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Protocol

Development and Testing of a Personalized Web-Based Diet and Physical Activity Intervention Based on Motivational Interviewing and the Self-Determination Theory: Protocol for the MyLifestyleCoach Randomized Controlled Trial

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Abstract

Background: Unhealthy dietary patterns and insufficient physical activity (PA) are associated with negative health outcomes, such as cardiovascular diseases, type 2 diabetes, cancer, overweight, and obesity. This makes the promotion of healthy dietary and PA behaviors a public health priority.

Objective: This paper describes the development, design, and evaluation protocol of a Web-based computer-tailored (CT) dietary and PA promotion intervention, *MyLifestyleCoach*. A Web-based format was chosen for its accessibility and large-scale reach and low-cost potential. To achieve effective and persistent behavioral change, this innovative intervention is tailored to individual characteristics and is based on the self-determination theory and motivational interviewing (MI).

Methods: The 6 steps of the intervention mapping protocol were used to systematically develop *MyLifestyleCoach* based on the existing effective CT PA promotion intervention *I Move*. The *MyLifestyleCoach* intervention consists of 2 modules: *I Move*, which is aimed at promoting PA, and *I Eat*, which is aimed at promoting healthy eating. Development of the *I Eat* module was informed by the previously developed *I Move*. Both modules were integrated to form the comprehensive *MyLifestyleCoach* program. Furthermore, *I Move* was slightly adapted, for example, the new Dutch PA guidelines were implemented. A randomized controlled trial consisting of an intervention condition and waiting list control group will be used to evaluate the effectiveness of the intervention on diet and PA.

Results: Self-reported measures take place at baseline, 6 months, and 12 months after baseline. Enrollment started in October 2018 and will be completed in June 2020. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2020.

Conclusions: *MyLifestyleCoach* is one of the first interventions to translate and apply self-determination theory and techniques from MI in Web-based computer tailoring for an intervention targeting PA and dietary behavior. Intervention mapping served as a blueprint for the development of this intervention. We will evaluate whether this approach is also successful in promoting eating healthier and increasing PA using an randomized controlled trial by comparing the intervention to a waiting list control condition. The results will provide an insight into the short- and long-term efficacy and will result in recommendations for the implementation and promotion of healthy eating and PA among adults in the Netherlands.

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KEYWORDS

diet; physical activity; eHealth; computer-tailoring; intervention mapping; self-determination theory; motivational interviewing

Introduction

Background

Unhealthy lifestyle behaviors such as insufficient physical activity (PA) and unhealthy nutrition increase the risk of developing a variety of diseases, such as cardiovascular disease, type 2 diabetes, osteoporosis, cancer, and depression [1-3]. The Dutch PA guidelines state that adults should accumulate at least 2.5 hours of moderate-intensity PA every week and carry out muscle- and bone-strengthening activities at least twice a week. Daily sedentary behavior should be limited [4]. The Dutch guidelines on diet state that adults should consume at least 200 g of fruit and 250 g of vegetables daily, eat fish at least once a week, and limit intakes of energy and saturated fat by, for example, consuming fewer snacks [5,6]. Unfortunately, many adults in the world, including Dutch adults, do not follow these recommendations (eg, 50% of the Dutch adults do not meet the PA guidelines and Dutch adults consume only about 120 g of vegetables per day), and the proportion who fail to do so is higher in groups with low socioeconomic status (SES) [7-9]. As a consequence, promotion of PA and healthy dietary intake is of great importance to public health.

Effective interventions with a large reach (ie, reaching the entire population at risk because of an unhealthy lifestyle) are needed to achieve improvements in lifestyle at population level. If an intervention is to be effective and produce long-term, sustainable behavioral changes, it is important that people are able to choose their own goals and modules, that is, have a degree of autonomy within the context of the intervention, as this improves engagement and motivation for behavioral change [10,11]. A PA intervention that meets these requirements has already been developed and evaluated, and it is called *I Move*. *I Move* was successful in increasing PA levels in Dutch adults [12-14]. It is a computer-tailored (CT) intervention that can provide a large number of people with individualized feedback, taking their choices into account, at a relatively low cost. *I Move* is based on the self-determination theory (SDT) and uses the communication techniques of motivational interviewing (MI) to guide participants toward behavioral change [12]. The general idea is that by supporting the basic psychological needs for autonomy, competence, and relatedness, individuals are stimulated to develop more autonomous forms of motivation toward adoption and maintenance of targeted behavior [15]. More detailed information regarding the theoretical framework of SDT and the practical application of MI is provided in the Results section (see Step 3: Program Design). The success of this program has led to calls for the approach to be extended to other behaviors such as healthy eating, in the form a comprehensive healthy lifestyle program.

Study Aims

We developed *MyLifestyleCoach*, a combined Web-based intervention intended to improve diet and increase PA using the intervention mapping (IM) protocol. *MyLifestyleCoach* consists of 2 modules: (1) *I Eat* (*Ik Eet*), which is intended to (increase users' motivation to) eat healthily and (2) the pre-existing *I Move* (*Ik Beweeg*), which is intended to (increase motivation to) become more physically active. The intervention combines computer tailoring with the theoretical insights of SDT and practical applications of MI. The intervention is specifically aimed at people with a low SES. People with a low SES have the highest levels of risk behaviors and are least responsive to existing lifestyle interventions [16-18]. The purpose of this paper is to describe the development process, design, and evaluation protocol of the general program *MyLifestyleCoach* and the systematic development of the *I Eat* module (as the *I Move* program has already been developed and tested) according to the principles of SDT and MI. This insight is useful for the development of future dietary and PA interventions.

Methods

MyLifestyleCoach is a Web-based, CT intervention that consists of 2 modules, *I Eat* and *I Move*, that are aimed at improving the diet and PA levels of Dutch adults, respectively. We used an adaption of the original version of I Move (see Step 4). Detailed information about the development of *I Move* can be found elsewhere [12]. *I Eat* was developed specifically for *MyLifestyleCoach* using SDT and MI, as in the development of *I Move*. The *MyLifestyleCoach* intervention was developed through the systematic adaptation and extension of *I Move*, using IM to increase the chance of producing an effective intervention [19,20]. The IM protocol consists of 6 steps, each comprising several tasks that can be used as a guide for theory and evidence-based decision-making during the design, implementation, and evaluation of a new intervention [19]. Table 1 provides a description of the steps and tasks that have to be undertaken in each step.

Table 1. Overview of the intervention mapping steps and the corresponding tasks.

Intervention mapping step	Task
Step 1	Needs assessment
Step 2	Program goals
Step 3	Program design (theory and practical applications)
Step 4	Program production
Step 5	Implementation plan
Step 6	Evaluation plan

In the Results section, we elaborate on these 6 steps of the IM protocol and how *I Eat* has been developed. Then, we describe the integration of these 2 modules (*I Eat* and *I Move*) in *MyLifestyleCoach*.

Results

Step 1: Health Problem and Needs Assessment

The *first step* of the IM protocol involves carrying out an assessment of the health problem and related behaviors. Unhealthy dietary habits, such as a low intake of fruit and vegetables and a high fat intake, carry serious health risks, for example, an increased risk of many adverse health conditions such as various types of cancer, cardiovascular diseases, and type 2 diabetes [1]. According to the World Health Organization, an adult should eat at least 400 g of fruits and vegetables a day. Less than 10% (5% for additional health benefits) of the total energy intake should come from free sugars and less than 30% from fats, preferably unsaturated fats; industrial trans fats (often found in snacks) should be avoided. Finally, one should consume less than 5 g of salt per day [21]. The Dutch recommendations for a healthy diet differ slightly and are unique in a way that they are formulated in terms of the foods rather than nutrients or food and nutrients. For example, a consumption of at least 250 g vegetables and 2 portions of fruit per day is recommended along with weekly consumption of oily fish [5,6].

Using guidelines or recommendations to prompt behavioral change is more likely to induce extrinsic types of motivation than other methods, but to achieve long-term behavioral change, it is important to satisfy the basic psychological needs in an individual to induce more autonomous forms of motivation. To this end, we conducted a pilot study to tailor *MyLifestyleCoach* to the needs of the target population and to identify behavioral targets. We asked Dutch adults (N=78) to define healthy eating using their own words and to describe what they considered a healthy diet. Most participants described healthy eating in terms of content (eg, consumption of fruit and vegetables) and approach to eating (eg, consumption of a variety of foods). Preliminary results showed that the food items mentioned most frequently in connection with healthy eating were fruit and vegetables; (limiting) sugar and fat intake were also mentioned quite frequently. We had decided that our intervention would refer to foods rather than nutrients, and so we decided to target daily consumption of energy-dense snacks. Energy-dense snacks are generally high in sugar and/or fat and could, therefore, serve as a proxy for these 2 nutrients [22]. Fish consumption was also chosen as a target outcome, as this was mentioned quite frequently in the pilot study as a way to eat (more) healthily and it was a measurable dietary outcome; in addition, according to the Dutch dietary guidelines, one should consume fish once a week.

On the basis of these results, our aim was to design *I Eat* to produce a sustained increase in the consumption of vegetables, fruit, and fish and a sustained reduction in consumption of unhealthy snacks (and to maintain these new levels) in *I Eat*. Intake of these food products would be assessed with validated questionnaires. In line with SDT, participants would decide which behaviors they wanted to change and set their own goals; thus, the intervention would meet the basic need for autonomy.

Step 2: Program Outcomes and Objectives; Logic Model of Change

In the *second step* of IM, we defined 2 overall program goals. The first outcome was to improve the diet of adults not following a healthy diet, defined here as consumption of 250 g of vegetables and 2 portions of fruit per day, complete avoidance of unhealthy snacks, and consumption of fish once a week. The program was not designed to encourage users to achieve this outcome; instead, in line with the SDT and MI principles (see Step 3: Program design), participants would choose which dietary behaviors they want to improve. They might decide to consume more vegetables or target all 4 of the food groups mentioned in our definition of a healthy diet. The second outcome was to maintain or further improve the diet of adults who followed a healthy diet (depending on the participant's preference—eg, a participant might decide to try to consume even more fruit). Next, we broke these goals down into smaller steps (performance objectives): to decide to eat more healthily, to improve one's diet, and to maintain a healthy diet. Thereafter, we identified change objectives, that is, the skills individuals would need to learn to reach the performance objectives. These change objectives were formulated taking into account the basic psychological needs (autonomy, competence, and relatedness) specified in SDT and the important concepts of MI [10,23]. Examples of the change objectives in the *I Eat* module are "adults can explain why eating more healthily is important for them," "adults are able to create an eating behavior action plan that takes into account their personal preferences," "adults are confident that they know how to eat more healthily," and "adults have strategies for coping with barriers to healthy eating." See Table 2 for a selection of the change objectives.

Table 2. Selection of change objectives for eating more healthily.

Performance objectives	Determinants		
	Autonomy	Competence	Relatedness
Decide to eat more healthily			
Monitoring personal diet	Getting an insight into their current personal diet in an autonomous way, with little external control	Feeling confident to monitor personal diet	Feeling comfortable to think over and discuss their current diet in communication with the program
Getting an insight into personal importance	Getting an insight into their personal importance by themselves, with little external control	None[a]	Being at ease to think over and discuss the importance of increasing their diet in the program
Adults improve their diet			
Remaining aware of the importance of eating more healthily	Remaining confident to increase their diet in an autonomous way (not imposed)	Feeling confident to eat more healthily	Feeling comfortable to think over and discuss personal confidence issues in the program
Defining clear, achievable goals with regard to improving their diet	Defining clear, achievable goals with regard to improving their diet in an autonomous way, without being coerced to do so	None[a]	Accepting help defining clear, achievable goals with regard to eating more healthily in the program
Adults maintain their healthy diet			
Developing a (coping) plan about how they can best achieve their goals and how they can deal with difficult situations	Developing a plan about how they can best maintain their diet in an autonomous way, without being coerced to do so	Feeling confident to develop a plan about how they can best maintain their diet	Accepting help developing a plan about how they can best achieve their goals in the program
Evaluating whether goals have been achieved	Evaluating whether goals have been achieved in an autonomous way, without being coerced to do so	Feeling confident to evaluate goals in an honest way	Feeling at ease to think over and discuss personally their current diet in the program

[a]No change objectives are specified for this particular determinant.

The next step in this phase was to analyze the determinants of the selected target behaviors based on SDT and MI. Although many studies have analyzed the determinants of dietary behavior (eg, see Cox et al [24]), we conducted a second pilot study to obtain a better understanding of the current beliefs of Dutch adults regarding the importance of eating more healthily and confidence in eating more healthily (2 important constructs of SDT and MI) in their own words. Overall, 66 participants were asked to respond to a Web-based questionnaire that asked them to describe, in their own words, why healthy eating is important for them and reasons why they are confident in eating more healthily, factors that are critical to behavioral change according to the principles of MI. People may have their reasons for wanting to eat more healthily yet not succeed in changing their behavior, and therefore, we also asked respondents why it was *not* important for them to eat more healthily. In addition, we asked them to describe factors that might undermine their ability to eat more healthily or make it easier to do so. The results can be found in Multimedia Appendix 1.

This information about the beliefs and perceptions of the target users and the language they used was helpful in tailoring the *MyLifestyleCoach* and its communication style, so that it met users' needs for relatedness and autonomy. Providing suggestions about how to overcome barriers to healthy eating might increase users' confidence in their ability to eat healthily (self-efficacy), which is an important predictor of intention to eat healthily [25]. The support suggestions given by the pilot study participants were incorporated into the *I Eat* tailoring messages.

Step 3: Program Design

The *third step* of IM involves selecting theoretical ideas relevant to modification of target behaviors and practical ways of achieving such modification. A method is a theory-based general process that influences behavioral determinants [19]. One important determinant of sustained behavioral change, including changes in eating patterns, is autonomous motivation [26].

SDT is a macro theory of human motivation [10,23]. It focuses on the extent to which behavior is autonomous rather than controlled. Different types of motivation are placed on a continuum, ranging from amotivation to intrinsic motivation. Amotivation is the relative absence of motivation. External regulation involves performing a behavior to conform to other people's demands ("my partner wants me to eat more healthily"). Introjected regulation is used to describe behavior performed by an individual in response to an internal pressure to avoid feeling an emotion such as shame and guilt ("if I don't eat healthily, I feel bad") or to obtain self-worth. Identified regulation involves engaging in a behavior because one understands and accepts its importance (eg, the studies by Deci and Ryan [27]; "eating more healthily is important for my health"). Intrinsic motivation involves engaging in an activity for the pleasure and satisfaction inherent in it ("I enjoy eating healthily"). The central distinction here is between autonomous motivation (identified regulation and intrinsic motivation) and controlled motivation (external regulation and introjected regulation). Autonomous motivation is associated with greater commitment and longer-term maintenance of behavioral changes

than the other forms of motivation, and this may apply to changing to a healthier eating pattern [10,11,23,26,28]. Promoting internal motivation to eat healthily is expected to differ from promoting internal motivation to exercise. Physical activities may be performed because they are intrinsically enjoyable or because one enjoys the challenge, but people have an innate preference for palatable (unhealthy) food [29]. Therefore, it is helpful to focus on identified regulation (autonomous motivation) for eating healthily. Once people achieve this type of motivation, they may be more likely to find activities and experiences related to eating healthily, such as preparing healthy food for the family or enjoying tasteful healthy foods, to be more intrinsically motivated.

SDT postulates that providing conditions that support the basic psychological needs facilitate the development of more autonomous forms of motivation [10,11,23,30]. The basic psychological needs are need for autonomy (to engage in behavior as a matter of choice), competence (to feel competent and confident), and relatedness (to feel connected to others and understood by them) [10,11,23,31-34].

The widely adopted MI counseling style has been found to be useful in providing individuals with the change strategies they need to modify to the extent to which the basic psychological needs of the SDT are satisfied [15]. MI is defined as "a collaborative conversation style for strengthening a person's own motivation and commitment to change" [35]. The spirit of MI is captured in 4 terms: partnership, acceptance, compassion, and evocation. The practice of MI consists of 4 recursive processes: engaging, focusing, evoking, and planning [35]. Engaging is "the process by which both parties establish a helpful connection and a working relationship," and focusing is "the process by which you develop and maintain a specific direction in the conversation about change." Evoking involves eliciting the client's own motivations to change. Planning encompasses both the development of a commitment to change and the formulation of a specific plan of action. The 4 major counseling skills required for MI are asking open-ended questions, affirmation, reflective listening, and summary reflections [35]. This widely adopted counseling style has strong parallels with SDT because of its client-centered approach. It is assumed that MI generates change strategies that will fulfill the client's basic psychological needs for competence (eg, through the use of strategies to boost confidence), autonomy (eg, because it allows clients to discover their own reasons for wanting to change), and relatedness (eg, because the interviewer is compassionate) [15,35-37].

Evidence suggests that MI is a promising way of encouraging individuals to increase their PA, although reported effect sizes (ESs) vary [30,38]. However, there is still little evidence on how effective the SDT and MI approach is in promoting healthy eating alongside an increase in PA [38], but some empirical studies have demonstrated that utilizing MI as part of a dietary modification intervention is effective: People who received MI via phone or face to face reported, for example, an increase in fruit and vegetable intake [39,40]. Furthermore, it has been demonstrated that a tailored, text-based fruit and vegetable intervention based on constructs from SDT and MI can be successful [41]. So far, it is not known whether this SDT and MI approach is also successful in promoting a healthier diet when implemented in a Web-based environment, using computer tailoring. There are differences between a Web-based environment and a face-to-face MI. In a Web-based setting, nonverbal communication is less feasible than it is in a face-to-face counseling setting. A face-to-face setting allows the interviewer to use and register social cues such as smiling or responding to very subtle expressions of motivation, which may lead to a better understanding of the client and hence more effective encouragement of behavioral change. However, Web-based, CT MI has a potentially large reach and could be a means of providing people with individualized feedback at a relatively low cost. In comparison with text-based, CT MI, Web-based, CT MI may better simulate an interactive, collaborative conversation. Other benefits of a Web-based environment over a text-based format are the instantaneous feedback and the ability to use different types of media, such as videos [42].

Thus, the SDT and MI approach also seems a promising way of improving diet. We will decide to use the skills, processes, and spirit of MI to support users' basic psychological needs (autonomy, competence, and relatedness) and to explore and resolve ambivalence, thus increasing the chances that they will achieve behavioral change. The same skills and processes that were used in *I Move* (see [12]) were applied to the promotion of healthier eating in *I Eat*.

The 4 key concepts or *spirit* of MI (partnership, acceptance, compassion, and evocation) were implemented in the following ways. In general, participants are asked to give their opinion or reflect on statements they made earlier. They receive specific tailored feedback, and the language of the program and feedback messages is empathetic and accepting. Multimedia Appendix 2 describes in detail how we applied the MI spirit in our Web-based CT intervention.

MI comprises 4 processes. The first process is engaging and is used to establish a working relationship. We integrated a video coach into the intervention to facilitate the development of a social relationship between a user and the program. We also included several videos telling the stories of *former participants* to provide users with an opportunity to feel connected to others. The second process is focusing, which involves seeking and maintaining the direction of the conversation and consultation. Participants are informed before they enter the intervention, through advertisements and website information, that the intervention is designed to promote healthy eating and PA. The third process is evoking, in which the participant's own motivation for change is elicited. This process is important to elicit change talk. Several methods are used: importance and confidence ruler, value clarification, looking forward toward the consequences of eating (more) healthily if one decides to do so and maintains this new behavior, and looking back to a difficult situation and identifying how the person has managed to deal with this situation and how he or she felt afterward. Regarding the rules, follow-up questions mainly focused on eliciting change talk (eg, why did you not choose a lower number). The last process is planning. This is the bridge to change and involves giving participants the opportunity to create a specific action plan that they can try out and evaluate. These

4 processes are sequential, as each process builds on the one before; however, the counselor may go back to earlier previous processes at any point during the helping relationship (ie, the process can also be recursive). Multimedia Appendix 3 provides detailed information about these MI processes and how they were implemented in our Web-based CT intervention.

Several core communication skills are applied in the intervention: open-ended questions, reflective listening, affirming, summarizing, and informing and advising. Open-ended questions are frequently used to encourage participants to come up with their own ideas. This is essential to encourage change talk, which consecutively strengthens self-determined motivation [35]. Reflective listening is implemented using a structured approach. First, the participant is asked an open-ended question, following which he or she is asked to respond to a multiple-choice question that best reflects his or her answer. We developed unique feedback messages for each combination of multiple-choice answers. Affirming was incorporated, for example, by focusing on positive behaviors and rewarding the participant for trying and by using an empathetic style in the feedback messages. Furthermore, the participants often get summaries of their previous responses. They also receive a PDF attachment after each session; this summarizes the main content of the session. Participants are given information without being judged, and sometimes, they are asked if they want more information about a certain topic, for example, dietary recommendations. Participants are also given the opportunity to receive information through several short, expert videos. Multimedia Appendix 4 describes how these core MI skills were implemented in the Web-based environment.

Step 4: Program Production

In *step 4* of IM, the program is produced and pretested. In the sections below, we describe the specific content of the intervention, the adaptation of the program components, and the pretest.

Scope and Sequence

MyLifestyleCoach consists of an introductory session (opening session) and the modules *I Eat* and *I Move*. The program is designed in such a way that participants can choose which behavioral change module (or no module) they want to follow and if they are interested in following both modules, which module they want to visit first and when they want to use the other module. See Figure 1 for the structure of the program. Both *I Eat* and *I Move* consist of 4 sessions. Figure 2 presents the content of all the sessions (this figure has been adapted, with permission from Friederichs et al [12]).

Figure 1. Overview of the *MyLifestyleCoach* intervention. FFQ: Food Frequency Questionnaire; SQUASH: Short QUestionnaire to ASsess Health.

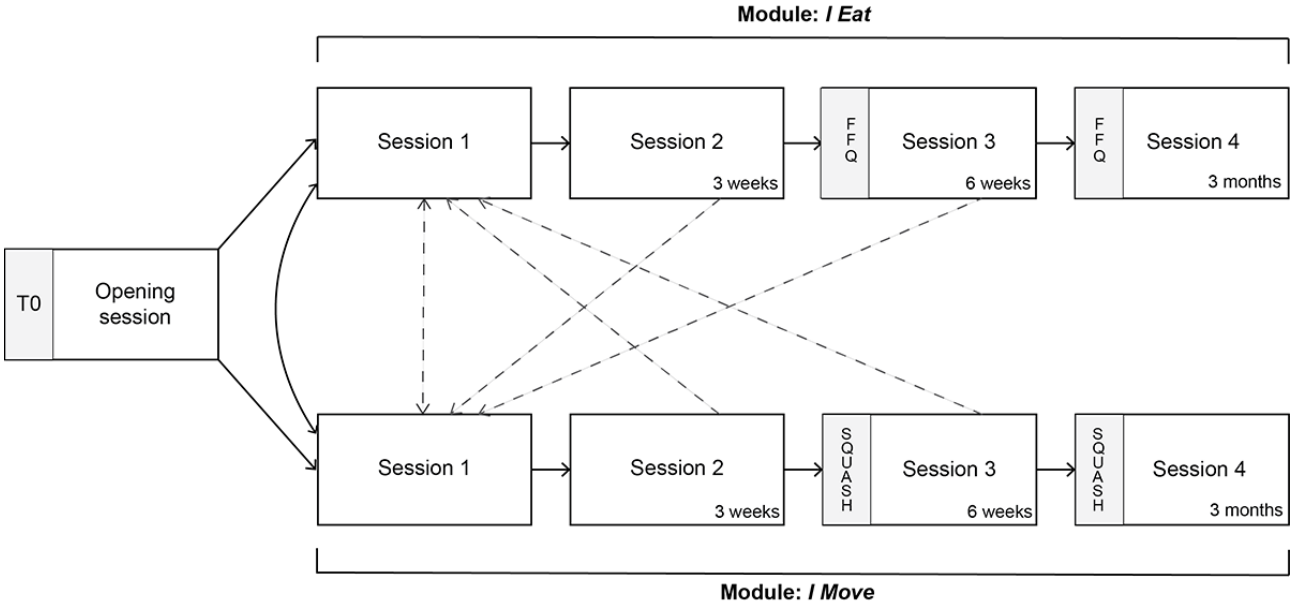
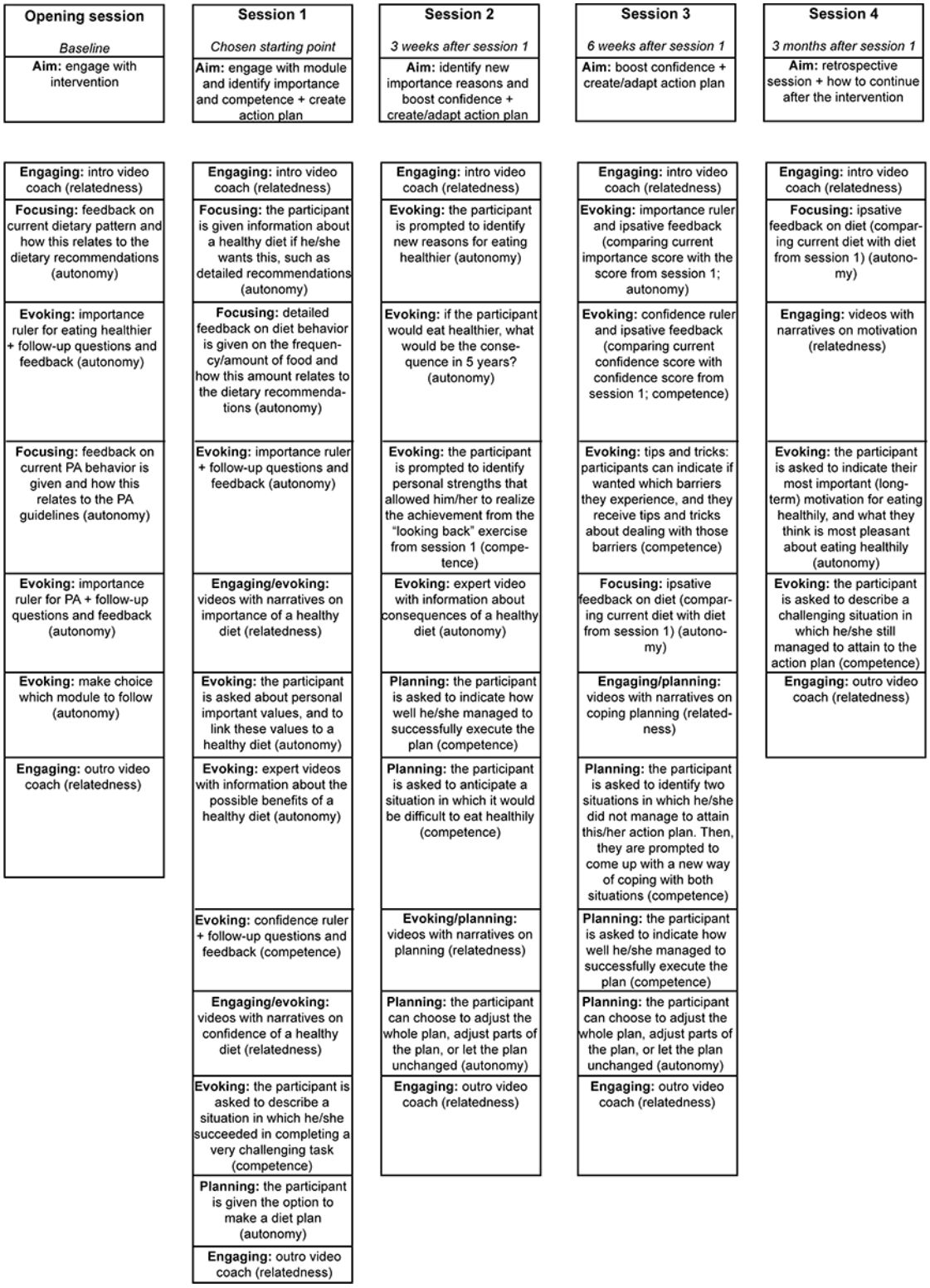


Figure 2. Overview of the content of the sessions of *I Eat*. PA: physical activity.

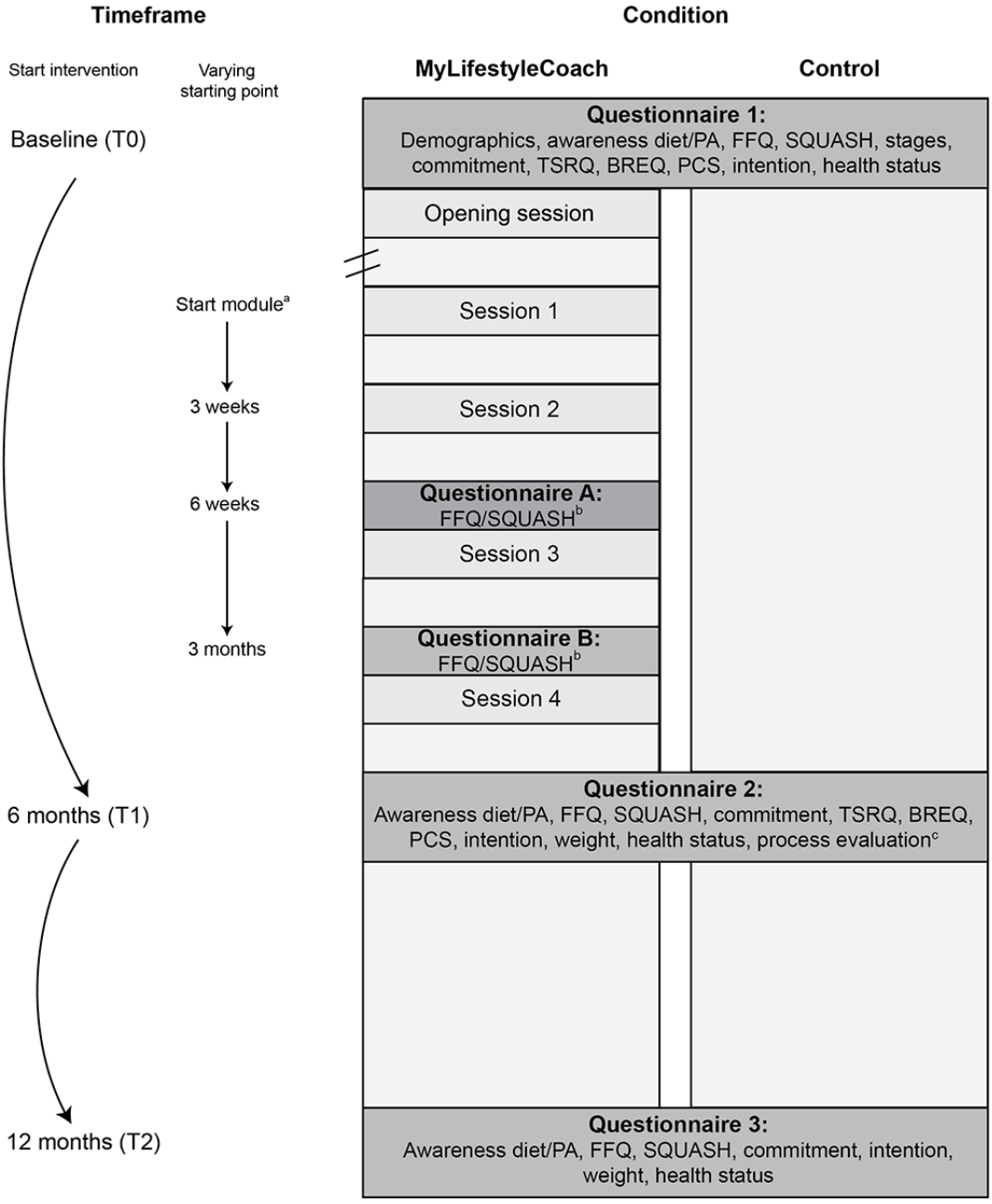


Opening Session

Before using the opening session, participants have to complete a questionnaire on several topics, including current dietary behavior and PA level, so that feedback about these behaviors can be provided. In the introduction to the opening session, participants become acquainted with the content of the program and meet the video coaches who will guide them through the program. These video coaches are used to create a sense of relatedness. Furthermore, participants receive general feedback about their current diet and PA level based on the results of the baseline questionnaire they completed beforehand. Feedback is provided using a traffic light system: The color of the light that is displayed indicates how closely their current PA level and diet correspond to health recommendations and which module (*I Eat* and/or *I Move*) is advised to use. The traffic lights are purely meant to provide participants with an insight into what they could change and are not necessarily intended to

induce compliance with PA guidelines and dietary recommendations. When participants received a green traffic light advice (in line with the guidelines), they received the message that following the correspondent module was not of high priority. Nevertheless, they were free to have a look at the module. When participants received an orange traffic light advice, they received the message that following the correspondent module might be relevant to them. When participants received a red traffic light advice, they received the message that following the correspondent module might be highly relevant to them. For both the orange and red traffic light advice, they were told that they were free to have a look at the module by choosing it in the program later. Participants also have to use the importance ruler to rate how important they feel it is for them to eat more healthily and become more physically active. They are given feedback tailored to their ratings. Subsequently, participants receive a short, combined summary of their current dietary behavior and PA level, and again are given advice on which module to use. Thereafter, they have to choose whether they want to participate in *I Eat* and/or *I Move*. They are also asked whether they want to start immediately or wait (waiting is restricted to a maximum of 14 days to avoid that the follow-up questionnaires, see Figure 3 [*Start module*], and the sessions of the intervention are intertwined). Figure 3 has been adapted with permission from Friederichs et al [12]. Next, we describe the sessions of the *I Eat* module.

Figure 3. Evaluation design of MyLifestyleCoach. BREQ: Behavioral Regulation in Exercise Questionnaire; FFQ: Food Frequency Questionnaire; PA: physical activity; PCS: perceived competence scale; SQUASH: Short QUestionnaire to ASsess Health; TSRQ: Treatment Self-Regulation Questionnaire.



I Eat Session 1

Session 1 is the most extensive of the 4 interactive sessions. It starts with an introduction, which includes the Dutch definition of a healthy diet, and is intended to engage participants. Thereafter, participants' awareness about their current dietary behavior is raised through the provision of detailed feedback (in terms of daily amount of vegetables, portions of fruit, consumption frequency of snacks, and weekly consumption of fish). The importance participants place on changing their behavior and their confidence in their ability to do so are critical to autonomous motivation. We assess how important they perceive healthier eating to be and how confident they are of achieving this using the importance and confidence ruler (1-10 scale) [43]. Follow-up questions are then asked based on the scores given. For example, "How important would you say it is for you to eat healthier on a scale ranging from 1 to 10?" For example, scores of less than 4 in response to the question "How important would you say it is for you to eat more healthily on a scale ranging from 1 to 10?" prompt the following: "It looks as if healthy eating is not your top priority, but perhaps there are still reasons why eating more healthily is important to you. Why could eating more healthily be important to you?" (see Multimedia Appendix 3 for more detailed information regarding these applications). Finally, intention to change (which is related to intrinsic motivation) is addressed. Users who say they intend to change are asked whether they want to make an action plan for eating more healthily. Participants are asked to formulate their goal in a concrete and realistic manner, formulate their most important motivation for eating (more) healthily, the location(s) of their choice, and on which moments they want to execute their activity. If desired, the participants can also indicate with whom they want to execute this action plan (*relatedness*) and what preparations they need to undertake before being able to implement their plan. In a pilot study of the *I Move* intervention, 85% to 90% chose to make such a plan for increasing their level of PA [44]. If the participant decides to make an action plan, the program stimulates him or her to execute it. The following sessions evaluate participants' execution of their action plan. Participants who do not want to make a plan at this stage are given the opportunity to do so in the following sessions. At the end of this session (as well as at the end of sessions 2 and 3), participants who chose to do just the *I Eat* module are asked if they would like to start the *I Move* module as well. Those who express an interest in doing so are then asked whether they want to start immediately or select a start date up to 14 days thereafter. If they choose to start the *I Move* module immediately, they are taken to session 1 of *I Move* once they have completed their current session. If they decide to start later with *I Move*, they receive an email on the day they have selected containing a link to session 1 of the module.

I Eat Session 2

Three weeks after session 1, participants receive an email inviting them to session 2. Session 2 looks back at the participant's perception of the importance of healthy eating. Participants are also asked whether they have identified new reasons to eat more healthily. In addition, participants are asked about what effects they think it would have if they started eating more healthily at this point. After that, participants are asked to think of situations in which they would find it difficult to eat healthily and to think of strategies they might use to cope with these situations. Thereafter, the participants are invited to identify personal strengths to boost their confidence. They are asked to elaborate on how their personal strengths (such as perseverance) are helpful in dealing with such difficult situations. This is a helpful strategy in the change process. Finally, the participants who made an action plan to help them eat more healthily in the previous session are given the option to evaluate how well they have succeeded in following it. They are given the opportunity to alter their plan and formulate additional coping plans. Those who did not make a plan are again given another opportunity to do so.

I Eat Session 3

At 6 weeks after session 1 (ie, 3 weeks after session 2), participants receive an email invitation to session 3. This session begins with assessment of participants' current perception of the importance of healthy eating and their confidence in their ability to do so, which is carried out using the rulers. Subsequently, participants are given feedback about how their perceptions compare with their perceptions at the start of *I Eat* (session 1). After the feedback message concerning confidence, the participants are asked to think back to a difficult situation in which they struggled to eat healthily but managed to overcome their difficulties. This is supposed to boost their self-efficacy and give them more confidence in their ability to eat more healthily. They are then given some tips for eating healthily in situations where it is difficult to do so, which are derived from the pilot study. After this topic, participants receive feedback on whether they have made progress toward a healthier diet (comparison of current and preintervention diet, based on the self-assessments). Finally, participants are once again given the option of evaluating and adapting their plans and formulating coping plans. If they have not yet made a personal healthy eating action plan, they are once again given the opportunity to do so.

I Eat Session 4

At 3 months after session 1, participants can enter session 4. This is a session in which several topics from previous sessions are covered. Participants can choose which of several topics they would like to pursue. The available topics are feedback on their dietary behavior, long-term personal motivation and confidence, how to deal with difficult situations, and information on how to maintain their new behavior after the end of the program. Participants can opt to skip one or more topics.

I Eat Videos

The program gives participants the option of viewing various prerecorded videos during the sessions that are mainly text based. Previous research has shown that this type of interactive video counseling has promise as a technique for public health interventions [45-48]. These videos include a human video coach who guides the participant through the program, short videos telling the stories of 4 putative *former participants* of *I Eat* (an older nurse, a younger cleaning lady, an older production assistant, and an elementary school teacher), and videos in which a dietician talks about the positive effects of eating healthily. Giving participants the opportunity to select the videos they

want to see instead of making them start automatically at a certain point in a session is in line with MI practice and with the principles of SDT, which suggest that the individuals' need and desire for information should be assessed before it is provided. The videos were scripted, and a film producer was hired to produce them. A real dietician provided feedback on the dietician's script. An advertisement was placed on a casting website to recruit actors for these videos. To increase the credibility of the actors appearing in the videos, several colleagues in the health psychology department were asked to choose the actors (from a preselection of actors that responded to the advertisement) who were most representative of a certain description. The videos were recorded in different settings, including a green screen, hospital, high school, and domestic setting.

Modification of I Move

Effectiveness and reach are key to the impact of a program. *I Move* was innovative because it was one of the first interventions to integrate SDT and MI into a Web-based, CT intervention. Although *I Move* was effective in increasing PA, it was recognized that improvements were necessary to reduce the high dropout rate (607/987 participants, 61.5%, did not complete the 12-month questionnaire) and to broaden the intervention by adding a healthy nutrition module. We fine-tuned the tailoring of the feedback messages and language used to make it more suitable for people with limited education. For example, we changed passive sentences into active sentences. Furthermore, the tailored feedback was updated, so that it was consistent with the new Dutch guidelines for PA (150 min of moderate-intensity PA per week; the original *I Move* intervention focused on the accumulation of 30 min or more of moderate-intensity PA over at least 5 days per week). Finally, we made the guidelines less explicit to encourage users to set their own targets for increasing PA level rather than simply trying to achieve the recommended level.

Delivery Channel

As unhealthy dietary patterns are prevalent, it is important to design and implement an intervention that can reach large numbers of people. Computer tailoring can be used to create interventions with some degree of personalization to potentially reach a large population at relatively low costs. Computer-tailoring has been defined as "the adaptation of health education materials to one specific person through a largely computerized process" [49]. It could especially be beneficial in the Netherlands, where the overwhelming majority (97%) of the population aged 12 years and above has access to the internet [50], including low SES groups [51]. There are several reasons to keep computer tailoring as a technique, similar as in *I Move*, to deliver the intervention. First, the CT intervention *I Move* has been shown to be effective in increasing PA [13,14]. Research has also indicated that Web-based, CT dietary interventions are more successful in changing people's intake of fruit, vegetables, and fat than provision of general guidance or no information [49,52-57]. Finally, CT interventions have also been found to be effective among low SES groups [58].

MyLifestyleCoach was developed using the TailorBuilder software (OverNite Software Europe) [59]. This software is designed to generate tailored feedback based on algorithms. The intervention is integrated into a website that provides information about the intervention and answers to frequently asked questions [60].

Pretest

We will conduct 2 pretests. The first will be a 3-part paper-and-pencil pretest covering (1) the design of the website, (2) evaluation of the baseline questionnaire, and (3) the opening session (N=10). The first part will use 5-point Likert scales to evaluate several possible website designs in terms of appeal and appreciation. Participants will also be asked to suggest possible improvements. The second part will focus on clarity of the questions and instructions in the baseline questionnaire. The third part will consist of several questions about the content of the opening session, the clarity of explanation of the program structure, the clarity of traffic-light feedback about dietary and PA patterns, and feedback about the importance of eating more healthily and being more physically active. We will also ask which module(s) the participants would choose to follow and why. We will ask about several attributes of the videos, such as how easy it is to relate to the content and narrators and whether they are interesting to watch. The second and third parts of this pretest will be completed once the participant has walked through the opening session on the Web.

In the second pretest, we will test the module *I Eat* (N=16). Overall, 10 participants will test the intervention at home using their own devices. They will receive a printed questionnaire to assess the user experience, which they should fill in as they proceed through the intervention. We will also conduct a qualitative evaluation with 6 other participants and will use the think-aloud method while testing the intervention. The results and suggestions from the pretests will be used to improve and finalize the intervention for the randomized controlled trial (RCT).

Step 5: Program Adoption and Implementation Plan

The development of an implementation plan to enable adoption, implementation, and maintenance of the program is central to Step 5 of IM. As *I Eat* is also one of the first dietary interventions to integrate MI into a Web-based, CT format, the evaluation study (ie, the assessment of its effectiveness) will focus on the adoption and implementation of *MyLifestyleCoach*.

For adoption of the program in the context of the evaluation study (ie, the intention to use it and subscription to the program), we will provide information about the program through an advertisement that will be distributed via an internet research panel to recruit the participants for this study. Facilitation of program use (for implementation and sustainability) was already taken into account in the first step of the development. Minimal human action is required to participate in the intervention. Individuals who want to participate in the intervention can register to do so on the website. After registering, they will automatically receive invitation emails when a new session is available. Furthermore, several small pilot studies and interviews have been conducted with members of the target population to identify their preferences and needs regarding the content and appearance of the intervention and the intervention has been

adapted accordingly. Once we have demonstrated that the program is effective in delivering the intended outcome, that is, eating (more) healthily, we may consider further implementation possibilities, such as targeting other program outcomes in other domains of public health (eg, smoking), and the use of advertisements in mass media, social media, newsletters, or certain websites for sustainability purposes.

Step 6: Evaluation Plan

Step 6 in IM will deal with the planning of the evaluation of the combined nutrition and PA intervention. A 2-group RCT will be conducted to evaluate the efficacy of the intervention by comparing diet and PA in an intervention group and a waiting list control group. Figure 3 shows the evaluation design. Participants will be randomized over conditions; the participants who are placed in the waiting list control group will be given the opportunity to use the intervention once the study has ended. Measurements will take place on the Web at the study website at baseline (T0) and at 6 months (T1) and 12 months (T2) after baseline. In addition, 6 weeks and 3 months after the start of a module, participants in the intervention conditions will also be asked to fill in a questionnaire assessing dietary behavior or PA, depending on the chosen module (Figures 1 and 3). Participants will be given tailored feedback on their diet and/or PA in sessions 3 and 4 based on the results of these questionnaires. At the beginning of the study, all eligible participants will be given information about the study and asked to sign a Web-based informed consent form. Data collection started in October 2018 and will be completed in June 2020.

This study has been reviewed and approved by the Committee for Ethics and Consent in Research of the Open University of the Netherlands (reference number: U2018/07266/SVW). It was judged that the study is not within the scope of the Medical Research Involving Human Subjects Act; therefore, this study did have to undergo a review by an accredited Medical Research and Ethics Committee or the Central Committee on Research Involving Human Subjects. This study is registered in the Dutch Trial Register (NL7333).

Participants

The inclusion criteria for the participants are age between 18 and 70 years, an adequate understanding of the Dutch language, possession of a computer or tablet with access to the internet, and no participation in the *I Move* intervention or pilot studies. Participants who are not willing to sign the informed consent will be excluded.

Given the modifications made to the original *I Move* intervention, we expect to improve the ES for PA to 0.30 at 12 months [13,14]). There are no estimates of ES in an MI-planning CT dietary intervention. A review indicates that in clinical settings, MI has produced ESs of up to 0.57 [61], but this is the first Web-based MI-planning CT intervention targeting both PA and dietary habits. It might be possible to find additive effects when participants decide to start with both modules, *I Eat* and *I Move*, so we will use a conservative estimate of the ES (0.30). We expect an ES of 0.05 in the control condition. On the basis of these data, a power calculation (ES=0.25; power=0.80) indicates that a total of at least 400 participants is needed for this study (200 per condition). On the basis of an expected dropout rate of 50%, we would need to enroll at least 800 participants. We do not expect all participants to decide to do both modules, and as we want to analyze the level of participation of the modules, we will enlarge the sample size to at least 1200 participants in total. A research panel will be used to recruit these participants. The sample will be representative of the population in terms of age and gender, but we will strive for an overrepresentation (about 50% instead of the 31% in the population [62]) of people with a low educational level, which will be used as a proxy for SES.

After passing the inclusion questions and providing informed consent, two-thirds of the participants will be randomized into the intervention condition and one-third will be randomized into the waiting list control condition. We will oversample the intervention group, as we expect that many participants will not participate in both modules; oversampling provides the option to conduct separate analyses per module. After that, participants will fill in the baseline questionnaire (dietary and PA parts) and continue with the intervention. The path they follow will depend on the choices they make.

Attrition Prevention

Attrition from internet-delivered health interventions is a subject of particular concern. In addition to the use of SDT and MI principles, tailoring, and personalized videos, we will implement several strategies to reduce attrition. First, the participants who complete each questionnaire will enter into a draw for 50 prizes of up to US $55 (a total prize pot of US $1100). Those who complete all sessions and questionnaires, including the follow-up questionnaires at 6 and 12 months after the baseline measurement, will enter into a draw to win 1 of 2 tablet computers [63]. Second, follow-up questionnaires at 12 months will be brief, only aiming to assess diet and PA behaviors, commitment and intention [64]. Third, as up to 10% of dropouts in a previous study could be attributed to changes of email address, we will ask participants to provide telephone numbers so that we can contact people who change their email address [65]. Provision of a telephone number will be optional, and we will ask explicitly for permission to use the number.

Measurements

The primary outcomes of this study are diet (ie, number of portions of fruit and daily consumption of vegetables [in g]; the consumption frequencies for fish and unhealthy snacks) and PA behavior (minutes of moderate-to-vigorous activity). Diet will be assessed with a validated Food Frequency Questionnaire (FFQ) [66]. Our FFQ only includes the items about fruit, vegetables, fish (1 question assessing the consumption frequency per week), and snack foods (unsalted nuts, dried fruits, chocolate, sweets, cookies, chips, ice cream, and savory pastries); see Coumans et al [67] to know how snacking consumption frequency was determined. We added questions assessing the size of vegetables and fruit portions based on Willems et al [68]. PA behavior is assessed using the validated self-administered Dutch Short QUestionnaire to ASsess Health [69]. Furthermore, several secondary outcomes will be measured. Motivation (amotivation, controlled motivation, and autonomous motivation) is measured using the 2 Treatment

Self-Regulation Questionnaires (TSRQs): one that addresses dietary behavior and the other PA behaviors [34]. As the TSRQs do not differentiate between the specific forms of autonomous motivation, we will include 2 *intrinsic regulation* subscales from the Dutch Behavioral Regulation in Exercise Questionnaire (BREQ-2) to determine intrinsic motivation for both dietary and PA behaviors, as this is the only fully self-determined form of motivation [70]. The original BREQ-2 is used to measure intrinsic motivation for exercise (but we translated exercise to *bewegen* which means *to be physically active*); we will use an adapted version of the BREQ-2 to measure intrinsic motivation to eat healthily in which we have replaced *exercise* in all items with *eating healthily* to compare intrinsic motivation for engaging in PA with a healthy diet as closely as possible. Competence will be assessed using 2 specific Perceived Competence Scales for becoming more physically active and eating more healthily [71]. Other secondary outcomes are awareness about current dietary behavior and amount of PA, stage of change for nutrition and PA, intention [72] and commitment [73] to eating more healthily and becoming more physically active, and health status, measured using a 100-point thermometer-style visual analogue scale. For the purposes of a process evaluation, participants from the intervention group will be asked what marks (1-10) they would give to the program (ie, *MyLifestyleCoach* and the module(s) they followed) [68]. Furthermore, we will assess the extent to which the intervention supports the basic psychological needs using several items from the study by Walthouwer et al [74]: 1 item on competence, 2 items on autonomy, and 3 items on relatedness.

Discussion

Principal Findings

This paper describes the systematic development of *I Eat* and how it has been combined with the pre-existing *I Move* program to create a Web-based intervention *MyLifestyleCoach* aimed at promoting healthy diet and PA behavior. We also describe the protocol for the design and evaluation of *MyLifestyleCoach*. This intervention combines computer tailoring with the theoretical insights of SDT and practical techniques of MI. It is specifically aimed at people of low SES. We developed the intervention using the IM protocol [19] because a systematic approach is more likely to yield an effective intervention [20]. Following the IM protocol gave us an insight into the steps needed to develop an intervention based on the adaption of an existing intervention *I Move* [12-14].

Unhealthy diet and lack of PA carry similar health risks (eg, increased risk of developing various types of cancer, cardiovascular diseases, and type 2 diabetes [1-3]). The process of changing one's diet might be quite different from the process of changing one's level of PA and may be even more complex. Activities concerning PA could be more related to intrinsic motivation, as they can be pursued for being enjoyable, whereas this link with intrinsic motivation may be less clear for eating (more) healthily. Other than the obvious benefits of eating more healthily (eg, losing weight), new eating behaviors may not have much immediate added value [26]. Furthermore, people have an innate preference for unhealthy (palatable) foods that are also known to enhance mood by activating reward systems, although some may enjoy the taste of healthy food as well [29]. For these reasons, the satisfaction of the basic psychological needs may be even more critical to achieve a healthier diet. We conducted a new needs assessment using 2 Web-based pilot studies because the performance and change objectives for interventions promoting increased PA and healthier eating are different. We made a point of eliciting free-text responses to gain an insight into the language used by the target population when talking about diet, foods, and eating behavior. The results were used to formulate the performance objectives. Thereafter, we specified the change objectives, which were formulated in terms of the basic psychological needs of SDT. MI counseling techniques seem to be general rather than domain specific, making them suitable tools for working toward different program goals. This made it straightforward to implement MI techniques in *I Eat*, as they could be integrated using the same approach as in *I Move* [12]. The opening session, which is designed to interest users in eating healthily and being physically active, was built from scratch. We used *I Move* as a template for the design of *I Eat*, replicating the structure and inclusion of SDT and MI elements (eg, feedback on current behavior and the importance ruler). This was done to keep the balance between the fidelity to the original design of *I Move* (thus retaining the elements that made *I Move* effective) and the adaptations required because of the difference in domain. Nevertheless, creating the *I Eat* module was the most time-consuming part of development of the intervention. After pretesting the program, we will recruit participants using an internet-based research panel. The intervention's effectiveness will be evaluated in an RCT (intervention vs waiting list control condition). Validated questionnaires will be used to assess diet, and the evaluation will also include questionnaires covering possible moderators, mediators, and determinants of diet and PA.

Unhealthy dietary habits and inadequate PA levels are a public health concern; therefore, many interventions that attempt to improve diet and PA levels have been developed; however, the effects have often been small and lacking in persistence [55]. This may be because traditional interventions induce extrinsic motivation instead of more autonomous forms of motivation [52,55,75]. Interventions based on SDT and MI, which recognize intrinsic motivation as a key factor in sustained behavioral change, may be a better method of achieving long-term behavioral change [10,76-79]. However, this approach is innovative and challenging in both theoretical and practical terms. Previous research has demonstrated that MI can be used outside of intensive counseling contexts, for example, by telephone [80-82]. Other studies have shown that MI principles can indeed be successfully translated to computer-based formats [13,14]. However, there is only limited evidence on whether this approach is also likely to be successful in the diet domain [41,83]. *MyLifestyleCoach* is innovative, as it is among the first attempts to apply MI techniques in a Web-based, CT intervention with objectives in 2 domains, PA and diet, that allows users to choose which domain(s) they would like to target. The effectiveness of this approach is yet to be evaluated.

Challenges and Limitations

One challenge in the development of *MyLifestyleCoach* was translating the spirit, processes, and skills of face-to-face, counseling-style MI to a Web-based environment. One of the difficulties is that a human counselor delivering face-to-face counseling may excel at expressing empathy, providing insightful reflection, and responding to very subtle expressions of change talk. It may not be possible to implement these behaviors fully in a Web-based environment. Our aim was to mimic face-to-face counseling situation as closely as possible by using a variety of MI skills and tools (importance ruler, looking back, specific empathic noncoercive feedback messages, and a combination of open and closed questioning) that could be implemented effectively within the constraints of a Web-based environment [11].

Although this is one of the first interventions targeting diet and PA based on SDT and MI developed using the IM protocol, there are several potential limitations to be noted. The time-consuming aspect of developing an intervention following the IM protocol is risky, especially in the field of electronic health. Owing to rapid technology developments, it could be that Web-based interventions may already be outdated once they have proven to be effective. Nonetheless, it is a valuable tool to develop or adapt (existing) interventions. The program is especially developed and tested in people who have the necessary digital skills. The risk could be that this study will take place in a select sample, that is, as people with a low SES or older people have highest levels of risk behaviors and are least responsive to existing lifestyle interventions, they may be less likely to be targeted [16-18]. Another limitation is that we have not addressed (yet) how the intervention will be spread to the targeted population once this intervention is shown to be effective. Another limitation is that we are recruiting our participants via a research panel. We have not yet addressed how the intervention will be spread to the targeted population once this intervention is shown to be effective.

Conclusions

This paper describes the development of a Web-based CT intervention *MyLifestyleCoach* that is intended to motivate Dutch adults to eat more healthily and to become more physically active. We hope that by inducing more autonomous forms of motivation than traditional interventions, *MyLifestyleCoach* will elicit sustained changes in diet and PA. This is one of the first attempts to integrate SDT and MI into a Web-based, CT intervention addressing both diet and PA. Results from the RCT will provide an insight into the efficacy of the approach and could be used in the development and optimization of future Web-based interventions in several public health domains.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of the beliefs for (no) importance, (no) confidence, support, and difficult situations toward eating healthier.
[DOCX File , 20 KB - resprot_v9i2e14491_app1.docx]

Multimedia Appendix 2
Translation of the motivational interviewing spirit into our Web-based computer-tailored intervention.
[DOCX File , 20 KB - resprot_v9i2e14491_app2.docx]

Multimedia Appendix 3
Translation of motivational interviewing processes into our Web-based computer-tailored intervention.
[DOCX File , 29 KB - resprot_v9i2e14491_app3.docx]

Multimedia Appendix 4
Translation of core motivational interviewing skills into our Web-based computer-tailored intervention.
[DOCX File , 21 KB - resprot_v9i2e14491_app4.docx]

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Abbreviations

BREQ: Behavioral Regulation in Exercise Questionnaire
CT: computer-tailored
ES: effect size
FFQ: Food Frequency Questionnaire
IM: intervention mapping
MI: motivational interviewing
PA: physical activity
RCT: randomized controlled trial
SDT: self-determination theory
SES: socioeconomic status
TSRQ: Treatment Self-Regulation Questionnaire

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Protocol

The Effects of a Humanoid Socially Assistive Robot Versus Tablet Training on Psychosocial and Physical Outcomes of Persons With Dementia: Protocol for a Mixed Methods Study

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Abstract

Background: New technologies, like socially assistive robots (SARs), may have the potential to support caregivers at home. Still, the evidence for people with dementia in home care is unclear because a lot of studies are performed in a laboratory or institutional setting, and mainly use robots in prototype stages.

Objective: This study aims to explore the effects of the refined, commercially-available, humanoid SAR Pepper combined with a tablet PC–based dementia training program (Coach Pepper) versus an exclusively tablet PC–based dementia training program on psychosocial and physical outcomes of people with dementia living at home, including caregivers and dementia trainers. We hypothesize that Coach Pepper has a more positive effect on the primary outcome motivation (stable or decreased apathy) of people with dementia.

Methods: A mixed methods study will be performed, including a randomized controlled, parallel, 2-arm study with a complementary qualitative part. This sample includes 40 PWD living at home and 40 relatives, each complemented with five professional caregivers and dementia trainers. The intervention group will receive Coach Pepper (a SAR connected with a tablet PC–based dementia training program), and the control group will receive exclusively tablet PC–based training without the SAR. The duration of the intervention will be three weeks per household. Data will be collected at baseline and during and after the intervention by standardized questionnaires, sensor data of the robot, and tablet PC, as well as semistructured interviews, focus groups, and observation.

Results: To date, no results are available for this study protocol. The study intervention started in May 2019 and will end in Spring 2020.

Conclusions: The intervention of this study can be seen as a nonpharmacological intervention, including cognitive and physical training by a robot. This study will help to further refine SAR for the specific needs of people with dementia living at home.

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KEYWORDS

dementia; socially assistive robot; home care; caregiver; dementia trainers; motivation; physical training; cognitive training; care burden; humanoid robot

Introduction

Background

Dementia rates are increasing worldwide and consequently burden global health care resources to a serious degree [1,2]. On the other hand, there is a decreasing number of available caregivers to provide (nursing) care [3-5]. (Nursing) care of people with dementia usually takes place at home, especially in the early stages [6]. Owing to the progression of dementia and growing (nursing) care needs because of increasing care dependency (eg, in mobility, social contacts, and learning ability), (nursing) care problems (eg, incontinence and malnutrition), professional care (eg, by nurses) and a possible nursing home transition become increasingly necessary [6-8]. One of the most important aims in (nursing) care for people with dementia is to promote their independence according to their stage of dementia and individual abilities. Such (nursing) care can counteract a galloping progression of care dependency [9]. It is in this context that new technologies, such as socially assistive robots (SARs), may constitute a supportive device for caregivers because they have the potential to promote the independence and well-being of older people [10,11].

SARs can be defined as representing an intersection of assistive robots (giving aid or support to a human user) and socially interactive robots (social interaction through speech and gestures) [12]. The goal of SARs is to create a close and effective interaction with a human user by giving assistance through social interaction (eg, in activities of daily life ranging from cognitive to physical tasks or to encourage emotional expression, conversation, and gestures) [12]. The appearance of the SARs can vary. They can look like a mechanoid with a machine-like appearance, or like a humanoid, such as Pepper by Soft Bank Robotics, which is designed with an unrealistic but still human-like appearance so that users can identify it as a robot. They can also look like an android with an almost realistic human-like appearance, or, in the case of animal-like SAR, can look like an animal, such as Paro, the seal baby [13,14]. In this study, the humanoid SAR Pepper (see section Interventions) is used.

Results of various reviews (literature, scoping, and systematic) show that research on SAR in the context of older people with and without dementia is most often conducted on SAR with an animal-like appearance, such as Paro, which was designed with the appearance and behavior of a baby seal, AIBO, the robotic dog, or NeCoRo, the robotic cat [13,15]. However, there is a wealth of studies relating to other robot types, like humanoid SAR [15,16].

Until now, the effectiveness of SAR in all care settings, especially in-home care, has generally been unspecified. Studies show that these robots may have a positive impact on affect, cognition, physiological parameters, use of medications, social contacts, and quality of life with respect to well-being and behavior [13,15,16]. Regarding behavior, apathy, which is defined as a loss of motivation [17], is one of the most common behavioral and psychological symptoms (BPSD) in people with dementia, with an overall mean prevalence of 49% [18].

Measurements from research studies have demonstrated that people with dementia have lower capacities for motivation processes [19]. Current models of motivation identify and discriminate two phases: (1) goal setting; and (2) goal pursuit. The latter requires self-regulatory capacities for decision-making, regulation of activation, and regulation of motivation. Forstmeier and Maercker [19] concluded from their research that cognitive and physical training should be complemented by motivation-supporting training strategies, such as goal-setting and self-motivation [19]. In addition, motivation-oriented interventions support the reduction of neuropsychiatric symptoms, such as depression and apathy (loss of motivation). The study described in this protocol implemented motivation-oriented strategies into the overall technological Coach Pepper concept in the shape of a humanoid SAR, which worked to motivate the people with dementia by means of social interaction to perform daily dementia training on a tablet PC (all functions of Coach Pepper are shown in Figure 1).

Figure 1. The functions of Coach Pepper.

It is necessary to focus on the motivation of people with dementia, because loss of motivation (apathy) could entail a decline in cognition, problems in activities of daily living (ADL), decreased quality of life, increased morbidity, greater mortality, and for caregivers, a greater caregiver burden [20-22]. In a systematic review by Pu et al [15], only two studies were found which included apathy as an outcome measure of SAR interventions. Only one of these studies included a humanoid SAR as an intervention for people with dementia. None of these two studies were performed in home care, which is a setting where a lack of research with SAR is still prevalent.

In their scoping review, Buhtz et al [23] identified 19 studies that included SAR for care-dependent people at home. Most of these robots were in a prototype stage and were tested mainly for technical aspects and operability in predominantly exploratory or piloting studies. Thus, there is a recommendation to explore the effectiveness of SAR [15,23] in well-designed randomized controlled trials with larger sample sizes [23,24]. In home care, often no more than ten older people with or without dementia are included in studies using SAR [25-28]. This is not surprising, because the home care setting can be seen both in technical and scientific terms as one of the most challenging and complex scenarios for SAR. A household with people and objects that seemingly unpredictably vary their position presents SAR with enormous challenges and hurdles [23]. But research of SAR in home care is extremely important, because many older people with and without dementia would like to live at home as long as possible. SAR, as an innovative intervention, has the potential to support care independency (in various ADL) at home and may help to avoid or delay institutional care (eg, nursing homes).

Overall Aim

The overall aim is to explore the effects of a humanoid SAR versus an exclusively tablet PC–based dementia training on psychosocial and physical outcomes of people with dementia living at home, including caregivers and dementia trainers.

Primary Aims

The primary aims of this study include exploring the effect of Coach Robot Pepper on motivation (in the sense of increased, decreased, or stable apathy) of people with dementia versus the tablet PC–based training, and exploring the effect of Coach Robot Pepper on the care burden of relatives compared with the tablet PC–based training.

Secondary Aims

There are several secondaru aims of this study, one of which is exploring the effect of Coach Robot Pepper on acceptance, usability, quality of life, cognition, mobility, depression, behavioral problems, and care dependency of people with dementia versus the tablet PC–based training. We would also like to explore the effect of Coach Robot Pepper on depression, quality of life, affect and acceptance, and usability of relatives versus the tablet PC–based training. There will also be a supplementary investigation of the acceptance and usability of robot Pepper and the tablet PC–based training in dementia trainers and caregivers, a supplementary observation of people with dementia to get an insight into how to handle a robot and the tablet PC–based training in home care (including usability), and supplementary interviews (focus groups or individual interviews) to obtain a deeper understanding of the experience (including usability) of all participants using Coach Robot Pepper in home care.

The description of the study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guideline [29].

Methods

Design

A mixed method study with embedded design will be performed. The quantitative part will be a randomized, controlled, parallel, two-arm study, and the complementary qualitative part will include semistructured, guideline-based interviews. This design was chosen to not only obtain quantitative results but also to get a deeper insight into the experiences of using a SAR in home care for people with dementia.

Setting and Sample

Setting

This study will be performed in the private households of people with dementia living in Styria, which is one of the 9 federal states of Austria, with 1,239,153 inhabitants [30] in 540,800 private households and an average household size of 2.25 people [31].

Sample

We will include people with mild and moderate dementia as the main sample. We will also include their main relative as well as their nursing staff (nurses and nursing assistant) and dementia trainers. The inclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion criteria.

Persons with dementia

- adults
- living at home
- all types of dementia (except frontotemporal dementia)
- mild or moderate dementia (Mini Mental State Examination 10 and above)
- mild dementia: living alone or with a relative at home (if alone, the relative should live in the neighborhood and be in daily contact with the person with dementia)
- moderate dementia: living with a relative at home
- receive professional or nonprofessional care or no care
- speak and understand German
- have no physical, auditory, or visual restrictions, which would make the application of the interventions impossible
- do not take any dementia-specific medication or have been taking dementia-specific medication for at least 3 months; condition stable and no change expected during the study period
- do not take antipsychotics and antidepressants or have been taking them for at least 14 days before study start
- children and pets in the household after previous individual discussion

Relatives

- relatives of the participating people with dementia (adults)
- living or not living with the person with dementia in the same household (in the case of moderate dementia, relatives must live in the same household)
- person with dementia receives or does not receive professional care
- relative provides or does not provide care
- if the people with dementia receive paid 24-hour care (regardless of whether they have mild or moderate dementia), a relative still has to be recruited as a participant (this relative must live in the same house or household and be in daily contact with the person with dementia)
- speak and understand German

Nursing staff

- adults
- nurses or nursing assistants
- speak and understand German

Dementia trainers

- adults
- trained as Morbus Alzheimer Syndrome trainer
- train the participants with dementia at home
- speak and understand German

Sample Size

There are currently no comparative studies investigating the influence of humanoid robots on the motivation of people with dementia. Therefore, no results can be used to calculate an optimal sample size. However, to gain insight about what is feasible with our sample size, we estimated the possible effect size. For simplicity, sample size considerations are based on a Student's *t* test. A sample size of 20 in each group will have 80% power to detect an effect size of 0.91 using a two-group *t* test, with a 5% two-sided significance level. For example, if there is a mean difference of 10 between the groups and a standard deviation of 11 (the latter being assumable according to the literature [32]), the effect size would be 0.91. As a drop-out rate of 20% to 30% can be assumed, 20 people with dementia per group was planned (40 in total). This is the maximum number of people that can be realized with two robots during the study period of 10 months. Beside the people with dementia, their main relatives will be included (n=40, 20 each group) and as a supplement five nurses, nursing assistants, and dementia trainers, respectively, will be included. A small sample size of nursing staff and dementia trainers were chosen because a minimum of three people are necessary for usability tests (which is one focus in the study), if there are more than three

groups included [33]. The inclusion of these further two groups was necessary to get an in-depth understanding of using robots in home care.

Recruitment

The recruitment of the participants will be carried out by project members of a social nonprofit organization in the community. The sampling method will be convenience sampling. This organization runs the first dementia service center in Styria and offers advice and consultation for relatives providing care at home. They also offer Morbus Alzheimer Syndrome training in private households. All potential participants will be contacted personally or by telephone by the nonprofit organization. Interested participants will be offered a home visit to inform them in detail about the study by means of an information folder (including detailed information about the study) and a short video about the robot Pepper. For the recruitment, flyers will be placed at the service points of the social nonprofit organization, at the organization's regional events, in waiting rooms of medical practices, and on social media platforms. Only participants who were willing to be assigned to either the intervention or control group were included.

Randomization and Blinding

A randomization plan will be prepared by the Institute of Medical Informatics, Statistics and Documentation at the Medical University of Graz. For that, randomization software will be used. Only authorized people will be able to randomize patients, and the allocation to the intervention and control group will be balanced. There are two robots available for simultaneous use in the study, therefore, four people will always be randomized (two for intervention and two for the control group) two weeks before the next round starts. This will be done until all 40 people have been randomized. A single blinding will be performed. The clinical health care psychologist who will perform data collection before and after the interventions will be blinded.

Ethics Approval and Consent to Participate

This study follows the Declaration of Helsinki and received ethical approval from the Ethics Committee of the Medical University of Graz, Austria (Approval Number: 30-401ex17/18). For all participants, written informed consent by project members of the social nonprofit organization will be obtained. If people with dementia have a legal representative, the written informed consent will be given by them. If a person with dementia is not able to give written informed consent by themselves and has no legal representative, he or she will be not included in the study. Every person with dementia and all robots will be insured during the study. The participants can drop out of the study at any time, and in the event of health hazards, the study will be stopped immediately for the affected person.

Interventions

Robot Pepper

Pepper is a humanoid SAR from the company SoftBank Robotics. Pepper is 1.20 m tall and weighs 28 kg. Pepper has four microphones, two high definition cameras, and a depth-perceiving sensor that gives Pepper three-dimensional sight of his surroundings. Pepper talks in different languages like English, French, and German, and it has a touchscreen tablet on its torso. An internal gyro sensor gives Pepper information about the position of its body. Pepper can make fluid and expressive movements with its arms, and while the hands are equipped with touch sensors, Pepper is unable to pick up objects. Furthermore, Pepper has 3 bumper sensors and laser sensors as well as sonars to estimate distances to obstacles. Omnidirectional wheels enable Pepper to move and rotate on the spot. Robot Pepper is not able to navigate in rooms because of software restrictions. Peppers' operation time is about 12 hours. For this study, the functions of Pepper were refined according to the results of a prior qualitative study with the aim of exploring the needs of people with dementia and a follow-up pilot study where the first refined prototype was tested (mainly for acceptance regarding the robot's usability). The functions of the refined Robot Pepper can be seen in Figure 1.

Tablet PC–Based Dementia Training

The training program was developed in a prior study for people with dementia living at home or in institutional care. The training includes a serious game with a cognitive and physical training program, and the training can be tailored to an individual (eg, content, level of difficulty adapted to the stage of dementia, procedure, and time). The training always starts first with physical exercises (eg, balance, motor skills, and coordination), which are explained by text and video on a tablet PC. This is followed by cognitive exercises, including quizzes, spot-the-difference puzzles, puzzles, looking for picture pairs, cloze tests, mathematical tasks, listening tasks, and songs.

Intervention Group (Coach Pepper)

For the intervention group, the robot Pepper is virtually connected via Web interfaces with the dementia training program on an additional tablet PC. Therefore, the intervention group is called a Coach Pepper group (Figure 1).

The total study duration is 10 months (three weeks per household). The planned start is May 2019. Because there are two Pepper robots in the study, the robot is transported from the first two private households to the next two private households. This means that the intervention starts with the first two people with dementia, who receive Coach Pepper for three weeks. Thereafter, there is a break of one week when the training and individual adaptation of the robot for the next two households takes place. After this, the next two people with dementia receive the intervention for three weeks. This happens until all 20 people with dementia have received their interventions. Table 1 shows the time schedule of the study.

Table 1. Time schedule: an example of two study rounds.

Study phases	Enrollment (Ongoing)	Randomization/allocation (2 weeks before intervention)	(Break)	Study round 1			(Break)	Study round 2			(Break)
			Week 0	Week 1	Week 2	Week 3	Week 0	Week 1	Week 2	Week 3	Week 0
Enrollment											
Eligibility screen	✓[a]	—[b]	—	—	—	—	—	—	—	—	—
Informed consent	✓	—	—	—	—	—	—	—	—	—	—
Randomization/allocation	—	✓	—	—	—	✓	—	—	—	✓	—
Interventions											
Coach Pepper	—	—	—	✓	✓	✓	—	✓	✓	✓	—
Tablet PC–based dementia training	—	—	—	✓	✓	✓	—	✓	✓	✓	—
Assessments											
Questionnaires	✓	—	✓	—	—	—	✓	—	—	—	✓
Sensor data	—	—	—	✓	✓	✓	—	✓	✓	✓	—
Observation	—	—	—	✓	—	✓	—	✓	—	✓	—
Interviews, focus groups	—	—	—	—	—	—	✓	—	—	—	✓

[a]Time of enrollment, intervention, and assessment tasks.

[b]Not applicable.

Due to robot Pepper's restricted mobility (navigation is not possible), the robot will stand on a previously defined place in the household (eg, living room) where the person with dementia spends most of the day. Pepper will start communication proactively when the user is in proximity (person in proximity recognition and proactive dialogs) or by a date and time previously entered (time-triggered proactive dialogs). Pepper will encourage the people with dementia to use the tablet PC–based dementia training, and will guide them through the training with speech, gestures, music, and dance. The physical exercise videos as well as the correct answers for the cognitive exercises will be displayed on robot Pepper's Tablet. Furthermore, Pepper will motivate the participants to use further functions of Pepper itself. However, it is also possible for people with dementia or their relatives to start Coach Pepper at any time.

During the test phase, a dementia trainer comes to the household once a week for one hour to perform the dementia training together with the people with dementia. A nurse or nursing assistant will also come as a visitor in the first and last week of the test period to perform a one-hour observation of the people with dementia. Outside of these times, the participants can independently use Coach Pepper. In addition, all households will receive regular calls from the research team to discuss questions or issues. For all participants, measurements are taken before, during, and after the intervention period (see Multimedia Appendix 1).

Control Group (Tablet PC–Based Training)

The control group will exclusively receive the tablet PC–based dementia training, without the robot. Otherwise, it will be the same procedure as in the intervention group. In total, two people with dementia start the intervention for three weeks, and there will be one week's break with training for, and adaptations of, the tablet PC–based dementia training for the next two people. Then, a three week test period will happen again with the next two people. This will happen until all 20 people have received the control intervention. Just as in the intervention group, a dementia trainer comes to the household once a week for one hour and a professional caregiver comes twice (first and last week of testing) for observation. Outside these times, people with dementia and their relatives can use the tablet PC training as often as they like. Regular control calls will also be made. For participants in the intervention and control group, it is forbidden during the study to use (similar) devices (eg, robots, tablets, and smartphones) including any cognitive or physical training.

Training

Pepper Master Training

Before the intervention, all responsible project members (eg, dementia trainers, project assistants, and technical people) will receive Pepper Master Training, which will be carried out by the project partner Humanizing Technologies. In this training, Pepper will be presented with its functionalities, including how to unpack, put into operation, and repack the robot. Important notes about the system, daily use, maintenance, and troubleshooting will also also discussed. The training will last two hours. The trained people will be responsible over the course of the project to handle questions/problems from the participants with regard to robot Pepper.

Training Data Collection Methods, Course of Study

To ensure consistent data collection, all data-collecting people will be trained by the researchers of the Institute for Nursing Science regarding the course of study, as well as all data collection methods. The duration will be about four hours.

Intervention Training

The social nonprofit organization will train their dementia trainers and nursing staff on the interventions with the tablet PC–based training and Coach Pepper. The duration will be about four hours. They will also train the people with dementia and their relatives. The training will be in the private household of the participants on the day of delivery of Coach Pepper or the exclusively tablet PC–based training (first day of intervention, always on Monday). The duration of the training depends on the individual needs of the participants. Every household will receive an operating manual for Coach Pepper and the tablet PC–based training program.

During the study, a hotline will be set up for participants' questions and problems. Home visits will be offered if problems cannot be solved on the telephone. Furthermore, control calls will be performed regularly by project members to ensure that participants can handle Coach Pepper and the tablet PC–based training program.

Measurements

An overview of the following data collection methods is outlined in Multimedia Appendix 1. If a participant drops out after randomization, the minimum amount of data collected by this person are the sample characteristics (eg, age, gender, and education). All important changes of measurement methods will be indicated in the trial register. The measurements are shown in Multimedia Appendix 1.

Primary Outcome Measurements

Motivation

The Apathy Evaluation Scale (AES) will be used to measure motivation because apathy can be understood as a loss of motivation. The scale has 18 items (4-point Likert scale), and a total of 18-72 points can be obtained. Higher scores correspond to a higher degree of apathy, and therefore lower motivation [34,35].

Care Burden

The Zarit Burden Interview will be used to measure the subjective care burden of the relatives. The instrument has 22 items (5-point Likert scale), and a total of 0-88 points can be obtained. Higher scores indicate greater caregiver distress [36-38].

Secondary Outcome Measurements

Quantitative Measurements

Quality of Life

The Dementia Quality of Life Questionnaire will be used to measure the health-related quality of life of the people with dementia. The questionnaire consists of a self-rating version for people with dementia with 28 items and a proxy version for their relatives with 31 items. Each version also has an additional item to capture the global quality of life of the person with dementia [39,40]. Both versions are applied during an interview, thus capturing the emotions, memory, and everyday life of the person with dementia during the last week [39,41]. A 4-point Likert scale is used to collect responses and a higher overall total score reflects a better health-related quality of life [38]. For the relatives, the World Health Organization Quality of Life Scale-BREF will be used. It has 26 items and 4 domains (physical health, psychological, social relationship, and environment). For every item, 1-5 points can be obtained. In general, higher domain scores indicate a higher quality of life [42,43].

Care Dependency

The Care Dependency Scale will be used to measure care dependency of people with dementia. The scale has 15 items (5-point Likert scale). In total, 15-75 points can be obtained, and lower scores indicate a higher degree of care dependency [44].

Mobility

The Timed UP and GO Test (TUG) will be used to measure mobility in people with dementia. The test measures the time (in seconds) an individual needs to stand up from a standard arm chair, walk a distance of 3 m, turn, walk back to the chair, and sit down. Interpretation: <10 seconds=completely unrestricted; 10-19 seconds=less mobile, but still unrestricted; 20-29 seconds=limited mobility; >30 seconds=pronounced mobility restriction; 14 seconds and more has been shown to indicate a high risk of falls [45].

Cognitive State

The Montreal Cognitive Assessment will be used to assess cognition in people with dementia. The instrument has 30 items in 8 domains of cognitive functioning: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. In total, 0-30 points can be obtained, and lower scores indicate a higher degree of cognitive impairment [46,47].

Depressive Symptoms

The Geriatric Depression Scale will be used to assess depressive symptoms in people with dementia. The scale has 15 items (yes/no answers). In total, 0-15 points can be obtained, and higher scores indicate a higher level of depressive symptoms [48-50]. For the relatives, the Center for Epidemiological Studies Depression Scale will be used. The scale has 20 items (4-point Likert scale), and a total of 0-60 points can be obtained. Higher scores indicate a higher level of depressive symptoms [51,52].

Acceptance and Usability

The Technology Usage Inventory will be used to measure acceptance in all included participants. It captures technology-specific and psychological factors that contribute to the use of a technological device. The instrument includes 8 main dimensions (curiosity: 4 items; anxiety: 4 items; interest: 4 items; usability/user-friendliness: 3 items; immersion: 4 items; utility: 4 items; skepticism: 4 items; and accessibility: 3 items) with 30 items in total (7-point Likert scale). For every dimension, 1-21 or 28 points can be obtained. Furthermore, the

instrument includes a ninth dimension (intention to use with 3 items). This ninth dimension is measured on a visual analog scale, including a 10-centimeter long horizontal line with two endpoints (agree and disagree). A cross on the line indicates the degree of agreement. For the evaluation, the distance from the right endpoint (disagreement) to the answer across the line is measured. This distance (in millimeters) is determined and summed up for all 3 items (maximum: 300, minimum: 0). For all 9 dimensions, higher levels on the respective dimension indicate a higher level of expression in the respective construction [53].

Affect

The Positive and Negative Affect Schedule will be used to measure effect of the relatives. The instrument has 20 items (5-point Likert scale) with two dimensions (positive affect and negative affect). In total, 20-100 points can be obtained, and higher scores indicate higher positive or rather negative affect [54].

Behavioral Problems

The Neuropsychiatric Inventory (NPI) will be used to measure behavioral problems of people with dementia, and information will be obtained from a caregiver who is familiar with the patient's behavior. The instrument has 12 domains (delusions, agitation/aggression, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, sleep and night-time behavior disorders, appetite, and eating disorders). The NPI assesses the presence, frequency, and severity of each behavior in the previous month, as well as the level of caregiver distress as a result of each of the neuropsychiatric problems. The domain score is obtained by multiplying the frequency and severity scores. The total NPI score is finally the sum of all individual domain scores (thus, ranging from 0-144). The caregiver distress level is not part of the total NPI score. Higher scores indicate greater psychopathology [55,56].

Sensor Data

Furthermore, sensor data from the robot platform Pepper and the theratainment app will be continuously collected during the study period. The objective is to extract key features from the sensor data and investigate correlations with the scores from the used questionnaires (AES, Montreal Cognitive Assessment, and TUG) to apply advanced machine learning techniques to research the potential of developing statistics-based estimators to predict motivation, cognitive state, and mobility/physical activity.

Qualitative Measurements

Open, semistructured observation of people with dementia interacting with the robot at home will be conducted by professional caregivers to explore how they handle the robot during the study period. Besides individual interviews with the people with dementia and relatives, focus groups will also be organized with the professional caregivers and dementia trainers to obtain more in-depth knowledge about their experience with the robot.

Data Management

The sensor data of robot Pepper will be processed directly for the interaction and not be stored. A connection to Pepper from outside (eg, tablet PC–based training program) is only possible via a secure connection and with a user ID or password. During the study, sensor data is immediately forwarded to the appropriate project partners for processing via secure connections. All sensor data are analyzed anonymously and result in anonymized feature data. The videos themselves are deleted immediately after extracting the features. For each completed dementia training exercise, the tablet PC stores data reflecting the performance of each participant with dementia (eg, wrong/correct answers, quizzes, and time). All data will be analyzed anonymized.

The questionnaires and interviews will be handed over by project members of the social nonprofit organization either personally or via a secure server (protected password) to the Medical University. All personal data of participants will be treated confidentially and interviews will be anonymized during transcription. All participants will be assigned a code. The Medical University and Joanneum Research (research partner) have access to the final data set for analysis. To ensure data quality, all data from paper-pencil questionnaires will be entered into the statistical software by one researcher and will be scanned for errors after data entry by the same person. Furthermore, sample checks for data errors by a second researcher are planned, and the statistician will also perform a plausibility check of the data before starting the analysis.

Analysis

Quantitative Analysis

Statistical analyses of the results will be performed following the intention-to-treat principle. Descriptive statistics of the data will be presented as a mean and standard deviation, or median and quartile, depending on the nature of the distribution. To describe categorical data, absolute and relative frequencies will be used. To answer the primary question as to whether the motivation differs between the two intervention groups, a median regression is planned. Therefore, it can be adjusted for the degree of dementia and depression. For differences between the intervention groups for the secondary outcomes, the ordinal scale data will be analyzed with median regression. For metric data, a covariance analysis is planned, which also adjusts to degrees of dementia and depression. Changes in pre- and postintervention outcomes concerning relatives will be analyzed by a paired *t* test or a two-tailed Wilcoxon signed-rank test, depending on the distribution of the data. For the sensor data, correlations with the scores of questionnaires will be performed. Furthermore, a skeleton-based analysis of human activity will be applied on the video frames of the physical exercises [57]. The estimated increase of kinetic energy of the movements is intended to provide cues for the increase of motivation [58]. In addition, the video data will be analyzed for nonverbal expressive features which provide analytics about the state of mobility. The significance level will be set to alpha=0.05. For the evaluation, SAS 9.4 (SAS Institute Inc, Cary, North Carolina, United States) will be used.

Qualitative Analysis

The qualitative interviews (individual interviews with people with dementia and relatives; focus groups with caregivers and dementia trainers) will be organized in the MAXQDA software program (VERBI GmbH, Berlin, Germany), and coded and analyzed by means of qualitative content analysis according to Schreier 2012 [59] by the Institute of Nursing Science.

Results

As this is a study protocol with the study still in the intervention stage, no results are available as of yet. The study started in May 2019 and 18 participants with dementia (8 per group) have already finished the intervention. The study will end in spring 2020.

Discussion

The overall aim of this study is to explore the effect of a SAR on psychosocial and physical outcomes of people with dementia living at home, including caregivers and dementia trainers. We hypothesize that the robot has a positive effect on the primary outcome motivation (stable or decreased apathy) of people with dementia.

A Lack of Commercially Available and Tested Socially Assistive Robots

Research with SAR is a relatively young field [60], especially in people with dementia. A systematic review by Ienca et al [61] focusing on intelligent assistive technologies (including SAR) for people with dementia identified only 17/539 studies that included SAR. Furthermore, many studies were testing SAR in an (early) prototype stage [23,62]. Bedarf et al [62] identified in a review focusing on older people that, in general, only 6/107 robots were already commercially available. Buhtz et al [23] identified 3/13 SAR which are commercially available for older people in home care. In our study, the commercially available robot Pepper by SoftBank will be tested, which was refined for home care by our research team before this study according to the results of a qualitative study using a content analysis of interviews that included 80 participants (not yet published), and a first prototype test in home care with 12 participants (ClinicalTrials.gov Identifier: NCT03823066, results not yet published), including people with dementia, caregivers, and dementia trainers. The refined robot is illustrated in Figure 1. According to Alzheimer's Disease International [1], in the absence of a medical solution for dementia, we need more research and innovation around care.

Reasons of Institutionalization and Socially Assistive Robots as Nonpharmacological Home Care Intervention

Most often, research with robots like SAR is performed in laboratories and institutional settings such as nursing homes [13,15,63]. However, the home care setting is of high importance [1] because about 80% of people with dementia, especially in the early stages of the condition, receive care at home mainly through their relatives, with or without professional support [6,64,65]. Caregiver burden and the inability of informal caregivers to perform care on the person with dementia, beside neuropsychiatric symptoms/BPSD (especially apathy [66]), care dependency (in various ADL), mobility and cognition problems of the person with dementia, are some of the main reasons for institutionalization (eg, nursing home) [66-68]. Andel et al [69] stated that people with dementia are admitted earlier into a nursing home than people without such an illness. This situation shows that it is important to support caregivers of people with dementia in home care so that people with dementia can stay at home as long as possible. Our study includes cognitive and physical training by robot Pepper that belongs to the area of nonpharmacological interventions, where studies show that cognitive interventions may have a positive benefit for cognition and ADL, and physical training may improve or maintain ADL and may have a benefit for neuropsychiatric symptoms/BPSD [70-73].

Relevance to Include Personal Views of People With Dementia

In our study, we included the personal experience of people with dementia because from the point of view of older care-dependent people, there is a scarcity of knowledge about the use of robots like SAR in real care situations [63]. It is highly recommended to include people with dementia and cognitive impairment in the design iteration cycles [74-77] because their feedback is very relevant for the appropriate and user-friendly development of novel technologies [76]. Furthermore, people with dementia are indeed able to learn to make use of robot technologies [77,78].

Limitations of the Study

The study focuses only on people with mild to moderate dementia. Therefore, the results cannot be used for people with severe dementia. People with frontotemporal dementia were not included in the study because of known aggressive behavior. Therefore, we will not be able to obtain information as to whether people with this dementia type may benefit from a robot-based intervention. The study is performed only in home care, and results cannot be generalized to other settings, like nursing homes or hospitals.

Results and information of the ongoing study will be disseminated via our project homepage.

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the design of this study and will neither have any role during its execution, analyses, interpretation of the data, nor on the decision to submit results.

Authors' Contributions

SS was the major contributor to the manuscript, compiling the first draft. LP, LL, MH, and JZ complemented the content in the manuscript. SS, LP, MF, and JZ were responsible for the research design. SS, JZ, JS, and SPR were responsible for the recruitment strategy. SB, LC, LL, DP, and SR refined and developed the functions for the robot and tablet PC training program. JZ, SPR, SB, LC, and LL designed training (materials) for the interventions. MH and SS designed the randomization plan and participant numbers. MH, LP, GL, and SS designed the analysis methods. All authors critically reviewed the manuscript and gave feedback for further revisions. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measurements and time of data collection.
[DOCX File , 42 KB - resprot_v9i2e14927_app1.docx]

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Abbreviations

ADL: activities of daily living
AES: Apathy Evaluation Scale
BPSD: behavioral and psychological symptoms of dementia
NPI: Neuropsychiatric Inventory
SAR: socially assistive robot(s)
TUG: Timed UP and GO Test

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Protocol

Beating Cancer-Related Fatigue With the Untire Mobile App: Protocol for a Waiting List Randomized Controlled Trial

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Abstract

Background: Many cancer patients and survivors worldwide experience disabling fatigue as the main side effect of their illness and the treatments involved. Face-to-face therapy is effective in treating cancer-related fatigue (CRF), but it is also resource-intensive. Offering a self-management program via a mobile phone app (ie, the Untire app), based on elements of effective face-to-face treatments, might increase the number of patients receiving adequate support for fatigue and decrease care costs.

Objective: The aim of this protocol is to describe a randomized controlled trial (RCT) to assess the effectiveness of the Untire app in reducing fatigue in cancer patients and survivors after 12 weeks of app use as compared with a waiting list control group. Substudies nested within this trial include questions concerning the reach and costs of online recruitment and uptake and usage of the Untire app.

Methods: The Untire app study is a waiting list RCT targeting cancer patients and survivors who experience moderate to severe fatigue via social media (Facebook and Instagram) across 4 English-speaking countries (Australia, Canada, the United Kingdom, and the United States). The Untire app includes psychoeducation and exercises concerning energy conservation, activity management, optimizing restful sleep, mindfulness-based stress reduction, psychosocial support, cognitive behavioral therapy, and physical activity. After randomization, participants in the intervention group could access the Untire app immediately, whereas control participants had no access to the Untire app until the primary follow-up assessment at 12 weeks. Participants completed questionnaires at baseline before randomization and after 4, 8, 12, and 24 weeks. The study outcomes are fatigue (primary) and quality of life (QoL; secondary). Potential moderators and mediators of the hypothesized treatment effect on levels of fatigue and QoL were also assessed. Link clicks and app activation are used to assess reach and uptake, respectively. Log data are used to explore the characteristics of app use. Sample size calculations for the primary outcome showed that we needed to include 164 participants with complete 12-week measures both in the intervention and the control groups. The intention-to-treat approach is used in the primary analyses, which refers to analyzing all participants regardless of their app use.

Results: Participants were recruited from March to October 2018. The last participant completed the 24-week assessment in March 2019.

Conclusions: This mobile health (mHealth) RCT recruited participants online in multiple countries to examine the uptake and effectiveness of the Untire self-management app to reduce CRF. Many advantages of mHealth apps are assumed, such as the immediate access to the app, the low thresholds to seek support, and the absence of contact with care professionals that will reduce costs. If found effective, this app can easily be offered worldwide to patients experiencing CRF.

Trial Registration: Netherlands Trial Register NL6642; https://www.trialregister.nl/trial/6642.

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KEYWORDS

RCT; mHealth; app; intervention; fatigue; quality of life; cancer patients; cancer survivors; psycho-oncology

Introduction

Background

The most common and distressing long-term side effect of cancer and its treatment is cancer-related fatigue (CRF) [1-3]. CRF can be defined as "a distressing and persistent subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with daily functioning and is not relieved by sleep or rest" [3,4]. A third of the patients with cancer suffer from fatigue on a daily basis [5,6], which can persist for up to 10 years after diagnosis [4] with a considerable impact on their lives [2]. Besides the personal impact of CRF, the economic impact of CRF is substantial. A recent European health economics study has indicated that over 75% of patients with cancer who were employed changed their employment status, and 28% stopped working. A US study reported that 30% of patients reduced their work hours, with an overall average of 4 days per month per patient [5].

Most patients with cancer (74%) and oncologists (80%) perceive fatigue as a symptom impossible to manage or to treat successfully [7]. Oncology practice lacks an adequate approach to address the consequences of CRF. Usually, physicians inform patients with cancer about the risks of cancer treatment, including the possibility of becoming fatigued [8]. However, patients assume that treatment for CRF is not available or not effective, which often discourages patients from asking for help. Also, when physicians make recommendations to assist patients in addressing CRF, these recommendations tend to be nonspecific as 40% of physicians recommended doing nothing, followed closely by prescribing rest (37%). About 9% of the physicians in this situation used prescription drugs, which regularly have severe adverse effects [8]. The inadequate provision of care is not solely due to the lack of education about fatigue treatment, but also due to the complex origin and underlying mechanisms of fatigue. The etiology of CRF is multidimensional, involving physiological, biochemical, and psychological systems [9].

When it comes to the psychosocial treatment of CRF, therapist-guided face-to-face interventions have shown to be effective [10]. Such therapies include energy conservation, activity management, optimizing restful sleep, mindfulness-based stress reduction (MBSR) techniques, psychosocial support, and cognitive behavioral therapy (CBT) [4,11,12]. However, face-to-face treatment approaches are limited in reach and resource-intensive, as 1 therapist can only treat 1 patient or patient-group at a time. Therapist-guided electronic health (eHealth) interventions in which health care is delivered over the internet via technologies are offering a more flexible and low-threshold approach [13]. Another advantage of eHealth is that due to Web-delivery, also patients with little time and energy can take part in the treatment [14,15].

One example of a therapist-guided eHealth intervention to reduce fatigue in cancer survivors is the *More fit after Cancer* (*Fitter na Kanker* in Dutch) intervention in which patients received Web-based mindfulness-based cognitive therapy via a psychologist. This intervention showed strong evidence in reducing fatigue in survivors of cancer [13]. Although eHealth interventions involving therapist-guidance can be offered effectively over the internet reaching many patients worldwide, these interventions are still limited by the availability of specialized psychologists.

One way to reach many patients worldwide is to make use of self-management interventions delivered via the mobile phone (mobile health [mHealth], which is a subbranch of eHealth) in the form of an app. Advantages of mHealth apps concern the reach (ie, apps are widely and easily accessible by many patients), the low threshold intensity to engage in apps as compared with face-to-face treatment, and the low resource-intensity of the care provided (ie, it does not require input from a therapist as it can function as a self-management tool) [16]. As mHealth permits treatment of participants worldwide without having contact with health care professionals, online recruitment might be an effective way to reach out to a large number of potential mHealth users within a short time [17].

Inspired by the academic research and clinical practice from the Helen Dowling Institute (HDI) for psycho-oncology including the aforementioned *More fit after Cancer* trial, the start-up Tired of Cancer BV (Utrecht, The Netherlands) developed the so-called Untire app, with the goal to deliver an effective self-management tool to improve CRF and quality of life (QoL) of patients and survivors of cancer who feel fatigued. The Untire app is built for smartphones and tablets for both mobile operating systems iPhone (Apple Inc) and Android (Google). The intervention is based on the aforementioned successful elements of face-to-face therapy for CRF, that is, energy conservation, activity management, optimizing restful sleep, MBSR, psychosocial support, CBT, and physical activity exercises [9] and in line with the guidelines of the National Comprehensive Cancer Network [18]. The app aims to create awareness by providing psychoeducation, to give insight into one's energy levels, thoughts and behaviors about fatigue, and to help users to challenge unhelpful thoughts (eg, catastrophizing thoughts) and behaviors (eg, increase physical activity) by means of exercises. It is hypothesized that creating awareness and adjusting unhelpful thoughts and behaviors will lead to improvements in CRF and QoL. The current international study aims to examine whether the use of the Untire app has the potential to reduce CRF and improve QoL in patients and survivors of cancer. Until 2017, as far as we know, no mHealth interventions were developed to decrease CRF in patients with cancer and survivors [4,19].

Aims of the Research

The primary aim of this waiting list randomized controlled trial (RCT) is to assess the effectiveness of the Untire app in reducing fatigue in patients and survivors of cancer after 12 weeks of app access as compared with patients in a waiting list control group.

Secondary aims are to assess the effectiveness of the Untire app in improving QoL in patients and survivors of cancer after 12 weeks of app access as compared with patients in a waiting list control group; to examine the reach and costs of online recruitment, study drop-out, and uptake and usage of the Untire app; and to determine which factors moderate (ie, age, gender, and country) and mediate (ie, mindfulness, physical activity, depression, sleep, pain interference, and fatigue catastrophizing) the hypothesized effect of the intervention.

Methods

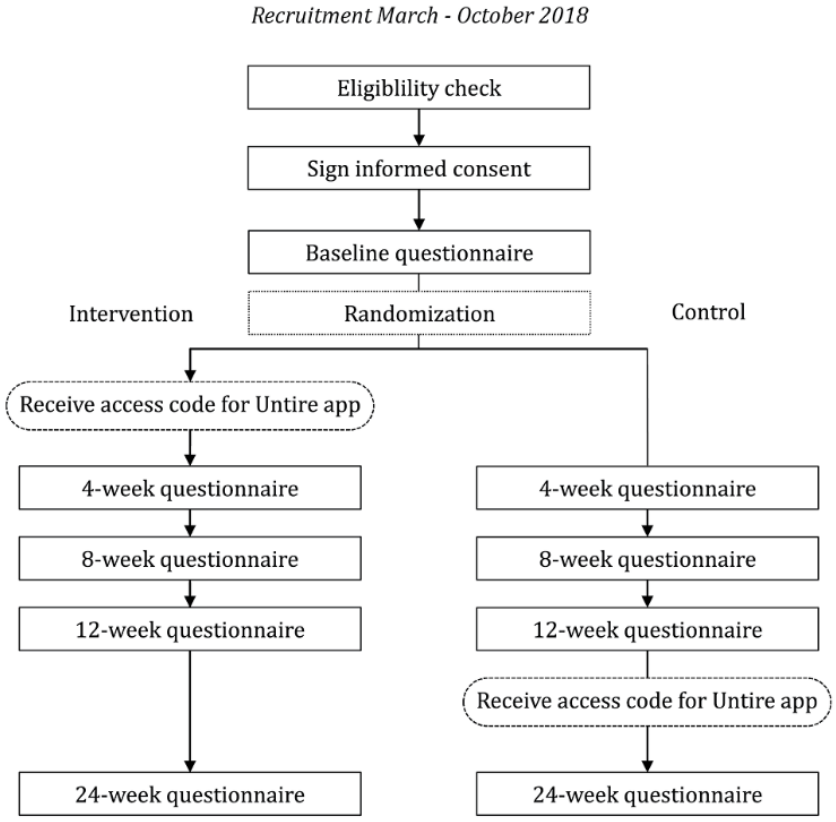
Approval

The Untire app study has been approved by the Medical Ethical Committee of the University Medical Center Groningen (UMCG), the Netherlands. Hereafter, the study received either ethical approval or a waiver from authorized institutions in the 4 English-speaking countries targeted (ie, Australia, Canada, the United Kingdom, and the United States; see Multimedia Appendix 1 for a detailed overview of ethical review and approval by country). The trial has been registered on 29/11/2019 on the Netherlands Trial Registry (NL6642).

