ATN (eg, Vicodin instead of acetaminophen-hydrocodone). Explanatory prompts were added owing to the self-interview format required for most ATN studies. The data collection on opioid use was augmented by the addition of 2 questions regarding the specific use of heroin during the current epidemic in the United States [29]. The data collection on alcohol use was augmented by the addition of 2 questions derived from the Alcohol Use Disorders Identification Test (AUDIT-C) to assess binge drinking owing to its prevalence in adolescent populations [29,30]. The definition of binge drinking used for the data collection was taken from the National Institute of Alcohol Abuse and Alcoholism [31].

For each class of substance, the harmonized measures assess the lifetime use (item 1) and aspects of usage over the past 3 months (items 2-5). Per the recommendation of the Substance Use and Abuse Working Group, ATN studies can also collect data on the aspects of usage using a frame of reference of the past 12 months to better align with the NHBS study, if desired. Substance use data are collected by the ATN for 2 purposes as follows: (1) to quantify the prevalence of substance in the populations studied; and (2) to facilitate risk adjustment in analyses that are more central to ATN research aims. The ASSIST provides an appealing solution for the second purpose. Each question on the ASSIST has a set of responses to choose from, and each response from questions 2-7 has a numerical score. The scores from questions 2-7 are added across each substance (eg, tobacco, alcohol, or cannabis) to produce an ASSIST risk score for each substance. In technical reports and papers, this score was referred to as the specific substance involvement score for each drug class. More details on scoring can be found in the ASSIST manual [4]. The translation of individual survey responses to a summary risk score is appealing for the ATN as this provides a standardized framework for performing risk adjustment for relevant analyses in ATN studies. In contrast, survey items from large national surveys, such as Monitoring the Future [22,23,32], assess substance use for the primary purpose of characterizing the prevalence of use in US adolescents and, therefore, may be less useful for research aims that are of primary importance to the ATN.

HIV-Negative Cascade

The HIV-Negative Cascade focuses on the prevention of HIV among adolescents and includes measures related to HIV testing, STI testing, PEP and PrEP awareness, utilization, adherence, and barriers to PrEP utilization and adherence (Table 4 in Multimedia Appendix 1). General HIV testing and STI questions for the HIV-Negative Cascade were taken from the NHBS questionnaire. The Centers for Disease Control and Prevention (CDC), in collaboration with 25 state and local health departments, began the NHBS in 2003. The NHBS was designed to conduct behavioral surveillance among persons at high risk for HIV infection and surveyed the 3 populations at highest risk for HIV in the United States—MSM, intravenous drug use, and high-risk heterosexuals [20,33]. PEP and PrEP awareness and utilization questions were taken from the University of California at San Francisco HIV risk assessment tool, NHBS [5], and assessments used in the ATN's Scale It Up [12] and CARES studies.

For studies planning to collect more detailed information related to PrEP, the AC recommended harmonized measures from the Motivational PrEP Cascade as additional measures (Table 9 in Multimedia Appendix 1). The NHBS instrument might also be considered for studies that will collect measures related to the HIV-Negative Cascade at a more detailed level than the required harmonized measures [5]. This questionnaire makes extensive use of skip patterns to ask questions specific to gender identity and sexual orientation. The NHBS data provide behavioral

context trends in HIV surveillance data and describe populations in the United States at increased risk for HIV infection.

HIV-Positive Cascade

This domain was developed with the goal of identifying key characteristics among HIV-infected participants that correspond to steps along the HIV Continuum of Care, using common definitions developed by the Health Resources and Services Administration HIV/AIDS Bureau and the CDC. The steps in the continuum are typically defined using biomedical data collected during clinical care for HIV-infected patients, including the CD4 count and HIV viral load before and after initiation of antiretroviral therapy (ART). Linkage to care, for example, is defined as having ≥1 documented CD4 or viral load measures within 30 days (1 month) of diagnosis, while retention is defined as having ≥2 viral load or CD4 tests in the last year, performed, at least, 3 months apart.