Study Design and Setting

The Untire app study is a large-scale international waiting list RCT aimed to examine the effectiveness of the Untire app in improving CRF and QoL in patients and survivors of cancer. The Untire self-management app was launched worldwide from March 2018, where study enrollment took place until October 2018. Also, after the recruitment period, the app remained available. Participants randomly allocated to the intervention group received the Untire app at the start of the trial (Figure 1). After 12 weeks, also the control participants received the intervention (ie, 1 year of free app access). During the waiting time, control participants were allowed to seek or accept other treatments for their fatigue. The eligibility check and all other assessments, including demographics of participants, were carried out by using Questback's Web-based questionnaire system *EFS-survey*.

Figure 1. Study design to test the effectiveness of the Untire app in 4 English-speaking countries.



Study Population

The Untire app study targeted patients and survivors of cancer of 18 years or older, who experienced persistent fatigue at moderate or severe levels (ie, an average composite score of >3 on items 1, 2, and 3 of the Fatigue Symptom Inventory (FSI) [20,21]) and owned a smartphone, tablet, or iPad. Exclusion criteria were a diagnosis of and receiving treatment for a severe mental disorder (ie, major depression, psychotic disorder, anxiety disorder, or addiction) as these persons may need more intensive treatment than offered by the app. Also excluded were persons having a diagnosis of chronic fatigue syndrome, myalgic encephalomyelitis, or fibromyalgia as the app focusses on improving physical activity, which is not recommended and could potentially be harmful to these patients [22].

Procedure and Recruitment

We approached potential participants over the internet via social media advertisement campaigns (Facebook and Instagram). Multiple advertisement campaigns were created to promote the link to the study page. Both female and male patients and survivors of cancer of all age groups >18 years, and who have shown interest in topics related to cancer, fatigue, and cancer survivorship were targeted in the first advertising campaigns. On the basis of participant characteristics of those who showed interest (ie, clicked on the advertisement link), comparable participants (ie, look-alike audiences) were approached in subsequent advertisement campaigns.

Interested persons were directed to the landing page of the Web-based survey tool (ie, Questback) that was used for data collection. Participants were screened for eligibility, and if eligible, they received an information letter and gave digitally informed consent. Hereafter, participants completed a baseline questionnaire, after which they were randomized into the intervention or control group. Next, participants received an email with the information letter (see Multimedia Appendix 2) and their digital signed consent (see Multimedia Appendix 3). Intervention participants received a second email with a unique access code that could be used to activate the Untire app after downloading it from the app store, enabling free usage. Subsequently, participants received email invitations and reminders at 4, 8, 12, and 24 weeks to fill in the questionnaires. Once control participants completed the 12-weeks survey, they also received an email with a unique access code that could be used to activate the app after downloading it from the app store, enabling free usage. The 24-weeks follow-up assessment was used to assess maintenance of the expected decline in fatigue in the experimental group. Assessments did not last longer than 15 min.

Randomization and Blinding

Participants who completed the baseline questionnaire were randomized 2:1 by the Web-based academic survey tool (ie, Questback) into the intervention and control groups. The randomization ratio was chosen for two reasons. First, we expected that intervention participants were less likely to complete the 12-weeks assessment after receiving the incentive for participation (ie, the free access to the Untire app) already at baseline, as compared with control participants who received the incentive after completing the 12-weeks measure. The 2:1 randomization increased the likelihood of a balanced number of completed 12-weeks measures. Second, in case the drop-out rate in the intervention group was higher than expected at the 12-weeks measures, it was considered convenient to have large enough numbers in the intervention group for in-depth app use analyses. Due to the character of the intervention, it was not possible to blind participants and assessors to intervention or control allocation.

Intervention

Participants in the intervention group were instructed to work through the app at their own pace and could freely choose modules to work on. Although daily use of the Untire self-management app was recommended, participants were instructed to use the app at least once a week. Users who had not been active for 5 days were sent a reminder. Users who opened the app at least seven times within 10 days received a rating pop-up (ie, to assess satisfaction and ask for feedback).

After opening the Untire app for the first time, participants received a short introduction on how to use the app. Participants were informed that every time they revisit the app (ie, reopen the app), a (new) daily program will be presented. The daily program consists of the 4 following core components: (1) *My themes*, (2) *My exercises*, (3) *Tip of the day*, and (4) *My physical activity* (Figure 2). Participants also received information about the weekly assessments of their fatigue and related components, the so-called *Quick scan*. The *Vase of Energy* is an integral part of the Quick scan. Participants were also invited to think about informing a friend or family member, a so-called *buddy*, to help or motivate them to work with the app. All the modules are explained below in detail (also see Table 1 and Figure 2).

Figure 2. The Untire self-management app: (a) mindfulness-based stress reduction audio exercises, (b) psychoeducative themes, (c) the daily program, and (d) the vase of energy.

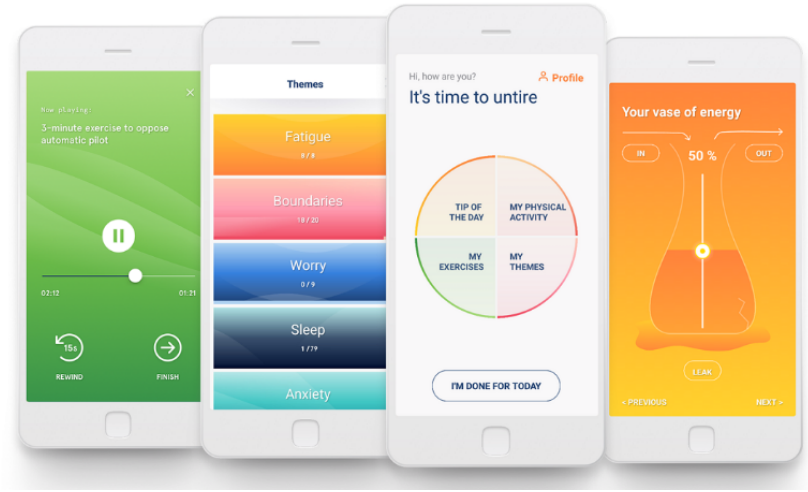


Table 1. Daily and weekly Untire app components, description, and use.

Untire app components	Description
Daily program	
My themes	Receive psychoeducation and exercises on topics such as fear, worry, anxiety, and sleep.
Basics	Get basic education about different sources of fatigue (ie, the other themes) and receive an overview of how to work with the Untire app, including the rationale of the *vase of energy*.
Fatigue	Receive psychoeducative and medical background information and exercises about cancer-related fatigue.
Anxiety	Receive information on the physiology and the harmlessness of anxiety, as well as several tips on how to cope with fear.
Worry	Learn to distinguish between thoughts and facts, and learn that thoughts are malleable. Furthermore, participants receive challenging questions to explore their thoughts.
Boundaries	Learn to accept that energy levels are often lower as compared with before your disease. Furthermore, learn to understand that time-outs may be needed and that you can actively manage your boundaries. Gain insight into your boundaries to prevent crossing them repeatedly.
Sleep	Learn about different factors related to sleep problems and the vicious circle of insomnia, which may influence (quality of) sleep. Receive suggestions on how to improve your sleeping behavior.
Self-care	Improve your self-compassion by receiving 20 suggestions for self-care.
Nutrition	Receive general information on healthy nutrition based on the latest scientific research.
My exercises	Engage in 17 different mindfulness-based stress reduction exercises to identify, manage, and release stress (ie, *attention to the breath* or body scan).
Tip of the day	Tips are ideas or quotes based on positive psychology, which should help to get into a good mood (eg, *Gratitude*).
Eg, gratitude	For instance, receive a gratitude writing tip and exercise, in which you write down 3 moments of the day that you felt grateful. The gratitude tip will support you in adopting a positive thinking style.
My physical activity	Receive information and exercises on 3 different aspects of the Untire physical exercise training program to increase levels of physical activity and muscle strength.
Planning	Receive several exercises and tips to deal with limited levels of energy, such as agenda taking and indicate how the upcoming days will be about activities and energy levels.
Build up energy	Build up your energy by carrying out daily physical activity based on guidance in 30 min a day (daily increasing difficulty). Receive guidance in improving sedentary behaviors through information, exercises, and tips.
Power	Receive guidance to build up power and muscle strength through information, exercises, and tips.
Assessments	
Quick scan	Receive weekly evaluations involving 4 questions about well-being as well as 3 questions about energy (part of the *vase of energy*). Via the personal profile, you can see your progress anytime.
Fatigue	How was your fatigue last week?
Burden	How was your burden last week?
Happiness	How happy have you been last week?
Satisfaction	How satisfied have you been last week?
Vase of energy	Receive 3 questions presented visually by the vase of energy: What gives you energy? What costs you energy? What is your energy leak? The weekly pattern provides insights into energy levels.

My Themes

My Themes is 1 of the 4 core components of the Untire app, which serves the overarching purpose of providing patients and survivors of cancer with background information about various aspects of their CRF. Psychoeducation is known as a crucial element of face-to-face therapy for patients with CRF [4]. Themes that are often associated with CRF include fatigue, anxiety, worry, boundaries, sleep, self-care, and nutrition. Participants started with a theme called Basics, which taught them essential introductory information on CRF and explained the rationale behind the Vase of Energy. Hereafter, participants could choose the themes based on their interests. The themes mostly consist of articles to read or listen to (audio) and small related exercises (eg, listing realistic activities).

My Exercises—Mindfulness-Based Stress Reduction

Stress-reduction exercises involving relaxation techniques and meditation exercises are often used in mindfulness-based cognitive therapy for patients and survivors of cancer (Table 1) as reduced stress is generally associated with a reduction of CRF [4,23-26]. Participants are offered 1 of 17 stress-reduction exercises. Participants could choose to do a new exercise or also redo earlier completed exercises. *My exercises* include

stress-reducing mind-body activities such as breathing techniques and body scans. All exercises are audio-guided.

Tip of the Day

Tips are provided to foster insights and tricks to improve the daily mood of patients and survivors. One example is the tip of the day called *gratitude*, in which participants are instructed to write down 3 aspects that they are feeling genuinely happy about that day. Participants are instructed to continue this exercise for the upcoming days. Every day the tip component is revisited, a new tip is displayed and accompanied by a motivational image or catchphrase.

Physical Activity

The physical activity part aims to increase participants' physical activity levels and muscle strength and, even more important, gives insight into the management of energy levels and activities. The app teaches 3 methods to improve the participant's energy balance, supported by video-guided strength exercises (Table 1). Positive effects of physical activity and gaining fitness are explained, and participants learn that, even though they feel tired, exercise might improve their feeling of tiredness. Also, a schedule is presented as an example of how to build up to 30 min of physical activity a day, which is the recommended duration of physical activity per day [27].

Quick Scans

Apart from the 4 core components, every week, participants are assessed on their level of fatigue and related aspects in a weekly quick scan. The quick scan aims to evaluate to what extent participants experienced fatigue and related aspects in the previous week. In this way, participants are expected to gain insights into their patterns and progress of fatigue and energy levels over time. The quick scan is solely for informing participants; the app does not offer any personalized feedback based on participants' answers. The quick scan consists of 4 items assessing the level of fatigue, fatigue burden, satisfaction, and happiness on a visual analog scale: *How was your fatigue this last week?How was your burden of fatigue this last week*? *How satisfied with life have you been this last week? How happy have you been this last week?* Every week, participants have to fill in once their *Vase of energy.* The vase of energy is a visual presentation tool helping participants to track and visualize personal energy levels. Participants gain insights into factors leading to a reduction or increase in energy levels. Apart from that, so-called energy leaks are explored, which can pertain to a constant drain (eg, pain, anxiety, and stress). Participants indicate what was lowering their energy levels, as well as what was giving them energy and what caused a consistent energy leak.

Content Delivery Forms

The content of the Untire app is presented in different forms. Patients and survivors of cancer can read educative articles, but often also an audio option is available, as listening to the material instead of reading it might be less tiring for patients with CRF. Besides reading texts and listening to audio texts or exercises, the Untire app contains numerous video animations aimed to explain complex aspects and exercises in an easy to understand and visually attractive way. Apart from the form of content delivery (ie, text, audio, and video), also persuasive elements (eg, motivational pictures in between blocks of text) are used to visualize key aspects (eg, the biological clock for sleeping quality). Other persuasive elements include progression bars, rewards, badges, and constant encouragements. To encourage participants to use the app at their own pace, they receive gentle reminders to take a break after going through 5 pages within a theme. The app fosters social commitment by supporting participants to invite a so-called *buddy*. In this way, participants can manage their fatigue together with a family member or friend. Furthermore, participants are also invited to join the Untire community on Facebook, which provides a platform for the exchange of thoughts and allows socializing in a broader social environment.

App Version

The study used version 2.1 of the app, which has been developed based on a pilot and feasibility study with version 1.0, and a usability study with 19 users and 9 professionals focusing on the content, use, and technical aspects of version 2.0. For version 2.1, improvements were made in the onboarding system, tone-of-voice, and presentation of content. For the improvements in the onboarding system, an additional 5 users participated in a UX usability test. During the study, only minor technical updates and changes (ie, mostly bug fixes) have been made.

Outcome Assessment

Data in this study have been collected by means of Web-based questionnaires and in-app log data. Table 2 presents a complete overview of the variables assessed by the Web-based questionnaires at each measurement wave for the intervention and control participants, respectively. Variables were assessed by either using validated questionnaires, using a selection of items of a validated questionnaire, or by items specifically created for this trial. We realize it may be a burden for patients with CRF to fill out all these assessments. To enhance patients' commitment to the study and to reduce attrition, we carefully selected a limited number of questionnaires and items to include.

Table 2. Questionnaires to assess the primary outcome, secondary outcomes, moderators, mediators, and explanatory factors (including background attitudes, experiences of app use, and cost-effectiveness).

Variables	Measurement (number of items)	Measurement in weeks				
		0 (baseline)	4	8	12	24
Primary outcome measure						
Fatigue symptoms	FSI[a] (15): Severity Scale (4) and Interference Scale (7)	I[b]C[c]	IC	IC	IC	IC
Secondary outcome measures						
QoL[d]	EORTC-QLQ-30[e]—Past week (1) and QoL—On Average (1)	IC	IC	IC	IC	IC
Moderators						
Demographic and health characteristics	—[f]	IC	—	—	—	—
Mediators						
Mindfulness	MAAS-5[g] (5)	IC	IC	IC	IC	IC
Physical activity	(3)	IC	IC	IC	IC	IC
Depression	PROMIS-29[h] (4)	IC	IC	IC	IC	IC
Sleep						
Quality	PROMIS-29 (1)	IC	IC	IC	IC	IC
Disturbance	SLC-90-R[i] (3)	IC	IC	IC	IC	IC
Fatigue catastrophizing	FCS[j] (13): Rumination (4), Magnification (3), and Helplessness (6)	IC	IC	IC	IC	IC
Explanatory factors						
Patients expectancy	(3)	I	—	—	C	—
Patients motivation	(2)	I	—	—	C	—
Patients support in environment	WHYMPI/MPI[k] (5)	IC	IC	IC	IC	IC
Pain interference	RAND-36[l] (2)	IC	IC	IC	IC	IC
Experienced changes	(5)	—	—		IC	IC
User experience of the app	(19)	—	—	—	I	C
Cost-effectiveness	(6)	—	—	—	IC	—

[a]FSI: Fatigue Symptom Inventory (fatigue severity scale, fatigue interference scale).

[b]I: intervention measurement.

[c]C: control measurement.

[d]QoL: quality of Life.

[e]EORTC-QLQ-30: European Organization for Research and Treatment for Cancer Quality of Life Questionnaire.

[f]Not applicable.

[g]MAAS-5: The Mindful Attention Awareness Scale.

[h]PROMIS-29: Patient-Reported Outcomes Measurement Information System (depression scale, sleep scale).

[i]SLC-90-R: Symptom Checklist-90-Revised (sleep disturbance scale).

[j]FCS: Fatigue Catastrophizing Scale (fatigue catastrophizing—adapted from PCS: Pain Catastrophizing Scale; rumination, magnification, and helplessness scales).

[k]WHYMPI/MPI: The West Haven-Yale Multidimensional Pain Inventory.

[l]RAND-36: Research and Development (pain interference scale).

Primary Outcome Measure

The primary outcome is the change of fatigue severity and fatigue interference from baseline to 12 weeks, which was assessed with the self-report questionnaire FSI [20,21]. Fatigue severity was assessed by calculating the average of 3 severity items (FSI items 1-3: *Rate your average level of fatigue during the past week; Rate your level of fatigue on the day you felt most fatigued during the past week; Rate your level of fatigue on the day you felt least fatigued during the past week*) on an

11-point Likert-scale ranging from 0 (not at all fatigued/no interference) to 10 (as fatigued as I could be/extreme interference). Fatigue interference was assessed by calculating a composite score of the average of 7 interference items (FSI items 5-11: *Rate how much, in the past week, fatigue interfered with your general level of activity, ability to bathe and dress, normal work activity [includes both work outside the home and housework, ability to concentrate, relations with other people, enjoyment of life, mood]*). A higher score indicates stronger severity or interference.

Secondary Outcome Measures

The secondary outcome is change in QoL from baseline to 12 weeks, which was assessed with the 1-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (*How would you rate your overall quality of life during the past week?* [28]) as well as a self-constructed item of overall QoL (Overall QoL: *How would you rate your overall quality of life on average?*) on a 7-point Likert-scale ranging from 0 (very poor) to 7 (excellent). A higher score indicates a better QoL.

Moderating Factors

Demographic data were gathered on age, gender, country of residence, level of education, employment status, relationship status, and illness-related characteristics, such as being a patient or survivor of cancer, time since diagnosis, and type of treatment received.

Mediating Factors

The following potential mediating factors were assessed: mindfulness, physical activity, depression, sleep, and fatigue catastrophizing. Mindfulness was measured with the Mindful Attention Awareness Scale [29]. To measure physical activity, we constructed 3 questions regarding engagement in light, moderate, and vigorous physical activities. Depression was measured with the depression subscale of the Patient-Reported Outcomes Measurement Information System (PROMIS-29) [30]. Sleep was measured with the 1-item sleep quality subscale of the PROMIS-29, and 3 items of the sleep disruption subscale of the Symptom Checklist-90-Revised [31]. The fatigue catastrophizing scale was adapted from the Pain Catastrophizing Scale [32], and measured by the rumination, magnification, and helplessness subscales.

Explanatory Factors

Explanatory factors were included as these were assumed to be potentially helpful for the interpretation of the study results. Patients' attitudes were assessed with questions about their expectations, motivations, and experienced support in their environment. Furthermore, as a proxy of impaired physical functioning, pain interference was assessed. Pain interference was measured with 2 items of the Research and Development Health Survey [33]. Perceived changes in levels of fatigue, overall QoL, physical activity, mood, and sleep were assessed with 1-item questions. User experience with the app was assessed to explore patients' attitudes toward and experiences with the Untire app. Cost-effectiveness was assessed to explore the costs and benefits of the Untire app (see Table 1).

In-App Log Data

Log data are used to explore the characteristics of app use. Once participants activated their unique access code and gave consent to the privacy terms in the Untire app, participants were registered, and their log data were stored anonymously. Log data are automatically stored data about the activities and assessments (ie, Quick scans and the Vase of Energy) that participants perform, and registers the date on which activities and assessments were performed. App use can be described based on (1) the duration of app use in days and (2) the degree of app use. Log data will indicate the first, and the last time a participant completed an activity and the number of days between the first and last activity will be used as a proxy for the duration of app use. The number of completed activities will be counted and will be used as a proxy for the degree of app use, with a higher number of completed activities indicating more app use.

Data Management

Data collection took place over the internet on the secured and password-encrypted server of Questback. Anonymous back-ups were saved on the secured and encrypted server of the UMCG, permitting only access to the involved researchers.

Statistical Analyses

Preparatory Analyses

We will present baseline characteristics (ie, demographics, disease, and treatment characteristics) for each variable side by side for the intervention and control groups by the mean (standard deviation), or frequencies and percentages.

Main Analyses

Does the Untire App Reduce Fatigue Significantly After 12 Weeks of App Access?

To examine a treatment effect of the app on fatigue, the data collected via Questback's Web-based survey of fatigue severity and interference will be analyzed using General Linear Mixed Models (GLMM) for 4 repeated measures (baseline, 4 weeks, 8 weeks, and 12 weeks), and 2 groups (intervention and control), following the intention-to-treat (ITT) approach. The ITT approach refers to analyzing all participants, regardless of app use, and is the primary approach in all outcome analyses. Assumptions of linearity, homogeneity of variance as well as the normal distribution of residuals of the model will be tested. The individual measures of fatigue ratings over time (level 1) are nested within each patient (level 2). The default GLMM model without a country factor will be compared with a model with a country factor concerning the best model fit using the Bayesian information criterion.

On the basis of previous studies testing health-related apps targeting behavior [34-39], we estimated the percentage of participants that would lose interest in the app or study assessments, and, therefore, would be lost to follow-up (eg, the 12-weeks measurement), at 60%. For the data analysis, we will, therefore, employ a model that can take missing data into account (ie, GLMM). A comparison of the outcomes of the model run in the ITT approach and the outcomes of a model

run among those who have completed at least the 12-week assessment (T12-completers) will demonstrate the robustness of the findings.

In addition to the model validation, we will carry out sensitivity analyses to determine whether the duration and the degree of app use are related to the degree of change in fatigue severity and interference over time. Outcomes of active users will be compared with less-active users. Active and less-active users are categorized according to the duration and degree of app use. The dose-response relationship of app use and treatment effects will be explored in a three-way interaction (time×group×activity level), using GLMM.

Secondary Analyses

Does the Untire App Improve Quality of Life Significantly After 12 Weeks of App Access?

To examine the treatment effect of the app on QoL, the data derived from the 2 QoL questions will be analyzed following the same analytic procedure as described above in the main analyses.

What Are the Reach, Costs of Online Recruitment, and What Is the Uptake and Usage of the Untire App (Study)?

To explore the number of participants reached using Web-based social media campaigns, we will use the number of Web-based advertisement link clicks, leading to the study landing page. To determine the costs of recruitment, the number of link clicks will be compared with the budget spent on social media campaigns. We will calculate the total costs of recruitment, the costs per person who clicked the link, and the costs per person that completed the baseline (study) assessment. To examine how many participants completed the assessments, activated the app, and used the app in the first 12 weeks of the study, percentages and count data will be used. Log data will indicate how many participants activated their unique access code, the number of days a participant has been active in the app, and the number of activities performed.

Which Factors Moderate, and Which Factors Mediate the Hypothesized Effect of the Intervention?

Moderating factors (ie, age, gender, and country) of the intervention effect of the app on CRF and QoL will be explored as a three-way interaction (time×condition×moderator variable) using GLMM as described above to gain insights into whether the intervention effect varies among different groups of participants, for example, patient with cancer versus survivor. Moreover, we will examine via longitudinal mediation analysis, whether levels of mindfulness, physical activity, depression, sleep, pain interference, and fatigue catastrophizing mediate the hypothesized effect of the intervention.

Sample Size

Sample size calculations for the primary outcome of fatigue showed that we needed to include 164 participants with complete 12-weeks measures in the intervention and the control group (total N=328) to detect a between-group difference in change from baseline to 12 weeks with a minimal effect size of η^2=0.10 (alpha=.05, 1−beta=.95). The sample size was calculated using the simplest between/within-group comparison (F tests—repeated measures analysis of variance [with within-between interaction]) in G*Power 3.1. With the inclusion of 820 participants (410 intervention participants; 410 control participants) and an estimated drop-out of (492/820) 60.0%, 164 participants are expected to remain in the intervention and 164 in the control group at the 12-week primary outcome measurement. The total baseline completer sample size of N=820 can be taken as a conservative upper bound as the final analyzes will be carried out using GLMM. GLMM takes more information into account and, thus, requires a smaller sample size given the same power.

Results

Throughout March and October 2018, patients with cancer and survivors (N=1137) were eligible and gave consent to participate in this trial. Of these, 847 participants started with the baseline questionnaire and were randomized into two conditions, following a 2:1 randomization with 545 participants assigned to the intervention group and 302 participants assigned to the control group. The last participants completed their 24-week assessment in March 2019.

Discussion

Principal Findings

This protocol describes an RCT to assess the effectiveness of the Untire app in reducing fatigue in patients and survivors of cancer after 12 weeks of app use as compared with a waiting list control group. Substudies nested within this trial include questions concerning the reach and costs of online recruitment and uptake and usage of the Untire app. There are advantages of stand-alone mHealth apps assumed, such as the immediate access to the app, the low thresholds to seek support via an app, and lower costs in supporting patients as compared with therapist-guided treatments.

The Untire app is based on a face-to-face therapy protocol, which was developed by the HDI in the Netherlands [25]. Although successful therapeutic elements have been used continuously over the years (eg, psychoeducation, CBT, physical activity, and mindfulness) [40], new ways of treatment delivery are increasingly being explored. For example, face-to-face treatment protocols have been effectively adapted to fit therapist-guided internet therapy [13]. More recently, the ingredients of the *More fit after Cancer* protocol were used to develop an adapted version in the form of a stand-alone app. The key therapeutic ingredients remained, but no supervision of a therapist is available. Apart from this shift to self-management, the app offers flexibility as the patients are allowed to choose from the entire library of education and exercises instead of following a structured week-by-week program. Although the app includes proven successful therapeutic elements, it is important to test its effectiveness as the delivery mode differs from previously tested interventions. If we do find the app to be effective, it can easily be offered worldwide to patients with cancer and survivors experiencing fatigue.

The findings will not only show whether or not the app is effective in reducing fatigue and improving QoL but will also provide more insight into the underlying mechanisms. Several routes may lead to a reduction in fatigue. For example, participants may gain vitality through improvements in the quality of their sleep, increases in physical exercise, and better management of their physical activities (eg, balancing activities throughout the day) [13]. Participants may also improve because they learn to better manage their unhelpful or catastrophizing thoughts about their fatigue, possibly through mindfulness [13]. Previous diary research has shown that such catastrophizing thoughts are associated with increases in negative affect and fatigue during the day [41]. This study will demonstrate whether improvements in these factors mediate hypothesized improvements in fatigue. Patients with specific problems concerning sleep or physical activity, or with respect to unhelpful and catastrophizing thoughts may benefit specifically from improvements in the respective areas.

Strengths and Limitations

The design of the study has both strengths and limitations. Strengths are its international focus and large scale, which will not only provide insight into the effectiveness of the app but also valuable information on the costs of online recruitment across different countries, the reach of patients who are interested in mHealth as a form of treatment for fatigue, and the uptake of the app. Costs of online recruitment might be hard to predict, as Facebook advertising campaigns cannot be targeted to patients with cancer directly. Patients with cancer can only be targeted indirectly based on shared interests in the field of cancer (eg, diagnosis, impact, and treatment of cancer). Furthermore, on the basis of the number of patients to be included, we hope to be able to conduct moderator analyses to determine whether the hypothesized intervention effect varies among different groups of participants (eg, patients with cancer versus survivors of cancer) and the context in terms of country where the intervention is delivered. The study contains a self-report eligibility check to include only patients with moderate and severe levels of fatigue, as these patients are hypothesized to benefit from the intervention. A drawback of our online recruitment procedure is the lack of access to hospital records, meaning that we cannot validate medical information (eg, type, duration, and treatment of cancer). Another study limitation is that remotely conducted automated mHealth studies regularly show large attrition rates [42]. Although high drop-out rates and sparing app use may be a natural characteristic, as the choice to discontinue usage is uncomplicated easy owing to the impersonal nature of the Web-based study and app assessments. We hope to counteract this mechanism by sending personal reminder emails to reinvite participants to complete the respective study assessments. Finally, the waiting list RCT will help to demonstrate causality (ie, can patients benefit from treatment versus no-treatment) and control for potential spontaneous improvements during the study period, but we cannot disentangle the effects of therapeutic elements and common factors (eg, attention). A drawback of using waiting list control designs might be that it artificially inflates intervention effect estimates as control participants could be influenced by design to literally *wait-to-change* and, thus, do not improve [43]. Using an active control condition could overcome this shortcoming but was not possible as an equivalent Web-based intervention was not available, and a comparison with therapist-guided treatment was not feasible owing to the international and large-scale character of the study.

Conclusions

This large-scale international RCT examines the effectiveness of the Untire app aimed at improving fatigue and QoL in patients and survivors of cancer. To provide more insight into the process of change, the study also tests the influence of several potential mediators such as physical activity, catastrophizing, and mindfulness. Moderator analyses will further our understanding of who benefits more depending on, for example, age, gender, and disease status. These findings will further improve the theoretical notions of fatigue in relation to other variables involved in facilitating or moderating change. In terms of practical implications, the findings will enable us to further improve the Untire app and similar interventions, for example, by giving more or less weight to specific therapeutic elements.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Ethical review and approval by country.
[DOCX File , 13 KB - resprot_v9i2e15969_app1.docx]

Multimedia Appendix 2
Subject information for participation in scientific research.

[DOCX File , 17 KB - resprot_v9i2e15969_app2.docx]

Multimedia Appendix 3
Informed Consent.
[DOCX File , 14 KB - resprot_v9i2e15969_app3.docx]

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Abbreviations

CBT: cognitive behavioral therapy
CRF: cancer-related fatigue
eHealth: electronic health
FSI: Fatigue Symptom Inventory
GLMM: General Linear Mixed Models
HDI: Helen Dowling Institute
ITT: intention-to-treat
MBSR: Mindfulness-Based Stress Reduction
mHealth: mobile health
PROMIS-29: Patient-Reported Outcomes Measurement Information System
QoL: quality of life
RCT: randomized controlled trial
UMCG: University Medical Center Groningen

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Protocol

Text Message Behavioral Intervention for Teens on Eating, Physical Activity and Social Wellbeing (TEXTBITES): Protocol for a Randomized Controlled Trial

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Abstract

Background: Obesity is among the most significant health challenges facing today's adolescents. Weight gain during adolescence is related to cardiovascular disease, type 2 diabetes, and some cancers in later life. Presently, adolescents living in Australia have limited access to age-appropriate obesity prevention services.

Objective: This study aims to investigate whether a two-way text message program, with optional telephone health counseling, improves body mass index (BMI) *z* score and lifestyle outcomes in adolescents who are overweight.

Methods: This study will be a single-blind randomized controlled trial (N=150) comparing a two-way text message intervention, with optional telephone health counseling, to usual care in adolescents (13-18 years old, inclusive) who are overweight (recruited from a pediatric weight management clinic and the broader community in Sydney, Australia). The intervention group will receive a six-month text message program, which consists of two-way, semipersonalized, lifestyle-focused text messages (four messages/week) in addition to usual care. The control group will be assigned to receive usual care. The study also includes a follow-up at 12-months. The primary outcome is a change in BMI *z* score at six months. Secondary outcomes are changes in waist-to-height ratio, diet, physical and sedentary activity levels, sleep quality, quality of life, self-esteem, self-efficacy, social support, and eating disorder and depression symptoms. Also, we will examine acceptability, utility, and engagement with the program through a study-specific process evaluation questionnaire, semi-structured telephone interviews, and an analysis of health counselor communication logs. The analyses will be performed by the intention-to-treat principle to assess differences between intervention and control groups.

Results: The study opened for recruitment in December 2019. Data collection is expected to be completed by December 2021, and the results for the primary outcome are expected to be published in early 2022.

Conclusions: This study will test the effectiveness of an interactive two-way text message program compared to usual care in improving BMI *z* score and lifestyle outcomes in adolescents with overweight. This interactive, innovative, and scalable project also aims to inform future practice and community initiatives to promote obesity prevention behaviors for adolescents.

Trial Registration: Australia New Zealand Clinical Trials Registry (ANZCTR) ACTRN12619000389101; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377158&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/16481

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KEYWORDS

obesity; adolescents; nutrition; physical activity; text message; randomized controlled trial; mHealth

Introduction

The global prevalence of obese and overweight adolescents has significantly increased over the last five decades, with 18% of the global population of children and adolescents being overweight or obesity in 2016 [1]. No developed countries have successfully halted the continuing upward trend in the prevalence of obesity and being overweight since 1980 [1]. For example, in 2017-2018, 25% of adolescents aged 12-17 years old and living in Australia, were overweight or obese [2]. Among older adolescents (16-17 years old) residing in Australia, there has been a 57% increase in the incidence of obesity in the last three years [2]. In the United States of America, 20.6% of adolescents aged 12-19 years old had obesity in 2013-2014 [3].

Preventing obesity during adolescence is important because adolescence is a life stage when risk factors and lifestyles are established [4,5]. Once obesity is established, weight loss and weight maintained after weight loss are difficult to achieve [6]. Consequently, gaining excess weight during adolescence is likely to lead to being overweight and obese in adulthood [7]. Weight gain during adolescence is associated with higher risk and earlier onset of cardiovascular disease [8], type 2 diabetes [9], and some cancers [10]. Moreover, adolescent obesity has adverse psychosocial outcomes, including weight stigma [11] and reduced quality of life and self-esteem [12]. Long term weight regulation is related to diet and physical behaviors that are adopted during adolescence and track throughout life [4]. Therefore, to halt the rise in the prevalence of overweight and obese adolescents, scalable, low-cost, and engaging strategies are needed.

Several lifestyle risk factors have been associated with excess weight gain during adolescence, and adolescents that are living in developed countries are not achieving national recommendations. Firstly, consuming the recommended intake of fruits and vegetables may prevent unhealthy weight gain [13], yet only 4% of adolescents living in Australia, aged 12-17 years old, meet national guidelines for fruit and vegetable intake [2]. Secondly, adolescents remain the highest consumers of discretionary foods and sugar-sweetened beverages, despite the evidence that consumption increases the risk of obesity and being overweight [14,15]. In Australia and the United States, over 60% of adolescents drink a sugar-sweetened beverage daily, adding 143 kilocalories per day. Moreover, discretionary foods account for a significant portion of adolescents' total energy intake (>40% in Australian adolescents) [16]. Finally, short sleep duration [17], insufficient physical activity levels, and increased screen time are associated with an increased risk of obesity [18,19]. Both physical activity and sedentary screen-based behavior guidelines are met by less than 4% of adolescents aged 13-17 years old [20], and night-time technology use can have harmful effects on adolescent sleep duration [21].

Despite the apparent risk for weight gain during adolescence, evidence to inform effective interventions for this population is lacking. A 2019 Cochrane review of 31 randomized controlled trials (RCTs) testing the effectiveness of a range of interventions, which included diet or physical activity components or both, designed to prevent obesity in adolescents found limited effective interventions for adolescents aged 13-18 years old [22]. There has been more investment in childhood obesity prevention research, with over 85 RCTs conducted in children aged 6-12 years old. Moreover, the diet and physical activity strategies delivered to adolescents in the studies did not reduce their body mass index (BMI) *z* score, and there has been limited investigation of digital intervention modalities. Current attrition rates for traditional, in-person obesity prevention and management interventions in adolescents remain highly variable, with 27% to 73% of participants dropping out of interventions for reasons including the intervention not meeting the adolescent's expectations [23,24]. Digital technology has been identified as an engaging intervention modality for overweight and obese adolescents [25]. Thus, mobile phone interventions hold promise for delivering interventions that are scalable, low-cost, and engaging.

Currently, over 90% of adolescents living in Australia and the United States own a mobile phone [26,27], and text messaging remains a primary means of communication between adolescents [27]. There is a small body of evidence which indicates one-way text message interventions can promote weight loss in adults [28]. Emerging research has shown that text messages are a feasible and acceptable form of communication in interventions for adolescents with obesity [29-32]. However, there is limited high-quality evidence for the role of two-way text messages to improve obesity prevention behaviors in adolescents who are overweight. Therefore, the primary aim of this study is to test the effectiveness of a two-way, semipersonalized text message program, with optional health counseling, compared to usual care for improving adolescents' BMI *z* score. This study also aims to determine if the text message program can improve lifestyle outcomes. The study will also examine acceptability, utility, and engagement with the program.

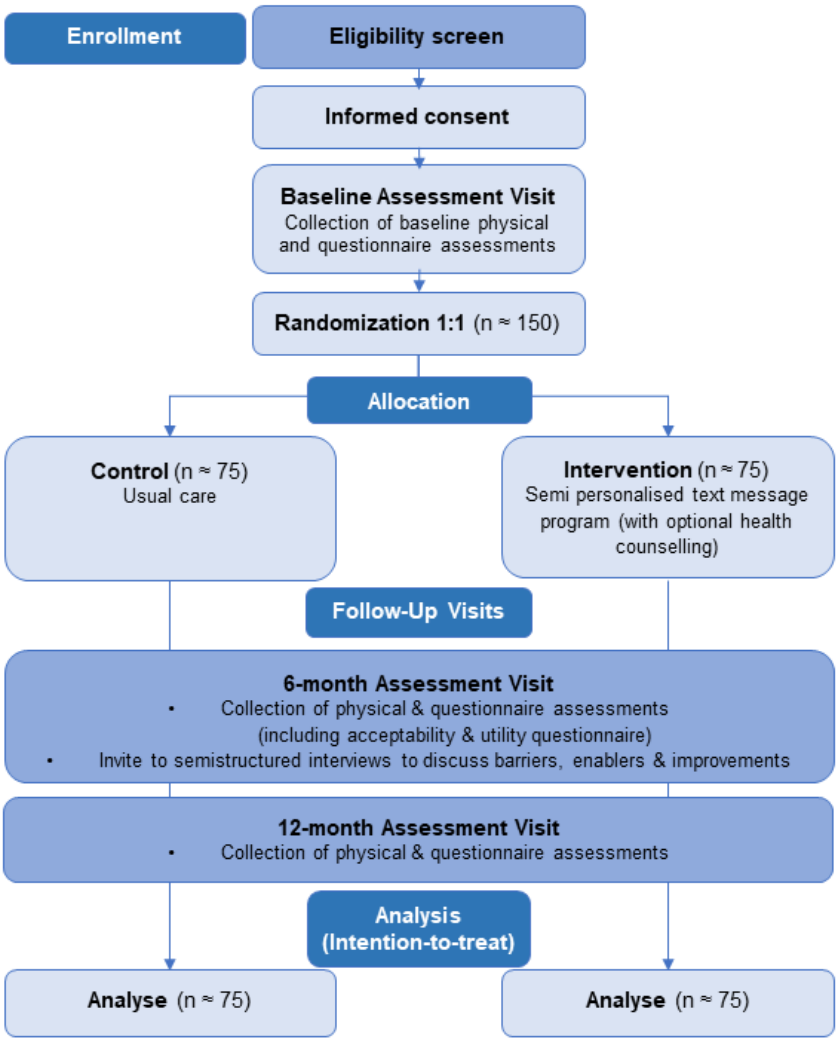
Methods

Study Design

The TEXTBITES (TEXT message Behavioral Intervention for Teens on Eating, physical activity, and Social wellbeing) study is a single-blind, multi-center, randomized controlled trial, which delivers a six-month obesity prevention program via text messages to adolescents who are overweight. The study also includes a twelve-month follow-up (Figure 1). The sites include

public hospitals and a pediatric weight management clinic at a public children's hospital in Sydney, Australia. Participants will be recruited via referral from the pediatric weight management clinic, and from the local community via print and digital advertisements at community centers, high schools, and tertiary education providers. A log of all recruitment strategies utilized will be kept. The target sample size is 150 adolescents aged 13-18 years old inclusive, who are overweight. Participants will be randomly allocated to either a control or intervention group. The control group will be assigned to receive usual care. For this study, usual care is defined as accessing available health services and information for adolescent obesity prevention. The intervention group will be allocated to receive the six-month, two-way text message program for obesity prevention that provides practical tips and information, motivation, and support for lifestyle modification for healthy eating, physical activity, and mental wellbeing behaviors, in addition to usual care. Trained research personnel blinded to the group allocation will conduct assessments at baseline, six-, and twelve-months during a face-to-face interview.

Figure 1. Flow chart of study design. Adolescent participants 13-18 years, with overweight are considered for inclusion in the study and randomization is single blind, with allocation determined and initiated by the computerized program.



Randomization and Blinding

After obtaining written informed consent from adolescents and their parents or guardians (if <18 years old) and completing the baseline assessment, the research assistant will enter the data into a secure web-based database. Then randomization will occur via a centralized, computerized randomization program in a uniform 1:1 allocation ratio (control: intervention). Randomization is based on a permuted randomized block design, where the strata are gender, age, and recruitment site. The randomized block method contained block sizes of 2 and 4 in a ratio of 2:1 to minimize imbalance in small strata groups. A randomization list was generated by an independent statistician using RandomiseR package [33] within the R computing environment (The R Foundation, Vienna, Austria). For each participant, the computer system automatically produces a study identification number, which will be used on all study documents. On the following Monday, after the baseline visit, the computer system automatically sends the assigned text message program to the participant. Therefore, the researcher conducting all face-to-face assessments remains blind to the study allocation. As an additional precaution and for safety

purposes, there will be an independent, unblinded researcher monitoring all incoming text messages.

A 20% (30/150) subsample of participants will be randomly assigned to wear an accelerometer for seven days to validate the self-reported physical activity questionnaire. These participants will receive a second layer of randomization, which will be nested within each treatment arm at a ratio of 1:5. A total of 15 participants with accelerometers will be in the text message intervention group, and 15 participants will be in the control group.

Study Population

Participants will be eligible to participate if they are: (1) 13 to 18 years old inclusive; (2) are overweight, defined by the International Obesity Task Force as equivalent to an adult BMI of 25.0-29.9 kg/m^2 [34,35]; (3) own an operational mobile phone that is capable of sending and receiving text messages; and (4) provide written informed consent themselves or provide written informed consent from their parents or guardians (if <18 years old).

Participants will be excluded if they: (1) have a diagnosis of Type 1 diabetes or Type 2 diabetes; (2) have a medical condition or psychiatric illness that would not allow the participant to give informed consent or would preclude the participant's ability to comply with the study protocol; (3) a history of disordered eating, including being diagnosed with, or treated for, Anorexia nervosa or Anorexia athletica, Binge Eating Disorder, or Bulimia nervosa; (4) are pregnant, or are planning to become pregnant within the next 12 months; (5) are on weight loss medications or any medications known to cause weight gain; (6) are enrolled in an alternative randomized weight management program; (7) are already participating in a text message-based study; or (8) cannot speak English. The team will keep recruitment and screening logs for those people who are ineligible or decline to participate, with basic demographic information and reasons for nonparticipation.

Control Group

The control group will receive usual care. For this study, usual care is defined as accessing available health services and information for adolescent obesity prevention, as outlined in the clinical practice guidelines for overweight and obese adults, adolescents, and children in Australia [36]. Participants in the control group will receive an initial text message welcoming them to the study. However, they will not receive the text message support program or health counseling telephone calls. The control group will also receive a text message reminder approximately six- and twelve-months after their enrolment, notifying them that they will be contacted to schedule their six- and twelve-month follow-up visits, respectively. Participants in the control group will be offered the opportunity to receive the text message support intervention (no health counseling) at the end of the study (twelve-month visit) if they wish.

Intervention Group

Overview

The intervention group will receive usual care, plus a text message support program that includes a series of text messages focused on lifestyle modification for obesity prevention, as well as an opportunity to speak with an English-speaking health counselor over six months, as detailed below.

Message Content, Frequency, and Sequence

The text message content was co-designed with adolescents and research/health professionals and using established scientific methods [37]. The bank of 107 unique text messages are based on seven behavior change techniques with demonstrated effectiveness in adolescent obesity prevention interventions [38], and on evidence-based health information found in current national obesity prevention, nutrition, and physical activity guidelines [36,39,40]. Findings from previous text message development research with adolescents were also applied to ensure the text message style and language were appropriate and engaging for adolescents [31,32,41,42].

Each intervention participant will receive a customized and semipersonalized set of text messages sent on four random days per week, including one weekend day, and at random times (Table 1). Each unique text message will only be sent only once during the 6-months. If the participant is attending high school, the weekday text messages will only be sent before or after school hours (8:00 AM to 9:00 AM or 3:30 PM to 7:30 PM). Text messages are based on four priority areas, namely, healthy eating behaviors (n=26), physical activity behaviors (n=18), mental wellbeing (n=21), and general behaviors (n=34), and a total of 6 text messages prompt communication with the health counselor. One welcome message and one final text message are included in the bank of 107 text messages. General behavior messages are focused on the environmental impact of eating and activity, food environment, time management, and practical tips.

The text messages will be semipersonalized by using the participant's name and selecting text message content relevant to the participant's characteristics, such as age. Participants can also update their personal information (eg, mobile phone number or change in school attendance) throughout the study. Messages are sent at no cost to the participants; however, text message replies to the study team will be paid for by the participant at standard short message service (SMS) rates set by their mobile phone provider. The intervention will encourage two-way communication, with participants monitored by the health counselor on weekdays. All replies and responses will be reviewed in regular weekly team meetings.

Table 1. Examples of text messages sent to the intervention group.

Text message category	Example text message
Introductory	*Hi [pref_name][a], welcome to the TEXTBITES[b] study. We hope you find the program fun and helpful. If you have any questions throughout the program, text us or call. We are here to support you! If you ever want to stop the messages, respond STOP to opt-out.*
Physical activity	*Need a dose of some happy hormones? Stretching can release endorphins, reduce your stress and make you feel great. The best part? You can do it anywhere, even while watching TV or YouTube. Check it out: tinyurl.com/stretchyout.*
Nutrition	*Corn isn't just a tasty snack, it's multi-purpose! It can be used to make fireworks, glue, paint & plastic. But let's face it, popcorn is one of the best uses, check out some recipe ideas here: tinyurl.com/airpopcorn.*
Mental wellbeing	*Your brain has 86 billion thinking cells (called "neurons") & 80 billion or so supporting cells. Wow, that's a lot! No wonder they need a break at night to rest & recover. Make sure to give them 8-10 hours rest each day!*
General behaviors	*Want to get your homework or study done in record time? Do power bursts! Put your phone on do not disturb and power it out for 25 min. Take a 5 min break (yep, you can check your phone) and repeat until your work is done!*
Health counselor	*How is everything going, [pref_name]? Text back if you would like to chat with our health counsellor about all things food, exercise and wellbeing and we will get back to you soon.*
Final	*This is your last message from the TEXTBITES study. Thank you for being a part of the program, we couldn't have done it without you! We will contact you shortly to arrange your 6-month follow-up interview. Thanks again from the TEXTBITES study team!*

[a]pref_name: participants preferred first name

[b]TEXTBITES: TEXT message Behavioral Intervention for Teens on Eating, physical activity, and Social wellbeing

Role of the Health Counselor

Once a month, over six months, intervention participants will be sent a text message encouraging them to call the university-qualified health counselor to ask questions or request additional information (Table 1, example, two-way communication messages). The health counseling calls will employ complementary theoretical approaches to the text messages, including motivational interviewing, goal setting, self-monitoring, barrier identification, and problem-solving [43,44]. The personalized health counseling calls will last 10-15 minutes and will be delivered according to a standardized protocol. The university-qualified health counselor (allied health professional) will monitor and respond to participants' request for a call each month, either via text message or phone call, within three working days. Participants are allowed a total of six health counseling calls in total over six months. The health counseling calls will enable participants to set behavioral goals, discuss barriers and enablers to behavior change, and their overall progress. This part of the intervention is based on the evidence based TEXTMEDS (TEXT messages to improve MEDication adherence and Secondary prevention) study for secondary prevention of heart disease [45].

Text Message Management System

The text message management system was developed in conjunction with the text message intervention to support women's physical and mental health after breast cancer treatments study and has similar processes [46]. Each week messages will be selected from the message bank by the software sequencer system that ensures that participants are receiving the correct messages (intervention vs control). Both intervention and control groups will receive a welcome text message at the beginning of the study and a concluding message at the end of the 6-months. Each text message will have a unique signature to ensure that participants know these messages are from the TEXTBITES study. All participants will be given brief training at baseline on how to read, delete, and save a text message, and how to unsubscribe if required. Training will also include safe and acceptable times to read the text messages (eg, reminding participants they must not read the text messages or use any other mobile phone functions if they are driving). All participants will also be provided with the research personnel's contact details and will be contacted at least once during the intervention period to organize the six-month follow-up assessment and once during the follow-up period to facilitate the twelve-month follow-up assessment.

A researcher will manage a study mobile phone, and a record will be kept of any incoming messages from participants, and all out-going replies from the study health counselor throughout the study. Any analysis of these incoming text messages will be performed at the group level, except for reporting examples of individual quotes, which will be anonymized to protect the participant's identity. Participants from either group can withdraw from the study at any time with or without giving a reason by replying "STOP" to any of the messages or contacting a member of the research team, which will activate a process of review and withdrawal from the study. If a reason for withdrawal is provided, it will be recorded.

Data Collection and Study Outcomes

The in-person follow-up assessments will occur at the end of the six-month intervention period and the end of the six months post-intervention (twelve months from baseline). The primary outcome, secondary outcomes, and their assessments are presented in Table 2. The primary outcome is a change in BMI *z* score (units BMI is above or below average for age- and

sex-specific reference values) measured using calibrated stadiometer and electronic scales. BMI is calculated as weight (kg)/[height (meters)^2]. Bodyweight and height will be measured to the nearest 0.1 kilogram and 0.1 centimeter, respectively, at each assessment time point by the research assistant, who is blinded to participant allocation and is using a standardized protocol [47]. Waist-to-height ratio will be measured to the nearest 0.1 centimeter using a nonstretch plastic waist measurement tape, midway between the iliac crest and the lowest rib, and a calibrated stadiometer.

Table 2. Description of TEXTBITES study outcomes and assessments.

Outcome	Assessment
Primary outcome	
BMI[a] *z* score	Units BMI is above or below average for the age- and sex-specific reference values measured using calibrated stadiometer and electronic scales [47].
Secondary outcomes	
Waist-to-height ratio	The midway measurement between the iliac crest and lowest rib and height, measured using a non-stretch plastic waist tape and a calibrated stadiometer [47].
Adherence to dietary guidelines	Short questions adapted from the New South Wales Population Health Survey [48]
Diet quality, food choices and food patterns	ACAES[b] Survey [49]
Physical activity	Validated short physical activity question and study-specific sports participation questions [50]
Sedentary activity	Modified ASAQ[c] [51-53]
Objective physical activity	Actigraph GT3X+ activity monitors worn for seven days [54,55]
Sleep quality	PSQI[d]-Short [56,57]
Quality of life	PedsQL[e] Version 4.0 Generic Core Scales questionnaire [58]
Self-esteem	Rosenberg Self-Esteem Scale [58]
Self-efficacy	Short questions adapted from the Project Eat Survey II [59]
Social support	Short questions adapted the social support and eating habits survey [60] and Social Support Scale for Physical Activity [61]
Eating disorders	EDE-Q[f] [62]
Depression	CESDR-10[g] [63]

[a]BMI: body mass index

[b]ACAES: Australian Child and Adolescent Eating Survey

[c]ASAQ: Adolescent Sedentary Activity Questionnaire

[d]PSQI: Pittsburgh Sleep Quality Index

[e]PedsQL: Pediatric Quality of Life Inventory

[f]EDE-Q: Eating Disorder Examination questionnaire

[g]CESDR-10: Centre for Epidemiological Studies Depression Scale-Revised-10

The following questionnaire-based assessments have demonstrated validity and reliability in adolescent populations and will be completed online at the in-person follow-up assessment. Diet quality, food choices, and food patterns will be measured using the Australian Child and Adolescent Eating Survey (ACAES) [49], and adherence to dietary guidelines will be measured using short questions adapted from the North-South Wales Population Health Survey [48]. Physical activity and sedentary behaviors will be measured using a validated short physical activity question, study-specific sports participation questions [50], and a modified version of the Adolescent Sedentary Activity Questionnaire (ASAQ) [51-53]. For data quality, physical activity and sedentary behaviors will also be objectively assessed in a random 20% (30/150) subsample of participants using Actigraph GT3X+ activity monitors worn for seven days [54,55]. Sleep quality, quality of life, and self-esteem will be measured using the Pittsburgh Sleep Quality Index Short (PSQI-Short) [56,57], the Pediatric Quality of Life Inventory (PedsQL) Version 4.0 Generic Core Scales questionnaire [58], and the Rosenberg Self-Esteem Scale [58], respectively. Self-efficacy will be assessed using a questionnaire adapted from Project Eat Survey II [59], and social support will be assessed using a questionnaire adapted from the social support and eating habits survey [60] and the Social Support Scale for Physical Activity [61]. Eating disorders will be measured using the Eating Disorder Examination Questionnaire (EDE-Q) [62], and depression will be measured using the Centre for Epidemiological Studies Depression Scale Revised-10 (CESDR-10) [63]. The schedule of enrolment, interventions, and assessments are presented in Table 3.

Table 3. TEXTBITES study schedule of enrolment, interventions, and assessments.

	Enrolment	Allocation	Postallocation		
Assessments	Before baseline ($-t_1$)	Timepoint 0	Baseline (t_1)	6-months (t_2)	12-months (t_3)
Enrolment					
Eligibility screen	✓				
Informed consent	✓				
Allocation		✓			
Interventions					
Intervention group			✓	✓	
Control group			✓	✓	
Assessments					
BMI[a] *z* score			✓	✓	✓
Waist-to-height ratio			✓	✓	✓
Adherence to dietary guidelines			✓	✓	✓
Diet quality, food choices and food patterns			✓	✓	
Physical activity			✓	✓	✓
Sedentary activity			✓	✓	✓
Objective physical activity			✓	✓	✓
Sleep quality			✓	✓	✓
Quality of life			✓	✓	✓
Self-esteem			✓	✓	✓
Self-efficacy			✓	✓	✓
Social support			✓	✓	✓
Eating disorders			✓	✓	✓
Depression			✓	✓	✓

[a]BMI: body mass index

Process Measures

The adolescents' acceptability, utility, and engagement with the two-way semipersonalized text message intervention and interaction with a health counselor will be measured using a study-specific, process evaluation questionnaire, and semistructured telephone interviews. All intervention participants will be asked to complete the process evaluation questionnaire at their 6-month follow-up assessment. The questionnaire will include questions regarding acceptability and utility that require Likert responses from strongly agree to strongly disagree. It also includes open-ended questions about the most useful and least useful components of the program, as well as suggestions to improve the program. Measures of engagement with the program will be extracted from the text message management system, including the number of text messages sent and replies received. At the 6-month follow-up, both control and intervention participants will be asked if they accessed any other health-related information or programs regarding weight management or lifestyle behavior change. Intervention participants will be invited in person, or by telephone, to take part in a semistructured telephone interview at six-months. A minimum of 15 interviews will be conducted and will be consecutive until no new themes or categories emerge (thematic saturation). However, it is anticipated that at least 30-40 participants will be invited to take part. These interviews will be conducted by telephone and will last approximately 30 minutes. Participants will be purposively selected to ensure that a variety of views are explored and to obtain a mix of participants in terms of age and ethnicity.

Statistical Considerations

Modest reductions in BMI *z* score (0.01-0.15) in adolescents have been associated with improvements in several cardiovascular risk factors and are considered to be clinically meaningful [64]. The population SD for this power calculation was obtained from a contemporary Australian RCT in adolescents [65]. To test for a change in BMI *z* score of 0.15 (SD 0.27) [65] in the intervention group at six-months, compared with the control group, for 80% power (type I error=5%, two-sided test), 1:1 randomization, and accounting for a conservative 30% dropout-rate based on a recent systematic literature review [66], we will require 150 participates (75 participants per group).

Baseline demographic characteristics, attrition rates, and the average number of text messages sent and received for

participants will be tabulated and compared using descriptive statistics. Categorical variables will be summarized using totals numbers and percentages. Continuous variables will be summarized using mean and standard deviation for normally distributed data, or median and interquartile range for data that are not normally distributed. The baseline characteristics of completers and noncompleters will be compared to examine attrition bias, using two-tailed *t* tests for continuous variables and chi-square tests for categorical variables. Actigraph GT3X+ accelerometer data will be captured in 1-15 second epochs to capture the intermittent activity patterns of adolescents and downloaded using the ActiLife software into an excel spreadsheet. Time spent in different physical activities will be evaluated by classifying the intensity level using count thresholds specific to adolescents [54,55].

The primary analysis will include all available participant data and will be performed at the end of the study after all the data has been collected. The analysis of the primary and secondary outcomes will be conducted according to the intention-to-treat principle. Continuous outcomes will be analyzed at six- and twelve-months using analysis of covariance (ANCOVA), adjusting for baseline measurement of the outcome, gender, and recruitment site/strategy. Categorical outcomes will be analyzed at six- and twelve-months using log-binomial regression and adjusting for baseline measurement of the outcome, gender, and recruitment site/strategy. Planned subgroup analyses will investigate interactions between treatment and subgroups, including categories of age, socioeconomic status, and ethnicity, to explore trends for future studies. A significance level of 0.05 will be used. All analyses will be undertaken using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, United States).

Process evaluation data, including questionnaire data, interview data, and text message management data, will be analyzed using mixed methods. Descriptive analysis will be used to examine questionnaire data and software analytics. Interviews will be conducted by a trained qualitative interviewer, digitally recorded and transcribed. Interview data will be analyzed thematically, and coding based on emergent themes using the NVIVO Software program, version 12 (QRS International Pty Ltd, Victoria, Australia).

Dissemination

The study findings will be disseminated via peer-reviewed publications and presentations at national and international conference meetings. Results will also be presented and communicated appropriately to relevant adolescent and consumer groups.

Ethical Approval and Consent to Participate

Formal ethical approval for this study has been obtained from the Sydney Children's Hospitals Network Human Research Ethics Committee (approval number HREC/18/SCHN/374). The current protocol version is Version 2.0 (March 20, 2019). Written and informed consent will be collected from all participants and their parents/guardians (if they are <18 years old). The study is sponsored by the University of Sydney and managed by staff based there. The sponsor has no role in the study design, the collection, management, analysis, and interpretation of data, the writing of the findings, or the decision to submit the findings for publication. The design and conduct of the study will be overseen by a steering committee (authors). This study will adhere to the Australian National Health and Medical Research Council ethical guidelines for human research, and the study will follow the Consolidated Standards of Reporting Trials guidelines [67].

Results

Recruitment for the trial will start in December 2019 and is expected to run until the end of 2020. Data collection is expected to be complete by December 2021, and dissemination of trial results is planned after that. The results on the primary outcome are expected to be ready during early 2022.

Discussion

Primary Findings

The study will evaluate an innovative means of delivering a simple obesity prevention program to adolescents who are overweight and are at risk of obesity using an RCT. It is hypothesized that the intervention group will see improvements in primary and secondary outcomes compared to control post-intervention (six-months) and at follow-up (twelve-months). If effective, this study will inform translational research to improve BMI and lifestyle outcomes for adolescents, and to prevent the transition to obesity in young adulthood. Results of the process evaluation will assess the barriers and enablers to widespread implementation of the text message program, with the ultimate goal of providing adolescents with age-appropriate, evidence-based, and accessible obesity prevention services.

The simple and innovative text message program addresses a critical gap in obesity prevention for adolescents, given their risk of future chronic diseases. Text messages are an appropriate and accessible intervention delivery modality for this population group. The benefit of text messages is that they do not require an internet connection to receive, offer an interactive modality to communicate with health professionals, can be delivered with minimal personnel, and may provide a socially equitable intervention for most adolescents. As such, text message interventions show the potential to reduce socioeconomic disparities in health care and deliver a scalable, low-cost intervention to a wide population. To date, there have been only eight RCTs investigating text messages for obesity prevention or management in adolescent populations [30,68-74]. The interventions were mostly multicomponent mobile health interventions, and there was limited process evaluation data to help understand the effects of the text message component. Taken together, currently, there is limited high-quality research investigating obesity prevention interventions delivered via text message for adolescents. Hence, the TEXTBITES study aims to address this research gap.

Conclusion

This study will test the effectiveness of a six-month text message intervention to improve BMI and lifestyle outcomes for adolescents who are overweight and at risk of obesity. If

effective at improving BMI and lifestyle outcomes, the results will provide evidence to inform future practice and community initiatives to promote obesity prevention behaviors for adolescents, and ultimately be translated to help all adolescents nationally and internationally.

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Authors' Contributions

All authors were involved in the conception of the study design and reviewing the final manuscript; KH informed the sample size calculations and analysis methods; ethical approval was sought by SRP, KH, AG, CC, and JR. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACAES: Australian Child and Adolescent Eating Survey
ASAQ: Adolescent Sedentary Activity Questionnaire
ANCOVA: analysis of covariance
BMI: body mass index

CESDR-10: Centre for Epidemiologic Studies Depression Scale-Revised
EDE-Q: Eating Disorder Examination questionnaire
PedsQL: Pediatric Quality of Life Inventory
PSQI-Short: Pittsburgh Sleep Quality Index Short
RCT: randomized controlled trial
SMS: short message service
TEXTMEDS: TEXT messages to improve MEDication adherence and Secondary prevention
TEXTBITES: TEXT message Behavioral Intervention for Teens on Eating, physical activity, and Social wellbeing

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Protocol

A Smartphone App for Self-Monitoring of Rheumatoid Arthritis Disease Activity to Assist Patient-Initiated Care: Protocol for a Randomized Controlled Trial

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Abstract

Background: Telemedicine based on self-measurement of disease activity could be one of the key components to create the health care system of the future. Previous publications in various medical fields have shown that it is possible to safely telemonitor patients while reducing the number of outpatient clinic visits. For this purpose, we developed a mobile phone app for patients with rheumatoid arthritis (RA), which allows them to self-monitor their disease.

Objective: The objective of this study is to assess the safety and efficacy of self-initiated care assisted by a smartphone app in patients with RA.

Methods: This is a randomized controlled trial that will be performed for 1 year. A total of 176 patients with RA will be randomized to either self-initiated care with only one scheduled follow-up consultation assisted by our app or usual care. The coprimary outcome measures are the number of outpatient clinic consultations with a rheumatologist taking place during the trial period and the mean disease activity score as measured by the disease activity score 28 (DAS28) at 12 months. The secondary outcomes are patient satisfaction, adherence, patient empowerment, and cost evaluation of health care assisted by the app.

Results: Recruitment started in May 2019, and up to 18 months will be required for completion of recruitment. Thus far, 78 patients have been randomized, and thus far, experiences with the app have been positive. The study results are expected to be published by the end of 2021.

Conclusions: The completion of this study will provide important data regarding the following: (1) safety of self-initiated care supported by a smartphone app in terms of DAS28 and (2) efficacy of lowering health care usage with this new strategy of providing health care.

Trial Registration: Netherlands Trial Register NL7715; https://www.trialregister.nl/trial/7715

International Registered Report Identifier (IRRID): DERR1-10.2196/15105

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KEYWORDS

smartphone app; telemonitoring; rheumatoid arthritis

Introduction

Background

Rising health care costs, increasing elderly population size, and shortage of medical personnel have forced us to think about alternative ways to organize our health care system. The use of information technology tools (eHealth) may lead to better outcomes while reducing costs [1]. One suggested use for eHealth is asynchronous telemonitoring. In this form of telemonitoring, patients are monitored without face-to-face or real-time contact with a physician. Various studies with asynchronous telemonitoring have been performed in patients with inflammatory bowel disease (IBD) [2], asthmatic diseases [3,4], and diabetes mellitus [5], with positive results. However, for patients with rheumatoid arthritis (RA), clinical evidence for the use and safety of asynchronous telemonitoring is lacking [6].

Currently, patients are monitored in outpatient clinics according to the European League Against Rheumatism (EULAR) treat-to-target guidelines for RA. The guidelines state that measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently, such as every 6 months, for patients with sustained low disease activity or those in remission [7]. On one hand, the value of most consultations is low, as 75% of patients in routine clinical follow-up have low disease activity or show remission [8]. On the other hand, individuals with RA may experience occasional increases in inflammation between routine clinical visits, which are associated with worsening symptoms, and these are referred to as flares [9]. Moreover, patients with RA characterize flares as unpredictable intense episodes that make them feel helpless [10]. Frequent self-monitoring of disease activity combined with self-initiated care could lead to the early identification of flares and treatment intensification while reducing appointment frequency for stable patients. Furthermore, with implementation of such measures, patients with RA may benefit from reduced travel time, less work leave, and possibly reduced health care costs.

There are already many smartphone apps available for self-monitoring of RA. However, high-quality apps are lacking [11]. For instance, integration with electronic medical record (EMR) systems is practically nonexistent. Therefore, we developed a new app. The developed app requests patients to fill in a Routine Assessment of Patient Index Data 3 (RAPID3) questionnaire weekly for self-measurement of RA disease activity [12,13]. If disease activity assessment indicates flares, patients are instructed to contact the outpatient clinic through the app. We expect the app to support self-initiated care and to help achieve better disease activity management between scheduled clinic visits.

Objective

The objective of this paper is to report a protocol for a randomized controlled trial (RCT) that will test if we can safely (noninferiority in terms of Disease Activity Score [DAS] 28) reduce the number of outpatient clinic visits in patients with RA who self-monitor their disease. If the results confirm our hypothesis, we aim to implement our telemonitoring strategy in the Dutch health care system.

Methods

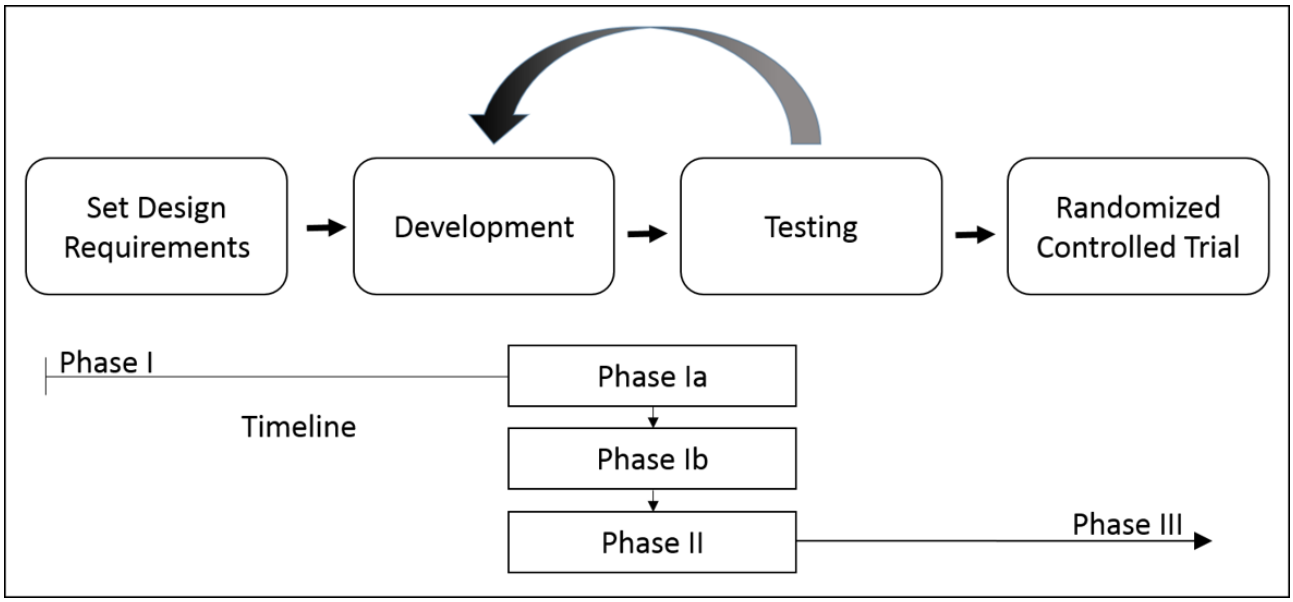
Overview

The study will take place at Reade, a secondary rheumatology clinic in Amsterdam, the Netherlands. Reade developed the smartphone app together with the software company Brightfish BV (Amsterdam, the Netherlands), which offers advice and assistance to ensure that important standards for cybersecurity, software design, and software maintenance are met [14]. The city of Amsterdam along with its surroundings is an ideal setting for this study, as network coverage in the Netherlands is excellent, reaching as high as 96.8%, overall, and 100% in Amsterdam [15]. Furthermore, over 87% of the Dutch adult population owns a smartphone, and the mobile download speed currently ranks sixth worldwide [16,17].

Design, Test, and Redesign

Following the Medical Research Council guidance for developing and evaluating complex interventions, the development and evaluation of the app was carried out in three distinct phases, which will be described in detail elsewhere (manuscript in preparation) [18]. The process is presented in Figure 1. Only the protocol for an RCT (phase III) will be reported here. The manuscript of the development process and pilot studies is in preparation [19].

Figure 1. The design, test, and redesign approach in three distinct phases. In phase I, the app was developed and tested twice. A prepilot check (Ia) was performed to test usability. Subsequently, the app was tested in a mixed-methods pilot study (Ib). In phase II, further development was performed and the new app was re-evaluated with another mixed-methods pilot study (manuscript of pilot studies in preparation) [19].



Phase III: Protocol for a Randomized Controlled Trial

In the third phase of the development process, an RCT will be performed. In this 1-year study, the safety and efficacy of self-initiated care assisted by our app will be evaluated. The proposed work process has been thoroughly evaluated with physicians, researchers, and two patient partners. Multiple meetings have been held to adjust and improve the process, with involvement of patients and rheumatologists in each step. Ultimately, all stakeholders agreed on the strategy, and therefore, we anticipate successful implementation of this proposed renewed health care design, if it is clinically proven to be successful.

The trial has been registered at Trialregister.nl, a publicly available and freely searchable register for studies in the Netherlands. The study has been approved by the research ethics committee of the Amsterdam UMC. A total of 176 patients will be recruited at the outpatient clinic of Reade, a center for rehabilitation and rheumatology in Amsterdam, the Netherlands. As over 3000 patients with RA are currently receiving outpatient clinic care at Reade, adequate recruitment is expected to be feasible.

MijnReuma Reade App (MyRheumatism App)

The built app aims to collect self-assessment questionnaire data every week (Table 1). The user is prompted by weekly reminders sent by the app to fill out the questionnaire. If the user does not fill out the questionnaire, another reminder is sent after 24 hours. If the questionnaire is still not complete, another reminder is sent 1 week after the initial reminder. The app presents outcomes over time in a graph and provides access to patient medical records and information regarding RA (Figure 2). When a user completes the questionnaire, the data from the app are transmitted securely (transport layer security) to secure servers on the hospital premises. The servers are connected to the Reade EMR system. Data handling is fully compliant with all relevant Dutch privacy and security laws, including ISO27001 and General Data Protection Regulations. In the EMR system, numerical scores and a graph of the self-assessment questionnaire data over time can be viewed by Reade health care professionals (Figure 3).

Table 1. Self-assessment questionnaire in the MijnReuma Reade App.

Domain	Measure	Number of questions
Function[a]	mHAQ[b]	10
Pain[a]	NRS[c] (0-10)	1
Patient-Global[a]	NRS (0-10)	1
Fatigue	NRS (0-10)	1
Morning stiffness	Minutes	1
Social participation	Likert scale (0-3)	1
Sleep	Likert scale (0-3)	1
Anxiety	Likert scale (0-3)	1
Stress	Likert scale (0-3)	1
Flare question	Yes/no	1

[a]These items together form the Routine Assessment of Patient Index Data 3.

[b]mHAQ: modified health assessment questionnaire.

[c]NRS: numeric rating scale

Figure 2. The MijnReuma Reade App. Five separate screenshots illustrate the simple and comprehensive design and interface of the app. The second screenshot from the left portrays one of the disease activity graphs.

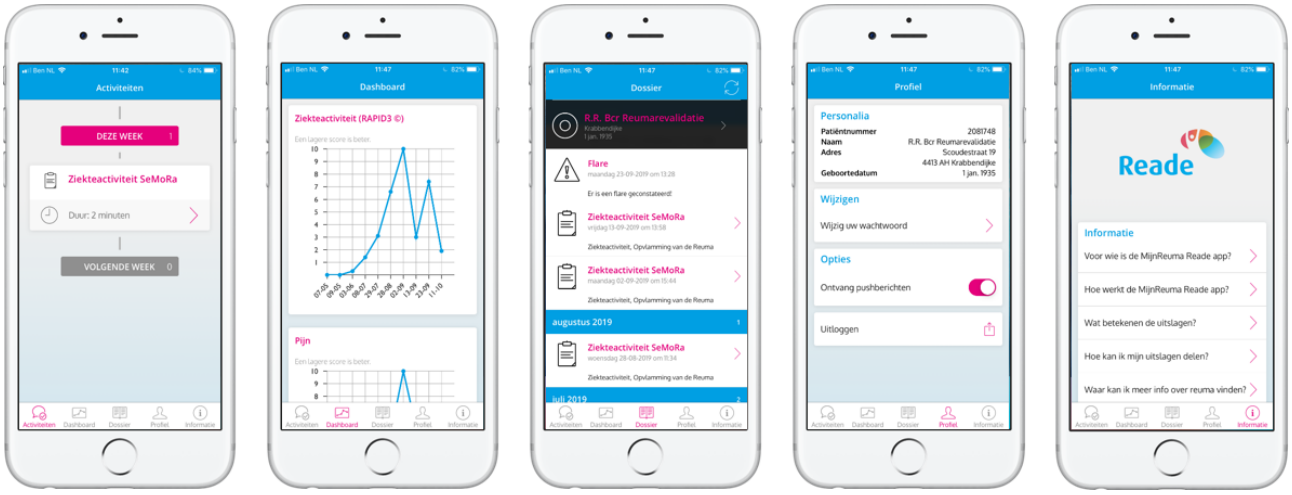
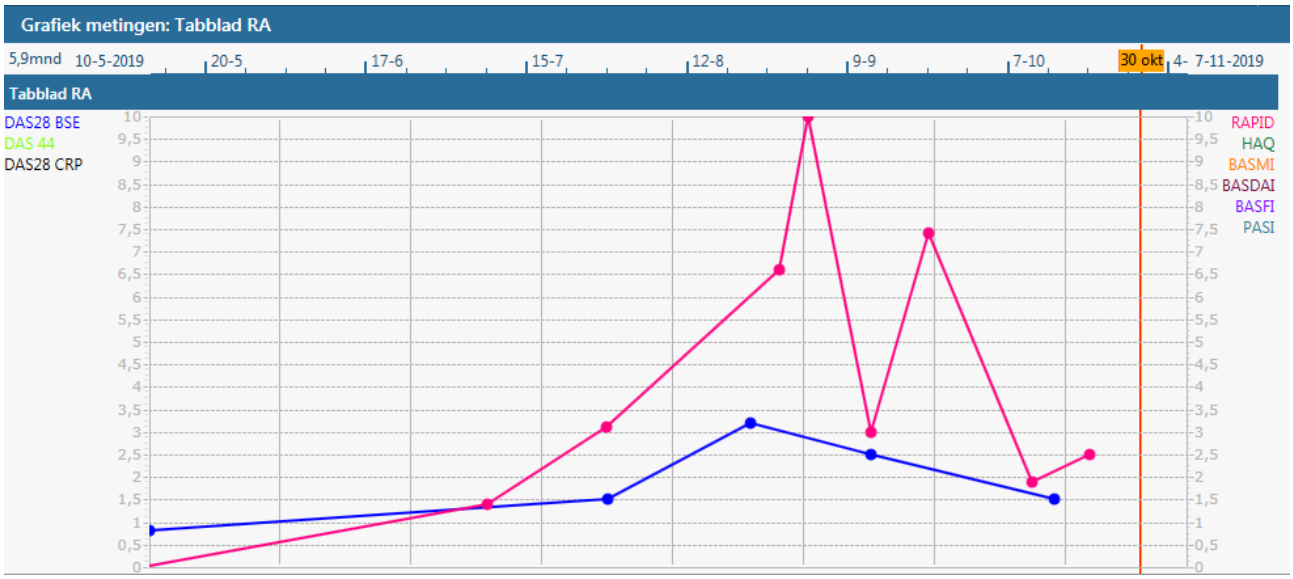


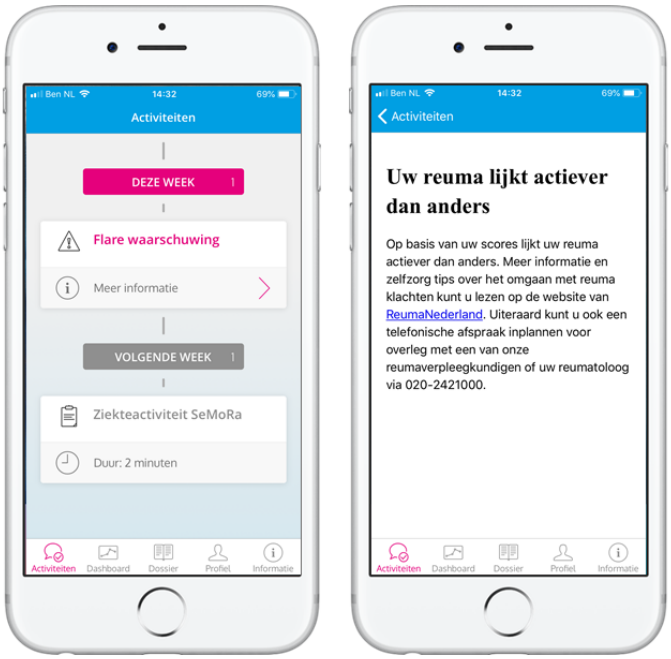
Figure 3. EMR dashboard. The EMR dashboard displays the results collected with the app. The data originate from the EMR itself, where they are stored in real-time after questionnaire completion in the app. The graph displays disease activity over time as measured by the RAPID3 (red) and DAS28 (blue). DAS28: Disease Activity Score 28; EMR: electronic medical record; RAPID3: Routine Assessment of Patient Index Data 3.



Algorithm

The app sends an alert to the user when the algorithm recognizes a flare (Figure 4). The alert notifies the user of a possible flare, provides links to self-management tips, and advises the user to contact a rheumatology nurse if necessary. The alert is generated when the RAPID3 value of the user increases by more than 2 points from the previous value and the current RAPID3 value is >4 points. This threshold has been determined on the basis of the findings in previous studies, in which a flare according to the DAS28 corresponded with a RAPID3 increase between 1.5 and 2.3 points [9,20]. Furthermore, the cutoff of 4 points corresponds very well to the patient- and physician-defined flare cutoffs of 4.33 and 4.27, respectively [20]. Receiver operating characteristic curve analysis showed that a RAPID3 value >4.27 had 77.3% sensitivity and 77.6% specificity for patient-defined flare and that a cutoff of 4.33 had 67.6% sensitivity and 85.3% specificity for physician-defined flare. The discussed alternatives included the RA flare questionnaire (RA-FQ) and FLARE-RA score [9,21]. As remission criteria are not available for both these assessments, three out of five RA-FQ domains are captured with the RAPID3, and RAPID3 values and FLARE-RA scores are highly correlated (r=0.77), it was ultimately decided to use the RAPID3-based algorithm [22]. An anchor question regarding the presence of an RA flare (yes/no) was included in the weekly self-assessment questionnaire (Table 1) to evaluate the appropriateness of the threshold in this study [9].

Figure 4. Flare algorithm. The app generates an alert with a link to self-management tips and advice to contact the outpatient clinic in case of an increased disease activity. Left: "Flare warning". Right: "Your disease appears to be more active".



Eligibility Criteria

The inclusion criteria are as follows: diagnosis of RA by a rheumatologist; disease duration of at least 2 years; low disease activity or remission (DAS28 <3.2) at the time of inclusion; use of a disease-modifying antirheumatic drug (DMARD); owning a mobile device with an Android or iOS operating system (implying mobile phone literacy); age of at least 18 years; and ability to read and speak Dutch.

The exclusion criteria are as follows: medication change involving initiation or discontinuation of a DMARD (conventional [methotrexate, cyclosporine, cyclophosphamide, gold injections, hydroxychloroquine, leflunomide, mycophenolate, sulfasalazine, and corticosteroids] or biological) in the last 6 months and participation in another interventional study.

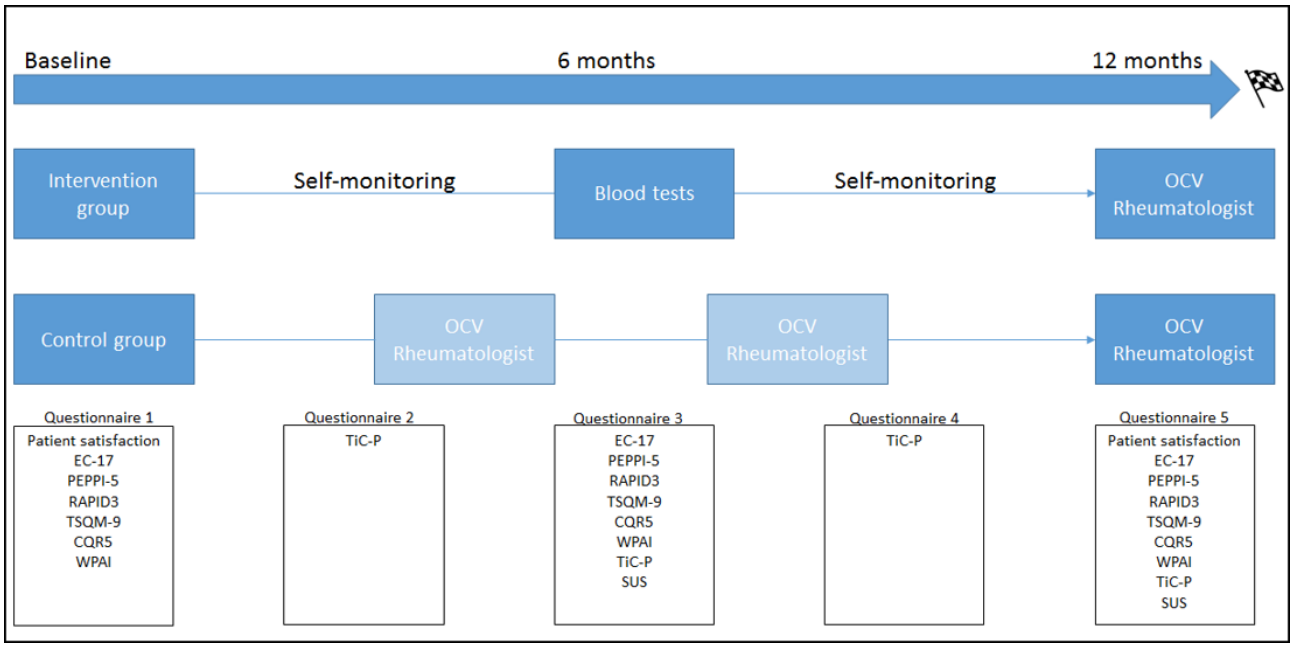
Study Design

Outpatient clinic patients will be informed about the study by their rheumatologist. If consent is given, they will be contacted by the trial physician (BS). They will be invited for a study visit to discuss the study, sign the informed consent form, and undergo screening for eligibility. The selected patients will be randomized to one of the following two parallel groups: control group and intervention group. Patients randomized to the control group will continue usual care, and outpatient clinic visits are planned as usual by their rheumatologist, on average 2-3 times a year. For patients randomized to the intervention group, only one outpatient clinic visit is planned at the end of the trial period (after 12 months). They will receive a username and password for the app to allow monitoring of their own symptoms. If necessary, they will be provided help to download the app from the appropriate app store. During the first study visit, they will be instructed on how to complete the weekly questionnaire through the app. Additional follow-up visits will be scheduled at the occurrence of flares as recognized by the app or at the request of individual patients. Furthermore, at 6 months of the intervention, the blood of the patients will be tested (erythrocyte sedimentation rate [ESR], hemoglobin level, leukocyte count, aspartate aminotransferase level, and alanine aminotransferase level) at the outpatient clinic. Patients will receive the results of the blood tests over the phone. If trial patients do not complete the weekly questionnaire for 4 weeks, they will be contacted to investigate the reason for nonadherence. Nonadherence will not lead to discontinuation of the trial for trial patients.

After 12 months, all patients will be seen by the trial physician for the second and final study visit. During the visit, a tender and swollen joint count will be performed by a blinded research nurse or a rheumatology resident. For patients in the intervention group, the number of flare reports will be collected and, if applicable, the reason for not contacting the outpatient clinic will be recorded.

During the trial, all patients will complete validated self-reported questionnaires at 0, 3, 6, 9, and 12 months, using a web-based system (Figure 5).

Figure 5. Study design and outcomes over time. The control group continues regular care, usually with two or three preplanned outpatient clinic visits (OCVs) (light blue box). The intervention group has only one preplanned OCV (blue box) and monitors symptoms using a smartphone app. All patients complete five questionnaires during the study to compare secondary outcomes. CQR5: Compliance Questionnaire for Rheumatology 5; EC-17: Effective Consumer Scale 17; PEPPI-5: 5-item Perceived Efficacy in Patient-Physician Interactions; RAPID3: Routine Assessment of Patient Index Data 3; SUS: System Usability Scale; TiC-P: Treatment Inventory of Costs in Psychiatric Patients; TSQM-9: Treatment Satisfaction Questionnaire for Medication 9; WPAI: Work Productivity and Activity Impairment.



Flare

All patients, irrespective of the algorithm results or randomization arm, will be allowed acute outpatient visits if needed. If patients seek health care during the study, they will be seen by a rheumatology nurse. Patients will be asked about possible flares, associated symptoms, and medication adherence. If the rheumatology nurse cannot manage the flares, the patient's own rheumatologist or the on-call rheumatologist (when the

patient's own rheumatologist is absent) will be notified by the rheumatology nurse for further treatment.

Power Analysis

To evaluate the safety of app-supported self-initiated care, we aim for noninferiority in terms of disease activity, as measured by the difference in the mean DAS28 score between the two study groups. Furthermore, we aim for superiority in terms of the number of outpatient clinic visits, with a lower number indicating a better result. Two sample size calculations are performed to determine an appropriate sample size for both hypotheses.

A sample size of 70 patients in each group has 90% power to detect noninferiority using a one-sided two-sample *t*-test. The margin of noninferiority is −0.3, and it corresponds to half of the minimal clinically important difference of 0.6, according to the EULAR response criteria. The true difference between means is assumed to be 0.0. The significance level (alpha) of the test is .05. The data are drawn from populations with a standard deviation of 0.60, which can be generally assumed in a stable group of patients with RA.

As the number of visits will be analyzed and each patient might have multiple visits, the sample size calculation needs to take the exposure-adjusted rate into consideration to power the study. Therefore, a Poisson test has been performed. The expected decrease in visits is approximately 50%, as a recent telemonitoring study in RA showed a decrease in visits of 58% [23]. A sample size of 22 patients in each group has 90% power at the 5% significance level to detect a difference of 25% (half the expected difference) with the use of a one-sided two-sample Poisson test. The exposure time is set at 6 months in the calculation, but with an actual follow-up of 1 year, the power will be even higher.

A sample size of 70 patients in each group will have sufficient power for both the clinical outcome and reduced appointment frequency. Considering these calculations and accounting for follow-up loss of 20% of patients, we plan to include 88 patients in each group (total 176 patients).

Randomization Procedure

Participants will be randomized 1:1 to self-initiated care with our app (intervention) or standard care (control). Randomization and allocation will be performed by the author BS, using a web-based randomization tool (Castor EDC, Ciwit BV, Amsterdam, the Netherlands) to obtain variable blocks of two, four, or six, with stratification for treatment (conventional or biological DMARD). Castor builds the allocation sequence and performs randomization for the researcher, which can be considered centralized randomization, without the risk of allocation bias [24].

Blinding

The 28-joint tender and swollen joint count for the primary outcome measure will be determined by a blinded research nurse or rheumatology resident. These individuals have no treatment relationship with the participants and will be instructed not to look at the patient files prior to the examination. The nurse or resident will be called during the study visit to perform the examination. As in most eHealth trials, it will not be possible to blind patients and health care providers caring for their patients to treatment allocation.

Outcome Measures

The primary outcome measures are health care utilization, as measured by the number of outpatient clinic visits with a rheumatologist during the 12-month trial period, and disease activity, as measured by the DAS28-ESR at 12 months. A list of secondary outcome measures and their assessment time points are presented in Table 2 and Figure 5, respectively. The key secondary outcomes include cost evaluation of the intervention and adherence. Health care costs in the intervention group will be compared with usual care costs from a societal perspective as measured using the Treatment Inventory of Costs in Psychiatric Patients questionnaire, which is adjusted for use in RA patients, and medical information retrieved from the Reade EMR system [25]. Furthermore, explorative analysis will be performed to evaluate the relationship between user adherence and disease activity.

Table 2. Secondary measures.

Secondary measure	Scale
Patient satisfaction	10-point Likert scale
Patient empowerment	Effective Consumer Scale 17
Disease activity	Routine Assessment of Patient Index Data 3
Treatment satisfaction	Treatment Satisfaction Questionnaire for Medication 9
Medication adherence	Compliance Questionnaire for Rheumatology 5
Work productivity	Work Productivity and Activity Impairment
Overall cost	Treatment Inventory of Costs[a]
Adherence	Questionnaire completion rates
Qualitative data	N/A[b]

[a]Adjusted for use in rheumatology.

[b]Not applicable.

Results

Recruitment is currently underway. We started recruitment in May 2019, and it will continue until the goal of 176 participants is reached. Thus far, 78 patients have been randomized and, empirically, experiences with the app have been positive. Data release in the form of a research paper is estimated by the end of 2021.

Discussion

Summary and Strengths

This study will be the first randomized trial to test the safety and efficacy of self-initiated care supported by a smartphone app in patients with RA. Although several apps to monitor disease activity exist and some of these apps have been tested, to date, no studies have reported on the use of an app to support patient-initiated care [26-28]. This study has been performed in accordance with the relevant domains of the model for assessment of telemedicine applications, as advised by the European Commission guidelines, and meets the requirements of the checklist on how to report health interventions using mobile phones [29,30].

In a recent systematic review of mobile apps for monitoring disease activity, a lack of high-quality apps was reported [11]. The review suggested that apps should use validated questionnaires and have a user-friendly interface. With the design and redesign strategy and patient feedback in all stages, we were able to develop a mobile app that meets the review requirements. The app is easy for patients to use, visually presents data, and incorporates useful information for physicians. Furthermore, we secured technical support during the trial period, as one of the developers of the app is a part of the project team (FC). Additionally, we have ensured that this system is integrated with the existing Reade EMR system to optimize clinicians' workflow in their busy daily clinical practice. Integration of the app and its patient-reported outcome (PRO) data with the existing EMR system has enormous research potential. This has been recognized before but is often not accomplished [31].

Expectations

We anticipate that the app will facilitate better comanagement of the disease by rheumatologists and patients. This will result in early identification of disease flares and will lead to possibly better interventions for patients requiring treatment adaptation. Moreover, we expect a reduced appointment frequency for patients, as unnecessary consultations will be prevented [23]. Furthermore, self-monitoring will improve patient engagement and empower patients to manage their own illness. We expect a fair amount of missing data from the app owing to varying engagements from our patients [32]. Our primary objective is not to use the PRO data in statistical analyses, but to ensure that the data are useful to patients and rheumatologists for monitoring and understanding the disease. Even if patients enter data only once every 4 weeks, they will still have 4-6 times more data about their disease status when compared with the data obtained on visiting the rheumatology outpatient clinic every 4-6 months.

Limitations

This study has several potential limitations. First, there is a possibility of a ceiling effect of the secondary outcome measures, as all participants will have low disease activity at baseline and a disease duration of at least 2 years and might score well in several of the secondary outcome measures, as is often the case in the Dutch health care system. Second, the addition of a third arm (patient-initiated care without the app) has been discussed to allow evaluation of the effect of the app. However, we opted against the inclusion of a third arm because this would mean that information about disease activity could be lacking for a full year, which is against current EULAR guidelines. To avoid this unethical design, we selected a design similar to that used in the study by de Jong et al, in which the telemedicine system IBDcoach led to a reduction in outpatient clinic visits when compared with usual care [2]. Third, generalizability is limited for three reasons. Firstly, we only include patients who are in remission, and thus, patients with high disease activity are excluded from this intervention. Nevertheless, we think that this intervention is still very relevant, as there are unmet needs to reduce the number of outpatient clinic visits and detect flares early. Secondly, only patients who own a mobile device and therefore are likely receptive to mobile technology are included. However, we anticipate that this selection excludes only a small percentage of individuals, as the proportion of adults with a smartphone is growing and is already at 87% [16]. Thirdly, the MijnReuma Reade App is only accessible to patients at Reade presently, which limits delivery at scale. We have however granted everyone access to the prototype app, which other hospitals can incorporate into their own EMR systems.

Conclusion

Following a design, test, and redesign approach, we have developed an app that allows patients with RA to monitor their own disease activity. We anticipate that our app will safely lower the need of patients for outpatient clinic visits. If proven safe and effective in an RCT, our aim is to implement our telemonitoring strategy in the Dutch health care system.

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Authors' Contributions

BFS and WHB wrote and edited the manuscript, BFS was responsible for study procedures including obtaining informed consent, WB, LR, and DvS initiated the project, WHB, MA, and SDSR were responsible for the pilot studies, and all other authors provided feedback and edited the manuscript.

Conflicts of Interest

The software for the smartphone app is owned by Brightfish BV, and author FC is cofounder of Brightfish BV.

Multimedia Appendix 1
The SPIRIT checklist.
[PDF File (Adobe PDF File), 148 KB - resprot_v9i2e15105_app1.pdf]

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Abbreviations

DAS28: disease activity score 28
DMARD: disease-modifying antirheumatic drug
EMR: electronic medical record
ESR: erythrocyte sedimentation rate
EULAR: European League Against Rheumatism
FQ: flare questionnaire
IBD: inflammatory bowel disease
PRO: patient-reported outcome
RA: rheumatoid arthritis
RAPID3: Routine Assessment of Patient Index Data 3
RCT: randomized controlled trial

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Protocol

A Theoretically Based Mobile App to Increase Pre-Exposure Prophylaxis Uptake Among Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: HealthMindr is a mobile phone HIV prevention app for men who have sex with men (MSM). In a previous pilot study, HealthMindr was found to be acceptable among users and to demonstrate preliminary effectiveness for increasing pre-exposure prophylaxis (PrEP) uptake among MSM. PrEP is a highly effective HIV prevention intervention; however, uptake remains low.

Objective: The aim of this study will be to assess the efficacy of a mobile app for increasing PrEP uptake among MSM in the southern United States.

Methods: In this randomized controlled trial, we will assess the efficacy of HealthMindr for increasing PrEP uptake among MSM in the following three southern US cities: Atlanta, Georgia; Jackson, Mississippi; and Washington, DC. In total, 657 men will be recruited and randomized to intervention and control arms in a 2:1 ratio. Participants in the intervention arm will receive access to the full HealthMindr app, with information and resources about PrEP (eg, frequently asked questions, risk assessment tool, and PrEP provider locator), other HIV prevention information, ability to order free HIV/sexually transmitted infection test kits, and additional resources related to substance use and mental health. Participants in the control arm will use the HealthMindr app but will only have access to the study timeline and a message center to communicate with study staff. Participants will complete quarterly surveys to assess self-reported PrEP uptake over 12 months of follow-up. Self-reported PrEP uptake will be verified by dried blood spot testing and/or uploading a photograph of a PrEP prescription.

Results: Participant recruitment began in January 2020.

Conclusions: This trial will determine whether the HealthMindr app can increase PrEP uptake among MSM in the southern United States.

Trial Registration: ClinicalTrials.gov NCT03763942; https://clinicaltrials.gov/ct2/show/NCT03763942

International Registered Report Identifier (IRRID): PRR1-10.2196/16231

(JMIR Res Protoc 2020;9(2):e16231) doi:10.2196/16231

KEYWORDS

men who have sex with men; pre-exposure prophylaxis; mobile health; electronic health; HIV

Introduction

In the US HIV epidemic, men who have sex with men (MSM) experience disproportionately high HIV prevalence [1-4] and incidence [5-7]. MSM are the only US risk group in which HIV incidence increased after 2000 [6], and the increase is especially alarming among young MSM [5] and MSM of color [8]. MSM aged 13-24 years and 25-34 years are the only MSM groups in which new diagnoses increased after 2009 [9]. The prevalence of HIV infection among MSM is 67 times greater than that among other men in the US population [10]. There are estimated to be more than 4,700,000 MSM in the United States [10], and over 800,000 of these men are estimated to be current candidates for pre-exposure prophylaxis (PrEP) [11].

In the United States, daily oral PrEP is available for MSM as emtricitabine/tenofovir disoproxil fumarate and emtricitabine/tenofovir alafenamide. Despite the effectiveness of PrEP for preventing HIV seroconversion [12,13], there are a number of barriers to PrEP uptake, including cost, awareness, and underestimation of the self-perceived HIV risk [14,15]. Manufacturer payment assistance programs are available to help offset the cost of PrEP; however, these programs do not cover the costs of necessary laboratory tests and can be difficult for patients to navigate [16].

Multiple models of HIV incidence in MSM suggest that to substantially decrease HIV incidence in MSM, it is needed to achieve 40%-50% coverage of multiple prevention services and interventions (eg, condom promotion, HIV testing, PrEP, and treatment as prevention) in at-risk MSM [17-19]. Currently, uptake of many prevention services among MSM is low. HIV testing within the past 12 months, as recommended by some health jurisdictions [20] and the Centers for Disease Control and Prevention (CDC) [21], has been reported by 71% of men in 21 National HIV Behavioral Surveillance cities [22]. However, only 58% of respondents in the American Men's Internet Survey (AMIS) [23], a national survey that includes more rural MSM and MSM living in smaller cities, reported HIV testing in the past 12 months. In Atlanta, Georgia; Jackson, Mississippi; and Washington, DC, AMIS data indicate that there are significant deficits in annual HIV testing and PrEP knowledge and uptake. Data from the 2017-2018 AMIS surveys indicate a substantial unmet need for PrEP; 51%, 46%, and 58% of HIV-negative MSM in Atlanta, Jackson, and Washington, DC, respectively, are behaviorally eligible for PrEP but have never taken it (unpublished data). Considering the estimated population of HIV-negative MSM in each city [24] and the proportion of PrEP-eligible men and prevalence of PrEP use from AMIS data in each city, we estimate that the unmet need for PrEP among MSM in these three cities is greater than 70,000 MSM.

Electronic health (eHealth) tools provide an opportunity to facilitate uptake of HIV prevention services. A recent summary of eHealth tools for HIV prevention in MSM noted that certain types of prevention services are most amenable to provision through new technologies. Services for which indications can be determined through an algorithm are good candidates to bring to scale with technologies [25]. For example, well-described criteria and algorithms exist to identify individuals with behavioral indications for PrEP [26,27]. Moreover, using technology to administer PrEP eligibility screening could highlight the need for more accessible PrEP services for rural MSM [25]. Furthermore, the indications of men for PrEP change over time [28,29], so efficient use of PrEP among MSM will require periodic reassessment of the HIV risk. Assuming 6-monthly PrEP eligibility screenings for HIV-negative MSM, approximately 8 million PrEP eligibility screenings would be needed in the United States annually to identify PrEP-eligible MSM. Technologies that allow men to conduct periodic self-screening and opt-in to clinical screening when indicated have the potential to substantially reduce health-care system burden.

The HealthMindr app is an eHealth tool designed to promote HIV prevention among young MSM in the United States. HealthMindr is grounded in Social Cognitive Theory [30], particularly the components of self-efficacy, goal setting, outcome expectation, and feedback/self-regulation [31]. HealthMindr is designed to be a comprehensive HIV prevention app with information and links to resources that involve a combination prevention approach (eg, HIV/sexually transmitted infection [STI] testing, PrEP information and provider locators, and condom promotion). Additional details of the app and its components are presented in the Methods. In a pilot study conducted in Atlanta, Georgia and Seattle, Washington, HealthMindr was found to have high acceptability among MSM over a 4-month follow-up [31]. We incorporated feedback from the pilot participants to improve the app, including the inclusion of graphics and videos, additional frequently asked questions (FAQs), and customizable reminders (eg, to order a HIV test and schedule an appointment with a PrEP provider). Although not a primary outcome of the pilot study, 9% of PrEP-eligible participants initiated PrEP over the follow-up period. The primary goal of this study is to assess the efficacy of HealthMindr for increasing PrEP uptake in a randomized controlled trial (RCT) in the southeastern United States. The primary aim of this study is to assess the efficacy of HealthMindr for increasing self-reported PrEP uptake among MSM aged 18-34 years in the three cities of Atlanta, Georgia; Jackson, Mississippi; and Washington, DC in the southern United States, which have a high HIV incidence among young MSM. Participants will be randomized to an intervention arm and provided access to HealthMindr or to a standard-of-care (information only) control arm. Participants in the control arm will be provided access to an app that allows them to manage their study progress and complete surveys but contains no HIV prevention information. The primary outcome will be PrEP uptake, as measured by self-report on quarterly follow-up

surveys. PrEP uptake will be verified by dried blood spot testing and/or prescription verification. Secondary outcomes will be to assess app components contributing to PrEP uptake measured via app usage data (ie, paradata), conduct in-depth interviews (IDIs), and measure HIV and STI incidence and PrEP adherence and persistence.

Methods

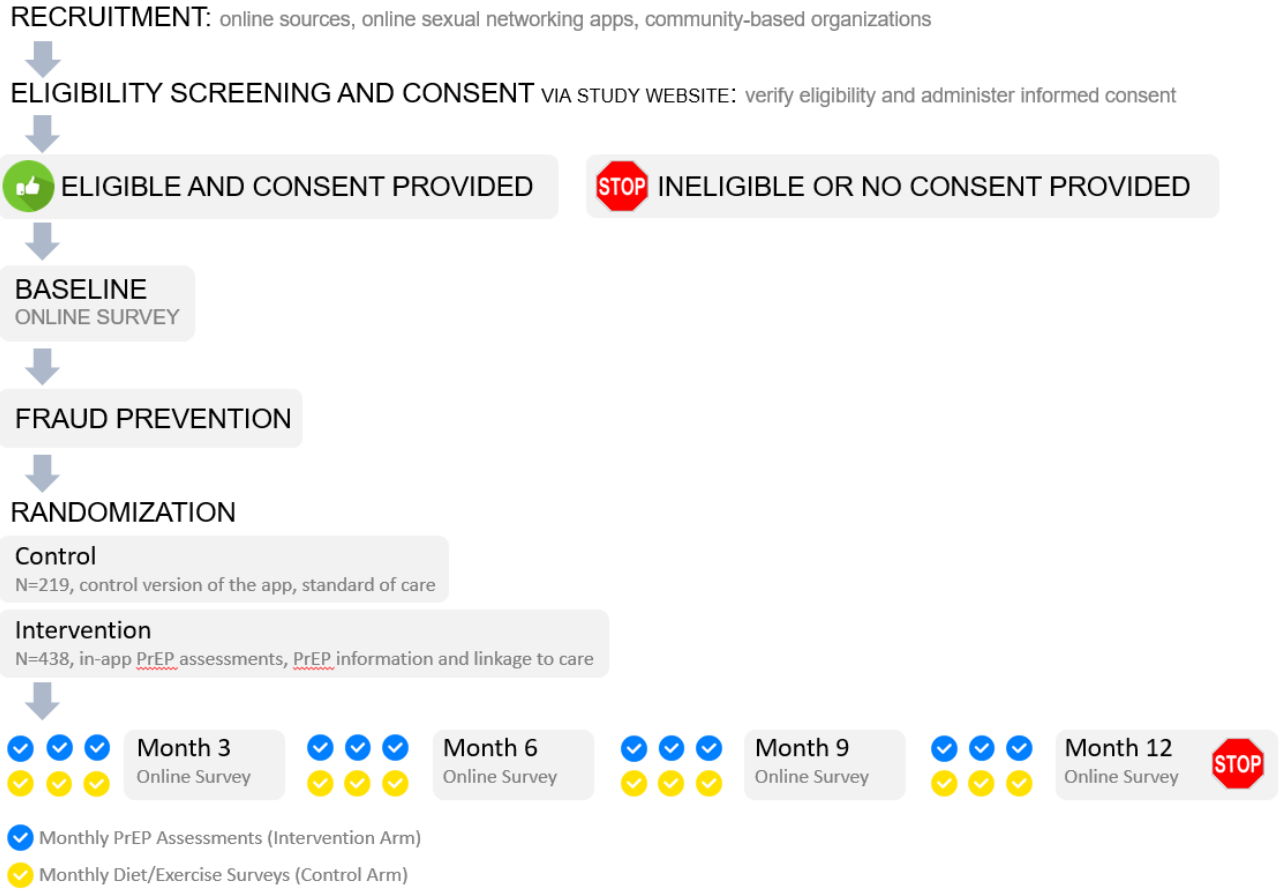
Study Design

We will conduct a mixed-methods RCT with two arms. Participants in the intervention arm will receive access to HealthMindr with enhanced HIV prevention services (HIV test planning and test locator; initial risk/PrEP eligibility assessment; HIV treatment locator; and ordering of free condoms, HIV test kits, and at-home STI specimen collection kits); information about PrEP; PrEP provider locator; initial local PrEP navigator referral; and monthly PrEP eligibility assessment and PrEP navigator referral. The app also provides links to health insurance exchanges, where eligible men can seek health insurance (all cities), Medicaid (DC only), or payment assistance programs. The control arm will be provided standard-of-care HIV prevention and PrEP information upon enrollment and will receive access to the control version of the HealthMindr app. The control version of the app prompts participants to complete a monthly mobile phone–administered attention control survey about diet, exercise, and prescription medications (to assess PrEP uptake) of the same length as that of the monthly PrEP assessment given to the intervention arm in order to maintain the same frequency of contact as that among intervention participants. Participants in the control arm will not have access to the HIV prevention information and services available in HealthMindr used in the intervention arm.

Study participants will be followed for 12 months, and primary and secondary outcome measurements will be performed at 3-month intervals in both arms. A schematic of the study design is presented in Figure 1. Surveys will be distributed to all participants through the mobile app at baseline and quarterly. Quarterly surveys will take approximately 30 minutes to complete; to limit survey duration, non–time-varying survey elements will not be assessed at each time point. Quarterly surveys will be identical for men in both arms; however, the final survey will include questions on acceptability of HealthMindr only for men in the intervention arm. The surveys are optimized for smartphones to allow them to be completed on participants' phones. The survey measures represent a comprehensive set of previously validated measures that will characterize the population, allow for assessment of randomization adequacy, document important outcomes, and allow for exploration of possible moderating factors.

During and after follow-up, participants will also be purposively sampled to participate in an IDI to obtain additional insights into the role that HealthMindr plays in decisions to start or not start PrEP during the study period.

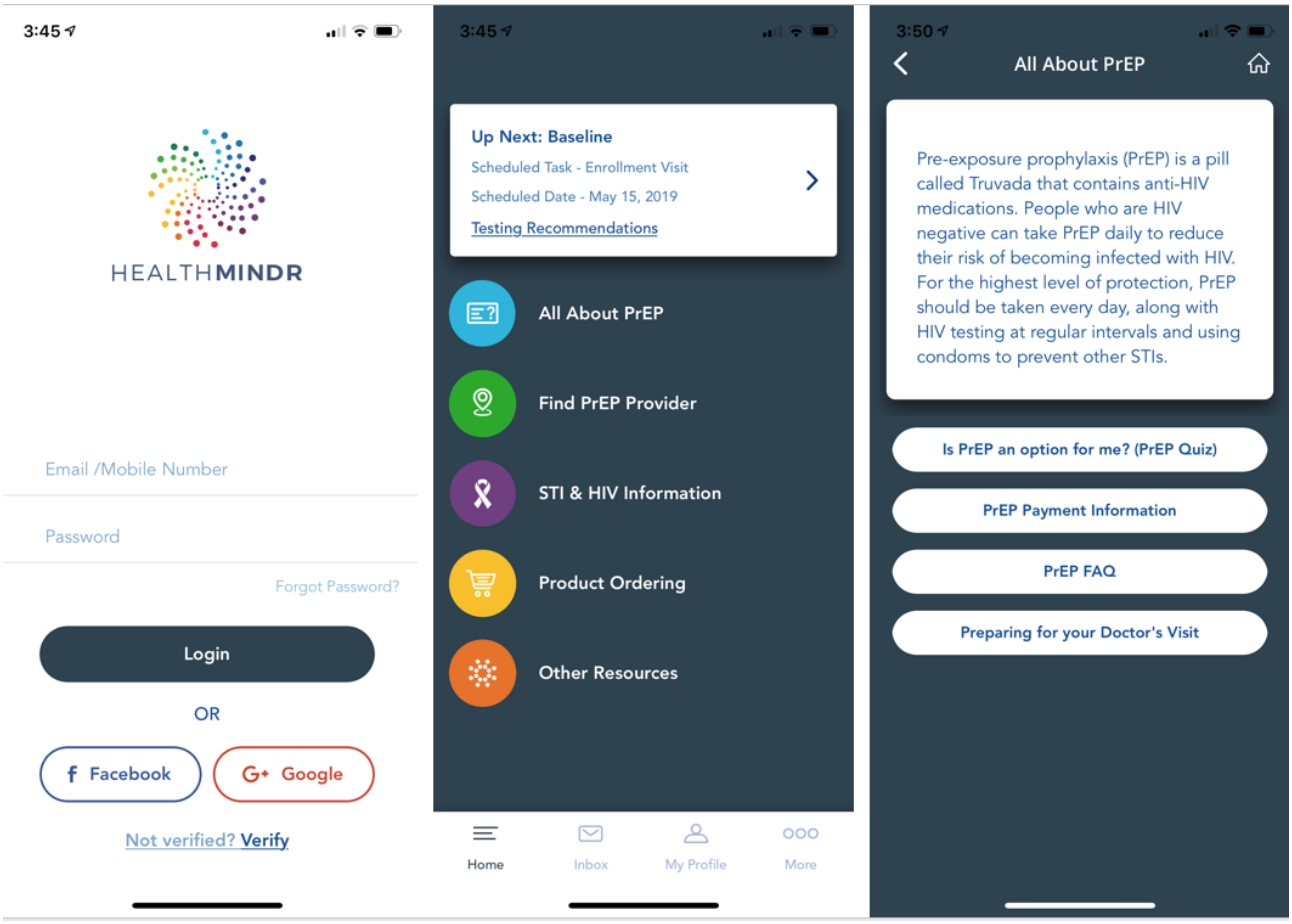
Figure 1. Study schema depicting planned enrollment in each arm and the schedule of surveys and monthly self-assessments. PrEP: pre-exposure prophylaxis.



Study App

HealthMindr is a mobile app designed to be a HIV prevention portal for MSM, and it was developed using an iterative community-driven process [32]. As previously described, the app development is grounded in Social Cognitive Theory, particularly the components of self-efficacy, goal setting, outcome expectation, and self-regulation. Participants in the intervention and control arms will download the HealthMindr app (Figure 2). The version of HealthMindr used in this study has been updated and modified according to feedback obtained in a previous pilot study [31]. Following randomization, the HIV prevention features of HealthMindr will become available to participants assigned to the intervention arm. The control version of the app is designed to support an attention control that maintains the same schedule of contact as that among intervention participants and provides a secure method for participants to communicate with study staff. The common features available to all participants and HIV prevention features available to intervention participants are described below.

Figure 2. Screenshots of the splash screen, home page, and all about PrEP screen of the HealthMindr app. FAQ: frequently asked questions; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.



Participants in the control arm will have access to the control HealthMindr app with limited functionality, which includes the following features:

- Secure messaging: Participants will be able to send and receive secure messages and communicate with study staff. When participants receive a message from study staff, they will have the option of receiving a nonspecific alert (eg, You have a message) on their phone.
- Study timeline: A study timeline will be displayed so that participants can see all study activities (eg, surveys and self-assessments) and seen when they are due.
- Surveys and self-assessments: Participants will be able to follow links to complete all study surveys and self-assessments within the HealthMindr app via a SurveyGizmo API.
- Profile: Participants will be able to create a basic profile to keep their contact information up-to-date.

Participants in the intervention arm will have access to the features described above, as well as the below-mentioned HIV prevention functions. Where appropriate, we have mapped functions to the relevant components of Social Cognitive Theory (eg, goal setting, self-regulation, and self-efficacy).

- HIV testing: Participants will be able to learn more about testing options, plan with built-in reminders to test 2-4 times in the coming year, locate possible places for the tests, and schedule reminders (goal setting).
- Behavioral risk assessment: Participants will be able to complete a short behavioral risk assessment (eg, HIV risk behaviors: sex while drunk or high, unprotected anal intercourse with a positive or unknown HIV status partner, total number of sex partners, recent STI diagnosis, and methamphetamine or popper use and protective behaviors: HIV testing, STI testing, and consistent condom use; feedback/self-regulation). Participants will be prompted to

complete the risk assessment monthly but will have the option of completing it at any time on-demand.

- Nonoccupational postexposure prophylaxis (nPEP): Participants will have access to nPEP information, nPEP self-assessment [27], nPEP locator services [33], and PrEP referral for those who evaluate multiple exposures for nPEP indication (goal setting and outcome expectation) [34].
- Product ordering: Participants will be able to order condoms, condom-compatible lubricants, at-home STI specimen collection kits (urethral and rectal gonorrhea and chlamydia, and syphilis; goal setting), and at-home HIV test kits (OraQuick; goal setting). Orders are filled through Amazon fulfillment services.
- Pre-exposure prophylaxis: Participants will have access to PrEP self-assessment at the first app use, monthly rescreening for PrEP eligibility, PrEP recommendations adapted from CDC criteria, PrEP provider locator services, transport or driving directions to providers, and PrEP FAQs. The PrEP self-screener assesses certain key elements of behavioral eligibility (potential indicators of ongoing high risk for HIV acquisition) and recommends potentially eligible MSM to visit PrEP providers for further clinical assessment, with help locating nearby providers and transport directions (self-efficacy, goal setting, and outcome expectations). Locator services will be provided via PrEPLocator.org, which allows users to locate nearby PrEP providers and navigators. PrEP navigation will not be explicitly offered by study staff; however, participants who request PrEP navigation assistance will be directed to resources in their area.
- Substance use and mental health screeners: Participants will have access to brief screeners to conduct self-assessments for anxiety, depression, and substance use problems.
- Substance use and mental health provider directory: Participants will have access to a list of local resources available for treatment, rehabilitation, and counselling. This will allow participants to search the directory of substance use and mental health counseling providers included in the Substance Abuse and Mental Health Services Administration online directory [35].

Participants and Recruitment

The target enrollment for this study is 657 participants (438 intervention and 219 control participants) across the three study sites. Power analyses are described in detail below. The eligibility criteria for this study are as follows: (1) cisgender male (male at birth and currently identifies as a male); (2) age 18-34 years (inclusive); (3) resident in one of the study metropolitan statistical areas (MSAs; Atlanta, Georgia; Jackson, Mississippi; or Washington, DC); (4) intention to reside in one of the study MSAs for the duration of the trial; (5) available Android or iOS phone with active service and willingness to download the study app; (6) English speaker; (7) report of having anal sex with a man in the past 6 months; and (8) report of being HIV-negative or never having been tested for HIV. Men who report currently being on PrEP will be considered ineligible; however, past PrEP use will not be exclusionary.

Recruitment strategies will aim to recruit MSM who are diverse in terms of race/ethnicity and maintain comparability across sites. Black and Hispanic MSM will be oversampled with the goal of enrolling at least 50% of the study population from these disparately impacted groups. The primary method of recruitment will be via online venues, including social networking sites (eg, Facebook, Instagram, and Twitter), sexual networking apps (eg, Grindr and Scruff), and banner advertisements on websites frequented by MSM (eg, Queerty, Towleroad, and Adam for Adam). In a previous study in Atlanta, Georgia, minimal differences were observed between men recruited online and men recruited via venue-based time-space sampling [36]. We will target men aged at least 18 years, who live in MSAs in Atlanta, Georgia; Jackson, Mississippi; or Washington, DC. Additional metropolitan areas in the southern United States might be added if needed to achieve our recruitment goal. When men click on a banner advertisement, they will be taken to a page containing basic study information that includes a short description of the study activities. If they click on a button to advance, they will progress through screening, consent, and enrollment. These procedures are described below. No user data will be collected from the referral site (eg, Facebook and Grindr); however, unique tracking links will be used to allow identification of the referral site. Recruitment yields from each source will be monitored, and recruitment strategies will be adjusted as needed to reach the target population number.

In addition to online recruitment strategies, participants will be recruited by posting flyers and promoting the study through community partners (eg, community-based organizations and drop-in centers) in the three MSAs. Those recruited through these flyers will be directed to a website for eligibility screening.

Screening, Consent, and Enrollment

Participants who click on an online recruitment advertisement or follow the URL on a community-based advertisement will be taken to an eligibility screening survey hosted on SurveyGizmo.com, a Health Insurance Portability and Accountability Act-compliant web-based survey platform. Eligible participants will complete an online informed consent form, with the option to view a video summary of the informed consent form [37]. After providing informed consent, participants will be directed to a link to authenticate their smartphone and download the HealthMindr app from either the Google Play Store or Apple App Store. Initially, the app will display a study timeline with a link to the baseline survey, which participants will complete in the app. After the baseline survey is completed, a standardized fraud check procedure will be completed. Participants who pass the fraud check will be randomized and enrolled into the study. Following randomization, the HIV prevention features of HealthMindr will become available to participants assigned to the intervention arm (ie, all participants will have the same HealthMindr app, with additional content made available to participants in the intervention arm).

Baseline Survey

The baseline survey will take approximately 30 minutes to complete. The measured domains will include demographics; sexual behavior in the past 6 months; PrEP awareness,

knowledge, attitude, use, and stigma; HIV/STI testing, diagnosis, and treatment history; health care access and utilization; substance use [38]; intimate partner violence; and mental health. The full survey is included in Multimedia Appendix 1.

Fraud Prevention Procedures

To avoid fraudulent registrations, the eligibility criteria will not be revealed to prospective participants prior to screening, IP addresses will be assessed to block duplicate screening attempts, and CAPTCHA will be used to prevent bots. Payment of initial baseline incentives will be delayed for 2-3 business days to allow routine checks for duplicate IP addresses, names, email addresses, or phone numbers. Some demographic questions (eg, age and ZIP code) will be repeated in the eligibility screener and baseline survey for verification. All participants will be contacted by phone prior to enrollment. If duplicate contact information or discrepancies between eligibility and baseline survey data are detected, the study staff will attempt to resolve concerns during this phone call and clarify how the situation arose. If duplicate registrations are detected, the records will be inactivated and deemed invalid.

Randomization

After providing informed consent, downloading the study app, completing the baseline survey, and passing the fraud check, participants will be randomized to the intervention and control arms in a 2:1 ratio (438 intervention and 219 control participants), with stratification by city to ensure balance of the study arms across the three study sites [39]. The 2:1 randomization is designed to ensure that the trial includes enough app users to conduct planned secondary analyses of intervention efficacy according to the level of app usage. Within each city, a computer program will randomly assign each participant to the next treatment allocation from a random-permuted block randomization sequence.

Follow-Up Survey Schedule

All participants will be asked to complete monthly self-assessments and quarterly surveys. Monthly self-assessments will differ between the study arms. The participants in the intervention arm will complete a PrEP eligibility self-assessment that is intended to promote PrEP uptake (Multimedia Appendix 2). After PrEP initiation, the monthly survey will include the same PrEP eligibility self-assessment to encourage continual awareness of changing HIV risks and four additional questions assessing PrEP adherence. The participants in the control arm will complete an exercise and general health self-assessment (Multimedia Appendix 2). The purpose of the self-assessment in the control arm is to equalize the frequency of participant contact with study procedures across the follow-up period. Quarterly surveys will be used to measure labile demographic characteristics and study outcomes. Participants will receive incentives in the form of electronic gift cards for completion of the baseline and follow-up surveys according to the following schedule: baseline, US $50; months 3 and 6, US $40; month 9, US $50; and month 12, US $60. The graduated increase in the incentive amount over the follow-up period is designed to increase participant retention over the entire follow-up period. Any participant who reports a reactive HIV test result will be contacted to assist with linkage to care.

Statistical Analysis

The main analysis will use four standard survival analysis techniques to compare the rate of PrEP initiation between the study arms and estimate the effect size and statistical significance for observed differences. This approach will account for loss to follow-up, study termination owing to competing events (eg, HIV seroconversion), and other forms of censoring [40]. The first analysis will use Kaplan-Meier methods to characterize the empirical survival distribution, which is the time-dependent probability of remaining PrEP uninitiated over the follow-up period. This method will yield estimates of the median time to PrEP initiation and cumulative incidence with 95% confidence intervals. In the second analysis, log-rank or related (eg, Harrington-Fleming) statistical tests will be used to test the null hypothesis of no difference in the rate of PrEP initiation between the study arms, with a cutoff *P* value of .05 used to determine significance [41]. In the third analysis, a Cox proportional hazards model will be used to estimate the hazard ratio associated with the study arms in order to characterize the strength of the causal effect of app use. The primary model will include an independent exposure variable for the study arms as randomized (ie, standard intent-to-treat analysis), and covariates of interest (including those related to the four domains along the PrEP continuum) will be included in the model to increase precision [42]. In the fourth analysis, parametric survival models (eg, under exponential or Weibull distributional assumptions) will be used to characterize the rate of PrEP initiation overall and by study arm. Participants will be analyzed according to the randomized arm (ie, intention-to-treat analysis).

Primary Outcome

The primary outcome will be the rate of PrEP uptake as measured by self-report in the app-based surveys at months 3, 6, 9, and 12. Additionally, all participants reporting PrEP initiation will be asked to submit confirmation of self-report either by laboratory testing for the presence of tenofovir diphosphate via dried blood spots submitted by mail or uploading a photograph of their PrEP prescription or pill bottle via HealthMindr. Tenofovir diphosphate, although conventionally used as a measure of PrEP adherence, will be interpreted as a qualitative (yes/no) indicator of having taken PrEP. Participants who opt to verify their PrEP uptake will be incentivized with an electronic gift card for submitting a dried blood spot (US $40 incentive) or uploading a photograph of their prescription or pill bottle (US $15 incentive).

Secondary Outcomes

App paradata (eg, number of unique times the app is accessed and time spent on each app page) will be recorded on the server side when users access app content. To prevent overestimation of the time spent in the app and to protect participant privacy, the app will automatically log out after 3 minutes of inactivity whether left in the foreground or background of the mobile phone. The server will record a log of all activities the user completes in the app. These data will be used to summarize

typical usage patterns of the app, including frequency of overall app usage; frequency of use of individual app components, including monthly check-in surveys to assess PrEP eligibility; and typical time spent on the app. These data will also be used to inform secondary per-protocol analyses of intervention efficacy.

HIV and STI diagnoses will be assessed in multiple ways. Participants in the intervention arm will be able to order HIV and STI at-home test kits. Those who order HIV test kits will be asked to self-report their results via the app. STI test kits will contain biospecimen collection tools that participants will use to self-collect samples to test for syphilis and pharyngeal, rectal, and urethral gonorrhea and chlamydia. STI test kits will contain prepaid envelopes that participants will use to return samples for laboratory testing. STI results will be provided to participants by study staff. Negative results will be delivered via in-app messages, and positive results will be delivered via a phone call. Staff will attempt to link participants having positive STI diagnoses to treatment. Participants in the intervention arm will be able to report HIV/STI tests received outside of the context of the study. Finally, all participants will be asked about recent HIV/STI diagnoses at the baseline and quarterly surveys.

Among participants initiating PrEP, we will assess self-reported adherence (ie, number of doses missed in the past 30 days) and persistence (ie, time on PrEP) at each quarterly survey.

Power Analyses

Power calculations are conducted for the main analysis of time to PrEP initiation comparing the intervention arm with a control condition. Regarding estimates of PrEP uptake in four quarters spanning 2014 to 2015, 4507 men started PrEP in the United States [43]. Assuming all of these men are MSM, which is an overestimate, and using the number of MSM estimated by the CDC to be eligible for PrEP as the denominator [11], only 0.6% (4507/813,970) of eligible MSM started PrEP between mid-2014 and mid-2015. Thus, our assumption that at most 2% of men in the control arm will initiate PrEP during the study period is conservative. According to our preliminary pilot data, men using the app initiated PrEP at a rate of 9% in a 4-month period, and we conservatively estimate that men in the intervention period would initiate PrEP at a rate of 9% in a year. We will enroll 438 intervention and 219 control participants, which will provide 91% power (α=.05) to detect a 4.5-fold increase in the rate of uptake in the intervention arm when compared with the control arm. If the effects were less than our conservative estimates, we would retain reasonable power (4-fold: 80% power; 3.5-fold: 74% power). These power calculations assume 20% annual attrition.

The power calculations mentioned above were conducted at the time the study was proposed. However, recent data from the AMIS [44] indicate that approximately 3% of MSM initiated PrEP in the past year in the three study MSAs (data unpublished). Changing the calculations above to reflect 3% uptake among control participants, we would have 69% power to detect an intervention effect.

In-Depth Interviews

Up to 30 IDIs (approximately 10 per site) will be conducted within 1 month of PrEP initiation among participants in the intervention arm who start PrEP. Up to 20 additional IDIs will be conducted within 1 month of study completion among participants who fit the following criteria (maximum of five for each criterion): initiated PrEP, did not initiate PrEP, initiated PrEP but stopped PrEP prior to the end of follow-up, and cycled on and off PrEP during follow-up. Participants undergoing IDIs will be purposively sampled to ensure representation of men who access the app at least once during follow-up and receive a PrEP recommendation. Participants who initiate PrEP and are interviewed after 1 month of follow-up will not be eligible to be reinterviewed at the end of the study. The IDIs will be conducted by trained qualitative interviewers and will follow semistructured interview guides. The IDIs will assess the extent to which app components facilitated or inhibited PrEP uptake. Central to the IDIs will be understanding the participants' use of the app. Participants who initiate PrEP will be asked to describe the role that the app played in their decision and which app components were most integral to their decision. Participants who do not initiate PrEP will be asked if there are additional components (eg, better linkage to providers and other information) that could be included in the app, which might cause them to change their mind about initiating PrEP. HealthMindr is designed to address known barriers, including individual risk perception (via monthly PrEP self-assessments) and financial costs (via PrEP FAQs and payment information), and participants will be asked to comment on whether they accessed these sections of the app. Participants who do not initiate PrEP will be asked to demonstrate how they used the app and which components of the app were not used. Participants who stop and do not restart PrEP or who cycle on and off PrEP during follow-up will be asked to describe how HealthMindr influenced their decision to initiate PrEP and whether additional functions or support might have influenced their decision to discontinue PrEP.

Additional IDIs will be attempted with participants who report testing HIV-positive during follow-up. These IDIs will follow a structure similar to that described above. Additional questions will be added to explore the factors related to PrEP and seroconversion. Interviews will explore attitudes toward HIV prevention generally and PrEP specifically. Participants will be asked to comment on why they did or did not use PrEP and mention any barriers to PrEP they might have experienced.

Qualitative Analysis

All IDIs will be digitally recorded, transcribed verbatim, and deidentified. Transcripts will be entered into MAXQDA (VERBI GmbH, Berlin, Germany), which facilitates the processes of coding, annotating, and retrieving text such that analysts might note patterns in the textual data across themes. Data analyses will be conducted using a phenomenological inquiry framework [45,46]. Phenomenology is focused on describing what a given group of people have in common when they experience a phenomenon and is an inductive analytic approach that allows the patterns, themes, and categories of analysis to emerge from data [45,46]. Data are then presented through textual phenomena

descriptions based on summaries of experiences described by respondents. Composite descriptions offer explanations of underlying structures that exist across the respondents' experiences [45,47].

Trial Registration and Institutional Review Board Approval

This study has been reviewed and approved by the Institutional Review Board at Emory University (#IRB00102006), and the Institutional Review Boards at George Washington University and University of Mississippi Medical Center have agreed to rely on this decision. This study has been registered at ClinicalTrials.gov (NCT03763942).

Results

Participant enrollment began in January 2020. Study results are expected to be available in 2022.

Discussion

PrEP is a highly effective HIV prevention intervention, and with widespread use and high levels of adherence, it has the potential to drastically reduce HIV incidence among MSM in the United States. Despite its promise, PrEP uptake has been slow since receiving Food and Drug Administration approval in 2012 [48,49]. Its uptake has been the slowest among population groups that are most disproportionately affected by the HIV epidemic, including black and Hispanic MSM [50,51]. Innovative interventions that can be brought to scale are needed to increase PrEP uptake among disproportionately impacted populations.

HealthMindr is innovative in its approach of promoting PrEP in the context of a package of HIV prevention information and services delivered via a theory-based app. In addition to PrEP-specific content, HealthMindr provides information on HIV/STI testing, nPEP, and condom use; allows ordering of HIV/STI test kits, condoms, and personal lubricants; provides substance use and mental health resources; and provides service locators for STI/HIV testing and substance use and mental health counselors. These components form the backbone of a combination HIV prevention approach and provide multiple motivations for users to return to the app over time.

This study is subject to limitations and challenges. Despite our intention to oversample MSM of color, including Latinx MSM, HealthMindr is only available in English. Thus, language barriers might prevent otherwise eligible men from participating in this study. Currently, only oral tenofovir disoproxil fumarate/emtricitabine and emtricitabine plus tenofovir alafenamide are approved for use as PrEP in the United States. Approval of other formulations or modalities (eg, injectables) may necessitate changes to the protocol for the measurement and verification of PrEP uptake.

The results of this study will be useful for understanding the extent to which a mobile app designed to promote HIV prevention interventions for MSM, with a focus on PrEP, can increase PrEP uptake. If effective, as our preliminary data indicate, this smartphone-based intervention will be scalable to increase PrEP access to MSM across the United States.

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We gratefully acknowledge the contributions of the HealthMindr participants. We recognize the expert contributions of many dedicated public health professionals who worked to design, launch, and monitor the study and to provide services to participants at Emory University, George Washington University, and the University of Mississippi Medical Center. Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number R01DA045612. The original HealthMindr app was developed with support from the MAC AIDS Fund. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest

JDS reports involvement in HPTN 069/ACTG A5305 in which Gilead and ViiV contributed study medications and attending a Gilead Latinx Advisory Board Meeting in 2018. LAM reports funding from Gilead Sciences, Merck, ViiV Healthcare, and Roche.

Multimedia Appendix 1
Baseline survey for the HealthMindr randomized controlled trial.
[DOCX File , 71 KB - resprot_v9i2e16231_app1.docx]

Multimedia Appendix 2
Monthly check-in surveys to assess pre-exposure prophylaxis eligibility (intervention arm) and diet and exercise (control arm).
[DOCX File , 17 KB - resprot_v9i2e16231_app2.docx]

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Abbreviations

AMIS: American Men’s Internet Survey
CDC: Centers for Disease Control and Prevention
FAQ: frequently asked question
IDI: in-depth interview
MSA: metropolitan statistical area
MSM: men who have sex with men
nPEP: nonoccupational postexposure prophylaxis
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
STI: sexually transmitted infection

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Protocol

Nurse-Delivered Cognitive Behavioral Therapy for Adherence and Depression Among People Living With HIV (the Ziphamandla Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: There is an unmet need to develop effective, feasible, and scalable interventions for poor adherence and depression in persons living with HIV in low- and middle-income countries (LMIC).

Objective: This study aims to investigate the effectiveness of a nurse-delivered cognitive behavioral therapy (CBT) intervention for adherence and depression (CBT-AD) among persons living with HIV who are failing first-line antiretroviral therapy (ART) in Cape Town, South Africa.

Methods: This study is a 2-arm randomized controlled trial of CBT-AD integrated into the HIV primary care setting in South Africa. A total of 160 participants who did not achieve viral suppression from their first-line ART and have a unipolar depressive mood disorder will be randomized to receive either 8 sessions of CBT-AD or enhanced treatment as usual. Participants will be assessed for major depressive disorder using the Mini International Neuropsychiatric Interview at baseline and 4, 8, and 12 months. The primary outcomes are depression on the Hamilton Depression Scale (HAM-D; as assessed by a blinded assessor) at the 4-month assessment and changes in ART adherence (assessed via real-time, electronic monitoring with Wisepill) between baseline and the 4-month assessment. Secondary outcomes are HIV viral load and CD4 cell count at the 12-month assessment as well as ART adherence (Wisepill) and depression (HAM-D) over follow-up (4-, 8-, and 12-month assessments).

Results: The trial commenced in August 2015 and recruitment began in July 2016. Enrollment was completed in June 2019.

Conclusions: Results of this study will inform whether an existing intervention (CBT-AD) can be effectively administered in LMIC by nurses with training and ongoing supervision. This will present unique opportunities to further explore the scale-up of a behavioral intervention to enhance ART adherence among persons living with HIV with major depression in a high-prevalence setting, to move toward achieving The Joint United Nations Programme on HIV/AIDS 90-90-90 goals.

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International Registered Report Identifier (IRRID): DERR1-10.2196/14200

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KEYWORDS

major depressive disorder; cognitive behavioral therapy; HIV; medication adherence; integrated treatment; task shifting

Introduction

Background

The global HIV epidemic has disproportionately affected low- and middle-income countries (LMIC) and Southern Africa in particular [1]. In this region, South Africa has the highest rate of HIV infection and the highest number of persons living with HIV (PLWH) [1]. Coupled to this, it also has the largest antiretroviral therapy (ART) treatment program [2]. Successful management of the epidemic in these high-prevalence settings requires effective interventions across the care cascade. In 2017, it was reported that only approximately 30% of HIV-infected individuals in South Africa had achieved viral suppression [3]. One key aspect of effective viral suppression are behavioral adherence factors, including the management of mental disorders, such as major depressive disorder (MDD).

Depressive disorders are highly prevalent among South Africans in general, with the lifetime prevalence of MDD being 9.8%, whereas PLWH are at increased risk of developing a depressive disorder [4]. Rates of 10% of major depression and nearly 30% of minor depression have been noted in PLWH in South Africa [5]. Mental health services are not geared to address depressive disorders in general in PLWH in primary health settings, resulting in a large treatment gap—only 25% of persons affected by a common mental disorder ever obtain treatment [6]. Reasons for this treatment gap include the burden of large patient numbers and few mental health professionals, limited treatment options, and a general focus on hospital-based services as opposed to clinic- or community-based ones where the focus is often on severe mental disorders [7-9]. Counseling and psychotherapy for depressive disorders are not readily available in primary health care because of constraints in skills and resources [10,11]. As qualified psychologists are in short supply in South Africa, the use of mental health nurses, who staff the community mental health clinics, represents an opportunity to transfer critical cognitive behavioral therapy for adherence and depression (CBT-AD) skills more widely.

The impact of untreated MDD includes several adverse health outcomes, such as HIV disease progression and mortality [12], as well as reduced quality of life, disability, and increased time out of role [13,14]. A significant mediator of these outcomes in the context of untreated MDD is poor medication adherence [15]. PLWH in South Africa face several psychosocial challenges known to increase the risk for depressive disorders [16] and also several stressors unique to living with HIV, such as stigma, loss, and the challenges of living with a chronic disease [17,18]. Strategies to improve depression and coping with living with HIV within primary health care are, therefore, imperative.

In LMIC, there is a lack of consensus on how best to provide mental health care for PLWH [19,20]. Owing to resource constraints, such as a lack of qualified clinical psychologists to deliver evidence-based psychosocial treatments and a lack of psychiatrists to evaluate and further treat by utilizing the available medications in LMIC, health systems have utilized task-sharing approaches, with varied success [21,22]. The delivery of evidence-based psychotherapy for a combination of MDD and adherence difficulties by paraprofessionals would represent a significant step forward in addressing this issue among PLWH [23].

CBT is an effective treatment for MDD, with a strong evidence base [24]. In the context of MDD in chronic disease care, there are data to support its use to improve both MDD and adherence [25-27]. There is growing evidence that CBT for both adherence and MDD (ie, CBT-AD) might be effective in LMIC and in South Africa in particular. In an open case series of 14 sessions of CBT for depression in HIV clinics in Cape Town [28], 6 participants experienced a marked reduction in depressive symptoms during the course of treatment. This study established initial feasibility and acceptability for CBT for depression applied to PLWH in South Africa with a CBT psychologist as the interventionist. A further pilot study of 14 participants evaluated a shortened, nurse-delivered, integrated CBT-AD intervention adapted to the South African context [29]. Although improvements in adherence and mood were robust, there were challenges in provider fidelity to the intervention, which required intensive training and supervision. Further work to develop an effective, yet scalable, CBT-AD intervention is, therefore, necessary. In addition to the key issues of adherence and remission of depression, the issue of task-sharing of the intervention to nonpsychologists needs to be explored.

Trial Objectives

The goal of this trial is to investigate whether CBT-AD administered by nurses is effective for reducing depression and improving ART adherence among PLWH with adherence difficulties and MDD in primary health care in Cape Town, South Africa.

The primary objective is to compare the effectiveness of an isiXhosa-adapted, nurse-delivered CBT-AD intervention integrated into the HIV care setting in individuals who are failing, or have failed, first-line ART. The CBT-AD treatment is being compared with enhanced usual care (enhanced treatment as usual [ETAU]) at 12 months. ETAU consists of participants' medical providers being furnished with a referral letter indicating the psychiatric conditions they meet diagnostic criteria for including MDD. Primary study end points include depression scores on the Hamilton Depression Scale (HAM-D; as assessed by a blinded assessor) at the 4-month assessment and changes

in adherence scores (assessed via the electronic Wisepill device) between baseline and the 4-month assessment.

Secondary outcomes include HIV viral load and CD4 cell count at the 12-month assessment as well as adherence (Wisepill) and depression (HAM-D) over follow-up (4-, 8-, and 12-month assessments).

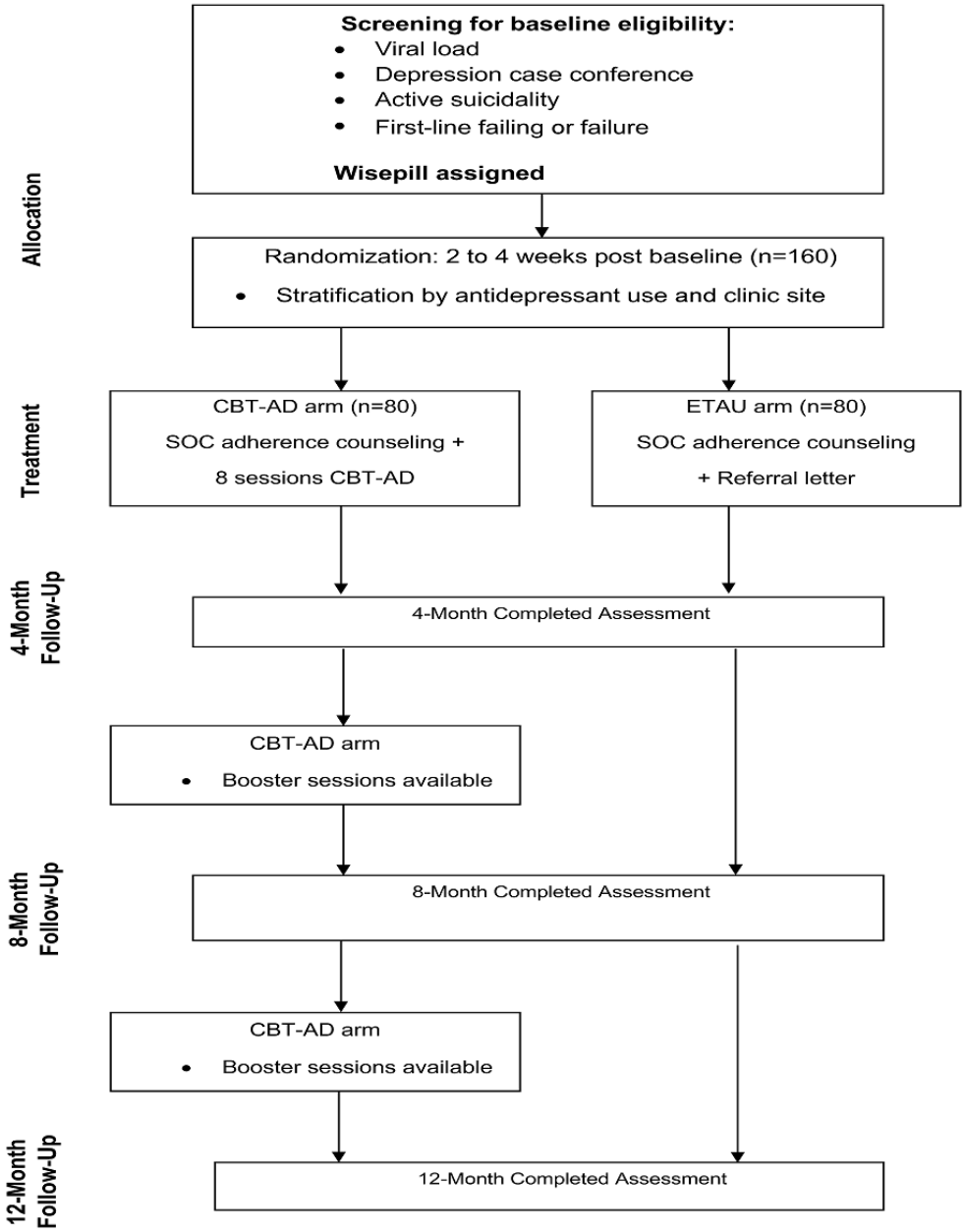
Methods

Trial Design

Project Ziphamandla (meaning *to be empowered* in isiXhosa) is a 2-arm, randomized controlled trial comparing CBT-AD with ETAU among PLWH who are failing, or have failed, first-line ART (see Consolidated Standards of Reporting Trials diagram in Figure 1).

Before randomization to treatment condition, participants complete a diagnostic assessment, clinician-rated measures of depression, and a self-report psychosocial assessment battery. We aim to randomize 160 participants to either CBT-AD (8 sessions) or ETAU. For participants in both conditions, treatment providers receive letters summarizing the results of the participants' diagnostic assessments. At this point, their treatment providers may further diagnose or treat (with antidepressants) MDD in the participants. Randomization follows approximately 1 month after the baseline assessment, so that stratification can occur by those who may or may not have commenced antidepressants as part of their care, following this letter. The 1-month period from baseline to randomization also allows for a baseline assessment of ART adherence using Wisepill real-time electronic adherence monitoring. For participants in both arms, there are 4 major study assessment points: baseline, post intervention (4-month), 8-month, and 12-month.

Figure 1. Consolidated standards of reporting trials diagram. CBT-AD: cognitive behavioral therapy for adherence and depression; ETAU: enhanced treatment as usual; SOC: standard of care; 4M: 4-month; 8M: 8-month; 12M: 12-month.



Study Sites and Participants

Recruitment

All participants are enrolled at primary HIV care clinics located in periurban areas of Cape Town. Potential participants are identified by their HIV primary care clinic as not responding to their current antiretroviral (ARV) treatment regimen (defined per local clinic standards as viral load >400 copies/mL). Research assistants (RAs) and other study staff situated at the primary care clinics work with staff in the HIV clinics to identify potential participants as they wait for their appointments. RAs are isiXhosa-speaking staff recruited locally for the study based on their research and clinical experience. They are extensively trained in the study protocol and supervised weekly by the project director who is a PhD-level clinical psychologist. The team also makes use of recruitment materials (eg, fliers) to describe that the study is for individuals who are managing depression and are not responding to their current ARV treatment regimen. Potential participants are screened using the MDD module of the Mini International Neuropsychiatric Interview (MINI) [30]. If individuals screen positive for MDD, but they do not have a recent (1 month) viral load, they are asked to undergo a blood draw to determine if their viral load is unsuppressed (ie, >400 copies/mL).

To be eligible for the study, participants must (1) be HIV seropositive, (2) have a current diagnosis of MDD (meets threshold for diagnostic severity based on the MINI), and (3) not have attained viral suppression from first-line ART. Participants are excluded if they (1) are unable or unwilling to provide informed consent, (2) have active untreated major mental illness (untreated psychosis or mania or high suicide

risk) that would interfere with CBT-AD, (3) have received CBT for depression, or (d) are aged <18 years.

Procedures and Study Assessments

Baseline

At baseline, participants complete the informed consent process and sign the release of information form to allow access to their medical record for most recent viral load and CD4 and current ART regimen. The nurse interventionists conduct the clinical assessment and administer the HAM-D and the remaining MINI modules. The RAs administer the battery of psychosocial assessments and other self-report questionnaires. The study team, including 2 clinical psychologists, meets to discuss each case and confirm that participants meet diagnostic criteria for MDD.

Participants also provide consent to allow the study staff to contact them for up to 1 year after completion of the study (ie, 1 year after the 12-month follow-up visit) for additional study purposes. The team makes use of mobile phones as well as meets participants at clinics when they attend other clinic appointments, as phone numbers do change frequently. In addition, participants also consent to allow the study to continue to access medical records at their clinic (eg, viral load and CD4 cell count) for a period of 5 years following completion of the study. We anticipate that approximately 1000 prospective participants need to be screened and consented to randomize the sample of 160 fully eligible individuals.

Randomization

Approximately 1 month after the initial baseline assessment, participants return for their randomization visit. At this visit, participants are randomly assigned to either CBT-AD or ETAU. Randomization is determined by a computer-generated chart, using the Research Electronic Data Capture (REDCap) randomization module [31]. Study staff enter stratification information (specifically, antidepressant use and site) and click randomize. Antidepressant use is confirmed by paper medical record review. Once the condition has been assigned in REDCap, this field is locked and cannot be changed.

As the study team sends a letter to HIV providers documenting the participants' depression, regardless of study arm, participants are given the opportunity to start using antidepressant medication outside of the study if they are not already using them. Therefore, at the randomization visit, we stratify randomization by whether or not the participant is taking an antidepressant (2 levels). We are also stratifying by which study site the participant is seen at (2 levels). Note our Data Safety and Monitoring Board (DSMB) reviews baseline data annually for adequacy of randomization.

Retention

The RAs track participant retention, which is reviewed weekly by the on-site project director. Procedures to maximize retention include reimbursing participants for their transport costs, providing participants with an appointment card, contacting participants to remind them of their scheduled appointments, and offering a R200 grocery voucher to participants who complete the full course of treatment. We also collect extensive locator information (eg, contact information of 2 significant others with whom the participant is in regular contact). We make efforts to maintain contact with individuals who move to a nonstudy site for their HIV care but are still willing to complete follow-up.

Following baseline, there are 3 further major assessment visits: post intervention (4 months), 8 months, and 12 months. At the 4-, 8-, and 12-month follow-up assessments, an independent assessor (IA), blind to study condition, repeats the clinician-rated assessments and administers the self-report measures to the participants. Bloods are drawn to determine viral load and CD count (unless available through medical chart proximal to the visit). The follow-up assessments occur at the study sites. However, in the event that a participant is unable to attend the study sites, the assessment may be conducted telephonically and arrangements can be made to have bloods drawn at the closest local facility.

All participants receive standard HIV and ART adherence counseling, comprising 3 to 4 sessions as part of standard of care at the clinic. Participants randomized to the integrated intervention (CBT-AD) receive their first intervention visit following randomization and receive up to 8 intervention sessions (plus optional booster sessions).

Interventions

Intervention Training

Before starting the study, nurse interventionists completed a weeklong training in the intervention that was conducted by the US and South African investigators. The South African investigators then provided further training until the nurses were deemed competent to begin administering the intervention. Since the nurses started administering the intervention to participants, the project director and the other South Africa–based clinical psychologist provide weekly supervision for an hour with support from the US investigators when needed. Moreover, 1 therapy session from each interventionist is orally translated by the RAs during the week it occurred and is listened to by the clinical psychologists in preparation for supervision. Approximately yearly, interventionists have booster training with the US and South African investigators to prevent drift and enhance fidelity and competence to the protocol.

Standard of Care—Enhanced Treatment as Usual

The clinic nurse provides feedback to the participant and to their clinic doctor (via a letter) about their MDD diagnosis. In addition, all participants undergo standard of care adherence counseling in the clinic, which may include several sessions with a clinic counselor. The letter specifically states that they are not restricted in terms of referral or treatment of MDD for their patient with respect to antidepressant medications or other interventions available.

Treatment Intervention—Cognitive Behavioral Therapy Intervention for Adherence and Depression

The intervention is the specific version that we have adapted to this setting based on a series of pilot studies [29]. Adherence and self-care issues are incorporated into each session. In early sessions, we employ motivational interviewing and

psychoeducation to establish confidence in, and credibility of, the treatment and to increase motivation for retention in the study. In addition, information specific to the participant is gathered during this interactive process, with careful attention to the role of specific life stressors that may influence case conceptualization. After session 1, which focuses on adherence counseling, at the start of each session, the nurse interventionist discusses adherence and depressed mood over the past week, reviews the results from the Wisepill as a graph depicting actual adherence in the past week, and discusses any adherence issues. This review allows for a discussion of progress and consideration of any problem solving or enhancements to the homework and coping plan assigned in previous sessions. To integrate CBT for depression with adherence skills, participants review adherence problem solving before starting the weekly CBT-AD sessions that focus on both depression and adherence/self-care. For this study, to maximize fidelity to the intervention, it is delivered in the form of a flip-book that the interventionist and participant both see, with additional notes on one side for the interventionist and visual depictions for the participant.

Session 1: Life-Steps

Life-Steps [32,33] is a single-session intervention based on general principles of CBT as well as more specific principles of problem-solving therapy. The adapted Life-Steps incorporates 13 informational, problem-solving, and cognitive behavioral components: (1) psychoeducation, (2) transportation to appointments, (3) obtaining medications, (4) formulating a daily medication schedule, (5) plan for storing medications, (6) plan for obtaining medications when away from home, (7) identifying social supports, (8) identify motivation for adherence and create association with reminders, (9) plan for coping with medication side effects, (10) communication with treatment team, (11) plan for taking medication when using substances, (12) responses to slips in adherence, and (13) review of plans. In each step, the participant and clinician define the problem, generate alternative solutions, make decisions about the alternatives, determine the optimal solution, and develop an action plan to implement that solution.

Session 2: Psychoeducation and Motivational Interviewing

A major focus of the first session involves gathering and presenting information in a way that promotes credibility and confidence in the treatment for participants [34]. Following principles of culturally informed functional assessment and case conceptualization [35-37], the nurse interventionist and the participant go over the CBT model of depression and, using motivational interviewing, identify specific motivations for behavior change and attempt to resolve participant ambivalence.

Sessions 3 and 4: Behavioral Activation

This module addresses depression-related withdrawal from pleasurable activities and social interactions. Participants learn to rate their mood with respect to the activities of their life and learn to systematically program *pleasure*- and *mastery-based* activities back into their lives. This module has been extensively adapted for patients with very limited resources who are living in poverty, including an isiXhosa-translated and locally adapted pleasant events checklist.

Sessions 5 and 6: Problem Solving

This involves teaching participants how to define and approach problems; generate and rank order alternative solutions; and implement optimal solutions. Participants are also taught how to break down a complex problem into manageable steps. This approach is used for the treatment of depression [38] and coping with chronic illness [39] and was reviewed positively by patients in our pilot study [29].

Session 7: Relaxation Training

Progressive muscle relaxation and diaphragmatic breathing are used to support management of negative mood and stress. Progressive muscle relaxation comprises tensing and relaxing particular muscle groups to learn to distinguish between the feelings of tensed versus relaxed muscles. Ultimately, the goal is to enable the participant to cue their muscles to relax when they start to feel anxious. These relaxation techniques are also widely used in behavioral medicine approaches to managing body pain, headache, and nausea [40], all of which can be side effects of ART and can interfere with adherence.

Session 8: Review and Relapse Prevention

One goal of CBT is to transition patients to *be their own therapists* and continue to use the skills after the active intervention ends. Accordingly, this session makes such plans and involves discussing how the participant may continue to cope with emergent life stress.

Booster Sessions

After completing the 8 sessions outlined above, participants randomized to the CBT-AD treatment condition also may attend up to 9 optional booster sessions throughout follow-up. Booster sessions comprise topics and skills from the previous 8 sessions to address any additional difficulties with adherence and/or depression, tailored to the individual and based on notes of their sessions.

Nurse Interventionist Protocol Integrity

The integrity and feasibility of the specific protocol is assured empirically. All intervention sessions are digitally recorded and subsequently translated into English by the RAs. Each session of 1 hour takes approximately 2 hours to translate. Participants provide consent for this but are not excluded if they refuse this aspect. Monitoring of the intervention takes into account both therapist adherence and competence [41]. We have developed a rating checklist to evaluate the nurse counselors adherence to CBT-AD, including whether the specific treatment components were, in fact, delivered.

Measures

Diagnostic Evaluation

The MINI 7.0 for Diagnostic and Statistical Manual of Mental Disorders-5 is one of the most widely used diagnostic instruments to reliably determine psychiatric disorders in clinical populations [42-45]. The MINI is designed to be used by clinicians but can be administered by nonclinicians with

appropriate training and supervision. The recruiters conducting the screening, the nurse interventionists, and the IA received training and weekly supervision on the MINI.

Primary Outcomes

Depression

The nurse interventionists at baseline and the IA at the follow-up assessments complete the HAM-D [46], one of the most widely used clinical measures of depression in psychiatric research that has strong psychometric reliability and validity. It has also been used in several antidepressant medication trials in South Africa [45,47,48]. Assessors are trained by certified trainers and licensed psychiatrists/psychologists on the study. The self-reported Center for Epidemiologic Studies Depression Scale [49] is also used. This measure has been translated into isiXhosa and used successfully in South Africa.

Assessment of Adherence to Antiretroviral Therapy

Wisepill is a real-time, electronic adherence monitoring system that comprises a pillbox container fitted with a global system for mobile communication chip. Using mobile phone technology, the Wisepill transmits a real-time signal to the Wisepill Web server each time the pillbox is opened. The Wisepill Web server can be securely accessed from any computer via the Wisepill Technologies website with the use of a designated log-in and password. It captures real-time data on device openings and, hence, provides the results of weekly assessments for longitudinal modeling. For the purposes of this study, we did not establish a *window* for missed doses; they were just counted as whether or not they opened the device the required number of times (ie, if they opened the device on 2 separate occasions for a twice daily regimen, it would be counted as fully adherent for the day, and if they opened it once for a twice daily regimen, it would be counted as 50% for the day). To ensure the Wisepill device is working properly, we check in with participants at approximately half-way between major study visits (ie, at approximately 2, 6, and 10 months in study participation). In addition, we monitor Wisepill functionality between the baseline visit (when the device is issued) and the randomization visit. To ensure the device is working properly, if no signal is detected from the Wisepill device for 3 or more days in a row within the first week after the device has been issued, we contact the participant to ascertain if they are experiencing any issues with their device. The purpose of these check-ins is solely to enquire about any difficulties using the Wisepill device. The Wisepill Web server also monitors device battery levels, and participants whose devices had low battery are contacted to remind them to charge the Wisepill device.

Secondary Outcomes: HIV Viral Load and CD4 Cell Count

Absolute CD4 cell count and number of HIV viral copies per milli liter of blood are extracted from the participants' medical record at baseline (to assess the first-line treatment failure inclusion criteria) and at 12-month follow-up. This allows for a calculation of the proportion of patients with virologic suppression. Participants who do not have viral load test results within 1 month of the baseline assessment or 4-, 8-, and 12-month follow-up undergo a blood draw for assay using the COBAS AmpliPrep/TaqMan HIV-1 test (range: 20-10,000,000 copies/mL) [50].

Psychosocial Self-Report Assessment Battery

Participants complete a demographic questionnaire including items regarding age, sex, sexual orientation, educational history, and employment status. National Institutes of Health (NIH)–defined categories are used to assess participant race and ethnicity, although we anticipate mostly (if not only) isiXhosa-speaking black South African participants. We also obtain data on mode of HIV infection, using a single-item (AIDS Clinical Trials Group) question assessing risk factors for likelihood of means of HIV infection.

Medications

During baseline assessment, participants will provide information regarding all of their medications (psychiatric, HIV, and other). When completing assessments at every study visit thereafter, patients are asked to report any changes to their medication regimen. These changes are recorded on adherence questionnaires and cross-checked with clinic chart review. Any initiation or changes to antidepressant medications are tracked across all participants and will be used as covariates in analyses.

Data Analysis

Primary Outcome Measures

The primary outcome analyses compare changes in depression (HAM-D; continuous measure assessed by a blinded assessor) and adherence scores (continuous measure assessed via Wisepill) from baseline to the 4-month assessment.

Secondary Outcome Measures

Secondary outcome measures include viral load, analyzed categorically (suppressed vs not) at the 12-month outcome, using <400 copies/mL as suppressed (consistent with recent work analyzing chart-extracted viral load data from the same clinics in Khayelitsha). CD4 is analyzed continuously at the 12-month outcome. In addition, HIV medication adherence and depression scores over time are examined as secondary outcomes using the 4-, 8-, and 12-month assessment time points.

The ultimate data analytic approach will depend on the distribution of the data. We anticipate that we will use generalized linear models), which are estimated using generalized estimating equations with robust standard error estimates to account for repeated measures of the outcome. For the primary outcomes, we will examine adherence scores longitudinally using the Wisepill data and Hamilton scores using the 2 time points (baseline to 4 months) comparing the 2 study arms. For outcomes assessed at the 4 major assessments (ie, baseline and 4, 8, and 12 months), we will use repeated measures analyses. For 12-month viral load, we will test the proportion of those who are suppressed using Fisher exact test. If continuous viral load data are analyzed, we will make log transformations and examine viral load using repeated measures. To reduce bias, the intention-to-treat principle is utilized, where individuals are analyzed according to the condition they were randomized, regardless of their fidelity to that condition.

Exploratory Outcomes

We examine the possible effects of alcohol and substance use by means of the World Health Organization's alcohol, smoking, and substance involvement screening test [51]; the alcohol use disorders identification test [52]; and the MINI [30], and we examine demographic factors as moderators to the effects of the nurse-delivered CBT intervention. For these analyses, we fit interaction terms to the models. We also separately assess effects of the treatment in subgroups defined by these factors. If results indicate that the intervention significantly increases adherence, we then assess the extent to which this effect operates through possible mediators (eg, depression, coping, and social support). In the first set of models, we add the main effects of alcohol (as an example) and time (ie, the different assessment time points), in addition to an intervention by alcohol use interaction and intervention by time interaction. We conduct a product of coefficients test for the effect of each mediator as an intervening variable [53]. Statistical significance of the mediated effect will be determined by the asymmetric distribution of products test. This test is conducted separately for the other mediators.

Sample Size Considerations

The study is powered to detect differences in the depression outcome as well as virologic suppression, and accordingly, a sample size of 160 randomized participants is appropriate. Using repeated measurements with a medium effect, we will have almost 90% power to detect a 10% difference in depression with complete retention at randomization, and assuming 20% attrition, we will have 84% power to detect a difference. On the basis of our earlier efficacy trial that was completed when this study was being designed, for those who entered the study with detectable viral load (in this study, all participants entering will have detectable virus), there was a 20% difference in the proportion of those who had undetectable virus at 12-month follow-up: 40% of those in the control condition compared with 60% of those in the experimental condition [27]. On the basis of these effect sizes, for this study, with a sample size of 160, we are powered to detect differences in the secondary binary outcome, virologic suppression, as follows: we will have >90% power to detect at least a 25% difference and >80% power to detect at least a 20% difference in the proportion of those with detectable viral load. These calculations assume a 20% attrition rate that occurs during the active treatment phase of the study, that the proportion of subjects with viral suppression in the usual care comparison condition is 0.4, that the type I error rate is 5%, and that the correlation between observations on the same subject is 0.5.

Data Safety and Monitoring Board

The study team has constituted a DSMB including several leading investigators. DSMB members were recruited because of expertise covering behavioral intervention development, global mental health, and implementation. The DSMB meets at least annually and is provided with a report on study progress and enrollment and details of all adverse events. The DSMB includes open and closed sessions.

Ethical Considerations

The trial was approved by the Human Research Ethics Committees (HREC) of the University of Cape Town (HREC 010/2014) and the Institutional Review Board (IRB) of the University of Miami (IRB Study Number: 20150399). The City of Cape Town research office also approved the study (6584/10530). The trial is registered with ClinicalTrials.gov. Informed consent is obtained from all potential participants before enrollment. Prospective participants are informed of all foreseeable risks of study involvement, that participation is voluntary and does not affect their clinical care, and that they may withdraw their consent without this affecting their medical care. The consent forms are available in English and isiXhosa, the main languages spoken in these clinics. To ensure confidentiality, a unique participant identification number is assigned to participants, and this deidentified number is used on all data collection forms. We collect data using the REDCap electronic data collection platform that transmits data in real time to a central secure database, enhancing data safety. All data not stored electronically, such as copies of consent documents, are stored in locked filing cabinets in designated locked offices. Forms with personal identifying information are stored separately from case report forms. Study records are not available to participants' health care providers unless requested and documented that participants give consent to this release. We, however, ask participants' consent to obtain relevant medical information including HIV RNA viral load test results from their clinic folders.

The main risk associated with this study is the initial worsening of symptoms and risk of suicide arising from issues uncovered during counseling [54]. To minimize this potential harm, we train staff to screen all participants who report or display signs of distress for risk of suicide and to provide referrals (based on severity of risk) to appropriate services. These cases are discussed with the study clinicians. There are also potential benefits to participation. All participants benefit from screening for MDD and referral to mental health care as appropriate. We hypothesize that participants in the intervention arm will experience improvements in their mental health, adhere better to ART, and reduce their risk of treatment failure.

Results

The trial commenced in August 2015 and recruitment began in July 2016. To date, we have screened over 900 participants and randomized 139 participants. A total of 45 participants have exited the study at 12 months. Recruitment continued till July 2019, with the final participant exiting 12 months later in June 2020.

Discussion

The development of interventions to improve HIV outcomes in the care cascade has become critical to the success of global ART programs. More specifically, attainment of the 90-90-90 The Joint United Nations Programme on HIV/AIDS goals will require a concerted effort, across testing, care engagement, and effective ART adherence. Individuals enrolled onto ART may struggle to adhere for various reasons, but the detection and

treatment of depressive illness is a major treatment gap, with potential for significant health and health-economic benefits. In addition, behavioral interventions, especially in LMIC, must be scalable and cost-effective. Scalable means that the intervention can be integrated into primary health care and delivered by nonmental health specialist providers (where professional psychiatrists and psychologists are too few). Cost-effective means that there needs to be a clear benefit to the overall health care and economic system to justify directing resources to recruiting, training, and sustaining interventionists.

The proposed study is unique in that it attempts to address several of these key questions. Most notably, the intervention targets both adherence challenges and depressive symptoms simultaneously. This patient-level integration of ART medication adherence and depression is key to the success of the program. Although the relationship between mental disorder (specifically MDD) and poor adherence is clear, there are few randomized controlled trials demonstrating clear benefits of behavioral interventions on biological outcomes in LMIC. Furthermore, the intervention is being delivered by clinical nurse practitioners with experience in mental health. Nurses are central figures in the growth and development of the South African health care system and, indeed, many LMIC primary health care programs. This is evidenced by the South African Nurse-Initiated Management of Antiretroviral Treatment program [55].

The inclusion of both behavioral and biological outcomes is a major strength of this study. These combined outcomes strengthen the case for improving mental health care services, which have been historically underfunded in many LMIC. Recent data suggest that electronic medication adherence tools (such as Wisepill) are not used uniformly across study samples and, therefore, cannot be used a sole measure of medication use. Successful demonstration of medium- to long-term benefits to sustained viral suppression is key to the efforts in individual- and community-level programs.

It is hoped that a positive outcome in this trial would influence health systems policy not only in South Africa but also in other LMIC. With this in mind, using nurses as interventionists represents a novel approach to complex disorders. Nurses, particularly those with mental health training or experience, may be uniquely suited to fill an important gap in existing task-sharing models, including expanding local capacity for training and supervising nonprofessional providers in CBT and treating more complex, treatment-resistant patients in stepped-care models that also include lay counselors at lower tiers of care. Furthermore, training lay counselors in more complex CBT techniques may be challenging [56] and may not be suitable for more complicated clinical cases. We, therefore, believe that nurses are a provider group uniquely positioned to support scale-up of behavioral interventions to support the needs of more complicated individuals with poor adherence and comorbid psychiatric disorders as well as increase local capacity for training and supervision in CBT in task-sharing models that use lay health workers.

Potential challenges to the success of this trial include difficulties in identifying and recruiting individuals in busy clinic settings, with both virological failure and MDD. To successfully randomize participants, we confirm that the 1-month viral load is >400 copies and that criteria for MDD are met. To address this challenge, we make allowance for additional blood draws in depressed individuals. We work tirelessly with clinic staff in their busy HIV clinics to identify potential participants. A second potential challenge is participant retention through both the acute (intervention) component and the long-term (12 months) outcome period. In this study, PLWH live in periurban areas and may struggle to attend regular planned therapy visits because of casual employment, sickness, or migration. We ensure that we obtain maximal and contemporaneous contact information and work hard to develop rapport with participants across the study. Participants who miss visits are tracked through the clinic system and approached on visit days, and those who migrate may be allowed to complete major assessments by telephone. Hopefully, this will mitigate the risks of attrition. Finally, although previous studies have reported limited or variable success with task-shared behavioral interventions because of poor fidelity, limited skills, or insufficient supervision, major components of this study are intervention supervision (which is performed weekly in a face-to-face fashion), fidelity assessment, and session monitoring. We also note that although we are stratifying for antidepressant prescription across both arms, it is possible that the study itself may result in a change in prescribing behavior. We do not anticipate that this will be a marked effect but will report on this when a final medical record review is conducted at study completion.

In summary, this study has the potential to address several key questions regarding how effective behavioral interventions might be delivered and integrated into primary health care settings in LMIC with high HIV prevalence. Our findings might be used to inform how patients with adherence difficulties and HIV nonsuppression might be effectively treated in primary care, which is critical to motivating to health authorities for scale-up.

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Authors' Contributions

JJ is the coprincipal investigator of the Ziphamandla study, and SAS and CO are multiple principal investigators. The study was conceived by SAS, COC, LSA, and JJ. This manuscript was drafted by JJ, LSA, RSA, JM, JSL, and SAS.

Conflicts of Interest

SAS receives royalties from Oxford University Press on CBT manuals addressing adherence and depression in chronic illness. He also receives royalties from Oxford University Press, Guilford Publications, and Springer/Humana Press for books that address the delivery of CBT and related issues. The other authors declare that they have no conflicts of interest.

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Abbreviations

ART: antiretroviral therapy
ARV: antiretroviral
CBT: cognitive behavioral therapy
CBT-AD: cognitive behavioral therapy intervention for adherence and depression
DSMB: Data Safety and Monitoring Board
ETAU: enhanced treatment as usual
HAM-D: Hamilton Depression Scale
HREC: Human Research Ethics Committees
IA: independent assessor

IRB: Institutional Review Board
LMIC: low- and middle-income countries
MDD: major depressive disorder
MINI: Mini International Neuropsychiatric Interview
NIH: National Institutes of Health
NIMH: National Institute of Mental Health
PLWH: persons living with HIV
RA: research assistant

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Protocol

A 21-Day School-Based Toothbrushing Intervention in Children Aged 6 to 9 Years in Indonesia and Nigeria: Protocol for a Two-Arm Superiority Randomized Controlled Trial

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Abstract

Background: The World Health Organization reports that dental cavities affect 60% to 90% of children globally. FDI World Dental Federation and Unilever Oral Care have developed public health programs to improve brushing habits over their 12-year partnership. The last of these (phase III) named Brush Day & Night aimed to educate children on brushing twice daily with a fluoride toothpaste and gave useful information for a new project, phase IV. The 21-day Brush Day & Night program is an intense education activity designed to establish the habit of brushing day and night with a fluoride toothpaste. The program involves daily brushing instruction and includes free toothpaste and toothbrushes.

Objective: The main objective of the study is to evaluate the impact of a 21-day school program on children's oral health. As a secondary objective, we aim to evaluate the impact on the knowledge, behavior, toothbrushing habits, and quality of life in school children aged 6 to 9 years after a 21-day school program and compare with baseline and a control group as measured by the self-reported questionnaires issued to children (in particular, the self-reported brushing frequency and positive responses on fluoridated toothpaste use). The enduring nature of the program will be determined by the inclusion of 8- and 24-week time points.

Methods: The study is a 2-arm superiority randomized controlled trial. Clusters in this study are infant and junior schools in Indonesia and Nigeria. The study aims to recruit 20 schools with children aged 6 to 9 years in each country. At baseline, children in both intervention and control schools will answer a questionnaire and have their clinical oral health assessed using the Simplified Oral Hygiene Index (OHI) and Decayed Missing and Filled Teeth index. Children in the intervention schools will then take part in a structured 21-day Brush Day & Night intervention. Children in the control schools will be provided with free toothpaste and toothbrushes but will not receive the 21-day intervention. The questionnaires and OHI assessments are repeated after the 21-day program is completed and again 8 weeks later and 24 weeks later for all participating children. Parents/carers/guardians of all children will sign the informed consent and complete questionnaires on their own experience and attitudes toward oral health and toothbrushing routine at each of the four times points (baseline, 21 days, 8 weeks, and 24 weeks). The study will be conducted by the national dental associations of Indonesia and Nigeria and was approved by the ethics committees of both countries.

Results: The study is ongoing. Recruitment of schools started in Indonesia in February 2018 and in Nigeria in April 2018 for the first part of the study, which concluded in Indonesia in September 2018 and in Nigeria in November 2018. The second part of the study (the second half of the schools) started in November 2018 in Indonesia and December 2018 in Nigeria.

Conclusions: We expect to collect all the data during 2019 and publish findings from the study by March 2020.

Trial Registration: ClinicalTrials.gov NCT04001296; https://tinyurl.com/selxraa

International Registered Report Identifier (IRRID): DERR1-10.2196/14156

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KEYWORDS

school children; oral health; OHIs; DMFT; school program; knowledge transfer; behavior change

Introduction

Prior Work

The Brush Day & Night (BDN) program is the result of a 12-year partnership between FDI World Dental Federation (FDI) and Unilever. It is an intense education activity designed to establish the habit of brushing day and night with a fluoride toothpaste. The program involves daily brushing instruction and includes free toothpaste and toothbrushes (see Multimedia Appendix 1 for more information).

The program was designed based on the theories of behavior change. Behavior change interventions and the formation of health promoting habits is thoroughly reviewed by Lally et al [1] and specifically in the context of interventions to improve tooth brushing by Claessen et al [2]. This and other research was crystallized into the Unilever 5 levers of change model [3], which is the foundation for the design of this particular intervention. The first step of the model is to identify barriers, triggers, and motivators to adopting a new behavior. Those insights are considered in designing a new behavioral intervention in 5 steps:

- Make it understood
- Make it easy
- Make it desirable
- Make it rewarding
- Make it a habit

This is a 21-day intervention, a duration chosen to reflect past research [4] that repetition of between 12 and 15 times is necessary to make a habit change, and 21 calendar days is 15 school days. The choice of schools within which to implement the program was influenced by the work of Pine et al [5] that states schools can be an optimum place for behavior change interventions where both parents and teachers may be involved in the intervention. The duration of 21 days was also chosen to avoid the program becoming overly onerous for the schools and teachers implementing the program.

Previous work has shown that the 21-day BDN program is effective in improving children's toothbrushing knowledge and habits [6]. A study conducted in 10 countries with 7991 children aged between 2 and 12 years revealed that 25% more of the school children brushed their teeth twice a day at the close of the 21-day intervention. The program was found to be more effective among the 7 to 9 year age group.

Rationale for the Study

The importance of preventing oral diseases to achieve good oral and general health is well known [7]. Regular twice-daily toothbrushing with a fluoride toothpaste is widely recommended for all age groups [8,9] and is effective in improving gingival health and preventing caries. It has been demonstrated that the successful adoption of good brushing habits in childhood can be effective in reducing dental caries risk for the longer term [10].

The 21-day BDN school program is a behavioral change intervention targeting primary school age children [6]. It is an immersive program designed to be delivered by dentists, dental nurses, or teachers at schools. This new study using the 21-day BDN school program aims to build on the previous results [6], with a new design. The previous study used nonprobabilistic convenience sampling with an intervention group only. Additionally, due to differences in evaluation time points which varied between 6 to 12 months, no quantitative conclusions could be drawn from the plaque index score. The study power and robustness of the methodology were cited as necessary improvements in a future investigation.

Study Objectives

The main objective of the study is to evaluate the impact of a 21-day school program on children's oral health. The primary objective is to evaluate the impact on knowledge, behavior, and toothbrushing habits in school children after a 21-day school program and compare with baseline and control group. Subsequent objectives will examine the impact on oral health, durability of the intervention, and any wider benefits on parent/carer and child well-being. The specifics of the objectives are outlined in Textbox 1.

Textbox 1. Study objectives.

- Primary: measure the impact on knowledge, behavior, and toothbrushing habits in school children after a 21-day school program and compare with baseline and control group
- Secondary: measure the impact on oral health via plaque levels at baseline and after a 21-day school program with children and compare with children in their control group
- Tertiary: evaluate the longer term impact of the 21-day program on knowledge, behavior, and oral health in children after a period of 8 weeks and 24 weeks (ie, approximately 7 months in total)
- Quaternary: provide evidence that the 21-day school program is effective in getting parents and carers to also improve their brushing habits and to brush day and night
- Quinary: measure the change in quality of life, well-being, and social measures of school children after a 21-day oral health program

Methods

Intervention

Children participating in the 21-day BDN school program are each provided with toothpaste and a toothbrush and follow brushing instruction, supervised brushing, and the singing of songs to facilitate learning the importance of brushing day and night, with stickers and calendars to track progress. A celebration is held at the end of the program with certificates and rewards. The program is supported by colorful materials with bespoke cartoon characters. Parents are provided with educational leaflets.

Study Design

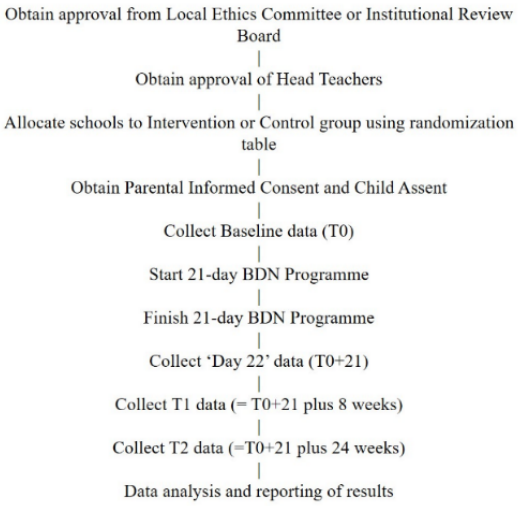
This study is a 2-arm, superiority cluster randomized trial. Clusters in this study are infant and junior schools in Indonesia and Nigeria. Schools will be matched into pairs by location and then randomized to intervention and control groups using a randomization table.

The study will look to recruit children aged 6 to 9 years in school grades 1, 2, and 3 to participate in the study. Children who assent to take part in the study (see Multimedia Appendix 2 for form), meet the selection criteria, and have the informed consent of their parents (see Multimedia Appendix 3 for form) will be enrolled in the study. The study flowchart is shown in Figure 1.

The T0 (baseline), T0+21 (end of 21-day intervention), T1 (8 weeks after the end of the intervention), and T2 (24 weeks after the end of the intervention) data collection time points will consist of questionnaire completion and a clinical assessment of plaque level evaluation using the Simplified Oral Hygiene Index (OHI-S) and an additional caries evaluation at T0 and T2 using the Decayed, Missing, and Filled Teeth index (DMFT). For the control group, the same flowchart will be followed, but the "Start 21-day BDN program/Finish 21-day BDN program" is replaced by only providing toothpaste and toothbrushes to school children.

The delivery of the intervention program relies on Unilever materials including toothpaste and toothbrushes as well as all the necessary educational materials. These materials are produced and delivered by Unilever locally. Translations of the materials to a local language will be completed if necessary. Toothpaste provided in Indonesia will be a commercially available and marketed product manufactured by Unilever Indonesia containing 1450 ppm fluoride as 1.12% sodium monofluorophosphate in a chalk base (Pepsodent Anti-Cavity or similar). In Nigeria, a commercially available and marketed toothpaste sold by Unilever Nigeria containing 1450 ppm fluoride (0.32% sodium fluoride) in a silica abrasive (Pepsodent Cavity Fighter Gel or similar) will be provided.

Figure 1. Study flowchart.



Selection of Schools

This is a cluster randomization trial with schools being the clusters, randomized to intervention or control groups. Schools need to be matched in terms of setting (city, suburb, rural) and socioeconomic status. The sample size calculation determined the number of schools that would be required to detect a difference between the test and control groups. The response of interest is an improvement in brushing behavior.

For Nigeria, it is assumed that 30% of the children are already brushing twice a day [6]. The trial is designed to detect a minimum 35% difference in the number of children brushing day and night at day 22 between the intervention group and the control group. It is assumed that the control group will see a 20% increase in proportion of children brushing twice a day due to the free toothpaste and toothbrushes they are given (Hawthorne effect). The interclass correlation has been set low at 0.05 and 0.10 (ie, low interpupil correlation) as we do not expect the children to influence each other in their brushing behavior because brushing will be carried out at home.

For Indonesia, it is assumed that 84% of the children are already brushing twice a day [6]. The trial is designed to detect a minimum 30% difference in the number of children brushing day and night at day 22 between the intervention and control group. It is assumed that the control group will have 40% of

children brushing twice per day as a result of the Hawthorne effect. Again, the interclass correlation has been set at 0.05.

Therefore, for both Nigeria and Indonesia, the target number of schools is 20 (10 intervention and 10 control schools) calculated using power 80% and a significance level of .05. This number of clusters should also be sufficient to detect a difference of 0.5 in the OHI-S (plaque) at the same power and significance level. About 30 children in each class, in each grade, are anticipated, and for each child, the participation of a parent completing the questionnaires at each time point will be requested.

Recruitment and Management of Participants

Rollout

After written approval from the ethics or education authority has been received, local study coordinators (LSC) will visit each school to obtain the head teacher's permission to attend schools to deliver the 21-day BDN program and collect data. The LSCs are also responsible for the full delivery of the program from recruiting and matching the schools and composing the dental teams to training the teachers. A dental team is generally composed of 2 to 4 trained and certified dentists and nurses. Dentists will also receive appropriate training and be calibrated for the oral health examinations. A trained and calibrated dental team will be responsible to collect the answers from the self-reported questionnaire and complete the clinical observation of oral health statuses recording the plaque index at all study end points and the caries DMFT index at baseline and at the end of the study (T2). In addition, the LSC will be in charge of training the teachers to deliver the 21-day BDN program over 21 days.

The LSC will be given a list of unique user IDs generated for each school, for each class, and for each child participating in the program. The head teacher will be asked by the LSC to provide a list of the children attending years 1, 2, and 3 in their schools. The list should include first and last name, gender, and date of birth (dd/mm/yyyy) for each child plus the name of the child's parent.

A member of the study staff will explain the details of the study in person to parents. If parents wish their child to participate, the parent will sign the appropriate informed consent form. Two copies of the informed consent will be completed, one copy will be kept by the parents and one copy returned to the national dental association team. Each LSC is responsible for leading the dental teams. The LSC will assign an ID to each child participating in the study. This ID only plus the exact date of birth will be used to report data, so the data collected will be anonymous once reported.

Selection Criteria

A list of inclusion and exclusion criteria will be defined to manage participants in the study. Children in school year grades 1, 2, and 3, aged 6 to 9 years, in good general health, willing and able (eg, to brush teeth and understand and respond to questions) to participate in the 21-day BDN activities at school and at home, and planning on attending their currently registered school for at least the next 12 months will be included.

Exclusion criteria include failure of parents to provide written informed consent, children scheduled for medical or dental procedures during the duration of the study, children who have a known allergy to any toothpaste ingredients, children with obvious signs of gross or untreated caries or of significant periodontal disease which in the opinion of the dentist would affect the scientific validity of the study, or children whose well-being would be affected by the study. Children and their families should have no affiliation (eg, employee) with either FDI or Unilever.

Participant Restrictions

A list of restrictions is also set on participants, such as children should not take part in any other form of oral health education for the duration of the study (ie, those that might be delivered at community health centers). Parents should inform their child's class teacher if they receive any form of dental treatment during the study duration or if they have been prescribed any medicines.

Participant Withdrawal

Participants can withdraw from the study at any time, and parents will be advised at the start of the study that they may withdraw their child and family from the study at any time without giving a reason. If a parent withdraws a child from the study, the parent will also be considered withdrawn. Children will be withdrawn from the study analysis if they miss more than 5 days of school during the 21-day intervention period. School attendance during the 21-day period will be checked against the school register.

Ethics and Quality Standards

The study was presented to the local ethics committees in Nigeria and Indonesia to receive ethics agreements for health research using humans as research subjects. In Nigeria, the study was granted approval by the State Universal Basic Education Board before enrollment of the schools. In Indonesia, the study was granted approval by the Health Research Ethics Commission at the Faculty of Dental Teaching, Trisakti University, also before the enrollment of the schools. The study was registered with ClinicalTrials.gov (NCT04001296).

It is the responsibility of the LSC to ensure that the study is conducted in accordance with the principles of Good Clinical Practice, 2008 version of the Declaration of Helsinki, and applicable local laws and regulations concerning studies conducted on human subjects that are outside of the definition of a medicinal product or medical device. Quality assurance audits may be performed by the sponsor or any ethics committee or regulatory authority during the course of the study or at study completion.

Study End Points

Assessment of Behavioral Change Impact

The objective of this study is to evaluate the impact of educational school programs in improving the oral health of local communities. The primary objective of the study analysis will be to measure the impact on knowledge, behavior, and toothbrushing habits in school children in Indonesia and Nigeria after a 21-day school program. This will be evaluated using three questions (specifically questions on behavior and

knowledge) from the children's questionnaire at all evaluation points (T0, T0+21, T1, T2). Improvement in knowledge and behavior will be calculated based on the percentage of positive change. Positive change is considered when a child selects the correct answers of twice daily brushing with a fluoride toothpaste.

The secondary objective employs the use of the OHI-S to assess plaque levels. More frequent brushing will result in lower plaque levels compared with baseline and compared with control groups. Plaque levels will be used to validate reported brushing frequency with assessments timed to align with questionnaire completion (how well are the children retaining and acting on the information/motivation delivered by the 21-day intervention?). To evaluate the longer term impact of the 21-day program on knowledge/behavior and oral health in children after periods of 8 weeks and 24 weeks, the children in the test group should report higher levels of brushing frequency and reduced plaque levels compared with children in the control group. To provide evidence that the 21-day school program is effective in getting parents and carers to also improve their brushing habits and to brush day and night, parents' own brushing frequency, use of fluoride toothpaste, amount of toothpaste, and toothbrushes purchased should increase when compared with baseline and compared with parents in the control group. To measure the change in quality of life, well-being, and social measures of school children after a 21-day oral health program, children may report less dental discomfort/pain and need to take fewer days off school as a result. Additionally, at baseline (T0) and T2, all children will be scored for their caries prevalence using the DMFT index. No direct conclusions on the caries can be made but it is important descriptive information that is often not available in these two countries and could serve further research.

Questionnaires

This study aims to understand, to a greater extent, the impact of the 21-day BDN program on quality of life–related outcomes and, thus, includes more detailed questions and addresses some aspects of the new oral health definition [11].

The parent questionnaire includes 14 main questions addressing aspects on oral health behavior and knowledge, socioeconomic factors, well-being, and quality of life–related outcomes. Most of the parent questions were taken from validated questionnaires, namely the World Health Organization oral health surveys, Global Oral Health Assessment Index, and Positive Oral Health and Well-being 15-term [12-14]. Other questions were developed through a process in which an expert group identified topics included in similar surveys and developed questions on these topic areas adapted to the study objectives and setting. Parent questions can be found in Multimedia Appendix 4.

The children's questions were derived from the parent questions and adapted for children's comprehension and to obtain the required information as set by the objectives of the study. In addition, building on learning gained in the previous study [6], the questionnaire was further refined to remove overlapping answers encountered that required some retrospective reinterpretation prior to analysis.

The children's questionnaire includes 8 main questions to address the primary objective of improvement in behavior and knowledge, adapted to their comprehension.

- Did you brush your teeth yesterday?
- If yes, how many times?
- Did you brush your teeth today?
- If yes, how many times?
- How often do you brush your teeth at home?
- Most days, do you brush your teeth both in the morning and the evening?
- Do you think it is important to brush your teeth every day?
- If yes, how often should you brush your teeth every day?

An intense immersion into a fun and engaging 21-day BDN program will inform children of the importance of twice a day brushing with a fluoridated toothpaste and motivate improved brushing frequency. This will be seen in results of questionnaires issued to children at time points throughout the study. All children's questions can be found in Multimedia Appendix 5.

Simplified Oral Hygiene Index

The OHI-S [15] is a rapid method for evaluating oral cleanliness of population groups. In this study, the following permanent teeth will be scored: 16, 11, 26, 46, 31, and 36. However, due to the specific target age group of the study, the equivalent deciduous teeth 55, 51, 65, 85, 71, and 75 will be scored when the above-mentioned permanent teeth are not present.

Decayed, Missing, and Filled Teeth Index: Tooth Level

The DMFT index [14] has been used for more than 70 years and is well established as the key measure of caries experience in dental epidemiology. The DMFT index can be applied to both the permanent and primary dentition. Table 1 shows the full schedule of study end points by time point and intervention for this study. The schedule is the same for control and intervention groups.

Table 1. Study end points by time point and intervention.

Group and end point	Baseline T0	T0+21[a]	T1[b]	T2[c]
Children				
Questionnaire	x	x	x	x
OHI-S[d]	x	x	x	x
DMFT[e]	x			x
Parents/carers				
Questionnaire	x	x	x	x

[a]T0+21: end of 21-day intervention.

[b]T1: 8 weeks after the end of the intervention.

[c]T2: 24 weeks after the end of the intervention.

[d]OHI-S: Simplified Oral Hygiene Index.

[e]DMFT: Decayed, Missing, and Filled Teeth index.

Data Management

Data Exclusion

All school data will be used, and where a school has been significantly noncompliant (eg, a school has not sufficiently followed and completed all elements of the 21-day BDN program) with the protocol, this will be registered. Minor deviations may be included at the discretion of the LSC. Participants who missed more than 5 days (one school week) of the 21-day BDN program will have this information registered in the analysis.

Data Handling and Record Keeping

Paper forms (Multimedia Appendix 6) will be used to collect all questionnaire answers from parents and children as well for reporting the oral health indicators used, the OHI-S and DMFT. All collected data will be compiled using SPSS Statistics (IBM Corp) software for study analysis.

The LSC will keep a separate confidential enrollment log that matches identifying codes with children's names and addresses. The LSC will maintain these documents at the site. It is the responsibility of the LSC or designee to maintain adequate clinical study records. Copies of all clinical study material must be archived for a period of at least 15 years after the end of the study (or more as legally required). All documents must be archived in a secure place and treated as confidential material. The anonymous data will be made available to researchers upon request.

Statistical Analysis

As outlined in Table 2, five outcomes measures have been prepared and prioritized to evaluate the effect of the 21-day program. At each time point, summary statistics will be calculated for intervention and control schools and include within- and between-group analyses.

Each of the mentioned measures in Table 2 will be compared between T0 and T0+21 and between T0 and T0+21 and T1 and T2 for the intervention and control groups. The mean change will be reported, with 95% confidence interval and associated *P* value. Longitudinal models will be used. Multinomial logistic regression will be performed when the outcome variables have a nominal level of measurement. For ordinal and interval outcome variables, we will use either ordered logistic or linear regression as appropriate. To measure positive change, we will convert nominal or ordinal independent variables using dummy variables where each dummy will be measuring the effect of one answer category on the reference category.

Each of the above measures will be compared between the intervention and control group at T0, T0+21, T1, and T2 using analyses of covariance, mixed models, and generalized estimating equations as appropriate. Mean differences will be reported, with 95% confidence interval and associated *P* value.

In addition to analyzing the impact of the program on various beneficiaries through behavior and health change, the global impact of the 21-day program will be analyzed. This analysis will be performed by multivariate analysis, which measures the influence of each outcome variable on the others and of each independent variable on the relevant outcome variables. We will also measure some of the variables with a measurement model such as factor analysis. All statistical analyses will be performed using SPSS Statistics software.

To minimize bias in the results, the intention to treat principle will be applied and every randomized participant will be analyzed. The school structure is helping us to minimize missing data, but it may still occur due to the longitudinal aspect of the study and number of follow-ups. In this case, carrying the last data forward should be the best approach.

Table 2. Study objectives as they relate to the statistical analysis plan.

Objective	Outcome variables	Results observed for	Hypotheses
Primary: measure the impact on knowledge/behavior and toothbrushing habits in school children after a 21-day school program and compare with baseline and a control group	Child questionnaire: reported brushing frequency, knowledge of the need to brush twice a day, reported use of fluoride toothpaste	within-group analysis: T0+21 vs T0; between-group analysis: T0, T0+21	Immersion in a structured 21-day school program will inform children of the importance of twice a day brushing with a fluoridated toothpaste and motivate improved brushing frequency.
Secondary: measure the impact on oral health via plaque levels in school children after a 21-day school program and compare with baseline and a control group	Child clinical observation: plaque levels (OHI-S[a]) will be used to validate reported brushing frequency with assessments timed to align with questionnaire completion (how well are the children retaining and acting on the information/motivation delivered by the 21-day intervention?)	within-group analysis: T0+21 vs T0; between-group analysis: T0, T0+21	More frequent brushing will result in lower plaque levels compared with baseline and compared with their control group.
Tertiary: evaluate the longer term impact of the 21-day program on knowledge/behavior and oral health in children after a period of 8 weeks (T1) and 24 weeks (T2) or approximately 7 months total	Child questionnaire: reported brushing frequency at T1 and T2; knowledge of the need to brush twice a day and reported use of fluoride toothpaste at T1 and T2; and OHI-S at T1 and T2 compared with baseline, after 21 days, and with control group	within-group analysis: T2 vs T0, T0+21, and T1 vs T0, T0+21; between-group analysis: T0, T0+21, T1, T2	Children in the intervention group will report higher levels of brushing frequency and reduced plaque levels compared with the children in the control group. This can be attributed to the 21-day intervention.
Quaternary: provide evidence that the 21-day school program is effective in getting parents and carers to also improve their brushing habits and to brush day and night.	Parent questionnaire: reported brushing frequency, reported use of fluoride, renewing toothbrush frequency, amount of purchased toothpaste	within-group analysis: T0+21 vs T0; between-group analysis: T0, T0+21	Consenting for their children to participate in a toothbrushing program will likely trigger a reflection upon their own oral care habits, and parents' own brushing frequency, use of fluoride toothpaste, amount of toothpaste, and toothbrushes purchased should increase when compared with baseline and compared with parents in the control group.
Quinary: measure the change in quality of life, well-being, and social measures of school children after a 21-day oral health program	Child questionnaire: reported absenteeism for oral health issues	within-group analysis: T0+21 vs T0; between-group analysis: T0, T0+21	Children may report less dental discomfort/pain and a need to take fewer days off school as a result.

[a]OHI-S: Simplified Oral Hygiene Index.

Safety Monitoring

Adverse Event

An adverse event (AE) will be considered as any untoward medical occurrence in a subject that is new in onset or an exacerbation of a preexisting condition, whether related to study product or procedures or not. However, medical occurrence resulting from a pretreatment AE (ie, any medical occurrence that occurs after informed consent but before the start of the intervention) will be considered as medical history and only recorded as an AE if it worsens during the study. Similarly, a medical occurrence resulting from preexisting medical condition (ie, events that occur with comparable frequency and severity to the subject's baseline condition) is reported as medical history and not AE. Relatedness—the likelihood that an AE is related to the study product or study procedure—of an AE is defined in Table 3. An AE will be recorded only once, with the most extreme severity:

- Mild: awareness of symptoms that require minimal or no treatment and do not interfere with daily activity
- Moderate: discomfort or low level of interference that is enough to interfere with but not prevent daily activity
- Severe: interrupted or unable to perform usual daily activity; usually requires treatment

Table 3. Relatedness of adverse events.

Relatedness	Definition
Not related	AE[a] is clearly due to an alternative cause, even if this cannot be definitely identified. Alternative causes include diseases and environmental factors.
Unlikely	Connection between AE and the study product or procedure is unlikely: • AE has a relationship in time to the study product or procedure • Alternative cause (eg, disease or environmental factor) is the most likely explanation, even if this cannot be identified
Possibly	Connection between AE and the study product or procedure cannot be ruled out with certainty: • AE has a relationship in time to the study product or procedure • Alternative cause (eg, disease or environmental factor) seems likely or possible or there is significant uncertainty about the cause of the AE
Probably	There is a high degree of certainty that the AE is related to the study product or procedure: • AE has a relationship in time to the study product or procedure • Possible alternative cause may be present • AE disappears or decreases on withdrawal or reduction of study product or procedure (if performed)
Definitely	AE is clearly related to the study product or procedure: • There is a strong relationship in time • Alternative cause is unlikely • AE disappears or decreases on withdrawal or reduction of study product or procedure (if performed)

[a]AE: adverse event.

Serious Adverse Event

A serious adverse event (SAE) is an AE that results in any of the following outcomes: death, life-threatening event, in-patient hospitalization, persistent or significant disability/incapacity. Any other important medical event may be considered an SAE when the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed. A stable preexisting condition is not an AE, and hospitalization for elective treatment (eg, cosmetic or dental procedure) of a preexisting condition that did not worsen from baseline is not an SAE.

Reporting of Adverse Events

AEs will be monitored, reported, and followed up to the public health authorities. All AEs will be recorded and submitted to the FDI global team at the end of the study. The LSC will maintain source documents to fully record all AEs.

Additionally, SAEs and clusters of AEs that may affect the safety or continued participation of participants in the study will be reported immediately using a more detailed form. An SAE will be reported to FDI within 24 hours of the LSC becoming aware of the event.

Follow-Up of Adverse Events

If an AE is ongoing at the end of the study, follow-up will be performed until the AE has resolved, unless decided and agreed that no further follow-up will be necessary. Follow-up may take the form of subject visits, referral to another specialist, site telephone calls to the subject, or letters from the treating physician. For expedited AEs, if applicable, the LSC will submit follow-up reports. The LSC will comply with the specific reporting requirements of the ethics committee, reporting as a minimum any serious unexpected adverse reaction that is an unexpected SAE that may be related to study product or procedure.

Results

This protocol is being retrospectively published with the information shared with the two participating countries on January 19, 2019. In the meantime, the trial was set up, and the study is ongoing. Recruitment of schools and participants started in Indonesia in February 2018 and in Nigeria in April 2018 for the first part of the study, which concluded in Indonesia in September 2018 and in Nigeria in November 2018. The second part of the study (the second half of the schools) started in November 2018 in Indonesia and December 2018 in Nigeria. We expect to collect all the data during 2019 and publish findings from the study by March 2020.

Discussion

This new study will include both intervention and control schools and children and ensure that evaluations (knowledge, behavior, plaque levels, and dental caries) are made within a clearly defined time window to facilitate data analysis.

Children in the control group will not receive the 21-day school program intervention. This will allow a full evaluation of the benefit of the intervention. The OHI-S will be used to score plaque. This is a 4-point scale and hence will be more discriminatory than the 2-point (visible plaque index) scale used previously. This is the first time that the 21-day BDN program has been evaluated in a study with a set of control schools. The impact of such a program on parents is also being studied for the first time. We expect this study will increase knowledge of the effectiveness of this intervention in bringing immediate and sustained change in knowledge, behavior, toothbrushing habits,

oral health, quality of life, and well-being in children aged 6 to 9 years and their parents. We aim to publish the results in a special edition of the International Dental Journal by March 2020. In addition, results will be presented at conferences and disseminated among project leaders as guidance for the development and continuation of implementation of school programs in their countries.

Acknowledgments

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Conflicts of Interest

SM and AR are employed by Unilever Oral Care. Unilever is funding this study through an unrestricted educational grant. Unilever local brands are supporting the study in both countries by providing necessary materials such as toothpaste, toothbrushes, and educational materials (calendars, stickers, leaflets, and certificates). There will be no intervention by Unilever in the results and analysis.

Multimedia Appendix 1
[DOCX File , 15 KB - resprot_v9i2e14156_app1.docx]

Multimedia Appendix 2
Child assent form—English.
[DOCX File , 17 KB - resprot_v9i2e14156_app2.docx]

Multimedia Appendix 3
Parent informed consent form—English.
[DOCX File , 18 KB - resprot_v9i2e14156_app3.docx]

Multimedia Appendix 4
Parent questionnaire—English.
[DOCX File , 44 KB - resprot_v9i2e14156_app4.docx]

Multimedia Appendix 5
Child questionnaire—English.
[DOCX File , 49 KB - resprot_v9i2e14156_app5.docx]

Multimedia Appendix 6
Decayed missing filled tooth index and simplified oral hygiene index: paper form for data collection.
[DOCX File , 274 KB - resprot_v9i2e14156_app6.docx]

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Abbreviations

AE: adverse event
BDN: Brush Day & Night
DMFT: Decayed, Missing, and Filled Teeth Index
FDI: FDI World Dental Federation
LSC: local study coordinator
OHI-S: Simplified Oral Hygiene Index
SAE: serious adverse event
T0: baseline
T0+21: end of 21-day intervention
T1: 8 weeks after the end of the intervention
T2: 24 weeks after the end of the intervention

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Protocol

A Mobile Intervention to Improve Uptake of Pre-Exposure Prophylaxis for Southern Black Men Who Have Sex With Men: Protocol for Intervention Development and Pilot Randomized Controlled Trial

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Abstract

Background: The uptake of pre-exposure prophylaxis (PrEP) has been slow for young black men who have sex with men (BMSM) living in the southern United States. This is a significant issue because 8 of the 10 states with the highest rates of new HIV infections are in the South. Jackson, Mississippi (MS), the site of this project, has the second highest AIDS diagnosis rate in the nation and the highest rate of HIV infection for young, urban BMSM. This study will develop and test an engaging, interactive, and cost-effective mobile messaging intervention to improve engagement in PrEP care for BMSM aged 18 to 35 years living in Jackson, MS.

Objective: The goals of this mixed methods study are to (1) conduct qualitative interviews with young BMSM in Jackson, MS, to understand individual, community, and structural barriers affecting engagement in PrEP-related care, (2) assemble a PrEP mobile messaging intervention that includes text messages with publicly available internet content (websites and YouTube videos) that provide factual information, motivational materials, and behavioral skills related to PrEP and HIV prevention, and (3) evaluate the preliminary efficacy of the intervention in a randomized controlled study with PrEP-eligible BMSM receiving care in STI/HIV testing clinics in Jackson, MS.