The participant questions in this domain primarily address medical appointments with HIV providers, missed visits, CD4 and viral load testing, and adherence to ART, using questions derived from several sources, including the NHBS and prior ATN studies (Tables 5 and 6 in Multimedia Appendix 1). In addition, the HIV-Positive Cascade Working Group developed 4 additional questions for data harmonization that capture participants' characteristics corresponding to reengagement and retention in care based on missed appointments over time.

Furthermore, the NHBS survey instrument might be considered for studies that will collect measures related to the HIV-Positive Cascade at a more detailed level than the required harmonized measures [5]. For studies collecting CD4 count from biomedical data, it is recommended that investigators collect the CD4 collection date, $CD4^+$ T-cell absolute count (cells/mm^3), CD4-T-cell percent (%), and data source (similar to Viral Load Data Source; Table 6 in Multimedia Appendix 1).

Additional Domains

Mental Health

In the United States, anxiety and depression are among the most common mental health disorders for adolescents and young adults [34]. For HIV-positive youth, anxiety and depression have been associated with poorer medication adherence and decreased viral suppression [35-40]. Furthermore, direct and indirect relationships between depression and anxiety and increased sexual risk behaviors among youth have been identified in several studies [41], though other studies have found null or conflicting findings.

The Mental Health domain collects data on anxiety and depression using a 2-step approach. All study participants complete the 2-item Patient Hospital Questionnaire (PHQ-2) and the 2-item Generalized Anxiety Disorder Scale (GAD-2), which are used to screen for depression and anxiety, respectively. The PHQ-2 consists of the first 2 items of the 8-item version of the questionnaire, the PHQ-8, and assesses the 2 core criteria for depressive disorders. The PHQ-2 has good operating characteristics (eg, sensitivity and specificity) for detecting depressive disorders [6,7]. The GAD-2 includes the first 2 items of the 7-item version of the scale, the GAD-7, and assesses the 2 core criteria for generalized anxiety disorder. In addition, the GAD-2 items have been found to be appropriate screening items for panic, social anxiety, and posttraumatic stress disorders. The GAD-2 has good operating characteristics for screening for all 4 types of anxiety disorders [7,8]. For study participants who screen positive on the PHQ-2 or GAD-2, the remaining items of the PHQ-8 or GAD-7 are administered to determine the symptom severity (described in Table 7 of Multimedia Appendix 1). Furthermore, the longer PHQ-8 and GAD-7 with broader scoring ranges may be useful for examining changes in depression and anxiety over time. Both the PHQ-8 and the GAD-7 have been shown to be reliable and valid measures [7-10].

Social Support and Isolation

The Social Support and Isolation domain uses the PROMIS short-form versions of the Social Relationships scales to measure perceived social isolation and social support [42]. PROMIS, an NIH initiative, uses rigorous processes to develop and test item banks that measure physical, mental, and social health components [11]. The 5 Social Relationships short-form scales, each with 4 items, measure domains of social isolation and social support, including companionship, emotional support, informational support, and instrumental support [42]. The Social Support and Isolation measures are included in Table 8 of Multimedia Appendix 1.

Motivational Pre-exposure Prophylaxis Cascade

The Motivational PrEP Cascade domain and measurements utilize the Transtheoretical Model of Change framework to assess the psychological stages HIV-negative individuals determine their willingness, intentions, uptake, and adherence to PrEP [43]. The development of the Motivational PrEP Cascade was based on the formative work suggesting that, among individuals *willing* to take PrEP (ie, those for whom PrEP acceptability is high), there was wide variability in behavioral *intentions* to do so [44]. The Motivational PrEP Cascade complements the HIV-Negative and HIV-Positive Cascades with the overall goal of identifying facilitators and barriers to the PrEP uptake needed for addressing implementation issues. The measurements have been tested on a national sample of HIV-negative gay and bisexual men in the United States with results identifying fewer than 1 in 10 as currently using and adhering to PrEP [12]. Based on this initial work, questions were adapted for youth and a reduced 15-item version of the scale containing only questions considered essential to estimating progress along the PrEP Cascade was selected for inclusion in the harmonized ATN measures (Table 9 in Multimedia Appendix 1).