Methods: This research protocol will be conducted in 2 phases. A development phase will involve in-depth interviews (n=30) with PrEP-eligible BMSM who receive care in STI/HIV testing clinics in MS. These interviews will allow researchers to select the texted material that will be sent out during the intervention. The second phase will consist of an unblinded, small, randomized controlled trial among 66 new participants to examine the preliminary efficacy of the intervention compared with enhanced standard of care (ESC) on attendance at a PrEP services appointment (the first step in initiating PrEP care) and receipt of a PrEP prescription, based on self-report and electronic medical records. The free, publicly available material will be sent to PrEP-eligible BMSM in 8 to 16 interactive text messages over 4 weeks. Study assessments will occur at enrollment and at 4- and 16-weeks postenrollment and can be completed online or in person. All participants will be recruited from a local clinic.

Results: Institutional review board approval was received on January 16, 2017, and research activities, subsequently, began in February 2018. Recruitment for the study concluded in November 2019. In total, 65 participants were randomized with 33 being assigned to the intervention and 32 to ESC. Collection of follow-up data is ongoing.

Conclusions: This PrEP mobile messaging intervention aims to increase uptake of PrEP by BMSM in the southern United States. This intervention uses interactive, tailored text messaging and appealing free Web content (publicly accessible educational

websites and YouTube videos) to promote linkage to PrEP care and increase HIV preventative behaviors. A cost-effective PrEP mobile messaging intervention has great potential to improve information about PrEP, improve motivation to use PrEP, and decrease stigma and structural barriers that often prevent engagement in PrEP-related medical care.

Trial Registration: ClinicalTrials.gov NCT03308097; https://clinicaltrials.gov/ct2/show/NCT03308097

International Registered Report Identifier (IRRID): DERR1-10.2196/15781

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KEYWORDS

pre-exposure prophylaxis (PrEP); HIV prevention; men who have sex with men (MSM)

Introduction

Background

The strategy of using antiretrovirals as a form of HIV prevention, known as pre-exposure prophylaxis (PrEP), has received considerable attention and holds tremendous promise [1,2]. Despite the advancements supporting PrEP efficacy and its availability, uptake of PrEP by many men who have sex with men (MSM) has been slow. In particular, uptake has been slow for young black MSM (BMSM) who live in the southern United States [3-8]. This is a significant issue because BMSM living in the South have particularly high rates of HIV. Eight of the ten states with the highest rates of new HIV infections are located in the South, and estimates suggest that BMSM in the South are 5 times more likely than white MSM in the South to become infected with HIV [9]. The site of this proposed project, Jackson, MS, has the highest prevalence of HIV among urban MSM living in the United States (39.5 per 100 MSM) [9]. The premise of this project is to develop a targeted mobile messaging intervention to improve linkage to PrEP care for young BMSM in Jackson, MS, who are at high risk for HIV infection. Interventions that improve linkage to PrEP care are urgently needed for BMSM in the South.

Truvada (tenofovir disoproxil fumarate/emtricitabine) for PrEP was approved by the US Food and Drug Administration as an HIV prevention method in July 2012 for individuals aged 18 years and older and in 2018 for adolescents weighing at least 77 pounds [10]. Despite this, knowledge and access to information about PrEP remains low in many MSM communities. This has restricted linkage and uptake of PrEP and, ultimately, the effectiveness of PrEP at the community level [3-7,11-13]. To use PrEP, individuals must have accurate knowledge, understand its risks and benefits, and be willing to take it. Studies show that many high-risk individuals who would be excellent candidates for PrEP have not taken it simply because their knowledge about it is limited [3,11]. In one study conducted among young MSM in 2013, only 27% of study participants were aware of PrEP [11]. Knowledge about PrEP has increased recently [13,14]; however, some studies show that awareness remains markedly lower among men of color, those who live in southern and rural areas in the United States, and those whose primary care providers are not aware that they have sex with men [15]. Among 436 BMSM surveyed in Atlanta, GA, from January 2012 (6 months prior to PrEP approval) to March 2014 (20 months after approval), only 20.5% were aware of PrEP before approval and only 23.4% were aware of PrEP after approval [3]. Improving southern, young BMSM's knowledge about PrEP is critical for successful linkage to PrEP care.

Strengthening the relationships young BMSM have with providers is critical for successful PrEP uptake. Young BMSM who are at highest risk of HIV infection are historically underserved by the health care system [16-19]. Therefore, engaging patients in care is challenging and requires support for doctors and patients [19,20]. Brooks et al [6] found that heightened concerns over potential side effects to PrEP pose a significant barrier to engagement and linkage to PrEP care for BMSM. In the southern United States, homophobia, stigma, and clinician/patient communication all influence initiation of PrEP [21-23]. Eaton et al [3] surveyed 398 HIV negative BMSM at a black Gay Pride event in the southeastern United States. Among this sample, 60% agreed that they were uncomfortable talking to a health care provider about having sex with men. Race-based medical mistrust was also identified as a barrier to engaging in PrEP. Around 1 in 5 participants reported that "people of my race cannot trust doctors and health care workers" (21%), "people of my race should be suspicious of information from doctors and health care workers" (19%), and "people of my race should be suspicious of medicine" (19%). Strengthening communication and connection between medical caregivers and the young BMSM community are crucial components to improving linkage and initiation of PrEP care in the South [12,14,18,23]. Accurate information about PrEP and issues such as potential side effects will need to be shared in a method that considers a history of mistrust to effectively allay concerns among southern BMSM [18].

Furthermore, addressing structural/economic barriers to receiving PrEP-related care is imperative for BMSM. Effective interventions to improve PrEP must assist individuals when navigating insurance companies and enrolling in medication co-pay assistance. In 2014, approximately 21% of African Americans did not have health insurance, compared with 12% of whites [24]. The situation is particularly concerning for southern BMSM since some of the highest levels of poverty in the United States are in the South. Mississippi has the highest poverty level (28%) in the United States, which directly impacts health care access. Southern states also have the most restrictive Medicaid eligibility criteria and provide fewer Medicaid benefits than other regions in the country [25]. Interventions that help navigate the economics of getting on PrEP, such as PrEP co-pay and full medication assistance programs, are essential to the successful implementation of PrEP in the South, where poverty is highest.

Last, decreasing stigma about PrEP and HIV can improve linkage and initiation of PrEP-related care for BMSM. Participants in PrEP demonstration studies have reported that stigma affects their decision to initiate PrEP care [19,20,26-30]. Gay men have reported a fear of being labeled as promiscuous by doctors and "Truvada whores" by friends. These stigmatizing labels infer that PrEP is associated with unbridled sex and may be a barrier to care [20,27,30]. Furthermore, the only currently available PrEP method, Truvada, is the same medication used to treat those infected with HIV. In the South, where HIV-associated stigma is high and HIV is prevalent, being seen with Truvada can be perceived as being HIV-infected, which is a further barrier [19,30]. HIV-related stigma is particularly widespread in the South [11,12,20,31]. Interventions must replace negative community attitudes about individuals using PrEP with positive impressions of PrEP users as individuals who take care of themselves and others [32].

PrEP and HIV prevention interventions for young BMSM need to be interactive, cost effective, and easily integrated into existing clinical care. We will use interactive, tailored text messaging and appealing free Web content (publicly accessible educational websites and YouTube videos) to promote linkage to PrEP care and increase HIV preventative behaviors. A cost-effective, interactive intervention that uses mobile technology is particularly compelling for use with young MSM. MSM make greater use of cell phone technologies than heterosexuals [33], and there is evidence that mobile phone teledensity (ie, number of phones per person) in black southern communities has outpaced black communities in the northeast [34-37]. On a monthly basis, young black adults in the United States spend nearly 56 hours using smartphone apps or internet browsers and 2.5 hours watching videos on their smartphones [38]. With such widespread use of mobile technologies, it is not surprising that data supports the use of mobile technology to improve health [39-41]. Meta-analyses have shown that mobile interventions are most effective when they are interactive and tailored [39-41]. The widespread appeal and use of smartphones and promising data supporting mobile messaging interventions for health promotion create a unique opportunity. Information about PrEP and HIV prevention can be delivered to young, southern BMSM during their leisure time, outside of the sexually transmitted infection (STI)/HIV clinic, and in a manner that is cost effective and easily scalable [34,35,38,42-46].

Theoretical Framework for Intervention

The information-motivation-behavioral skills (IMB) model is a well-established conceptualization for improving engagement in care and decreasing HIV risk behaviors. HIV prevention interventions and linkage/engagement in care interventions based on the IMB model have demonstrated efficacy [47,48]. Reviews have suggested that interventions guided by theory are more efficacious than those not driven by theory [47-50]. According to the IMB model, health information, motivation, and behavioral skills are the fundamental determinants of health behavior. For a PrEP-related intervention to be successful, a person must learn information that is directly relevant to HIV prevention and treatment with PrEP. Knowledge is a necessary but not sufficient condition for change. Personal motivation to engage in HIV preventative behavior or engage in treatment regimens (attitudes about health) and motivation (perceived social, cultural, and structural support for performing these acts) are essential for change. Finally, skills for performing healthy behaviors and a sense of self-efficacy must be easily applied to an individual's cultural, social, and structural setting [47-50]. Engagement in PrEP care can be facilitated by accurate knowledge of medication benefits, self-efficacy for care, and structural support [51,52]. Our intervention, and the online material it is composed of, will address these factors within the IMB model and the local/geographic, structural, and racial context. The IMB model is broadly applicable and can be used to organize and guide theoretically consistent and culturally and structurally informed intervention content [53].

Aims and Objectives

This mixed methods study will develop an online PrEP mobile messaging intervention for PrEP-eligible BMSM at the STI/HIV testing clinics in Jackson, MS. The intervention will be created with the help of in-depth interviews with 30 young BMSM in MS that will seek to understand individual, community, and structural barriers affecting IMB factors relevant to engagement in PrEP-related care. We will then conduct a randomized controlled pilot study with 66 PrEP-eligible BMSM seen at STI/HIV testing clinics. This pilot will evaluate the preliminary efficacy of the PrEP mobile messaging intervention compared with enhanced standard of care (ESC) on improving HIV-related knowledge and attitudes, attendance at a PrEP services appointment, and receipt of a PrEP prescription. These data will provide preliminary evidence of the intervention's impact and inform a larger randomized controlled trial (RCT), if needed, as a test of the intervention.

Methods

Trial Registration and Institutional Review Board Approval

The research and ethics presented in this study were approved by the institutional review board of Rhode Island Hospital and University of Mississippi Medical Center (UMMC). This study is registered on ClinicalTrials.gov (NCT03308097).

Design

This research protocol will be conducted in 2 phases. A development phase will involve in-depth interviews (n=30) with PrEP-eligible BMSM who receive care in STI/HIV testing clinics in MS. Interviews will be conducted by LB, LW, or a trained senior research associate in a private area of the UMMC STI/HIV testing clinic. These interviews will allow researchers to select and adapt the material that will be sent out through the PrEP mobile messaging intervention. The material will be composed of free, publicly available links to websites and YouTube videos that provide factual information, motivational materials, and behavioral skills related to PrEP and HIV prevention. The second phase will consist of a small, unblinded, parallel, randomized controlled pilot study among 66 new participants in the clinics to examine the preliminary efficacy of the intervention compared with ESC on attendance at a PrEP services appointment and receipt of a PrEP prescription.

Participants will be randomized using the block randomization method designed to randomize subjects into groups that result in equal sample sizes (1:1). This method is used to ensure a balance in sample size across groups over time. Blocks will be small and balanced with 6 participants assigned to each block. Blocks will be generated using an internet application and saved on a secure drive accessible only to Rhode Island Hospital staff. A research assistant at Rhode Island Hospital will randomize participants after they are enrolled by UMMC staff. The intervention material will be sent to PrEP-eligible BMSM in 8 to 16 interactive text messages over 4 weeks. Study assessments will occur at enrollment and at 4 and 16 weeks postenrollment.

Participants

Young BMSM, aged 18 to 35 years, who visit the STI/HIV testing clinics in Jackson, MS, and who are eligible for PrEP according to current treatment guidelines [54] will be eligible for enrollment in each phase of the study according to the following criteria: (1) English speaking, (2) eligible to receive prophylactic antiretroviral treatment, (3) not enrolled in another PrEP-related study or HIV prevention study, and (4) able to give consent/assent and not impaired by cognitive or medical limitations as per clinical assessment. Clinical assessment will occur by members of the proposed research team, as they have substantial prior clinical (medical and psychiatric) and research experience in care of young adults and adults. While having a smartphone or computer is not an eligibility criterion, participants without regular access to this technology must be willing to come to the clinic twice a week if they are randomized to the intervention arm to access intervention content. There will not be overlap between subjects in the developmental and RCT phases. We are enrolling only BMSM between the ages of 18 to 35 years, because they are the subgroup most at risk for acquiring HIV in Jackson, MS. Limiting the study to young BMSM will allow for the development of a mobile intervention that is targeted, acceptable, and engaging for this specific population.

Description of Intervention Content

The PrEP mobile messaging intervention employs graphics, characters, and video content specifically chosen to be appealing to young BMSM. Text messages and accompanying Web content will target IMB constructs. These IMB-consistent messages and content all aim to increase knowledge and engagement in PrEP care and decrease HIV risk behaviors. Examples of the IMB-informed texts include: “Do you want to see a cool website with more information about PrEP? Check out this website” which provides information, “Hear from Dr. Mena, who works in Jackson. You can take PrEP and still have fun” which enhances motivation, and “Hear tips for taking PrEP each day and how to get PrEP easily in Jackson” which teaches behavioral skills.

Interviews will ensure that the intervention material is relevant to community context (eg, stigma, structural barriers). Currently, the intervention is composed of 8 text messages with 1 to 2 links to publicly available Web content in each message. Participants will be sent 2 text messages per week over 4 weeks. The timing and length of the texts and Web activities are based on the timing and length of the efficacious Center for AIDS Research HIV prevention project reviewed in preliminary studies [55]; however, the length and frequency of the intervention and intervention activities will be assessed and edited during the development stage. Each text message will have a link to Web information, quizzes, and games focused on providing facts about PrEP and HIV transmission and prevention and on correcting misperceptions about HIV and PrEP. Videos that are publicly available online and that specifically address engagement in PrEP-related care and HIV prevention information deficits identified with BMSM will be part of the modules. Pictures and graphics have been selected to appeal to BMSM. Young, black male role models are used to impart information and address attitudes, stigma, and social norms concerning engagement with providers, PrEP, and HIV risk. Accurate information will reduce PrEP misconceptions that fuel stigma. Videos that show BMSM discussing the positive aspects of PrEP for them, their partners, and their communities will also help reduce stigma. The intervention will also address structural barriers. Mobile-ready information has been selected to help participants navigate health insurance, medication assistance programs, and co-pay assistance programs. Figure 1 shows sample text messages with pictures of accompanying IMB Web content.

Preliminary material will either be confirmed or adapted following in-depth interviews with 30 BMSM eligible for PrEP seen at STI/HIV testing clinics in Jackson, MS. Thus, these interviews finalize the links and digital material that will be sent out by the mobile messaging intervention during the RCT.

Figure 1. Preliminary intervention text messages developed from publicly available internet content.

Developmental Phase Qualitative Interviews

Qualitative interviews will be conducted by LB, LW, or a trained senior research associate, who have experience with interviews used to develop behavioral interventions and health care provider training. Interviews will be digitally recorded and recordings uploaded to a secure file location on the Rhode Island Hospital server that will only be accessible to project staff.

Developmental phase participants will be recruited from the UMMC STI/HIV testing clinics. They will be screened for eligibility by UMMC research assistants by phone or in person. Those eligible and interested will arrive the day of the focus group or interview, and research staff will review the consent form with them. Those who sign the consent form will proceed with the interview.

Interview questions were developed to reflect the IMB model. Questions focus on the relevance and utility of the presented content and its appeal and will solicit suggestions for potential improvements. Feedback will be elicited after exposure to mobile material in a secure clinical space at the UMMC STI/HIV testing clinics. We will ask about general reaction to the preliminary Web content and all texted queries. Participants will be asked about the acceptability and relevance of texts and mobile content, actions, and graphics as they relate to race, culture, and structural factors. We will also concentrate on deeper, or more complex, emerging themes. For example, if there are particular barriers to engagement in PrEP care, such as misconceptions about the perceived risk of HIV, more content will target this misperception [56-58]. If other barriers to engagement in PrEP-related care, such as misinformation about side effects or mistrust of the medical community, are identified, more content will target these issues. For example, participants will be asked "As a black, gay male, how worried are you about getting HIV? How effective do you think PrEP is at preventing someone from getting HIV?" and "How comfortable do you feel talking to your doctor about sex, HIV, and PrEP?" After viewing preliminary Web content, participants will be asked, "Which parts of this website or YouTube video would influence how concerned you are about HIV?" "Do any parts of this website or video help you feel prepared to start PrEP?" "Do any parts of this website help you to know how to pay for PrEP?" and "How could these messages be made more relevant to you, your friends, and your partners?" Major topics and subtopics from the interviews will be coded. Additional codes will be generated for topics that invariably arise and that may have significance to the project. Qualitative data will be analyzed using the qualitative software package NVivo version 11 (QSR International). In order to maintain scientific adequacy and confirmability, we will perform semistructured interviews on a sufficient number of participants from each relevant subgroup defined by age (divided at 25 years); level of interest in starting PrEP; and identifying as gay, bisexual, or neither until there is redundancy in themes and general feedback. All interviews will focus on how sexual orientation, race, stigma, culture, age, and

structural factors influence IMB for the major targets of the intervention.

After the first 15 qualitative interviews, another draft preliminary PrEP mobile messaging intervention will be assembled. This draft intervention will be assessed with another group of young BMSM using the similar qualitative procedures. Interviews will continue until thematic redundancy is achieved. These iterative design efforts will provide an intervention that is culturally acceptable and theoretically informed. Throughout the developmental phase, members of the research team will iteratively review and assess the clinical utility of all intervention components via the BMSM participants' qualitative feedback and audiotaped session materials. The team will assess the strengths and weaknesses of intervention components and indicate revisions. Specifically, we will assess the intervention content's accuracy and suitability, ability of the intervention content to engage MSM, and ability to target STI/HIV-related behavioral change with material and techniques consistent with the IMB model. Additionally, the team will review the intervention material for relevance, conceptual clarity, and potential technological problems.

Pilot Randomized Controlled Trial

Overview

We will evaluate the impact of the IMB mobile PrEP/HIV intervention compared with ESC in an RCT with 66 newly recruited BMSM. Recruitment will take place at local STI/HIV testing clinics using flyers and word of mouth. Flyers list the eligibility criteria and provide contact information of the UMMC research assistant they can contact if they would like to participate in a study to test a new mobile messaging tool that provides information about PrEP. Those interested in participation will be screened either in person or over the phone by research assistants in MS. Those interested and meeting all eligibility requirements will be scheduled to complete consent and baseline assessment if it does not occur on the same day. Research staff will then go over the consent form (Multimedia Appendix 1) in a private area of the STI/HIV testing clinic, and participants will fill out the consent and locator forms. Participants will then complete the baseline survey and be placed in either the intervention or ESC group using computerized, block randomization. We will compare conditions on attendance at a PrEP services appointment and receipt of a PrEP prescription at 16 weeks using data from the electronic medical record and by self-report. Conditions will also be compared by self-report on PrEP and HIV-related knowledge, attitudes, skills, and risk behaviors at baseline, 4 weeks (immediately postintervention), and 16 weeks.

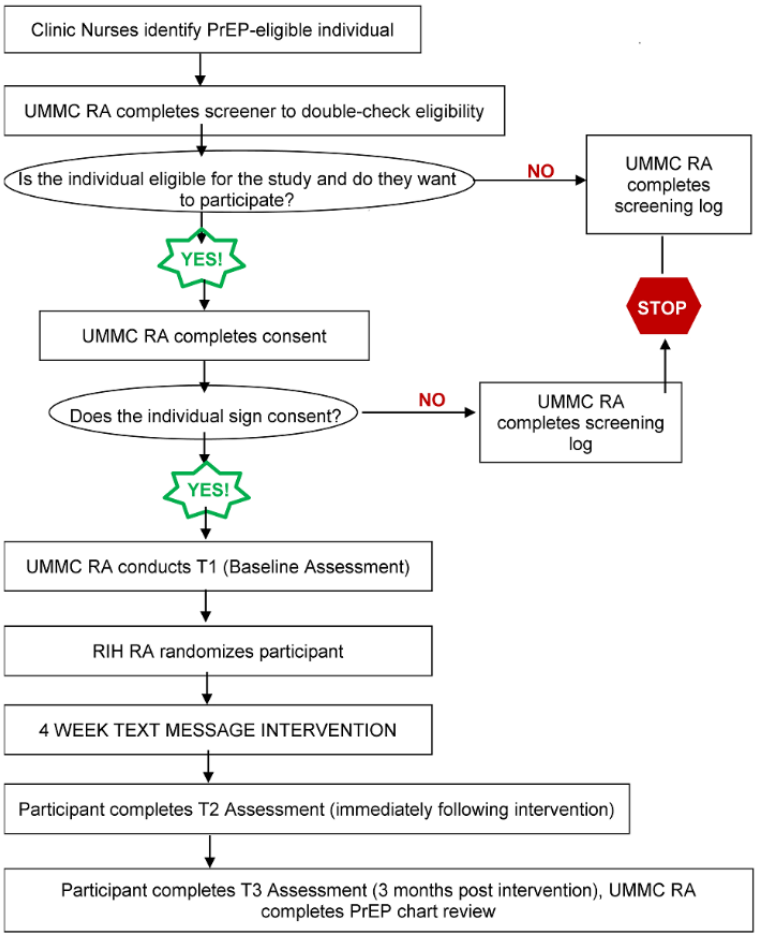
Pre-Exposure Prophylaxis Mobile Messaging Intervention

Participants in the intervention will receive text messages with intervention content over 4 weeks on their smartphones. Mobile phones will not be provided by the researchers; therefore, participants must have their own working smartphone or computer or be willing to come into the clinic regularly to access content to be eligible to participate. The intervention is composed of 8 to 16 texts with links to Web content. Texts will be sent twice a week over 4 weeks by a research assistant using the Health Insurance Portability and Accountability Act (HIPAA)-compliant Study Management and Retention Toolkit (SMART) developed by Emory University [59]. While there is minimal human involvement in the intervention, participants have the option to contact research staff by phone or SMART if they have any questions or concerns. Based on feedback from the developmental phase, intervention content was selected to be less tailored to the population and more diverse and inclusive. Videos were also included that were perceived as more accurate representations of social interactions in the south. The preliminary timing and length of the texts and Web activities are based on the timing and length of the efficacious Center for AIDS Research HIV prevention project reviewed in preliminary studies (PI: LW). Each mobile link sent to participants will take between 5 and 10 minutes to read, listen to, or interact with. Participants can engage with text message material on their phones at any place that is convenient and comfortable.

Enhanced Standard of Care Condition

The impact of the intervention will be compared with ESC. At both STI/HIV testing clinics in which subjects are recruited, the medical director and his staff assess patients for PrEP eligibility and HIV risk (as defined by the Centers for Disease Control and Prevention [CDC] guidelines) [54]. Feedback is given to each patient on their current risk behavior and future plans (personal risk summary). Patients are given a CDC informational handout with basic PrEP facts; shown a brief, 5-minute, free/publicly available online video about PrEP; and given contact information for the clinic care coordinator. These procedures are consistent with CDC guidelines for PrEP, and because of the handout, personal risk summary, and video, the procedure can be considered ESC. The medical director and his team have used the handout and video for the past 2 years. The video is colorful, informative, and well received but has not been chosen with specific qualitative feedback from BMSM. Patients in both conditions will receive the ESC clinical encounter described here and be followed for assessments. Only patients in the IMB mobile messaging intervention will receive the additional 8 to 16 text messages (Figure 2).

Figure 2. Study flow diagram of the randomized controlled trial phase.



Measures and Assessments

Assessments

Assessments will occur at baseline, immediately postintervention (4 weeks), and 3 months postintervention (16 weeks) and will take 45 minutes to complete.

Measures

A computer self-interview using Research Electronic Data Capture (REDCap) will be used to assess behavior since it is confidential, allows for complex branching/skip patterns, and detects greater rates of risk behavior [60]. Participants will be emailed the REDCap surveys 2 days prior to their appointments, but they may also opt to complete the surveys on a computer at the UMMC STI/HIV testing clinics. Standard items will be administered to gather demographic data (including age, educational level, sexual orientation, socioeconomic status, race, ethnicity, and stability of housing). The measures below will be used to evaluate HIV- and PrEP-related knowledge, attitudes, and behavior (see Table 1 for linkage between constructs and intervention).

Table 1. Linkage between constructs, intervention foci, and assessment instruments.

IMB[a] construct	Description of construct	Intervention foci	Assessment instruments
Information	PrEP[b] and HIV risk knowledge	Increased HIV/PrEP knowledge, perceived vulnerability to HIV/STIs	HIV/PrEP Knowledge Scales
Motivation	Risk attitudes, intentions, and self-efficacy for starting PrEP and engaging in PrEP-related medical care	Improved motivation for PrEP and related medical care, increased motivation for safer sex, decreased perceived structural and stigma barriers	IMB PrEP Care Motivation Scale, Self-Efficacy for PrEP Care, Rollnick's Readiness Ruler
Behavior	Attendance at PrEP prevention appointment, sexual risk	PrEP prevention appointment, safer sex skills	Attendance at PrEP services appointment, receipt of PrEP prescription, and sexual risk self-report

[a]IMB: information-motivation-behavioral skills.

[b]PrEP: pre-exposure prophylaxis.

Outcomes

Primary Outcome

With participant consent, staff at the STI/HIV testing clinic will abstract from the electronic medical record any PrEP services appointment and any PrEP prescription received around 20 weeks (4 weeks after final assessment). Participants will also be asked to self-report if they are currently taking PrEP for each assessment. This study is occurring in the only two PrEP clinics in Jackson, and both are affiliated with UMMC. Participants are recruited from the STI/HIV clinics run by the same medical staff. PrEP is unavailable elsewhere in Mississippi, so virtually no one will begin PrEP at another location. While study inclusion criteria do not restrict to only those living in Jackson, MS, we anticipate that accessibility to the recruitment sites will lead to a predominately local sample.

Secondary Outcomes

The following self-report scales on secondary outcomes will be asked on all three questionnaires. We will assess how responses to these measures change over time.

HIV/Sexually Transmitted Infection and Pre-Exposure Prophylaxis Knowledge

The HIV Knowledge Scale assesses knowledge about issues such as risks for HIV using 18 items with true, false, or do not know response options. Test-retest reliability (r=.73) and internal consistency (reliability coefficient=.90) were both satisfactory in studies with at-risk young adults [61]. The STI Knowledge Questionnaire uses similar response options with 10 items assessing risk for and treatment of sexually transmitted infections. Test-retest reliability (r=.88) and internal consistency (reliability coefficient=.86) were both satisfactory in studies with at-risk young adults [62]. Because there is no PrEP knowledge scale with published psychometrics, we will use a 15-item questionnaire to assess knowledge (true/false/don't know) based on facts from the CDC and the San Francisco AIDS Foundation websites concerning PrEP. The items will be tested for readability and relevance with the target population in the qualitative phase of the study. Items will be revised if needed for the RCT portion of this study.

Personal and Social Motivational Readiness for Pre-Exposure Prophylaxis Care

Rollnick's Readiness Ruler [63] will be used to assess motivation for engaging in PrEP care. Respondents rate how ready they are to (1) attend a PrEP services appointment, (2) begin PrEP, and (3) go to PrEP-related medical appointments on a scale from 1=not ready to 10=ready to engage. Participants will also complete the 10-item, Likert-style IMB PrEP Motivation Scale from the LifeWindows Project Team. It has been modified to assess personal and social (culture and structure) motivations for PrEP rather than antiretroviral therapy and is used in our ongoing study of PrEP adherence (1R34 MH104068) in consultation with Dr Jeffery Fisher, one of the developers of the IMB model [64].

Pre-Exposure Prophylaxis and Appointment Self-Efficacy

This measure was developed based on Bandura's theory of self-efficacy [65] and was shown to have strong reliability (alpha>.80) [66]. The instrument consists of Likert-style items (with 5 response options). Three items assess self-efficacy for taking PrEP as prescribed and attending PrEP-related medical appointments. The IMB PrEP Behavioral Skills Scale has 14 Likert-style items (modified to address PrEP rather than antiretroviral therapy). This measure assesses information, motivation, and perception of behavioral ability to perform the necessary PrEP skills. It has an internal consistency of .90 when used with infected adults [64].

Risk Behavior Assessment

The risk behavioral assessment (used in LB's other federally funded projects) is a reliable and valid computer-assisted structured interview assessing self-reported sexual behaviors. It assesses types of sexual behavior (ie, anal, oral, vaginal) in the past 3 months, frequency of sex, age of sexual debut, and number and gender of partners. Additional questions cover use of barrier method contraception, sex with high-risk partners, transactional sex, reasons for condom nonuse, frequency and quantity of substance use, and having sex while using alcohol and drugs [67].

Statistical Analysis

Hypothesis One

The PrEP mobile messaging intervention, developed with participant feedback, will be judged by participants to be feasible, appealing, relevant, and useful. Intervention links that receive a mean score of less than 30 on the session evaluation form or less than 24 on the client satisfaction questionnaire will be discarded.

Hypothesis Two

A total of 66 participants will be randomized to 2 conditions. Those in the IMB PrEP mobile messaging intervention condition will show improvements in each of the IMB domains: information (HIV and PrEP knowledge), motivation (motivational readiness for PrEP and medical care, improved self-efficacy, and improved attitudes for PrEP and medical treatment), and behavior (HIV risk behavior score and engagement in PrEP). Information, motivation, and HIV risk scores will be evaluated at 4 and 16 weeks using linear mixed-effect models, which will account for the 3 assessments (0, 4, and 16 weeks) being nested within individuals [68,69]. We will test for differences in linear change over time between intervention and control groups on each outcome variable. For the PrEP uptake outcome, we will evaluate difference between conditions in the proportion of participants who engaged in PrEP (attended a PrEP medical visit, received a PrEP prescription, or self-reported starting PrEP). Propensity scores (ie, inverse probability of treatment weighting) will be used to account for any imbalance in baseline characteristics between conditions [70]. Hierarchical linear modeling analyses are robust if missing data amount is small. If missing data amount is larger, last observation carried forward techniques will be used for

missing scale data. Outcomes such as engaging in PrEP care (attending a PrEP medical visit or receiving a PrEP prescription) can be obtained from the medical record regardless of subject attrition.

As this is an intervention development study and the impact of the experimental intervention is not known, there may not be adequate power to determine the efficacy of the IMB PrEP mobile messaging intervention, and pilot studies are not designed to provide accurate estimates of effect sizes upon which to base large trials [71]. Nevertheless, the small pilot RCT may provide a signal of impact on its major outcomes. We conservatively assume that retention of 66 participants over 16 weeks is 85% based on previous clinic trials. Power analyses were run with Optimal Design 3.01 (open source, University of Michigan) [72]. The model assumed 3 assessments nested within cases. The hierarchical linear modeling analyses with alpha of 0.05 and power of 0.80 will be able to detect an effect size of 0.38 SD for change in the information and motivation outcomes. If the alpha is 0.10 (as is appropriate in exploratory research), then the power is 0.80 to detect an effect size of 0.34 SD. Power to detect a difference in the proportion of participants beginning PrEP by 16 weeks is 0.80 if 10% of the ESC group begin PrEP (similar to our preliminary studies) and 39% of the intervention group begin PrEP. Because chart review will extend to 24 weeks, actual power should be somewhat greater.

Incentives

For their involvement in this study, developmental phase participants will receive $50 gift cards as an incentive. During the RCT, subjects will receive $50 gift cards for completing the baseline assessment and $40 for the 4- and 16-week assessments. Participants who confirm contact information and research appointments prior to the 4- and 16-week assessments will receive an additional $10 per appointment. Receipts for this payment are offered to participants should they deem it necessary.

Ethical Considerations

To protect participants from potential risk of breach in confidentiality, the following measures will be taken. Participant research data will be identified by numeric ID only and any records containing potentially identifying information will be kept separate from any research data. All research data (written records and audiotapes of program sessions) will be kept in a locked file, and electronic data will be password-protected. All of the study-related materials will only be accessible to research staff. All data collection will take place in secure and supervised clinical settings or with HIPAA-compliant software (REDCap). All study personnel have completed training and received certification in Human Subjects Research Protection (Collaborative Institutional Training Initiative Program) and HIPAA regulations and will continue to renew this training in compliance with hospital policies.

To further protect the privacy of the study participants, we will obtain a Certificate of Confidentiality from the US Department of Health and Human Services. With this certificate in place, the researchers cannot be forced to turn over identifying information about a study participant in any federal, state, or local criminal, administrative, legislative, or other proceedings. This certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Results

This is an ongoing study. The developmental interviews took place from February to April 2018. Recruitment for the RCT phase began in November 2018 and closed in November 2019. Follow-up data is still being collected. Therefore, analysis of the RCT has yet to begin.

Based on input from the qualitative interviews, content was selected to be more diverse and inclusive and less tailored to young BMSM. Participant preference for videos that more accurately reflected social interactions in the South was also considered when choosing content for the RCT. Furthermore, interview participants were asked what time of day they would want to receive the texts, so texts are sent between 11 am and 4 pm. There have been no significant changes to the videos and links that are given as intervention content since the beginning of the study. However, in the initial protocol, participants were to receive follow-up queries on days they received content asking them to rate the links. Lack of participant interest in responding to queries led the team to remove this from procedures. Currently, there are no prompts to remind participants to engage with content.

At the conclusion of recruitment, 65 participants were randomized in total (33 to the intervention and 32 to ESC). The goal was to randomize 33 participants to each arm of the study (66 in total). However, three individuals who completed baseline were withdrawn from the study prior to randomization. Demographics for the 68 participants, taken at baseline, are presented in Table 2. The average age of participants is 23.9 years. Individuals predominately identify as male; black, African American, or Haitian; and not of Hispanic or Latino descent, which reflects the eligibility criteria. Most of the sample received a high school diploma or General Educational Diploma and are either currently employed or a student. While yearly income ranges from less than $10,000 to $79,999, many participants make less than $40,000.

Of those who have been randomized, 3 were withdrawn from the study, 2 were removed from the intervention arm for seroconverting during the trial, and 1 was removed from the ESC arm for no longer self-identifying as an MSM. Until follow-up concludes, we cannot determine the effect of treatment assigned on the desired outcomes.

Table 2. Pre-exposure prophylaxis mobile randomized controlled trial demographics (n=68).

Variable	Value
Age in years, mean (SD)	23.9 (4.8)
Gender identity, n (%)	
Male	67 (99)
Gender nonconforming	1 (2)
Race, n (%)	
American Indian or Alaskan Native	3 (4)
Black, African American, or Haitian	62 (91)
Multiracial	3 (4)
Hispanic or Latino, n (%)	
Yes	1 (2)
No	67 (99)
Highest level of education, n (%)	
Some high school	1 (2)
High school graduate or GED[a]	42 (62)
College degree or higher	20 (29)
Other	5 (7)
Employment status, n (%)	
Employed full-time	28 (41)
Employed part-time	13 (19)
Student	13 (19)
Disabled/unable to work	1 (2)
Unemployed	13 (19)
Annual income, n (%)[b]	
$0-$9,999	28 (47)
$10,000-$19,999	11 (18)
$20,000-$29,999	9 (15)
$30,000-$39,999	7 (12)
$40,000-$49,999	3 (5)
$50,000-$59,999	0 (0)
$60,000-$69,999	1 (2)
$70,000-$79,999	1 (2)

[a]General Educational Diploma.

[b]Eight participants (12%) did not provide information on annual income.

Discussion

Review

The PrEP mobile messaging intervention aims to inform BMSM in the southern United States on the purpose and beneficial impacts of PrEP while reducing stigma about this method of HIV prevention. Through digital material aligned with an IMB theoretical framework, the intervention attempts to motivate participants to engage in PrEP-related care. This cost-effective, easy-to-use, interactive PrEP/HIV prevention mobile messaging intervention could provide BMSM in the southern United States with the information and motivation they need to schedule a PrEP services appointment and take preventative measures in the high-risk environment of the South. No other study has sought to improve this aspect of PrEP-related care, yet attendance at a PrEP services appointment is a crucial first step in the prevention timeline.

Moreover, the intervention is cost effective and easily adapted and tailored to participants. Free and publicly available online content will be selected through in-depth interviews. Selected online material will address information, motivation, behavioral

skills, cultural barriers (such as stigma), and structural barriers (such as payment). In this way, the PrEP/HIV prevention mobile messaging intervention is made to be more effective for its target population.

Despite being developed for BMSM, the addition of diverse and inclusive material based on developmental feedback allows the intervention to be generalizable to other populations. Furthermore, the protocol's low cost and ease of use would make the intervention easy to apply in routine settings outside of a small RCT. However, to do so would likely require a shift from the SMART platform to local agencies sending texted information by cellphone. More individuals would then need to be trained on the protocol.

Limitations

Some limitations should be noted regarding this protocol. This trial is unblinded, which may lead participants to alter how they report on study outcomes since they are aware of their treatment group. They may also be more or less inclined to seek out additional information or be lost to follow-up. While the follow-up questionnaire asks participants how many of the links or videos they watched, this report may be inaccurate due to social desirability bias. Therefore, it will be difficult to ascertain if results are biased due to nonuse of intervention content.

Conclusion

With the large numbers of youth possessing smartphones, the PrEP mobile messaging intervention is a promising route in the effort to increase PrEP uptake for BMSM living in the southern United States. Digital systems cross geographic and interpersonal barriers and can engage at-risk populations. The results of this study can signify the role that interactive digital interventions can play in HIV prevention and clinical care.

Acknowledgments

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Conflicts of Interest

LM has received honoraria for advisory boards and speaker bureau participation from Gilead Sciences, ViiV Healthcare, and Merck, and his institution has received grants from these companies. Members of the study team are not associated with the creators of many of the intervention links; however, team members were responsible for the creation of some intervention links that provide local resources and information.

Multimedia Appendix 1
Consent to participate in research.
[PDF File (Adobe PDF File), 91 KB - resprot_v9i2e15781_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report from the National Institutes of Health.
[PDF File (Adobe PDF File), 151 KB - resprot_v9i2e15781_app2.pdf]

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Abbreviations

BMSM: black men who have sex with men
CDC: Centers for Disease Control and Prevention
ESC: enhanced standard of care
HIPAA: Health Insurance Portability and Accountability Act
IMB: information-motivation-behavioral skills

MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture
RCT: randomized controlled trial
SMART: Study Management and Retention Toolkit
STI: sexually transmitted infection
UMMC: University of Mississippi Medical Center

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Protocol

A Web-Based Human Papillomavirus Vaccination Intervention for Young Gay, Bisexual, and Other Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Gay, bisexual, and other men who have sex with men experience several disparities related to human papillomavirus (HPV) infection, including high incidence rates of anal cancer. Although the HPV vaccine is currently recommended for young adults, HPV vaccine coverage is modest among young gay, bisexual, and other men who have sex with men (YGBMSM).

Objective: We describe the design and methods for a randomized controlled trial (RCT) to rigorously evaluate *Outsmart HPV*, a population-targeted, individually tailored, Web-based HPV vaccination intervention for YGBMSM. The RCT is designed to determine the efficacy of the intervention, the mechanism by which the intervention has an effect (ie, mediation), and whether efficacy varies by participant characteristics (ie, moderation).

Methods: *Outsmart HPV* was previously developed and pilot-tested. This study is a 3-arm prospective RCT that will enroll a projected 1995 YGBMSM who are aged 18 to 25 years, live in the United States, and have not received any doses of the HPV vaccine. Participants will be recruited by means of paid advertisements on social media sites and randomized to receive (1) standard information on the Web about HPV vaccine (control group), (2) *Outsmart HPV* content on the Web with monthly unidirectional vaccination reminders sent via text messages, or (3) *Outsmart HPV* content on the Web with monthly interactive vaccination reminders sent via text messages. Participants will complete Web-based surveys at 4 time points during the study: baseline, immediately after engaging with Web-based content, 3 months after randomization, and 9 months after randomization. Primary outcomes will include both HPV vaccine initiation (ie, receipt of 1 or more doses of the HPV vaccine) and completion (receipt of all 3 doses recommended for this age range). We will examine constructs from the intervention's theoretical framework as potential mediators and demographic and health-related characteristics as potential moderators of intervention effects.

Results: The institutional review board at The Ohio State University has approved the study. Materials have been developed and finalized for all study groups. Recruitment for the RCT began in fall 2019.

Conclusions: If shown to be efficacious, *Outsmart HPV* has the potential to fill an important gap by promoting HPV vaccination among a population at increased risk of HPV infection and HPV-related disease.

Trial Registration: ClinicalTrials.gov NCT04032106; http://clinicaltrials.gov/show/NCT04032106

International Registered Report Identifier (IRRID): PRR1-10.2196/16294

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KEYWORDS

human papillomavirus; human papillomavirus vaccination; gay or bisexual; men who have sex with men; intervention; young adult

Introduction

About 45% of men in the United States have a current genital infection with at least one type of human papillomavirus (HPV) [1]. Infection with oncogenic HPV types can cause several types of cancer among men (eg, anal, oropharyngeal, and penile cancers), and infection with nononcogenic types can cause genital warts [2,3]. Several HPV-related disparities exist among gay, bisexual, and other men who have sex with men (GBMSM). Past research has shown that up to about 66% of GBMSM who are HIV negative have a current genital HPV infection, with prevalence estimates being even higher among those who are HIV positive [4]. Anal cancer incidence rates among GBMSM have ranged to more than 60 cases per 100,000 population, which is much higher than the national rate of about 2 cases per 100,000 population for men [5-9].

Although the Advisory Committee on Immunization Practices (ACIP) began recommending routine HPV vaccination for females in the United States in 2006 [10], routine vaccination was not recommended for males until 2011 [11]. The ACIP now recommends routine HPV vaccination for both male and female adolescents aged 11 to 12 years and recently voted unanimously to support catch-up vaccination for persons through the age of 26 years who are not vaccinated [12]. Before this recent update, catch-up vaccination was recommended only for males aged 13 to 21 years, although routine HPV vaccination was still recommended for men who have sex with men (including those who identify as gay or bisexual or who intend to have sex with men) through the age of 26 years [13]. The recent update also now recommends that adults aged 27 to 45 years make shared decisions with their doctors about getting the HPV vaccine [12]. The HPV vaccine series consists of 2 doses if it is initiated before the age of 15 years and 3 doses if it is initiated after the age of 15 years [13]. HPV vaccination is currently approved to prevent anal cancer and genital warts among males [14].

Despite recommendations, HPV vaccine coverage is modest among young gay, bisexual, and other men who have sex with men (YGBMSM) in the United States. Studies have shown that about half or fewer YGBMSM have received any HPV vaccine doses, and fewer than 20% have received all recommended doses [15-22]. Although HPV vaccine coverage may be slighter higher among GBMSM than among heterosexual men [16,23], the suboptimal coverage is still somewhat surprising, given that most GBMSM have expressed a willingness to get vaccinated [24-28]. YGBMSM have reported numerous barriers to HPV vaccination, including lack of knowledge about HPV and the HPV vaccine, concerns about vaccine safety, concerns about cost and/or health insurance, perceived stigma around the vaccine (eg, the vaccine is only for females), fear of potential health care discrimination, and lack of a health care provider recommendation to get vaccinated [17,20,29]. Given that many YGBMSM remain unvaccinated, efforts to increase HPV vaccine coverage among these men are needed.

We recently developed and pilot-tested a Web-based HPV vaccination intervention for YGBMSM called *Outsmart HPV* [30]. During the pilot test, we recruited 150 unvaccinated YGBMSM from the United States through social media [31]. We randomized participants to receive either standard information about the HPV vaccine (control group) or population-targeted, individually tailored content about the HPV vaccine and monthly unidirectional vaccination reminders (*Outsmart HPV* intervention group). The results of the pilot test showed that HPV vaccine initiation was higher among participants in the intervention group (34/76, 45%) than those in the control group (19/74, 26%; P=.02) [30]. We also observed a trend toward HPV vaccine completion being higher among the intervention group (8/76, 11%) than among the control group (2/74, 3%; P=.07) [30], and the intervention group reported larger changes in several attitudes and beliefs about HPV and the HPV vaccine [32]. Participants in the intervention group reported high levels of acceptability and satisfaction with *Outsmart HPV* [32].

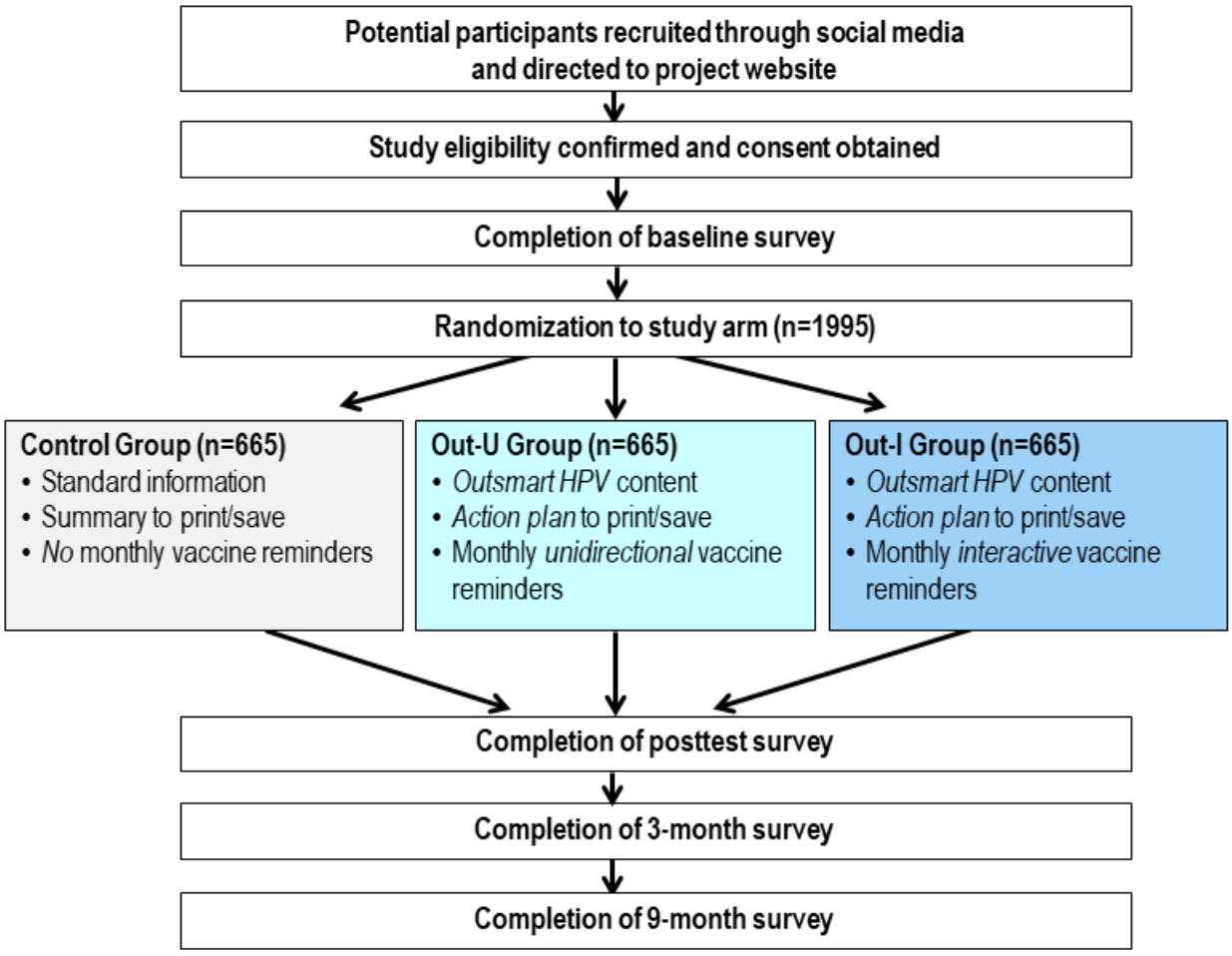
The next step in this line of research is to implement a well-powered randomized controlled trial (RCT) to determine the efficacy of *Outsmart HPV*. It is important to also identify the mechanism by which the intervention has an effect (ie, mediation) and determine how efficacy may vary by participant characteristics (ie, moderation). This study describes the protocol for a study that will accomplish this by comprehensively evaluating *Outsmart HPV*.

Methods

Trial Overview

This study is a 3-arm prospective RCT that will enroll a projected 1995 YGBMSM (Figure 1). Participants will be randomized to receive (1) standard information about the HPV vaccine (control group), (2) *Outsmart HPV* with monthly unidirectional vaccination reminders (Out-U group), or (3) *Outsmart HPV* with monthly interactive vaccination reminders (Out-I group). Each group is described in detail in the following sections. We will follow up with the participants for 9 months and use an intent-to-treat approach to determine the effects of *Outsmart HPV* on HPV vaccination.

Figure 1. Overview of the randomized controlled trial for the *Outsmart HPV* intervention. HPV: human papillomavirus; Out-I group: *Outsmart HPV* that includes monthly interactive vaccination reminders; Out-U group: *Outsmart HPV* that includes monthly unidirectional vaccination reminders.



Recruitment and Eligibility

We will recruit YGBMSM through paid advertisements on social media sites. Social media sites will include Facebook and Instagram, with the potential for expanding to other sites if needed. About 90% of adults aged 18 to 29 years in the United States use social media, with Facebook and Instagram being 2 of the most popular platforms for these ages [33,34]. For the pilot test, we also recruited by means of social media advertisements, and it resulted in a sample of participants who were demographically similar to nationally representative samples of YGBMSM [31].

Advertisements will link potential participants to the project website, which is a mobile-friendly website accessible by desktop, laptop, tablet, or smartphone (iOS and Android). Eligibility will be based on responses to a Web-based screener. Potential participants will be eligible if they (1) are cisgender male; (2) are aged between 18 and 25 years; (3) self-identify as gay, bisexual, or queer; report ever having oral or anal sex with a male; or report being sexually attracted to males; (4) live in the United States; (5) have not received any doses of the HPV vaccine; and (6) did not participate in the pilot test of *Outsmart HPV*. We specify the age of 25 years instead of 26 years as the upper age limit so that participants do not *age out* of the recommended age range for routine vaccination [12,13] during the study. We will also require men to read English and be able to provide informed consent, both of which will be inferred by completion of the eligibility screener and consent form. After completing the screener, eligible men will provide informed consent and create a project account (eg, establishing a username and password and providing an email address and text message number to allow for study communications).

Initial Website Session and Randomization

After account setup, participants will begin their initial project website session. This will consist of completing a baseline survey on the Web, engaging with Web-based content about the HPV vaccine (either *Outsmart HPV* or control group materials), and then completing a posttest survey on the Web. Immediately after completing the baseline survey, participants will be randomized using a 1:1:1 allocation scheme to receive (1) standard information about the HPV vaccine (control group), (2) *Outsmart HPV* that includes monthly unidirectional vaccination reminders (Out-U group), or (3) *Outsmart HPV* that includes monthly interactive vaccination reminders (Out-I group). Recruitment will continue until a projected 1995 YGBMSM are randomized (about 665 per study group).

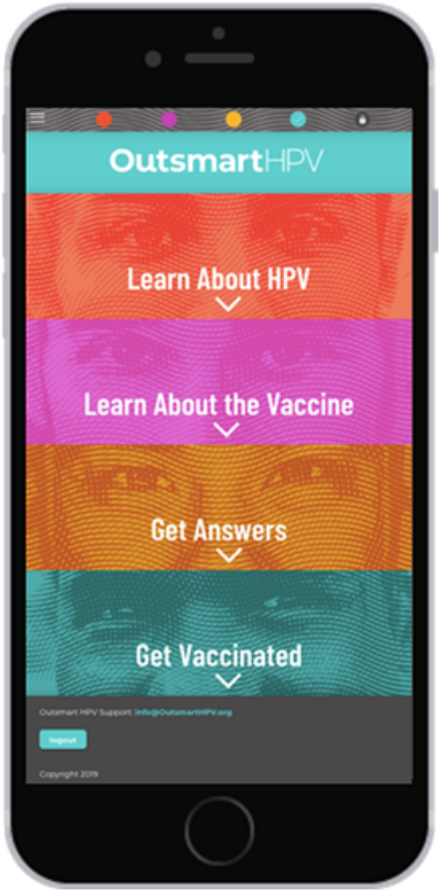
Study Materials

Materials for all study groups are patterned heavily after those from our pilot test [30,32]. To further help ensure the appropriateness of study materials, we conducted focus groups of YGBMSM before the RCT to review and discuss study materials. The project website will deliver materials to all study groups.

Outsmart HPV With Monthly Unidirectional Vaccination Reminders

Outsmart HPV was developed using a framework that included aspects of the Protection Motivation Theory [35], Information-Motivation-Behavioral Skills Model [36], and the Minority Stress Model [37]. The intervention for the Out-U group will consist of 2 components: (1) population-targeted, individually tailored *Outsmart HPV* content on the Web and (2) unidirectional monthly HPV vaccination reminders sent via text messages. The Web-based content will be presented in 4 sequential sections (Figure 2) that contain infographics, other visual formats, and tailored testimonials. The 4 sections are as follows:

Figure 2. Screenshot from a smartphone of the *Outsmart HPV* intervention showing the 4 sequential sections. Both intervention arms (*Outsmart HPV* that includes monthly interactive vaccination reminders and *Outsmart HPV* that includes monthly unidirectional vaccination reminders groups) will receive this content.



1. *Learn About HPV* provides population-targeted information about HPV prevalence, transmission, and HPV-related diseases among GBMSM. For example, this section provides information about the occurrence of anal cancer among GBMSM. At the end of this section, participants are asked to identify what they think is the most important thing they learned about HPV.
2. *Learn About the Vaccine* provides information about the HPV vaccine, including its dosing schedule, recommendations for administration, effectiveness, and safety. This section also includes population-targeted information about the HPV vaccine among YGBMSM (eg, the acceptability of the vaccine reported by YGBMSM in past research) [17]. The end of this section then prompts participants to identify their motivations for wanting to get the HPV vaccine.
3. *Get Answers* uses a question-and-answer format to address barriers and concerns about HPV vaccination (Figure 3). The barriers and concerns include those that have been commonly reported by YGBMSM in past studies [17,20,24,29,38,39]. The website uses information from the baseline survey to prioritize and individually tailor the presentation of content in this section. For example, the potential barriers and concerns indicated by a participant on the baseline survey will appear at the top of this section to highlight this salient content. Following this prioritization, participants will be able to access all remaining questions and answers.

4. *Get Vaccinated* provides content about the logistics of getting the vaccine. This includes resources for accessing the HPV vaccine (eg, a weblink to a lesbian, gay, bisexual, transgender, and queer–friendly provider directory [40]), information about vaccine cost and health insurance, and strategies for talking with a provider about getting vaccinated. This section also asks participants to identify potential questions they have for a doctor about the HPV vaccine. The website then prompts participants to create a customized Action Plan (Figure 4). The plan includes a goal date for getting their first dose, schedule for subsequent doses, next steps for getting vaccinated, and individually tailored information for taking these next steps (eg, resources addressing potential barriers and concerns and potential questions to ask a doctor). It also includes brief information about the HPV vaccine and participants' motivations for wanting to get vaccinated.

Figure 3. Screenshot from a tablet computer of the Get Answers section of *Outsmart HPV*. Presentation of content is individually tailored to prioritize participants' barriers and concerns about the human papillomavirus vaccine, as indicated on the baseline survey.

The monthly vaccination reminders for the Out-U group will be unidirectional, meaning that participants will not have the option to respond to the reminders. The unidirectional reminders will be sent via an automated process and contain only text. The text will provide information about HPV and the HPV vaccine, steps for getting vaccinated (eg, making an appointment with a health care provider), and content addressing common barriers and concerns about the HPV vaccine. After completing their posttest survey, participants will have the ability to print or save a version of their *Action Plan*. Participants will also be able to log back into the project website and review the Web-based content throughout the study, except when completing surveys.

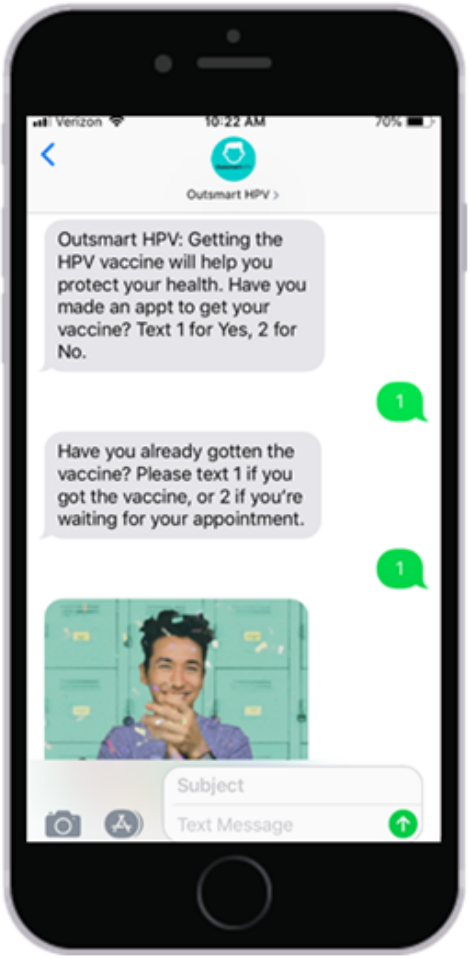
Figure 4. *Outsmart HPV* Action Plan on a desktop computer and a tablet computer. The plan is informed by participants' engagement with the project website and includes a goal date for getting the first dose of the human papillomavirus vaccine series, schedule for subsequent doses, next steps for getting vaccinated, and tailored information for taking these next steps. Participants may revisit the plan on the study website or save/print a copy for future reference.

Outsmart HPV With Monthly Interactive Vaccination Reminders

The intervention for the Out-I group will consist of 2 components: (1) population-targeted, individually tailored *Outsmart HPV* content on the Web and (2) interactive monthly HPV vaccination reminders sent via text messages. Thus, the interventions for the Out-I and Out-U groups will be identical except in the type of monthly vaccination reminders sent to participants: participants in the Out-I group will have the option to respond to and/or ask questions to obtain additional tailored information and resources. Research suggests that interactive reminders may be more preferable and effective than unidirectional reminders [41,42], which could be partly because of their ability to obtain additional information/resources and increased participant engagement. Communications for the interactive reminders will be sent through a combination of automated and manual processes, as described further below. To increase participant engagement, some of the interactive reminder text messages will also contain a meme or brief animation in Graphics Interchange Format (GIF). Similar to the approach taken in other technology-based interventions with adolescents and young adults [43], the memes and GIFs are intended to be funny or motivational and reinforce behavior. The text portion of the messages will focus on areas similar to those described above for the Out-U group.

For each month, the initial text message sent to participants will be automated and include a question that prompts a response (Figure 5). Including a prompted message can increase participant responsivity compared with texts with unprompted messages [44]. Depending on how a participant responds to this initial communication, additional automated communications with information and resources will be sent to participants. Participants will then have the opportunity to text further open-ended questions that they may have to the study team (participants can ask as many questions as needed). A study team member will review the received questions and manually send an appropriate response based on a library of example responses that has been developed for this study. Responses to unanticipated questions not included in the library will be discussed and agreed upon by members of the study team. Participants will be notified that it could take up to a few days for the study team to respond to questions.

Figure 5. Example of an interactive human papillomavirus vaccination reminder that includes an initial prompted message and subsequent communications. As shown, some of the communications will contain a meme or brief animation in Graphics Interchange Format.



Control Group

Participants in the control group will receive standard information about the HPV vaccine that is closely modeled after the Vaccine Information Statement (VIS) for the HPV vaccine. The VIS is created by the Centers for Disease Control and Prevention to provide easy-to-understand information about the HPV vaccine that is publicly available [45]. We modeled the control group content after the VIS because health care providers are required to give a copy of the VIS to patients before vaccination [45]. We formatted the VIS content to match the color and font scheme of the project website. Similar to the Out-U and Out-I groups, participants in the control group will have the ability to print or save a summary of their viewed content after completing their posttest survey, and they will be able to log back into the project website and review their materials throughout the study (except when completing surveys).

Follow-Up Surveys and Medical Record Release

After the initial project website session, participants will be asked to complete follow-up surveys 3 and 9 months after randomization, for a total of 4 surveys during the course of the project. The final survey will occur 9 months after randomization to allow participants ample time to receive all 3 doses of the HPV vaccine during the study period. To improve retention, participants in all study groups will be sent automated email and text message notifications to complete their surveys.

Participants who indicate they have received 1 or more doses of the HPV vaccine on the 3- or 9-month survey will be asked to complete a medical record release (MRR) form on the Web. Completion of the MRR is optional; participants who do not complete one will still continue in the study. At the conclusion of the study, the study team will contact the health care providers of participants who complete an MRR form to verify their HPV vaccination status. No additional health information beyond HPV vaccination status will be requested from health care providers, which is indicated to participants during the MRR form process.

Incentives

Participants will be able to earn up to US $95 in gift cards for this study. This includes a US $40 gift card for completing the initial project website session (ie, baseline survey, engaging with *Outsmart HPV* or control group materials on the Web, and posttest survey), a US $20 gift card for completing the 3-month survey, and a US $35 gift card for completing the 9-month survey. No additional incentives will be provided to participants for completing an MRR form. All incentives will be sent to participants via email.

Measures

Primary Outcomes

Our primary outcomes will include both HPV vaccine initiation (ie, receipt of 1 or more doses of the HPV vaccine series) and completion (ie, receipt of all 3 doses recommended for this age range [13]) during the 9-month follow-up period. The 3- and 9-month surveys will assess how many HPV vaccine doses participants have received. To help maximize the quality of data on our primary outcomes, HPV vaccination status will be confirmed by and based on data from medical records for all participants who complete an MRR form. For those who do not complete an MRR form or who remain unvaccinated during the study, HPV vaccination status will be based on self-reported data from these surveys.

Potential Mediators

The results of our pilot test suggest that several theoretically informed constructs may mediate the intervention's effects on vaccination outcomes [32]. Guided by these previous findings, we will examine several constructs as potential mediators, including *perceived vulnerability* to HPV-related disease (3 items with a 4-point response scale ranging from *no chance* to *high chance*), *perceived severity* of HPV-related disease (3 items with a 4-point response scale ranging from *not at all* to *very*), and *response efficacy* (eg, perceived effectiveness of the HPV vaccine; 2 items with a 5-point response scale ranging from *strongly disagree* to *strongly agree*). Additional constructs will include *rewards of the maladaptive response* (eg, negative social norms of getting the HPV vaccine; 2 items with a 5-point response scale ranging from *strongly disagree* to *strongly agree*), *self-efficacy* to get the HPV vaccine and to talk with a health care provider about the HPV vaccine (2 items with a 5-point response scale ranging from *strongly disagree* to *strongly agree*), *response costs* of getting the HPV vaccine (ie, perceived barriers; 2 items with a 5-point response scale ranging from *strongly disagree* to *strongly agree*), and *intention* to get the HPV vaccine (1 item with a 5-point response scale ranging from *strongly disagree* to *strongly agree*). We will also assess *knowledge* about HPV and the HPV vaccine (7 items with response options of *yes*, *no*, and *I don't know*), *worry* about getting HPV-related disease (3 items with a 4-point response scale ranging from *not at all* to *a lot*), and *stigma* around HPV (3 items with a 5-point response scale ranging from *strongly disagree* to *strongly agree*). These constructs will be assessed at each survey time point with existing measures and those used in our past studies [17,28,32,46,47].

Potential Moderators

The baseline survey will assess demographic and health-related characteristics that we will examine as potential moderators of intervention effects. Demographic characteristics will include participants' age, race/ethnicity, socioeconomic status, relationship status, sexual orientation (eg, sexual identity, behavior, and attraction), and urbanicity. Health-related characteristics and experiences will include health insurance status, health care utilization, perceived experience of discrimination in receiving health care, disclosure and concealment of sexual orientation to their health care provider, sexual history (eg, number of sexual partners and age at first sexual intercourse), history of HPV-related disease, and HIV status (as some HIV-positive participants may not be aware they can receive the HPV vaccine [13]). The baseline survey will also assess participants' attitudes about vaccines in general [48] and electronic health literacy [49] (which may affect participants' understanding and perceptions of the study materials).

Acceptability and Additional Survey Measures

The posttest survey will assess acceptability of the Web-based content about the HPV vaccine across the 3 study groups [50]. Survey items will ask about participants' perceptions of the information viewed (eg, understandability and relevance) and quality of the website (eg, appearance and usability). The 3-month survey will ask participants in the Out-U and Out-I groups about their acceptability of the *Action Plan*, and the 9-month survey will ask these participants about the acceptability of the monthly vaccination reminders (eg, understandability and helpfulness). Study surveys will also examine participants' communication and information seeking about the HPV vaccine.

Engagement

We will measure engagement using administrative data from the project website about study processes and participants' interaction with study materials (ie, *paradata*). This information will assist in examining whether dosage influences intervention efficacy, which in turn will help inform future dissemination efforts [51]. Paradata will include counts of website log-ins, duration of each log-in, parts of the website visited, duration on each part of the website visited, and functions utilized. For the Out-I group, these data will also include the number and nature of communications that occur during the interactive vaccination reminder process.

Sample Size and Power

Our target analytic sample size is 1398 YGBMSM (466 per study group). To achieve this analytic sample size, we will randomize a projected 1995 men (665 per study group) and expect 70% retention over the 9-month follow-up period (based on our pilot test [30]). Once randomized, participants who do not complete a given survey can still continue in the study and will be given the opportunity to complete any subsequent surveys. Our target analytic sample size will give us excellent power for making all pairwise comparisons across study groups for our primary outcomes of HPV vaccine initiation and completion, even with a Bonferroni corrected 2-sided alpha of .017 to control the overall type I error rate. For example, assuming an HPV vaccine initiation rate of 20% in the control group, 35% in the Out-U group, and 45% in the Out-I group, we will have 80% power to detect this difference between the Out-U and Out-I groups and more than 99% power to detect this difference between the control and the Out-U groups.

Statistical Analysis

Efficacy

We will examine descriptive statistics for participants' baseline characteristics and make comparisons across study groups.

Using an intention-to-treat approach, we will then use logistic regression models to determine intervention efficacy, with separate models for HPV vaccine initiation and completion. For each outcome, we will perform all pairwise comparisons across study groups. Logistic regression models will produce odds ratios (ORs) and 95% CIs. Sensitivity analyses will include adjusting for possible residual confounders and a tipping point analysis and multiple imputation to examine the impact of any missing outcome data.

Mediation

We will examine theoretical constructs as potential mediators using structural equation modeling. We will examine HPV vaccine initiation and completion separately and use a probit link to transform each binary outcome to a standard normal scale [52]. For each outcome, we will fit 2 models using a maximum likelihood approach: a *full* model and a more parsimonious *final* model. The *full* model will include the study group and all theoretical constructs examined. We will assess the overall model fit of the *full* model through the root mean square error of approximation (RMSEA) and other metrics (eg, chi-square test) [53,54]. We will consider an RMSEA of less than 0.07 to indicate an acceptable fit [54]. To create the *final* model, we will remove pathways (ie, associations) from the *full* model based on effect size and the chi-square test for nested models. This process will continue until removing pathways no longer improves the model. The resulting model will be the *final* model. Structural equation models will produce standardized path coefficients that estimate the direct and indirect effects of study group and the theoretical constructs.

Moderation

To examine moderation, we will use logistic regression models that include an interaction term between each potential moderator and study group. These logistic regression models will produce ORs and 95% CIs. We will consider moderation to be present if an interaction term has $P<.05$.

Results

The project has been funded by the National Cancer Institute of the National Institutes of Health under Award Number R37CA226682 (originally awarded as R01CA226682). The institutional review board at The Ohio State University has approved this study (study number 2019C0028). The Ohio State University served as the reviewing institution with other study sites ceding review. We have also registered this clinical trial (NCT04032106). Recruitment and enrollment for the RCT began in Fall 2019.

Discussion

There are several potential challenges and limitations to our forthcoming RCT. First, although we will confirm participants' HPV vaccination status through medical records when possible for primary outcomes, we will use self-reported data for participants who do not provide a signed MRR. We will also rely on the participants' self-reported HPV vaccination status in determining study eligibility. However, previous research suggests that most young adults can accurately report their HPV vaccination status, with only a 2.2% net bias in self-reported HPV vaccination data among this age group [55]. Second, as we attempt to recruit a large sample size of YGBMSM and follow up with participants for 9 months, it is possible that we may encounter challenges with our recruitment and retention goals. To address this, we will recruit participants through multiple social media sites, aid both recruitment and retention by offering incentives, and further aid retention by using automated notifications for the completion of follow-up surveys. Third, a concern for Web-based health research is the presence of fraudulent accounts (eg, users with multiple accounts). We will use several recommended strategies [56] for minimizing this concern, including inspecting account information for similarities between accounts, requiring potential participants to verify their text message number as part of the project account setup process (and not allowing the same text message number to be used for multiple accounts), inspecting survey data for illogical responses, and providing incentives only after study activities are completed. We will review new accounts on a regular basis during recruitment to monitor for fraudulent accounts, and accounts suspected of being fraudulent will be deactivated immediately. Fourth, we acknowledge the chance of contamination occurring in health behavior interventions. We believe the chance for contamination is low for this study because we will recruit throughout the United States, the project website will require log-in, and participants will receive only the study materials for their randomized study arm. Finally, this RCT will focus on cisgender males, but if the intervention is shown to be efficacious, it will be important for future efforts to also include transgender individuals.

The goal of *Outsmart HPV* is to increase HPV vaccine coverage among YGBMSM. This study is a critical step toward achieving this goal because it will comprehensively evaluate *Outsmart HPV*. The results will provide an understanding of the intervention's efficacy (including any potential differences between the use of unidirectional and interactive vaccination reminders), mediators, and moderators. If proven efficacious, *Outsmart HPV* has the potential to fill an important gap by providing a Web-based intervention that allows YGBMSM to learn about HPV vaccination and promotes vaccination.

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Conflicts of Interest

PR has received research grants from Merck Sharp & Dohme Corp and Cervical Cancer-Free America through an unrestricted educational grant from GlaxoSmithKline. EP has received research grants from Merck Sharp & Dohme Corp. These funds were not used to support this research study. None of the other authors have any conflicts of interest to declare.

Multimedia Appendix 1
Peer-reviewer report from the National Institutes of Health.
[PDF File (Adobe PDF File), 162 KB - resprot_v9i2e16294_app1.pdf]

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Abbreviations

ACIP: Advisory Committee on Immunization Practices
GBMSM: gay, bisexual, and other men who have sex with men
GIF: Graphics Interchange Format
HPV: human papillomavirus
MRR: medical record release
OR: odds ratio

Out-I group: Outsmart HPV that includes monthly interactive vaccination reminders
Out-U group: Outsmart HPV with monthly unidirectional vaccination reminders
RCT: randomized controlled trial
RMSEA: root mean square error of approximation
VIS: Vaccine Information Statement
YGBMSM: young gay, bisexual, and other men who have sex with men

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Protocol

Impact of Geriatric Hotlines on Health Care Pathways and Health Status in Patients Aged 75 Years and Older: Protocol for a French Multicenter Observational Study

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Abstract

Background: In France, emergency departments (EDs) are the fastest and most common means for general practitioners (GPs) to cope with the complex issues presented by elderly patients with multiple conditions. EDs are overburdened, and studies show that being treated in EDs can have a damaging effect on the health of elderly patients. Outpatient care or planned hospitalizations are possible solutions if appropriate geriatric medical advice is provided. In 2013, France's regional health authorities proposed creating direct telephone helplines, "geriatric hotlines," staffed by geriatric specialists to encourage interactions between GP clinics and hospitals. These hotlines are designed to improve health care pathways and the health status of the elderly.

Objective: This study aims to describe the health care pathways and health status of patients aged 75 years and older hospitalized in short-stay geriatric wards following referral from a geriatric hotline.

Methods: The study will be conducted over 24 months in seven French university hospital centers. It will include all patients aged 75 and older, living in their own homes or nursing homes, who are admitted to short-stay geriatric wards following hotline consultation. Two questionnaires will be filled out by medical staff at specific time points: (1) after conducting the telephone consultation and (2) on admitting the patient to a short-stay geriatric medical care. The primary endpoint will be mean hospitalization

duration. The secondary endpoints will be intrahospital mortality rate, the characteristics of patients admitted via the hotline, and the types of questions asked and responses given via the hotline.

Results: The study was funded by the National School for Social Security Loire department (École Nationale Supérieure de Sécurité Sociale) and the Conference for funders of prevention of autonomy loss for the elderly of the Loire department in November 2017. Institutional review board approval was obtained in April 2018. Data collection started in May 2018; the planned end date for data collection is May 2020. Data analysis will take place in the summer of 2020, and the first results are expected to be published in late 2020.

Conclusions: The results will reveal whether geriatric hotlines provide the most effective management of elderly patients, as indicated by shorter mean hospitalization durations. Shorter hospital durations could lead to a reduced risk of complications—geriatric syndromes—and the domino chain of geriatric conditions that follow. We will also describe different geriatric hotlines from different cities and compare how they function to improve the health care of the elderly and pave the way toward new advances, especially in the organization of the care path.

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KEYWORDS

aged; health care; hotline; emergency department; general practice medicine

Introduction

The world's populations are aging, which represents a serious public health issue. There are many consequences categorized into four main types: (1) demographic, with increasing numbers and proportions of people older than 65 years with increased life expectancy; (2) epidemiologic, with an accumulation of chronic diseases, incapacitating conditions, and disabilities; (3) economic, with increased health costs and accelerated health care reforms; and (4) social.

The organizational model of hospitals is one of the first elements to be affected by population aging. Over time, the elderly will become the central focus of all hospitals. But how will these establishments address this issue? In France, emergency departments (EDs) are the fastest and most common means for general practitioners (GPs) to cope with the complex issues presented by elderly patients with multiple conditions [1,2]. These services are already overwhelmed, and studies show that being treated in EDs can have a damaging effect on the health of elderly patients [3]. These emergency services can be traumatizing for the elderly and cause the many different complications that are commonly grouped together as "geriatric syndromes" [4-10]. When treated in EDs, the elderly are at higher risk of functional decline due to falls, drug iatrogenesis, and incontinence [11-13].

For emergency physicians, treating elderly patients with multiple pathologies, who often arrive alone, proves to be challenging. Treatment is rendered even more difficult by the lack of time emergency physicians have at their disposal due to EDs being more and more overburdened.

Studies have reported that in 20% to 35% of cases, there was no real need for admission to EDs, and outpatient care or planned hospitalizations would have been possible if appropriate geriatric care was available [14]. Therefore, nearly a quarter of these hospitalizations could have been anticipated and prevented. Some studies on hospitalization durations report that patients with initially planned hospitalizations seem to experience longer times being seen and treated in EDs. Furthermore, this significant number of hospitalizations creates financial issues. According to the French High Council for the Future of Health Insurance, an estimated €2 billion are lost due to the segmentation and inadequacy of response, along with unnecessary hospitalizations [15]. Overall, the literature highlights the need to better coordinate outpatient care with hospital services to provide the elderly with access to more effective care [16].

To improve interactions between GP clinics and hospitals, France's regional health authorities first organized the area as a unit focused on hospital centers incorporating both EDs and short-stay geriatric wards enabling immediate admission. In parallel, the regional health authorities created telephone hotlines designed to enhance GP clinic-hospital interactions with the aim of reducing the number of hospitalizations, particularly by improving the quality of response. The desired outcome was to improve both the care pathways and health status of the elderly. This hotline service was a recent creation (2013) and is still in an experimental form and not yet widespread. Its use still varies widely across the country, and we have yet to gauge its real value.

The primary objective of this study is to describe the health care pathways and status of patients aged 75 years and older hospitalized in short-stay geriatric care and referred via the hotline. The study population will be from different geriatric care hotlines from around France.

The aims of this study are to describe and compare how the geriatric medicine hotlines function with the goal of standardizing their use and defining ways they can be improved. We will also analyze the principal responses provided to GPs who call the hotlines and improve awareness of this tool. We hypothesize that geriatric hotlines will lead to reduced mean durations of hospitalizations by helping prevent time spent in EDs when it is unnecessary and potentially a risk. Through the use of a direct geriatric hotline diagnostic tool, we believe

elderly patients will experience better health care pathways that no longer involve multiple trips to EDs. The hotlines may facilitate better adapted and more appropriate responses to situations that do not necessarily need hospitalization and provide better alternatives (eg, therapeutic medical and social care, outpatient care, consultations, ambulance services, telemedicine).

Methods

Design and Setting

This will be a multicenter descriptive study conducted in seven French investigating centers (including university centers, across three different regions) with subgroup analysis (Table 1). Participating establishments will all be voluntary. To participate in the study, the center must have a specific and separate telephone line for doctor-doctor communications. Only calls originating from health care professionals will be included. The study will last for 24 months (May 2018 to May 2020). The course of the study and its design are presented in Figure 1.

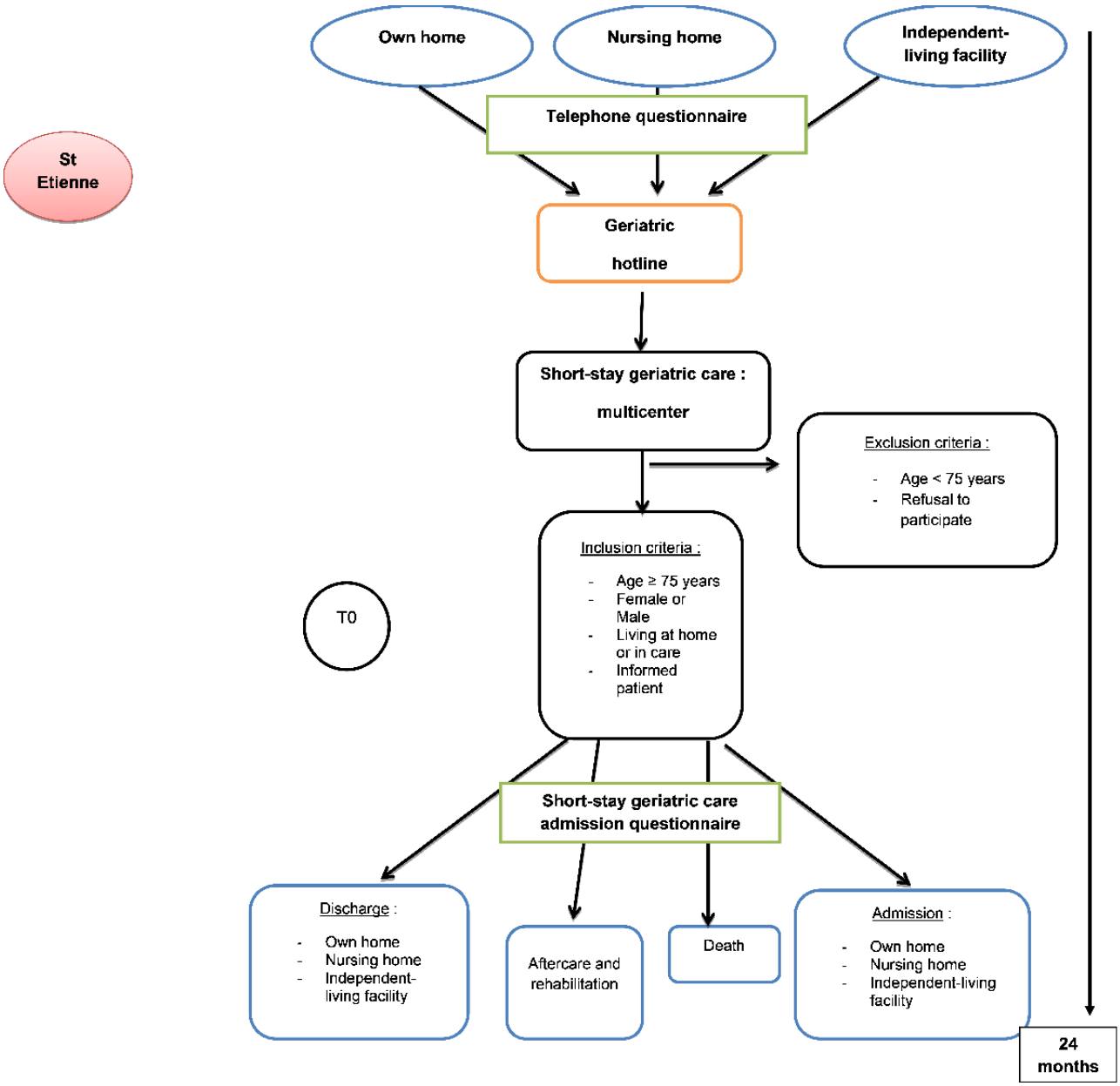
Two questionnaires will be distributed at two distinct time points: after telephone consultation (hotline) and after admission to a short-stay geriatric ward. The first questionnaire will be filled out via the hotline by the geriatric specialist answering the call. A second questionnaire will then be filled out during the patient's hospitalization by the treating geriatric specialist.

Table 1. Description of geriatric care offered by different participating centers.

Paticipating center	Residents, n	Hospital beds, n	Short-stay geriatric care	Postdischarge care	Long-term rehabilitation care	Consultation	Outpatient clinic	Ambulance care	Telemedical consultation
Bordeaux	252,000	3076	x	x	x	x	x	x	x
Clermont-Ferrand	141,400	2136	x	x	x	x	x		
Saint Etienne	171,100	1819	x	x	x	x	x	x	x
Angers	151,500	1445	x	x	—[a]	x	x	x	x
Lyon Sud	513,300	1038	x	x	x	x	x	x	—
Saint Chamond	34,870	710	x	x	—	x	—	x	—
Firminy	16,840	475	x	x	x	x	x	x	—

[a]Service not offered.

Figure 1. Flowchart of the study protocol.



Participants

The study population will be people aged 75 years and older, living in their own home or a care facility (including independent-living facilities), hospitalized in short-stay geriatric care and referred by the hotline in one of the investigating centers. All participants will be fully aware of the study and their rights regarding their participation. All participating patients will give their consent. Participants or a legally authorized representative will receive informational brochures and give their informed oral consent (more visual difficulties and writing for the elderly). All participants will be able, at any moment and by any method, to withdraw from the study.

Inclusion Procedure

When the patient is admitted to short-stay geriatric care, the investigators in each hospital of the study will first check the inclusion and noninclusion criteria of the patient. Then, they will explain the study to the patient and give the patient an information form. This will all be the responsibility of each center independently.

Selection and Exclusion of Participants From Study

The inclusion criteria will be patients aged 75 years and older, male or female, living in their own home or a care facility (including independent-living facilities), hospitalized in short-stay geriatric care, and with confirmed receipt of information on the study and their rights, as stipulated by articles L.1122-1 of the French public health code, by 57 of the “Informatique et Libertés” data protection act, and by MR-003 of the French data protection and civil liberties authority (CNIL). The exclusion criteria will be patients aged younger than 75 years or refusing to participate.

Monitoring

This study will involve no extra examinations or treatment besides traditional practices. The only difference will be the digitization of all medical findings for analysis. Data will be

kept confidential and anonymized for analyses. This study will be noninterventional. All interventions will be carried out following normal clinical practices. There will be no unusual risk or specific constraint for participating patients.

Study Endpoint

The study endpoint will correspond to when the patient is discharged from short-stay geriatric care. The duration of study participation for each patient will be the duration of their short-stay geriatric care.

Evaluation Criteria

The primary endpoint is the mean duration of hospitalization in short-stay geriatric care. The secondary endpoints are hospital mortality rate, assessment of health status of elderly patients hospitalized in short-stay geriatric wards using different criteria and their outcomes following discharge, describing and comparing how the different hotlines across France function, analyzing the principal responses provided to doctors using the hotline, and improving awareness.

Recorded Variables and Source Data

The study data will be collected directly from the questionnaires as the study progresses. For the first questionnaire (context of calls and solutions proposed), filled out by the hotline geriatric specialist (Textbox 1), health and administrative information will be collected for the study. The health data collected will include the identification of both speakers on the call, patient age, reasons for calling, degree of emergency as perceived by the geriatric specialist and the calling doctor (evaluated by simple scale from 0 to 10; 0 being a null degree of urgency and 10 an absolute urgency), and the responses offered by the geriatric specialist. The administrative data will include call duration (in minutes).

This questionnaire will be anonymous with no identifying criteria. It will be filled out every time contact is made via the hotline, irrespective of what responses are offered by the doctor (referrals to short-stay geriatric care or not).

For the second questionnaire, filled out by the geriatric specialist treating the patient during their hospitalization in short-stay geriatric care following referral from the hotline (Textbox 2), the sociodemographic, health, family, living situation, and location information will be collected for the study.

Sociodemographic data will include the first and last name of the patient, Patient Permanent Identification number, and patient age. These data will be anonymized on entry.

The health data collected will be the reason for hospitalization; number of hospitalizations during the past year; polypharmacy (four or more medications at the same time); biological data [17], including albumin and C-reactive protein levels for assessing nutritional status; and Charlson Comorbidity Index calculation using patient history for assessing the comorbidities of our geriatric population [18-20]; evaluation of activities of daily living (ADL) before hospitalization according to the validated ADL (/6) [21] and instrumental ADL scales (/4) [22]; evaluation of cognitive status using the Mini-Mental State Examination score (/30) [23]; and recommended referral after hospital discharge.

We chose the Charlson Comorbidity Index because it is a validated, reproducible, and simple comorbidity score that measures the impact of age (as there is excess mortality according to age), weighting by age from 1 (50-59 years) to 5 (90-99 years). This score is widely used for geriatrics publications.

Family or marital status data will include single or with a partner, and with or without children. The living situation data will be the residence of the patient (own home, independent-living facility, nursing home). Type of living area will be urban, semiurban, or rural.

Textbox 1. Context of calls and solutions proposed.

Caller

- General practitioner
- Hospital physician
- Other

Hotline responding doctor

- Assistant physician
- Hospital practitioner

Reason for calling

- Advice
- Emergency department hospitalization
- Emergency geriatric department hospitalization
- Consultation request
- Deferred hospitalization

Patient age (years), mean (SD)

Degree of emergency perceived by the hotline doctor, mean (SD)

Degree of emergency perceived by the calling doctor, mean (SD)

Response

- Simple advice
  - Medical
  - Social-medical
  - Therapeutic
- Emergency admission
  - To emergency department:
  - No beds in short-stay geriatrics
  - Emergency care required
- Short-stay geriatric care: allocated bed
  - Yes
  - No
- Deferred hospitalization (days), mean (SD)
- Nonhospital ambulance services
- Outpatient care
- Consultation
- Teleconsultation
- Temporary nursing home

Call duration (minutes), mean (SD)

Textbox 2. Sociodemographic participant characteristics.

Mean age (SD)

Sex

- Male
- Female

Mean hospitalization duration (SD)

Type of living area

- Urban
- Semiurban
- Rural

Reason for hospitalization

- Fall
- Fainting
- Frailty
- Difficulties coping at home
- Pain
- Stroke
- Change in general status
- Confusion or behavioral problems
- Breathing difficulties
- Sepsis
- Other (specify)

Residence type

- Own home
- Nursing home
- Independent-living facility

Family or marital situation

- With a partner
- Alone no children
- Alone with children
- Other

Polypharmacy (>4)

- Yes
- No

Charlson Comorbidity Index score, mean (SD)

Previous autonomy

- Mean activities of daily living (SD)
- Mean instrumental activities of daily living (SD)
- Mean blood albumin (SD)
- Mean C-reactive protein (SD)

Cognitive disorder

- Mean Mini-Mental State Examination score (SD)
- Diagnosed dementia

Walking difficulties

- Walking aids
- History of falls

Outcomes

- Return home
- Return to nursing home
- Long-term rehabilitation
- Follow-up care then nursing home
- Admission to nursing home
- Admission to independent-living facility
- Death
- Return home with planned help (specify)

Statistical Analysis

This is a pilot study. Given the need for subgroup analyses and information concerning the activities conducted at the investigating centers participating in this study, approximately 250 patients are required per center (ie, 2000 in total). This goal is attainable in 24 months, which represents the entire duration of the study. Statistical analysis will be done by statisticians. Different measures will be used depending on the desired descriptive statistics. All analyses will be conducted on the entire included population and each investigating center.

Univariate analysis, descriptive analyses of the study population, will involve recorded variables, comparison of subjects included via the hotline according to sex, and type of discharge using parametric or nonparametric tests and according to the distribution of variables (chi-square tests for quantitative variables, Student *t* tests for qualitative variables, test significance set at 5%).

Multivariate analyses will include analyses of mean values (ANOVA), the use of a generalized linear model, the use of a mixed model for taking into account the random effect of choosing seven centers. A multiple-component analysis will be used to identify different patient groups (patient profile analysis).

Results

The study was funded and peer reviewed by the National School for Social Security Loire department (École Nationale Supérieure de Sécurité Sociale) and the Conference for funders of prevention of autonomy loss for the elderly of the Loire department in November 2017, and obtained institutional review board approval in April 2018 by the committee for the protection of persons of Sud Est V of Grenoble University Hospital Center (registered under 18-CETA-01 No.ID RCB 2018-A00609-46). Data collection started in May 2018. The planned end date for data collection is May 2020. Data analysis will take place in the summer of 2020. First results are expected to be published in late 2020.

Discussion

This study will enable us to determine whether a geriatric hotline offers effective management of elderly patients. Could planned hospitalizations be the best solution for our elderly? Will this approach lead to less geriatric syndromes [4-10]?

Wargon et al [4] demonstrated that the elderly spend more time in EDs, which is a potential source of dysfunction in the organization care offered by these services and lowers chances of positive outcomes for the patient. Therefore, there is interest in enabling the assessment of geriatric health status to limit visits to EDs as much as possible and improve the care pathways offered to elderly patients. In a retrospective study, Mazière et al [8] demonstrated that elderly admissions to EDs are independently associated with functional decline in terms of daily activities. The findings of these studies indicate that improving interactions between GP care and hospital services could enable more direct referrals of patients to multidisciplinary care in short-stay geriatric wards, consequently improving the functional prognosis of elderly patients and avoiding geriatric syndromes secondary to ED care.

The study has several strengths. It is a multicentric study covering a large patient sample. The diversity of the participating investigating centers (across three different regions) and their populations is also likely to offer diverse responses. Is the time spent in ED consultations greater in the larger centers? Does this lead to more cases of geriatric syndrome? Are there closer, more effective ties between GP clinics and hospitals in areas with a lower population density? Do these areas (with a lower population density) benefit from better understanding and communication of this type of care? The analysis will be conducted across subgroups (town by town) to avoid confusion bias. The overall population will be sourced from different types of regions (ie, rural, semiurban, urban) to

reveal whether this factor has an impact on the knowledge of or access to the hotline [24]. The analysis will enable evaluation of GP clinic-hospital interactions [25] according to population centers, and the need for links between these health care areas, to determine the strengths and limitations and to reinforce GP clinic and hospital collaboration with the aim of reducing ED admissions [26].

By analyzing center by center, we will be able to describe each center with the different responses they offer. Ideally, this will help to improve the function of the geriatric hotline for the entire country and pave the way to new advances, especially in the organization of the care path in the long run.

The analysis also will be conducted in two sections. First, the call to the hotline will be analyzed. Did the experience of the doctor responding to the call influence the type of care recommended and the response offered? Does a high level of perceived emergency correlate to hospitalization via the ED? Is the hotline solely used by general medicine doctors? Would it be a good idea to roll out access to the hotline to other hospital specialties? Given the growing issue of population aging, the current geriatric services are not enough to care for all the elderly. This is why specialists are turning more toward other fields for geriatric assessment (eg, oncology, orthopedics). This study will reveal the different responses that can be provided by this tool (the hotline), from therapeutic or medical advice to referrals for hospitalization, ambulance call-outs, consultations, telemedicine, and more.

Second, we will study the profile of patients referred for hospitalization via the hotline to determine the characteristics of those the hotline recommends for admission to improve their health care approach. Does this tool lead to direct hospitalization in short-stay geriatric care for the less-fragile patients who still have some autonomy? Are the motives for admission less serious? We hypothesize that the mean duration of hospitalization will be shorter in cases in which it is planned, which leads to the question of whether the future of hospitalization is influenced by the ways patients are admitted. In their study involving 520 patients, Dijon et al [27] demonstrated that the intrahospital care pathways of geriatric patients referred directly to short-stay geriatric care are shorter and more effective than those experienced by patients who first went through EDs, with significantly shorter mean hospitalizations achieved through direct hotline-referred admissions (11.6 days versus 14.1 days with ED consultation; $P<.05$). Patients admitted to short-stay care via EDs were also the quickest to be rehospitalized in the future.

Another advantage of our study is its innovative character because there are currently very few studies analyzing geriatric hotlines [25]. In addition, it is observational in nature, which enables many types of procedures from across the country to be analyzed, leading to more standardized approaches.

The study does have limitations, notably its nonrandomized nature. There is no comparison because it is a descriptive study. The quality of the responses will be operator-dependent. Eventually, the goal will be to conduct a second study aiming to compare profiles of elderly patients hospitalized in short-stay geriatric wards via EDs versus those referred via a geriatric hotline. Through the first questionnaire, we will analyze the different responses provided by the hotline (eg, call-outs, consultations, telemedicine, day hospital). We will evaluate the number of hospitalizations avoided or deferred in time following the use of the hotline to reduce inappropriate passage through EDs.

This first study will demonstrate if managing patients by means of a geriatric hotline offers the most effective approach and results in shorter mean hospitalization durations and thus fewer complications and geriatric syndromes and fewer trips to EDs. It will also describe and compare the function of different geriatric hotlines across France to improve health care pathways for the elderly and pave the way toward future advances, such as new modalities of patient management, the development of more appropriate responses to this population, and the reduction of inappropriate visits to emergencies, which we know can be deleterious for the elderly.

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Authors' Contributions

The chief investigator of the study, RG, as well as LM, NL, MB, TC, LG, CA, NS, NJ, JM, MT, EO, RJ, and BB were responsible for determining the research question, the design, methodology, and follow-up of the study; obtaining ethics approval; acquiring financial support; and writing the paper. BB and LG contributed the development of the methodology and statistical analysis. All authors helped draft and revise the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from Comite de Protection des Personnes Sud est V.
[DOCX File , 19 KB - resprot_v9i2e15423_app1.docx]

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Abbreviations

ADL: activities of daily living
ED: emergency department
GP: general practitioner

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Protocol

Effectiveness of an Educational Intervention in Reducing New International Postgraduates' Acculturative Stress in Malaysian Public Universities: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Universities around the world, including Malaysia, have attracted many international students from different countries. Research has reported that acculturative stress resulting from international students' attempts to adjust to the cultures of host countries is one of the most challenging issues that affects their lives in general and academic lives in particular.

Objective: This study aims to examine the effectiveness of an educational intervention on acculturative stress among new postgraduate international students joining Malaysian public universities.

Methods: A cluster randomized controlled trial design with Malaysian public universities as the unit of randomization will be used in this study. Public universities will be randomized in a 1:1 ratio to be either in the intervention (educational program) or control group (waiting list). Participants in the intervention group will receive 7 sessions in 9 hours delivered by an expert in psychology and the researcher. The control group will receive the intervention once the 3-month follow-up evaluation is completed.

Results: The data will be analyzed using the generalized estimation equation with a confidence interval value of 95%; significant differences between and within groups are determined as $P<.05$. The results of the study underlie the effectiveness of educational program in decreasing acculturative stress of new international students and enabling them to cope with a new environment. The results of this study will contribute to previous knowledge of acculturative stress, acculturation, and adjustment of international students. Furthermore, such results are expected to play a role in raising university policy makers' awareness of their postgraduate international students' acculturative stress issues and how they can help them avoid such stress and perform well in their academic life.

Conclusions: We expect that the intervention group will score significantly lower than the wait-list group on the immediate and 3-month postintervention evaluation of acculturative stress and achieve a higher level of adjustment. Results will have implications for international students, policy makers at universities, the Malaysian Ministry of Higher Education, and future research.

Trial Registration: Clinical Trials Registry India CTRI/2018/01/011223; http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=21978&EncHid=&userName=Muhamad%20Hanafiah%20Juni

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KEYWORDS

acculturative stress; acculturation; international students; adjustment; protocol; cluster; randomized controlled trial

Introduction

Background

Previous research has identified the challenges and needs of international students during their higher education outside their native countries [1-6]. The most challenging issue faced by international students is adaptation to the new environment, especially the new culture of the host country [7-10]. Other challenges include difficult living circumstances; different foods, climate, cultural norms, and customs [2,8,11-14]; and stressful interactions with local students and the host environments [15]. International students also face academic or educational challenges such as an unfamiliar educational system and language barriers [2,8,11,16]. These stressors can lead to a kind of stress commonly referred as acculturative stress, defined as a psychological and physical discomfort experienced by an individual in a new cultural environment [17].

A causality relationship between a high level of stress experienced by international students and deteriorating health conditions and even more serious health problems has been reported [18,19]. The combination of lack of social relations, financial support, and stress results in students' feelings of anxiety [5], depression, physical illness, and wasted potential [20-22], leading to depression [23], negatively affecting their academic achievements [24], reducing their academic performance, and even leading them to drop out of university [22,25], especially when it becomes excessive [19]. In this regard, preventing student dropout is a challenging task in higher educational institutions [26]. Pal [27] suggested that programs should be employed in higher educational institutions to address student levels of stress and intention to drop out. Furthermore, research has indicated there is a significant positive relationship between acculturative stress, social support, and sociocultural adjustment of international students [28]. Other studies reported a positive relationship between acculturative stress and psychological adjustment [29,30]. Acculturative stress was found to have a negative relationship with positive acculturation. Acculturative stress is negatively correlated with social support. Consequently, lower levels of acculturative stress are associated with both positive cultural associations and higher levels of social support [31], and acculturation is negatively associated with acculturative stress [32]. In terms of students' social support and their adjustment, studies on international students in the Malaysian context [32-34] and overseas [28,35] reported that social support significantly affects international students' adjustment by lowering the level of stress. Similarly, studies have found that social support has positive impacts on sociocultural adaptation as it acts against the stress of cultural adaptation of international students [36,37].

Malaysia has attracted many international students, which has positioned it 11th in world ranking in hosting international students [38]. The increasing number of international students coming from other regions, including the Middle East [39], and the plan to increase intake to 250,000 students by 2025 (Malaysia Education Blueprint 2015-2025: Higher Education) raises the need for enhancing the quality of services and enabling higher educational institutions to meet the needs and requirements of the students, especially in health care. The number of international students has increased from 18,242 to 83,633 in the years 2001-2013, however, making this a challenge. In addition, while the government aims to make the country of Malaysia an international hub for higher education excellence by 2020, research on international postgraduates is still limited. There are only a few studies on international postgraduates that explore the challenges they face in academic and social adjustment in Malaysia [40,41]. Cross-cultural adaptation is crucial for postgraduates in order to overcome the various challenges and become able to psychologically and socioculturally adapt to the new environment [42]. Acculturative stress is caused by stressors such as language barriers, academic barriers, racial discrimination [43,44], perceived surrounding environment, attitudes toward the host country among international postgraduate students [45], cultural shock, homesickness, and perceived hatred [46]. While Rajab et al [46] found that international students' acculturative stress is moderate, Par et al [47] reported that almost 40% of international postgraduate students joining Malaysian universities experience a high level of acculturative stress, which could affect their academic achievement in higher educational studies [48].

Although the above studies in Malaysia are useful for investigation of international students' acculturative stress, these studies have focused on describing stress merely from student perception and self-reported reflections, and they are scant and general in comparison with those studies carried out in other host countries [49]. For instance, while research on international student acculturative stress and adaptation has reached its third phase of development in other host countries like Australia [50], in the Malaysian context, such research is still in the early phase of development [49]. In addition, studies in the Malaysian context have ignored the importance of implementation of stress coping interventions. Further empirical investigations into issues pertaining to international student requirements are needed to enable students to improve achievement and performance in higher educational institutions [51]. Based on the above issues, gaps addressed in earlier research, and the need to address stress and adjustment in international students, our study proposes an educational intervention program that can assist international postgraduates to cope with and overcome the different aspects of acculturative stress.

Theoretical and Conceptual Frameworks

The literature highlights several acculturation models developed by scholars over time, one of which is the bidirectional model of acculturation widely accepted in previous research [52]. Specifically, Berry's model of acculturation [53] places emphasis on two distinct aspects: the person's identification with their native culture and identification with the host culture.

However, early views and perspectives of acculturation can be valuable in theoretically explaining and discussing the process of acculturation. According to the first view, acculturation is seen as a term covering issues resulting from first-hand contact of individuals with people of different cultural backgrounds. This view also stresses that the consequence of acculturation is changes in the individual's native or original cultural patterns and behaviors. Based on this view, there is a distinction between acculturation and cultural change in the sense that acculturation encompasses such cultural change as one of its aspects, and assimilation, which is at times a phase of acculturation [54].

The second view emphasizes acculturation as a cultural change initiated by the conjunction of two or more autonomous cultural systems. Thus, acculturative change can result from direct cultural transmission or it can be a result of noncultural aspects, including modification of ecological or demographic characteristics by an impinging culture, and it may be delayed. Hence, acculturation can appear in the form of an internal adaption after the individual accepts alien cultural patterns or behaviors or it can emerge in the individual as a kind of reactive adaptation of traditional modes of life [54,55]. In addition, as defined by Graves [56], psychological acculturation is a process of changes taking place in an individual who participates in a culture-oriented contacting situation directly affected or influenced by the new or external culture and by the changing culture to which they belong. According to Redfield et al [57], acculturation comprises various changes in different forms, identified by Berry [58] as biological, social, and physical changes.

Based on the model of stress developed by Lazarus and Folkman [59], Berry [60] and Berry et al [61] developed an acculturative stress model. The main idea of the framework is that acculturative stress results from situations in which a person's experiences and appraisal become problematic due to the person's inability to deal with them and failure to adjust to them through behavioral changes. This implies that acculturative stress is a response of the individual to life events which are grounded in the experience of acculturation [54]. However, not all acculturation changes are assumed to lead to acculturative stress because how acculturation is experienced, perceived, and interpreted by the individual can be influenced by moderating and mediating factors, including personal characteristics such as age, gender, and social support prior and during acculturation [53,62].

In their systematic review of the theoretical frameworks used in research on international students' sociocultural adaptation to host countries between 2012 and 2017, Sarmiento et al [63] found that 82.2% of the research papers and articles provided a description of particular theoretical frameworks on students' adaptation. Moreover, 69.3% of these articles reported treating nonspecific frameworks. What was interesting in this review paper was that the majority of the reviewed research papers focused on investigation of international students' issues related to acculturation and adaption based on the acculturation model. Acculturation should also be approached from the perspective of cross-cultural psychology. As pointed out by Berry [64], acculturation should be investigated in its cultural contexts. In such contexts, researchers can obtain a better understanding of the cultures and individuals in contact. Therefore, such investigation seeks to link the acculturation of a given group of people to which an individual belongs and the individual's psychological acculturation.

Berry's [65] acculturation model describes cross-cultural adaptation as a process that involves the individual's or group's behavioral and psychological changes in life resulting from their contacts with others from different cultures. Whereas psychological changes are related to one's modified attitudes, perceptions, and beliefs, behavioral changes are pertinent to their external behavior toward those typical of the host society or mainstream [65]. In a previous study, the term psychological dimension was defined as the person's perceived acculturative stress which was attributed to their cross-cultural adaptation (eg, how they perceived unfamiliar social cultural customs) [66]. On the other hand, psychological adaptation is often associated with the person's emotional and affective satisfaction about their integration into a new social environment, while sociocultural adaptation encompasses the process in which the person fits in a new environment and effectively interacts with it [63]. Therefore, our study is framed within the theoretical perspective of acculturation and acculturative stress developed by Berry et al [61] and Berry [53] and further expanded by Berry [65,67,68].

Study Aims

This study aims to develop, implement, and evaluate the effectiveness of an educational intervention in reducing acculturative stress and improving adjustment among new international postgraduates joining Malaysian public universities. Specifically, the study aims to (1) describe participants' sociodemographic characteristics, acculturation, acculturative stressors, and social support at the baseline; (2) determine the level of acculturative stress, adjustment (psychological and sociocultural), and intention to drop out of university among new international postgraduates at the baseline; and (3) determine the effect of the educational intervention on acculturative stress, adjustment, and intention to drop out between and within the control and intervention groups at the immediate and 3-month postintervention follow-up.

Study Hypothesis

In order to achieve the above research objectives, the study attempts to test the following null research hypotheses: (1) the intervention group will score significantly higher than the wait-list group on the immediate and 3-month postintervention evaluation of acculturative stress, adjustment, and intention to drop out measures (between groups) and (2) the acculturative stress, adjustment, and intention to drop out scores for the intervention group at the immediate and 3-month postintervention follow-up will be significantly higher than scores of the baseline or preintervention (within groups).

Methods

Overview

The design, conduct, and reporting of the study will adhere to the Standard Protocol Items: Recommendations for

Interventional Trials (SPIRIT) [69], Consolidated Standards of Reporting Trials (CONSORT) guidelines [70], and Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth (CONSORT-EHEALTH) [71].

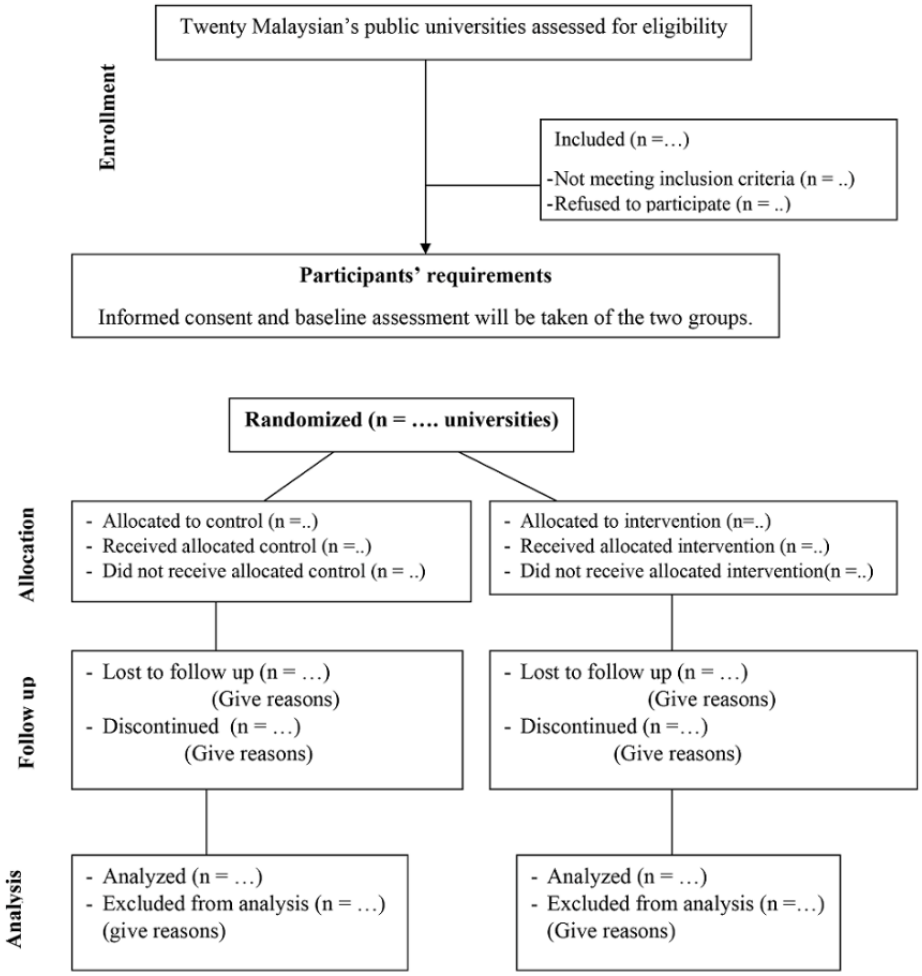
Study Location

Malaysia is the context of this study since it is the host country for many international students coming from different countries. The target participants in this study will be those new international postgraduate students joining Malaysian public universities. The study includes 20 well-known public universities that attract large numbers of new international students who will be screened according to the inclusion criteria.

Study Design

This study is quantitative in nature and experimental in design. Specifically, the study employs a cluster randomized controlled trial (RCT) design. Figure 1 summarizes the study design. Selection of such an experimental design is based on its strength and effectiveness [72]. A cluster design will be employed as the randomization and intervention at the level of the university, and the primary outcome measures are related to students' acculturative stress, while the secondary outcomes refer to their adjustment and intention to drop out of university. Public universities will be randomized to either a control (wait-list) or intervention (educational intervention) group. In order to determine the effectiveness of the intervention program, the primary and secondary trial outcomes will be assessed through surveys of new international postgraduates at 3 time points: baseline (time 1) before the intervention, immediately postintervention (time 2), and at 3-month follow-up after the intervention (time 3).

Figure 1. Flowchart of study.



Participants

Public universities that will be eligible to participate in the study should satisfy the following criteria: acting or serving as the main campuses for international students in Malaysia and having more than 40 new international postgraduates in their first semester in Malaysia. For students, only new international postgraduates entering the selected universities in their first academic semester will be eligible to participate.

Recruitment

For the purpose of eligibility assessment, the researcher will approach all public universities in Malaysia and invite only those universities that are eligible through formal invitation letters issued by the researcher's university. The letters will be directed to the high authorities of the selected universities through emails seeking their permission for the researcher to conduct his study among international postgraduates. Moreover, the researcher will obtain lists of new international postgraduates joining these universities, including necessary information about the students including contact details, faculty, nationality, and academic program.

Procedures for recruiting public universities will be based on several strategies that have been reported to be useful for maximizing research participation, including prenotifying universities of the study, providing opportunities for participation, visiting persons in charge at the universities, contacting potential participants using telephone and other contact methods, accessing research staff for further clarification on participation, and using dedicated research staff to manage the recruitment process. Specifically, an invitation letter will be directed to a university contact person (deputy vice chancellor for academic and international affairs, deputy vice chancellor for research and innovation, and dean of postgraduate studies) in each eligible university.

Once the letters are sent, the above-mentioned persons in the universities will be contacted by telephone to confirm eligibility based on inclusion criteria and assess interest in participating in the study. This will be followed by several calls until the decision on informing international postgraduates of participation in the study is made and the researcher is informed of such decision. However, such decision, in some cases, will be made through meeting among academic and research staff and consultation with the management committee of a given university. At the end of this process, a confirmation email will be sent to each university, confirming and thanking them for agreement to participate in the study. Each participating university will be given hard and electronic copies of the information and invitation letters for the selected postgraduates in that university.

Student recruitment will use a random sampling procedure to select students from the list of the new postgraduates for each selected university based on probability proportional to size method in order to reduce possible sampling bias. The respondent's information and consent sheets will be given to the sampled students to get their agreement to participate. In order to maximize response rates, representatives of the international students will be requested to seek the selected postgraduates' consent.

Randomization and Blinding

Prior to randomization, the researcher will start collecting baseline data. This will be followed by assigning the universities as the unit of randomization. Universities will be randomized in order to reduce contamination between groups [73,74]. However, to ensure allocation concealment, the allocation sequence of the universities selected at the previous stage will be assigned to a control group and an intervention group by the ratio 1 to 1. The purpose of this is to ensure that the number of universities allocated to each group will remain approximately equal (see Figure 1 flowchart) [75-77]. This will be achieved by employing a simple randomization procedure. The researcher will use a computer-generated list of random numbers. It is exclusive to the researcher who will allocate the 10 universities to the two groups. In addition, no one in the control groups will know what the experimental groups will be offered. The statistician who will perform the primary analyses will be blinded to group allocation. This study will follow a CONSORT chart [73] as shown in Figure 1 (study flowchart).

Sample Size

The total sample size needed will be calculated by applying the formula for two population means [78] as seen in Figure 2. Means and standard deviation used for the intervention group and control group were based on the estimation offered in a previous RCT [79]: μ1=2.58, μ2=2.07, SD1=1.08, SD2=1.08, n1=24, n2=30. Therefore, the total sample (n) will account for 71 participants. Calculation of the required sample size in this study was performed based on the guidelines in the CONSORT for cluster RCTs [73]. By considering the account intraclass correlation coefficient (ICC), it is necessary to multiply the sample size in RCTs by design effect=1+(m–1)*ICC, where m is the average cluster size [80-83]. Thus, the average class size is assumed to be 40 participating students, and an ICC of .05 could be expected. This would result in design effect N=1+(m–1)*ICC=1+(40–1)*.05=2.95. Based on the sample size required by the formula, the required minimum sample size for each group after adjusting for design effect is n=71*2.95=209, and the total sample size required is 209 participants per arm.

Figure 2. Sample size formula for two population means.

$$\frac{2\sigma^2\left[Z1-\frac{\alpha}{2}+Z1-\beta\right]^2}{(\mu1-\mu2)^2}$$

To factor in 20% attrition, if (n) is the sample size required as per formula and (d) is the dropout rate, adjusted sample size N new is obtained as N1=n/(1–d) [84]. Therefore, the total required per group after adjusted for dropout rate is N1=209/(1–0.2)=261; hence, a total of 522 new international postgraduate students will be needed for the sample size in both groups.

Intervention

Intervention Development

The intervention is developed based on the acculturation and acculturative stress models integrating with a cognitive behavioral theory with the aim of focusing on cross-cultural sessions and social and behavioral issues in order to improve social and psychological adjustment and reduce acculturative stress and intention to drop out among international students, especially those who have just arrived at the new hosting

environment. Most of these models highlight important variables, including acculturation experience, acculturation strategies, and social support, which have an effect on decreasing acculturative stress and a positive impact on the adjustment of students in host cultures [68,85,86]. Therefore, this study developed an intervention that targets individual variables such as acculturation, social support, and coping strategies, as these factors have the potential to mitigate acculturative stress and, consequently, the international students' adjustment and intention to drop out.

The educational intervention was developed based on previous experimental studies on the implementation of intervention programs such as Excellence in Experiential Learning and Leadership developed by Mak et al [87], a cultural transition course for international students by Brunsting et al [88], a behavioral intervention to improve cross-cultural relationships consistent with the acculturation models developed by Pritchard and Skinner [89], a cognitive behavioral group intervention on acculturation by Pan et al [90], a group psychological intervention to enhance coping and acculturating by Smith and Khawaja [91], and further intervention and support programs aiming to improve international students' sociocultural and psychological adjustment and reduce their acculturative stress and intention to drop out of the university [92-94]. Taking into consideration the limitations of these previous intervention studies, development of the intervention in this study is based on the creative use of cross-cultural activities in a program, using a clear quantitative evaluation of the effectiveness of the program and including components that directly target international students' psychological and sociocultural adjustment and acculturative stress. The intervention was also developed based on the results of previous studies.

Berry's model [68] for acculturation places an emphasis on individuals' cognitive appraisal of acculturative life changes as another factor that has an impact on acculturation. For instance, a given person is likely to appraise a life change as a chance or, alternately, as a stressor that is conducive to acculturative stress. Berry's model provides a clear picture of the instance or case in which a person appraises a life change as a stressor. Moreover, they may make an additional appraisal of the sufficient coping resources that they have in order to overcome the stressor. Thus, acculturative stress will become low when a person possesses adequate coping resources. As a result, they will be able to psychologically and socioculturally adjust to the new host country. Therefore, the model adopted in this study guides development of the intervention (identifying the necessary components of what an efficient intervention that reduces acculturative stress and improves adjustment should be). These are cognitive appraisals of acculturative life changes, acculturation experience, stressors, acculturative stress, and coping strategies including social support [95]. To achieve this, the study adopts a cognitive behavioral framework for acculturation and acculturative stress since it suits the purpose of this effective intervention. The framework addresses cognitive appraisals and increases coping resources in the cognitive and behavioral domains.

Intervention Content

The proposed program will cover a period of 7 sessions and will be conducted over a period of 9 hours in each university of the intervention group. Core modules of the Acculturative Stress Educational Intervention Program will include (1) introduction to the intervention program, (2) introduction to Malaysia and Malaysian culture and customs, (3) study abroad in Malaysia, (4) understanding acculturation, (5) acculturative stress, (6) coping strategies, and (7) adjustment strategies. In each session, participating international students will be offered different topics with experiential and interactive methods of delivery and materials. Websites; videos; demonstrations; in-group activities and interaction; interchanging of cultural background, experience, and intracultural communication; and critical incidents with analysis, reflection, and discussion on different cases and scenarios of international students' experience with acculturative stress and adjustment will be used for enabling students to engage with the program.

Intervention Implementation

The aim of the intervention program is to transfer knowledge and gain skills, and the program will cover two parts: (1) a seminar session with PowerPoint (Microsoft Corp) presentation covering the 7 sessions, providing knowledge about different aspects of Malaysia and Malaysian culture, acculturation, and acculturation strategies and (2) knowledge and activities will be provided about acculturative stress, the sources for acculturative stress, adjustment, coping strategies, and social support. In this part, group exercises and activities will be used for enabling the students to engage with the program and gain knowledge and skills. Therefore, the intervention program will be delivered through seminar sessions, a PowerPoint presentation, videos, group activities, a printed booklet, and other printed materials that are available on the website during the intervention and study but can be accessed only by the intervention group using codes. Website, email, and WhatsApp are the primary methods to deliver the educational materials to the intervention group. These technological tools will be used to send short reminder messages and encourage participants to take part in the intervention and control groups. Participants in the study will be provided useful information about the topic and how to cope and adjust in the new environment. The second phase focuses on participants' independent processing and implementing of information provided in the first phase as they begin to use the information in their personal lives and develop the skills necessary for enhancing their situation.

Study Variables and Instruments

This study will use a self-administered questionnaire consisting of 8 sections measuring the sociodemographic, independent, and dependent variables (study outcomes). The questionnaires will be completed at time 1, time 2, and time 3.

Primary Outcome: Acculturative Stress

Stress is defined as a state of a person that results from their interaction with their surroundings and is regarded as a threat to the well-being of the individual. Since this study focuses on international students' acculturative stress as the primary outcome, we conceptualize acculturative stress as stress that a

person suffers from reaction or response to stressful events of life relevant to the process of acculturation [65] as well as the psychological difficulties in the new culture [96]. Acculturative stress is also a psychosocial result of the individual's lacking familiarity with the customs and social norms of the host culture [97,98]. Hence, one of the focuses of the investigation in this study is the acculturative stress experienced by international students in the Malaysian context [99-101].

This study uses the Acculturative Stress Scale for International Students (ASSIS) for measuring the primary outcome, international students' acculturative stress. The measure is effective in examining international students' cross-cultural adjustment, specifically the extent to which they find their involvement in everyday social situations as difficult due to cultural differences. ASSIS is widely used in studies on international students' acculturative stress in Malaysia, and the scale is also highly reliable and valid as reported in early research [29,32,66,101-106]. The overall score for the ASSIS is in the range of 36 to 180. The use of the total score of the ASSIS is highly encouraged by Sandhu and Asrabadi [103]. In the case of using the total scores, high scores mean that the individual's perceived acculturative stress is high [46,104-106].

Secondary Outcomes: Adjustment and Intention to Drop Out

Adjustment is known as a short-term and dynamic process experienced by the individual in relation to the new cultural environment; it also refers to the degree to which a certain university meets the demands or requirements of international students [107-109]. According to Ward and Kennedy [110], there are two dimensions of adjustment: sociocultural and psychological.

First, sociocultural adjustment is a process in which individuals with different cultural backgrounds become skilled and able to engage in negotiating the host culture and effectively interacting with its local people [111]. Assessment of the individual's sociocultural adaptation is based on a 20-item version of the Sociocultural Adaptation Scale (SCAS) [110]. Participants will be asked questions regarding the degree of difficulty experienced by them in a number of areas [110,112-115]. This is based on a 5-point Likert scale for rating the difficulty of 20 daily situations adapted by the participating international students in the Malaysian context. Initial use of the SCAS was documented in a previous study that indicated it was reliable, with scale alphas ranging from .75 to .91, indicating good internal consistency and construct validity [110-115]. The SCAS is regarded as a flexible research instrument and measure that is easily modified based on characteristics of the sojourning sample, and it can be adapted to different cultural contexts [34].

Second, the Satisfaction with Life Scale (SWLS) is used to measure psychological adjustment and the cognitive component of subjective well-being [116] through 5 items. Consistent with the standpoint of the World Health Organization on health, psychological adjustment is seen as state of well-being and not merely the absence of disease [117]. Hence, its specific focus is on evaluating individuals' perceived satisfaction with life as a whole based on their criteria and views [118,119]. The items on the SWLS are based on a 5-point scale on which respondents are asked to agree or disagree with 5 statements (eg, "In most ways my life is close to my ideal"). The scale is available in a range of languages and has been used in cross-cultural research [118], and its internal consistency for psychological adjustment has proved to be very good [34,42,109,119].

Finally, the international students' intention to drop out of the university is also a secondary outcome. This variable describes the international students' intended behavior concerning their persistence of studies in the host country. It will be measured using this single item: How likely is it that you will withdraw from university (for whatever reason)? This question underlying the dependent variable of students' intention to drop out is known to be the best predictor of students' actual behavior and can be used in the absence of behavioral data [120,121]. In our study, this question is intended to seek participating students' responses to whether they were thinking of or had already thought of dropping out of university.

Sociodemographic Information Questionnaire

All participants will be asked to provide sociodemographic information including their gender, age, marital status, educational level, duration of stay in Malaysia, country of origin, prior traveling experience, native language, and self-reported proficiency of language. Self-reported proficiency will also be assessed using a composite score from the following questions: (1) What is your present level of English fluency? (2) How comfortable are you communicating in English? (3) How often do you communicate in English? This method of measuring and assessing English language proficiency has been documented previously by several researchers [122-125]. For this study, participants will be asked to rate their perceived proficiency in speaking, understanding, writing, and having a conversation in Malay and English, as language skills are said to enable sojourners to interact with host nationals and engage in interpersonal relationships, which, in turn, influences their adaptation [125,126].

Other Independent Variables and Measurements

This study focuses on other independent variables that directly or indirect affect study outcomes: acculturation, social support, and acculturative stressors.

Acculturation is a process of adaptation or adjustment to a new cultural context that imposes behavioral, cultural, and psychological changes on the individual in an attempt to be in contact with other individuals or even groups coming from diverse cultural backgrounds [65,127]. Participants' acculturation will be measured using the Acculturation Index (AI) [128]. The AI was adopted from the two-dimensional acculturation model of Berry et al [61]. These two basic dimensions of acculturation are students' identification with their heritage culture and their relationship with the host culture. The scale comprises 21 cognitive and behavioral items (eg, food, language, recreational activities, social customs, pace of life, religious beliefs). The instrument is intended to identify acculturation strategies used by participants [110,115,128,129]. Participants will be given two questions on their current lifestyles in two cultures: "How similar are your experiences and behaviors to members of your culture of origin?" and "How

similar are your experiences and behaviors to members of Malaysian culture?" This instrument makes use of a 5-point, partly anchored, Likert-type scale ranging from 1=not at all similar to 5=very similar. Independent scores for the two dimensions are in the range of 0 and 105, and higher scores are indicative of the participants' stronger identification with the host culture. In previous studies, internal consistencies and reliabilities were illustrated by Cronbach alphas ranging from .91 to .94 and .89 to .97 for the heritage culture and host culture, respectively. These reliabilities were confirmed by studies using this measure among sojourns from different cultures living in different populations [115,128,129].

While acculturative stressors are those related to international students' acculturative process at the biological, social, functional, cultural, and physical/environmental levels [130], other related stressors include reentry issues. Acculturative stressors will be measured by the International Student Acculturative Stressor Scale (ISASS) developed by Eustace [131] for the purpose of capturing the degree to which each acculturative stressor represents an issue or difficulty for the international students participating in this study. Respondents will be provided with a 5-point Likert-type scale with 13 items that allow them to rate their degree of difficulty of the different acculturative stressors. The options ranged from 1=not difficult at all to 5=very difficult. The total scores for the 13 items ranged between 13 and 65. Higher scores indicate higher levels of difficulty of such acculturative stressors.

Perceived social support is another dependent variable, defined as the individual's impression of the available resources that are supportive for them during their experience of stress and symptoms experienced. Social support encompasses three different dimensions: family, friends, and significant others. Whereas family and friends are recognized as self-explanatory, significant others might be a supervisor, peer, colleague, or any other person with whom the stressed person has constant contact [42,132,133]. In this study, the Multidimensional Scale of Perceived Social Support (MSPSS) aims to measure international students' perceived social support. It was designed and developed by Zimet et al [132] based on adult samples. Several studies have used the MSPSS with the aim of measuring perceived social support across different cultures [119,132,134-136]. It is reported to be a short, clear, and accurate scale that can be used for measuring social support. The MSPSS is also relatively free of the biases of social desirability [137]. Using this scale, respondents select from the 5-point Likert-type scale choices ranging from 1=strongly disagree to 5=strongly agree. In a previous study, the factor loadings of these items were relatively high, and the measure had internal consistencies (Cronbach alphas) of .79, .81, and .82 for family, friend, and significant other support, respectively. In another study in the Malaysian context, internal consistency results were reported of .88, .64, and .87 for family support, friend support, and the availability of a special person [42,109,119].

Quality Assessment

Prior to distributing the questionnaires to the targets of the study, the researcher conducted a pilot study as recommended by scholars to reduce ambiguity, validate the instrument, and evaluate the educational intervention program before conducting the study [138,139]. For the validation of the intervention module and educational materials, the researcher constructed the basis of each statement, information, guideline, or strategy in the educational module from credible published scientific sources. A panel of experts then engaged in reviewing all sources and the newly developed educational intervention before providing it to the study sample. The experts read the references used in developing the module and educational materials and were asked to provide their evaluation and suggestions for enhancement. This was followed by resending the final module to the panel of experts for a second review. This resulted into the final version of the educational module and educational materials that will be used in this study.

After the educational module and materials were designed, a group of experts in psychiatry and education (3 experts from the psychiatric department, faculty of medicine, and 3 from the faculty of education) rated the content validity of the educational module and materials from the proposed educational intervention in terms of its accuracy, currency, and appropriateness of content using a 5-point scale: 1=extremely unsuitable to 5=extremely suitable. They will be also asked to identify areas of items that need to be improved, removed, or modified [140]; we will then pretest the educational module and materials among new international students in a private university to evaluate the reliability of the educational module and materials.

Statistical Analysis

We will use SPSS Statistics version 25.0 (IBM Corp) to analyze the data. Statistical significance will be considered as a *P* value of less than .05. Analysis of the data will take into account clustering of students within universities. The study will use statistical analyses, including descriptive statistics of the respondents' sociodemographic characteristics, chi-square test for nonparametric variables, and 2-tailed *t* test for continuous variables, to compare between the control and intervention groups on sociodemographic variables and primary and secondary outcome measures. Complete case analyses, intent-to-treat analyses, and completer status analyses will be conducted according to the initial allocation of universities to either intervention or control groups. In relation to the missing data, we will follow the guidelines for analyzing and reporting cluster RCTs with missing data established by Fiero et al [141] and Díaz et al [142].

The effectiveness of the intervention will be assessed using the generalized estimation equation (GEE). Specifically, the differences in the research hypothesis in terms of students' acculturative stress, adjustment (sociocultural and phycological), and intention to drop out will be compared at 3 points—time 1 (preintervention), time 2 (immediately postintervention), and time 3 (3-month follow-up)—between and within the intervention and the control groups adjusted for covariate variables. The GEE method was chosen because of its efficiency in appropriately modeling the structure of the correlations of the pre-post repeated measures and its low degree of reliance on the assumption of normality in the distributions of data for the variables in the analysis. Furthermore, in the context of RCT

research, multilevel models such as the GEE are the most appropriate model because they permit the estimation of treatment effects (ie, group differences) across multiple time points within a single statistical model [143].

However, there is no default option in the GEE analysis for eta squared to obtain the intervention effect size that can be expressed as a standardized effect size. Therefore, two popular measures, Cohen d and eta squared, will be used in this study. Cohen d = beta ÷ standard deviation, with beta representing the difference between two means for the two groups relative to their standard deviation obtained from the pooled variance to compute the effect size within group and between group [144-146]. Hence, d = (mean 1 – mean 2) / (the average standard deviation of the two groups). The eta squared indicates how much of the total variance is explained by the difference between the means. Therefore, we will convert the effect size d to eta squared with the equation $\eta^2=d^2/d^{2+4}$. The reported effect size d is also interpreted by Cohen [147] as adopted by many previous studies, specifically intervention as well in terms of the practical or clinical significance of the effect, 0.2 (small effect), 0.5 (moderate effect), and 0.8 (large effect), and similarly for eta squared 0.01 (small effect), 0.06 (moderate effect), and 0.14 (large effect) [146,148-151].

Results

The trial protocol of this study was approved by the Universiti Putra Malaysia Ethics Committee for Research Involving Human Subjects (reference: JKEUPM [FPSK-P104] 2017). The trial was registered at Clinical Trials Registry India [CTRI/2018/01/011223]. Approval for participation in the study was obtained from the authorities of the selected public universities. The study results will be reported at the cluster and individual levels, including information about the level of acculturative stress, adjustment, intention to drop out of the university, effectiveness of the intervention, estimated effect size and its precision, and ICCs for each primary and secondary outcome. Initial results are expected to be submitted for publication by the end of the first semester 2019/2020, and the paper will be presented at national and international conferences.

Discussion

Summary

This study investigates acculturative stress, adjustment, and intention to drop out among new international postgraduates joining Malaysian public universities. Specifically, the focus of the study is on the effectiveness of a proposed educational intervention in reducing new international postgraduates' acculturative stress in the host country of Malaysia. Due to the fact that Malaysia is becoming one of the important host countries for postgraduates in the Asian region, it is important to investigate acculturative stress and adaptation of new international postgraduates to the culture and environment. The study is expected to contribute to previous studies and existing knowledge about the challenges and barriers faced by postgraduates entering higher education in Malaysia. As an experimental study, the results will inform us of the stressors that cause acculturative stress and strategies that can be used by international postgraduates to adapt to the new environment. Another contribution of this study is the implemented intervention program that can be used as a guide for further studies among new international students. These results will provide good insight into this important research topic and be of value for international postgraduates, academics, authorities, policy makers in higher education, and researchers interested in exploring issues and challenges among postgraduates in different higher educational contexts.

Conclusions

This trial is expected to provide valuable insight into the implementation and effectiveness of educational intervention programs in reducing new international postgraduates' acculturative stress and improving their adjustment to the host culture. The aim of designing the initial cluster RCT is also to provide information regarding the feasibility of potential future full-scale trials in order to optimize the intervention and design approach. Process evaluation outcomes will provide contextual information about implementation decisions of international students, researchers, and higher education stakeholders.

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Authors' Contributions

MA, MH, HK, MS, LS, and SI have been involved in the study concept including formulating the study design and will be responsible for overseeing the work undertaken including intervention development, data collection, and analysis. HK, LS, and MA will take part in analyzing the data through statistical analyses and reporting the results. MH, MS, and SI will be involved in the intervention development and implementation. All authors have contributed to refining, drafting, and revising the current protocol in a critical way as to improve its important intellectual content and reach the final version of the protocol.

Conflicts of Interest

None declared.

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Abbreviations

AI: Acculturation Index
ASSIS: Acculturative Stress Scale for International Students
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
GEE: generalized estimation equation
ICC: intraclass correlation coefficient
ISASS: International Student Acculturative Stressor Scale
MSPSS: Multidimensional Scale of Perceived Social Support
RCT: randomized controlled trial
SCAS: Sociocultural Adaptation Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SWLS: Satisfaction with Life Scale

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Protocol

Use of Apps to Promote Childhood Vaccination: Protocol for a Systematic Review

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Abstract

Background: The decline in the uptake of routine childhood vaccinations has resulted in outbreaks of vaccine-preventable diseases. Vaccination apps can be used as a tool to promote immunization through the provision of reminders, dissemination of information, peer support, and feedback.

Objective: The aim of this review is to systematically review the evidence on the use of apps to support childhood vaccination uptake, information storage, and record sharing.

Methods: We will identify relevant papers by searching the following electronic databases: PubMed, Embase by Ovid, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and Education Resources Information Center (ERIC). We will review the reference lists of those studies that we include to identify relevant additional papers not initially identified using our search strategy. In addition to the use of electronic databases, we will search for grey literature on the topic. The search strategy will include only terms relating to or describing the intervention, which is app use. As almost all titles and abstracts are in English, 100% of these will be reviewed, but retrieval will be confined to papers written in the English language. We will record the search outcome on a specifically designed record sheet. Two reviewers will select observational and intervention studies, appraise the quality of the studies, and extract the relevant data. All studies will involve the use of apps relating to child vaccinations. The primary outcome is the uptake of vaccinations. Secondary outcomes are as follows: (1) use of app for sharing of information and providing vaccination reminders and (2) use of app for storage of vaccination information; knowledge and decision making by parents regarding vaccination (ie, risks and benefits of vaccination); costs and cost-effectiveness of vaccination apps; use of the app and measures of usability (eg, usefulness, acceptability, and experiences of different users: parents and health care professionals); use of technical standards for development of the app; and adverse events (eg, data leaks and misinformation). We will exclude studies that do not study an app. We anticipate a limited scope for meta-analysis and will provide a narrative overview of findings and tabular summaries of extracted data.

Results: This project was funded by the Sir David Cooksey Fellowship in Healthcare Translation at the University of Oxford, Oxford, United Kingdom. We will submit the full systematic review for publication in the *Journal of Medical Internet Research*.

Conclusions: This review will follow, where possible, the Cochrane Collaboration and the Centre for Review and Dissemination methodologies for conducting systematic reviews. We will report our findings based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review results will be used to inform the development of a vaccination app.

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KEYWORDS

app; smartphone technology; vaccination; vaccines; immunization; children; mobile phone

Introduction

Description of the Issue

Outbreaks of vaccine-preventable diseases, such as the measles, mumps, rubella, and diphtheria, have risen over the past decade [1-3]. While mortality rates of vaccine-preventable diseases are relatively low, certain groups, including children under 5 years of age and people with a compromised immune system, are at greater risk of severe complications [2]. The decline in the uptake of routine childhood vaccinations has been identified as a cause for outbreaks of vaccine-preventable diseases. Immunization coverage has declined for nine routine childhood vaccinations measured at different child ages in England; vaccination rates fell by 0.2%-1% in 2018-2019 compared to the previous year [4].

There are numerous interrelated reasons for the decline in childhood vaccinations, including concerns about side effects, fear of autism, objection against many injections, moral or religious grounds, costs, access, and other reasons [3]. A commonly mentioned reason is misinformation and false evidence, for example, claims by the discredited ex-physician Andrew Wakefield who linked the measles, mumps, and rubella (MMR) vaccine to autism in 1998 [5]. Religious and philosophical reasons have been used by certain groups to decline vaccination of their children [6]. Particular communities have been consistently difficult to engage, for example, male-dominated societies often resist vaccination against human papillomavirus (HPV) [7,8]. The seriousness and relative rarity of these illnesses has reduced some people's awareness of the importance of vaccination. Visiting a health clinic for vaccinations might be an inconvenience or may also be forgotten about [3], particularly as reminders to attend a clinic for vaccinations are not part of routine health care in all countries.

Description of the Intervention

There have been several initiatives to improve the uptake of childhood vaccinations in different settings [9,10]. These include a range of informational, behavioral, and environmental initiatives. Health care provider initiatives have focused on patient counseling, maximizing the opportunities of each visit, combination vaccines, and automated electronic patient record reminders. Community-based approaches to increase vaccination rates include increasing outreach and educational programs, using recall and reminder strategies, providing financial incentives, and offering vaccinations at nontraditional sites [3].

Over the past decade, public and private organizations have developed tools to improve vaccination coverage, including vaccination information websites and apps [11]. These apps help health care providers and patients to access reminders for recommended immunization schedules and related vaccine resources and websites; they also allow for changes in the schedules through app updates.

How the Intervention Might Work

Vaccination apps can be used as a tool to provide reminders, information, peer support, and feedback [12]. A cluster randomized controlled trial showed that an app used by village doctors, which included text messages to caregivers, improved full vaccination coverage in China. Village doctors using the app reported improved efficiency in managing childhood vaccinations [13]. A quasi-experimental pre-post study using an app to electronically register child births and sending text message reminders to parents about upcoming vaccinations showed improved vaccination coverage in rural hard-to-reach and urban street dweller communities in Bangladesh [14].

Why It Is Important to Do This Review

A systematic review that assessed interventions to improve immunization coverage in England concluded that current practice is insufficient [15]. Vaccination apps might be used to help improve immunization coverage but, to our knowledge, no recent systematic reviews have assessed the evidence on childhood vaccination apps. A systematic review on the design of a vaccination reminder app identified two publications on mobile apps, but the search was limited and conducted in 2015 [12]. Furthermore, this review did not assess all important quality indicators, including whether the app was secure, usable, engaging, efficacious, and cost-effective [16].

Objective

Our objective is to systematically review the evidence on childhood vaccination apps by assessing the following:

1. The uptake of vaccination.
2. Knowledge and decision making by parents: risks and benefits of vaccination.
3. Costs and cost-effectiveness.
4. Use of the app and measures of usability (eg, usefulness, acceptability, and experiences of different users: parents and health care professionals).
5. Use of technical standards for development of the app.
6. Adverse events (eg, data leaks and misinformation).

Methods

Overview

This is the protocol for a systematic review of the literature that will be reported, where possible, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P), as provided in Multimedia Appendix 1 [17]. Our review will follow, where possible, the Cochrane Collaboration [18] and the Centre for Review and Dissemination [19] methodologies for conducting systematic reviews.

Criteria for Considering Studies

Types of Studies

We will include observational studies, such as cross-sectional surveys, cohort studies, qualitative studies (eg, interview studies and focus groups), and intervention studies, such as randomized controlled trials and nonrandomized studies (eg, nonrandomized controlled trials, before-and-after studies, and interrupted-time-series studies). We will only include studies reported in English and published after 2008, when the first smartphone was launched.

Types of Participants

We will include studies involving children up to 18 years of age, the children's parents or guardians, and health care providers in any country. We will exclude studies focusing on vaccination of adults.

Types of Interventions

We will include any studies assessing apps designed to support childhood vaccination uptake, information storage, and record sharing (see Table 1). We will exclude studies that do not involve the use or study of an app for childhood vaccinations and that solely focus on other ways of delivering vaccination interventions, such as text messaging, telephone calls, or a website [20,21].

Table 1. Childhood immunization schedule: Ireland example.

Child's age	Where vaccination is given	Vaccine
Birth	Hospital or clinic	Bacille Calmette-Guerin (BCG) vaccine: a vaccine to protect against tuberculosis disease
2 months	General practitioner	6 in 1: vaccines against diphtheria, tetanus, whooping cough (ie, pertussis), polio, *Haemophilus influenzae* type b (Hib), and hepatitis B provided in one single injection
		Vaccines against pneumococcal disease, meningococcal B, and rotavirus disease
4 months	General practitioner	6 in 1: vaccines against diphtheria, tetanus, whooping cough (ie, pertussis), polio, *Haemophilus influenzae* type b (Hib), and hepatitis B provided in one single injection
		Vaccines against meningococcal B and rotavirus disease
6 months	General practitioner	6 in 1: vaccines against diphtheria, tetanus, whooping cough (ie, pertussis), polio, *Haemophilus influenzae* type b (Hib), and hepatitis B provided in one single injection
		Vaccines against pneumococcal disease and meningococcal C
12 months	General practitioner	Measles, mumps, and rubella (MMR) vaccine
		Vaccine against meningococcal B
13 months	General practitioner	Vaccines against meningococcal C, *Haemophilus influenzae* type b (Hib), and pneumococcal disease
4-5 years	General practitioner or school	4 in 1: vaccines against diphtheria, tetanus, whooping cough (ie, pertussis), and polio
		Measles, mumps, and rubella (MMR) vaccine
11-14 years	School	Tetanus and low-dose diphtheria and pertussis (Tdap) booster
		Meningococcal C booster
		Human papillomavirus (HPV) vaccine (2 doses)

Types of Comparators

We will include any type of comparator interventions.

Types of Outcome Measures

The primary outcome of this review is the uptake of vaccination. Secondary outcomes are knowledge and decision making by parents (ie, risks and benefits of vaccination); costs and cost-effectiveness; use of the app and measures of usability (eg, usefulness, acceptability, and experiences of different users: parents and health care professionals); use of technical standards for development of the app; and adverse events (eg, data leaks and misinformation).

Information Sources

Relevant articles will be identified by searching the following electronic databases: (1) PubMed, (2), Embase through Ovid, (3) Web of Science, (4) Cochrane Central Register of Controlled Trials (CENTRAL) [22], (5) ClinicalTrials.gov, and (6) Education Resources Information Center (ERIC).

Search Strategy

A draft search strategy can be found in Multimedia Appendix 1. This will be tailored to the different databases, with the assistance of a medical research librarian. No study design filter will be used, as both quantitative and qualitative studies are to be included. We will use the titles, abstracts, and keywords of a set of articles that we know meet our inclusion criteria to define a search strategy that will return all these articles without an unmanageably large number of irrelevant articles.

Data Management, Collection, and Analysis

Selection of Studies

Studies that meet the inclusion criteria will be included in the review. Two reviewers will screen titles and abstracts against the inclusion and exclusion criteria. Where duplicates or publications from the same study are identified, articles will be

screened and the more recent publication or the one with the most detail will be selected for inclusion in the review. Two reviewers will assess full texts for eligibility; any disagreement will be resolved through discussion with a third reviewer. Study selection will be demonstrated using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Data Extraction

We will pilot the data extraction form on a small number of studies to develop the final data extraction form. One reviewer will extract data from the included studies, which will be validated by a second reviewer. The data extraction form will be based on the minimum requirements as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [18]. The data extraction form will be comprised of a Microsoft Excel form and will include the following about the studies: general information (eg, title, authors, and date); characteristics (eg, study design, aim, duration, and inclusion and exclusion criteria); risk of bias, depending on study design; samples (eg, description, geographic location, and setting); interventions; outcomes, as specified above; and results (eg, outcomes and times of assessment).

Assessment of Methodological Quality and Risk of Bias

Quality assessment will be undertaken by two reviewers. Any disagreements will be resolved by consensus and by including the opinion of a third reviewer. The methods specified in the Cochrane Collaboration's tool for assessing risk of bias will be used. Three bias assessment categories will be used: low, high, and unclear risk, as specified in the Cochrane Handbook for Systematic Reviews of Interventions [18]; as specified in this handbook [18], an adapted version of these domains will also be used for nonrandomized studies. For other types of studies, we will use adapted versions of the following: Cochrane's Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool [23], the Critical Appraisal Skills Programme (CASP) tool for qualitative studies [24], and the Appraisal tool for Cross-Sectional Studies (AXIS) [25].

Assessment of Heterogeneity

We anticipate a limited scope for meta-analysis due to differences in study populations, interventions, and outcomes. If a sufficient number of studies are found, we will explore heterogeneity through consideration of the study populations, methods, and interventions by visual inspection of results. Also, in statistical terms, we will assess the chi-square test for homogeneity and the I^2 statistic. We will define statistically significant heterogeneity as $P<.10$. The I^2 will be assessed with the following levels of inconsistency: I^2 of 0%-25% represents a low level of inconsistency; I^2 of 26%-50% represents a moderate level of inconsistency; and $I^2>50\%$ represents a high level of inconsistency.

Data Synthesis

If a meta-analysis is not possible, we will provide a narrative overview of the findings and tabular summaries of extracted data. If a meta-analysis can be performed, this will allow us to estimate a summary measure of effect on relevant outcomes. For dichotomous outcomes, odds ratios will be used as the summary statistic. For continuous outcomes, mean difference will be the summary statistic. Standard pairwise meta-analysis will be conducted when more than one randomized controlled trial is identified.

Subgroup Analyses

If appropriate, we will provide a narrative overview of subgroups, including different interventions, participants, and geographic regions.

Results

This project was funded by the Sir David Cooksey Fellowship in Healthcare Translation at the University of Oxford, Oxford, United Kingdom. We will submit the full systematic review for publication in the *Journal of Medical Internet Research*.

Discussion

We will systematically review the evidence on apps to facilitate the vaccination process. Our review will follow, where possible, the Cochrane Collaboration and the Centre for Review and Dissemination methodologies for conducting systematic reviews. We will report our findings based on guidelines from the PRISMA statement. A comprehensive search of the evidence will be conducted. A potential limitation of this review is that the quality and quantity of studies using similar methods and interventions may be limited. The review results will be used to inform the development of a vaccination app.

Acknowledgments

This work was funded by the Sir David Cooksey Fellowship in Healthcare Translation at the University of Oxford, Oxford, United Kingdom.

Authors' Contributions

MM and EM conceived the study topic. EM and CdC set initial search parameters. MHVV drafted the protocol. EM, MMI, CdC, and MM revised and edited the drafted manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Reporting checklist based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines and draft searches.
[DOCX File , 21 KB - resprot_v9i2e16929_app1.docx]

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Abbreviations

AXIS: Appraisal tool for Cross-Sectional Studies
CASP: Critical Appraisal Skills Programme
CENTRAL: Cochrane Central Register of Controlled Trials
ERIC: Education Resources Information Center
HPV: human papillomavirus
JMIR: *Journal of Medical Internet Research*
MMR: measles, mumps, and rubella
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols
ROBINS-I: Risk Of Bias In Non-randomized Studies-of Interventions

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Protocol

Optimizing Low–Socioeconomic Status Pregnant Women's Dietary Intake in the Netherlands: Protocol for a Mixed Methods Study

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Abstract

Background: Although the importance of maternal nutrition is evident, adherence to dietary guidelines is limited in pregnant women, especially in those with a low socioeconomic status. Promotion of a healthy diet in midwifery practice is promising. As prenatal diet affects both maternal and child health, pregnant women are open to dietary changes during this critical transition, and midwives are their first and most important source of information. Unfortunately, nutrition communication by Dutch midwives is limited.

Objective: The objective of this study is to optimize the dietary intake of low–socioeconomic status pregnant women by contributing to the further development and adjustment of a tool or toolbox to support midwives in providing nutrition communication.

Methods: This interdisciplinary, mixed methods study includes 2 phases, in which quantitative and qualitative research are complementary. In phase 1, we will conduct a literature study and interviews to gain insight into midwives' knowledge, needs, and practice. We will obtain data on the dietary intake of low–socioeconomic status pregnant women and factors influencing this intake from another literature study, an interviewer-administered meal-based food frequency questionnaire, and qualitative interviews with pregnant women. We will identify the availability of suitable tools to improve pregnant women's dietary intake from the literature, interviews, focus groups, and expert meetings. In phase 2, we shall adapt an existing tool or develop a new tool(box), depending on the results of phase 1, and implement it in 5 midwifery practices. Ultimately, a process evaluation will provide insight into barriers and facilitating factors playing a role in the implementation of the tool(box).

Results: The main outcome of this study will be a tool(box) to optimize the dietary intake of Dutch pregnant women. We anticipate that the developed or adjusted tool(s) will be available in February 2020. After we implement the tool(s) and evaluate the implementation process, the final results should be available by February 2021.

Conclusions: This study is scientifically and socially relevant, as we will study low–socioeconomic status pregnant women's contextual dietary intake in-depth from an ecological perspective on health. The results obtained will lead to recommendations for multidisciplinary strategies to promote a healthy maternal dietary intake in low–socioeconomic status populations.

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KEYWORDS

pregnant women; midwifery; nutrition; social class; healthy diet; health promotion

Introduction

Background

The importance of maternal nutrition for optimal fetal development and lifelong population health is increasingly recognized. A healthy dietary intake during pregnancy supports the physical and mental development of the fetus and may prevent congenital malformations, premature birth, and low birth weight or small-for-gestational-age babies [1-4].

Pregnancy provides opportunities to improve dietary intake, as it is a critical transition in the life course during which women consider nutrition important [5]. Nulliparous pregnant women, in particular, show an increased interest in nutrition, although their nutrition-related information-seeking behaviors depend on the time at which they start to feel like a mother [6]. Unfortunately, pregnant women's adherence to dietary guidelines still appears to be limited [7-9], especially in low–socioeconomic status (SES) populations [10]. Low-SES pregnant women face additional barriers to healthy eating compared with higher-SES groups and experience multiple stressors that may prohibit the instigation and maintenance of a healthy dietary intake [11]. This warrants further study of contextual, behavioral, and psychosocial characteristics of low-SES pregnant women and the associations of these characteristics with dietary intake [11].

The World Health Organization (WHO) claims (pg xii) that interventions improving maternal nutritional status in low-SES populations are among the most effective and sustainable means to achieve positive impacts on health and to reduce health inequalities across generations [4]. In such interventions, diet quality in terms of adherence to dietary recommendations, including supplement use, should be considered, as well as energy balance in relation to gestational weight gain. Successful adoption of a healthy dietary intake depends not only on pregnant women's nutrition knowledge, but even more so on their ability to decide on, act toward, and sustain a healthy dietary intake given the often stressful or disempowering contexts in which they live [11]. The WHO advocates an inclusive approach to public health and nutrition, such as through support for practitioners to ensure that they understand low-SES pregnant women's circumstances without stigmatizing them when discussing diet and physical activity [4].

Midwives are an important source of nutrition-related information for most pregnant women in the Netherlands and could potentially play a significant role in improving the dietary intake of low-SES pregnant women [6,12]. Szwajcer et al showed that 80% of Dutch pregnant women were more interested in nutrition information during the first trimester than they were before [6]. Moreover, this study showed that 28% of Dutch women in the first trimester of their pregnancy considered the midwife to be an important channel for pregnancy-related information, including nutrition [6]. Dutch pregnant women considered the midwife to be a trusted source of nutrition information, valued the interactive character of consultations, and perceived the ambiance as pleasant [13]. Dutch midwives independently provide care during normal pregnancy, childbirth, and the early postpartum period. In 2016, 86.8% of pregnant women started consultations in primary prenatal care, and 30.0% of women eventually delivered their child with their primary care midwife. Referral from primary to secondary care during pregnancy or during birth took place in 35.2% and 21.5% of all cases, respectively [14].

Baron et al [12] suggested that a certain amount of proactivity from midwives in providing information may be justified, to increase awareness of beneficial health behaviors and shape positive health behaviors. Although Dutch midwives receive some training in nutrition as part of their education and appear motivated to discuss nutrition in their consultations, their actual nutrition communication appeared limited, was often general in nature, and focused primarily on risks (eg, food safety) and problems (eg, nausea) [12,13]. Midwives seemed to lack essential resources such as expertise, self-efficacy, and time [15,16]. To be more effective, midwives should be able to provide tailored nutrition communication throughout pregnancy and take into account women's family situation and culture, as well as their current dietary intake [17-19].

Tools could provide support in tailored nutrition communication. Although a variety of tools informing pregnant women about healthy nutrition are available, no evidence-based tools are being used routinely by Dutch midwives to improve pregnant women's dietary intake. This lack of tools has also been acknowledged by the Royal Dutch Organization of Midwives (*Koninkelijke Nederlandse Organisatie van Versloskundigen*; KNOV), the Dutch Association of Dietitians (*Nederlandse Vereniging van Diëtisten*; NVD), and the Netherlands Nutrition Centre (NNC), and in several scientific papers [20-22]. Tools that could be used may range from pocketbooks to educational videos and workshops [23]. Dietary assessment instruments, including digital ones, might also be helpful for increasing awareness of dietary intake, motivating people to adopt healthy eating habits, or providing support in dietary self-monitoring [24].

Therefore, we will address several omissions in current research and practice in this study. First, we aim to gain insight into the dietary intake of low-SES pregnant women in the Netherlands, including the dynamic interplay between pregnant women and their sociocultural environment. Second, we will study midwives' current practice and their capability and willingness to provide nutrition communication. Third, we will provide an overview of tools that could support midwives in optimizing pregnant women's dietary intake. Based on findings on these information gaps, we will either select and adapt or newly develop 1 or more tools fitting best with pregnant women's and midwives' needs for implementation in concurrent prenatal practice.

Objectives and Research Questions

The objective of this study is to develop a tool or toolbox for midwives to promote healthy nutrition among pregnant women, taking into account insights into factors influencing the dietary intake of Dutch low-SES pregnant women. To explore the needs of both pregnant women and midwives and to identify best practices, the main research question is 2-fold:

> *(1) What is low-SES pregnant women's contextual dietary intake?*

(2) Which tools or methods can midwives use in their daily practice to improve their nutrition communication in order to improve pregnant women's dietary intake?

In the first part of the project (2.5 years), we will answer 3 research questions and, based on the results, we will develop a tool(box):

(1) What individual (eg, food preferences, information-seeking behavior), interpersonal, and sociocultural (eg, family, social networks, social media) factors drive low-SES pregnant women's dietary intake? (RQ1)

(2) What resources do midwives need to improve their nutrition communication in order to improve pregnant women's dietary intake? (RQ2)

(3) What adequate and feasible tools to improve low-SES pregnant women's dietary intake are available or should be developed? (RQ3)

In the second part of the project (1.5 years), we will implement a newly developed or adapted tool and address a fourth research question will be addressed:

(4) What are the barriers and facilitating factors in relation to using tools or methods to assess and optimize pregnant women's contextual dietary intake in line with concurrent prenatal care by midwives? (RQ4)

Methods

Study Design

We will conduct interdisciplinary, mixed methods research to comprehensively address the research questions. We will collect data in the first part of the research (RQs 1-3) through systematic literature research, interviews with midwives and pregnant women, a diet history questionnaire, focus groups, and expert consultations. In the second part of the study, we will conduct a process evaluation of the implementation of the tool(box) throughout the Netherlands.

Stakeholder involvement is key in this study in order to develop a tool(box) that fits the needs of low-SES pregnant women and is feasible for midwives to use. Midwives, pregnant women, and relevant stakeholders identified in the process will therefore be actively engaged in the research activities. Furthermore, we will involve project partners KNOV, NVD, and NNC in all stages of the research.

Conceptual Framework

The design of this study is focused on what creates health and well-being rather than on preventing disease. This is encompassed by the concept of salutogenesis, used to explore sources of adaptability and resilience [25]. In this study, we will use 3 building blocks for salutogenic research [26]: (1) taking a holistic orientation to food (nutrition), including physical, mental, and social dimensions of health; (2) supporting a healthful life orientation; and (3) facilitating health-directed learning processes through positive interactions and experiences with food [26].

The first building block is addressed by means of a socioecological model (Figure 1) and an integral model (Figure 2). Both models provide frameworks for a holistic approach, as they help to elucidate how multiple levels of influence shape a person's dietary intake [27,28] and to unify multidisciplinary thinking, practice, and evidence gathering [29,30]. The socioecological model allows for categorization of personal, cultural, and environmental factors [31,32], whereas the integral model distinguishes between subjective and objective factors of influence on both the individual and the collective level [30].

The second building block advocates an orientation toward health rather than disease, as conceptualized by the salutogenic model of health. The core constructs of the salutogenic model are sense of coherence and general resistance resources. Sense of coherence comprises the 3 constructs comprehensibility, manageability, and meaningfulness. Comprehensibility encompasses a feeling of confidence that stimuli deriving from one's internal and external environments are structured, predictable, and explicable; manageability, that resources to meet the demands posed by these stimuli are available; and meaningfulness, that demands are challenges, worthy of investment and engagement [33].

Sense of coherence is inherently related to general resistance resources: resources within an individual or the environment that can be used to counter the stressors of everyday life [34]. From the salutogenic model perspective, it is argued that health promotion activities should focus not only on changing beliefs, knowledge, or intentions, but also on empowering people to mobilize and reflect on resources already available to them [35]. It should be noted that it is not only pregnant women who need to be empowered, but also their midwives. To enable the empowerment process, their relationship should resemble a partnership rather than a traditional hierarchical relationship [36]. In our study, we will use the salutogenic model as a guiding perspective. We will address related concepts of empowerment and reflection in research activities with professionals and pregnant women and in the development or adjustment of a tool(box).

The third and final building block describes health-directed learning processes. Swan's recommendations include engaging participants and taking into account participants' social environment or changes in their environment [26]. The best practice framework by Ng and De Colombani comprises these aspects and provides guidance on defining criteria for tools and methods to be used in midwifery practice, with regard to context, process, and outcomes [37]. The framework addresses relevance, community participation, stakeholder collaboration, ethical considerations, and replicability, as well as effectiveness, efficiency, and sustainability. The practice-based evidence available in this framework helps to build on existing tools and practices.

Figure 1. A variation of Bronfenbrenner's socioecological model adapted to include factors influencing dietary intake based on Fitzgerald and Spaccarotella and Robinson.

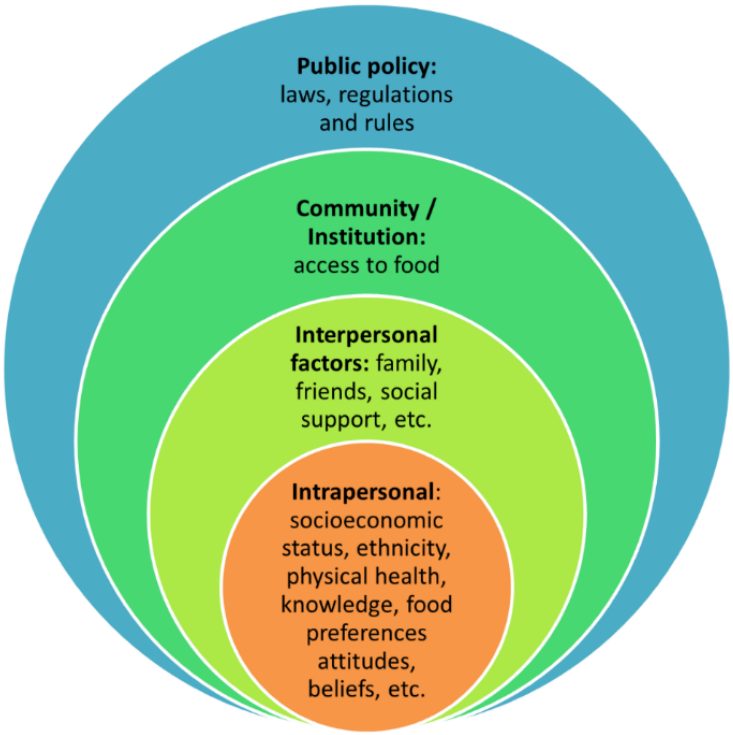
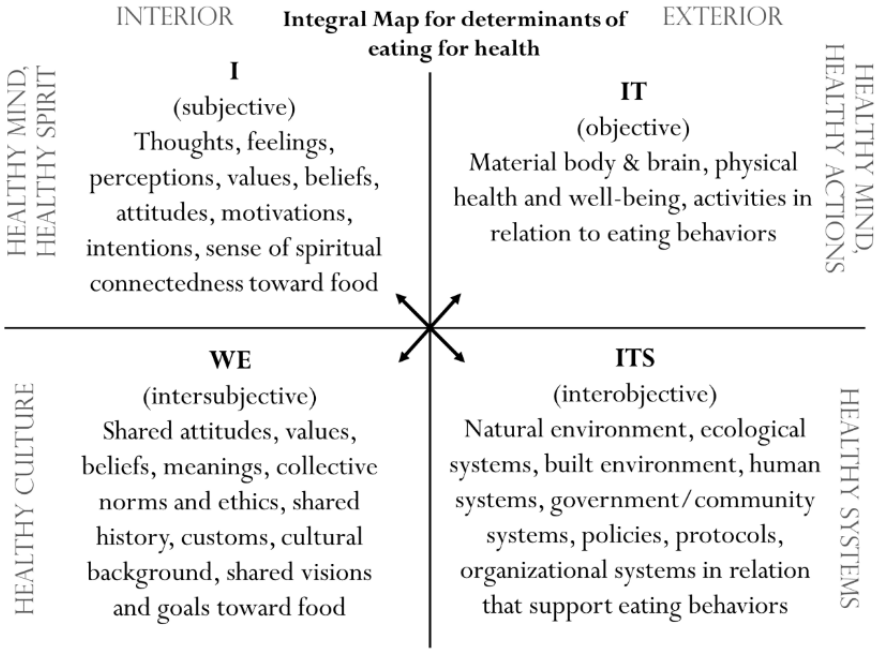


Figure 2. An integral map for integral study of healthful eating by Swan (adapted from Lundy).



Study Setting

This study includes low-SES pregnant women and midwives living and working in the Netherlands, as well as stakeholders identified in the process (eg, family members and health professionals, other than midwives). We will collect data on educational level, occupational status of both the participant and, if applicable, her partner, and individual and household income in a general questionnaire to capture the multidimensional nature of SES.

Recruitment

We will recruit midwives through a combination of convenience sampling and purposive sampling. First, we will approach midwives in the network of project partners, including a midwife, a gynecologist, and the KNOV for participation. Second, we will select midwifery practices located in disadvantaged neighborhoods (both rural and urban) based on postal code, as defined by the Dutch Healthcare Authority [38]. We will approach all midwives selected through the network or through postal code by telephone and email and invite them to participate in an interview and to recruit low-SES pregnant

women, or they may opt for just 1 of these activities. We estimate that we will need 20 midwives to reach data saturation. In case we do not reach data saturation, we will conduct more interviews.

We will recruit pregnant women (n=50) through the midwives using a purposive sampling technique. Midwives will receive oral as well as written instructions for the recruitment of pregnant women. We will use highest educational attainment as the primary indicator of SES, as education is a relatively permanent aspect of SES [39] commonly used in nutrition and health research and often included in midwives' intake questionnaires. Pregnant women will preferably be interviewed as early as possible in pregnancy, as the intervention to be developed will also have to be implemented in the first trimester. All participants taking part in interviews or focus groups should be proficient in Dutch and have a Western dietary pattern. Additionally, we will post flyers and posters in midwifery practice waiting areas to reach pregnant women directly. On these flyers, educational level is communicated positively: "Have you graduated from or are you currently following prevocational or vocational education?:

Ethics Approval and Consent to Participate

Ethics approval was given by the Social Sciences Ethics Committee of Wageningen University & Research, Wageningen, the Netherlands. The committee thereby declares that the proposal deals with ethical issues in a satisfactory way and that it complies with the Netherlands Code of Conduct for Scientific Practice. Informed consent will be obtained from each participant, after the nature and possible consequences of the study have been explained.

Data Collection

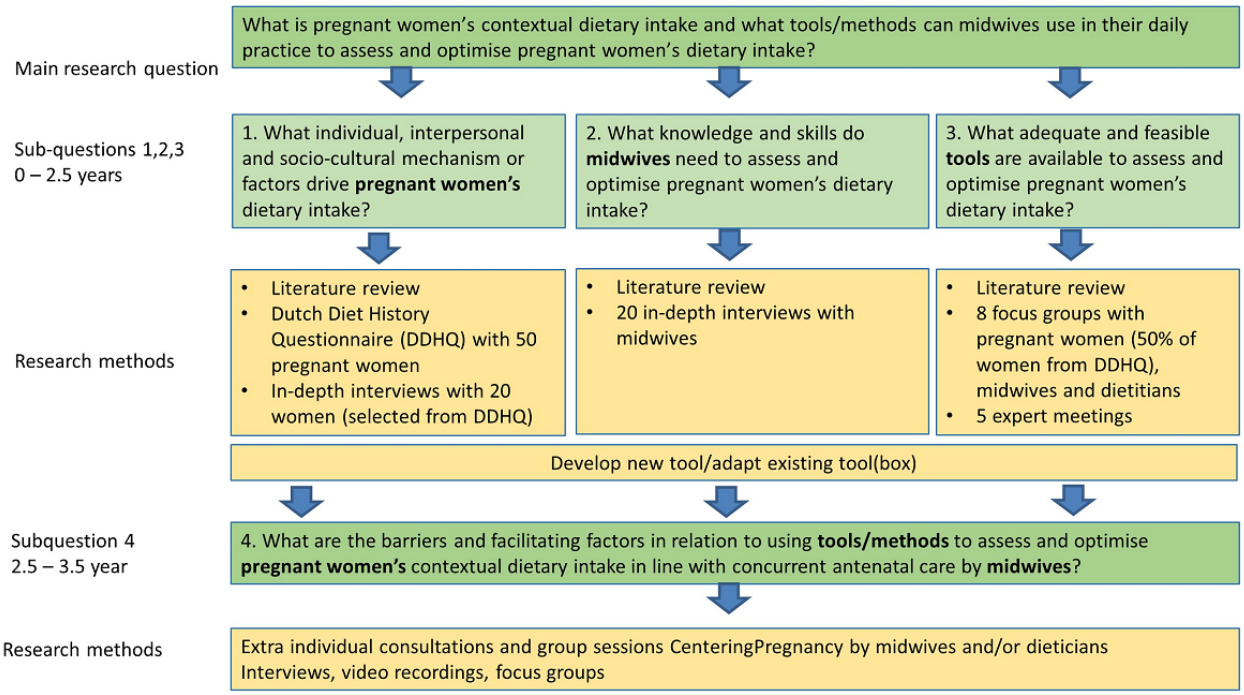
Overview

We will collect phase 1 data (RQs 1-3) through systematic literature reviews and interviews and focus groups (n=8) with both pregnant women and midwives. These data will provide insight into factors influencing the dietary intake of low-SES pregnant women (RQ 1); midwives' current practice, perception of their role, and resources needed to provide nutrition communication (RQ 2); and available tools to optimize pregnant women's dietary intake, particularly that of low-SES women (RQ 3). Phase 2 will involve implementation of a tool(box), developed or adjusted depending on the results of phase 1, together with all stakeholders, and a process evaluation (RQ 4). Table 1 summarizes the methods and tools for each research question and Figure 3 provides an overview of participant recruitment per research method.

Table 1. An overview of research questions, key outcomes, and methods.

Research question	Outcome	Method(s)
What individual, interpersonal, and sociocultural factors drive low–socioeconomic status pregnant women's dietary intake?	Usual dietary intake	Dutch Diet History Questionnaire
	Factors influencing dietary intake	Literature review, interviews with pregnant women
	Demographics, anthropometrics, health, and lifestyle factors	Questionnaire
What resources do midwives need to improve pregnant women's dietary intake?	Current nutrition communication by midwives	Interviews with midwives and pregnant women
	Resources needed by midwives to provide nutrition communication	Interviews with midwives
What adequate and feasible tools to improve low–socioeconomic status pregnant women's dietary intake are available or should be developed?	Needs and expectations with regard to tools	Interviews with midwives and pregnant women, focus groups, expert meetings
	Available tools	Literature review, interviews, expert meetings
What are the barriers and facilitating factors in using tools and methods to assess and optimize pregnant women's dietary intake in line with concurrent prenatal care by midwives?	Successes and failures in implementation: reach, dose delivered and received, fidelity, context, recruitment, and satisfaction	Pilot study, process evaluation: interviews, video recordings

Figure 3. Research questions and participant recruitment per method.



Literature Reviews

We will systematically review the literature for RQs 1 to 3, using the online databases Scopus, Web of Science, and PubMed. The aim of the first literature review is to identify factors influencing pregnant women's dietary intake. Because few articles focus on pregnant women with a low SES, this review will include articles on pregnant women in general, but will report on differences for SES groups if these are identified in the literature. We will use the second literature review to gain insight into midwives' perceptions of their role in nutrition communication and resources that they need to optimize pregnant women's dietary intake. The third and last literature review will identify existing tools and methods to provide nutrition communication to pregnant women. In all reviews, we will exclude articles from low- and middle-income countries, as the results will inform further research activities and the development of a tool(box) for the Dutch setting.

Dietary Assessment in Low–Socioeconomic Status Pregnant Women

We will conduct a comprehensive dietary assessment to gain insight into the dietary intake of low-SES pregnant women in the Netherlands. To our knowledge, dietary intake in this specific population has not been studied to date. Obtaining these data will allow us to assess the quality of Dutch low-SES pregnant women's diet and identify inadequate micronutrient intakes. We will recruit a sample of approximately 50 low-SES pregnant women, based on the research objective, feasibility, and funding [40], and based on previous studies that showed that a sample size of as few as 30 participants can provide a major increase in the width of corrected confidence intervals of associations in a mixed population [41].

To estimate overall usual dietary intake, we will use the diet history method with a reference period of 1 month. To standardize this method, we recently developed a questionnaire, the Dutch Diet History Questionnaire (DDHQ), which is meal based and includes 185 food items. The DDHQ has been developed by trained dietitians and experts in the field of dietary assessment, with a question format based on an existing, validated food frequency questionnaire (FFQ) developed previously at Wageningen University & Research. Food items and portion sizes were adjusted to the target population by analyzing dietary data collected previously among pregnant women [42] and women of reproductive age [43]. A small-scale pilot study (n=7) was conducted to test the face validity and acceptability of the DDHQ in the target group and to improve the comprehensiveness of the food list, as well as its comprehensibility and feasibility. The Dutch FFQ tool was used to generate the computer-based DDHQ [44].

The questionnaire includes an open question for each mealtime to allow for the addition of items missing from the questionnaire. It also includes an open question on supplement use, to assess brand, type, and duration of supplementation. Context is assessed using 3 predefined questions on usual location and timing of meals and social company at each mealtime.

The DDHQ will be administered by trained dietitians to enhance the feasibility of the method for the low-SES study population. Interviewer administration allows for cognitive support in estimating average intake over the reference period, portion sizes, food details, and preparation techniques. Involved dietitians will participate in regular reflection meetings to discuss coding issues, standardize procedures, and minimize interobserver bias. The interviews will last about 1.5 to 2 hours and will take place at the participant's home or at their midwife's practice location, depending on each participant's preference. All participants will receive a gift card for €25 (about US $28).

Interviews

Overview of Semistructured Interviews

We will conduct semistructured interviews to gain further insight into current eating practices of low-SES pregnant women and the need for nutrition advice as perceived by Dutch low-SES pregnant women and midwives. Topic guides will be based on the literature reviews and guided by the salutogenic model of health. We will use appreciative inquiry to create a positive and motivating conversation. Appreciative inquiry relates closely to the concept of salutogenesis and has proved to be effective in organizational life as well as in action research. It builds on participants' existing strengths and past achievements, rather than on solving a problem [25,45].

We will conduct the interviews both with midwives and with pregnant women until we reach data saturation or have included a maximum of 20 participants. We expect interview duration to be approximately 45 to 60 minutes. Interviews will take place either at the midwife's practice location or at the participant's home, according to each participant's preference. Midwives will receive a financial reward in line with standard hourly wages, and pregnant women will receive another gift card (€15; about US $17).

Interviews With Pregnant Women

We will conduct semistructured interviews with pregnant women in a subsample of participants from the DDHQ interviews. All DDHQ interview participants will be invited to participate in an in-depth interview. The interview will take place after the DDHQ interview and not necessarily in the first trimester, as women may be even more experienced or have a clearer view of their needs in retrospect.

We will use visual tools to support communication and represent the data, to summarize themes, and to visualize the data for participants [46]. Prior to the interview, participants will be asked to take a picture of something that is important to them in relation to nutrition during pregnancy. At the start of the interview, the participant will be asked to describe this picture and why it is important to her. This technique is derived from the photovoice method, a participatory action research method. The second visual tool includes picture cards. Cards will be either preprinted based on the topic guide or blank (to be filled out during the interview) and will be used to make a mind map representing factors influencing diet, mentioned throughout the interview. At the end of the interview, this completed mind map will be used for reflection and to determine the most important factors according to the participant.

Two interviewers will be present at each interview. One will primarily be conducting the interview, while the other will be observing, creating the mind map, and complementing the first interviewer by posing additional questions if needed.

Interviews With Midwives

We will conduct interviews with midwives to deepen our understanding of midwives' perceived role and the resources that they need or already use to provide nutrition communication. In addition to the salutogenic model and appreciative inquiry, we will use the 5 A's construct (or 5 A's model) in these interviews. The 5 A's—assess, advise, agree, assist, and arrange—will help to obtain insight into the extensiveness of current nutrition communication in midwifery practice, similar to Van Dillen and colleagues' method for general practitioners [47,48].

The interviews will be conducted by 2 trained researchers. One of the researchers will primarily conduct the interview, and the other will check whether all questions have been posed and pose additional questions at the end of the interview if needed. We will alternate these roles.

Focus Groups

We will organize 2 rounds of semistructured focus groups to complement the individual interviews, as group dynamics may allow for new ideas to arise. The focus groups will be activity oriented where possible, by incorporating choosing, listing, and ranking activities. Such activities can, for instance, be used to test participants' knowledge and stimulate more in-depth discussions and to make focus groups more enjoyable by doing things rather than just talking [49].

In round 1, we will conduct 2 focus groups of 4 to 12 participants for each study population (pregnant women, midwives, and dietitians) independently. In these focus groups, we will integrate data from the prior individual interviews with pregnant women and midwives and discuss the results (current practice, needs, tool suggestions, and so on) and any inconsistencies. Participants will be a combination of previous interviewees and new participants, to combine those who have already thought of the subject and those with new ideas.

After analyzing the data from the first round of focus groups, in round 2 we will organize 1 or 2 focus groups, attended by pregnant women, midwives, and dietitians combined. In this second round, we will integrate data from the previous focus groups for all participants to work toward a tool(box) together. The mixed focus groups are aimed at facilitating a cocreation process in which important stakeholders together develop the tool(box) based on the research findings.

Implementation and Process Evaluation

From the synthesis of the data obtained from the literature and from interviews and focus groups with pregnant women, midwives, dietitians, and experts in the field, we will develop a tool(box) or adjust an existing tool, or both. As the developed tool(box) will be cocreated with all stakeholders and based on the research findings, we cannot yet give an exact description of the tool(box). In addition, it is not yet clear in what setting or settings the tool will be implemented. The developed tool could become part of midwifery practices, be specifically directed at pregnant women, or be implemented by other health care professionals, or a combination thereof. Depending on the cocreation process, we will involve new stakeholders when needed to further develop and implement the tool(box). Experts will be mainly from the Netherlands, but we will also consult experts from countries with similar prenatal care systems.

We will pilot test the tool(box) in real-life practice, specifically for low-SES pregnant women. For the pilot, we will select 5 midwifery practices in different regions of the Netherlands, both

urban and rural. We expect that the process evaluation will include approximately 100 individual consultations and 20 CenteringPregnancy group meetings. CenteringPregnancy [50] brings up to 12 pregnant women together for their care and facilitates discussion and activities to address important health topics while leaving room for what is important to the group.

To provide insight into both successes and failures in the implementation of the tool(box), we will conduct a comprehensive process evaluation. In this phase, we may use multiple research methods to understand what works and why. Depending on the eventual tool or tools developed, the methods might include questionnaires, observations through video recording, in-depth interviews, and focus groups. The evaluation will cover common components of process evaluations in public health, such as the proportion of the intended target population participating (ie, reach), how often each part of the tool(box) was delivered by midwives and actually used by pregnant women (ie, dose delivered and received), and the extent to which the intervention was delivered as planned (ie, fidelity). Additionally, it will include environmental and socioenvironmental aspects that may influence implementation (ie, context) and a description of procedures used to approach and attract participants (ie, recruitment) [51]. Lastly, the compatibility of the tool(box) with midwives' and pregnant women's needs and expectations (ie, satisfaction) will show whether the involvement of stakeholders in the development of the tool(box) has paid off [52].

Data Management and Analysis

We will manage data according to Wageningen University's research data policy, based on the Netherlands Code of Conduct for Scientific Practice and the FAIR (findability, accessibility, interoperability, and reusability) principles. All participants will be assigned a unique study identifier to store data anonymously. We will use the study identifiers to link the quantitative and qualitative data of those participating in both the DDHQ and the in-depth interviews, allowing for investigation of associations between the quality of dietary intake and individual, interpersonal, and sociocultural factors.

We will audiotape the qualitative research data from the interviews and focus groups with the interviewees' permission through informed consent, transcribe the audio intelligent verbatim style, and analyze the data by means of thematic analysis [53]. The thematic framework used in the analyses allows for iterative use of both deductive and inductive approaches. Interviews will be coded independently by multiple researchers to reduce interobserver bias and thereby increase the internal validity of the method. We will use ATLAS.ti version 8 software (ATLAS.ti Scientific Software Development GmbH) for these analyses to manage data and optimize transparency.

Quantitative data derived from the DDHQ will be administered and stored in the online Dutch FFQ tool [44], then exported for analysis using SAS version 9.4 statistical software (SAS Institute Inc). Food items in the DDHQ are aggregations of food codes in the Dutch Food Composition Database [54]. Total energy and nutrient intakes will be calculated automatically in the tool by multiplying frequency of intakes by consumed amounts and nutrient composition per item using the same food composition database and standard Dutch food portion sizes. We will present all DDHQ data adjusted for energy to partially account for measurement errors.

Results

The main outcome of this study will be a tool(box) to optimize dietary intake of Dutch pregnant women. We anticipate that the developed or adjusted tool or tools will be available in February 2020. After we implement the tool(s) and evaluate the implementation process, the final results should be available by February 2021.

Discussion

Strengths and Limitations

This study relates to several concurrent health challenges and developments in the Netherlands, such as health inequalities, midwives' ambition to be strengthened in their role as public health professionals, and translating the first Dutch national dietary guidelines for pregnant women (by an ad hoc committee of the Health Council of the Netherlands) into practice.

This is, to our knowledge, the first time that the dietary intake of specifically low-SES pregnant women in the Netherlands will be studied. Gaining insight into determinants of dietary intake in pregnant women, and specifically low-SES pregnant women, will help to elucidate the factors that contribute to unhealthy habits or—from a more assets-based perspective—the factors that facilitate a healthy dietary intake. By including those pregnant women who would benefit most from nutritional education, this study will address socioeconomic inequalities in health, which are considered unfair and avoidable by, among others, the WHO and governments, in an early stage of life.

The diet history method, applied in an interview by trained dietitians, is the best method for a low-SES target group. However, it is a burdensome method and not well standardized. Therefore, we developed a meal-based questionnaire with food items covering at least 95% of the intake of women of reproductive age. As we will ask additional open questions about the intake of other foods not included in the questionnaire, we expect to cover the complete dietary intake of the women like that captured by the diet history method.

All stakeholders' perspectives need to be taken into account to generate an evidence base of what works and why in a real-life setting. The participation of multiple stakeholders (pregnant women, midwives, and other health professionals and experts) will be stimulated throughout the research, thereby generating context-sensitive and usable knowledge [55]. We will develop the tool(s) in close collaboration with pregnant women and midwives, KNOV, NVD, and NNC, taking into account their concurrent practices.

All research activities and project meetings conducted in the first phase of the research will contribute to the development of this tool(box) and its implementation and evaluation in the second phase. A limitation of this study is its inability to measure the effectiveness of the developed tool(box) within the

scope of the study. An evaluation of the effects on dietary intake, as well as maternal and child health outcomes, could be part of a follow-up study. If the adapted or newly developed tool(box) improves pregnant women's dietary intake, the impact on perinatal and postnatal outcomes may have health and social benefits, as well as economic benefits.

We will disseminate results to participants who express an interest in this, as inventoried at the end of the interviews. Project partners will be informed on progress, and results will be conveyed orally at least every 6 months by way of a group meeting or individual phone calls. All project partners have furthermore agreed to share the results of the research with their members, for example, through their websites or newsletters. To inform the scientific community, we will disseminate results in scientific journals, as well as at national and international conferences.

Anticipated Problems

The researchers involved in this study have ample experience with the successful recruitment of low-SES pregnant groups, such as the MetSLIM lifestyle intervention [56], SLIMMER diabetes prevention intervention [57], and Communities on the Move [58]. From these experiences, we have learned that considerable efforts are required to recruit low-SES groups, that too-strict inclusion and exclusion criteria hinder recruitment, and that a personal approach and trust in the recruiter are success factors. Therefore, in this study, we allow for sufficient time for recruitment activities and have budgeted for incentives. We will ask midwives to be gatekeepers in the recruitment of pregnant women, as they have strong trust relationships with their clients. A flexible recruitment protocol will be based on the needs and desires of low-SES pregnant women and their midwives, and incentives, as stated, are budgeted for.

Compared with other countries, in the Netherlands midwives play a central role in maternity care. In general, they are interested in research that will strengthen their profession. Unfortunately, they often experience a lack of time and receive numerous requests to participate in research. We have addressed this problem by holding interviews at their location, by trying to minimize midwives' time investment in recruitment, and by compensating them financially (based on regular hourly wages).

Ethical Considerations

Low-SES pregnant women may be considered a vulnerable population for several reasons. First, pregnancy is a time during which women (and their unborn babies) are physically vulnerable. Second, people with a low SES may have problems understanding information. We will instruct interviewers to ensure that participants understand information correctly if the interviewers doubt comprehension and to inform the main researcher about reconsideration of participation. Researchers involved in this project are experienced with research including low-SES groups. The research as a whole is specifically responsive to the health needs and priorities of low-SES pregnant women and ultimately aims to reduce health inequalities.

We are aware of pregnant women's dependence on midwives and shall therefore emphasize to midwives that all participants should enter the study freely. Participants will not run any physical, social, or political risk by participating in this research.

All participants will be informed about the aims of the research, duration of interviews, data preparation and anonymous data storage, the voluntary nature of participation, and their right to withdraw at any time prior to each research activity. After an opportunity to ask questions, written informed consent will be obtained from each study participant for each research activity. The term low SES, which sounds negative, will not be used in any communication with pregnant women.

Conclusion

To our knowledge, this will be the first study to address the dietary intake of low–socioeconomic status pregnant women in the Netherlands and to link dietary intake to contextual factors by using an ecological perspective on health. We hope the results obtained will inform multidisciplinary strategies to promote a healthy dietary intake in prenatal care, specifically in low–socioeconomic status populations in developed countries.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report #1 from the Edema-Steernberg Foundation.
[PDF File (Adobe PDF File), 172 KB - resprot_v9i2e14796_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report #2 from the Edema-Steernberg Foundation.

[PDF File (Adobe PDF File), 151 KB - resprot_v9i2e14796_app2.pdf]

Multimedia Appendix 3
Peer-reviewer report #3 from the Edema-Steernberg Foundation.
[PDF File (Adobe PDF File), 361 KB - resprot_v9i2e14796_app3.pdf]

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Abbreviations

DDHQ: Dutch Diet History Questionnaire
FFQ: food frequency questionnaire
KNOV: Royal Dutch Organization of Midwives
NNC: Netherlands Nutrition Centre
NVD: Dutch Association of Dietitians
SES: socioeconomic status
WHO: World Health Organization

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Protocol

Exploring Drivers of Work-Related Stress in General Practice Teams as an Example for Small and Medium-Sized Enterprises: Protocol for an Integrated Ethnographic Approach of Social Research Methods

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Abstract

Background: An increasing shortage of skilled personnel, including medical personnel, has been reported in many postindustrial economies. Persisting and growing trends in absenteeism and incapacity to work due to mental disorders are concerning and have increased political, economic, and scientific interest in better understanding and management of determinants related to the work environment and health.

Objective: This study protocol describes an integrated approach of social research methods to explore determinants of work-related stress in general practice teams as an example for micro, small, and medium-sized enterprises (SMEs).

Methods: The methods applied will allow an in-depth exploration of work practices and experiences relating to psychological well-being in general practice teams. An ethnographic approach will be used to develop an in-depth understanding of the drivers of work-related stress in general practice teams. We will combine participating observation and individual interviews with five to seven general practitioners (GPs), and five to seven focus group discussions with the nonphysician staff (3-4 participants per group) in approximately four GP group practices and one single practice in Germany. Data collection and analysis will follow a grounded theory approach.

Results: The Ethics Committee of the Medical Faculty, University Hospital of Tuebingen, Germany, has approved this study (reference number: 640/2017BO2). Recruitment has commenced with study completion anticipated in mid-2020.

Conclusions: The data from this project will be used in follow-up projects to develop and test an intervention to reduce and prevent work-related stress in GP practices and other SMEs.

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KEYWORDS

occupational health; work-related stress; small and medium-sized enterprises; general practice teams; ethnography; method triangulation; grounded theory

Introduction

Background

This study protocol describes an integrated approach of social research methods to explore work-related stress [1] in the primary care setting as an example for micro, small, and medium-sized enterprises (SMEs). We focus on general practice teams because they are particularly challenged by an increasingly complex, intense, and responsible working environment [2].

An increasing shortage of skilled medical personnel, including general practitioners (GPs) and physician's assistants, has been reported in many postindustrial economies, such as the United States [3], Canada [4], the United Kingdom [5], and Germany [6]. This development has been linked to demographic change in these societies and other macroeconomic, political, and structural processes (eg, digitalization), which results in changing and challenging working environments that affect the mental health and well-being of employers and employees in all economic branches [7]. Managing economic and human resources are integral components of organizational and institutional development. A shortage of staff, together with a persisting and growing trend in absenteeism [8] and incapacity to work, has initiated political, economic, and scientific interest in better understanding and management of work-related stressors or psychosocial risks [9,10] and resources [11,12].

A European survey with a focus on workplace risks collected responses from approximately 50,000 enterprises, including questions on psychosocial risks and their management [7]. The results show that the proportion of establishments having an action plan to prevent work-related stress ranges from 60% in the United Kingdom to 8% in the Czech Republic (Germany: 20%) [13]. Compared with larger companies, SMEs with fewer than 250 employees have tighter financial and human resources; hence, health and safety can be of low priority, particularly affecting issues concerned with mental health [14]. However, enterprises in the nonfinancial business economy (eg, manufacturing, construction) account for 99.8% (Germany: 99.5%) of all enterprises across all European Union (EU) countries, including Norway and Switzerland, and 66.3% (Germany: 62.9%) of total employment [15], emphasizing the pivotal importance of ensuring health and safety for personnel working in smaller businesses.

Primary care practices are established microenterprises that have to be maintained and developed to be economically viable. Usually organized as single or group practices with independent practice owners, these microenterprises face increasing financial competition from new emerging health business models, such as large group practices or medical care centers in which a growing number of physicians are no longer self-employed [16,17]. Similar to other SMEs [18,19], many GPs close to retirement have difficulties finding successors, which has been related to a variety of factors, including relatively little recognition for GPs compared with specialists and increasingly unmanageable workloads [20]. This can jeopardize the existence of the entire business, which is concerning because the provision of regional health care is put at risk, with the availability of primary care in rural areas particularly affected [21,22].

Theoretical and Legal Frameworks Concerning Work-Related Stress

Although the proportion of physically strenuous work has been declining in many economically developed countries, growing job insecurity accompanied by high demands on employees' flexibility and mobility have resulted in a shift from a hazardous physical environment to a more challenging and stressful psychosocial working environment [23]. Several relevant theoretical models have explained the development of work-related stress, such as the job demand-control model [24], the job demand-control-support model [25], the effort-reward-imbalance model [26], and the concept of organizational justice [27]. These models relate potentially harmful (eg, high workload and low scope of decision making) and beneficial working conditions (eg, social support and recognition, financial rewards, job security, organizational justice, or good leadership quality) to both physical and mental health (eg, cardiovascular diseases, depression) and health-related behaviors (eg, smoking and drinking) [7,9,28]. Therefore, these models play an important role in the development of concepts improving occupational health because they allow for the evaluation of measures preventing work-related stress.

From a legal perspective, the EU Agency for Safety and Health at Work provides guidelines for the improvement of working conditions implemented in European Health and Safety legislation based on Article 153 of the Lisbon Treaty [10,29]. Existing recommendations and guidelines concerning psychosocial factors in the working environment address both potentially harmful and protective dimensions [10,30-33]:

1. Work content (eg, job autonomy, completeness of tasks, variability of tasks, required qualification);
2. Work organization (eg, working time arrangements, possibility or need for communication or cooperation and delegation, working procedures, interruptions during specific tasks);
3. Social relations (eg, relationships between subordinates and leading personnel, hierarchies, leadership and managerial abilities);
4. Working environment (eg, workplace design and equipment) or working conditions (eg, noise, lighting); and
5. New forms of work (eg, increasing mobility, flexible and temporary working arrangements, telework, decreasing differentiation between work and leisure).

Work-Related Stress in Primary Care Practices

Higher levels of work-related stress have been reported in the health care setting compared with other economic sectors. Health care staff are exposed to a variety of well-established predictors of chronic stress, including high expectations in the workplace accompanied by insufficient resources (eg, time and personnel) and a lack of monetary, social, and work-related recognition [11,34]. A comparative study investigating work stress in primary care physicians across three different health care systems showed that the highest levels of physician work

stress—due to effort and lack of rewards—were reported by German GPs, followed by physicians in the United States and the United Kingdom [35]. The study also highlighted the importance of work-related rewards (salary, career opportunities, and recognition) compared with other factors promoting or preventing work-related stress. Further research from England [36] and Germany [37,38] demonstrated a relatively high prevalence of psychological distress, perceived chronic stress, and burnout among workers in general practices compared with the general population.

Recent studies investigating psychosocial risks or work-related stressors [9,10] in the primary care setting have included specifically the profession of physician's assistants. A recent systematic literature review highlighting career and job satisfaction in relation to burnout in physician's assistants summarized several work-related factors unique to the profession, including the practice setting, team dynamics, and career flexibility [39]. The authors concluded that there is a lack of high-quality studies investigating occupational well-being in health care teams. The number of studies addressing the primary care environment was relatively low (7 of 37), highlighting the lack of research in this area. However, we have identified studies from Germany that provide further evidence for the relationship between psychosocial working conditions and the well-being of physician's assistants [40-44].

Most studies to date have applied either quantitative (eg, cross-sectional research) or qualitative approaches (eg, interviews or focus group discussions). Participatory observation, an ethnographic approach, has also been applied in the health care setting to, for example, examine interprofessional communication within a clinical setting [45] or research complex interactions between doctors and nurses working in intensive care [46]. We identified very few studies in a medical setting in which ethnographic and other qualitative methods were applied in combination [46-49] to achieve a deeper understanding of aspects and circumstances related to occupational health. Furthermore, none of these were conducted in the general practice setting including both doctors and physician's assistants, although the majority of patients (>65% in Germany and >95% the Netherlands) are treated by their GP before they see a specialist [50]. Therefore, a better understanding of occupational health and safety of health care personnel outside the hospital setting is of importance to mitigate and manage health system challenges at the local level (eg, dealing with multimorbidity, chronic disease, geriatric conditions, obesity, tobacco and alcohol consumption, provision of a family health strategy and prevention programs), which are key tasks of personnel working in the primary care setting.

Aims and Research Questions

This protocol is for a study that is part of the research collaboration IMPROVE*job* funded by the German Federal Ministry of Education and Research (BMBF 01GL1751 A, B, C, and 01GL1851D) [51,52]. Researchers from four universities and six disciplines—occupational medicine, primary care, psychosomatic medicine, operations research, health promotion, and epidemiology—will collaborate within four consecutive work packages (see Multimedia Appendix 1). Within the research collaboration, we aim to develop a deeper understanding of factors related to the development and occurrence of work-related stress in primary care teams.

The focus of this protocol is related exclusively to the integrated qualitative approach that will be applied in work package 1. Modifiable, setting-specific factors considered relevant in this context are lack of leadership (eg, inexplicit description of responsibilities, poor prioritization), inefficient work processes (eg, long waiting times for patients, high frequency of interruptions), lack of communication (eg, within the practice team or with patients), insufficient implementation of occupational health and safety measures, and lack of occupational health promotion. The following questions will guide the analysis:

1. How is work organized within GP practice teams?
2. Which work-related resources and stressors are specific to the primary care setting?

Within the research collaboration IMPROVE*job*, the findings will inform the development of a participatory intervention for the prevention of work-related stress within primary care teams (work package 2). Applying a cluster randomized controlled trial, the effect of the intervention will be assessed (work package 3) measuring the primary outcome "job satisfaction" and several secondary outcomes before and after the implementation of the intervention comparing possible changes between the intervention and the control group [53]. Finally, options for the transfer of the results into other medical practices and SMEs of other economic branches will be evaluated (work package 4).

Methods

Qualitative Methods

For the last three decades, qualitative methods have become an integral part of health-related and health services research. They provide tools for a comprehensive understanding of complex environmental, social, and cultural relationships within a particular setting. Ethnographic research design has been established in other disciplines but has yet found little application in research related to occupational health and safety. The study design conforms to the consolidated criteria for reporting qualitative research (COREQ) [54].

Study Design: Ethnography and Grounded Theory

An ethnographic technique will be used, including participatory observation accompanied by interviews with the practice owners and focus group discussions with the physician's assistants. Observation will be guided by a theoretical framework developed through a transdisciplinary process [55,56] by the IMPROVE*job*-Consortium based on occupational health and safety guidelines [10,30-33], while also considering life course-specific aspects relevant in the working environment (eg, professional training, pregnancy, dealing with illness and/or care, retirement). We will accompany different GP practice teams over a sustained period. This will allow the mapping of everyday work practices in relation to stressors [9,10] and resources [11,12] as they occur. Based on the observations, we will be able to capture aspects which the participants themselves

are either not aware of or are unlikely to disclose in an interview situation, such as different forms of verbal and nonverbal communication (eg, gestures or impromptu responses to routine or nonroutine situations), as well as the dependency between work processes and work environment.

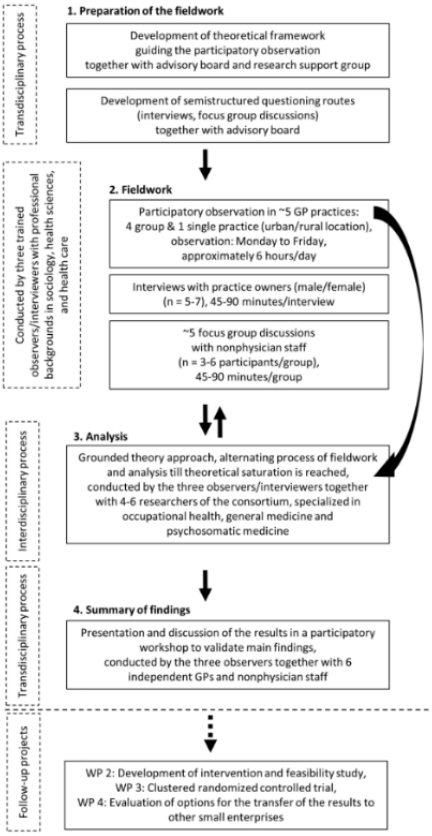
To further enrich the observational data, we will conduct a variety of interviews with the practice teams. Because we will experience teamwork and collaboration between the entire practice staff through observation, we decided to discuss additionally occurring aspects and themes separately with doctors and physician's assistants acknowledging their different roles. This will create an atmosphere as unaffected as possible by structures of hierarchy and dependency. These qualitative interviews will be performed either as single interviews used mainly to collect the practice owners' individual stories about everyday working life [57], or as focus group discussions [58] to capture the physician's assistants perspective on how work is organized within the team and which work-related stressors [9,10] and resources [11,12] affect their daily routines [58].

The analysis of all data will follow a grounded theory approach, which is suitable for less-studied and complex research questions comprising the construction, modification, and evaluation of knowledge created through the reciprocal relationship between researchers and participants [59]. Grounded theory provides a systematic method to address initially unstructured data from different collection methods. Data collection and analysis are carried out alternatingly, allowing for the continuous development of emerging codes and themes until no new conceptual insights occur, and theoretical saturation is reached [59,60]. We will apply a triangulation of methods [60] (observation, individual interviews, and focus group discussions) to compare different perspectives (researcher, GPs, and physician's assistants). Using these methods in combination, we expect to uncover different and potentially hidden work practices and interactions within the observed practice teams to understand, conceptualize, and evaluate how these relate to work-related resources and stressors relevant to the primary care setting.

Participatory Approach: Advisory Board and Research Support Group

To further ensure scientific rigor, an advisory board will offer guidance and support throughout the study. Members with a scientific and/or professional background in occupational health and safety, work design, or occupational health promotion, as well as scientists from two institutes of general medicine, will provide primarily theoretical and methodological expertise. The research support group, including GP practice staff (doctors and physician's assistants), will provide advice on the practicalities of applying the ethnographic approach in the general practice setting; furthermore, they will take part in the validation of the emerging codes and themes throughout the analysis to improve the rigor and reliability of the results providing communicative validation [60]. A summary of the methods is displayed in Figure 1.

Figure 1. Flowchart of the methods that will be applied in work package 1.



Setting and Inclusion Criteria

To capture a variety of primary care settings, we plan to recruit approximately five practices (expected number of practices until theoretical saturation is reached): one single and four group practices in three urban and two rather rural areas, managed by male and/or female practice owners (purposive sampling). Prior research has shown that workload, income, and practice patterns differ frequently to the disadvantage of primary care physicians managing single practices [37] in rural areas [61,62]. Moreover, there is evidence that leadership styles can differ between men and women [63]. Leadership styles have also been related to job satisfaction; for example, transformational leadership has been shown to impact positively on workplace empowerment in the hospital setting, which increased the job satisfaction of nurses and promoted better safety outcomes for both staff and patients [64]. Furthermore, some national [65] and international [66,67] research has shown differences in job satisfaction between male and female GPs, with women being generally more satisfied at work [68]. However, for the perception of chronic stress and burnout, younger, female GPs working part-time have been reported to be more affected than their male colleagues [37,38].

Recruitment

Access to GP practices is planned through selective sampling via the network of GPs of the Institute for General Medicine, University Hospital Essen (IFAM, Germany). This network is representative of the primary care setting in Germany [69]. All participating practices in this network are located in urban and rural areas of North-Rhine-Westphalia (largest cities: Cologne, Duesseldorf, Dortmund, Essen), one of the most densely populated districts in Germany (population in 2017: 524 per square kilometer) [70]. Suitable GP practices will be invited via post and contacted by telephone if they agree to participate. During the phone call, practice owners will receive detailed information on the study and a schedule for the participatory observation (one working week: Monday to Friday), and the times for the interviews with the practice owners and the focus group discussions will be decided.