There are 5 stages to the Motivational PrEP Cascade that reflect decision-making processes across time. The cascade is most appropriate for samples of objectively identified PrEP candidates based on the risk for HIV infection using the established CDC criteria [45]. The inclusion of individuals into the cascade who are not at risk for HIV infection may confound accurate prevention numbers. Stage 1 is PrEP precontemplation and includes individuals who are objectively identified as PrEP candidates, but do not view themselves as good candidates for PrEP or are unwilling to pursue PrEP. Those who do not meet

the criteria for stage 2 are considered PrEP precontemplation. Stage 2: PrEP contemplation includes those who identify themselves as PrEP candidates (Table 9: PrEP_Q1) and willing to pursue PrEP. Willingness was defined as those indicating they would probably or definitely take PrEP if they could get it for free and without their parent's knowing (Table 9: PrEP_Q6 and PrEP_Q7). Stage 3: Preparation includes those who intend to start PrEP but have not yet started (Table 9: PrEP_Q8) and who know of a medical provider that would prescribe PrEP (Table 9: PrEP_Q10). Those indicating they would definitely or probably start taking PrEP were coded as intending to begin PrEP. Those who had talked to a medical provider about starting PrEP and both thought they should start PrEP (Table 9: PrEP_Q11) and those who are currently on PrEP (Table 9: PrEP_Q2) are in Stage 4: PrEP Action. Stage 5: PrEP Maintenance includes those who are currently prescribed PrEP (Table 9: PrEP_Q2), adherent to their regimen (Table 9: PrEP_Q14), and receiving quarterly HIV or STI testing (Table 9: PrEP_Q15).

Discussion

The ATN developed guidelines for harmonizing standard measures for Demographics and Socioeconomic Characteristics, Sexual Behavior and Risk, Substance Use and Abuse, HIV-Negative Cascade, and HIV-Positive Cascade domains. In addition, guidelines for additional measures commonly collected among ATN studies were developed for Mental Health, Social Support and Isolation, and PrEP Cascade domains. The research goals of the ATN motivated many of the measures included in these standard domains, especially the measures for the HIV-Negative Cascade and HIV-Positive Cascade domains. AC and working group members referred to existing surveys and data collection tools, like YRBS, ASSIST, NHBS and PROMIS, to develop the ATN harmonization guidelines. As the ATN works to increase awareness of the HIV status and access to health care for adolescents diagnosed with HIV in the United States, the collection of selected key measures uniformly across studies facilitates the characterization of participant populations, comparisons between studies, and pooled analysis of data from multiple studies.

Moving forward, the ATN should periodically evaluate the utility of each of the harmonized measures currently being collected across ATN studies and update these data harmonization guidelines as needed. Some of the measures currently included are relatively new and do not necessarily have a robust evidence base supporting their validity and reliability, especially in adolescents and young adults in the United States. Therefore, it will be important for the ATN to reassess these harmonized measures in the future. In addition, gaps may be identified that warrant the inclusion of further measures. For example, the current harmonized measures do not consider stigma or cost-effectiveness. Related to cost-effectiveness, the ATN Modeling Core recently formed a working group to explore the feasibility of standardizing cost-related measures collected in ATN studies or developing guidelines for harmonizing cost-effectiveness analyses across the network. Like the continuously evolving HIV epidemic, the ATN-harmonized measures should evolve as well to ensure the collection of data most relevant to defeating the HIV epidemic among adolescents and young adults.

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Conflicts of Interest

ACS received a grant from Gilead Sciences.

Multimedia Appendix 1

The measures (variables) defined as part of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Data Harmonization Guidelines.

[PDF File (Adobe PDF File), 245KB - resprot_v7i12e11207_app1.pdf]

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Abbreviations

AC: Analytic Committee
ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
CDC: Centers for Disease Control and Prevention
EC: Executive Committee
GAD-2: Two-item Generalized Anxiety Disorder Scale
GAD-7: Seven-item Generalized Anxiety Disorder Scale
NHBS: National HIV Behavioral Surveillance System
NIH: National Institute of Health
PEP: postexposure prophylaxis
PHQ-2: Two-item Patient Hospital Questionnaire
PHQ-8: Eight-item Patient Hospital Questionnaire
PrEP: Pre-exposure prophylaxis
PROMIS: Patient-Reported Outcomes Measurement Information System
STI: sexually transmitted infections
YRBS: Youth Risk Behavior Surveillance

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