Preparation of the Field Work

In preparation for the fieldwork, all observers and interviewers will participate in a two-day methods course, which will include theoretical background on grounded theory and practical exercises concerning fieldwork and analysis. Each of the three female observers (with professional backgrounds in sociology, health sciences, and health care) will conduct a two-day trial observation in different GP practices to gain first impressions of the setting, its facilities, and organizational structures. The researchers will also have the opportunity to explore their role in the field and develop a feeling for suitable points of observation where they will attract as little attention as possible.

Data Collection and Sample Size

Data collection will take place in approximately five GP practices until theoretical saturation is achieved [71].

Participatory Observation

To allowing for comprehensive coverage during opening hours over the course of a workweek (Monday to Friday), each practice will be visited daily and in turn by two observers. According to previous studies [45,72], the observation time per person will be 2 to 4 hours to ensure the quality of the fieldwork. In agreement with the practice owners and the patients involved, the observers will attend as many situations and procedures as possible in areas such as reception, the waiting area, the kitchen, and in functional rooms (eg, laboratory, consultation room). Although the researchers will be in continuous contact with practice staff and patients, their aim is not to intervene actively in acute or sensitive events to avoid the disruption of procedures. If possible and appropriate, field notes will be taken, including the documentation of spontaneously occurring conversations with practice staff.

Interviews and Focus Group Discussions

All interviews and focus group discussions will follow up aspects that occurred over the course of the observations and will elaborate on particular situations, experiences, attitudes, and ambiguities. For both the interviews and discussions, we developed a semistructured questioning route including an introduction (short thematic intro, information on recording and data protection) and questions related to work content, work organization, social and working environment, as well as new forms of work [10,30-33]. Using a semistructured topic guide will provide the appropriate flexibility to guide the course of the interview. The researchers can clarify questions or can adapt the focus of the interview to further explore topics and phenomena that reoccur in different general practices. Depending on the availability of the practice staff, all individual interviews with the practice owners (approximately 5-7) and discussions (approximately 5, with 3-6 participants per discussion) are planned to last between 45 and 90 minutes. In agreement with the participants, all interviews and discussions will take place in the GP practices and will be digitally recorded, ensuring accuracy and completeness.

Data Management and Analysis

Observation protocols, complemented by material including spontaneous informal discussions with primary care staff and field notes, will be written by the participating researchers during or immediately following the fieldwork [73]. The transcription of the interviews and focus group discussions will be carried out by a professional company according to a simplified system whereby transcription is word-for-word, but not phonetic [74]. Quality checks, depersonalization, and pseudonymization of all data sources will be done by the team conducting the fieldwork. To facilitate the linkage and classification of all data sources, the software MAXQDA 2018 [75] will be used to organize the observational protocols, interviews, focus group transcripts, and emerging memos.

Data analysis will apply a grounded theory approach including open, axial, and selective coding as well as constant comparison of all material to develop codes, work out the relationships between the codes, and establish a narrative around selected core themes [76]. The analysis will be conducted by the

investigators carrying out the fieldwork supported by an interdisciplinary team of researchers from the IMPROVE*job* collaboration with expertise in general, psychosomatic, and occupational medicine.

Ethical Considerations

Individual declarations of informed written consent will need to be signed by all participating practice staff; each team member will have the opportunity to ask questions and revoke their participation at any time over the course of the study. Data management and storage will be subject to the EU General Data Protection Regulation. The data will be available only to persons involved in this research. Ethical approval for this study was obtained from the Ethics Committee of the Medical Faculty, University Hospital of Tuebingen, Germany (reference number: 640/2017BO2). This study complies with the Declaration of Helsinki, World Medical Association (1964), last revised October 2013 [77].

During fieldwork, all patients and other visitors will be informed about our study at the patient registration desk of the respective practice where a sign will refer to our study and the observing researchers. As working procedures involving patients are of interest only in terms of how work is organized and communicated within the GP team (eg, doctor-patient relationship), patients will be asked by the GP or physician's assistant whether they agree to the observers being present in the treatment areas, and the observers will sign a declaration of confidentiality. However, we will neither collect nor analyze any patient-related information because this study focuses exclusively on the collaboration within the practice teams. All data sources will undergo the process of pseudonymization.

Results

Recruitment has commenced, and study completion is anticipated in mid-2020. On behalf of the IMPROVE*job*-Consortium, the findings of this qualitative study (work package 1) will be disseminated via peer-reviewed publications, conferences, and workshops. The results will inform subsequent subprojects (work package 2-4) of the IMPROVE*job*-project, including the development and evaluation of a participatory intervention for the prevention of work-related stress within primary care teams as an example for other SMEs.

Discussion

Principal Findings

This study protocol describes an integrated qualitative approach of social research methods to explore drivers of work-related stress in the primary care setting as an example for SMEs, including microenterprises. Criteria to ensure quality have been established, including persistent observation, member checks, and triangulation [60,78,79]. The triangulation of methods applied in this study will allow an in-depth exploration of work practices and experiences in relation to psychological well-being from different perspectives over a sustained period across a variety of GP practice teams, providing particular insight into values and ideas that are inherently difficult to capture (eg, team spirit, attitudes concerning patient care, workplace atmosphere). This is relevant because there is little research to date that applies a comprehensive approach to the study of work-related stress in SMEs such as GP practices. Reducing and preventing work-related stress is an important dimension in protecting the health and safety of employees as well as reducing illness-related costs.

Benefits of Transdisciplinary Research

The combination of scientific and practical expertise is a central prerequisite for transdisciplinary cooperation [55,56]. Transdisciplinary research networks thrive when an interdisciplinary academic and a practical consensus results in the integration of research ideas and results throughout the entire research process so that jointly developed knowledge and products can be shared with and used by the target audience. It is expected that the entire IMPROVE*job*-project will have a positive effect on the prevention of work-related stress in not only the primary care setting. Other SMEs might benefit from the results learned from the experiences in the GP practices, which may eventually contribute to the promotion of psychosocial aspects of work-related health in other smaller businesses.

Limitations

From a practical and operational point of view, the recruitment of GPs for research has been shown to be challenging. This has been related to a variety of factors, including the high workload of GPs, skepticism in the applicability of the results, the feeling of being monitored and judged [80], and the sensitivity of the working environment regarding patient confidentiality and data security [81]. Furthermore, the ethnographic approach is prone to disrupting the usual working environment; researchers engage in participatory observation over a sustained period of time [82], which may cause an additional and unusual form of stress. Conducting this study within the collaborative research network, IMPROVE*job* will provide resources to mitigate or overcome some of the challenges described. Over the course of the entire IMPROVE*job*-project, the interdisciplinary research group will work closely together with the study's target group of GP practice teams. For this subproject, the practitioners of the research support group will provide practical insight into the primary care setting, which will support the researchers with the familiarization of the setting, the recruitment of participating practices, as well as the organization and execution of the ethnographic fieldwork. The researchers will be invited into different GP practices and accompany the team for a week; therefore, we expect all participants (researchers, GPs, and physician's assistants) to become familiar with this research approach so, ideally, it will cause as little disruption as possible.

Conclusion

It is expected that the entire IMPROVE*job*-project will have a positive effect on the prevention of work-related stress inside and outside the primary care setting. Other SMEs might benefit from the results learned from the experiences in the GP practices, which may eventually contribute to the promotion of psychosocial aspects of occupational health in other small businesses.

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Authors' Contributions

MR and CP developed the detailed qualitative research protocol. ER, ET, and SE contributed to the subsequent refinement of the analysis plan. MR, ER, SE, and ET were involved in obtaining approval from the Ethics Committee of the Medical Faculty, University Hospital of Tuebingen. ER is the primary investigator and drafted this study protocol with contributions from SE. All authors provided critical feedback on the manuscript and read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Evidence based for teams: aims of the transdisciplinary research consortium IMPROVEjob.
[PDF File (Adobe PDF File), 194 KB - resprot_v9i2e15809_app1.pdf]

Multimedia Appendix 2
Current and former members of the IMPROVEjob-Consortium.
[PDF File (Adobe PDF File), 85 KB - resprot_v9i2e15809_app2.pdf]

Multimedia Appendix 3
Review and proof ethics-English.
[PDF File (Adobe PDF File), 298 KB - resprot_v9i2e15809_app3.pdf]

Multimedia Appendix 4
Review and proof ethics-German.
[PDF File (Adobe PDF File), 607 KB - resprot_v9i2e15809_app4.pdf]

Multimedia Appendix 5
Review and proof of major funding - English.
[PDF File (Adobe PDF File), 294 KB - resprot_v9i2e15809_app5.pdf]

Multimedia Appendix 6
Original peer review from the Federal Ministry of Education and Research - German.
[PDF File (Adobe PDF File), 184 KB - resprot_v9i2e15809_app6.pdf]

Multimedia Appendix 7
Original peer review from the Federal Ministry of Education and Research - English.
[PDF File (Adobe PDF File), 150 KB - resprot_v9i2e15809_app7.pdf]

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Abbreviations

EU: European Union
GP: general practitioner
IFAM: Insitut für Allgemeinmedizin, Universitätsklinikum Essen (Institute for General Medicine, University Hospital Essen)
SME: small and medium-sized enterprise

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Protocol

Web-Supported Social Network Testing for HIV Among Men Who Have Sex With Men With a Migration Background: Protocol for a Mixed Methods Pilot Study

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Abstract

Background: Of newly diagnosed HIV positive men who have sex with men (MSM) in the Netherlands, 29% have a non-Western migration background (MSM-NW). Among MSM-NW, HIV positivity rates are high (0.8%-2.0%), as is the proportion of late stage infections (39%). Factors such as HIV and sexual orientation–related stigma may form barriers for timely testing. Innovative approaches for HIV testing are needed to better reach MSM-NW. Social network testing (SNT) for HIV is an evidence-supported approach where peer recruiters identify persons (network associates) who could benefit from testing in their social or sexual networks. Web-supported SNT might be particularly promising for reaching people who may not be reached by regular care.

Objective: The purpose of this paper is to describe the design of our pilot PREVENT (Peer-Empowered Voluntary Extended Network Testing). In this pilot, we will explore whether SNT using HIV self-tests is feasible and acceptable among MSM-NW in the Netherlands and whether it reaches those who were never or not recently tested for HIV (>1 year ago).

Methods: The project aims to include 50 to 60 MSM and MSM-NW peers who will distribute 4 to 5 oral HIV self-tests each aiming to reach 200 network associates (NAs). Enrollment of peers includes 4 steps: (1) fostering interest in becoming a peer by health care professionals at sexual health clinics, HIV treatment clinics, and community settings; (2) sending peer contact information to the peer coordinator; (3) registering peers and giving program instructions by the peer coordinator and referring to the Web-based training at time2test; and (4) receiving precoded HIV self-tests for distribution in the peers' networks. NAs who receive the self-test will log in with their test package code in the time2test application for step-by-step test instructions. After testing is complete, NAs receive tailored follow-up information depending on their test result.

Results: Between January and May 2019, 10 STI clinics and 7 HIV treatment clinics started recruiting peers. Results of the PREVENT pilot are expected in December 2020.

Conclusions: This is the first Web-supported peer-driven SNT pilot using HIV self-tests in the Netherlands and one of the first in Europe. Implementation is considered successful if it reaches MSM-NW who were never or not recently tested for HIV. Additionally, it may encourage conversations within the networks about risk behavior and barriers to HIV testing, potentially contributing to the Joint United Nations Programme on HIV/AIDS goal of zero HIV infections.

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KEYWORDS

HIV; social network testing (SNT); men who have sex with men (MSM); community-based testing; HIV self-testing

Introduction

People who are unaware of their HIV infection are more likely to be a source of HIV infection for others and are unable to benefit from (early) treatment [1,2]. Of HIV prevention interventions evaluated to date, increased HIV testing combined with early treatment resulting in viral suppression has been shown to have the most substantial effect on HIV transmission at population level [3]. In the Netherlands, men who have sex with men (MSM) account for the majority (68%) of new HIV infections. Of those, 29% have a non-Western migration background (MSM-NW). Among MSM-NW, HIV positivity rates are fairly high (0.8-2.0%) [4] with a high proportion (39%) of late stage infections (CD4 <350 cells/mm^3) [4-6]. High proportions of late stage infections may indicate that MSM-NW are not well reached by regular, provider-based test facilities. Innovative testing approaches not dependent on patient- or provider-initiated testing are needed to reach MSM-NW for HIV testing.

Peer-driven HIV testing in social networks is an evidence-supported approach to improve HIV testing rates in difficult-to-reach populations [7-9]. These social network testing (SNT) approaches can reach hidden individuals at high risk for HIV infection and those who are unaware of their HIV status, as shown in various studies mostly in the United States [10-14]. SNT is based on the concept that individuals with similar characteristics (sociocultural and behavioral) are linked together to form social networks with similar sexual (risk) behavior [9,15]. Persons within a network may encounter similar sexual situations or may influence each other's behavior. Some studies even showed that network-level variables were stronger predictors of risk behavior outcomes than individual-level variables [16]. Among networks in which HIV prevalence and sexual risk behavior are high, this interconnectedness between people can be used to roll out an intervention aimed at increasing testing uptake and locating people with undiagnosed HIV infection. When SNT is combined with HIV self-tests, this might overcome barriers to provider-based testing, such as fear of being seen at a clinic by people they know or reluctance to disclose their sexual identity to a health care professional [17-19]. Although several SNT studies for HIV testing in MSM networks have been published, it has not been attempted to great extent in combination with HIV self-tests and Web-based support. The HIV self-test with Web-based support enables the network associate (NA) to test anonymously in their home environment or another safe place, using step-by-step instructions, videos, and information tailored to their test result.

The main goal of our pilot, PREVENT (Peer-Empowered Voluntary Extended Network Testing), is to investigate whether SNT [8,10,20] is feasible and acceptable in MSM-NW networks in the Netherlands. The major target group is MSM with a non-Western migration background (eg, Central and Eastern Europe, Africa, Central and South America, and Asia). Transgender people are also invited to participate as they often encounter similar barriers to testing. Transgender female sex workers are at especially high risk for HIV infection and often exposed to physical and sexual violence [21,22].

PREVENT will focus specifically on the feasibility and acceptability of SNT using HIV self-tests. If we can recruit and support high-risk peers—HIV-positive or HIV-negative—to distribute self-tests among their social contacts, we can decrease rates of people never being tested, detect undiagnosed HIV infections earlier, and learn how SNT can be improved. Furthermore, the self-test could act as an object connecting people and improve conversations and openness about HIV.

PREVENT was developed as a blended intervention, combining face-to-face and Web-based strategies. It will include learning strategies for recruitment of instructing and motivating peers and NAs for SNT with HIV self-tests. Using a Web-based application for instructions and support for both peers and NAs has several advantages for SNT among MSM. Internet use is high for meeting sex partners or seeking health information [23], and the internet is available 24/7, allows anonymous participation, and enables the provision of tailored information and linkage with other Web-based sexually transmitted infection (STI) testing services.

This pilot intends to explore and understand HIV testing through social networks of MSM and MSM-NW with the primary aim being to study feasibility and acceptability of SNT using HIV self-tests. Secondary aims are to assess the effectiveness of SNT regarding diagnosing HIV and explore the effect of SNT on openness toward HIV and HIV testing.

Methods

Recruitment of Peers

MSM and MSM-NW will be recruited for the PREVENT pilot at 10 STI clinics and 7 HIV treatment clinics throughout the country. In the Netherlands, 24 STI clinics, mostly within public health services, provide free-of-charge STI/HIV testing and care for high-risk groups; 30% of all consultations are among MSM, with 45,553 consultations in 2017 [4]. In 2017 at these clinics, HIV positivity rates among Western MSM were 0.5% and 1.2% for non-Western MSM, with the highest percentages for MSM originating from Latin America (2.0%) and Eastern Europe (1.8%). Among transgender people, HIV positivity was 1.4% [4]. People newly diagnosed with HIV are referred to one of the 26 HIV treatment centers [6]. Additionally, recruitment

of peers will take place at community settings for lesbian, gay, bisexual, transgender, and intersex (LGBTI) persons, where HIV testing, hepatitis B vaccinations, and pre-exposure prophylaxis (PrEP) information are being offered by health care professionals or trained volunteers.

Recruitment of peers is accomplished in a stepwise process. MSM and MSM-NW who visit any of the recruitment sites are informed about the project and receive an information flyer. Inclusion criteria for peers include being aged 18 years or older, having a social network that includes MSM-NW, and being willing to distribute HIV self-tests to their NAs. A social network includes personal connections such as friends, acquaintances, (ex-)partners, sexual contacts, colleagues, etc. The size of a persons' network is not an inclusion criterion. Non-Western is defined as first or second generation Caribbean, African, Eastern/Central European, Asian, or Central/Latin American. MSM from Western Europe who have a network of MSM-NW can also participate as peers, as can transgender individuals.

Persons who are interested in participating are asked to provide an email address or telephone number to the health professional, who then sends the contact details to the peer coordinator. Potential peers who received the information flyer can also register themselves via the project website [24]. Subsequently, peers are contacted by the peer coordinator who provides them with project information and registers them in the Web-based time2test application. The application sends a website link for creating a peer account. After completing the informed consent and baseline questionnaire on their account page, peers follow a short training (e-learning tool of 20 minutes) to prepare them for SNT testing. After completion of the e-learning tool, participants indicate they will sign up to the program by clicking on a button "I sign up as a peer" or they click on "I changed my mind and do not sign up as a peer." If they sign up, they will receive a message telling them they will be contacted by the peer coordinator and will receive 5 precoded HIV self-tests by mail or at a nearby location (eg, closest STI clinic) for distribution in their social network.

Ethics and Consent

The study was presented to the medical ethics committee of the Amsterdam University Medical Center (multicenter study reference number NL61922.018.17). The committee concluded that ethical approval was not needed as the Dutch Medical Research Involving Human Subjects Act does not apply for this study. The trial was registered with the Netherlands Trial Registry [NL7424]. All participants in PREVENT provide online informed consent.

Sample Size

The primary objective of PREVENT is to assess the feasibility and acceptability of SNT among MSM-NW, and therefore a formal power analysis is not appropriate. However, we aim to enroll 200 NAs during a period of 12 to 18 months. To achieve this target, an estimated 50 to 60 peers who will distribute 4 to 5 test packages each should be recruited when they attend any of the participating sites. With these numbers, the pilot is expected to have 80% statistical power to observe differences of 15% in study outcomes (cross-sectional analyses) between subgroups, such as younger versus older age groups or by migration background and location of recruitment.

Development of the E-Learning Tool for Peers

The e-learning tool is part of the time2test website that was developed for the PREVENT pilot. Findings of a qualitative prestudy among MSM-NW were used for website content and to design the e-learning tool [19]. This qualitative study, in which 13 MSM of various migration backgrounds recruited from STI clinics were interviewed, was based on the capability, opportunity, motivation, and behavior (COM-B) model and was focused on barriers and facilitators of SNT for HIV [25,26]. It included network characteristics (ie, who could benefit from SNT), peer skills to apply SNT successfully, assessments of sexual risks, abilities to motivate NAs to test, cultural or social aspects, and practical requirements for implementation. MSM-NW who were interviewed thought that SNT with HIV self-test was feasible and needed. They also indicated a need for support of peers in case of emotional reactions or a positive HIV diagnosis among their NAs. Openness and trust were considered important elements for successful implementation of SNT [19].

From the prestudy, learning objectives and delivery strategy were determined by the research team of PREVENT. Examples of learning objectives: peer can explain HIV transmission routes, peer can explain how the OraQuick HIV self-test (OraSure Technology, Inc) works, peer is motivated to prioritize friends within his inner circle of trust (eg, those never tested for HIV, having a migration background, and/or at sexual risk), peer is able to start a conversation about HIV testing. The learning objectives were translated into applications: the 6 steps of the e-learning tool in which they receive information and instruction videos on how to recruit NAs and motivate them to test. As there is no one-size-fits-all approach, example instruction videos were used. The prestudy showed that almost all men had an idea of how they would approach their contacts [19]. Peers are free (and probably know best how) to tailor their approach to suit their NAs.

Content of the E-Learning Tool for Peers

In step 1, peers watch an animated video about HIV and how it is transmitted; in step 2, the use of the OraQuick HIV self-test is demonstrated (Figure 1). In step 3, the different test results of the oral HIV self-test are explained and illustrated by images of HIV positive, HIV negative, and failed test results. In step 4, peers watch a video in which two friends discuss how they selected their NAs for self-testing (Figure 2). It is explained that NAs are preferably unaware of their HIV status or not recently tested (>1 year ago). The video in step 5 discusses how they can start the conversation about HIV self-testing (Figure 3).

Figure 1. Screenshots of the time2test website showing animations on HIV (step 1 of e-tool, including an English voice over) and the oral HIV self-test (step 2).

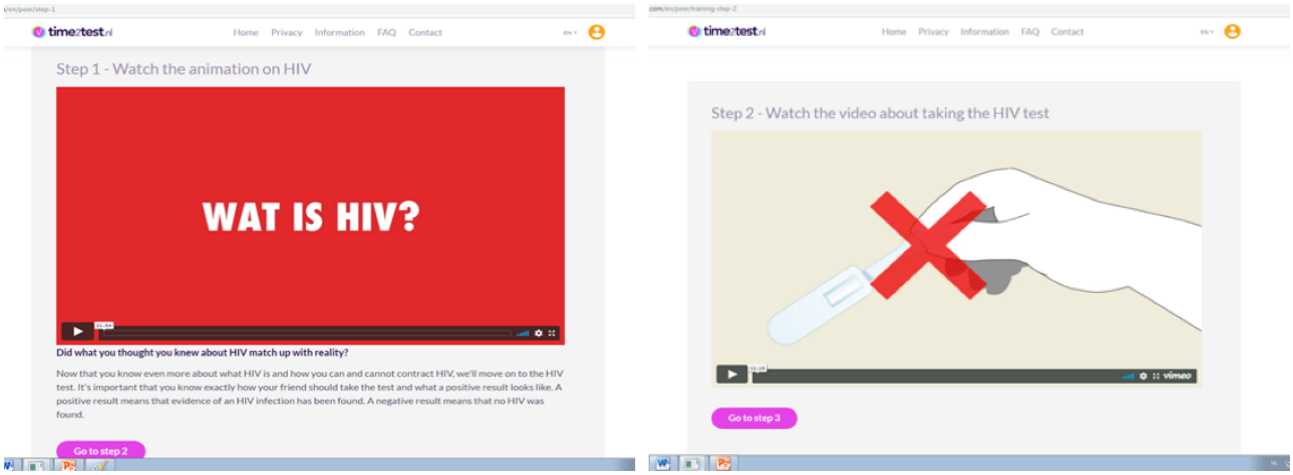


Figure 2. Screenshots of the time2test website showing the different test results (left) and a video explaining who to approach for testing (right).

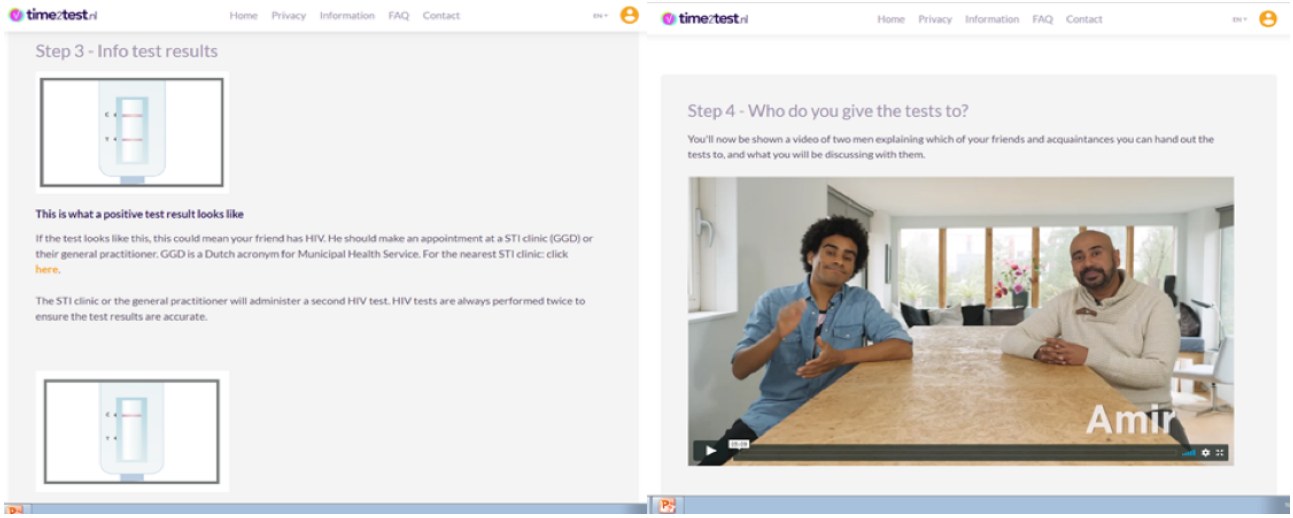
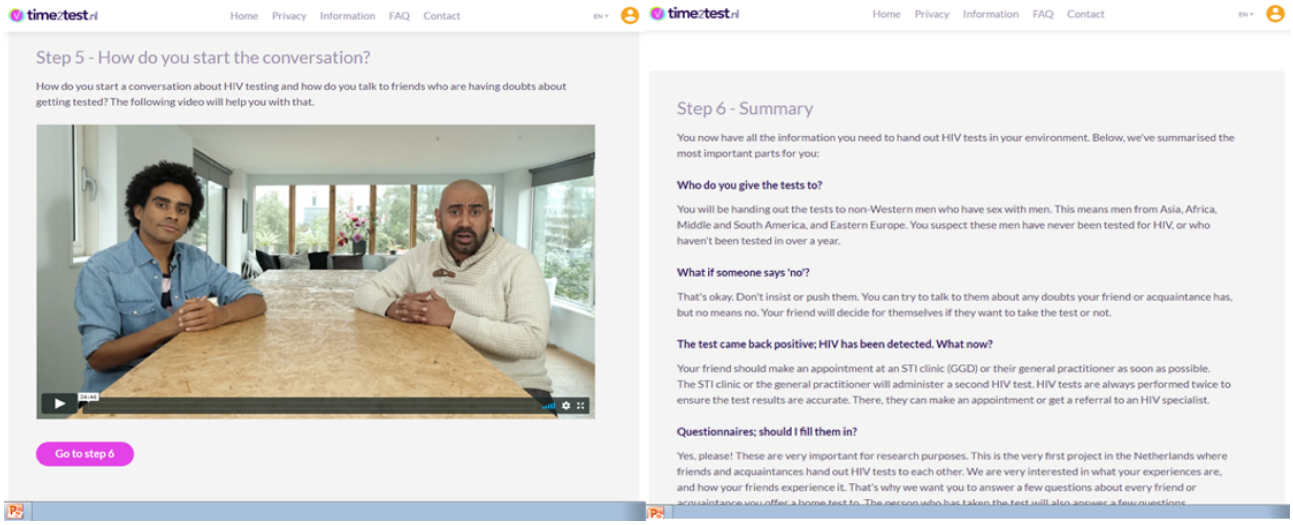


Figure 3. Screenshots of the time2test website showing a video on how to start a conversation about HIV self-testing (left) and a summary of information for peers (right).



At the end of the e-learning tool, the peer has learned the following:

- Explain what HIV is and how it is transmitted
- Select NAs (friends, acquaintances, sex contacts, etc) for HIV self-testing
- Motivate NAs to test with an HIV self-test

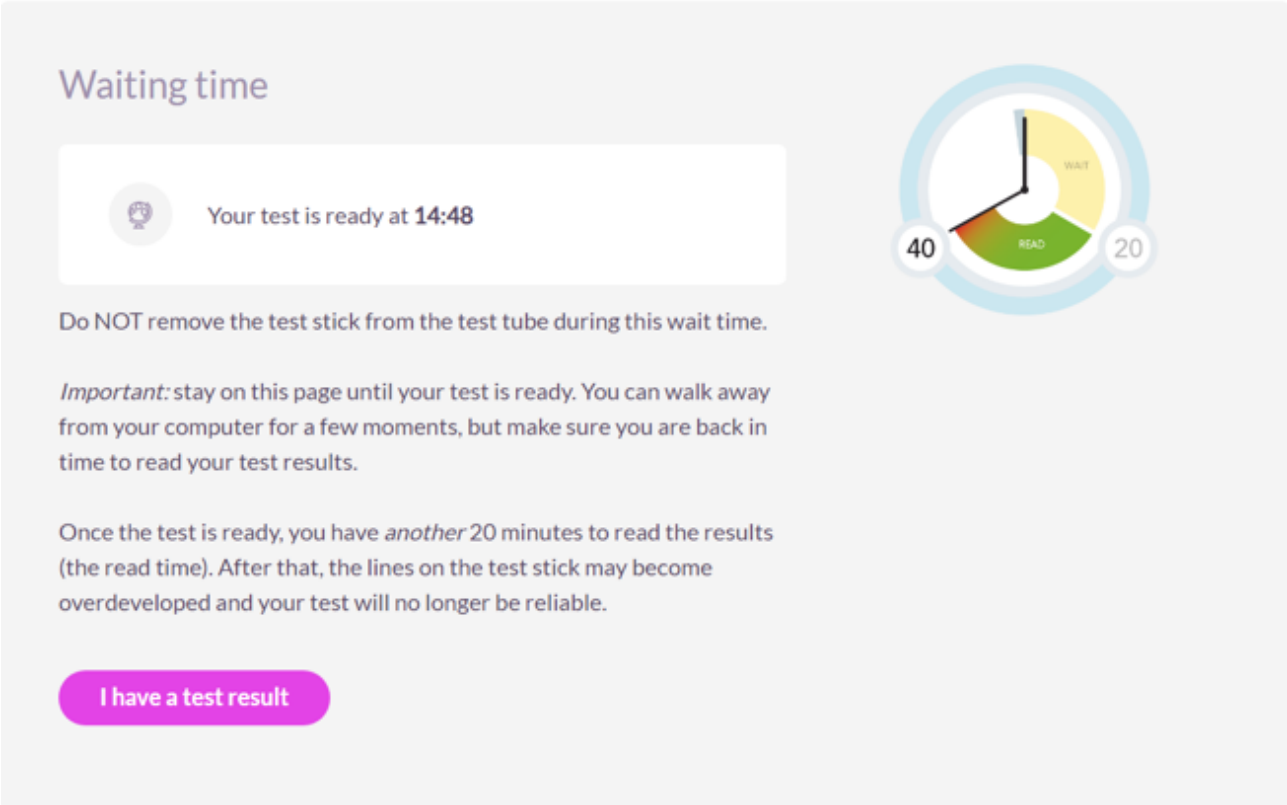
- Guide NAs to the website for test instructions and counseling
- Deal with doubts or negative reactions of NAs about HIV testing
- Ask for support from the peer coordinator

HIV Self-Testing for Network Associates

Network associates who accept the self-test from their peers log in to the time2test website (via a computer, tablet, or smartphone) with their test package number to create an anonymous test account based on a second code that is generated by the time2test application. The content of the time2test website as well as the instruction letters and manuals are provided in three languages (Dutch, English, and French).

After reading about the aims, terms of participation, and data privacy, they give online informed consent for participation by clicking on a button "I have read and understood the information above." Next, they are taken to the baseline questionnaire (12 questions) on demographics, sexual orientation, HIV testing history, and sexual behavior. After completing the questionnaire, participants watch an animation about the OraQuick HIV self-test and go to the step-by-step test instructions. The HIV self-test uses oral fluid from the gums to detect antibodies against HIV-1 and HIV-2. In an OraQuick HIV self-test usability study on 900 individuals, sensitivity was reported as 99.4% (152 out of 153 positive individuals correctly identified their result as positive) and specificity as 99.0% (717 out of 724 negative individuals correctly identified their result as negative) [27]. The window phase of the test is 3 months. Both peers and NAs receive clear test instructions about this window phase and how to interpret the results. Test instructions have proven sufficient in an earlier study (HIVTest@Home trial) of the Amsterdam public health service where people could buy the self-test online [28]. NAs are instructed to check the content of the test package that includes an instruction letter, the self-test, and paper test manual. The paper manual contains similar information on testing and follow-up steps for NAs without internet access. After sample is collected and placed in the tube, the test result is directly readable after 20 minutes. The website contains a timer that shows when the test is ready (Figure 4). After the waiting time, images appear with the possible test results (1 line, 2 lines, or no lines) that NAs can compare with their own test. NAs have another 20 minutes to read the result. For each image, tailored information is provided that explains the test result and various posttest counseling options.

Figure 4. Image of one of the online testing steps for the oral HIV self-test.



Follow-Up

NAs with a reactive (HIV positive) test are informed about the importance of having a confirmation test and preventing (possible) further transmission of HIV. They are referred for confirmatory testing to an STI clinic in their region (telephone numbers provided through the STI clinic finder) where they are given priority, or they can go to their general practitioner (GP). They can print or download a referral letter on their phone for the health care professional. The referral letter explains what HIV self-test was used and the need for confirmation testing. They can also bring the test manual from their test package. When the confirmation test is HIV positive, they are directly

referred to the nearest HIV treatment clinic as part of standard practice.

NAs with a nonreactive test are referred to the STI clinic, GP, or the Man tot Man (Testlab) website for repeated HIV testing after 3 months, testing for other STIs, and Web-based interventions aimed at reducing sexual risk behavior and increasing PrEP use.

In case the self-test failed, NAs can ask for a new test via their peer or they can send an email to the project mailbox that will be answered by the peer coordinator. NAs who have questions about the test procedure are referred to the Frequently Asked Questions page on the website or they can contact a health care professional by telephone through the STI clinic finder on the website.

Data Collection and Study Outcomes

Peers and NAs provide online informed consent for participation and data collection directly after the online project information page and prior to any online data collection. The baseline questionnaires inquire about age, migration background, educational level, sexual behavior (NAs only), and HIV testing history (NAs only) (Textbox 1). After peers complete the training, they receive 5 test packages. For each person they approach with the self-test, they record a few baseline characteristics (type of contact, age, ethnicity, education, HIV testing history) on the website. If the self-test is accepted, peers activate the test package number by clicking on the number of the test (out of a list with 5 package numbers). The next time that an NA accepts a self-test, the 4 remaining package numbers will appear, and this process continues until no packages are left. If the self-test is not accepted, peers record a reason for nonacceptance. Peers are offered the opportunity to ask for additional self-tests in case they are able and willing to distribute more tests.

After their SNT period, peers will be invited to participate in an evaluation survey and/or qualitative interview about their experiences with SNT, their role as a peer, and their relationship with the NAs they approached. We will examine factors supporting the acceptance of the social network approach, barriers that peers experience during the recruitment process, and outcomes on communication about HIV testing (eg, Did offering the test affect the relationship between the peer and NA in any way?).

NAs who used the self-test are asked to provide a voluntary email address in case they are willing to be contacted for a follow-up questionnaire after 3 weeks or become a peer recruiter themselves. The follow-up questionnaire contains questions about their experiences with SNT and the Web-based service for self-testing. Not giving consent to these options does not affect the ability to participate in the project in any way.

The following outcomes will be examined (by study aim):

- Study feasibility and acceptability of SNT using HIV self-tests:
  - Numbers of registered peers, peers finishing the training, peers starting SNT
  - Peer profiles (eg, age, gender, ethnicity, area of residence, education, location recruited as peer)
  - Network index (accepted/used tests divided by the number of peers)
  - Numbers of NAs rejecting, accepting, and using the self-test
  - NA profiles (eg, age, gender, ethnicity, homo/bisexual, years living in the Netherlands, residence status, HIV testing history, number of sexual partners in the last 12 months)
  - Types of relationships between peers and NAs
  - Locations of self-test offer
- Assess the effectiveness of SNT regarding diagnosing HIV:
  - Number of newly diagnosed HIV infections (self-reported and/or confirmed at STI clinic)
  - Network yield (newly diagnosed HIV infections divided by the number of NAs/peers)
  - NA characteristics associated with newly diagnosed HIV infections
  - Peer characteristics associated with the ability to identify NAs with undiagnosed HIV infection
- Explore the effect of SNT on openness toward HIV and HIV testing:
  - Encouragement of conversations about risk behavior and HIV (testing) within networks
  - Reasons for nonacceptance of HIV self-test
  - Positive or negative reactions by NAs
  - Peer support

Textbox 1. Data collection among peers and network associates in the PREVENT pilot.

Peers

- Inclusion:
  - Demographics (age, gender, ethnicity, residence, education level, location of recruitment)
  - Approval to participate as a peer
  - Approval for follow-up interview
- Follow-up:
  - Experiences with e-learning tool
  - Experiences with supervision by the peer-coordinator
  - Experiences with distibution of HIV self-tests
  - Reactions to the test offer
  - Shared test experience
  - Communication about HIV testing and sexuality
  - Willingness to distribute more self-tests

Approached network associates (completed by peers)

- Inclusion:
  - Demographics (age, gender, ethnicity, education level)
  - Sexual preference
  - Type of network contact
  - HIV testing history
  - HIV self-test acceptance and date of acceptance
  - Reason for nonacceptance and date of acceptance

Participating network associates

- Inclusion:
  - Demographics (age, gender, ethnicity, area of residence, education level, residential status, years in Netherlands)
  - Sexual behavior
  - HIV testing history
  - Approval for follow-up questionnaire
- Follow up:
  - Reason for acceptance of HIV self-test
  - Experience with the HIV self-test offer
  - Experience with conducting the HIV self-test
  - Would recommend the HIV self-test to others
  - HIV self-test conducted in presence of others
  - Location of conducting the HIV self-test
  - HIV test result
  - Location of confirmation test (HIV positive self-test only)
  - Result of confirmation test (HIV positive self-test only)
  - Visited HIV treatment clinic (if confirmed HIV positive)
  - Support by the peer
  - Sharing the test result with others

- Communication about HIV in social network
- Willingness to become a peer
- Willingness to be interviewed
- Changes over time in online visitors

Website tracking data

- Inclusion:
  - Frequency of log-ins
  - Number of webpages accessed

Data Analyses

Descriptive analyses will be used to examine participation rates and characteristics of peers and NAs. The databases containing epidemiological data of peers and NAs can be linked based on the test package number. Therefore, we can identify person profiles (sexual risk, HIV testing history) as well as social network profiles (types of relationships, types of sexual and/or social networks across migration backgrounds, etc) and link these with SNT outcomes. Factors associated with (un)successful distribution of HIV self-tests will be examined by stepwise (logistical) regression analyses.

Usability of the e-learning tool for peers will be evaluated by using mixed methods approaches (qualitative interviews and a follow-up questionnaire) to gain insight on its user friendliness, record characteristics of peers (not) finishing the e-tool, and support enhancements in the (re)usability of the e-learning tool. Quantitative data will be analyzed using SAS/STAT version 14.1 (SAS Institute Inc) or SPSS Statistics version 24 (IBM Corp). Interview data will be transcribed using f4transcript version 7 (Audiotranskription) and assisted by NVivo software version 9 (QSR International) according to the thematic analysis method [29].

Results

Between January and May 2019, 10 STI clinics and 7 HIV treatment clinics throughout the Netherlands (Amsterdam, Rotterdam, the Hague, Arnhem, Nijmegen, Utrecht, Flevoland, Groningen, Twente, and Brabant) began to recruit peers for the PREVENT pilot. A midterm and final evaluation will be conducted during 2019-2020.

Discussion

Aim

The PREVENT pilot is the first Dutch peer-moderated social network study using HIV self-tests and one of the first in Europe. This pilot intervention will provide insight on the feasibility and acceptability of SNT and its ability to identify undiagnosed HIV infections among MSM-NW in the Netherlands.

Strengths and Limitations

A potential strength of this Web-based SNT approach is that hard-to-reach populations receive a free HIV self-test at a very low threshold, literally handed over by their friends. PREVENT has not only the ability to reach high-risk MSM-NW hidden to current HIV testing practices, it may also encourage conversations about risk behavior, HIV, and (barriers to) testing within the networks. Ultimately, the project can promote normalization of HIV testing. Also, the integrated online data collection, where peers and NAs complete questionnaires, enables anonymous linkage between the two groups. This provides us the opportunity to keep track of the distributed and used HIV self-tests.

There are also challenges to the success of our implementation. The value of SNT depends on many contextual factors as shown in previous SNT studies [10-13]. For SNT, it is important to include motivated peers who are willing to contribute to HIV testing in their community, an essential condition for optimal implementation of this study design. Therefore, peers who encounter challenges during the recruitment process will be personally assisted by the peer coordinator. Furthermore, our pilot focuses on a hard-to-reach population, and including 50 to 60 peers and 200 NAs in 12 to 18 months' time is ambitious, especially due to the diversity of the target population in terms of cultural background, languages, educational levels, or socioeconomic statuses. Another concern is that the data collection on test results is more complicated when self-tests are used. Information on test results is provided by self-report in the follow-up questionnaire after 3 weeks and by collecting numbers of HIV confirmation tests conducted at the participating STI clinics. However, NAs might not be willing to report their test result. Also, NAs can go to their GP for a confirmation test or to an STI clinic outside the participating regions, which could lead to missing test results. Moreover, there is a possibility that NAs who accept the self-test will use the paper manual for instructions and not log in to the website. For them, epidemiological information and test results will also be missed. In addition, the evaluation process involves several small questionnaires that may be a barrier for NAs and peers. This could complicate a thorough evaluation of the outcomes of the pilot. Finally, language barriers are foreseen as the website and manuals are in three languages only. Peers could potentially bridge this barrier by helping NAs with the test and/or guiding them to the routine test locations. Hopefully, NAs who are tested

for the first time through SNT find it easier to test themselves again in other settings (online or at STI clinics or GPs).

Evaluation

During the evaluation of the pilot, we will focus on factors influencing all participation steps by peers and NAs, their feedback, and problem solving. We will also assess which peers reach the most NAs and who reaches NAs who have never tested before or tested positive. Factors include demographics, behavior, and process indicators. If needed, participation-enhancing strategies will be developed during the recruitment period. Creating general awareness for the pilot (ie, promotional material in the waiting room of the clinics) is already considered to stimulate engagement of peers in SNT. The first results may also support the need for further improvement of the content on the time2test website, the integrated e-tool for peers, or other elements of our pilot implementation. If SNT is acceptable and feasible among MSM-NW in the Netherlands, it can easily be adopted by other clinics and/or the website can be adjusted for future recruitment in other HIV risk populations.

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Authors' Contributions

EC, RS, CD, TH, UD, WZ, MV, HG, KV, and FZ are the core members of the PREVENT research team who designed and implemented the study. EC wrote the initial draft of the manuscript, and CD, TH, HG, RS, KV, UD, and FZ edited the manuscript. JB, CD, FZ, RS, and EC designed the questionnaires. All authors approved the final manuscript.
PREVENT collaborators: Public Health Service of Amsterdam: Arjan Hogewoning, Elske Hoornenborg, Bart-Jan Mulder, Kees de Jong; Public Health Service Twente: Karlijn Kampman; Public Health Service Flevoland: Charlie van der Weijden; Public Health Service Rotterdam: Charlotte Lantinga, Liesbeth Vasen; Public Health Service Gelderland-Midden: Ferna Neienhuijsen; Public Health Service Nijmegen: Anne-Marijn Siemes, Noëmi Nijsten, Pushpa Hoppener, Public Health Service Groningen: Fetzen de Groot; Public Health Service Utrecht: Bas Boogmans; Public Health Service West-Brabant: Annemarie Dado; Amsterdam UMC: Hans van Eden, Marc van der Valk; DC klinieken: Hans-Erik Nobel, Loek Elsenburg, Arne van Eeden; OLVG hospital: Imke Hooijenga, Guido van den Berk, Kees Brinkman; Maasstad hospital: Jan den Hollander; Flevo hospital: Judith Branger, Tine Duijf; UMC Groningen: Wouter Bierman, Dorien De Weerd; Radboud UMC: Karin Grindjes; Aids Healthcare Foundation Amsterdam: Milo DeMoraes, and Anna Zakowicz.

Conflicts of Interest

FZ has received nonfinancial support (ie, HIVST kits) from OraSure Technologies for another investigator-initiated study concerning HIV self-testing.

Multimedia Appendix 1
Peer-reviewer report from Aidsfonds.
[PDF File (Adobe PDF File), 75 KB - resprot_v9i2e14743_app1.pdf]

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Abbreviations

COM-B: capability, opportunity, motivation, and behavior
GP: general practitioner
LGBTI: lesbian, gay, bisexual, transgender, and intersex
MSM: men who have sex with men
MSM-NW: men who have sex with men–non-Western
NA: network associate
PrEP: pre-exposure prophylaxis
PREVENT: Peer-Empowered Voluntary Extended Network Testing
SNT: social network testing
STI: sexually transmitted infection

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Protocol

Measuring the Effects of Sharing Mobile Health Data During Diabetes Consultations: Protocol for a Mixed Method Study

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Abstract

Background: There is rising demand for health care's limited resources. Mobile health (mHealth) could be a solution, especially for those with chronic illnesses such as diabetes. mHealth can increases patients' options to self-manage their health, improving their health knowledge, engagement, and capacity to contribute to their own care decisions. However, there are few solutions for sharing and presenting patients' mHealth data with health care providers (HCPs) in a mutually understandable way, which limits the potential of shared decision making.

Objective: Through a six-month mixed method feasibility study in Norway, we aim to explore the impacts that a system for sharing patient-gathered data from mHealth devices has on patients and HCPs during diabetes consultations.

Methods: Patients with diabetes will be recruited through their HCPs. Participants will use the Diabetes Diary mobile phone app to register and review diabetes self-management data and share these data during diabetes consultations using the FullFlow data-sharing system. The primary outcome is the feasibility of the system, which includes HCP impressions and expectations (prestudy survey), usability (System Usability Scale), functionalities used and data shared during consultations, and study-end focus group meetings. Secondary outcomes include a change in the therapeutic relationship, patient empowerment and wellness, health parameters (HbA_{1c} and blood pressure), and the patients' own app-registered health measures (blood glucose, medication, physical activity, diet, and weight). We will compare measures taken at baseline and at six months, as well as data continuously gathered from the app. Analysis will aim to explain which measures have changed and how and why they have changed during the intervention.

Results: The Full Flow project is funded for 2016 to 2020 by the Research Council of Norway (number 247974/O70). We approached 14 general practitioner clinics (expecting to recruit 1-2 general practitioners per clinic) and two hospitals (expecting to recruit 2-3 nurses per hospital). By recruiting through the HCPs, we expect to recruit 74 patients with type 2 and 33 patients with type 1 diabetes. Between November 2018 and July 2019, we recruited eight patients and 15 HCPs. During 2020, we aim to analyze and publish the results of the collected data from our patient and HCP participants.

Conclusions: We expect to better understand what is needed to be able to share data. This includes potential benefits that sharing patient-gathered data during consultations will have on patients and HCPs, both individually and together. By measuring these impacts, we will be able to present the possibilities and challenges related to a system for sharing mHealth data for future

interventions and practice. Results will also demonstrate what needs to be done to make this collaboration between HCPs and patients successful and subsequently further improve patients' health and engagement in their care.

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KEYWORDS

diabetes; patient-gathered data; mHealth; data sharing; therapeutic relationship

Introduction

How Patient Mobile Health Apps Are Changing Consultations

Mobile health (mHealth) technologies originally were designed for and used by patients to better understand and self-manage their health. For those with diabetes, this means tracking and understanding how many different factors, such as diet, exercise, and medication, affect their blood glucose levels. As a result of collecting and reviewing these data, patients are more empowered and knowledgeable, eager to take control and responsibility of their daily health, and more knowledgeable patients are able to better understand how their actions affect their diabetes health. Some information and subsequent decisions are more evident than others after reviewing their data. In other words, patients can only understand or explain a portion of the data that they collect without the medical expertise of health care providers (HCPs) to contextualize these data with known disease processes. Patients have begun to bring these data from their mHealth technologies to their health care consultations, hoping that the HCPs can provide explanations for the results seen in their gathered data [1].

Mobile Health Data Sharing

The expected benefits of mHealth integration and data sharing are to decrease health care costs, increase patient engagement and aid options, and improve clinical outcomes [2,3]. However, HCPs have traditionally relied on scientifically proven, professionally collected clinical data, such as laboratory test results and biological measures taken at consultations, to understand the patient's health status. There is evidence that by using these data to inform a clinical recommendation, HCPs can be confident that they have provided a relatively accurate diagnosis and that their treatment will produce a known clinical outcome [4]. Ideally, presenting app-collected data to HCPs would provide a greater understanding of the patient's situation. However, the data have not been collected, structured, or validated in relation to disease status like traditional laboratory data. The presentation and structure of the data (ie, dozens or hundreds of data entries), including many different types of data from a variety of different mHealth technologies, is a challenge to relate to from the HCPs' perspective.

Further, HCPs aim to use medical data in a slightly different way than patients use their patient-gathered data. In other words, each wants to know different things. The patient wants to know if their daily decisions are having a positive effect on their disease management, and the HCPs want to know how their clinical recommendations and medications are affecting the disease status. These priorities are complementary; as part of daily self-management, diabetes patients need to observe, understand, and respond to fluctuations in their blood glucose [5], often instantly for those with type 1 diabetes. The focus of HCPs is on the progress or trend to determine if a treatment modality or approach is a practical choice for that patient in the long run [6,7]. Therefore, for mHealth data sharing to be useful for patients and HCPs, the information should be presented in a way that both can understand, discuss, and use together to determine how best to maintain or improve treatment and self-management strategies. This is an example of shared decision making.

The Potential of Shared Decision Making

Shared decision making describes the communication and health care decisions made between patients and their HCPs [8]. When used in such a way, shared decision making is key to successful therapeutic relationships—those between patients and their HCPs—and, ultimately, patients' adherence and achievement of treatment aims [8]. Several studies have demonstrated that patients' improvement in HbA_{1c} (glycated hemoglobin) and perceived diabetes competence are associated with a medical environment where clinicians encourage patients' autonomy [9,10].

Sharing Mobile Health Data Enables Shared Decision Making

With mHealth, individuals have been presented with the opportunity to bring patient-relevant data to the conversation during consultations, as opposed to relying on only patient memory of their self-management and clinical test results. In doing so, true shared decision making between the HCP and patient is not only possible but necessary to effectively support and validate patient decisions in their self-management. For example, a patient may collect diet or exercise data that could explain fluctuations in clinical test results, such as lipid levels or imbalances between insulin and blood glucose levels during those periods. Patient-gathered data could even bring to light challenges that the patient faces in their self-management that are not evident from clinical test results, such as dangerous nightly hypoglycemic events. The result of bringing such information to the consultation is, for example, that the patient could provide concrete evidence of their challenges and self-management activities, with specific questions that would improve their understanding and ability to self-manage. Then the HCP could explain why adverse outcomes are occurring and give patient-tailored guidance about how to better deal with such situations in the future. Therefore, patient-gathered data from these devices could strengthen patient-clinician collaboration in tailored diabetes treatment.

How to Approach Mobile Health Intervention Research

The purpose of health intervention research is to develop and test the ability of such things as a new device, system, or service to improve patient health outcomes or experiences. To develop a solution that facilitates shared decision making using mHealth data, one must consider two main questions: (1) how to effectively present the mHealth-gathered data during consultations between patients and HCPs, and (2) how to promote conversation about the patient-gathered data in a way that leads to shared decision making. The goal of testing such a solution is typically to determine if a system can successfully convert patient-gathered data to a form that is understandable and useful for patients and HCPs and shows that the use of the data can produce positive clinical or experiential outcomes.

The Proposed Solution

To assess how mHealth data sharing comprehensively affects patients, their health outcomes, HCPs, and their therapeutic relationship, we must first have a suitable data-gathering and data-sharing platform that can facilitate and validate this new situation. As the data-gathering platform, we use a mobile phone app, the Diabetes Diary, which has been tested in several studies [11-14]. In the Full Flow of Health Data Between Patients and Health Care Systems project, we aim to design, develop, and test a system for sharing patient-gathered mHealth data with HCPs during diabetes consultations by iteratively involving both patients and providers throughout the research activities [15].

The Diabetes Diary app is a research tool that allows patient participants to register their self-gathered health measurements (eg, blood glucose and physical activity) and review previously registered data either as a summary or list (Figure 1). Patients then have the option to select the data they want to share with their HCPs, which is then displayed via the FullFlow System, a platform for sharing and presenting patient data.

The FullFlow System's Web interface allows both patients and providers to view together selected summaries and preliminary information about the set of shared data. This system also allows users to choose the summary forms to view, which is intended to be guided by the information about the patient's progress on their goals, measurements, and identified areas of possible concern illustrated on the home screen (Figure 2). The development details and initial clinical testing of the data-sharing system are described elsewhere [16,17].

Figure 1. Home screen of the patient-operated Diabetes Diary app (English version).

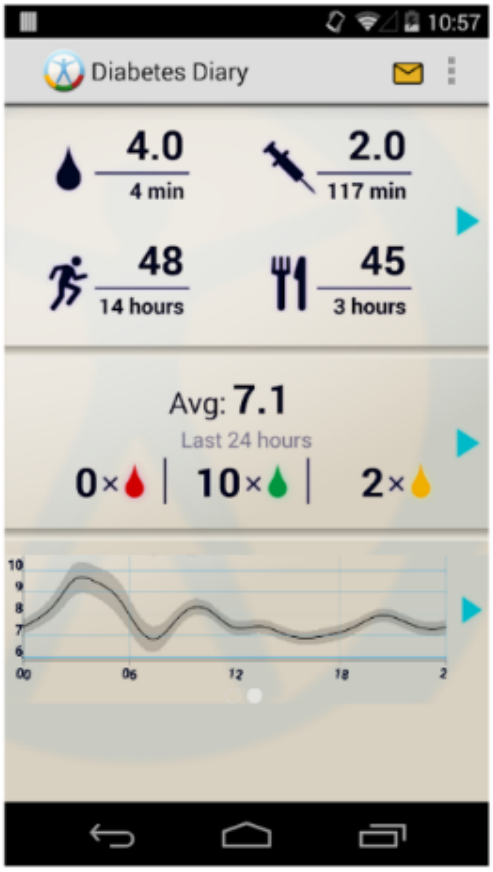
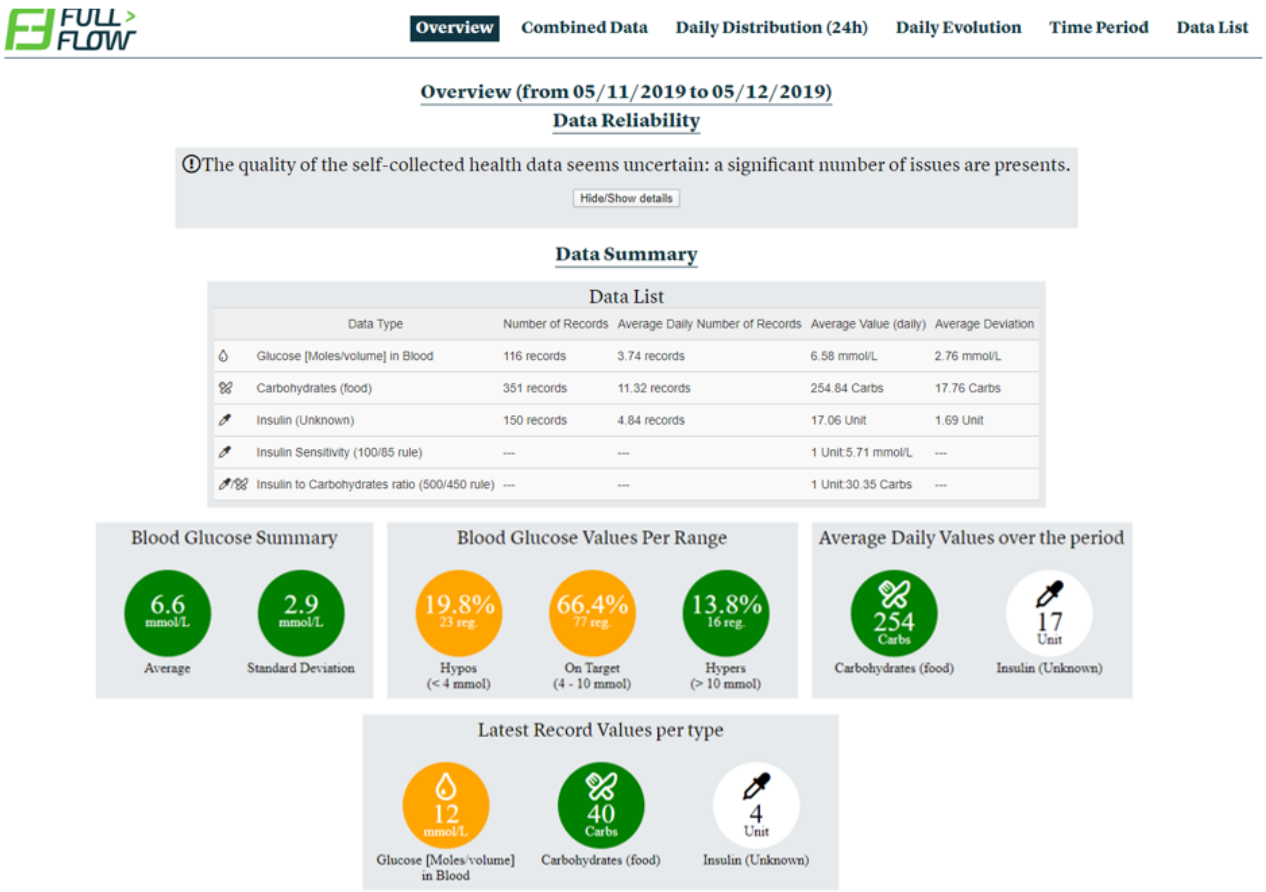


Figure 2. The FullFlow System's Web-based home screen (English version).



Study Aims and Objectives

A working version of the system was developed in 2018 [17-19]. We now aim to comprehensively measure its impacts on patients and providers and its role in encouraging patient-provider collaboration in diabetes care. Further, by using diverse measures (mixed methods) based on different research fields (eg, psychology, medicine, and technology), we can better understand which impacts mHealth can have on health care services.

The overall objective is to understand and test the effects of using a data-sharing system (exemplified by the FullFlow System developed in-house [17,20]) for patient-gathered mHealth data and the Diabetes Diary mobile phone app. We hypothesize that sharing such data, in the form of mutually relevant information, will enable patients and HCPs together to generate more tailored and concrete self-management recommendations for patients. This protocol includes a description and justification behind why the selected measures, evaluation methods, and study implementation methods were chosen.

Methods

Study Design

This protocol describes a six-month mixed method study, which is part of the larger Full Flow project [15], in which the FullFlow data-sharing system is used to enable the sharing of patient-gathered mHealth data during diabetes consultations. The design of both the data-sharing system itself and mixed method study structure (Figure 3) are based on developmental studies and activities within the Full Flow project, described elsewhere [16,18,19,21,22].

Traditionally, health studies report only the pre- and posteffects of interventions, perhaps with some participant-recalled experiences. However, human memory is prone to forgetfulness and mistakes. Using mHealth technology that can provide real-time recording of information about what patients did and how their health responded to their self-management is an invaluable resource for health studies. Therefore, in the described study, we include a comprehensive set of measures that take advantage of the reliability of clinical measures and standardized questionnaires with the record of how patients performed their self-management between consultations (see Table 1). In doing so, we aim to understand not only the pre- and posteffects of using such a system but also how patients performed their self-management between consultations.

Figure 3. Study design flowchart. HCP: health care provider; T1D: type 1 diabetes; T2D: type 2 diabetes.

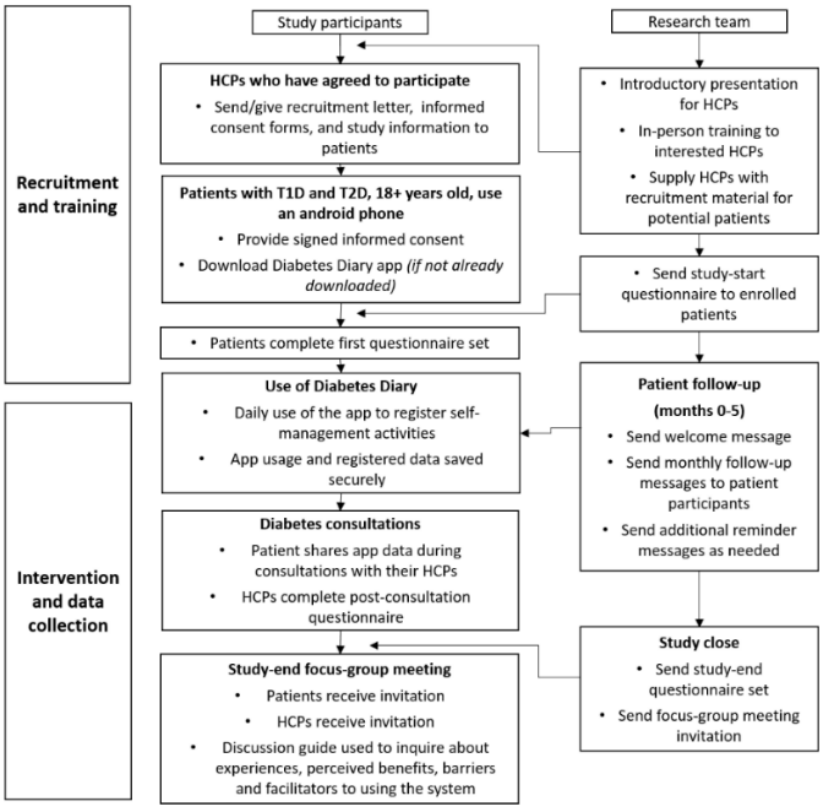


Table 1. List of data types, their sources, and purpose for measurement.

Data collection tools[a]	Purpose: to measure...	When collected
Primary outcomes		
Prestudy survey to HCPs[b]	HCPs' first impressions of the system and their expectations	Before study start
Postconsultation questionnaire	Functions of the system used, HbA_{1c}[c], and blood pressure of patients	After each consultation
Data displayed by the FullFlow System	What patients chose to share during consultations	At each consultation
Study-end focus group meetings[d]	Experiences, perceived benefits, barriers to, and facilitators for using the system	After study end
System Usability Scale [23]	Usability of the system for patients	After study end
Secondary outcomes		
Diabetes Empowerment Scale [24]	Patient engagement (ability)	Before and after the study
WHO-5 wellness [25]	Patient engagement (likelihood)	Before and after the study
Health Care Climate Questionnaire [26]	Therapeutic relationship	Before and after the study
Patient-registered health data (app)	Patients' self-measured health parameters: blood glucose, weight, diet, physical activity, and medication	Continuously throughout the study
App usage logs	Patients' interactions with the Diabetes Diary app	Continuously throughout the study

[a] Norwegian versions of all questionnaires will be used. The five-question World Health Organization Wellness Index (WHO-5) is the only Norwegian version of a questionnaire to be officially validated [27].

[b]HCP: health care provider.

[c]HbA_{1c}: glycated hemoglobin.

[d]Focus group sessions will be held in Norwegian, audio-recorded, transcribed, cleared of all identifiable information, and translated into English for analysis.

Online Study Administration and Management

The online study management platform provides a real-time overview of participants' progress through the study. The platform allows study administrators to deliver recruitment material and collect informed consent electronically. After it is confirmed that the patient has downloaded the app and entered the code, we can collect their data. Each participant is assigned an anonymous user ID, which is not directly linkable to the user's personal information (eg, personal email, sensitive personal information) that is stored elsewhere. Electronic questionnaires and direct follow-up messages can then be sent to these user IDs, directly to the app, and registered personal email. This direct channel with the app also allows the platform to collect both registered measurements and usage log data from the app. Preliminary and summative analysis is accessible via the system as well to identify data gaps, such as possible technology challenges that participants are experiencing that study administrators can efficiently respond with follow-up messages when necessary.

Study Population

We recruited general practitioners (GPs), diabetes nurses, and individuals diagnosed with either type 1, type 2, or other types of diabetes in the Troms and Finnmark region of Norway between October 2018 and July 2019. Inclusion to participate as a health care provider required that they had the ability and willingness to use the FullFlow data-sharing system during their consultation setting, which required an internet connection and a Web browser on their office computer. Persons with diabetes who were older than 18 years were eligible to participate. Inclusion required that they have a mobile phone with an Android operating system through which the Diabetes Diary app could be downloaded and used for data collection. Participants had to be willing to use the app to gather and share data during consultations, and to consider participation in a study-end focus group meeting. No restrictions were placed on applicants' disease duration or HbA_{1c} level. Exclusion criteria included any mental or physical illness that interfered with their ability to fulfill study expectations.

Recruitment and Training

Health Care Personnel

We require sets of patients and their health care professionals to agree to participate together; therefore, we will first approach diabetes nurses and endocrinologists through our research team's current network, including the University Hospital of North Norway and Hammerfest Hospital. A member of our research team will identify potential GP participants and cold-call them directly. Emails will also be used to request in-person recruitment meetings. Two representatives of our research team will give a brief lunch presentation to HCP offices accepting such meetings. For those interested in participating in the study, we will schedule one-hour training sessions to demonstrate the FullFlow data-sharing system in more practical detail on the HCP's own computer. The HCPs will be asked to complete a brief survey about their perceptions of the presented FullFlow System after these in-person training sessions.

As GP offices in Norway do not commonly have agreements or contracts with local or national research projects, we will provide additional compensation for the time taken outside of their regular work schedules for the training sessions for each patient enrolled and for any additional time spent on the study, such as study-end focus group meetings. These will follow standard reimbursement schemes for health care professionals in Norway.

Patients

When needed, we will also assist HCPs in identifying potential participants from their diabetes patient lists. We will provide both electronic and paper copies of the patient recruitment materials. HCPs will provide patients the recruitment letters and study information in-person during consultations, or they will mail the letters to those not scheduled to meet for consultation shortly after. Patients will be instructed to contact us if they are interested in enrolling in the study. Patient recruitment letters will contain a link to the study webpage where interested patients will be able to read and sign the informed consent form electronically (Multimedia Appendix 1). Patients who have not already downloaded the tailored version of the Diabetes Diary app, including an associated website and user guide [28], will be requested to do so to participate. We will also inform patient participants of their right to withdraw their data or participation from the study at any time. Patients will be reimbursed for travel and consultations if the meetings are scheduled in addition to their usual care.

All participants will be encouraged to participate in the study-end workshop. The participants are informed that technical support will be available via email or by visiting our office. Patient recruitment ended on July 1, 2019.

Sample Size

We plan to approach 14 GP clinics, with an estimated one to two interested GPs in each clinic, and two hospitals, with one to three nurses and one endocrinologist in each.

The GPs in the Troms and Finnmark regions of Norway have listed 1000 to 1500 patients [29]. The prevalence of type 2 diabetes is 4.7% [30]; therefore, our recruitment pool is expected to be 1234 patients with type 2. The average expected response rate is 15% (range 10% to 20%), and approximately 40% of these patients are estimated to meet the inclusion criteria. Therefore, we expect to recruit 74 patients with type 2 diabetes.

There are 511 patients with type 1 diabetes registered at University Hospital of Northern Norway (UNN) Tromsø and 62 registered at Hammerfest Hospital in the Norwegian Diabetes Registry for Adults [31]. With the same estimated response rate of 15% and 40% of these meeting the inclusion criteria, we estimate to recruit approximately 30 patients from UNN and three patients from Hammerfest Hospital.

Intervention Description

Diabetes Diary Application—Tailored Version

Our research team previously developed a tailored version of the Diabetes Diary app [32,33], which we will provide to all patient participants. We developed the app over several years

to act as the research platform for many projects [13,34,35]. The app itself allows patients to tailor the app to their diabetes type and self-management foci, including the ability to register and review the following data types: goals, blood glucose, medication, physical activity, nutrition, and weight.

For the study, both registered measurements and usage log data from this app will be continuously encrypted and transferred to the project's secure online study management platform [36], which was used during two previous projects [34,37]. However, for consultations, the patient will be able to control the data they share with their health care team via the tested FullFlow System.

The FullFlow Data-Sharing System

The FullFlow System will summarize and display information based on the data provided. If patients do not share data, patients and HCPs can plan goals together about which data to collect and discuss during future consultations. We have designed the dynamic, Web-based interface of the FullFlow System to facilitate easy navigation of this information. The FullFlow System will register the data that patients choose to share, which we will then qualitatively analyze after the study. A more detailed description of the FullFlow System itself is described elsewhere [17].

Consultations and Self-Management

We will ask that each patient-clinician team schedule at least one consultation by the sixth month of the study related to diabetes treatment. To the best of their ability, HCPs and patient participants should use the FullFlow System during these consultations. HCPs are requested to report the functions that were used, the usefulness of the FullFlow System, and the patients' HbA_{1c} and blood pressure via a postconsultation questionnaire (requiring three to five minutes).

We will send monthly messages to patients using the online study management platform. These messages will appear both in the participants' email and the Diabetes Diary app. We detail the scheduled messages (eg, reminders to schedule appointments and register data throughout the study) in Multimedia Appendix 2.

Data Collection

We will administer questionnaires through LimeSurvey [36,38] and our study management platform. Information about which data was registered in the Diabetes Diary app will be collected continuously through connection to our secure research platform.

We will request patient participants to report the following before study start: age, gender, level of education, disease duration, medication type, and delivery system (eg, pens, pumps, pills). We will also request data, described in the Evaluation Measures section and Table 1, about patients' self-management habits and perceived health status and challenges that they may have with the self-management of diabetes parameters.

Evaluation Measures

We chose to include standardized and validated questionnaires where possible, supplemented by measures specific to impressions of the use of the technologies involved. The combination of questionnaires was chosen to limit the number of questions because we are also asking them to track several other factors as part of the intervention on the mobile phone app. Table 1 introduces an overview of the purpose and selection of our data collection tools.

System Usability

We will assess the usability of the system with three data collection tools: the prestudy survey to HCPs, the System Usability Scale (SUS) [23], and the postconsultation questionnaires. The reason for combining these to measure usability is that responses from each build on one another. In other words, we measure not just overall satisfaction or dissatisfaction with the system, but information about how each pair of patients and providers used the system during each consultation.

The postconsultation questionnaires provide a specific indication of the functions the HCPs and patients chose to use (ie, which characteristics of the system contributed to their use).

Patient Well-Being and Health

Postconsultation questionnaires will also request that the HCP provide the laboratory values for each patient's HbA_{1c} and blood pressure. The participants' own app-registered health data (ie, measured values of blood glucose, administered insulin or other medication, weight, physical activity, diet, and goals) will provide a more continuous illustration of a patient's self-management foci and health. By comparing these recorded values to the other measures mentioned, we aim to explain how patient self-management habits contribute to measures of health, engagement, and communication with their providers.

The World Health Organization Wellness Index (WHO-5) is a five-question measure of an individual's subjective health during the previous two weeks using a six-point Likert scale [39]. We chose this measure based on its simplicity, brevity, and ability to cover a diversity of concepts related to well-being.

Patient Empowerment and Engagement

The Diabetes Empowerment Scale-Short Form (DES-SF) is an eight-item questionnaire that measures an individual's psychosocial self-efficacy [24]. Self-efficacy refers to a person's belief in their own ability to perform the activities necessary to achieve a specific level of performance; in this case, those necessary to maintain or improve their diabetes health. Although this is a measure of a person's belief and not actions, self-efficacy is strongly correlated to an individual's self-care actions in the case of diabetes [40,41].

The participants' own app-registered health data are evidence of their real-world self-management habits. Similarly, the interactions with the app (ie, app usage logs) indicate time spent using the app that includes not only time taken to enter values but also the use of other functionalities (eg, reviewing previously recorded materials).

Therapeutic Relationship

The Health Care Climate Questionnaire (HCCQ) is a six-item measure of patient perception of whether their HCP supports their autonomy [26,42]. In other words, the HCCQ measures

the relationship between patients and HCPs. This questionnaire is based on the concepts of self-determination or one's ability to choose their own actions [43]. The therapeutic relationship supports one's health self-management and has been shown to significantly contribute to an individual's health-related outcomes [44]. These concepts describe a collaboration based on mutual contribution to care decisions rather than a patient-provider relationship based on a hierarchy of knowledge and power. In combination with the other questionnaires listed, we can better understand how, and possibly why, a system that encourages communication, initiated by the patient's choice to share patient-gathered data, affects the patient's motivation, self-care actions, and health, as described previously.

Study-End Focus Group Meetings

We have chosen the presented questionnaires to limit "burnout" from answering too many written questions; however, we still expect there to be missing responses. In addition, as this is the first time these measures have been used together in a study for mHealth—to the best of our knowledge—we expect that we will have follow-up questions and clarifications about the patients' and providers' responses. Therefore, the study-end focus group meetings will focus on elaborating the participants' responses from the measures mentioned previously and encouraging the participants to share their experiences and opinions. We also aim to gather more specific input and explanation of the system's function, use, and suggested improvements.

Data Analysis

Baseline measures will be described using descriptive statistics. We assume that some variables will differ between participants with different types of diabetes due to the limited size of the study population.

Analysis of responses for all standardized tests will follow the scoring guidelines provided with each measurement tool. Postconsultation questionnaires will be assessed quantitatively and qualitatively, depending on the question type. The transcripts from the study-end focus group meetings will be analyzed using inductive thematic analysis to contextualize the quantitative results. Paired *t* tests will be used to compare all quantitative baseline (0 months) and study-end (6 months) measures. Correlation analysis will be used to assess relationships between quantitative and coded qualitative variables, when possible.

Results

Ethical Approval

The protocol, questionnaires, interview guides, recruitment material, and other adjoining study material have been submitted to the Regional Committees for Medical and Health Research Ethics for Northern Norway, who found the study exempt from their purview of approval. Instead, the study was declared and approved by the Personvernombudet (Personal Data Protection Officer) at UNN.

Funding

This study is part of the first author's PhD program and has been funded through a larger project, entitled "The Full Flow of Health Data Between Patients and Health Care Systems (2016-2020)," by the Research Council of Norway (number 247974/O70).

Progress to Date

Recruitment for this six-month study began in October 2018. As of September 2019, we recruited 13 GPs, two diabetes nurses at two hospitals, and eight patients. We expect all results to be collected by March 2020. We will then have results about patient and provider usage of the technologies, collected automatically, as well as their reported experiences. From these, we can identify whether the tested system met their individual needs and potential improvements needed to facilitate collaboration in diabetes care consultations. Results will also include the impact of collaborative use on the patients' clinically measured data from mHealth tools, as well as their measured health and wellness.

Discussion

Collaboration Between Patients and Providers

The described Full Flow mixed method study is the final phase of the Full Flow project. Previous phases of this project engaged individuals with types 1 and 2 diabetes, and a variety of HCPs, in iterative and experience-based activities to design the studied FullFlow data-sharing system. During these initial phases, the concepts of end-user perspective and collaboration between patients and providers, not only in clinical practice but also in research, was emphasized.

Although many studies and commercially available systems involving shared patient-gathered data focus on the provider's interpretation of the information, we believe that it is not only possible but necessary to encourage more collaboration between and contribution from both parties in mHealth interventions and care practice. Through our choice of methods and measures, we aim to exemplify the importance of accounting for the unique additional needs and opportunities of mHealth in research practice.

True Shared Decision Making

Shared decision making is described as patients and their HCPs working together to collaborate on the process of making health decisions [45]. However, most interventions describe this process with HCPs taking on the bulk of the decision making [46]. Instead, the patient is queried about their goals and preferences, acting mostly as an information source for the HCP. This lack of a true, equal partnership between patients and HCPs has been cited as mainly due to time constraints and lack of patient engagement or knowledge of their health situation [47]. This highlights the importance of using a patient's capacity and willingness to contribute to this process.

Today, patients' use of mHealth and the ability of these technologies to enable collecting and sharing of patient-gathered data make true shared decision making possible. Sharing patient-gathered data allows for a more balanced and

patient-initiated process of developing recommendations for self-management (ie, tasks that are performed by the patient on a daily basis).

Other Measures Are Needed

Within research, we must also adapt to the new situation that mHealth creates. A major challenge of understanding the effects of mHealth interventions is determining which traditional measures are applicable and which others are needed. The World Health Organization (WHO) is an example of several attempts to develop a comprehensive set of information that is needed from mHealth intervention studies. In addition to the traditional usability reports for new health technologies, the mERA (mHealth Evaluation, Reporting and Assessment) checklist also calls for evidence of barriers and facilitators to participants' access to the intervention (eg, "factors that may limit the users' ability to use the intervention") as well as its potential to be implemented into clinical care [48]. The dynamic network of interactions that mHealth represents calls for more than pre- and postintervention measurements. In this context, where patients can use several tools and services continuously in their everyday lives, it is no longer sufficient to merely understand what has changed and by how much [49]. This is our opportunity to invite not just patients and their devices but also their HCPs to participate in considering and understanding the interactions within and outside of clinical practice.

Not only has mHealth provided researchers with a more informed patient, it has also provided us with ways of tracking how they use mHealth (eg, by analyzing app and system's usage logs) [50]. These allow us to more effectively observe and record patients' self-management tasks and health measures, their data shared during consultations, and other factors that static questionnaires are not able to collect. One of these factors, which now plays an even more crucial role than before, is the motivation to be more involved in the data collection and sharing process. The relationship—now hopefully, collaboration—between patient and provider is not only something that can change but also something that can play a role in patients' motivation to engage in their health [51,52]. By including standardized psychological questionnaires with the other measures of patients' well-being, health, and self-management activity, we can contribute to a better understanding of this relationship. The planned study-end focus groups will allow us to elaborate on why some of these changes are happening and provide insight from all the participants about the context of their decisions.

Conclusion

In this study, we aim to address and understand the nuances of mHealth. By including measures of what has changed, including how and why, we can begin to more effectively and accurately explore the impacts of mHealth on not only the before and after measures but also events during the intervention itself. In addition to the relevant research communities, the information gained from this study will inform our electronic health record vendor partners and both The Norwegian Directorate of eHealth and overarching Ministry of Health and Care Services [53], which will better prepare Norway, and other countries, when forming future health systems that support mHealth integration.

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Authors' Contributions

Coauthors Bradway, Årsand, Joakimsen, Hartvigsen, and Giordanengo contributed to the application for funding, and many of the authors contributed to the study administration and design. All authors have approved the protocol and the presented manuscript. As part of their individual PhDs, Alain Giordanengo has been the main contributor to the working version of the FullFlow data-sharing system, and Meghan Bradway has been the main contributor to the methods and perspectives necessary for this mHealth intervention. Eirik Årsand serves as the project manager and main supervisor to the PhD candidate, Meghan Bradway, while Gunnar Hartvigsen is the main supervisor of Alain Giordanengo. Anne Helen Hansen played a significant role in the recruitment of the health care professionals, as well as insight into the general practitioners' working environment. Pietro Randine maintained the study administration platform and provided oversight of the data collection and structuring process in preparation for analysis. Astrid Grøttland was the project officer, overseeing practicalities, while Ragnar Joakimsen contributed to valuable insight into the hospital working environment and diabetes services offered to patients today.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.

[DOCX File , 41 KB - resprot_v9i2e16657_app1.docx]

Multimedia Appendix 2
Scheduled follow-up messages to patient participants.
[DOCX File , 17 KB - resprot_v9i2e16657_app2.docx]

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Abbreviations

GP: general practitioner
HbA_{1c}: glycated hemoglobin
HCP: health care provider
UNN: University Hospital of Northern Norway

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Original Paper

Identifying Barriers and Enablers to Attending Diabetic Retinopathy Screening in Immigrants to Canada From Ethnocultural Minority Groups: Protocol for a Qualitative Descriptive Study

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Abstract

Background: Immigrants to Canada belonging to ethnocultural minority groups are at increased risk of developing diabetes and complications, including diabetic retinopathy, and they are also less likely to be screened and treated. Improved attendance to retinopathy screening (eye tests) has the potential to reduce permanent complications, including blindness.

Objective: This study aims to identify the barriers and enablers of attending diabetic retinopathy screening among ethnocultural minority immigrants living with diabetes in Quebec and Ontario, Canada, to inform the development of a behavior change intervention to improve diabetic retinopathy screening attendance.

Methods: The research question draws on the needs of patients and clinicians. Using an integrated knowledge translation approach, the research team includes clinicians, researchers, and patient partners who will contribute throughout the study to developing and reviewing materials and procedures, helping to recruit participants, and disseminating findings. Using a convenience snowball strategy, we will recruit participants from three target groups: South Asian and Chinese people, and French-speaking people of African descent. To better facilitate reaching these groups and support participant recruitment, we will partner with community organizations and clinics serving our target populations in Ontario and Quebec. Data will be collected using semistructured interviews, using topic guides developed in English and translated into French, Mandarin, Hindi, and Urdu, and conducted in those languages. Data collection and analysis will be structured according to the Theoretical Domains Framework (TDF), which synthesizes predominant theories of behavior change into 14 domains covering key modifiable factors that may operate as barriers or enablers to attending eye screening. We will use directed content analysis to code barriers and enablers to TDF domains, then thematic analysis to define key themes within domains.

Results: This study was approved for funding in December 2017, and the research ethics board approved the conduct of the study as of January 13, 2018. Data collection then began in April 2018. As of August 28, 2018, we have recruited 22 participants, and analysis is ongoing, with results expected to be published in 2020.

Conclusions: Findings from this study will inform the codevelopment of theory-informed, culturally- and linguistically-tailored interventions to support patients in attending retinopathy screening.

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KEYWORDS

retinopathy; diabetes; eye screening; theoretical domains framework; integrated knowledge translation; patient engagement; behavior change; immigrant health; minority health; patient oriented research

Introduction

Diabetes is among the most common chronic diseases worldwide. In Canada, the prevalence of diabetes is higher in immigrants to Canada (8.1%) than in those born in Canada (7.1%) [1] and varies across ethnic groups. Ethnicity and immigration can increase the risk of developing diabetes and related complications, with South Asians, Hispanic-Americans, Chinese, and Africans having a higher risk of developing diabetes and diabetes-related complications than Europeans [2,3].

For people living with diabetes worldwide, diabetic retinopathy is the most common complication and is also a critical microvascular complication [4-6]. This vascular disease of the retina comprises three forms: nonproliferative diabetic retinopathy, macular edema and ischemia, and proliferative diabetic retinopathy. Diabetic retinopathy is the leading cause of blindness among working-age populations in the Western world [2,5], and approximately one-third of people living with diabetes worldwide are already affected by retinopathy. In Canada, most people with type 1 and over half of those with type 2 diabetes will develop a degree of retinopathy in their lifetime [7].

Diabetic retinopathy screening can reduce the risk and progression of vision loss [8]. It is also one of the most effective and least costly ways to reduce the severe complications associated with this disease [9]. Screening (including an eye examination with pupil dilation using drops) by an optometrist, a general ophthalmologist, or a retina specialist helps to detect the disease earlier and thus increases the effectiveness of treatment [9]. Several international studies and guidelines recommend annual screening for diabetic retinopathy [2,10,11]. Guidance recommends that screening should be initiated five years after the onset of type 1 diabetes, and at the time of diagnosis with type 2 [12]. Despite these recommendations, however, diabetic retinopathy screening rates are much lower in ethnocultural minorities despite them having a higher prevalence of diabetic retinopathy [13]. Immigrants who are members of ethnocultural minorities are less likely to be screened and treated for diabetic retinopathy than nonimmigrant members of those same minority groups [14]. Obstacles to accessing eye care may differ between ethnic groups due to a variety of factors [15].

Low diabetic retinopathy screening rates are a public health issue [16] with considerable economic burden [8]. In Canada, diabetic retinopathy accounts for 25% of vision loss in people of visible minorities compared to 4% across all ethnicities [17]. Complications from diabetes account for 80% of the costs associated with the disease [18], which in 2015 was estimated to be Can$14 billion dollars (approximately US $10 billion) in Canada alone [19]. If left untreated, diabetic retinopathy leads to the continued use of multiple health care services [20]. The economic burden rests on the indirect costs of the progressive loss of sight due to decreased individual productivity, the use of counseling or rehabilitation services, and the government's income assistance policies in the event of total or partial incapacitation [21]. In addition to these broader economic and social costs, diabetic retinopathy is also associated with significant psychological and social consequences [8], including feelings of fear, depression, anger [22], shame, or guilt [23,24] related to the irregular management of diabetes. Improved attendance of diabetic retinopathy screening can reduce permanent complications of diabetes as well as the associated financial burden and negative psychosocial consequences [20].

We previously conducted a systematic review of barriers and enablers to attending diabetic retinopathy screening [25] and showed that such barriers and enablers had been investigated and described in a variety of ways. Framing diabetic retinopathy screening attendance as a health behavior could help researchers to understand the barriers and enablers to attendance for minorities in terms of the modifiable and nonmodifiable factors affecting this health behavior. Doing so may facilitate drawing upon theories of behavior and behavior change to provide a basis for developing a cumulative evidence base of factors that impact diabetic retinopathy screening attendance, and for developing interventions best suited to address these barriers and enablers.

Our review of barriers and enablers to attending retinopathy screening [25] identified 69 studies and highlighted recurring factors that may impede screening attendance:

- environmental context and resources factors (identified in 52 studies), including issues of access, competing priorities, economic concerns, schedule, referral problems, and specialist service availability;
- social influences (35 studies) related to doctor-patient communication, including language, trust, community support, and stigma;
- knowledge (35 studies) about diabetic retinopathy, of the difference between routine eye tests and screening;
- memory, attention, and decision processes (34 studies), including the lack of symptoms, competing comorbidities, and forgetting to attend;
- beliefs about consequences (26 studies) that screenings provide important health status information but worry about the harmful effects of screening;
- and emotions (23 studies), including fear, defensiveness, and adding to the overall demands of diabetes self-management, causing a feeling of being overwhelmed [25].

While these barriers may affect people living with diabetes in general, some barriers and enablers may be especially relevant to immigrants from ethnocultural minority groups. Furthermore,

their experienced barriers/enablers may be underrepresented in the literature or not represented at all, leading to health care interventions that do not best serve their needs. Indeed, only 3/69 identified studies were conducted in Canada, and only one involved a minority group (First Nations Cree communities in Alberta). There is a need to better understand among the known barriers and enablers which are particularly salient among immigrants to Canada from different ethnocultural minority groups, and whether there are any as yet unidentified barriers that are relevant to specific groups. This will facilitate the development of services and support to meet their needs better and encourage higher screening attendance in those attending screenings at a lower rate.

We also completed a Cochrane systematic review of trials of interventions to improve retinopathy attendance [26]. Across the 66 trials identified (only 3 in Canada) [26], 56 of which compared intervention to usual care, screening attendance increased by 12% (risk difference 0.20 [95% CI 0.10-0.14]) [26]. We showed that specific behavior change techniques were associated with improved screening attendance, including goal setting (outcome) (0.26 [95% CI 0.16-0.36]) and feedback on outcomes of behavior (0.22 [95% CI 0.15-0.29]) in interventions targeting patients [26]. The review guides potential high-yield strategies for future implementation trials in principle, but these likely need to be tailored to address relevant barriers in different subgroups to ensure optimal fit between barriers and the interventions designed to address them [27]. Rather than assuming a generic intervention will solve this problem, a collaborative and patient-oriented approach is needed to understand how different vulnerable populations with a higher risk of diabetic retinopathy experience barriers to attending the screening.

A comprehensive theory-based approach may be particularly useful in providing a breadth and depth of factors to explore as barriers and enablers to screening attendance, which, for our study, is the Theoretical Domains Framework (TDF) [28,29]. The TDF synthesizes prevailing theories of behavior and behavior change, and the constructs within them, into a set of 14 theoretical domains that represent a breadth of factors demonstrated to affect or impact behavior and behavior change. The domains include knowledge, skills, social/professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory/attention/decision processes, environmental context and resources, social influences, behavioral regulation, and emotion. It has been previously used to understand the barriers and enablers to behavior across a range of settings and populations, including patients [30-33], was included in our systematic review of barriers and enablers to attending diabetic retinopathy screening [25], and will serve as the basis for identifying barriers and enablers in this study.

We aim to identify barriers and enablers to attending diabetic retinopathy screening in ethnocultural minorities, such as immigrants from South Asia or China and Francophone immigrants of African descent [34], in the provinces of Ontario and Quebec, Canada.

Methods

Study Approach

This study will use an integrated knowledge translation [35] approach, which involves partnering with clinicians and people living with diabetes at all stages of research. This includes the steps of defining or refining research objectives, collecting and analyzing data, disseminating results, and developing policies. An integrated knowledge translation approach better ensures that research incorporates the experiences and needs of patients. In this study, we plan to have up to 12 patient partners included in the research process. At least six people (two from each selected subgroup of immigrants from South Asia or China, or Francophone immigrants of African descent) will be members of the research team. They will be invited to take part in the discussions and decision-making processes as key members of the research team, contributing their expertise through their experience living with diabetes and accessing and attending diabetic retinopathy eye screening. The patient partners will be as diverse in age and gender as possible to help ensure a broader scope of opinions and experiences.

Theoretical Framework

The TDF will inform the content of the interview topic guides and subsequent directed content analysis. This will allow us to identify key theoretical domains likely to influence diabetic retinopathy screening attendance within each of our three subgroups. The use of the TDF will provide the capacity to draw upon evidence from the broader literature on barriers and enablers to diabetic retinopathy screening attendance, as well as the wider behavioral science literature. The use of a framework thus ensures contribution to a cumulative evidence base on modifiable factors to address to encourage higher attendance of retinopathy screenings.

Design

We defined the health behavior under study using the Target-Action-Context-Time principle: immigrants to Canada from South Asia or China, or of African descent with any diabetes (target) attending (action) diabetic retinopathy screening with an eye specialist (context) in the next year (time). We will then use the TDF to identify barriers and enablers to attending retinopathy in each ethnocultural group. We will conduct a descriptive qualitative study guided by the TDF. The qualitative approach provides a global perspective and interpretative understanding of the phenomenon while allowing theoretical and methodological adjustments throughout the research process. This ensures that we capture the breadth of potentially modifiable factors to inform subgroup-specific intervention development. We will use consolidated criteria for reporting qualitative research reporting guidelines [36] to report our eventual findings from this study.

Consistent with guidance [37], the TDF will be used as a basis for describing the topics to be addressed in the interview guide and to inform the analysis. The guide will be developed, and findings interpreted with our patient partners to ensure consistency with any ethnocultural features of interest. While the TDF will provide the theoretical structure, we will

incorporate open questions within the interview guides and an inductive theme-generation process for factors that may not directly fit within the TDF. See Multimedia Appendix 1 for examples of our topic guide.

Context

This study will take place in the provinces of Ontario and Quebec in Canada and will focus primarily on recruiting in Toronto, Ottawa, Montreal, and Quebec City. We may add other areas depending on referrals. Local team members will facilitate the selection of locations for data collection and recruitment of participants in collaboration with primary care (eg, family practice teams) and community organizations in both provinces. We will also collaborate with Diabetes Action Canada (DAC) and its Diabetic Retinopathy, Patient Engagement, and Knowledge Translation groups. DAC is one of five pan-Canadian research networks focused on a chronic illness and seeks to improve the lives of people living with diabetes through patient engagement and collaboration.

Participants

Study participants will be immigrants to Canada from South Asia or China, and French-speaking immigrants of African descent living with diabetes. While Canada is home to immigrants from many nations, these three ethnocultural groups represent the majority of ethnocultural minorities currently arriving in Canada annually [38] who have a higher prevalence of diabetic retinopathy. These groups also align with our study team members' linguistic abilities to ensure that interviews can be conducted with participants in their native language. The Francophone immigrants of African descent have been selected as they represent more than three-quarters of the Francophone immigrants that arrived in Canada in 2014 [39]. The term immigrants refers to "individuals who moved from their country of origin into a new country for the purpose of resettlement" [40]. This definition, according to the International Organization of Migration, includes those who arrive and stay through an irregular migration process such as "temporary foreign workers, foreign students, refugees and other involuntary migrants" [40].

This study will not include refugee populations since they experience unique barriers in accessing health care and health coverage. In our analysis, we will distinguish between recent immigrants (living in Canada for less than five years) and immigrants who have been established in the country for a longer period. Inclusion criteria for participation in the study include: (1) at least 18 years of age; (2) an immigrant from South Asia (native speakers of Urdu or Hindi) or China (native speakers of Mandarin), or a Francophone immigrant of African descent; (3) living personally with diabetes; and (4) agree to participate in the study. The exclusion criterion is to have a confounding severe ocular disease other than diabetic retinopathy, such as cataracts or glaucoma.

Participant Recruitment

Study participants will be recruited through the patient circles of Diabetes Action Canada, our team members' networks, primary care units, and community organizations serving immigrants or people living with diabetes in Ottawa, Toronto, Quebec City, and Montreal. We will contact selected organizations by phone or email to introduce ourselves and the research project.

We will establish contact with the primary care units and community organizations via a specified contact person working at each establishment. We will ask community organizations interested in collaborating with us to support the recruitment process by sharing recruitment messages on their websites, in their newsletters, and via email to clients of their organization. We will also ask to post a recruitment announcement on their premises and assist us in accessing a private space to conduct interviews with participants. This is a documented method for working with vulnerable and underserved groups and likely also to promote reaching groups who are medically underserved as well [41].

To date, we have partnered with Polycultural [42] in Toronto and Alliance des communautés culturelles pour l'égalité dans la santé et les services sociaux (ACCÉSSS) in Montreal for this study. They will assist us in recruiting participants and provide private workspace(s) to conduct individual interviews with participants if needed. We will continue to involve further community organizations as needed. We will also approach family doctor leads in primary care units regarding their interest in informing relevant patients about our research project and making study information, including recruitment text, available at their location(s). People who are interested in learning more about our study or who wish to participate will be invited to contact the study coordinators. People meeting all inclusion criteria will be selected to participate. If the number of people willing exceeds our needs, we will select participants using the maximum variation sampling procedure. We will provide Can$40 (US $30.40) as financial compensation in recognition of their participation and reimburse participants for travel costs.

Sampling

We will use a purposive sampling approach supplemented with snowball sampling. We will aim to recruit 13-20 people per subgroup (South Asian immigrants, Chinese immigrants, and Francophone immigrants of African descent). Purposive sampling will involve aiming to recruit participants according to a sampling frame that aims to balance recruitment across sex/gender, age, time since immigration (within the last five years or more than five years), and reported diabetic retinopathy screening attendance within the last year or not. This will facilitate comparing results between recent immigrants and those who have been in Canada for a longer time, as well as between people who attend/do not attend regular diabetic retinopathy screening.

Interviews will continue in each subgroup until thematic data saturation is reached, using the "10+3 rule" [19] whereby at least ten interviews in each subgroup will be conducted, followed by a further three interviews, and if the last three do not bring up new barriers/enablers, saturation will be judged to have been achieved. If a new barrier/enabler is identified, interviews will continue until three consecutive interviews do not bring up anything new. Based on previous studies, we expect to achieve saturation in each subgroup within 13-20 interviews [43].

Interview Procedure and Data Collection

A semistructured interview guide has been developed, based on the TDF, to identify barriers and enablers to attending diabetic retinopathy screening. One-on-one interviews (or accompanied by family/friend/caregiver, if appropriate) will be conducted by native speakers of each language (Hindi, Urdu, French, and Mandarin). Interviews will be conducted over the phone or, when feasible, in person, and will be approximately one hour in duration. The guide will be developed per published standards [37]. Interview topic guides will be initially developed in English, then translated into the languages mentioned above. Transcribed interviews will be reviewed by team members (research staff and patient partners) who speak the respective languages to ensure both retention of the theoretical meaning for each domain and, where appropriate, ethnocultural adaptations are maintained. In keeping with our integrated knowledge translation approach, we will include patient partners' input in developing and refining the interview guide.

Analysis Plan

Individual interviews will be audio-recorded, translated into English, transcribed, then analyzed using NVivo (QSR international, Doncaster, Australia). Transcripts will be analyzed using directed content analysis [44], a deductive approach that uses an established theoretical framework as a basis for coding responses. We will develop a coding manual and then independently double code barriers and enablers expressed by respondents into the TDF domain(s) best reflecting their views while leaving open the possibility that barriers/enablers might not fit into a given domain. Once views have been coded to TDF domains, we will conduct an inductive thematic analysis within each domain to identify specific emergent themes. The result will provide an indicator of key domains to target within each group for the development of a future intervention to support attendance to retinopathy screening. Consistent with established criteria and guidance for using the TDF, key domains will be determined based on how strongly expressed the barriers/enablers are by respondents, how often a given domain is represented, and whether there are discrepancy views between participants [32]. Any barriers and enablers not fitting within TDF domains will be identified and thematic analysis conducted.

Results

This study was approved for funding in December 2017, and the research ethics board approved the conduct of the study as of January 13, 2018. Data collection then began in April 2018. As of August 28, 2018, we have recruited 22 participants, and analysis is ongoing, with results expected to be published in 2020.

Discussion

This study will be among the first to explore barriers and enablers to attending retinopathy screening in ethnocultural minority immigrants living with diabetes from different socio-cultural backgrounds. It will allow us to determine whether and how barriers/enablers vary by group and whether they differ from known barriers/enablers elicited from the general population of people with diabetes. Should more specific barriers be identified, this would argue in favor of developing interventions tailored according to socio-cultural background. However, should similar barriers emerge as those of the wider population, this would suggest more general intervention strategies are needed.

Results from this study will also help to develop behavior change intervention strategies that are ready for rigorous evaluation. In a future study based on this project, our patient partners and we hope to work alongside Diabetes Action Canada's Patient Engagement, Diabetic Retinopathy, and Knowledge Translation groups to codevelop intervention components that address barriers identified in this study. We will consider feasible options for how to deliver the intervention (methods of delivery), by who and to whom, where, and how often, informed wherever possible by existing literature on effective strategies for particular barriers. Once prototype intervention materials and approaches are developed, we will evaluate reactions and feedback to intervention materials and processes [45].

Many people from minority ethnocultural groups who have immigrated to Canada are at higher risk of the complications of diabetic retinopathy, but to date, we know very little about the modifiable factors that impact their screening attendance. The present study aims to fill this gap across multiple groups, and through an active process of involvement and engagement, ensure that the research is conducted in a manner that best reflects the experiences of members of each of the three groups. We hope that this approach may also serve as an exemplar to other planned research involving similar under-represented groups to ensure that the foundations for developing interventions to improve care consider the perspectives of these groups.

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Authors' Contributions

MJD and JP are project co-leads. MJD led protocol development and oversaw all aspects of the study design, protocol drafting, and REB submission. MJD and JP led the drafting and revision and gave the final approval of this manuscript. JP brought methodological expertise and led training and interview guide development according to Theoretical Domains Framework, which is central to the study design. MJD is the first and corresponding author for this manuscript. CB and SA collaborated on drafting the original protocol and preparing REB submissions for approval. CB and SA, along with XW, developed the interview guide and translated it into French (CB), Urdu and Hindi (SA), and Mandarin (XW) according to the Theoretical Domains Framework and cultural-linguistic requirements. MB and OS are the clinical team based in Toronto for the project and reviewed this article for procedural accuracy and adherence to the protocol. MHB is a clinical ophthalmologist guiding the clinic and medical components of this study. OD, MZ, NM, and SL are research professionals involved in the project in Ottawa and Quebec. OD and MZ are members of MJD's team. OD coordinates Patient Engagement activities within Diabetes Action Canada, which is one of this study's funders. OD and MZ contributed to the study design and supported protocol drafting. MZ edited all revisions of this manuscript and prepared it for submission. NM and SL are members of JP's team and bring their knowledge of the Theoretical Domain Framework, behavior change, and health system research. JG, NI, and JP are experts in applying the Theoretical Domain Framework. FL, HOW, MCT and JS are patient engagement, knowledge transfer, implementation science, and community-based research scientists involved in the project. They advised on study design and integration of their methods within the study and manuscript. All authors substantially contributed to the study design, protocol development, and this manuscript. Due to the complexity of involving ethnocultural minority immigrants in research, it was imperative to have those with expertise in the methods selected and with the linguistic and cultural aspects of our three groups: South Asian and Chinese immigrants, and French-speaking persons of African descent.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Woman from ethnocultural minority undergoing a diabetic retinopathy screening.
[PDF File (Adobe PDF File), 1066 KB - resprot_v9i2e15109_app1.pdf]

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Abbreviations

ACCÉSSS: Alliance des communautés culturelles pour l'égalité dans la santé et les services sociaux
DAC: Diabetes Action Canada
TDF: Theoretical Domains Framework

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Protocol

Evaluation of a Rural Emergency Medical Service Project in Germany: Protocol for a Multimethod and Multiperspective Longitudinal Analysis

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Abstract

Background: German emergency medical services are a 2-tiered system with paramedic-staffed ambulances as the primary response, supported by prehospital emergency doctors for life-threatening conditions. As in all European health care systems, German medical practitioners are in short supply, whereas the demand for timely emergency medical care is constantly growing. In rural areas, this has led to critical delays in the provision of emergency medical care. In particular, in cases of cardiac arrest, time is of the essence because, with each passing minute, the chance of survival with good neurological outcome decreases.

Objective: The project has 4 main objectives: (1) reduce the therapy-free interval through widespread reinforcement of resuscitation skills and motivating the public to provide help (ie, bystander cardiopulmonary resuscitation), (2) provide faster professional first aid in addition to rescue services through alerting trained first aiders by mobile phone, (3) make more emergency physicians available more quickly through introducing the tele-emergency physician system, and (4) enhance emergency care through improving the cooperation between statutory health insurance on-call medical services (German: *Kassenärztlicher Bereitschaftsdienst*) and emergency medical services.

Methods: We will evaluate project implementation in a tripartite prospective and intervention study. First, in medical evaluation, we will assess the influences of various project measures on quality of care using multiple methods. Second, the economic evaluation will mainly focus on the valuation of inputs and outcomes of the different measures while considering various relevant indicators. Third, as part of the work and organizational analysis, we will assess important work- and occupational-related parameters, as well as network and regional indexes.

Results: We started the project in 2017 and will complete enrollment in 2020. We finished the preanalysis phase in September 2018.

Conclusions: Overall, implementation of the project will entail realigning emergency medicine in rural areas and enhancing the quality of medical emergency care in the long term. We expect the project to lead to a measurable increase in medical laypersons' individual motivation to provide resuscitation, to strengthen resuscitation skills, and to result in medical laypersons providing first aid much more frequently. Furthermore, we intend the project to decrease the therapy-free interval in cases of cardiac arrest by dispatching first aiders via mobile phones. Previous projects in urban regions have shown that the tele-emergency physician system can provide a higher availability and quality of emergency call-outs in regular health care. We expect a closer

interrelation of emergency practices of statutory health insurance physicians with the rescue service to lead to better coordination of rescue and on-call services.

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KEYWORDS

resuscitation; telemedicine; mHealth; smartphone-based alerting; emergency medical services; mobile applications

Introduction

Status of German Emergency Care

German emergency medical services (EMSs) are a 2-tiered system using ambulances and emergency response vehicles. Ambulances are staffed by 2 paramedics, whereas emergency response vehicles are staffed by a paramedic and an emergency physician [1]. For life-threatening emergencies, both ambulances and emergency response vehicles are alerted, whereas less-critical situations require only an ambulance [2], which relates to approximately half of all cases [3,4].

German EMSs are facing the challenge of responding to constantly rising numbers of call-outs with fewer and fewer emergency physicians—this is especially difficult in rural areas [5-8]. Simultaneously, legal requirements of an optimal response time from the rescue service are becoming difficult to meet. In fact, the rescue service law for the state of Mecklenburg-Vorpommern (Mecklenburg-West Pomerania) requires statewide compliance with the response time of 10 minutes for the first response vehicle on the scene [9,10] and 15 minutes for emergency physician. The response time (German: *Hilfsfrist*) is defined as the time between alerting the rescue services and their arrival on a passable road at the place of need. According to the legal requirements, the response time must be guaranteed in 95% of cases in cities of more than 20,000 inhabitants or in 90% of cases in rural areas.

For the district of Vorpommern-Greifswald, a region that belongs to the state of Mecklenburg-Vorpommern, calculations by the Chair of General Business Administration and Health Care Management at the University of Greifswald revealed that in 14 of the 36 areas, the emergency physician did not arrive within 5 minutes of the ambulance in 90% of cases (based on the official figures for 2014) [11]. Each year, numerous tourists visit the popular holiday region on a seasonal basis, leading to increased cases of emergencies and that also need to be guaranteed support in an emergency. This additional burden was not included in the calculations of simulations.

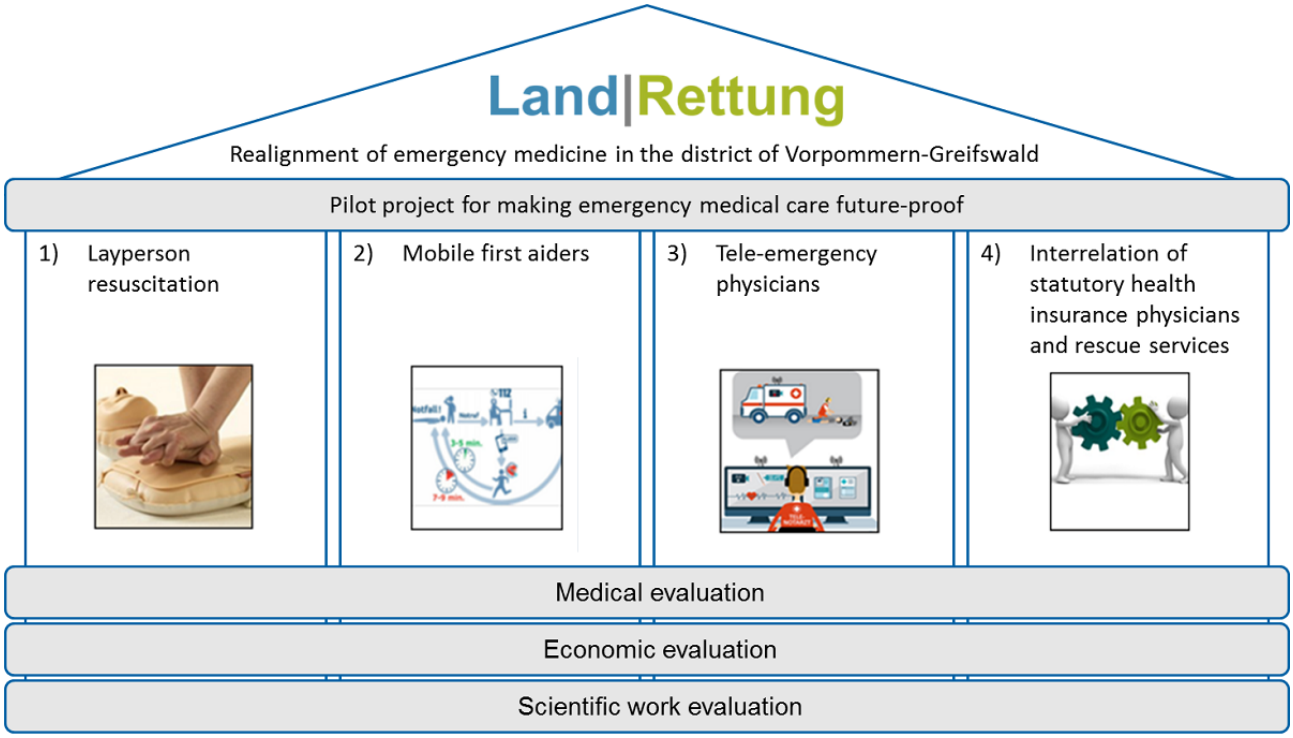
Call-outs due to cardiac emergencies are particularly urgent as, for example in cardiac arrest, vital organs such as the brain are no longer supplied with oxygen; the longer the time to first resuscitation measures, the lower the rate of survival [12]. Accordingly, compared with urban areas, in rural regions the chance of surviving a cardiac arrest substantially decreases due to longer travel time to the emergency site [13]. During a medical emergency, it is not only the response time of professional emergency services that is critical, but also the therapy-free interval—that is, the time from occurrence of the emergency to the start of qualified aid assistance [14]. To realign emergency medicine in rural areas, the project Land|Rettung (English: Rural|Rescue) is focusing on 2 solution approaches: (1) structuring professional rescue services using information and communication technologies to reduce the therapy-free interval, and (2) introducing layperson resuscitation, hence bridging the longer arrival times of professional services during an emergency situation [14,15].

Project Land|Rettung

To realign emergency services, Land|Rettung follows a multimethodological approach based on 4 pillars that also are the project's objectives (see Figure 1): (1) reduce the therapy-free interval through a widespread reinforcement of society's resuscitation skills and motivation to provide assistance using targeted training methods (ie, bystander cardiopulmonary resuscitation [CPR]), (2) provide fast professional first aid in addition to rescue services through the involvement of specially trained first aiders alerted via a mobile phone app (Land|Retter app), (3) provide faster and greater availability of emergency physicians through the establishment of the tele-emergency physician (TEP) system, and (4) more closely interlock emergency care through the realignment of emergency practices of statutory health insurance physicians and EMSs.

Being the first of its kind in Germany, this 4-module project will lead to a joint concept developed and established by all groups involved in emergency care: state government, districts, health insurers, rescue services, hospitals, and statutory health insurance physicians. Involving all relevant parties in the process of realigning emergency medicine in rural areas will also allow for the concept's transformation to other regions in Mecklenburg-Vorpommern and other states.

Figure 1. The project Land|Rettung (English: Rural|Rescue) and its 4 pillars.



Reducing the Therapy-Free Interval

As part of the project, we are implementing 2 interventions to reduce the therapy-free interval in cases of cardiac arrest.

First, in a cardiac emergency, medical laypersons who are in the immediate vicinity of the person affected are an important factor. Between 67% and 84% of cardiac arrests occur at home, and approximately that many are witnessed by bystanders [16,17]. Bystander CPR—that is, CPR given before the arrival of medical emergency personnel—is performed in Germany in about 37% (in 2017) of cases, which is low compared with other countries [18]. Therefore, not only knowledge but also the willingness to perform resuscitation among the population has to be increased [19]. Chest compressions ensure that oxygen is transported to the brain. Laypersons starting resuscitation can bridge the time until EMSs arrive and thus increase the likelihood of survival [20]. Resuscitation measures by the EMS lead to twice as good a result when layperson resuscitation has been conducted beforehand [21,22]. Resuscitation training in communities is associated with higher survival rates [23]. Layperson resuscitation is already promoted through Germanywide projects such as “Ein Leben retten” (save a life) [24]. Accordingly, one key objective of this project is the targeted promotion of layperson resuscitation.

Second, studies have proven that chest compressions performed by a highly trained first aider have a greater chance of success than those performed by a medical layperson [25,26]. Based on their professional or voluntary qualifications, these first aiders can include physicians, dentists, paramedic and rescue personnel, nursing personnel, medical service staff, company paramedics, fire department personnel, medical assistants, and students of medicine and dentistry. Their involvement can improve treatment of patients with cardiac arrest even before the EMS arrives [27,28]. The fact that approximately 11% of the German population is medically trained [29] increases the probability that a person trained in resuscitation is in the immediate proximity of a person with cardiac arrest. To involve and engage as many medical professionals as possible, we have developed a mobile phone–based app that connects the private mobile phone of the trained first aider with the alert system of the rescue directing center. As part of the intervention, first aiders are alerted by mobile phone and dispatched to resuscitate patients experiencing cardiac arrest nearby. Due to their closer proximity, first aiders could arrive on-site before the ambulance and start resuscitation [30].

Earlier Treatment by an Emergency Physician

In addition to first aid interventions, the project focuses on structuring professional rescue services using a variety of information and communication technology tools. To assure and to improve the quality of emergency care in districts covering large areas with a low population density, suitable strategies need to be developed guaranteeing continuous availability of both technical and individual resources.

Telemedicine in emergency medical care, such as a TEP system, can contribute to ensuring high-quality medical care in rural areas [31,32]. In emergency services with moving vehicles, however, the standard requirements for telemedicine are much higher than in areas where data transfer solely runs over local networks (eg, over a local area network or Wi-Fi) between physicians in the same field [33-35]. Even the technical aspect of data connection via mobile transfer media is challenging in rural areas. Equally challenging are the issues of new structures in work organization, employment law, liability law, and funding [36]. Previous pilot projects have been mainly oriented toward technical aspects but rarely have been translated into practice. There are, however, some exceptional projects where manufacturers of medical device technology and

telecommunication specialists have developed devices in cooperation with rescue service personnel, emergency physicians, and emergency departments. These devices have also been trialed in test operations to evaluate their effectiveness and safety in regular operations [37-40]. One example is the Aachen TEP system. This well-engineered concept, introduced in 2014, is composed of highly specialized training, selected medical device components, optimized transmission technology, and customized software modules [31,34,41]. Our Land|Rettung project is technically grounded in the Aachen TEP system, and we work closely together on technical realization and improvements (see Figure 2).

Figure 2. Tele-emergency physician station.

Interlinking of Statutory Health Insurance Physicians and Rescue Services

In Germany, prehospital emergency medical care is multilayered. Depending on the urgency of the medical problem, patients can contact 2 different systems: (1) the EMS and (2) statutory health insurance physicians [42-44]. While EMSs provide the care of patients with life-threatening or severe illnesses, statutory health insurance physicians take over the tasks of general practitioners outside regular hours by means of on-call medical services. Up to now, these 2 systems have operated independently of each other, as both are accessible through specifically installed telephone hotlines. While the EMS is easily accessible and is handling an increasing workload with a growing number of inadequate uses, statutory health insurance physicians are experiencing staffing problems and areas that are too large to cover [45]. In addition, emergency rooms are facing a growing burden of patients who are not hospitalized by a doctor, but who are seeking advice on their own initiative [46,47]. Overall, these 2 separate systems need to cooperate and should be interlinked [48] in order to achieve adequate patient control and optimal deployment of human resources.

Objective

Here we provide an overview of a rural EMS project in Germany, which is based on a multimethod and multiperspective longitudinal analysis.

Methods

A Multimethodological Approach From Different Perspectives

We will assess and evaluate the implementation and results of the project through a tripartite prospective and intervention study from (1) a medical, (2) an economic, and (3) a work and organizational perspective. First, as part of the medical evaluation, we will assess the influences of various project measures on the quality of care using multiple methods. For this, we will review the emergency services logs for general quality of monitoring and documentation, quality of analgesia and pain reduction, quality of diagnoses, and the rate of adverse events. We will gather indicators for tracer diagnoses on the quality of medical treatment and results. We are also planning an analysis of cases of stroke and acute coronary syndrome, regarding how often the tentative diagnosis in prehospital treatment matches with the diagnosis verified in hospital.

Second, in the economic evaluation we will include the number of call-outs, distribution between conventional and TEP call-outs, rate of calls for emergency physician reinforcements, actual response times, and overall call-out duration and engagement times for emergency physicians. In addition to the costs and time analyses, we will conduct an outcome analysis to evaluate the TEP system. Third, as part of the work and organizational analysis, we will analyze the necessary changes to work processes, workload, and satisfaction of all affected occupational groups; gather organizational, leadership, and cooperation structures; and assess regional effects, especially regarding cooperation between the occupational groups and the development of joint standards.

To assess and evaluate the project's results, each evaluation part consists of different procedures. All information relevant for data collection is available from the regularly kept logs for call-out documentation in rescue services (ie, emergency physician logs, TEP logs, and data from computer-aided dispatch), as well as data from hospitals providing follow-up care.

Medical Evaluation

The medical analysis will consist of 3 parts (see Table 1). The first part will focus on the documentation and treatment quality of the individual emergency cases. Second, we will assess how often the tentative preclinical diagnoses is concordant with that made by the hospital. Diagnostic capabilities are limited outside a hospital; for example, x-rays and laboratory tests cannot be conducted. For this reason, initial diagnoses made by the EMS remain tentative. As part of the project, we will examine how often the tentative diagnosis can be confirmed and how many false-negative or false-positive decisions are made. Third, we will gather and analyze important figures that characterize the general quality of treatment in rescue services.

Table 1. Medical analysis.

Subject of analysis	Criteria
Documentation and treatment quality of each emergency case	General monitoring quality
	Blood sugar measurements in cases of loss of consciousness
	Quality of analgesia or pain reduction
	Documentation quality of general medical history
	Specific documentation quality of allergies
	Specific documentation quality of previous medication
	Quality of diagnosis
Correctness of tentative diagnoses made by the emergency medical service	Patient was treated only by paramedics
	Patient was treated by paramedics and an emergency physician on-site
	Patient was treated by paramedics and a tele-emergency physician
General quality of treatment of the emergency medical service	Therapy-free interval for 6 selected tracer diagnoses (stroke, hypertensive emergency, acute coronary syndrome, asthma, exacerbated chronic obstructive pulmonary disease, and polytrauma)
	Bystander cardiopulmonary resuscitation rate
	Number of surviving patients who were discharged from hospital after resuscitation

Economic Evaluation

Similar to the medical analysis, the economic evaluation generally refers to data obtained from regularly kept logs for case documentation in rescue services, as well as from legally prescribed financial accounting or management accounting for rescue services. Accordingly, the economic evaluation will also consist of 3 areas of analysis (see Table 2). The first part will aim to calculate the total costs for each measure, divided into fixed and variable costs. We will collect data mainly from the EMS documents and contracts with external partners. Based on a break-even analysis, we will compare the total costs of the TEP concept versus standard care to find a cost-efficient solution for future implementation. This will further depend on the number of areas in which emergency care cannot be provided within the prescribed response time. The second part will analyze the influence of various project measures of central parameters of emergency rescue by means of pre-post comparison. After determination, we will compare the respective parameters separately with and without the TEP system being involved. As before, we will obtain data from regularly gathered call-out data for the rescue service. We will summarize and directly transfer the data before implementation of the project measures at regular intervals. The same applies to the data after implementation of the TEP system. We will check the EMS data for plausibility, calculate the necessary parameters, and compare the results specifically per group: pre-post, times of year, times of the day, areas, etc. The third part will focus on technical and temporal parameters of the first aider app. We will gather data from EMS logs and from app logs. We will focus on technical disruption of the TEP system and gather data from the TEP system logs.

Table 2. Economic analysis.

Subject of analysis	Criteria
Determination of costs (fixed and variable) for each measure	Investment costs
	Ongoing annual operating costs
Comparison of total costs of the tele-emergency physician concept and standard care	
Influence of various measures on the central parameter of emergency rescue	Response time
	Personnel engagement time during call-outs
	Transfer times
	Operational distances
	Total operating times
	Rate of subsequent calls for reinforcement of emergency physicians
Technical and temporal parameters of the first aider app and the tele-emergency physician system	Time between arrival of the mobile first aider and the rescue service
	Numbers of technical breakdowns of the tele-emergency physician system

In addition to the costs and time analyses, we will analyze patient outcomes based on the data resulting from the application of the project measures. Our main focus will be on the TEP system introduced at the start of the project. Based on the individual care pathways after a telemedically supported emergency treatment, we will compare the costs and the patients' individually perceived quality of life after the emergency incident versus standard care data. The main objective will be to determine whether telemedical emergency care has an effect on the individual and overall economic costs and whether it may lead to a life-related value for telemedically treated patients. We will gather the data for this evaluation from anonymized databases provided by the Eigenbetrieb Rettungsdienst Vorpommern-Greifswald.

Work and Organizational Analysis

The work and organizational evaluation will generally be based on a pre-post comparison and will differentiate 3 parts of the analyses (Table 3). In the first part, we will conduct expert panels at the beginning and at the end of the project to assess 4 clusters in 3 dimensions on a scale from 1 to 10 and importance on a scale from 1 to 10. We will hold the expert rounds for each of the 4 project pillars: (1) improvement in layperson rescue, (2) use of mobile first aiders, (3) the TEP system, and (4) cooperation between EMSs and statutory health insurance emergency care. In the second part, we will conduct a network analysis. Participants from the expert panel and other people nominated by them will anonymously enter their personal contacts and contacts to other organizations into a network matrix. Thus, we will be able to calculate network size, density, and centrality. The third part of the analysis will comprise a competence and transfer analysis based on surveys developed as part of knowledge transfer studies [49].

Design

This project is a multimethod and multiperspective longitudinal analysis and control group study. We will use a longitudinal approach not only to understand changes from implementing the 4-pillar concept but also, if needed, to intervene at an early stage. The control group design is essential, as insights into the transferability of the concept can only be gathered in this way. We will collect data across all 4 pillars: layperson resuscitation, mobile phone–based first aider alerts, the TEP system, and cooperation of emergency medicine providers. We will conduct pre-post comparisons of data before and after the introduction of the TEP system.

Table 3. Work and organizational analysis.

Subject of analysis	Criteria
Evaluating clusters made of (1) service providers, (2) suppliers, (3) training measures, and (4) new technologies in 3 dimensions of competitiveness (ie, regional, intraregional, international) and importance	Basic factors: • Infrastructure (building, accessibility, network expansion) • Resources (personnel, material, technology) Stakeholders: • Suppliers and supporters, cooperation and competition between organizations involved Area of care provision: • Care need (eg, deviations in the type and frequency of emergencies) • Transfer to other areas of care provision (intraregional cooperation and support)
Regional networks	Centrality (amount of connected links) Density (relationship of maximum possible links to actually available links)
Competence and transfer analysis Transfer of knowledge and competencies for social networks (ie, explicit, implicit, individual or joint use of knowledge) Type of knowledge and competence transfer (ie, types, sources, instruments)	Accuracy Availability Transparency Accessibility Comprehensibility Up-to-datedness Needs orientation Competence orientation Credibility Use Motivation to share knowledge Subjective perception of the strength of change

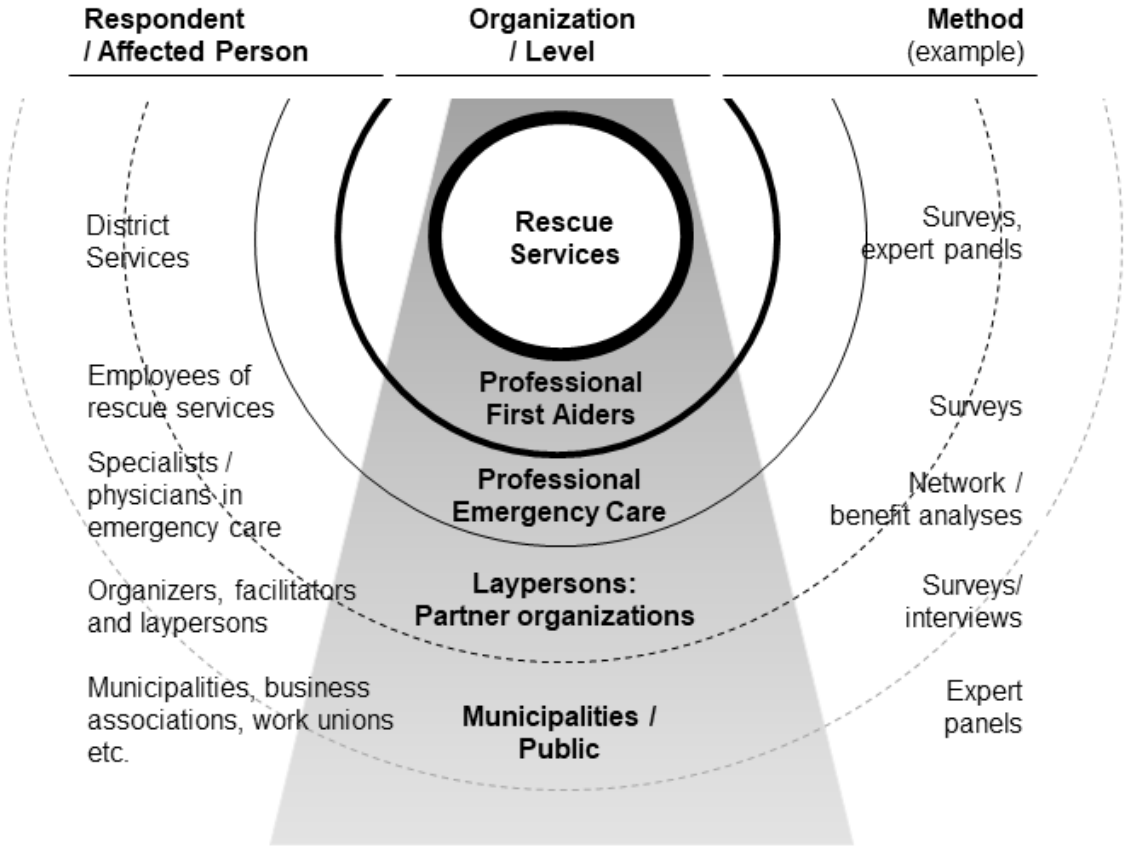
Participants

In the district of Vorpommern-Greifswald, the EMS is alerted to over 40,000 medical emergencies annually (as of 2017), with more than 15,000 alerts going to emergency physicians. Ambulances equipped with technology for the TEP system cover approximately 6500 of those cases annually. To achieve a sufficiently high power for subgroup analyses, we will consider emergency cases occurring over a period of 24 months (October 2017 to October 2019) prospectively within the evaluation process. With regard to general quality parameters for medical care and documentation, we will consider all cases handled by the TEP within the evaluation process as our intervention group. In addition to this overall analysis of TEP cases, we will create subgroups in accordance with the research question of interest. Before project enrollment, we conducted power analyses individually for each subgroup in order to estimate the sample size (ie, the number of patients needed).

As part of the control group, we will analyze emergency cases without telemedical support in a retrospective as well as a prospective design. We will also compare these cases with emergencies handled by the TEP in terms of parameters such as age, sex, and an injury severity score (National Advisory Committee for Aeronautics [NACA] score).

Depending on the organizational level, the work and organizational analysis will focus on different groups being affected by the project measures (see Figure 3). In the first instance, we will consider all employees of the emergency services except for professional first aiders in the analyses. As part of the network and cluster analysis, we will also consider representatives of partner organizations and municipalities.

Figure 3. Organizational levels, affected persons, and evaluation methods.



Statistical Analysis

We will apply statistical analysis in the medical evaluation to determine differences between the intervention and control groups and to measure the impact of potential influential factors. We will apply multiple regression models to describe and to assess interrelations of cluster strength (eg, emergency systems of 2 regions), network density, and centrality of people and organizations involved in the emergency system, but also to estimate the levels of intensity and time needed to transfer knowledge and competencies between individuals and teams. Overall, this method will help to identify relevant work and organizational factors contributing to the project's medical and economic success. As regression analyses confirm the expected relationships, we will conduct mutual discriminant analyses to examine the direction of the relationships. More specifically, mutual discriminant analyses will verify whether the coefficient of determination (r^2) is higher when medical or economic parameters are used to predict cluster and network data or levels of transfers, or whether, conversely, work and organizational factors predict economic or medical figures [50,51]. Furthermore, this analysis can be used to assess whether work and organizational factors account for medical and economic performance or whether high medical and economic performance determines the work and organizational factors.

Results

The project was started in 2017 and enrollment will be completed in 2020. We completed the preanalysis phase in September 2018. Data analysis is underway, and we expect to submit the first results for publication in 2020.

Discussion

Relevance

This multimethod and multiperspective longitudinal analysis uses an innovative approach that aims to realign emergency medicine in rural areas and to enhance the quality of medical emergency care in the long term. In particular, its consideration and involvement of all parties engaged in emergency care underlines the project's uniqueness. We expect the implementation of Land|Rettung to lead to a measurable increase in medical laypersons' individual skills and motivation to provide resuscitation, with an increasing rate of bystander resuscitation. Experiences from the layperson resuscitation campaign "Ein Leben retten" (save a life) [24], as well as initial training courses in Greifswald, have already indicated that the number of emergencies in which laypersons provided first aid significantly increased after they participated in the relevant courses [52]. Furthermore, the project is intended to decrease the therapy-free interval through the arrival of first aiders at an emergency before the rescue services. In some urban areas of

Germany, mobile phone apps that alert specially trained first aiders are already being used. Results show that, in up to 57% of all alerts, nearby professional first aiders are able to provide assistance [53]. With regard to our third objective, the TEP system has already shown a higher availability and quality of care as an integral part of the EMS in the city of Aachen, Germany [38,41]. Whereas Aachen offers an excellent infrastructure, with our project we intend to evaluate this concept in a rural area. We expect a closer interrelation between statutory health insurance physicians and the EMS to lead to better coordination of rescue and on-call services.

While the medical evaluation of treatment quality (ie, medical outcome) and the economic evaluation (ie, profitability calculation) will reveal whether transferring the concept is medically and economically feasible, the work and organizational evaluation will assess the transferability of the results. Thus, these 3 aspects of evaluation directly complement one another: while the medical and economic evaluation will check whether the measures implemented make medical and economic sense, the work and organizational evaluation will ensure their sustainability and universal adaptability. The establishment of an evaluation standard would be beneficial in 2 ways: (1) preclinical emergency medicine in the district of Vorpommern-Greifswald will be regularly evaluated with a reasonable effort, and (2) a standard would facilitate the introduction of this new treatment concept in other rural districts and ensure its effectiveness and sustainability.

Limitations

The project faces some challenges, such as ethical restrictions to conducting such research using digital resources without compromising the ethical or legal credibility and protections for human participants. Another constraint lies in the technical aspect of data connection via mobile transfer media and its limitations, especially in rural areas. With ongoing government investment programs and the interest of the industry, coverage by the Global System for Mobile Communications standard will increase over the next years. Especially in the initial stage of the project and in sparsely populated areas in particular, we recognized that some mobile phone app alerts were not being transmitted, even though specially trained first aiders were within the appl's radius. The provider's system data will provide further information on the app's functionality in different areas of Mecklenburg-Vorpommern. Overall, not all ambulance vehicles could be equipped with the TEP system. Although these systems are proportionally distributed, this factor may restrict the final number of our intervention group.

Conclusions

We are confident that this project presents an economically sensible and methodically innovative approach that will review the effects of project measures in terms of development of regional treatment networks, and of knowledge and experience transfer between occupational groups and decision makers. All in all, improved cooperation, the formation of a network, and better emergency care should ensure greater treatment provision reliability and increase the region's appeal. Due to the structural weakness of the region and the high importance of tourism with seasonal peaks, the implementation and evaluation of the concept are important not only for the local population, but also for the many tourists.

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Conflicts of Interest

None declared.

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Abbreviations

CPR: cardiopulmonary resuscitation
EMS: emergency medical service
NACA: National Advisory Committee for Aeronautics
TEP: tele-emergency physician

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Protocol

Preferences for Sun Protection With a Self-Monitoring App: Protocol of a Discrete Choice Experiment Study

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Abstract

Background: The incidence of sun-exposure-related skin conditions, such as melanoma, is a gradually increasing and largely preventable public health problem. Simultaneously, the availability of mobile apps that enable the self-monitoring of health behavior and outcomes is ever increasing. Inevitably, recent years have seen an emerging volume of electronic patient-generated health data (PGHD), as well as their targeted application across primary prevention areas, including sun protection and skin health. Despite their preventive potential, the actual impact of these apps relies on the engagement of health care consumers, who are primarily responsible for recording, sharing, and using their PGHD. Exploring preferences is a key step toward facilitating consumer engagement and ultimately realizing their potential.

Objective: This paper describes an ongoing research project that aims to elicit the preferences of health care consumers for sun protection via app-based self-monitoring.

Methods: A discrete choice experiment (DCE) will be conducted to explore how healthy consumers choose between two alternative preventive self-monitoring apps. DCE development and attribute selection were built on extensive qualitative work, consisting of the secondary use of a previously conducted scoping review, a rapid review of reviews, 13 expert interviews, and 12 health care consumer interviews, the results of which are reported in this paper. Following D-optimality criteria, a fractional factorial survey design was generated. The final DCE will be administered in the waiting room of a travel clinic, targeting a sample of 200 participants. Choice data will be analyzed with conditional logit and multinomial logit models, accounting for individual participant characteristics.

Results: An ethics approval was waived by the Ethics Committee Zurich. The study started in September 2019 and estimated data collection and completion is set for January 2020. Five two-level attributes have been selected for inclusion in the DCE, addressing (1) data generation methods, (2) privacy control, (3) data sharing with general practitioner, (4) reminder timing, and (5) costs. Data synthesis, analysis, and reporting are planned for January and February 2020. Results are expected to be submitted for publication by February 2020.

Conclusions: Our results will target technology developers, health care providers, and policy makers, potentially offering some guidance on how to design or use sun-protection-focused self-monitoring apps in ways that are responsive to consumer preferences. Preferences are ultimately linked to engagement and motivation, which are key elements for the uptake and success of digital health. Our findings will inform the design of person-centered apps, while also inspiring future preference-eliciting research in the field of emerging and complex eHealth services.

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KEYWORDS

preventive medicine; mobile health; health informatics; health economics; patient preferences; discrete choice experiment

Introduction

Background

As the mHealth market rapidly expands, digitally self-monitoring our health and well-being is easier than ever before. Inevitably, the volume of available electronic patient-generated health data (PGHD) grows exponentially. Defined as nonclinical health information, generated and controlled by consumers, patients, and their designees, PGHD are widely used across public health domains to facilitate primary prevention and strengthen health promotion [1-4]. Mobile phones and wearables come as fully functional measurement devices, accompanied by an abundance of apps that collect PGHD and provide prevention-relevant feedback [2,5]. Many of those apps are capable of capturing physical and contextual signals, as well as communicating risks and supporting behavior change [6]. With such an unprecedented number of self-monitoring apps comes an equally unprecedented need to understand how these should be designed and utilized for successful primary prevention.

Mobile Self-Monitoring for Sun Protection

Serious skin conditions related to sun exposure, such as melanoma, are on the rise. Melanoma—one form of skin cancer—is a potentially fatal malignancy of the skin arising from atypical melanocytes, primarily affecting young and middle-aged population groups [7,8]. While disease onset depends on multiple factors (eg, family history and genetics), exposure to UV light (eg, sun and indoor tanning) is considered a primary risk factor [7]. The global incidence of melanoma indicates upward trends, with most rapid increases recorded in western and Caucasian populations [7]. While the epidemiological trends of melanoma indicate a very present and most likely growing public health problem, targeted behavioral change in relation to sun protection can mitigate much of its burden [7]. With increasing popularity of mobile self-monitoring across prevention areas, including weight loss, physical activity, nutrition, smoking, alcohol consumption, and mental health, the use of PGHD is gradually gaining popularity in sun protection [1-4,9-13]. Mobile apps are designed to monitor behavior (eg, sunbathing intensity, use of sunscreen, and use of protective clothing), as well as environmental exposure (eg, UV-light intensity), and to combine that with behavior change techniques, such as tailored messages, sensitive reminders, motivational feedback, gamification, and education [11-13]. Acknowledging the need for person-sensitive and personalized primary prevention, the emergence of mobile self-monitoring is a unique opportunity and resource in reducing sun-related skin conditions, such as melanoma and other skin cancers.

An Emphasis on Health Care Consumer Preferences

A prerequisite of digital and mobile self-monitoring is the motivation of consumers to engage with technology. This is driven by individual, technical, social, and environmental factors, such as personal motivation, appropriate use, long-term engagement, and satisfaction [14,15]. While existing theories identify overall drivers of motivations of technology engagement, consumer preferences regarding concrete characteristics of technology have been less explored [16,17]. When it comes to one's health and well-being, as well as the prevention of malaise (ie, discomfort), focusing on health care consumer preferences is a central component of person-centered care. Person-centeredness requires a full focus on the needs, values, and desires of individuals, as well as their environments and social contexts [18,19]. Evidence suggests that person-centeredness can enhance satisfaction with, and acceptance of, health services while ensuring engagement and adherence [20]. Understanding preferences and their predictors is key to developing acceptable self-monitoring technologies.

This study outlines the methodology and preparatory qualitative results of a discrete choice experiment (DCE) that aims to elicit consumer preferences for facilitating sun protection with self-monitoring apps. Our findings target health app providers, practitioners, citizens, and policy makers, aiming to guide a more preference-sensitive development and use of self-monitoring apps.

Aims

Our study aims to assess the relative importance of modifiable elements of self-monitoring apps that focus on sun protection. We have identified the following study objectives:

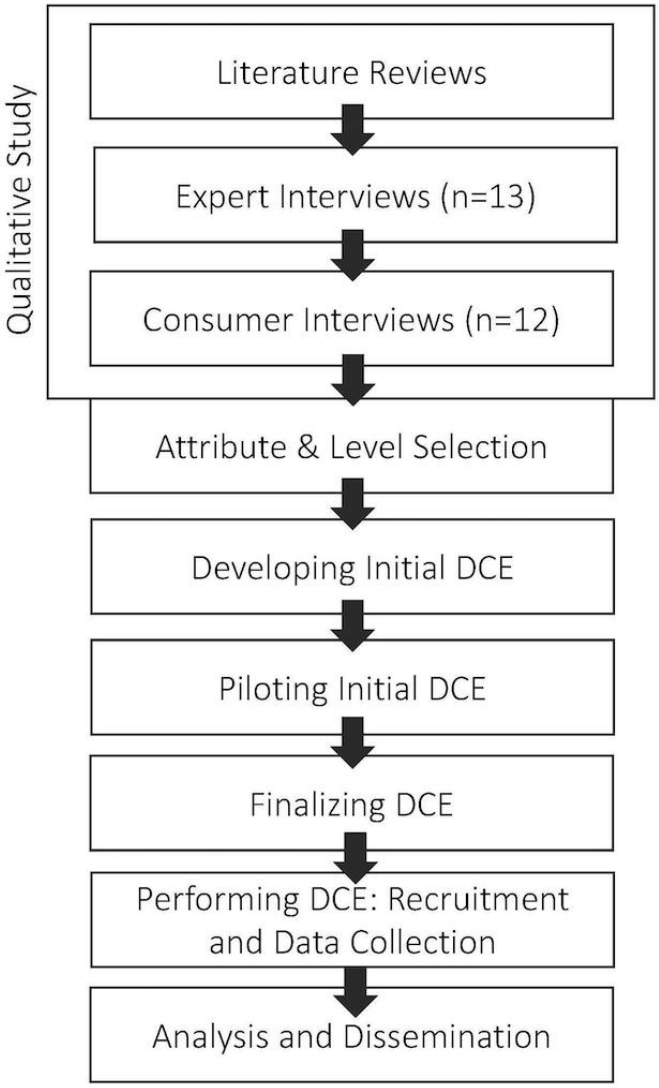
1. Identify and explore which elements of self-monitoring apps are deemed important by health care experts and health care consumers (qualitative results).
2. Among those preidentified elements, elicit the relative importance of health care consumer preferences (DCE results).
3. Determine whether those preferences vary across participant characteristics, including age, gender, education, health app attitudes, and perceived health (DCE results).

Methods

Overview of Approach

A DCE is a robust survey-based methodology that enables the elicitation of consumer preferences [21]. Rooted in psychometrics and based on strong theoretical grounds, DCEs have been widely used in economic research and are rapidly gaining popularity within health care [21-23]. The technique's core assumption suggests that any good or service consists of distinguishable characteristics, also known as attributes, from which consumers derive utility [21,24]. Each attribute can take alternative forms, often described as levels. The derived utility varies with changing levels of these attributes. Individual choices among alternatives of these characteristics are assumed to indicate a person's preferences, underlying values, and perceived service utility [21,24]. Developing a DCE and selecting appropriate attributes requires a range of preparatory qualitative steps [25]. We conducted literature reviews and interviews with health care consumers and experts, the results of which are detailed in this study [22]. Figure 1 provides an overview of the study's methodological steps.

Figure 1. Overview of the study's methodology. DCE: discrete choice experiment.



Rationale for Using a Discrete Choice Experiment

Both mobile self-monitoring and primary prevention rely on engaged health care consumers. Understanding their preferences is, therefore, key to the successful development and use of self-monitoring technology for preventive purposes. DCEs enable the identification of those relative preferences by asking consumers to choose between at least two versions (ie, scenarios) of a good or service, each consisting of different bundles of attribute levels [21,26]. Respondents are requested to make repeated choices, which provides enough information to statistically elicit those elements that are perceived to yield the highest utility [26].

In having to choose one scenario over another, thus, being requested to make trade-off choices, DCEs provide strong indices of preferences and are gradually gaining popularity in eHealth research [21]. For example, Cranen and colleagues used the methodology to elicit preferences of chronically ill patients regarding telerehabilitation, exploring attributes such as physician communication modes, feedback provision, and the use of digital monitoring tools [27]. Similarly, Kaambwa and colleagues applied a DCE to investigate the telehealth preferences of the elderly, identifying an inclination toward comprehensive and inexpensive eHealth services that target those who face constrained access to traditional care [28]. Using DCEs will enable us to identify which attributes of prevention-focused self-monitoring apps are considered important, as well as how consumer preferences are distributed across them [26]. DCEs require a thorough and well-conducted qualitative basis, which enables the selection of correct and appropriate attributes. The qualitative work and its results are presented in the following paragraphs.

Discrete Choice Experiment Scenario

Each DCE is framed around a hypothetical scenario that should be relevant to the targeted topic and specific enough to allow participants to make their choices accurately. For this DCE, each participant will be asked to imagine a mobile prevention app that targets sun protection and skin health by collecting information on the duration and intensity of sun exposure, followed by educational reminders on when and how to protect.

Discrete Choice Experiment Development: Methods of Qualitative Preparatory Work

Prior to developing the DCE, we completed a thorough three-step qualitative study, using existing literature and

stakeholder input to identify and select key attributes. We (1) used the output of a previous scoping review, (2) conducted a rapid review of systematic reviews on the use of electronic PGHD for primary prevention, (3) conducted 13 semistructured expert interviews, and (4) conducted 12 health care consumer interviews [29]. The literature reviews and expert interviews were merely meant to provide a preliminary basis of potential attributes and, therefore, had a broader scope on electronic self-monitoring for primary prevention. The health care consumer interviews were framed around sun protection and skin health, allowing us to identify attributes that are context specific.

Literature Reviews

Both reviews aimed at mapping current evidence on the use of electronic PGHD for prevention and health promotion, as well as associated barriers and facilitators. The previously conducted scoping review entailed searches in seven databases, complemented by multiple additional and grey literature searches, yielding 183 eligible primary studies [30]. The rapid review was conducted in two databases—PubMed and the Cochrane Database of Systematic Reviews—and was limited to systematic reviews, yielding 13 eligible studies. Data extraction was based on predefined templates and analysis was thematic, with raw data being thematically clustered and mapped. Multimedia Appendix 1 provides the rapid review's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, inclusion criteria, information on data extraction, and a list of all included studies [31].

Expert Interviews

The 13 semistructured expert interviews were conducted between March 12 and April 4, 2019, either face-to-face or via Skype. They aimed to expand on and validate the list of attributes identified in the literature. Our expert selection criterion entailed that after completion of the interviews, each of the following areas should be the expertise of at least one interviewee: eHealth research, self-monitoring, digital prevention, data science, eHealth and data ethics, primary prevention, clinical practice, and citizen science. The number of interviews was not prespecified but continued until saturation was reached. Interviews were guided by semistructured questions and a list of fixed topics that had to be addressed. Informed by the literature reviews, those topics included the following: (1) barriers and facilitators of digital self-monitoring for primary prevention, (2) the technical aspects of these barriers and facilitators, and (3) the broader components of self-monitoring-based primary prevention interventions, such as the use of behavior change techniques. In addition, experts were provided with a list of 22 attributes identified in the reviews and asked to comment on them, mention potentially missing ones, and expand on those perceived as highly important. Attributes were categorized according to the three above-mentioned (1-3) or newly emerging themes. All experts provided verbal consent for researchers to audiotape, transcribe, and analyze the interviews. Recordings were deleted after transcription, without linkages to any personal information.

Health Care Consumer Interviews

The 12 semistructured consumer interviews were conducted in Zurich, Switzerland, between May 15 and May 24, 2019. They aimed to capture which attributes of self-monitoring apps for sun protection are perceived as most relevant by health care consumers. Eligibility required a minimum age of 18 years and no chronic conditions. Participants were recruited at the University of Zurich Travel Clinic and selected purposively to ensure age and gender balance. Interviews were guided by semistructured questions and a list of fixed topics that had to be addressed, including (1) barriers and facilitators of self-monitoring for sun protection and skin health promotion and (2) all attributes that were identified in the reviews and expert interviews. In the interview's first part, participants were asked to discuss what would encourage or discourage them to electronically collect their health data for sun protection purposes. The second part consisted of a Likert-scale rating of a list of attributes that were identified by the literature reviews and expert interviews. Each interview required approximately 20 minutes and all participants provided prior written informed consent, including a confirmation of all eligibility criteria. All contact and personal identification information required for recruitment and invitation was deleted immediately after completion of the interviews and replaced by unique ID numbers. Multimedia Appendix 2 provides the interview schedule, participant demographics (eg, age and sex), and selected interview quotes.

Analysis of Expert and Health Care Consumer Interviews

All interviews were transcribed and analyzed with MAXQDA, version 18.2.0 (VERBI Software) [32]. Our analysis followed a hybrid approach of inductive and deductive coding [33]. Initial deductive coding was based on the above-mentioned fixed topics that guided the interviews, followed by an inductive, data-driven generation of new codes and their connection to subthemes and overarching themes. To ensure that our codes were understandable and complete, a random sample of three interviews was provided to an external coder who was instructed to use our code system and analyze the interviews independently. The coded interviews were compared and inconsistencies discussed and resolved. This led to a wording change for two codes, as well as the merging of two codes that were not distinguishable.

Discrete Choice Experiment Development: Results of Qualitative Preparatory Work

Combined, the literature reviews and 13 expert interviews yielded a list of attributes that were categorized into six groups, including (1) *effort and support*, (2) *trust and control*, (3) *data sharing*, (4) *technology and design*, (5) *prevention-related content*, and (6) *incentives and disincentives*. A more detailed account of these categories is provided in Multimedia Appendix 3.

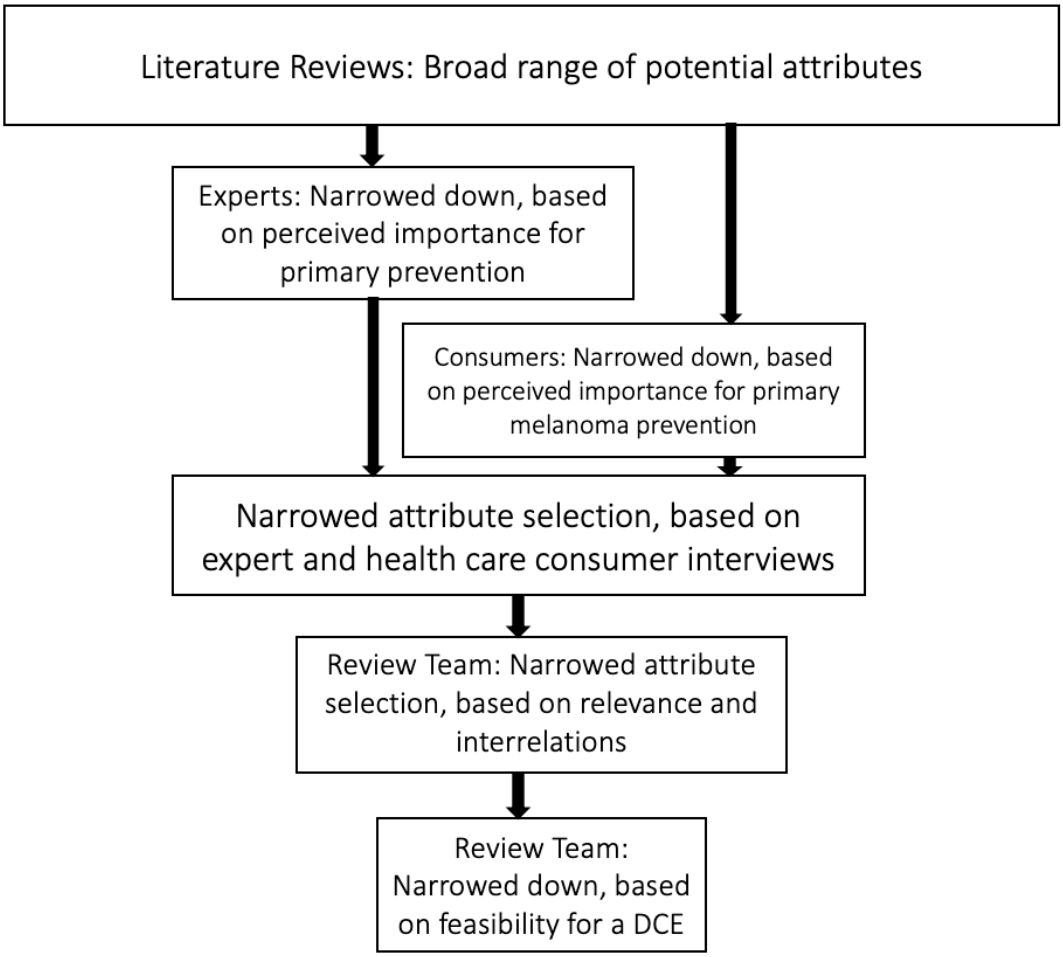
The 12 health care consumer interviews revealed six overall attributes that were perceived as important to the use of self-monitoring apps for sun protection; these included (1) *costs*, (2) *privacy and trust*, (3) *added value*, (4) *time and effort*, (5)

user-friendliness, and (6) *incentives*. A more detailed account is provided in Multimedia Appendix 3.

Selection of Attributes and Levels

The final list of all possible attributes, resulting from a synthesis of review and interview findings, was reviewed by the research team and one consulted health care consumer. The selection was based on three overall criteria, as outlined by Bridges and colleagues, including (1) research question relevance, (2) decision context relevance, and (3) interrelations between attributes. The group's choice was additionally guided by the importance of attributes, primarily by health care consumers, as well as by whether each attribute was realistic and could be defined for a DCE. We considered a realistic attribute to be compliant with current legal and policy regulations as well as with existing technology and primary prevention services. Consensus was reached on the following five attributes: (1) method of data generation, (2) privacy control, (3) data sharing with the general practitioner, (4) reminder timing, and (5) costs. The process and flow of attribute selection are provided in Figure 2.

Figure 2. Attribute selection process. DCE: discrete choice experiment.



We continued with assigning each attribute to realistic, relatable, and understandable levels. As suggested by Bridges and colleagues, we avoided ambiguous wording and tried to keep the number of levels to a minimum [22]. All attributes, levels, and descriptions were formulated in German and by native speakers. The wording has been reviewed by a native German speaker with a nonhealth background, ensuring ease of understanding and clarity. All included attributes and assigned levels are listed in Table 1.

We will additionally collect information on age, gender, highest attained education, attitudes toward health apps, and perceived health, as all of those factors have been previously associated with eHealth usage [34-37]. Perceived health will be measured with a widely used single-item measure, asking participants to rate their current general health on a 5-point scale from *very good* to *poor* [38,39]. Attitude will be captured with one reworded item on perceived usefulness, which was derived from previous research and asks participants to indicate their agreement on whether health apps are useful in promoting their health; they will rate their agreement on a scale from *totally agree* to *totally disagree* [40,41]. We chose single-item questions to keep that part of the questionnaire short and simple, considering that the actual DCE will require higher cognitive and time resources.

Table 1. Identified attributes, attribute levels, and prior assumptions.

Attributes	Descriptions	Attribute levels	Prior assumptions
1. Data generation method	How would you like your data to be collected?	(a) no manual entry (b) manual entry once a day	It is expected that most will prefer no manual data entry, as that is linked to lower effort. However, those who are more privacy-concerned might tend toward manual data entry.
2. Privacy control	If your data are being shared with third-party commercial entities, how would you like to control when and with whom your data are shared?	(a) I will only receive information on potential data sharing with third parties once and will be asked to provide informed consent once (b) I will be informed and provide consent whenever my data are provided to third parties	A clear a priori expectation is difficult to be formulated. Those who are concerned about constant push messages will likely prefer (a), and those who are more privacy-concerned will most likely choose (b).
3. Data sharing with general practitioner	Would you like to share the data collected with your general practitioner, to be discussed at your next visit?	(a) yes (b) no	A clear a priori expectation is difficult to formulate. We expect that those who have a trusting general practitioner relationship and lower perceived health will prefer (a).
4. Reminder timing	How would you prefer the times and frequency of your reminders to be set?	(a) I set the time and frequency of my reminders myself (b) the app sets the times and frequency of reminders automatically, based on my data	It is expected that most will prefer setting the time and frequency of reminders themselves, to avoid nuisance.
5. Costs	Are there any costs associated with downloading the app and, if yes, how high are these?	(a) free (b) one-time payment of 3 Swiss Francs	It is expected that most will prefer a free app. However, the cost might be accepted if combined with other desired attributes, such as low effort and high privacy.

Experimental Design and Choice Sets Selection

The combination of included attributes and levels, as shown in Table 1, results in a full factorial design of 2^5=32 possible distinct choice sets [42]. Limited time and cognitive capacities deem such a large survey design unrealistic. In our context, the time factor is particularly constraining, as questionnaires will have to be answered in the waiting room, often during short preconsultation windows. Although full factorial designs hold desirable features, such as perfect orthogonality and balance, it is common practice to use only subsets of those, known as fractional factorial designs. Thus, we developed a fractional factorial design, following D-optimality criteria and using R, version 3.5.3 (The R Foundation), the open-source software for statistical computing [43]. The 32 choice sets were reduced to a fractional factorial sample of eight. The quality of responses will be assessed through the inclusion of one additional choice set that will be identical to a previous one. In line with the axiom of completeness, participants that provide consistent answers are expected to choose the same alternative twice [22,44]. We will calculate percentages of inconsistent responses and assess their distribution across individual participant characteristics, as excluding participants is not recommended [22,45]. The final questionnaire version will include eight original and one repeated-choice set, yielding a total of nine choice sets.

Discrete Choice Experiment Piloting and Validity

The survey was piloted face-to-face with 8 participants recruited from the University of Zurich Travel Clinic, ensuring understandability and feasibility. Participants provided written informed consent and received written detailed information on the study's purpose, the research question, and all attributes. Participants were asked to complete the questionnaire in a think-aloud manner. The DCE's face validity was tested through a discussion on the survey's understandability and relevance, as well as on perceived ease of answering. Participants were asked to provide input on the survey's wording, content, and design, including the provided background material, pictures, pictographs, and choice of colors. Particular attention was given to the perceived relevance, formulation, and understandability of the sun protection scenario. Time to completion was measured to ensure that the survey is feasible within a given time frame. We additionally assessed whether overall results are in line with our hypotheses (see Table 1) [46]. The pilot was followed by subsequent DCE adjustments, ensuring that the final questionnaire is easy to comprehend and complete.

Participant Sampling, Recruitment, and Survey Administration

Estimating an adequate DCE sample size is lacking scientific consensus and remains a largely complex decision. Sample size decisions ultimately depend on multiple factors, such as task complexity, available resources, the sample's composition, and the target statistical precision of findings [22,47,48]. Although parametric approaches have been proposed, when it comes to identifying minimum sample sizes for specific hypotheses testing, they are considered unsuitable [48-50]. That leaves many researchers to use rule-of-thumb-based estimations [50]. Examples of those range from an overall sample of 100-300 participants to a minimum of 20 participants per choice set [47,50]. Carefully considering available time and financial resources, we utilized the rule of thumb proposed by Johnson and Orme, which depends on the number of choice tasks, alternatives, and analysis cells [51,52]. Aiming for a large enough sample size to identify the main effects and interactions, we will target a sample of 200 participants.

Participants will be recruited in the waiting room of the University of Zurich walk-in Travel Clinic. The clinic constitutes a hub for pretravel preventive consultation, as well as general preventive services, including vaccinations. The approximately 20,000 annual consultations render the travel clinic an ideal recruitment site. During recruitment days, everyone entering the clinic will be informed about the possibility to participate. Interested volunteers will be shortly briefed by a team member on the study's topic, purpose, and methodology; all this information will be additionally provided in written form. The completion of a DCE often poses high cognitive demands, for which the first pages will solely serve the purpose of preparing participants to answer the questionnaire. These first pages include information on (1) the study aims, (2) the study topic and key concepts, (3) detailed descriptions of each attribute, complemented by pictographs, and (4) instructions on how a DCE is filled out. Participants will have to confirm that all eligibility criteria are fulfilled, including a minimum age of 18 years, no chronic conditions, and mobile phone ownership. As the study does not include a follow-up session or any identifiable personal information, a signed participant informed consent form is not required. The survey will be administered in paper form and completed in a quiet room within the clinic. During recruitment and survey administration, a member of the staff will be present to answer questions and resolve uncertainties. We expect a survey completion time of about 10-15 minutes.

Analysis Plan

The DCE's main end points are the individual preferences of our participants, defined via the chosen attributes and their levels. Those will be assessed using a conditional logit model. This allows for the estimation of the relative importance of each attribute over the remaining ones, using the retrieved mean preference weights, as given by model coefficients [53]. To achieve this, our analysis will assess changes in weights within attributes—when changing from level (a) to level (b)—and the relative sizes of those across attributes [53]. The conditional logit model treats our findings as a function of the choice alternatives. It was developed by McFadden in 1973 and has been proven to be in accordance with the random utility theory, dividing a respondent's utility into a systematic and a random element [53,54]. We will use the R package *support.CEs* to convert our dataset to a form that is suitable for analysis [55].

We will additionally explore our data with mixed multinomial logit (MMNL) models, treating our findings as a function of choice alternatives and individual participant characteristics. Expecting some preference heterogeneity, we chose an MMNL model over a multinomial logit model, as the addition of the error term can adjust for unobserved heterogeneity and adds to the generalization of results [51]. In contrast to conditional logit modeling, mixed logit models provide preference-weight estimates and standard deviations of those, based on the assumption of an underlying distribution of preference weights and, thus, capturing preference heterogeneity among participants [53].

We will additionally assess the amount of missing data. If the percentage is considerable, we will use multiple imputation using chained equations, using the R package *mice*, assessing the impact of missingness on our findings. Goodness of fit will be assessed by looking at the distribution of the residuals and by calculating McFadden's pseudo R-squared [53]. Exploring variation, our analysis will test several individual characteristics for inclusion in our models, including age, gender, education, health app attitudes, and perceived health.

Results

An ethics approval was requested by the Ethics Committee Zurich and was waived since this study does not fall under the Swiss human research law, which only applies to clinical studies that involve a certain level of risk, as well as the collection of sensitive health data. The study began in September 2019, and estimated data collection completion is set for January 2020. Data synthesis, analysis, and reporting are planned for January and February 2020. Results are expected to be submitted for publication by February 2020.

Discussion

To the best of our knowledge, this is the first DCE that will explore health care consumer preferences for sun protection with self-monitoring apps. Our results will target technology developers, health care providers, and policy makers, potentially offering some guidance on how to design or use self-monitoring apps in ways that are responsive to consumer preferences and, thus, likely to maximize their engagement. Following good practice, our methodology is based on extensive and carefully designed qualitative work, ensuring that all included attributes are relevant and relatable. Nonetheless, the inclusion of all potentially relevant attributes is practically impossible in a DCE, as its feasibility depends on the required cognitive workload, as imposed by the number and nature of selected attributes. These should ideally be practical and limited to the most essential ones. This requires a careful and reasoned reduction process to allow for a small and feasible number of included attributes. Inevitably, this process includes trade-offs and the exclusion of attributes that might be relevant for a considerable proportion of the target population.

While DCEs constitute a robust and well-accepted approach for preference exploration, their focus on a limited number of variables inherently limits their capacity to capture broader factors that influence preferences toward sun-protection-focused self-monitoring apps. To fully understand the topic, our findings need to be followed up by qualitative and mixed-method research that will focus on understanding the individual and contextual factors contributing to certain preferences. Finally, as data collection will occur at the University of Zurich Travel Clinic and is subject to certain participant inclusion criteria, the data may not be fully generalizable to the entire Swiss or European population.

Despite these limitations, the attributes we have identified cover a considerable range of self-monitoring app characteristics, which are modifiable and, thus, adjustable to health care consumer preferences. Data collection effort, privacy, the flow of information, the sensitivity of push messages, and costs are all topics that are well-discussed in the literature and perceived

as key by health care consumers and experts, which signals their potential to enhance the impact of self-monitoring apps. Preferences are ultimately linked to engagement and motivation, which are key elements for the uptake and success of any digital health approach. Ultimately, our work and findings will inform the design of person-centered self-monitoring apps for sun protection, while also inspiring future preference-eliciting research in the field of emerging and complex eHealth services.

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Authors' Contributions

VN contributed to the conceptualization of the study and wrote and edited the manuscript. MM contributed to the conceptualization of the study, supervised the entire process, and edited the manuscript. MAP contributed to the conceptualization of the study, supervised the entire process, and edited the manuscript. The first author’s salary is funded by the Béatrice Ederer-Weber Fellowship.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Rapid review: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, inclusion criteria, information on data extraction, and list of included studies.
[DOCX File , 42 KB - resprot_v9i2e16087_app1.docx]

Multimedia Appendix 2
Health care consumer interviews: interview schedule, participant demographics, and sample quotes.
[DOCX File , 20 KB - resprot_v9i2e16087_app2.docx]

Multimedia Appendix 3
Attribute categories resulting from qualitative work.
[DOCX File , 14 KB - resprot_v9i2e16087_app3.docx]

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Abbreviations

DCE: discrete choice experiment
MMNL: mixed multinomial logit
PGHD: patient-generated health data
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Original Paper

Nonclinical Sexual Health Support for HIV, Viral Hepatitis, and Other Sexually Transmitted Infections in Gay, Bisexual, and Other Men Who Have Sex With Men: Protocol for a European Community Health Worker Online Survey (ECHOES)

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Abstract

Background: The term "community health worker" (CHW) can apply to a wide range of individuals providing health services and support for diverse populations. Very little is known about the role of CHWs in Europe working in nonclinical settings who promote sexual health and prevent HIV and other sexually transmitted infections (STIs) among gay, bisexual, and other men who have sex with men (MSM).

Objective: This paper describes the development and piloting of the first European Community Health Worker Online Survey (ECHOES) as part of the broader European Union-funded ESTICOM (European Surveys and Trainings to Improve MSM Community Health) project. The questionnaire aimed to assess the knowledge, attitudes, and practices of CHWs providing sexual health services to gay, bisexual, and other MSM in European settings.

Methods: ECHOES comprises three superordinate domains divided into 10 subsections with 175 items (routed) based on a scoping exercise and literature review, online prepiloting, and Europe-wide consultation. Additional piloting and cognitive debriefing interviews with stakeholders were conducted to identify comprehension issues and improve the clarity, intelligibility, accessibility, and acceptability of the survey. Psychometric properties, including internal consistency of the standardized scales used as part of the survey were examined. The final survey was available to 33 countries in 16 languages.

Results: Recruitment closed on January 31, 2018. Data from 1035 CHWs were available for analysis after application of the exclusion criteria. The findings of the ECHOES survey and the wider ESTICOM project, are now available from the ESTICOM website and/or by contacting the first author.

Conclusions: The findings of this survey will help characterize, for the first time, the diverse role of CHWs who provide sexual health services to gay, bisexual, and other MSM in Europe. Importantly, the data will be used to inform the content and design of a dedicated training program for CHWs as part of the larger ESTICOM project and provide recommendations for MSM-specific strategies to improve sexual health in general and to reduce the incidence and prevalence of HIV, viral hepatitis, and other STIs in particular.

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KEYWORDS

community health worker; ECHOES; Europe; MSM; gay men; HIV; hepatitis; sexual health; sexually transmitted infections; peer support

Introduction

Individuals who work in community-based settings have an important role to play in sexual health promotion and prevention of HIV and sexually transmitted infections (STIs) among gay, bisexual, and other men who have sex with men (MSM) [1-4]. In the United States [5-7] and elsewhere [8-10], such workers and volunteers are often characterized as community health workers (CHWs) - a workforce that has gained increased recognition, visibility, and legitimacy, and, in the United States at least, is now seen as an essential part of the public health system [11].

In a more global context, CHWs can be an important complement to underresourced health workforces, and thus can potentially be important to increase the availability of and access to health services [12,13]. Indeed, the evidence base regarding the positive contribution CHWs can make in the delivery of population-based health interventions is growing, particularly for child and maternal health, noncommunicable diseases, and infectious diseases [14].

In the countries of the European Union (EU) and European Economic Area (EEA; which includes EU countries as well as Iceland, Liechtenstein, and Norway), it is within the sphere of infectious diseases, specifically HIV and other STIs, that the concept and role of CHWs has recently come to the fore. MSM continue to represent the predominant mode of HIV transmission in the EU and EEA, accounting for 38% of all new HIV diagnoses in 2017 [15]. Although some countries have started to note a decline in HIV incidence among MSM (namely, Belgium, Greece, the Netherlands, Spain, and the United Kingdom), overall rates of HIV diagnoses among MSM continue to increase.

The reasons for MSM being disproportionately affected by HIV and other STIs, including viral hepatitis, are complex and vary along geographical and historical differences of the EU and EEA. Factors include (but are not limited to) the complex interactions between sexual behaviors; STIs; an increased biological vulnerability for HIV infections; social stigma associated with homosexuality; syndemics of mental health issues and substance use and misuse among MSM; structural, psychological, and provider-associated barriers experienced by MSM when accessing sexual health services; a lack of data and research on MSM in many countries; a lack of funding for MSM-targeted HIV and STI prevention and community-based HIV testing; advances in communication technologies and their impact on partner seeking and sexual behavior; and high internal and cross-border mobility (eg, [16]).

Historically, and in addition to the previous list, the public health sector in many European countries was slow in responding to the HIV epidemic (for example, due to conservative legislation around same-sex relationships and cultural and socioeconomic barriers fuelling stigma), leaving a void among other things in prevention and advocacy activities and service development [16]. This void was filled out of necessity by gay communities and nongovernmental organizations (NGOs), particularly in Western Europe, which proactively and progressively developed HIV prevention initiatives, programs, and services targeted to the most affected key populations, including MSM.

Unfortunately, such programs and services have been burdened over the years by insecure funding streams (eg, donations), poor linkage with formal health systems, lack of training and support for workers, fragmentation of purpose and roles, and competition for scarce resources with other actors and/or organizations. Together with a mixed and diverse nomenclature to characterize workers or volunteers (eg, HIV prevention worker, outreach worker, sexual health worker, health promoter, peer counselor, volunteer, health educator), this has led to a somewhat fractured and unstable workforce. For instance, in Europe the term “community health worker” (or “CHW”) is rarely used; instead, a plethora of disparate terms take its place (eg, [17-19]), which vary across organizations and countries. These definitional uncertainties result in a poor understanding of the precise nature of CHW work, practices, roles, knowledge, skills, and needs [3,20].

In 2015, as part of the European Commission’s Health Program 2014-2020, the Consumers, Health, Agriculture and Food Executive Agency (Chafea) issued a tender specification providing an important opportunity to not only strengthen the community response to tackling HIV and other STIs among MSM, but to also raise awareness regarding the persisting legal, structural, political, and social barriers hindering a more effective response to the syndemics of HIV, viral hepatitis B and C, and other STIs among MSM. The tender requested the development of a “behavioural survey for HIV/AIDS and associated infections, and a survey and tailored training [programme] for community-based health workers (CHWs) to facilitate access and improve the quality of prevention, diagnosis of HIV/AIDS, STI and viral hepatitis, and health care services

for MSM." In this tender, the term "CHW" was introduced for the first time, as far as we are aware, to refer to the workforce in Europe that supports the sexual health needs of MSM around HIV, viral hepatitis, and other STIs.

This paper is based on the pan-European 3-year project entitled ESTICOM (European Surveys and Training to Improve MSM Community Health) that was funded via this Chafea tender (no. Chafea/2015/Health/38). ESTICOM (2016-2019) aims to develop (1) a European online survey among MSM (European MSM Internet Survey—EMIS 2017); (2) a European online survey regarding the knowledge, attitudes, practices, and training needs of CHW who support MSM (ECHOES—the European Community Health Workers Online Survey); and (3) a training program for MSM-focused CHWs adaptable for all EU countries.

In this paper, we present the protocol for the ECHOES survey as a core part of the larger ESTICOM project, which is an extensive questionnaire that grappled with definitional complexities of CHWs who support MSM. The overarching aim of the ECHOES survey was to gather data from CHWs to help understand their role, including their knowledge, attitudes, and practices. Ultimately, the information should aid the potential development of the workforce through training, support, and policy development [21].

Methods

Design

A quantitative self-report questionnaire (ECHOES) was designed within the European Commission's funded ESTICOM project. The questionnaire was administered online using the survey tool provided by the Demographix platform.

Aim and Objectives

The overarching aim of the ECHOES study was to develop a multilingual, Europe-wide online questionnaire capable of assessing the knowledge, attitudes, and practices of CHWs providing sexual health services to gay, bisexual, and other MSM. Specifically, the research objectives were to (1) generate insight about who CHWs in Europe are, what they do, where they do it, and how and why they do it; (2) identify barriers and challenges to CHW activities; (3) identify skill and knowledge gaps and training needs; and (4) generate insights for the development of a dedicated training program for CHWs.

Study Population

ECHOES is the first survey of its kind in Europe that addresses CHWs who provide sexual health support to gay, bisexual, and other MSM. Therefore, the CHW study population is mostly unknown to researchers, an issue that the ECHOES survey was designed to address. Thus, given the term "CHW" is not well-known or used in Europe, a deliberately broad working definition was developed by the ECHOES development team to define the study population. Following an informal review of the relevant literature, this working definition was achieved through a consensus-based process with consortium partners using elements of the nominal group technique. The nominal group technique is essentially a group process involving problem identification, solution generation, and decision making. It can be particularly useful to ensure all parties are able to contribute and for use when the issue under question is controversial and/or the primary purpose is to come to clarification (rather than resolve differences of opinion). Thus, for ECHOES, a CHW was defined as "Someone who provides sexual health support around HIV/AIDS, viral hepatitis, and other sexually transmitted infections (STIs), to gay, bisexual, and other MSM. A CHW delivers health promotion or public health activities in community settings (not in a hospital or clinic)." [19] In other words, according to our definition, a CHW can be any person working with MSM around sexual health support (paid or unpaid) with or without a medical or health background as long as their work is conducted in community or nonclinical settings. Such a definition was intended to capture not only those more traditionally associated with supporting MSM, such as HIV outreach workers working in gay venues on behalf of NGOs, but also those providing sexual health support in a variety of different sectors (eg, educational, social care, housing, private sector) and in diverse ways.

Detailed plans to engage with the target population and recruit them to the survey were developed by the consortium partner AIDS Action Europe in collaboration with study partners. AIDS Action Europe is a network of national networks, AIDS service organizations, and community-based groups representing 415 NGOs in 47 countries in the World Health Organization (WHO) European Region. Briefly, activities included an initial Europe-wide consultation exercise to generate insight into the most useful communication channels to reach CHWs with 44 responses received from 32 countries (29 from countries eligible to be surveyed). Other strategies to recruit participants included direct mailing and emailing (eg, using translated email templates), website news items shared with pan-European HIV/AIDS organizations, paid social media promotion (Facebook), personal and professional contacts (eg, via events such as the HIV/AIDS, TB and Hepatitis Civil Society Forum), interviews and case studies published online "showcasing" the survey in specific countries, as well as a European webinar and marketing activities at relevant expert meetings and forums. ECHOES was also cross-promoted through a page delivered by the EMIS-2017 survey, which was launched at the same. This page used the same screening questions as ECHOES to identify if EMIS responders were also CHWs and, if so, to then direct respondents to the ECHOES survey.

Inclusion and Exclusion Criteria

The CHWs who satisfied the following criteria were eligible to participate in the survey if they (1) provided sexual health support for gay, bisexual, and other MSM in a community setting (not in a hospital or clinic) during the last 12 months; (2) provided support as a CHW in one of the 36 eligible countries (all 28 EU countries and neighbor countries: Bosnia Herzegovina, Iceland, Moldova, Norway, Russia, Serbia, Switzerland, and Ukraine); (3) were aged 18 years or older; and (4) consented to take part in the survey.

Questionnaire Development

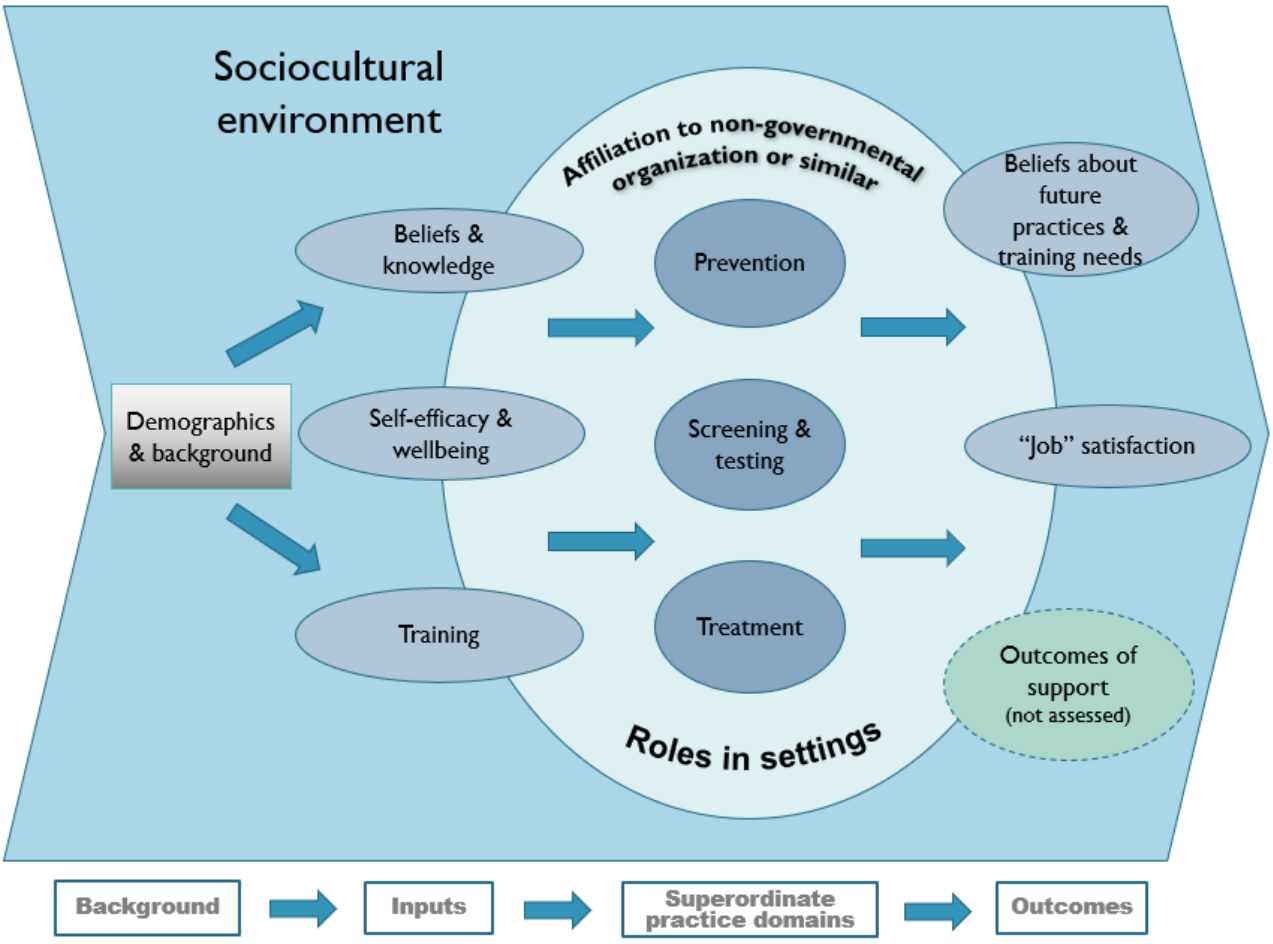
The ECHOES survey was developed primarily by a Brighton-based study team of five academics: three

psychologists specializing in MSM issues, behavioral medicine, survey design, and sexual health/HIV (NS, JH, CL); a social geographer with expertise in sexual and gender identities (NMG); and a former CHW/researcher (AP) in collaboration with colleagues from the wider ESTICOM project (particularly Objective Two partners OP, MK, MD, NL, CF, JC).

Before the survey was designed, a Europe-wide scoping exercise was conducted by the ESTICOM partners to review the extant literature regarding the knowledge, attitudes, and practices of CHWs concerning the sexual health of gay, bisexual, and other MSM [22]. Another more informal review was conducted by the ECHOES development team to develop a working definition of CHWs for European contexts and to explore the existence of any CHW surveys in Europe or elsewhere. An additional aim of this extra review was to consult with project partners to share any available national or regional questionnaires targeting CHW in any language. No national or regional questionnaires targeting CHW were submitted to the ECHOES development team. The outcomes of both scoping reviews were broadly consistent in showing a lack of both peer-reviewed and grey literature on CHWs involved in providing sexual health support aimed at gay, bisexual, and other MSM in Europe.

In parallel to the scoping activities, an initial conceptual model of the survey was devised drawing on a consensus-building exercise with project partners to collate their views as experts on a number of issues, including screening (who to include and exclude), the relative importance of different proposed areas of interest for the CHW survey (demographics, CHW activities and roles, settings, motivations, attitudes, knowledge, barriers, CHW development and support, training needs, and open text to propose any additional area), and estimates of the extent of data to be collected. Figure 1 shows the final conceptual model underlying the ECHOES survey, including all major components captured by the questionnaire. The conceptual underpinnings of the survey are informed broadly by ideas coming from the theory of planned behavior [23,24] and other conceptual frameworks, such as the health belief model [25], which suggest that action is strongly influenced by beliefs about benefits (and costs) of activities and barriers and facilitators.

Figure 1. Diagram of ECHOES conceptual model.



Based on the conceptual model, the questionnaire was structured around three superordinate practice domains of prevention, screening and testing, and treatment that form the core of the questionnaire (center of the model). These practice domains were shaped by (1) affiliation to organizations (NGO or similar) and (2) roles adopted in settings (eg, peer supporter, clinician working as a CHW within the community). Demographics, background variables, cognitions (beliefs and knowledge on HIV and other STIs prevention, screening and treatment), person variables (self-efficacy and well-being), and prior training and continuing professional development are inputs that shape practices. Beliefs regarding future practices (eg, providing

community-based voluntary counseling and testing) and training needs, job satisfaction, and outcomes in MSM (not measured) reflect on and are a reflection of the activities carried out by CHWs ("practices"). For the purposes of this paper, they are considered outcomes.

The ECHOES conceptual model will most likely aid analysis but should not be seen as capturing causal relationships. Based on our global or systems perspective and the evidence available, links exist between many elements and influences are frequently bidirectional and probably recursive. The conceptual model will inform the statistical analysis, but given the provisional and conceptual nature of this model, it will neither determine nor limit the analysis to links proposed by the model.

Piloting

Following the development of the conceptual model, the first full draft of the survey was developed on paper and online via Demographix in early 2017. A pretesting phase was initiated to make an initial assessment of this draft survey. Subsequent iterative rounds of small-scale online prepiloting were undertaken in February and March 2017, both informally and internally at the University of Brighton, as well as externally with CHWs known to the research team. Approximately 25 individuals participated in this pretesting phase, the purpose of which was to test out discrete sections of the questionnaire as they became available, checking for acceptability, completeness, comprehension, phrasing, and ease of use. As part of this process, respondents were asked to attempt to answer the draft sections followed by feedback to add, adapt, or delete questions as necessary to make them relevant to the target sample.

Following the completion of the series of online pretests, a broader consultation exercise was conducted using ESTICOM's wider networks. The draft ECHOES survey was sent out for its first consultation via MailChimp to 412 unique email addresses of ESTICOM subscribers from March to April 2017. Twenty-eight detailed responses were received from 18 countries representing 25 organizations, including European agencies, national government departments, and specialist NGOs (eg, in sexual health, HIV, and LGBTI issues), community-based voluntary counseling and testing, public health agencies, and other organizations. The consultation provided a very clear steer on modifying the ECHOES survey to develop it further for online piloting and finalization. In responding to the outcomes of the consultation, every nomination for amendment (eg, cut, add, or change), comment, and criticism was considered by the ECHOES development team. Respondents identified typos and routing errors that were subsequently rectified. Discussion by the research team led to the deselection, modification, and the addition of numerous questions.

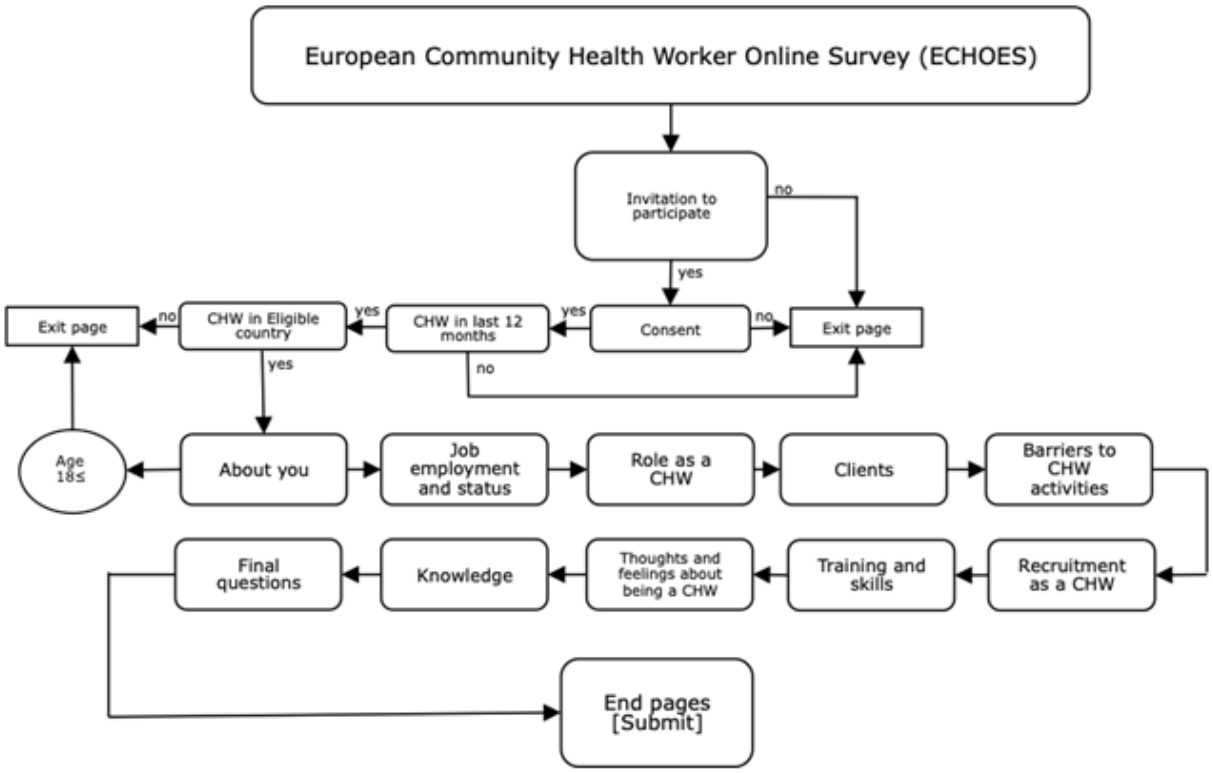
Following the pretesting phase, a small number (n=7) of cognitive debrief interviews were conducted by one of the authors (NMG) with participants experienced in CHW work and volunteering or appropriate fields of sexual health; recruitment was opportunistic, but heterogeneity was maximized. The aim of these interviews was to gather a rich evidence base to assess and improve the clarity, intelligibility, accessibility, and acceptability of the online survey. Data generated from the interviews was used to revise further the online survey before the wider online piloting.

Following the cognitive debriefing interviews, final adjustments were made to the survey and transferred into Demographix for the launch of a second pilot survey. The aims of the second pilot survey were to test the ECHOES survey in its most complete form and to provide sufficient data for validity checking of particular questions. Recruitment for the pilot test aimed for a sample size of 50 with a spread across European regions; however, the pilot was available in English only. The limited sample size was fixed to prevent potential exhaustion of the CHW population. The second pilot survey was opened for responses during three weeks in June 2017. An invitation to complete the pilot survey was emailed using MailChimp, and consortium partners were also asked to circulate the invitation through their own relevant networks. Reminder emails were sent on June 15 and 19, 2017. Fifty-four responses were received. Preliminary analysis of these pilot data demonstrated that the survey appeared to work well technically and could generate data that could answer the research objectives.

Final ECHOES Questionnaire Design and Content

With reference to Figure 1, the ECHOES survey comprised three superordinate domains, with 175 questions (heavily routed) divided into 10 subsections (see Figure 2); up to 250 data points were collected for each respondent. Approximately 10% of all questions were drawn from three validated scales documenting well-being, self-efficacy, and job satisfaction of CHWs [26-28]. The remaining 90% of questions were developed or adapted by the authors. The final survey was more than 27 pages, 13 of which contained core questions addressed to all respondents. Ten pages were conditional on the answers to preceding questions, and the remaining four were exit pages that showed when a participant was not eligible to complete the survey. Brief descriptions of each subsection of the questionnaire are provided subsequently; examples of questions for each section are provided in Textbox 1.

Figure 2. Flow diagram of ECHOES questionnaire structure.



Textbox 1. Examples of ECHOES questions per section.

About you

- Which of the following best describes how you think of yourself [gender identity response set]; ...is this what you were assigned at birth? [trans experience; y/n]
- Which of the following best describes how you think about yourself? (sexual orientation response set); Thinking about all the people who know you (including family, friends, and work or study colleagues), what proportion know this? [outness response set]

Job employment and status

- We know that many people do not use the term "community health worker." How would you describe your job title? [free-text]
- When working as a CHW, which of the following best describes the type of organization you work for/with? [organization response set]

Role as a CHW

- Tick all that apply:
  - For the purposes of prevention, I am involved in providing information about... [information response set (eg, safer sex, testing, vaccinations, chemsex)]
  - I am involved in providing these intervention activities.....[intervention response set (eg, supporting use of PreP/PEP, sexual health provision, mental health support)]
  - Where do you deliver prevention activities around HIV/AIDS, viral hepatitis and STIs to gay, bisexual and other MSM? [settings response set (eg, gay venues)]

Clients

- Which three of these populations of people do you most often work with in your CHW activities? [population response set]
- Thinking only about your work with gay, bisexual and other MSM regarding delivering sexual health support on HIV, viral hepatitis and other STIs, what age group do you most often work with? [age response set]

Barriers to CHW activities

- Think about all the activities you do in your role as a CHW. Please tick the main issues for you as an individual which hinder your activities [individual barriers response set]
- Please tick the main issues from your organization which hinder your activities [organizational barriers response set]

Recruitment as a CHW

- Why did you start to work/volunteer as a CHW? [motivation response set]
- How did you first become a CHW?

Training and skills

- Thinking about your current role as a CHW, have you received training in this role? If yes—What kind of training have you received? [training type response set]
- In order to be as effective as possible in your current role, which areas would you most benefit from additional training in? [training areas response set]

Thoughts and feelings about being a CHW

- Please think about your day to day life, including your role as a CHW. How true are the following statements? [true/not true response set]:
  - It is easy for me to stick to my aims and accomplish my goals.
  - I am confident that I could deal efficiently with unexpected events.
  - Thanks to my resourcefulness, I know how to handle unforeseen situations.
- Taking everything into consideration, how do you feel about your activities as a CHW as a whole? [satisfaction response set]

Knowledge

- Regarding HIV/AIDS and hepatitis B and C, how confident are you in your knowledge of... prevention; screening and/or testing; treatment and/or support? [HIV/AIDS/ Hepatitis B and C, confidence response set]

Final questions

- Have you ever been diagnosed with HIV?

- How good is your health in general? [general health status response set]
- Please indicate which is closest to how you've been feeling over the last two weeks: [time response set]:
  - I have felt cheerful and in good spirits
  - I have felt calm and relaxed
  - I have felt active and vigorous
  - I woke up feeling fresh and rested
  - My daily life has been filled with things that interest me

About You

The ECHOES survey is part of the larger EU ESTICOM project and was intended to sit alongside the EMIS 2017 survey; therefore, the demographic indicators were harmonized between the two surveys as much as possible. This section contained a total of 11 questions covering age, gender identity (inclusive of trans and gender-nonconforming identities), sexual identity (orientation), "outness," membership within an ethnic or racial minority, location of CHW activities, years in full-time education since the age of 16 years, perception of household income, and languages spoken (native and other). Linking with the final survey section (see Final Questions section), some of these items also assessed peer status; namely, whether the CHWs share characteristics with the populations they serve.

Job Employment and Status

This section asked about the CHW job role (paid or unpaid) in providing sexual health support to gay, bisexual, and other MSM. If not currently employed as a CHW, respondents were asked to answer about their most recent CHW role in the last 12 months. Given that "CHW" is an unfamiliar term in Europe, the first question asked participants to describe their job role (open question). Additional questions included employment status and job security (if part time, additional questions on status when not working as a CHW), and affiliated organization (if any) including its main purpose, size, and funding sources.

Role as a Community Health Worker

One of the key aims of the ECHOES survey was to find out what CHWs actually do. Therefore, this section asked respondents about their personal involvement in CHW activities over the last 12 months relating to sexual health support to gay, bisexual, and other MSM around HIV/AIDS, viral hepatitis, or other STIs. The cognitive debriefing interviews highlighted that CHWs work in a wide variety of organizations, beyond organizations specializing in gay, bisexual, and MSM sexual health and/or HIV/AIDS. Given the complexity of these CHW roles (practices) within diverse contexts, the wording of questions and data items throughout this section (and the wider survey) were designed to capture responses from those who have a CHW role as part of their wider job, those who volunteer unpaid, those who do not currently have a CHW role but did within the past 12 months, and those whose CHW role involved gay, bisexual, and MSM as well as those who did not fall into this grouping (eg, heterosexual men, women). This section comprised three large subsections, including prevention, screening and/or testing, and treatment and/or support, with each subsection containing multiple items. Each subsection covered specific CHW activities and their frequency as well as the settings in which they occur.

Clients

This included the people CHWs work with and their relationships with them. This section asked which populations the CHW worked with most often, including their approximate age band (<25 years, >25 years, even mix), how many clients they see in a seven-day period, and their perceptions of client trust in their support and associate organization (if relevant).

Barriers to Community Health Worker Activities

This section consisted of six questions about the issues that shaped or hindered their role and activities as a CHW at different levels (individual, organizational, societal/cultural), including how things might be improved.

Recruitment as a Community Health Worker

These eight items refered to how CHWs were recruited to their post when they first started as a CHW or first became involved with activities supporting gay, bisexual, and other MSM, including whether training, qualifications, and/or experience were required.

Training and Skills

A key part of the ECHOES survey was to identify training needs to inform the third objective of the ESTICOM project (development of a specific training program for CHWs). In this section, 11 questions explored training received, intensity (amount), on-going or not, and topic areas covered, including who identified and paid for the training, whether training was allowed in work time, and requirements (and priority) for future training.

Thoughts and Feelings About Being a Community Health Worker

This section included two validated scales, including (1) an adapted and shortened general self-efficacy scale (6 items) by Romppel et al [26] based on Schwarzer et al [27], and (2) a 10-item shortened version scale similar to Goetz et al [28] to assess job satisfaction including a global job satisfaction rating.

Knowledge

For practical purposes and because the ECHOES survey is designed to inform training needs, knowledge of HIV/AIDS, viral hepatitis, and other STIs as a CHW was assessed in terms of confidence judgments regarding core knowledge domains. CHWs were asked to rate how confident they were in their

knowledge of HIV/AIDS, viral hepatitis, and STIs on a scale from 1 (not confident at all) to 5 (very confident) in three different areas drawing on self-efficacy theory [29]: (1) prevention, (2) screening and/or testing, and (3) treatment and/or support (for a practical example see [30]).

Final Questions

The final 12 questions of the survey were designed to understand how CHWs may be connected to the communities they serve. Five of these comprised the WHO-5 Brief Well-Being Index [31] to assess general well-being and/or good emotional and positive aspects of mental health. A single question assessed overall health, and the remaining questions assessed aspects relating to whether CHWs share some characteristics with the populations they serve (eg, living with HIV, drug use).

Translation and Sociolinguistic Equivalence

To facilitate translation, the Demographix platform provided a custom interface for the translation of the signed-off English language version of the ECHOES questionnaire to all required languages. The interface allowed translators to enter the survey via a unique and personalized URL and to see a locked version of the original English version on the left of their screen while translating the survey directly over the top of a second version of the English original, on the right of their screen. Using this service ensured that all questions maintained the same routing and piping instructions in all languages, and all versions were structurally identical. Demographix also provided existing pretranslated survey completion instructions (eg, next, previous, submit) in all the required languages for ECHOES.

Multilingual proofreaders were asked to use a similar system to compare and contrast survey translations. Demographix also allowed simultaneous access to all ECHOES partners who needed to review a specific version of the survey before being published and launched. Translations were outsourced to translators suggested by the project's collaborating partners, thereby minimizing costs. Translations involved native-speaking stakeholders from the field (ie, experts in HIV prevention or LGBT health) as translators for each language. Two multilanguage proofreaders were involved when possible to compare the translations with the English original but also with one another. The proofreaders ensured a harmonized, multilanguage questionnaire, while deliberately maintaining certain differences identified as culturally appropriate, such as explicitness of language or the question of formal or informal address.

In ECHOES, the standardized scales used came with existing translations. The generalized self-efficacy scale and the WHO-5 Brief Well-Being Index were available in all languages required for the survey. The job satisfaction scale was available in English and German. Translators were asked to use the already translated versions when possible, and if translations did not exist, to provide their own translation.

The final questionnaire was available in the following 14 EU languages: Bulgarian, Croatian/Serbian, Czech, Dutch, English, Finnish, French, German, Greek, Italian, Polish, Portuguese, Romanian, and Spanish. ECHOES was also translated into Russian, because it is a major ethnic minority language, and into Ukrainian. After consultation with Scandinavian (Norway, Sweden, Denmark) and Baltic (Estonia, Latvia, Lithuania) country representatives, it was decided not to translate the ECHOES questionnaire into these languages because the few expected CHW in these countries were assumed to be able to understand and complete the English- or Russian-language questionnaires. Therefore, ECHOES was available in 16 languages in total.

Data Analysis and Management

In general, data analysis will be exploratory, although we will be exploring some issues in line with existing research findings. This includes a gradient across Europe (west to east) of intensifying stigma and discrimination. Scale scores will be created for the standardized instruments following published procedures. To ensure internal consistency of scales for the sample in this survey, internal consistency reliability will be checked with Cronbach alpha. Descriptive findings will be reported as means and standard deviations for continuous variables, and as numbers and percentages for categorical variables. Descriptive analyses will be run in SPSS using the overall ECHOES dataset, including all language versions of the ECHOES questionnaire. Bivariate analysis, including chi-square tests (or Fisher exact test when appropriate) and Mann-Whitney *U* tests, will be used to determine significant differences between groups, for categorical variables including demographics. Kruskal-Wallis tests will be used for continuous variables.

Only the ECHOES development team at the University of Brighton and the data analysis team at the Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT) in Badalona, Spain, will have access to the data during the study. After the study is completed, the University of Brighton and CEEISCAT will make the relevant data available to consortium partners for analysis as appropriate.

Ethics

Ethical approval for the initial questionnaire design and development activities (eg, cognitive debrief interviews, pretesting, piloting) was obtained from the University of Brighton's School of Health Sciences, School Research Ethics and Governance Panel. Additional approval to host the survey online and recruit participants was received from the Hospital Universitari Germans Trias i Pujol in Badalona, Catalonia (Spain) (PI-16-143), as the hosting institution of CEEISCAT.

Informed Opt-In Consent

Respondents who accepted the invitation to take part in the ECHOES study and used the link provided to access the survey Web page were taken to the survey introductory page. Participants were then provided with information about the project, confidentiality of the survey findings, and an outline of what participants were required to do and how long it would take to complete the questions. A statement was provided regarding data protection, including confidentiality and anonymity as well as a brief statement about the ESTICOM project consortium. Potential participants were asked to click on a box to confirm that they had read and understood the participant information before proceeding, a box to confirm that

they understood their participation would be voluntary and that they would be able to withdraw at any time, and a box explicitly requesting them to opt-in, thus confirming their agreement to take part in the survey.

Confidentiality

No personal data (such as names, addresses, date of birth) were collected from participants. The survey was completely anonymous; no IP addresses were stored or downloaded and no information regarding the origin of the "'click" was collected. No cookies were installed on the potential participant's computer or device.

Planned Dissemination

The results of the ECHOES survey will be published in consortium reports submitted to the Chafea, in peer-reviewed scientific journals, and via conference presentations. Results of the study will also be disseminated through the ESTICOM network via MailChimp and supported by AIDS Action Europe, as well as on the ESTICOM project website.

Results

The ECHOES survey (part of the ESTICOM project) is funded by Chafea of the European Commission. Survey enrollment closed on January 31, 2018. A total of 1181 participants responded to the survey. Responses were screened for key inclusion criteria. Those who did not deliver services to MSM in a community setting (n=107), work or were active in the countries included in the study (n=24), or meet the minimum age of 18 years (n=15) were excluded, resulting in a final sample available for analysis of 1035 CHWs. The findings of the ECHOES survey and the wider ESTICOM project, are now available from the ESTICOM website and/or by contacting the first author.

Discussion

To our knowledge, this study is the first internet-based self-completion questionnaire survey exploring the knowledge, attitudes, and practices of CHWs providing sexual health support to gay men, bisexual men, and other MSM in European settings. It is expected that the results will transform our understanding of who CHWs in Europe are; what they do; where, how, and why they do what they do; as well as identify the individual, organizational, and structural barriers and challenges to CHWs' activities. By gaining a deeper understanding of CHWs' knowledge, attitudes, and practices regarding their clients, and given that ECHOES is part of the much larger ESTICOM project that includes the EMIS-2017 survey, findings are also expected to generate insights for the development of the first European common training program for CHWs (aim 3 of ESTICOM). We expect this impact to be considerable, with findings highlighting important areas to strengthen and build the capacity of CHWs in all the 36 ECHOES-eligible countries (all 28 EU countries and neighbor countries, including Bosnia Herzegovina, Iceland, Moldova, Norway, Russia, Serbia, Switzerland, and Ukraine).

The questionnaire will also garner information about profile characteristics of CHWs, which may be important in supporting CHWs, allowing them to develop their professional profile and informing of psychosocial training needs. This will be supported by information on both general and emotional health, job satisfaction, and acceptance of gay, bisexual, and MSM people.

The pan-European nature of this study will provide a comprehensive dataset across participating countries that will enable analysis of variability observed in CHWs' knowledge, attitudes, and practices. As the output of a European Commission tender, it is anticipated that this knowledge of the variability among CHWs along with insights for the development of common training will be important in the development of future policy initiatives around promoting health, reducing new infections, and ultimately working toward global Sustainable Development Goals (goals 3, 10, and 11) and achieving the UNAIDS 90/90/90 targets.

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Authors' Contributions

All authors were involved in the conceptualization, drafting, and critical review of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

Chafea: Consumers, Health, Agriculture and Food Executive Agency
CHW: community health worker
ECHOES: European Community Health Worker Online Survey
EEA: European Economic Area
EU: European Union
MSM: men who have sex with men
NGO: nongovernmental organizations
STI: sexually transmitted infections
WHO: World Health Organization

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Protocol

Comparison of Housing First and Traditional Homeless Service Users in Eight European Countries: Protocol for a Mixed Methods, Multi-Site Study

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Abstract

Background: Homeless services expend considerable resources to provide for service users' most basic needs, such as food and shelter, but their track record for ending homelessness is disappointing. An alternative model, Housing First, reversed the order of services so that homeless individuals are offered immediate access to independent housing, with wraparound supports but no treatment or abstinence requirements. Although the evidence base for Housing First's effectiveness in ending homelessness is robust, less is known about its effectiveness in promoting recovery.

Objective: The objective of this research is to compare rehabilitation- and recovery-related outcomes of homeless services users who are engaged in either Housing First or traditional staircase services in eight European countries: France, Ireland, Italy, the Netherlands, Poland, Portugal, Spain, and Sweden.

Methods: A mixed methods, multi-site investigation of Housing First and traditional services will compare quantitative outcomes at two time points. Key rehabilitation outcomes include stable housing and psychiatric symptoms. Key growth outcomes include community integration and acquired capabilities. Semistructured interviews will be used to examine service users' experiences of environmental constraints and affordances on acquired capabilities to identify features of homeless services that enhance service users' capabilities sets. Multi-level modelling will be used to test for group differences—Housing First versus traditional services—on key outcome variables. Thematic analysis will be used to understand the ways in which service users make sense of internal and external affordances and constraints on capabilities.

Results: The study is registered with the European Commission (registration number: H2020-SC6-REVINEQUAL-2016/GA726997). Two press releases, a research report to the funding body, two peer-reviewed articles, and an e-book chapter are planned for dissemination of the final results. The project was funded from September 2016 through September 2019. Expected results will be disseminated in 2019 and 2020.

Conclusions: We will use the findings from this research to formulate recommendations for European social policy on the configuration of homeless services and the scaling up and scaling out of Housing First programs. From our findings, we will draw conclusions about the setting features that promote individuals' exits from homelessness, rehabilitation, and recovery.

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KEYWORDS

homeless services; Housing First; recovery; capabilities

Introduction

Background

The personal costs of homelessness are significant and multidimensional. Individuals who experience chronic homelessness are more likely to have mental health and/or substance misuse problems, experience victimization, and have fewer opportunities to develop positive identities or to participate in valued social activities than the general population [1-3]. European social policies that reverse homelessness rather than manage it have been quite limited and, as one consequence, homeless services expend considerable resources to provide for service users' most basic needs, such as food and shelter. Increasingly, researchers have begun to direct their efforts toward understanding how to improve the structure of homeless services so they can do more to reverse homelessness and ameliorate its costs to individuals and society [4,5]. The aim of this study is to examine the relationship of homeless services settings to service users' recovery experiences.

A growing body of evidence suggests that the traditional structure of homeless services, which follows a model of care that is variously referred to as "treatment first," "continuum of care," or "staircase," limits homeless individuals' potential for recovery in terms of both rehabilitation and growth [6]. A deficits model of homelessness, in which attributions for chronic homelessness focus on individuals' mental illness, substance misuse, and poor decision making, underpins the structure of treatment-first programs [7]. Consequently, the setting features of traditional services encourage compliance through treatment and sobriety prerequisites, a range of house rules and regulations, and the promise of independent accommodation [8]. Failure to comply with setting rules can result in moves back down the continuum to more restrictive housing arrangements or even eviction [6,9].

The underwhelming track record of traditional services was highlighted and critiqued by both the consumer and recovery movements; both questioned the assumptions that underpin the treatment-first model and its setting features [10,11]. An alternative model of homeless services delivery that is based in principles of consumer choice, empowerment, and recovery was introduced in New York City in 1992 [12,13]. Originally designed to serve chronically homeless adults with serious mental illness who may also have a co-occurring substance use disorder, Housing First reversed the order of services to provide independent, scatter-site apartments with no treatment preconditions or abstinence requirements. Support services are tailored to clients' preferences and needs and are provided 24/7 by either Assertive Community Treatment or Intensive Case Management teams. Housing First programs typically require service users to meet weekly with staff members, contribute 30% of their income toward the cost of rent, and comply with a standard lease agreement. Despite significant opposition to the model and skepticism from service providers and stakeholders [11,14], initial tests of Housing First returned impressive rates of stable housing [15,16] and cost-effectiveness [17,18] compared to traditional services. Critics' fears about increased substance use and psychiatric symptoms have not been supported by research findings [14,19]. There is evidence that greater consumer choice afforded to individuals in Housing First programs fosters greater personal mastery, which, over time, predicts fewer psychiatric symptoms [20].

Since its first implementation, Housing First has been disseminated across the globe. The first randomized and controlled trial was conducted in New York City, in which Housing First was compared to treatment as usual [21,22]. The largest randomized trial of Housing First thus far was conducted in Canada [23] and a third randomized trial was conducted in France [24]. The positive outcomes of these trials spurred widespread dissemination and nonexperimental pilot and demonstration projects [4,5]. Although the exact number of Housing First programs is unknown, it has been widely disseminated in North America, Europe, Australia, and New Zealand [25,26]. Despite Housing First's widespread reach and strong evidence base, most European homeless services continue to follow the treatment-first model [27]. Researchers and practitioners continue to work together to expand the evidence base for Housing First through rigorous experimental and observational trials. This study's comparison of Housing First and traditional services in eight European countries aims to demonstrate not only that Housing First reverses homelessness in these different contexts, but to identify the setting features that explain how it works and, in doing so, produce translational findings that may have widespread influence in policy and practice.

Homeless Service Features and Service Users' Recovery Experiences

When homeless services providers, stakeholders, and policy makers advocate for new Housing First programs, or for the reconfiguration of traditional treatment-first programs toward *housing-led* services, they tend to be motivated by ambitions to develop programs that facilitate service users' exits from homelessness; they are also motivated to promote service users' empowerment, personal growth, and freedom to participate in valued activities and roles [28,29]. Taken together, this goal can be conceptualized in terms of facilitating "a life worth living," which is defined in the capabilities approach as an individual's freedom to do and to be [30,31]. More specifically, capabilities are the opportunities that are realistically available to a person, which are determined by environmental and internal factors. Environmental factors can operate as either affordances or constraints on an individual's ability to develop, maintain, or exercise internal capacities to freely enact desired behaviors. Internal affordances and constraints include, but are not limited to, a person's intellectual abilities, physical and mental health, relationship to alcohol and illicit substances, skills, traits, motivations, and characteristic adaptations. For example, childhood poverty and neglect are environmental constraints that undermine an individual's ability to obtain adequate education or develop the kinds of intra- and interpersonal skills required for a range of occupations, roles, and activities [32]. Functionings are those capabilities that a person freely chooses to enact.

Situations of extreme social exclusion such as homelessness are environmental constraints; that is, they are forms of inequality and unfairness that block an individual's opportunities to develop new internal affordances or restore affordances that may have been lost. Indeed, homelessness has been described as capabilities failure [28] and capabilities deprivation [33]. Homeless services settings are important mediating structures that can broaden or constrict the environmental affordances on an individual's freedom to do or to be [28,29]. Homeless services can also facilitate or constrain a person's opportunities to develop the kinds of internal affordances, such as education, skills, psychiatric symptom management, or effective self-regulation of substance use, that are prerequisites to functionings in valued activities or socially valued identities and roles [28,29]. We aim to identify the setting features of homeless services (ie, environmental affordances and constraints) that affect service users' abilities to develop useful skills and abilities (ie, internal affordances) that broaden their capabilities sets and enhance their central functionings.

Although a growing evidence base reports the effectiveness of Housing First interventions for reducing homelessness for adults with complex support needs [22,34], there is more to learn about the specific setting features that operate as mechanisms through which these results may be achieved. Three important setting features are choice over housing and services, housing quality, and satisfaction with services. Previous research demonstrated that participants who were engaged with Housing First services consistently reported greater choice, better housing quality, and more satisfaction with services [5,18,35,36]. Among other important outcomes, consumer choice predicts greater mastery, stable housing, fewer psychiatric symptoms, and less problem-related substance use [15,16,35,37]. Perceived housing quality and service users' satisfaction with their input into the treatment and services they receive have both been associated with positive recovery-related outcomes, including engagement with supports [38] and reduced substance use [39].

This Study

In this paper, we describe the protocol for the Service Users' Experiences Study, one prong of a larger project called *Homelessness as Unfairness*, or HOME_EU, which takes an ecological approach to understanding long-term homelessness in Europe. Citizens' attitudes, social policy, service providers' experiences, and service users' experiences are each investigated in separate empirical studies. Our aim is to combine findings from the four studies into a body of translational knowledge that can be used to enhance European social policies so that countries may move beyond managing homelessness toward ending it.

In the Service Users' Experiences Study, we aim to investigate the features of homeless services hypothesized to function as key environmental affordances and constraints on service users' recovery and capabilities. We aim to understand how persistent homelessness thwarts individuals' basic liberties and equality aspirations. The capabilities approach [40] provides the theory-driven framework that guides our work on this project, which we will use to interpret our findings and propose practical guidelines to promote social justice in homeless policy and homeless services settings. The HOME_EU Consortium will combine findings from the Service Users' Experiences Study with findings from our studies with citizens, policy makers, and service providers. This will produce a translational multidimensional conceptualization of homelessness across eight European countries that will inform social policy at the European and national levels and encourage best practices in homeless services that promote recovery and inclusion in civil society.

Research Design

Our study uses a mixed methods design and is being conducted in eight European countries: France, Ireland, Italy, Poland, Portugal, the Netherlands, Spain, and Sweden. Our design is correlational and not randomized. We will recruit participants who are already engaged with either Housing First or traditional services and collect quantitative data via questionnaires at two time points: baseline (T0) and follow-up (T1). This will allow us to control for baseline nonequivalence on demographic characteristics and other individual differences, such as lifetime homelessness, length of time in current accommodation, alcohol and substance use, education, and physical health. A subset of participants from each country who completed the questionnaires will complete an in-depth, qualitative, capabilities interview. In this paper, we describe the core procedures and methods that will be completed across all eight study sites.

Objectives

The first objective of this study is to compare Housing First and traditional services regarding key service and support features hypothesized to promote recovery in terms of both rehabilitation

and growth. The second objective is to explore participants' subjective experiences of environmental and internal affordances and constraints on their functionings and capabilities, especially in the areas of valued social roles, activities, relationships, and responsibilities [28,30,31,41,42].

The specific objectives of the Service Users' Experiences Study are as follows:

1. Determine whether Housing First and traditional services are differentiated on key setting features previously demonstrated to be linked to recovery indicators.
2. Determine whether implementations of Housing First across eight different European contexts are consistent with one another and consistently differentiated from traditional services on these key setting features.
3. Determine whether setting features predict recovery outcomes at the second time point (T1), controlling for baseline (T0) scores.
4. Understand service users' subjective experiences of their own recovery of human rights, defined as capabilities, and the ways in which these experiences are afforded or constrained by their engagement with Housing First or traditional homeless services.

Methods

Quantitative Methods and Analysis

Recruitment and Data Collection

Overview

Consortium partners in each country will use their existing links to Housing First programs and traditional homeless services to recruit participants to the study. Partners in France, Ireland, Italy, Portugal, and Spain have been directly involved in Housing First pilot and demonstration projects, so they may directly contact participants to invite them to participate in this research. Researchers will liaise with key workers, team leaders, and program managers employed in either Housing First programs or traditional services for assistance with recruiting additional participants to the study so that we can achieve our target sample size.

Questionnaire Administration

Research interviewers will meet individually in a quiet location chosen by participants. After a short ice-breaker conversation intended to build rapport, the researcher will explain the study and obtain informed consent before administering the questionnaire. The 13 measures included in the baseline questionnaire are presented in Table 1. Research interviewers will read each item to participants using a standardized procedure and record participants' responses on the questionnaires. When the questionnaire is complete, the researcher will ask permission to contact the person to complete the questionnaire 6 months later.

Data Management

Participants' responses will be entered into a standardized SPSS, version 24.0 (IBM Corp), data file template that will be used in every site to ensure equivalence of data entry. Several steps will be, or have been, taken to ensure data quality. First, we will administer measures previously used with this population to maximize measure validity and reliability. Second, interviewers will follow a data entry protocol and receive ongoing support via telephone, email, and face-to-face meetings. Third, the type and range of data values and mandatory entry were built into entry fields in the database. Fourth, questions from interviewers were fielded centrally and decision rules were made where necessary and circulated to all partners. Fifth, the authority to change data elements will be restricted to a small team [43].

Sample Size and Retention Plan

Our target sample for the second time point (T1) is 480 participants (Housing First, n=240, and traditional services, n=240). Because we anticipate attrition between T0 and T1, we intend to oversample each group at baseline. Based on prior research [22,36], we anticipate greater attrition in the traditional services group, so we aim to sample 38 Housing First participants and 45 traditional service participants in each of the eight countries at T0 (N=664). In order to maximize follow-up, we have adapted Stefancic and colleagues' guidelines [44]. Specifically, at the baseline data collection meeting, researchers will ask participants to predict where they will be living 6 months later; to provide a range of contacts for family members, friends, and service providers; and to contact the research team if they change their phone number or move to a new residence. Participants will be compensated with a €20 shopping voucher for each questionnaire and interview they complete.

Participants

To be eligible to participate in this study, potential participants must meet the following inclusion criteria: be 18 years of age or older to legally consent to participate; have spent 6 or more months homeless in their lifetime; be currently engaged with homeless services, either Housing First or traditional services; and be sufficiently proficient in the language of the country in which they reside to understand all the questionnaire items. Exclusion criteria include the following: unable to provide consent at time of data collection because of active psychosis or inebriation, less than 18 years of age, have insufficient proficiency in the questionnaire language, have spent fewer than 6 months homeless in their lifetime, and not currently engaged with a homeless service.

Measures

Overview

The measures selected for this study are listed in Table 1 [36,45-57]. There are three main categories of measures: setting and support features, rehabilitation-related recovery, and growth-related recovery. Although some measures have already been translated into some of the languages represented in this study, most measures had to be translated into most languages. The Consortium agreed to adopt standard translation-back translation procedures for cross-cultural research [58]. Questions or disagreements about translation were discussed among Consortium partners until they reached consensus.

Table 1. Quantitative measures used for baseline (T0) and follow-up (T1) data collection.

Domain,Variables	Instruments
Setting and support features	
Working alliance	Working Alliance Inventory—Participant (Horvath and Greenberg, 1989) [47]
Service satisfaction	Self-Help Agency Satisfaction Scale (Segal et al, 2000) [46]
Housing quality	Choice in Housing and Services (Srebnik et al, 1995) [45]
Choice	Perceived Housing Quality and Choice/Control (Toro et al, 1997) [36]
Rehabilitation-related recovery	
Housing status	European Typology on Homelessness and Housing Exclusion (FEANTSA[a], 2005) [52]
Psychiatric symptoms	Colorado Symptom Index (Shern et al, 1994) [48]
Alcohol and drug use	Alcohol Use Disorders Identification Test (Babor et al, 2001) [49] Drug Use Disorders Identification Tool (Berman et al, 2005) [50]
Physical health	General Self-Rated Health (DeSalvo et al, 2006) [51]
Growth-related recovery	
Mastery	Mastery Scale (Pearlin and Schooler, 1978) [53]
Capabilities	Capabilities Scale
Recovery	Recovery Assessment Scale (Giffort et al, 1995) [54]
Community integration	Community Integration Measure (Aubry and Myner, 1996; Segal and Aviram, 1978) [55,56]
Distal social support	Distal Social Support Scale (Wieland et al, 2007) [57]

[a]FEANTSA: European Federation of National Organisations Working with the Homeless.

Setting and Support Features

Based on previous research on homeless services and theories of recovery, we identified four dimensions of service and support features to measure. These are subjective measures of service users' perceptions of the setting that assess choice over housing and services [45], housing quality [36], satisfaction with involvement with services [46], and working alliances with service providers [47].

Objective setting features were identified from the literature on Housing First and staircase services, as well as our own experiences of these environments. These include the following service setting features: congregate or scatter-site housing, private or shared bedroom, private or shared bathroom, mixed or segregated gender, tolerate alcohol use on-site or not, tolerate drug use on-site or not, tolerate intoxication on-site or not, fixed length of stay or not, treatment required or not, set meal times or not, and curfews or not.

Rehabilitation-Related Recovery

For homeless adults, rehabilitation-related recovery is often conceptualized as successfully maintaining independent accommodation, decreased psychiatric symptom frequency, decreased problem-related alcohol and drug use, and improved physical health. We selected measures with established validity and reliability to measure these rehabilitation-related recovery indicators, which are listed in Table 1. Specifically, we included the Colorado Symptom Index [48] as well as measures of alcohol and drug use [49,50] and physical heath [51]. We also created a measure of housing status based on the European Typology on Homelessness and Housing Exclusion [52].

Growth-Related Recovery

Growth-related recovery in homelessness is also multidimensional, so we included a range of measures to capture the dimensions that are commonly the focus of key stakeholders' attention. We included intrapersonal measures, such as mastery [53], hope, meaning of life, quality of life, and empowerment [54]. We also included interpersonal measures, such as community integration [55,56] and distal social support [57]. A measure of capabilities was developed and its content was validated for use in the Service Users' Experiences Study. It consists of 54 items adapted from the capabilities framework [42] and the Acquired Capabilities Questionnaire for Community Mental Health [59].

Statistical Analysis

We plan to compare participants who are engaged in Housing First programs to participants engaged in traditional services to determine whether they differ on service and support features, rehabilitation-related recovery outcomes, and growth-related recovery outcomes at baseline and at follow-up. Based on previous experience [60] in which participants chose to skip items and even entire measures, we expect to have missing data on most measures. We also expect attrition at T1 because participants have died, cannot be located, or do not wish to complete the questionnaire a second time. We will use Little's *missing completely at random* test to determine whether data is *missing completely at random*, *missing at random*, or *neither*. We will manage data that is *missing completely at random* or *missing at random* using one of two approaches, depending on the research question, statistical technique, and software package. In the first technique, we will use expected

maximization imputation techniques [61]. We will employ this technique with cross-sectional analyses of variance and multiple regression with SPSS, version 24.0 (IBM Corp). In the second technique, we will employ maximum likelihood in multi-level modelling with Mplus, version 8.2 (Muthén & Muthén) [62].

We will use T0 data to control for differences at baseline while examining patterns of association at T1. As individual data will be nested within program data, we will use multi-level modelling to account for Level 1 and Level 2 differences in intercepts, slopes, and intercept-slope covariances while controlling for baseline scores, country of residence, and demographic factors. If there are significant differences in the intercepts or slopes for recovery outcomes, we will determine whether these differences are accounted for by program membership—Housing First versus traditional services—and setting features.

Qualitative Methods and Analysis

Participants

From the full sample of participants who complete the quantitative questionnaire at T1, we will invite 10 participants in each country (Housing First, n=5, and traditional services, n=5) to complete a semistructured interview focused on the 10 domains of capabilities identified by Nussbaum [42]. Partners will select participants with an aim for gender and age balance, where possible. Given the demands of a qualitative interview, HOME_EU Consortium partners will be asked to select participants who, from their previous research encounters, seemed capable of engaging with questions and enjoyed talking but also those who were able to focus and effectively articulate their thoughts.

Partners will only recruit participants to the qualitative study if they consented to be contacted again about follow-up research. These potential participants will be invited to participate in a qualitative interview about their experiences of homeless services, either over the phone or in person. Participants will be told that the interview will take about 1 hour and will be audio recorded, their data will be anonymized, and they will receive a €20 shopping voucher in return for participation. If they agree, partners will arrange a time and place to meet the participant.

Semistructured Capabilities Interviews

One of the key objectives of *Homelessness as Unfairness* is to explore the capabilities sets [28,42,63] of homeless services users in Europe and to identify the ecological factors that enable or block these capabilities sets (eg, Maton, 2008 [64]). To achieve this objective, our aim for the qualitative interviews is to deeply explore the capabilities sets of 10 homeless services users (Housing First, n=5, and traditional services, n=5) in each country. We developed an interview guide to explore homeless services users' subjective accounts of their central functioning capabilities [42] (see Table 1 and Greenwood et al, 2013 [27]). In developing this interview guide, we followed Shinn's [28] suggestions to examine these capabilities sets in terms of participants' behaviors or activities that a person freely chooses to do or not to do. We also aim to explore their subjective understanding of internal and external affordances and constraints, which are intrapersonal factors and environmental factors that the person perceives to either facilitate or restrict the range of their realistically possible capabilities.

Sampling and Recruitment

Participant Selection

A total of 5 Housing First services-engaged participants and 5 traditional services-engaged participants who complete the T1 quantitative questionnaire will be recruited in each country to complete the qualitative interview. When choosing and recruiting these participants, we will aim for gender balance, where possible, and aim to have a range of ages represented in the sample. Because the capabilities interview addresses many abstract concepts, such as freedom and rights, ideal candidates for the qualitative interviews are participants who engaged well with the quantitative questionnaire, who are reflective on their lives, and are able to focus their attention and compellingly describe their experiences. Because we do not want the experience of completing the capabilities interview to influence participants' responses on the quantitative measures, the T1 questionnaire will be completed prior to the interview.

Procedures

Interviews will be prearranged to occur at a quiet location chosen by the participant. Research interviewers should greet the participant and have a short ice-breaker chat, then explain the purpose of the interview and give an indication of how long the interview will last. After obtaining informed consent, the interviewer will begin the interview. With the participant's consent, the interview will be digitally recorded.

Researchers will follow the semistructured interview guide (available upon request from the first author) in a way that adapts to each participant's responses. The interview guide is structured so that the interviewer can take the interviewee through a discussion of the domains of capabilities identified by Nussbaum [42]. The prompts for each of the domains are constructed so that the interviewer can gain insight not only into the types of choices that are made in these areas, but also the breadth of choices and the affordances and constraints on choices in each domain. The main purpose is to understand the "range of realistic possibilities" [28], that is, the capabilities set that is available to each interviewee, along with the forces they experience as either facilitating or constraining their capabilities.

The interviewers will ask the interviewees to describe themselves in terms of each domain, their range of capabilities in each domain, the things they could do but do not want to do in each domain, the things they cannot do in that domain but would like to, and the factors they experience as blocking or facilitating their capabilities in each domain. Once all the domains have been covered, the interviewer will ask the participant to reflect on the conversation and see if they have anything they would like to add or clarify. Participants will be thanked for their time and provided with a €20 shopping voucher in return for their contribution. They will be invited to contact the research team with any follow-up questions or comments.

Qualitative Analyses

Each digitally recorded interview will be transcribed verbatim and anonymized. A deductive coding scheme based on the

capabilities domains will be used by all Consortium partners to code each transcript (available upon request from the first author). Two independent coders will code each interview and then meet to agree on the codes. The coded excerpts will then be translated into English using the procedures agreed upon by Consortium partners [58]. The two independent coders will then agree on the English translation of the coded excerpts. The interview codes will be provided to the lead researchers on the Service Users' Experiences Study, who will collate the codes obtained in each country and enter them into NVivo 11 software (QSR International) for thematic analysis [65].

Data Synthesis

Qualitative and quantitative data from the Service Users' Experiences Study component of the HOME_EU study of *Homelessness as Unfairness* will be triangulated with findings from our studies with citizens, policy makers, and service providers. Our aim is to produce a holistic understanding of homelessness across eight European countries that can be used to shape national and European social policy, encourage best practices in homeless services, reverse unfairness and inequality associated with homelessness, and promote recovery and inclusion in civil society.

Ethics and Data Access

The *Homelessness as Unfairness* project received ethics approval from the lead partners' (JO and MJVM) home university's research ethics committee (ie, institutional review board). Each of the Consortium partners negotiated ethics approval with their home institutions. For example, the Irish team submitted evidence of approval from the lead partner's university, along with a description of the work to be carried out with participants in Ireland.

A separate ethics work package was developed to ensure research integrity and protection of participants and researchers. Access to the data will be controlled by each Consortium partner. Completed questionnaires will be anonymized and stored separately from signed informed consent forms. Anonymized data will be input into SPSS, version 24.0 (IBM Corp), files stored on password-protected computers. Data files will be shared electronically via a secure data-sharing program. Access to the data will be limited to core personnel working on the project.

Results

The study is registered with the European Commission (registration number: H2020-SC6-REVINEQUAL-2016/GA726997). Two press releases, a research report to the funding body, two peer-reviewed articles, and an e-book chapter are planned for dissemination of the final results. The project was funded from September 2016 through September 2019. Expected results will be disseminated in 2019 and 2020.

Discussion

We will use the findings from this research to formulate recommendations for European social policy on the configuration of homeless services and the scaling up and scaling out of Housing First programs. From our findings, we will draw conclusions about the setting features that promote individuals' exits from homelessness, rehabilitation, and recovery.

Authors' Contributions

The HOME_EU Consortium study group includes the following: José Ornelas (Principal Investigator), Maria J Vargas-Moniz, and Maria F Jorge-Monteiro from the Applied Psychology Research Center Capabilities and Inclusion (APPsyCI), Instituto Superior de Psicologia Aplicada (ISPA), Instituto Universitário, Lisbon, Portugal; Ronni M Greenwood, Rachel M Manning, and Branagh O'Shaughnessy from the Department of Psychology, University of Limerick, Limerick, Ireland; Inês Almas and Teresa Duarte from the Association for Study and Psychosocial Integration (AEIPS), Housing First Project (Casas Primeiro), Lisbon, Portugal; Francesca Disperati, Marta Gaboardi, Michela Lenzi, Massimo Santinello, and Alessio Vieno from the Department of Developmental and Social Psychology, University of Padova, Padova, Italy; Rita P Marques, Maria Carmona, and Américo Nave, Crescer-Community Intervention Association, Lisbon, Portugal; Frederik Spinnewijn from the European Federation of National Organisations Working with the Homeless (FEANTSA), Brussels, Belgium; Roberto Bernad, Borja Rivero, and Martin Julián from the Red de Apoyo a la Integración Sociolaboral (RAIS) Fundacion, Madrid, Spain; Anna Bokszczanin, Barbara Zmaczynska-Witek, Skałacka Katarzyna, and Aleksandra Rogowska from the Institute of Psychology, Opole University, Opole, Poland; Sandra Schel, Yvonne Peters, Tessa van Loenen, Liselotte Raben, and Judith R Wolf from Impuls - Netherlands Center for Social Care Research, Radboud Institute for Health Sciences, Nijmegen, The Netherlands; Ulla Beijer, Mats Blid, and Hakan Kallmen from Stockholm Prevents Alcohol and Drug Problems (STAD), Stockholm Center for Psychiatry Research and Education, Karolinska Institutet, Stockholm, Sweden; Teresa Bispo, Tiago Cruz, and Carla Pereira from Câmara Municipal de Lisboa (The Lisboa City Council), Lisbon, Portugal; Pascal Auquier and Junie M Petit from Centre d'Études et de Recherche sur les Services de Santé et la Qualité de Vie (CEReSS), La Timone Medical Campus, School of Medicine, Aix-Marseille University, Marseille, France; Sandrine Loubière and Aurélie Tinland from the Department of Research and Innovation, Support Unit for Clinical Research and Economic Evaluation, Assistance Publique-Hôpitaux de Marseille, Marseille, France.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Grant peer review and funding.
[PDF File (Adobe PDF File), 61 KB - resprot_v9i2e14584_app1.pdf]

Multimedia Appendix 2
Proposal evaluation form and peer-reviewer comments from the European Commission.
[PDF File (Adobe PDF File), 335 KB - resprot_v9i2e14584_app2.pdf]

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Abbreviations

FEANTSA: European Federation of National Organisations Working with the Homeless

T0: baseline, first time point
T1: follow-up, second time point

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Protocol

Improving Exposure Assessment Methodologies for Epidemiological Studies on Pesticides: Study Protocol

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Abstract

Background: Exposure to certain pesticides has been associated with several chronic diseases. However, to determine the role of pesticides in the causation of such diseases, an assessment of historical exposures is required. Exposure measurement data are rarely available; therefore, assessment of historical exposures is frequently based on surrogate self-reported information, which has inherent limitations. Understanding the performance of the applied surrogate measures in the exposure assessment of pesticides is therefore important to allow proper evaluation of the risks.

Objective: The *Improving Exposure Assessment Methodologies for Epidemiological Studies on Pesticides* (IMPRESS) project aims to assess the reliability and external validity of the surrogate measures used to assign exposure within individuals or groups of individuals, which are frequently based on self-reported data on exposure determinants. IMPRESS will also evaluate the size of recall bias on the misclassification of exposure to pesticides; this in turn will affect epidemiological estimates of the effect of pesticides on human health.

Methods: The IMPRESS project will recruit existing cohort participants from previous and ongoing research studies primarily of epidemiological origin from Malaysia, Uganda, and the United Kingdom. Consenting participants of each cohort will be reinterviewed using an amended version of the original questionnaire addressing pesticide use characteristics administered to that cohort. The format and relevant questions will be retained but some extraneous questions from the original (eg, relating to health) will be excluded for ethical and practical reasons. The reliability of pesticide exposure recall over different time periods (<2 years, 6-12 years, and >15 years) will then be evaluated. Where the original cohort study is still ongoing, participants will also be asked if they wish to take part in a new exposure biomonitoring survey, which involves them providing urine samples for pesticide metabolite analysis and completing questionnaire information regarding their work activities at the time of sampling. The participant's level of exposure to pesticides will be determined by analyzing the collected urine samples for selected pesticide metabolites. The biomonitoring measurement results will be used to assess the performance of algorithm-based exposure assessment methods used in epidemiological studies to estimate individual exposures during application and re-entry work.

Results: The project was funded in September 2017. Enrollment and sample collection was completed for Malaysia in 2019 and is on-going for Uganda and the United Kingdom. Sample and data analysis will proceed in 2020 and the first results are expected to be submitted for publication in 2021.

Conclusions: The study will evaluate the consistency of questionnaire data and accuracy of current algorithms in assessing pesticide exposures. It will indicate where amendments can be made to better capture exposure data for future epidemiology studies and thus improve the reliability of exposure-disease associations.

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KEYWORDS

pesticides; occupational exposure; epidemiology; algorithm; biomonitoring; urine; questionnaire

Introduction

Background

Exposure to certain pesticides has been implicated in the development of several chronic diseases such as some cancers, respiratory effects, reproductive effects, and Parkinsonism [1-5]. Determining any role of pesticides in chronic health diseases requires the assessment of historical exposures. However, exposure measurement data are rarely available to adequately cover the entire exposure time period. Therefore, assessment of historical exposures is frequently based on self-reported surrogate information such as a person's job title, duration of employment, whether they were ever exposed (yes or no) to pesticides. Naturally, such exposure measures have limitations, for example, the ability of a person to remember all their jobs, which may affect the conclusions of a study [6]. The large number of pesticide active ingredients and pesticide mixtures involved, their different toxicokinetics, seasonality of use, and a broad range of characteristics regarding their application and use further complicate the assessment of workers' exposure to pesticides as it is difficult to accommodate all these factors in a modeled assessment. Pesticide exposure intensity has also been understudied or underaccounted for but may be an important factor [7]; much of the current literature focusses on cumulative lifetime exposure. Understanding the performance of the applied surrogate measures in exposure assessment is therefore important to allow proper estimation of the risks.

Improving Exposure Assessment Methodologies for Epidemiological Studies on Pesticides (IMPRESS) is a collaborative project between the Institute of Occupational Medicine (IOM), the Health and Safety Executive's (HSE's) laboratory, the Institute of Risk Assessment Sciences at Utrecht University, and the Centre for Occupational and Environmental Health of the University of Manchester. The overall study seeks to improve understanding of the performance of pesticide exposure assessment methods (EAMs) used in previous epidemiological investigations, and to use this information to recommend enhancements in scientific practice for future studies. For this, the project will assess the reliability and external validity of the surrogate measures used to assign exposure within individuals or groups of individuals. Moreover, the size and impact of recall bias on the misclassification of exposure to pesticides and the associated health effects will be evaluated. Previous and newly collected exposure data from several existing epidemiological studies across 3 continents (including quantitative exposure measurements using biological monitoring methods) will be used in these evaluations. IMPRESS will also assess the performance of various EAMs used in epidemiology by comparing and contrasting them within existing epidemiological studies. A dedicated systematic review was performed to assist in the selection of relevant methods to be included in these comparisons [8].

The main outcomes of the IMPRESS project will include the following:

1. Mapping of the methods used for exposure assessment in occupational epidemiological studies [8];
2. An assessment of the ability of workers to remember their working history related to pesticide exposure over a range of time frames;
3. Evaluation of an easily adaptable semiquantitative individual-based EAM against measured levels of urine pesticide metabolites in a broad range of settings and;
4. The comparison of the reliability and performance of EAMs used to assign exposure to individuals (individual-based) or groups of individuals sharing common attributes (group-based) in the frame of existing epidemiological studies and against the same exposure history and health outcome data.

Protocol Aims and Objectives

This protocol outlines the methods to achieve the following 2 project aims:

1. Evaluate recall of exposure to pesticides and information on exposure determinants to estimate the size of any recall bias and its effect on misclassification in a few specific pesticide-using populations (described in Table 1). The primary mechanism for this will be to reinterview workers already enrolled within the existing epidemiological cohorts. This addresses outcome 2 above. As already mentioned, many epidemiological studies rely on questionnaire data to determine exposure and so the reliability of such recall is crucial to understanding the validity of the conclusions reported in such studies. This is referred to as recall bias subsequently in this paper.
2. Examine the reliability and validity of currently available individual-based EAMs for pesticide exposure. The main approach for this will be the collection and analysis of urine samples for selected pesticide metabolites from participants alongside details about the pesticide use. The derived results will be used as a comparative measure for the evaluation of the performance of the individual-based EAMs. This addresses outcome 3 and provides with a reference method for the benchmarking exercise included in outcome 4 above. The best studied algorithm (the Agricultural Health Study, AHS) was developed for US-style farming exposures; it is not clear how suitable this algorithm is for other farming

systems, such as small-scale (the United Kingdom) and low and middle income countries. IMPRESS will assess both of these situations. This is referred to as exposure assessment subsequently in this paper.

This protocol will be applied in a number of epidemiological studies, which are detailed below.

Briefly, the first project aim (point 1: recall bias) will be applied in the UK (using an ongoing epidemiological cohort (Prospective Investigation of Pesticide Applicators' Health [PIPAH] [9,10]), 2 historical cohorts (Pesticide Users Health Study [PUHS] [11] and Study of Health in Agricultural Work [SHAW] [7]) that analyzed the association between low-dose pesticide exposure and neuropsychiatric disorders [12] and some historical biomonitoring data [13]), and a study among Ugandan farmers (Pesticide use in tropical settings [PESTROP]) examining the association between pesticide exposure and health including the identification of methods for exposure prevention [14]. The second project aim (point 2: exposure assessment) will be applied in the UK PIPAH cohort, the Ugandan PESTROP cohort and a Malaysian cohort of farmers (Ahmad, personal communication).

Table 1. Existing studies to be included in *Improving Exposure Assessment Methodologies for Epidemiological Studies on Pesticides*.

Study	Project aims	Potential participants, N	Date of OQ[a]
UK Prospective Investigation of Pesticide Applicators' Health	Recall bias and exposure assessment	825 certified pesticide users	OQ 2016
UK Pesticide Users Health Study	Recall bias and exposure assessment	>500 certified pesticide users	OQ 2004-2006
UK Study of Health in Agricultural Work	Recall bias only	Up to 234 farmers	OQ 2002
UK Historical biomonitoring data	Recall bias only	Up to 115 pest control operatives, tree dippers, and orchard sprayers	No OQ, standardized one to be used
Malaysia	Exposure assessment only	150 small-scale farmers	No OQ
Uganda	Recall bias and exposure assessment	300 small-scale farmers	OQ 2017

[a]OQ: original questionnaire.

Prospective Investigation of Pesticide Applicators' Health Study

The UK PIPAH Study was established in 2013, with the aim of investigating whether there is any evidence of a link between working with pesticides and health. Men and women who are certified pesticide users are eligible to join the study. All the members of the National Register of Sprayer Operators (NRoSO) and the National Amenity Sprayer Operators' Register were invited to take part in the study. Members of HSE's other long-term health study on pesticides, the PUHS, were invited to join in 2014. Over 5700 baseline questionnaires have been completed to date and enrollment is ongoing. A pesticide use questionnaire was sent to the whole cohort in January 2017 with about 1500 responses received. We propose to recruit from the 825 NRoSO respondents to that questionnaire (asking about their pesticide use in 2016), excluding any PUHS recruits, who will instead be invited to participate in a rerun of the 2004-06 questionnaire (see below).

Pesticide Users' Health Study

The PUHS was established by HSE in the late 1990s. The aims of the study are to monitor the long-term health of individuals potentially exposed to low levels of pesticides on a long-term basis. From 1994 to 2003, anyone applying for certification (required by users of agricultural pesticides under the Control of Pesticides Regulations 1986) was invited to give their permission for HSE to access information relating to them for the purpose of medical research into pesticide use. Those who agreed became members of the PUHS (around 65,000 participants). From 2004 to 2006, HSE sent a questionnaire to all participants. As this is a historical cohort, only those participants who have been subsequently recruited into the PIPAH study and are currently active pesticide users will be contacted (>500 participants).

Study of Health in Agricultural Work

The SHAW was a study that commenced in 2002, designed to address the question of whether low-dose pesticide exposure was associated with neuropsychiatric disorders in UK farmers. A cohort of British farmers working in the 1970s was sent a screening questionnaire which asked about their health and work history. Questionnaires were returned from 1380 subjects; there was evidence that handling the pesticide concentrate for the treatment of sheep was associated with screen-positive ill health [7]. A subgroup of this cohort (n=234) was interviewed to obtain more detailed information on ill health and exposure history. This smaller group will form the basis of the recall bias recruitment. It should be noted that a substantial proportion of this population may have died since the original study, and hence pilot work will establish to what extent this population is still alive and are willing to participate.

United Kingdom Historical Biomonitoring Data

HSE has conducted a number of research projects looking at pesticide exposures in a range of sectors, using biological monitoring as an estimate of exposure. Suitable historical studies were identified: a permethrin survey (1992-93) looking at pest control operatives (N=30) and tree dippers (N=22), and an orchard spraying survey (1996-97; N=63). Although the original numbers (and therefore the number of likely respondents some 20 years later) are small in each case, the use of a standardized

questionnaire should allow some use of pooled responses and comparison with the same questions that appear in the newer cohorts.

The Malaysian Farmers Study

The Malaysian farmer's study is a prospective study of farmer's ill health in the pesticide spraying season in the Sabah region of Malaysia, which started in 2018. Farmers (approximately 150) were randomly selected from regional databases of farmers and were interviewed to provide baseline information on sociodemographic and occupational factors as well as their health. During the spraying season, farmers will collect spot urine samples, be observed (with videoing) by a trained researcher, and keep a diary on pesticide use and health symptoms.

Uganda: Pesticide Use in Tropical Settings

The PESTROP study consists of 300 smallholder farmers who were interviewed twice within an interval of 2 to 4 weeks in 2017 [14]. A structured questionnaire was used to obtain insights on sociodemographics, knowledge, attitude, and practices of pesticide use and corresponding protective behavior, as well as health history. An adapted pesticide exposure algorithm was developed [15]. In addition, a neurobehavioral test battery (eg, Purdue Pegboard and Finger Tapping Test) was administered, anthropometry (height, weight, and waist circumference) was recorded, erythrocytic acetylcholinesterase activity was measured, and urine, hair, and toenail samples were collected.

The protocol will be adapted as necessary to accommodate the specific requirements of each of these cohorts, with separate ethics approvals being sought.

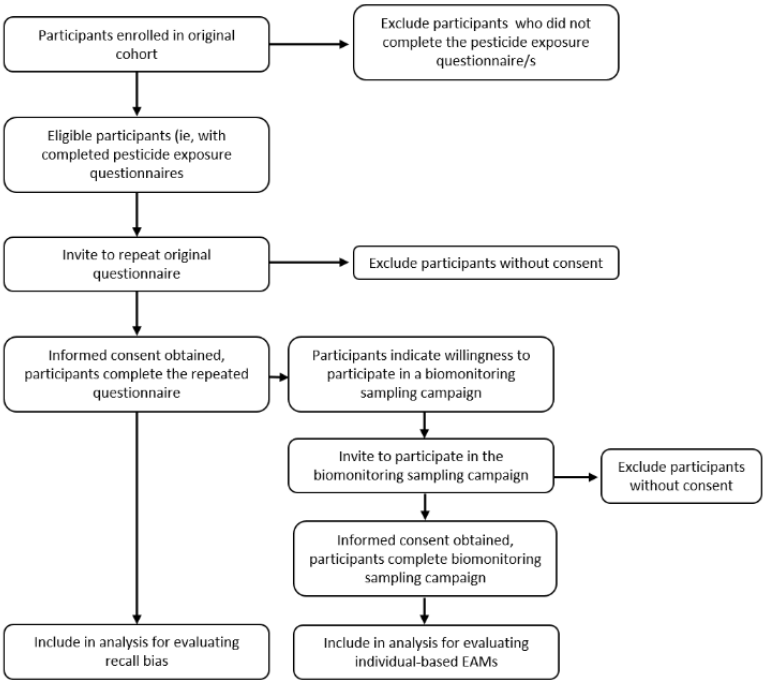
Methods

Study Design

Overview

For the epidemiological studies involved in both project aims (points 1 and 2 above, ie, PIPAH and Ugandan studies), participants will be recruited to address the first project aim (recall bias) and then invited to participate in the second project aim (exposure assessment). Figure 1 provides a schematic description of the enrollment and data collection process.

Figure 1. Summary of enrollment and data collection process. EAM: exposure assessment method.



Identification and Recruitment of Participants

Cohort participants who are aged 18 years or over, who are (*were* for SHAW and those included in the historical biomonitoring data cohorts) occupationally active in a job that involved direct (ie, handling or application) or indirect (ie, re-entry) exposure to pesticides during the original study period and completed the pesticide use questionnaire in the original study will be contacted to agree to complete a questionnaire relating to their previous participation in the cohort (all except the Malaysian cohort and the historical biomonitoring data), allow any data sources relating to them in the other identified cohorts to be combined (PUHS and PIPAH participants only) and, to be contacted concerning participation in the new cohort sampling as part of the second (exposure assessment) project aim (PIPAH study only, Malaysian and Ugandan participants recruited independently).

United Kingdom Cohorts

For the UK cohorts (PUHS, PIPAH, SHAW, and historical biomonitoring study data), survey packs will be sent out in mid-2019 to individuals fulfilling the inclusion criteria. Each survey pack will be customized to the particular cohort and will contain a letter of invitation, a participant information sheet, a consent form, a postage paid return envelope, and (for the PUHS, PIPAH, and historical biomonitoring data groups) the

questionnaire. The SHAW questionnaire is to be conducted by telephone interview and so will not be included in the survey pack, although the participants will be sent a copy of their work history from the time (mirroring the previous study).

Potential SHAW participants will be invited to provide their written informed consent to participate in the study, returning this in the postage-paid return envelope. For those who do not respond to the first mailing, a reminder survey pack will be sent to them within 3 months. For better consistency with the initial administration method (in-person interview), participants will be interviewed by telephone based on the original questionnaire survey material (it is not practical to reinterview face to face). It is anticipated that the telephone interview will take up to 1 hour to complete.

Potential PUHS, PIPAH, and historical biomonitoring study data participants will be invited to provide their written informed consent to participate in the study and complete the paper questionnaire sent to them, returning both of these in the postage-paid return envelope. For those who do not respond to the first mailing, a reminder survey pack will be sent within 3 months. Participants who give consent to take part in the second (exposure assessment) project aim will then be sent a new survey pack containing a letter of invitation, a participant information sheet, a consent form, a sampling kit with activity diary, and a postage paid return envelope.

Ugandan Cohort

For the Ugandan cohort, a local researcher will administer the survey material to participants who provided written informed consent, as per the original cohort study design (Fuhrimann, personal communication). The completion of the questionnaire will take place at the farm or workplace where participants are recruited. Later, participants will be invited to take part in the exposure assessment study, which will be conducted on a day when participants report spraying pesticides.

Malaysian Cohort

For the Malaysian cohort, a local researcher will supervise the urine sample collection and activity diary completion, as per the cohort study design. The completion will take place at the workplace where participants are recruited.

Data Collection

Evaluation of Recall Bias

Consented participants will be requestioned concerning the exposure information they had previously provided as part of the pesticide use questionnaires administered. Requestioning participants about both relatively recent and historical exposures will enable assessment of the consistency of recall where common questions exist across studies. Time frames for recall are 2 years (PIPAH and the Ugandan cohort), 6-12 years (PUHS), and up to 28 years (SHAW and historical biomonitoring study data). Participants will be administered a similar questionnaire as used previously (with the exception of those in the historical biomonitoring study), with slight modifications to highlight the time periods of interest to the IMPRESS project. In addition, all farmers in SHAW, in line with the original study protocol, will be administered the memory section of the Cambridge Cognition Examination instrument to allow for an assessment of their memory function [16]. The format and relevant questions will be retained but some extraneous questions from the original questionnaire (eg, relating to health) will be excluded for ethical (unused information) and practical (time taken to complete) reasons. The questionnaires will be completed in the same manner (or as near to) as previously administered to avoid any potential bias in their completion owing to different methodology being used. All written questionnaires are expected to take around 20 min to complete.

Evaluation of Currently Available Individual-Based Exposure Assessment Methods for Pesticide Exposure

Urine samples will be collected during the spraying season. Participants will be asked to provide samples after being involved in the use of, or indirect contact with, one or more pesticides. Activities targeted will be handling, spraying and re-entry with each participant providing samples for 1 of the 2 tasks. In general, sampling will occur irrespective of the pesticide involved except for the UK participants. UK participants will be asked to collect samples, if possible, when a pesticide from a list of preselected substances is used (see Table 1 for details). However, if those products are not routinely used, then UK participants will be asked to provide samples on any day when there is contact with pesticides and to record the product or active ingredients in the activity diary. This approach is intended to preserve statistical power by minimizing the number of different substances or metabolites measured while accounting for logistical constraints (ie, time spent in the field for studies where physical presence of investigators is required) and resources required for sampling material, storage, and analysis.

For every activity of interest, a spot sampling strategy of a pre- and a postactivity urine sample from each consenting participant will be followed. Preactivity samples will be collected before the activity commences (usually early in the morning), whereas postactivity samples will generally be evening voids. In the United Kingdom, postactivity samples will be collected at a standard time frame defined as between 6.00 pm and 8.00 pm. For re-entry tasks, sample collection will be attempted within 7 days of the performance of a crop spraying activity. Clear instructions on how to provide the urine samples in a manner to minimize potential cross-contamination will be given in a written (UK) or verbal (Uganda and Malaysia) and semipictorial form (all). Field blanks will be collected to assess any contamination of sample bottles by the worker. These will comprise empty vials, filled with tap or bottled water by the participants themselves, and will be included in approximately 10% of the samplings, with selection being made at random by the researcher.

Researcher-led (Uganda and Malaysia) or self-administered (the United Kingdom) diaries will be used to collect information on factors identified in the literature as important for determining the workers' level of pesticide exposure. This will include contextual information, for example, on activities involved and time spent on them, pesticide application and mixing methods, equipment used, where activities take place (indoor or outdoor),

cleaning, products and quantities used, and use of personal protective equipment (PPE). In the Malaysian study, farmers are also to be videorecorded during their normal working practices.

Each study pack provided to UK participants will include urine sample receptacles and appropriate packaging, a leaflet with simple instructions for the collection of the urine samples, the related activity diary, and a prepaid envelope to return the material. Study packs for non-UK participants will be in line with the developed in-study protocols including the urine sample receptacles, collection bags, and relevant guidelines whenever applicable.

Urine Sample Handling and Analysis

Laboratory analysis for all cohorts (including physical preparation, storage, and out of field handling and processing of the urine samples and collection materials) will be performed at the facilities of HSE's laboratory by dedicated and well-trained personnel of the institution.

Labeling and Tracking Samples

A comprehensive labeling and tracking system will be implemented to ensure that the contextual information from the collected diaries and questionnaires is clearly linked to the urine sample results and the participant. Given that the study population is sourced from ongoing epidemiological studies, existing identity numbers assigned to the participants are expected to play a key role on this sample tracking system.

Each study pack and included material (ie, diary, return envelope, and urine receptacles) will be prelabeled with a unique identifying number before being issued. This will include the (existing) participant's study ID, along with a sample number to reflect each consecutive sample provided with a prefix indicating the country population concerned (ie, UK [United Kingdom], UG [Uganda], and MY [Malaysia])—for example, UKXXXX-01 is the preactivity sample for UK participant ID number XXXX; UKXXXX-02 is the postactivity sample for the same participant.

Urine Sample Storage and Transportation

For UK participants, administration of urine samples and related survey material will be made by first class post as per standard practice, with prestamped envelopes for returning the materials being provided as part of the survey pack.

For Ugandan and Malaysian participants, urine sample receptacles will be provided at the time of the questionnaire interviews conducted according to the specific in-study designs. For Uganda, this will be in conjunction with the interviews performed as part of the first project aim (recall bias). Retrieval of the collected samples for these workers will be performed by the investigators. The researcher will log details of the samples, and the samples will be stored in a freezer at temperatures less than −15°C until transfer to the HSE's Laboratory in the UK for analysis. Transfer of samples will be performed in batches at intervals regulated by number of collected samples. The samples will be provided to the courier service responsible for the transfer in frozen study packs inside cool boxes with dry ice, thereby maintaining the cold chain (confirmed by an included data logger).

During every stage of the process, care will be taken to ensure that handling and transportation of the collected samples is undertaken in accordance with well-established protocols specific for the involved studies; this includes field blanks and spikes and stability testing [17]. At each stage in the chain, the integrity of the labels will be checked. If, at any stage, the label on the urine sample receptacle becomes damaged, a new label with the same sample ID number will be added. For each pack, the sample numbers on the urine sample receptacle and diary will again be checked to ensure they match. Details of the urine sample will then be logged as per HSE's laboratory standard practices, and the sample will be stored in a freezer with a temperature less than −15°C until extraction and analysis. During the storage period, conditions will be monitored with temperature entries being logged regularly.

Urine Sample Analysis

The collected urine samples will be analyzed for pesticide metabolite content using gas or liquid chromatography with mass spectrometric detection. The laboratory will follow ISO9001 record keeping and other relevant quality procedures. Metabolite concentrations will be expressed either as µg/L or corrected for creatinine concentration. Relevant urinary biomarkers will be selected based on the extent of use within the study populations, validity of biomonitoring methods (availability, specificity, robustness, and quality assurance), and knowledge of toxicokinetic parameters [18,19]. Analysis will follow recommendations from a recent study on this topic [20]. Preliminary information from within the participating studies (PIPAH, Uganda, and Malaysia) indicates that the pesticides listed in Table 2 are likely to be frequently used; all have well-established methods with the ability to detect low-level exposures found within general populations, so occupational exposures are expected to be readily detected. Where possible, samples will be collected according to use of the pesticides listed in Table 2. Where none of these are used, samples will be collected after pesticide use (active ingredient recorded) with a view to appropriate analysis where possible.

Quality control will be provided in the form of field blanks and spikes and laboratory spike samples prepared under standard procedures for the purpose. The field blanks and spikes will receive the same treatment as the normal samples in terms of handling, storage conditions, and analysis. Laboratory spikes serve as internal quality control material (pooled blank urine spiked with known quantities of relevant pesticide metabolite). This material will then be analyzed with every set of real samples to ensure consistency of analysis. It will also be used to determine the stability of urine samples under various conditions to represent the field situations. Where external quality assurance is available (eg, 3,5, 6-Trichloropyridinol, cis and trans isomers of 3-(2,2-dichloroethenyl)-2, 2-dimethylcyclopropane carboxylic acid, and 3-(2, 2-dibromovinyl)-2, 2-dimethyl-(1-cyclopropane) carboxylic acid; German External Quality Assessment Scheme For Analyses in Biological Materials), the laboratory will participate.

Analysts will be blinded to sample status (preexposure, postexposure, field blanks, and field spikes).

All samples and results will be logged into HSE's Biological Monitoring Database [13]. Samples will be identified by the anonymized sample identification number. The results of the urine sample analysis will be reported by sample ID number to the project team for data analysis.

Table 2. List of active ingredients to be prioritized for exposure assessment by biological monitoring.

Pesticide	Biomarker	Specificity
Chlorpyrifos	TCPyr[a]	Semispecific[b]
Chlorpyrifos-methyl	TCPyr	Semispecific[b]
Cypermethrin	DCVA[c]	Semispecific[d]
Deltamethrin	3-(2,2-dibromovinyl)-2,2-dimethyl-(1-cyclopropane)carboxylic acid	Specific
Glyphosate	Glyphosate	Specific
Pirimicarb	5,6-dimethyl-2-(methylamino)pyrimidin-4-ol	Specific
Lambda-Cyhalothrin	CFVA[e]	Semispecific[f]
Bifenthrin	CFVA	Semispecific[f]
Mancozeb, Maneb, and others	Ethylenethiourea	Generic
Chlormequat chloride	Chlormequat	Specific
Fluroxypyr	Fluroxypyr	Specific
Cyfluthrin	DCVA	Semispecific[d]
2-Methyl-4-chlorophenoxyacetic acid	2-Methyl-4-chlorophenoxyacetic acid	Specific
Acetamiprid	n-Desmethyl Acetamiprid	Specific

[a]TCPyr: 3,5,6-Trichloropyridinol.

[b]Specific to chlorpyrifos and chlorpyrifos-methyl.

[c]DCVA: cis and trans isomers of 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid.

[d]Specific to permethrin, cyfluthrin, and cypermethrin (and isomers).

[e]CFVA: cis-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropane carboxylic acid.

[f]Specific to lambda-cyhalothrin and bifenthrin.

Data Management

All data storage and handling within the project will be performed according to the specification and requirements of the European Union's General Data Protection Regulation (GDPR) 2018. Entry of the collected questionnaire data will be manual using an interface provided as part of the original study protocol (eg, Snap Surveys Ltd for the PIPAH and PUHS cohorts) or directly into a spreadsheet (for the other groups). There will be data entry checking (10% of the total number of records in a randomly selected manner) by another researcher not previously involved in the process. If errors are found in more than 5% of the examined records (ie, approximately 1% of the total sample), then all records will be rechecked against the original hard copies. The relevant comparison data from the original questionnaires will also be added to the spreadsheet or exported into a compatible format. Once completed, data for each cohort will be anonymized and exported into MS Excel or coma-separated value database before being transferred to IOM (in accordance with a project Data Transfer Agreement and the GDPR).

Access to identifiable information about an individual will be restricted to the institution responsible for the particular cohort and available only to a limited number of authorized employees responsible for administering their cohort. Hard copies of questionnaires and survey material will be securely stored by that institution. Any electronic files of questionnaires and other surveys will be held on a project folder on a secure server, accessible only to authorized employees. Data will only be shared with project partners in a pseudonymized format, with each cohort participant being allocated a unique identification number. This will be collated in a central database held by IOM for subsequent data analysis. Only members of the research team authorized by the project leader will have access to these databases.

All data related to the project will be retained for at least 10 years for quality assurance purposes.

Reporting and Participant Feedback

It is not intended to provide participants with details of their individual urinary biomonitoring results as only specific pesticide metabolites will be analyzed, and so we may not assess all pesticide exposure; we can only interpret the results in terms of exposure, not possible ill-health effects. Where a result is unexpectedly high, there will be a review by the scientific

advisory board to determine the implications of the result and the need for any action.

The overall study findings will be published as a publicly available report, peer reviewed publications, and conference presentations. The project website will post news about the project at regular intervals, as well as providing access to project publications and conference presentations. Participants will be advised of its URL. Where the original studies include community feedback (Uganda and Malaysia), the summaries of the urine results will be included in these activities.

No personal identifying details of individual participants will be disclosed in any publications or presentations arising from this work.

Statistical Analysis

Evaluation of Recall Bias

Analysis of the collected data will focus on the assessment of participants' ability to recall information regarding their previous use of pesticides during work over time. Commonly used determinants of exposure to pesticides, as available within study questionnaires, will be compared. These include the duration of use (days and hours per year), methods of mixing and application, products and areas of use, use of PPE during mixing and handling, and personal hygiene activity (eg, timing of personal washing and cleaning clothes). At first, comparisons will involve the newly collected questionnaire data against those already existing within each cohort, stratified by period of recall (ie, short-, medium-, and long-term recall defined as <2 years, 6-12 years, and >15 years since filling out the initial study questionnaire). Subsequently, and whenever possible, data will be pooled together using a standard database management system software (eg, ACCESS). Data pooling will be based on the similarity and meaning of the available questionnaire items across studies, and the included data will be comprehensively reviewed, cleaned, and prepared before the statistical analysis.

Following the initial data cleaning and processing, descriptive statistics will be applied, and the basic attributes of the measurement database will be described. The main analysis will be performed using standard statistical approaches such as the estimation of proportions of agreement and Cohen kappa statistics. The existing data will form the reference category in these comparisons. Standard statistical analysis software (eg, Stata, StataCorp LLC or SAS) will be used.

Evaluation of Currently Available Individual-Based Exposure Assessment Methods for Pesticide Exposure

Participants' daily average exposure will be estimated using the contextual information from the questionnaires and the exposure measurement surveys. Estimations will be based on mathematical equations (algorithms) developed by Dosemeci et al [21] as part of the exposure assessment of the AHS. Improvements were made to these algorithms through updating the assigned exposure-modifying factors and structural components [6,22-24], and a further adaptation of the general version of the AHS algorithm is now available [25].

Exposure predictions will be based both on the original Dosemeci et al [21] and the updated version of the AHS algorithm [25]. However, since the algorithms have been developed specifically for the AHS cohort, tailored adaptations of the updated general algorithm to the exposure situation specific to the populations in question will also be developed, for example, the Uganda cohort already has an adapted algorithm (Fuhrimann, personal communication). As with previous work, tailoring of the algorithms will be based on expert opinion and the available literature.

For each algorithm, 2 sets of intensity scores will be calculated. One will use the information derived from the participant's questionnaire responses, covering their usual working and exposure practices. The other will use the information collected from the self-reported diaries covering the actual working practices applied during work on the day of the measurements.

The performance of algorithms as tools for assessing exposure to pesticides will be evaluated through comparisons of the estimated intensity scores from all different versions applied on the same sets of information against the results of the collected biomonitoring data. These comparisons are expected to provide information on the exportability of the algorithm exposure assessment approach developed as part of the AHS study to new pesticide exposure populations and situations. The benchmarking of the different versions of the algorithm (ie, original AHS, updated AHS, and population specific) will inform about the gain in performance by the tailoring of the equations to the population and exposure situation at hand.

Data analysis will commence with an assessment of the shape of the distribution of the collected exposure data through graphical means and formal statistical tests. Where sample results are below the limits of detection, proper data processing methods will be selected based on the actual proportion of observed censored values and the available recommendations in the literature [26]. Appropriate transformations will be applied, and exposure measurements and algorithm intensity scores will be summarized using the corresponding central tendency measured. Differences between mean values of continuous variables will be evaluated, depending on the requirements, using paired or unpaired Student *t* tests, or analysis of variance regression for comparisons between multiple groups. If required, nonparametric statistical approaches will be applied. Chi-square tests will evaluate differences between groups in characteristics of a categorical nature. The associations between the different algorithm scores and the exposure measurements will also be explored using conventional regression analysis approaches including correlation analysis. Multivariate linear regression models with the exposure measurements as the dependent variable and the algorithm parameters or estimated scores as the independent variables will also be employed to allow the influence of the different parameters in the exposure to be examined.

Epidemiological studies frequently perform the analysis on the basis of exposure categories derived from the distribution of the objective exposure measurement results (eg, tertiles and quartiles). Therefore, analysis with the exposure intensity scores as a categorical variable will also be performed. Cutoffs for the exposure categories will be based on the distribution characteristics of the derived intensity scores and exposure

measurement results. The differences between the means of the measured exposure concentrations between the established categories of scores will be evaluated, and Chi-square tests for independence between the categories of the scores and the measurements will be performed. Classical agreement analysis between categorical variables will also be performed.

Power Calculations

Power calculations (see Multimedia Appendix 1) indicate that 150 to 216 questionnaire responses and at least 84 participants providing urine samples are required to provide 80% power for the various comparative analyses. Data from the ongoing PIPAH study suggest an expected response rate of 25% to 40% for the repeated questionnaire. We can therefore reasonably expect 125 to 200 questionnaire responses for the PIPAH study and, given that this is an engaged cohort, we might assume that many may also consent to the exposure assessment project aim. The Malaysian cohort has already recruited and sampled approximately 150 participants. The Uganda cohort will look to recruit >84 participants for the exposure assessment study. For the questionnaire recall, the number of participants recruited from the SHAW and historical biomonitoring populations cannot be guaranteed (owing to age of participants); it may therefore only be possible to analyze these data on a pooled basis.

Ethical Considerations

As previously stated, each cohort will seek separate ethical approval based on the same outline protocol. The IMPRESS project has also been registered on Research Registry (identification number 4292).

In addition, an advisory board comprising 4 independent experts has been appointed and will monitor the study progress throughout the project. They reviewed earlier versions of the study protocols for the work described in this manuscript.

Studies such as the one summarized in this paper may encounter a number of difficulties with recruitment and with the quality of information recorded by participants. Care must also be taken to avoid research fatigue (participants withdrawing owing to excessive demands from the projects). IMPRESS is based on existing cohorts whose participants have already demonstrated a commitment to participating in research and from that previous or ongoing involvement, they have some idea of what participation will entail. In the United Kingdom, following the initial response to the recall exercise, only 1 reminder will be sent to participants regarding the completion and return of the study material. Where participants expressed an interest in being contacted for the biomonitoring element of the project, after the initial approach, there will only be 2 reminders within 2 months during the spray season. In Uganda and Malaysia, recruitment is only attempted once, at the point of visiting the worksite.

We consider that there are no risks to participants in taking part in the research project, and we will take steps to minimize any burden that they may experience. In particular, the length and language used in the surveys will not be onerous. Participants will be asked to provide urine samples on specific days during the production or growing season which are relevant, where possible, to the use of selected pesticides. The provision of urine samples is not considered difficult or invasive.

The survey materials will not include any topics that might be considered sensitive, embarrassing, or upsetting and criminal or other disclosures requiring action are not considered as possible to occur during the study. If the field researchers observe dangerous practices, then they will advise the individual accordingly (this is not relevant to UK participants as their application practices will not be observed). Owing to the classic observational design (without any intervention) of this study, we also do not anticipate any specific health or other issues arising from it. Hence, there are no specific criteria for suspending or terminating participants in this study.

Finally, participants will not be compensated for their time incurred in participating in the IMPRESS project. This reflects the conditions offered in the original cohort studies.

Ethics Approval and Consent to Participate

PUHS and PIPAH: Ethical approval for the study has been obtained from the University of Sheffield's Research Ethics Committee (REC) for the assessment of recall bias (Reference Number HSL28) and the exposure assessment (Reference Number HSL29). The Greater Manchester Central REC gave approval for the PUHS to share individual-level data collected as part of the 2004-2006 Survey of Pesticide Usage with the PIPAH study (REC Reference number 14/NW/1042).

SHAW: Ethical approval has been obtained from the University of Manchester RECs (2019-5987-9976).

UK Historical biomonitoring data: Ethical approval was granted by the HSE's Research Ethics Panel (Impress_ERAC_140819).

Uganda: Ethical approval will be sought from Utrecht University in the Netherlands and the Higher Degrees Research and Ethics Committee at Makerere University in Uganda.

Malaysia: Ethical approval for the study has been obtained from the University of Manchester RECs (2017-0439-3979) and a Malaysian Medical REC (NMR-17-424-34635[IIR]).

Results

The project was funded in September 2017. Enrollment and sample collection was completed for Malaysia in 2019 and is on-going for Uganda and the United Kingdom. Sample and data analysis will proceed in 2020 and the first results are expected to be submitted for publication in 2021.

Discussion

To our knowledge, IMPRESS is the largest and most comprehensive evaluation of pesticide EAM used in epidemiological studies of working populations ever performed, with previous comparable exercises in farming populations being small either in terms of personal measurements involved (generally below 200 measurements per study) or EAMs or scenarios included [6,22,23,27-31]. The study builds on work already undertaken within the AHS [32], which looked at the impact of misclassification in 83 operatives using 2 active ingredients, concluding that misclassification may result in false-negative findings and hence underestimate exposure risks. It is anticipated that the knowledge obtained from the project

will assist in optimizing the way in which epidemiological studies of occupational pesticide exposures perform their exposure assessment. This is probably an important development considering that surrogate EAMs comprise the main exposure assessment in more than 70% of the epidemiological studies published within the last 25 years with increasing trends in use being observed for some of these methods within the same period [8].

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Authors' Contributions

KJ and IB are the lead authors responsible for the drafting and completion of the research protocol and also for the drafting of this manuscript. KG also assisted with the drafting of this manuscript. KG, IB, JC, KJ, HK, AP, MT, and RV were responsible for developing the original project proposal. All authors contributed to the development of the study protocol. KG is Principal Investigator of the IMPRESS project. AH is Principal Investigator of the PIPAH and PUHS studies, HK is Principal Investigator of the Uganda study, and AP is Principal Investigator of the SHAW and Malaysian studies. All authors have provided comments on the drafts and have read and approved the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary material – Power calculations.
[DOCX File , 50 KB - resprot_v9i2e16448_app1.docx]

Multimedia Appendix 2
Peer-reviewer report 1 from IMPRESS.
[PDF File (Adobe PDF File), 294 KB - resprot_v9i2e16448_app2.pdf]

Multimedia Appendix 3
Peer-reviewer report 2 from IMPRESS.
[PDF File (Adobe PDF File), 218 KB - resprot_v9i2e16448_app3.pdf]

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Abbreviations

AHS: Agricultural Health Study
EAM: exposure assessment method
GDPR: General Data Protection Regulation
HSE: Health and Safety Executive
IMPRESS: Improving Exposure Assessment Methodologies for Epidemiological Studies on Pesticides
IOM: Institute of Occupational Medicine
NRoSO: National Register of Sprayer Operators
PESTROP: pesticide use in tropical settings
PIPAH: Prospective Investigation of Pesticide Applicators' Health
PPE: personal protective equipment
PUHS: Pesticide Users Health Study
REC: Research Ethics Committee
SHAW: Study of Health in Agricultural Work

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Protocol

Adjuvant Alpha-Fetoprotein-Derived Peptide After Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma: Protocol for a Safety Study

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Abstract

Background: Hepatocellular carcinoma (HCC) is a worldwide health concern because of a continued increase in cases globally; furthermore, the prognosis for patients with HCC remains poor. Transarterial chemoembolization (TACE) has been established as the standard of care for the intermediate stage of HCC; however, no therapeutic agents are available to reduce the high rate of recurrence.

Objective: This study aims to evaluate the safety of alpha-fetoprotein (AFP)-derived peptides for patients with HCC post-TACE.

Methods: This will be an open-label, single-arm, multicenter study to evaluate the safety of AFP-derived peptides (AFP 357 and AFP 403), which contain histocompatibility antigen-A24-restricted cytotoxic T lymphocyte epitopes from tumor antigens expressed in HCC and is recognized at a high rate by lymphocytes in patients with HCC. Protocol treatment will consist of six courses of the subcutaneous administration of 3 mg each of AFP 357 and AFP 403. A total of 14 patients will be included in this study, the first 6 as a main analysis target group and an additional 8 as an extended cohort from three institutions in Japan. The primary endpoint will be the occurrence of serious adverse events (safety profile). The secondary endpoints will include time to progression, overall survival, completion rate, and adverse events (efficacy profile).

Results: We have recruited 14 patients with HCC as of December 2019. The final follow-up will be completed by March 2020.

Conclusions: In this study, we will evaluate the safety profile of AFP-derived peptides for patients with HCC post-TACE. We believe that this study will provide useful information and will help to design a subsequent phase II trial based on the results.

Trial Registration: Japan Registry of Clinical Trials jRCTs041180155; https://jrct.niph.go.jp/latest-detail/jRCTs041180155

International Registered Report Identifier (IRRID): DERR1-10.2196/17082

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KEYWORDS

hepatocellular carcinoma; alpha-fetoprotein-derived peptides; safety trial

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide [1]. Certain therapies are effective for treating different stages of HCC [2]. However, there is a high rate of metachronous and multifocal recurrence, even after curative treatment. Transarterial chemoembolization (TACE) has been established as the standard of care for the intermediate stage of HCC [3-6]. However, TACE is inferior to resection or percutaneous treatment in terms of curability and has a high rate of recurrence near the treated lesion, despite being judged

effective based on posttreatment imaging studies. Moreover, patients with HCC are often in a cirrhotic state, in which the underlying liver has high carcinogenic potential, and relapse occurs at a high rate at sites remote from the treated lesion. Therefore, attempts are being made to develop therapies to prevent such recurrence. Sorafenib [7,8], brivanib [9], and olantinib [10] have been tested in combination with TACE in an adjuvant setting, but none of these trials have validated their use. Therefore, observation is the standard treatment strategy for patients with HCC post-TACE.

Since the identification of the melanoma antigen-encoding gene in 1991, the human immune system has been shown to recognize tumor antigens and eliminate tumor tissue. The primary cell type responsible for tumor cell clearance is the T cell, which recognizes a peptide fragment complex composed of a major histocompatibility antigen present on the surface of the tumor cell and a protein produced by the tumor cell and exhibits cytotoxic activity. Several tumor-specific antigens and peptides, along with their amino acid sequences, have been identified, and immunotherapy based on these peptides has been attempted. Some immunotherapy approaches have been able to induce T cells to attack tumor cells in humans, demonstrating antitumor effects.

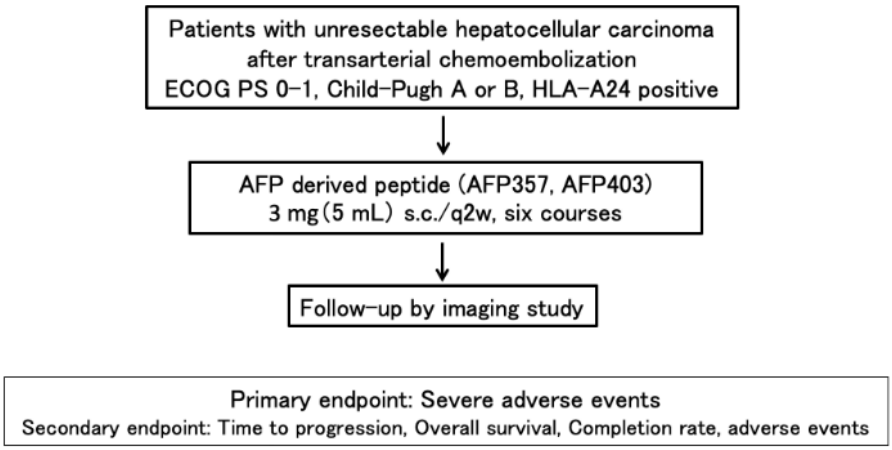
We have screened and compared many candidates as targets for immunotherapy strategies in HCC [11-13]. Based on these findings, two alpha-fetoprotein (AFP)-derived peptides, AFP 357 and AFP 403, were identified as attractive compounds to activate cytotoxic T cells in patients with HCC, and preclinical and clinical studies were conducted using these molecules. In a phase I study, AFP 357 and AFP 403 were administered to 20 patients with advanced HCC. In all patients, no serious adverse events were observed. Moreover, complete response was obtained in 1 patient and tumor control achieved in 8 patients, which was according to the Response Evaluation Criteria in Solid Tumors (RECIST). The immunological effects of AFP-derived peptides were confirmed in 5 of 15 patients (33%), for whom efficacy was evaluated after 3 or more doses [11]. Based on these findings, immunotherapy using AFP-derived peptides might be a promising therapeutic strategy for patients with HCC post-TACE as it is suggested for patients with more advanced HCC. The aim of this study, therefore, was to evaluate the safety of AFP-derived peptides for patients with HCC post-TACE.

Methods

Overall Study Design

This will be an open-label, single-arm, multicenter study (Figure 1). The primary endpoint of this study will be serious adverse events (safety profile); the secondary endpoint will include time to progression, overall survival, completion rate, and adverse events (efficacy profile). This study will be conducted in accordance with the Declaration of Helsinki, Clinical Trials Act, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable laws and guidelines in Japan. The protocol of this study was approved by the Institutional Review Board at Kanazawa University Hospital and is registered at the Japan Registry of Clinical Trials (jRCTs041180155).

Figure 1. Diagram of study design. ECOG: Eastern Cooperative Oncology Group; PS: performance status; HLA: human leukocyte antigen; AFP: alpha-fetoprotein.



Study Participants

We will first recruit 14 patients at Toyama City Hospital and Fukui-ken Saiseikai Hospital, subsequently adding those at the Kanazawa University Hospital, from October 2017 to December 2019. All patients will meet the inclusion criteria and no exclusion criteria will be applied (Textbox 1). Patients will be provided with comprehensive information about AFP-derived peptides and will provide written informed consent to participate in this study.

Textbox 1. Inclusion and exclusion criteria of this study.

Inclusion criteria

1. The patient was clinically diagnosed with hepatocellular carcinoma (based on histology or imaging)
2. Transarterial chemoembolization was performed because resection or percutaneous local treatment was not indicated due to multiple occurrences
3. It was confirmed that good embolic effects were obtained for nodules treated with transarterial chemoembolization
4. Patients whose adverse events associated with Transarterial chemoembolization have resolved or not worsened
5. Patients with human leukocyte antigen–A24-positive human tumor histocompatibility antigen
6. Child-Pugh classification is A or B
7. Age at entry (full age) is 20 years or higher
8. The Eastern Cooperative Oncology Group performance status is less than or equal to 2 (0–2)
9. The most recent test value within 14 days prior to enrollment satisfies all of the following: neutrophil count≥1000/mm3, hemoglobin level≥8.0 g/dL, platelet count≥40,000/mm3, total bilirubin level ≤3.0 mg/dL
10. The patient has provided written consent to participate in the trial

Exclusion criteria

1. The patient has refractory ascites and moderate or severe pleural effusion
2. The patient had a history of hepatic encephalopathy within 3 months before registration
3. Esophagogastric varices at risk of bleeding have been identified and no preventive measures have been taken
4. Active malignancy
5. Blood transfusions, blood products (containing a preparation of albumin), and blood-enhancing factor products such as granulocyte colony-stimulating factor administered within 2 weeks prior to enrollment
6. The patient received continuous systemic administration of steroids or other immunosuppressants (oral or intravenous administration)
7. Serious complications (including heart failure, renal failure, hepatic failure, bleeding peptic ulcer, intestinal paralysis, intestinal obstruction, and poorly controlled diabetes mellitus)
8. Infection (except for viral hepatitis) that requires systemic treatment
9. A woman who is pregnant, possibly pregnant, within 28 days after childbirth, or breastfeeding; a man who wishes to become pregnant with his partner
10. The patient is considered to have a psychiatric disorder or psychiatric symptom, and it is difficult for them to participate in the study
11. The patient has serious hypersensitivity to alpha-fetoprotein-derived peptides or components of adjuvants
12. Neither computed tomography nor magnetic resonance imaging with contrast agent can be performed due to drug allergy
13. The attending physician determines that participation in this study is inappropriate

Intervention

The treatment drug will be AFP-derived peptides (AFP 357 and AFP 403), which contain human leukocyte antigen (HLA)-A24–restricted cytotoxic T lymphocyte epitopes derived from tumor antigens expressed in HCC that are recognized by lymphocytes in patients with HCC at a high rate [11,13]. The AFP-derived peptides used in this study will be produced by Neo MPS Inc (San Diego, California) at Good Manufacturing Practice grade. One course of treatment will consist of the subcutaneous administration of 3 mg each of AFP 357 and AFP 403 on day 1 followed by 13 days of rest. Treatment will be repeated for up to six courses unless the following discontinuation criteria are applicable: obvious tumor progression based on radiological or physical findings, any adverse event that causes the discontinuation of protocol therapy, patient refusal, or death during protocol therapy. Before the treatment course starts, we will confirm that no grade 2 or higher adverse events exist. The administration of anticancer drugs other than AFP 357 and AFP 403 and procedures such as TACE, radiotherapy, hormonal therapy, or immunotherapy will not be permitted during the study. However, corticosteroids needed for fatigue; anorexia and emaciation; diuretics; amino acid preparations for ascites; hepatic edema; treatment of complications such as hypertension or diabetes mellitus; and antiemetics for nausea or vomiting will be permitted.

Follow-up Schedule

Table 1 shows the overall follow-up schedule. In this study, six courses of AFP-derived peptide administration are defined as the protocol treatment, and the entire study period is classified into the following three periods: pretreatment period, from consent to the start of treatment; treatment period, from the start of treatment to 30 days after the last administration (to assess adverse events related to protocol treatment); and follow-up period, from the end of the treatment period to death or to the final follow-up of this study. Before registration, hepatitis virus markers including hepatitis B virus antigen (HBsAg) and

hepatitis C antibody will be assessed. Hepatitis B virus-DNA will be checked in positive HBsAg results. Hepatitis B surface antibody and Hepatitis B core antibody will be checked if HBsAg results are found to be negative. Chest x-ray, electrocardiogram, and tumor markers including AFP and des-carboxy-prothrombin will be assessed prior to TACE treatment. Patient's general condition will also be evaluated using Eastern Cooperative Oncology Group (ECOG) performance status, body weight, encephalopathy, blood tests (complete blood count, blood chemistry, and coagulation), objective findings, contrast-enhanced computed tomography, and tumor markers within 14 days prior to registration.

Table 1. Follow-up schedule for trial protocol.

Assesments	Pretreatment period	Treatment period		Follow-up period
		During protocol treatment	Postprotocol treatment	
General condition				
Adverse events	14 days prior[a]	Date of administration[b]	1 month after[c]	N/A[d]
Height	Before registration	N/A	N/A	N/A
Body weight	14 days prior	N/A	N/A	N/A
ECOG[e] performance status	14 days prior	Date of administration	1 month after	N/A
Clinical examination				
WBC[f] (differential), hemoglobin, platelets	14 days prior	As needed	As needed	N/A
Albumin, bilirubin, aspartate transaminase, alanine transaminase, BUN,[g] creatinine, lactate dehydrogenase, alkaline phosphatase, CRP,[h] PT,[i] PT-INR,[j] PT activity levels	14 days prior	As needed	As needed	N/A
HBs[k] antigen, HCV[l] antibody	Before registration	N/A	N/A	N/A
HBs antibody, HBc[m] antibody, HBV[n]-DNA	As needed	As needed	N/A	N/A
Alpha-fetoprotein, PIVKA-II[o]	14 days prior	12 weeks after[p]	N/A	12 weeks with no progression[q]
Contrast-enhanced computed tomography	14 days prior	12 weeks after	N/A	12 weeks with no progression
Arterial blood gas	N/A	As needed	N/A	N/A

[a]Within 14 days prior to registration.

[b]Date of administration or the day before administration.

[c]1 month after discontinuation of protocol therapy or until the start of posttreatment.

[d]Not applicable.

[e]ECOG: Eastern Cooperative Oncology Group.

[f]WBC: white blood cell.

[g]BUN: blood urea nitrogen.

[h]CRP: C-reactive protein.

[i]PT: prothrombin time.

[j]INR: international normalized ratio.

[k]HBs: hepatitis B surface.

[l]HCV: hepatitis C virus.

[m]HBc: hepatitis B core.

[n]HBV: hepatitis B virus.

[o]PIVKA-II: protein induced by vitamin K absence or antagonist-II.

[p]12 weeks after enrollment (allow ± 2 weeks of change).

[q]12 weeks after enrollment in cases of no apparent disease progression.

During the treatment period, patients' general condition including ECOG performance status, encephalopathy, and adverse events will be evaluated at every visit for the safety profile. Blood tests, chest X-ray, or electrocardiogram will also

be performed if needed. Contrast-enhanced computer topography (CT) and tumor markers will be evaluated for the efficacy endpoint every 12 weeks after enrollment. Contrast-enhanced CT and tumor markers will also be evaluated until tumor progression is confirmed during the follow-up period.

Endpoints

The primary endpoint of this study will be the occurrence of serious adverse events (safety profile) during the treatment protocol. Serious adverse events are defined as any adverse events causing death, life-threatening condition, hospitalization (initial or prolonged), disability or permanent damage, or congenital anomaly/birth defect outcomes. Adverse events will be evaluated according to the Common Terminology Criteria for Adverse Events v 4.0 JCOG Version (Japanese translation of the NCI-Common Terminology Criteria for Adverse Events v 4.0) (CTCAE v 4.0 - JCOG). Each adverse event will be graded based on the definitions of grades 0-4. If a specific procedure is described based on grade, it will be graded for its clinical need. For example, if a patient has increased pleural effusions and oxygen or chest drainage is indicated, the patient may refuse. In such cases, the grading will be based on the medical judgment of what should have been performed rather than whether treatment was actually administered.

The secondary endpoints will be the efficacy profile including time to progression, overall survival, and completion rate as well as adverse events. The efficacy profile will be evaluated according to the Revised RECIST guidelines for the evaluation of the therapeutic efficacy of solid tumors Version 1.1 every 12±2 weeks after registration. The efficacy will be evaluated based on the same examination conditions as the baseline evaluation, such as slice width if imaging results are available. However, plain radiography and contrast studies with different modalities will be acceptable if a contrast allergy is detected prematurely and testing with the same modality cannot be continued.

Data Monitoring

Selected monitoring staff will conduct centralized data monitoring. The trial database will be monitored and reviewed annually by the selected monitoring staff, and data queries will be raised if necessary.

Sample Size

We first calculated the sample size for this study based on our in-house data on patients with HCC. Kanazawa University Hospital conducted TACE for 350 patients with HCC from January 2005 to December 2011. In this group of Japanese patients with HCC, approximately 60% of the individuals were HLA–A24-positive, and approximately 30% of the candidates were expected to drop out based on eligibility criteria and exclusion criteria. Considering that this is a safety confirmation study, the rate of obtaining consent for this study was suggested to be 30%, and as such, approximately 8 patients were expected to be recruited annually. On January 2019, the safety profiles of the 6 cases included in this study were reviewed by authorities of the Ministry of Health, Labour and Welfare, and the safety of the treatment protocol was confirmed. Based the advice of the Efficacy and Safety Committee, the 6 cases were designed as the main analysis target group for the safety confirmation part. Registration of additional cases continued at Fukui-ken Saiseikai Hospital, Toyama City Hospital, and Kanazawa University Hospital until December 31, 2019. The target number of patients in this extended cohort was set at 8 based on the expected number of patients at the cooperative research institution. In total, we included 14 patients from three hospitals.

Statistical Analysis

Safety profiles will be summarized using appropriate descriptive statistical methods. If necessary, we will obtain an accurate 95% confidence interval based on the binomial distribution. Time to progression is defined as the period from the date of enrollment to the date of evaluation of tumor progression. Tumor progression includes both “progressive disease” based on imaging examination, evaluated according to RECIST version 1.1 (radiological progression), and tumor progression that cannot be confirmed by imaging examination (clinical progression). The date of the tumor progression evaluation will be determined by when imaging examination is performed for radiological progression and clinical judgement is made for clinical progression. Overall survival is defined as the period from the date of enrollment to the date of death from any cause. Cumulative survival will be estimated using the Kaplan-Meier method. Completion rate will be calculated as the number of patients receiving six courses of AFP-derived peptide divided by the number of patients enrolled.

Results

We recruited a total of 14 patients with HCC and ended recruitment in December 2019. The final follow-up will be completed in March 2020. Then, we will perform data analysis and disseminate the study results in late 2020.

Discussion

We previously reported the safety and efficacy of these AFP-derived peptides for patients with HCC who were intolerant or refractory to standard therapy, or in other words, those with advanced-stage HCC [11]. Recently, numerous agents have been developed and subjected to ongoing clinical trials for such patients, and some of them were found to prolong survival in large phase III trials [14-16]. However, no agents have proven their ability to suppress metachronous and multifocal recurrence in patients with HCC post-TACE [7-10]. Due to the large number of patients experiencing recurrence, there is a need for further research.

As another rationale for the target population, we previously found that more advanced-stage patients harbor more antitumor suppressor cells [17,18], which suggested that it was better to select patients at an earlier stage to maintain their antitumor immunity and maximize the efficacy of cancer peptide therapy. Moreover, earlier-stage patients are considered suitable in terms of feasibility and safety, because patients with more advanced-stage HCC tend to experience deterioration of hepatic reserve or general condition [19]. With these considerations, we set the target population as patients post-TACE administration for this study.

The primary aim of this study is to evaluate the safety profile of AFP-derived peptides, namely AFP 357 and AFP 403, for patients with HCC post-TACE. We will also evaluate feasibility and efficacy endpoints to obtain helpful information for the design of a subsequent phase II trial. We believe that this study will show the safety of AFP-derived peptides for patients with HCC post-TACE, and we plan to design the subsequent phase II trial based on its results.

Conflicts of Interest

None declared.

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Abbreviations

AFP: alpha-fetoprotein
CT: computer topography
ECOG: Eastern Cooperative Oncology Group
HBsAg: hepatitis B virus antigen
HCC: hepatocellular carcinoma
HLA: human leukocyte antigen
RECIST: Response Evaluation Criteria in Solid Tumors
TACE: transarterial chemoembolization.

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Protocol

Willingness to Seek Help for Depression in Young African American Adults: Protocol for a Mixed Methods Study

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Abstract

Background: In the United States, among those living with mental illness, 81% of African American (AA) young adults do not seek treatment compared with 66% of their white counterparts. Although the literature has identified unique culturally related factors that impact help seeking among AAs, limited information exists regarding the development and evaluation of interventions that incorporate these unique factors.

Objective: This study aims to describe a study protocol designed to develop a culturally relevant, theory-based, psychoeducational intervention for AA young adults; to determine if exposure to the intervention impacts AA young adults' willingness to seek help; and to determine whether cultural factors and stigma add to the prediction of willingness to seek help.

Methods: The Theory of Planned Behavior (TPB) and Barrera and Castro's framework for cultural adaptation of interventions were used as guiding frameworks. In stage 1 (information gathering), a literature review and three focus groups were conducted to identify salient cultural beliefs. Using stage 1 results, the intervention was designed in stage 2 (preliminary adaptation design), and in stage 3 (preliminary adaptation tests), the intervention was tested using pretest, posttest, and 3-month follow-up surveys. An experimental, mixed methods, prospective one-group intervention design was employed, and the primary outcomes were participants' willingness and intention to seek help for depression and actual help-seeking behavior.

Results: This study was funded in May 2016 and approved by the University of Texas at Austin institutional review board. Data were collected from November 2016 to March 2016. Of the 103 students who signed up to participate in the study, 70 (67.9%) completed the pre- and posttest surveys. The findings are expected to be submitted for publication in 2020.

Conclusions: The findings from this research are expected to improve clinical practice by providing empirical evidence as to whether a culturally relevant psychoeducational intervention is useful for improving help seeking among young AAs. It will also inform future research and intervention development involving the TPB and willingness to seek help by identifying the important factors related to willingness to seek help. Advancing this field of research may facilitate improvements in help-seeking behavior among AA young people and reduce the associated mental health disparities that apparently manifest early on.

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KEYWORDS

African American young adults; depression; willingness to seek help; Theory of Planned Behavior

Introduction

Background

As the leading cause of disability in the United States, depression impacts 15.7 million US adults and represents a significant health problem [1,2]. Although lifetime prevalence of depression is higher among whites compared with African Americans (AAs), 17.9% and 10.4%, respectively, AAs live with significantly more persistent, chronic, impairing, and disabling depression compared with whites [3,4].

Despite high levels of persistent and disabling depression, treatment among AAs is suboptimal. This higher disease burden is especially concerning when disparities in mental illness treatment are considered. There is evidence that AAs are less likely to receive treatment compared with whites [5,6]. It is estimated that 70% of AA adults living with mental illness received no treatment compared with 53% of white adults [5]. Moreover, lack of help seeking among young AA adults was higher, with 81% receiving no treatment, compared with 66% of young white adults [5]. Therefore, despite an estimated lower prevalence of depression, AAs live with more persistent, chronic, and disabling depression that is more likely to be untreated.

The literature identifies lack of perceived need, financial costs, the desire to handle the illness on one's own, and stigma as common reasons why US adults do need to seek help [7-9]. Although these factors impact help seeking across racial and cultural lines, the literature has also identified unique cultural factors that impact help seeking among AA adults and young adults. These unique cultural factors include culturally embedded stigma, attitudes toward treatment, the influence of family and friends, medical mistrust, self-reliance, and religiosity [10-25]. To date, much of the literature evaluating these unique cultural factors have been descriptive in nature. Research is needed to address the influence of culturally-linked barriers and interventions targeting culturally linked barriers that may impact help seeking. If left unaddressed, the lack of help seeking among AAs may lead to greater disparities in depression treatment, which could lead to suboptimal outcomes such as suicide [26,27], which is the third leading cause of death among AA young adults (aged 18-25 years) [28].

Psychoeducational interventions have been identified as a tool to improve mental health help seeking. Psychoeducational interventions are a type of psychosocial treatment that combines psychotherapeutic and educational interventions using a collaborative and patient empowerment approach [29,30]. These interventions have been delivered in person, over the phone, through written patient information, and over the internet [31-34]. Psychoeducational interventions typically provide factual didactic information and can also include interactive activities and consumer educators. Psychoeducational interventions have demonstrated utility in preventing major depressive disorder [35], decreasing symptom burden [35-37], decreasing the risk of depression relapse [37], improving the quality of life [36], and improving global functioning [37]. Mental Health First Aid (MHFA) is such an intervention and is recognized as a Substance Abuse and Mental Health Services Administration (SAMHSA) national evidence-based program. It has demonstrated effectiveness in increasing mental illness knowledge, decreasing stigma, and improving help-seeking intentions and behaviors [33,38,39]. MHFA is an 8-hour course designed to provide members of the community with skills to assist during a mental health crisis and to help someone who may be developing a mental health problem [39]. MHFA is framed by two theoretical principles: (1) stigma can be reduced through awareness raising and education and (2) social support is instrumental in reducing risk for mental illness and in assisting a person with a mental health problem [40,41]. In addition to its standard form, MHFA has been successfully adapted for other populations (eg, rural populations and Aboriginal Australians) [33,42-46]; however, no such adaptation exists for AAs.

Despite the success of psychoeducational interventions and the identification of cultural factors that are unique to AAs, limited research has addressed the influence of culturally-linked barriers and interventions targeting culturally linked barriers that may impede help seeking [13,32,47]. Interventions in the literature report limited success and have typically not documented the utilization of a theoretical foundation for intervention design. Therefore, a gap currently exists regarding culturally relevant, theory-based psychoeducational interventions for AAs. Research is needed to address this gap, as this type of intervention represents an opportunity to target culturally embedded stigma and other culturally related factors and improve help seeking among a vulnerable and at-risk population. Furthermore, considering that AA young adults are more likely to not seek help and that suicide represents the third leading cause of death among AA young adults (aged 18-25 years) [28], this subgroup represents an even more vulnerable and at-risk population. In addition, most literature evaluating cultural factors related to help seeking and psychoeducational interventions in AAs have focused on AA adults, leaving cultural factors and interventions among AA young adults less understood. Given the factors related to AA help seeking (eg, attitudes, cultural factors, family and friends, and barriers), the Theory of Planned Behavior (TPB) is the proposed mechanism of action and guiding framework for this study.

Objectives

The overall objective of this study is to understand how a culturally relevant, theory-based, interactive psychoeducational intervention can impact depression help-seeking willingness and subsequent behavior among AA college students. The central hypothesis is that the culturally adapted psychoeducational intervention will significantly improve willingness to seek help for depression.

Specifically, the aims are as follows:

- Aim 1: To develop a culturally relevant, theory-based, interactive psychoeducational intervention for AA college students. The intervention, guided by MHFA, a SAMHSA National Evidence-Based Program, was created through incorporating findings from the literature and qualitative focus groups.
- Aim 2: To determine if exposure to a culturally relevant psychoeducational intervention impacts AA students'

willingness to seek help, attitude toward seeking help, perceived behavioral control over seeking help, depression stigma, and actual help-seeking behavior. We hypothesized that after the intervention, participants would be more willing to seek help for depression, have more favorable attitudes, and report increased perceived behavioral control and less stigma regarding depression.

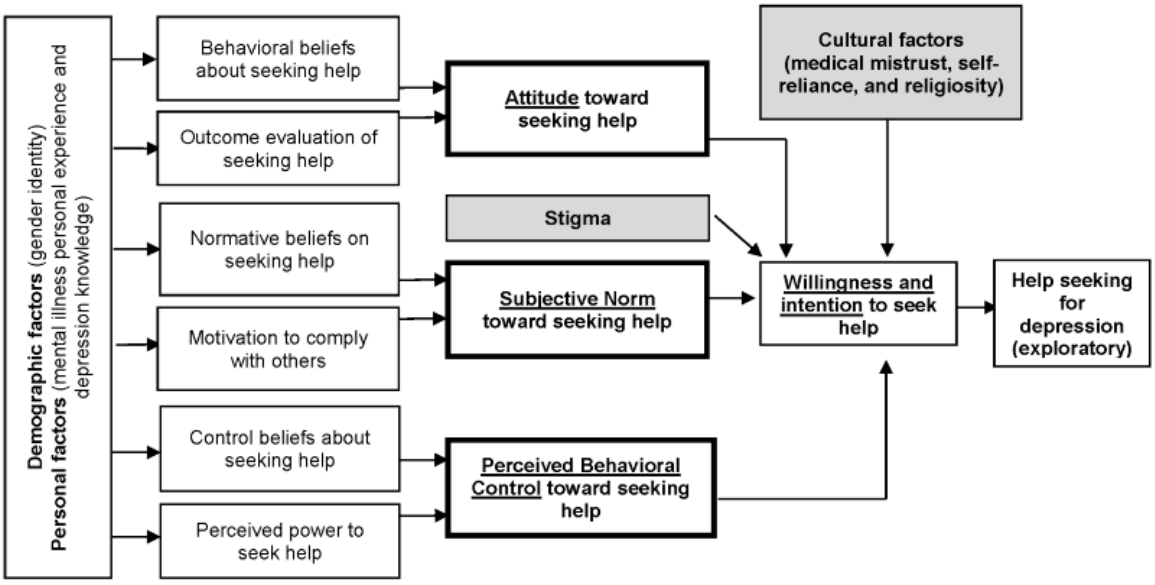
- Aim 3: To determine whether stigma and the cultural variables (ie, medical mistrust, self-reliance, and religiosity) add to the prediction of the TPB constructs (ie, attitude, subjective norm, and perceived behavioral control) in predicting AAs' willingness to seek help.

Methods

Intervention

The study intervention was developed using the TPB and Barrera and Castro's [48] framework for cultural adaptation of interventions. The TPB posits that behavioral intention directly predicts actual behavior (see Figure 1 for study conceptual model) [49]. The TPB is an expectancy value–based attitude-behavior model designed to explain behaviors in which people are able to exert self-control [49,50]. In this study, behavioral intention or willingness to seek help for depression is determined by attitudes toward seeking help, subjective norms associated with seeking help, and perceived behavioral control over seeking help. Attitude, subjective norm, and perceived behavioral control are determined by composites of related beliefs. Attitude comprises behavioral beliefs and outcome evaluations. Subjective norm comprises normative beliefs and the motivation to comply with others. Finally, perceived behavioral control comprises control beliefs and perceived power. The TPB was selected as a guiding framework because of its success in examining factors that impact other various health-related behaviors (eg, condom use, exercise behavior, dietary behavior, breastfeeding, and health screenings) [51-55]. In addition, factors that impact AA help seeking that were identified in the literature closely align with the TPB variables (eg, attitude toward treatment, influence of family and friends, and barriers such as lack of knowledge). Studies using the TPB in mental health help seeking have reported models that explain 42% to 93% of the variance in willingness or intention [56-59]. Among these studies, although samples did include some AAs, no sample consisted solely of AAs. At present, limited TPB studies in AA-only samples exist; however, no known studies exist in the area of mental health care help seeking [60-63].

Figure 1. Conceptual model: using the Theory of Planned Behavior to predict willingness to seek help.



Barrera and Castro's [48] cultural adaptation framework was also used as a guiding framework. It suggests that researchers and clinicians undertake the following steps to adapt an intervention: (1) information gathering, (2) preliminary adaptation design, (3) preliminary adaptation tests, and (4) adaptation refinement [48]. Researchers begin with the *information gathering* stage, which involves reviewing the literature and conducting quantitative or qualitative studies to understand and identify ideas that have the most potential to close the existing disparity gap. With a thorough understanding of the unique issues facing a particular population, researchers then draft an intervention adaptation (ie, *preliminary adaptation design*). Next, in the *preliminary adaptation tests* stage, researchers conduct pilot studies and use a mixture of quantitative and qualitative measures to evaluate the success of the adaptation. In addition, in this stage, researchers should assess "sources of program non-fit, implementation difficulties and difficulties with program content or activities." [48]. Finally, in the *adaptation refinement* stage, data collected from the previous step are used to revise the intervention. This project focused on the *information gathering*, *preliminary adaptation design*, and *preliminary adaptation tests* stages. The results from this study, which will be available in 2020, will assist with the revision of the intervention in the *adaptation refinement* stage. The cultural adaptation steps related to this study are detailed in the following sections.

Study Overview, Sample, and Recruitment

An experimental, mixed methods, prospective, pretest, immediate posttest, and 3-month follow-up, one-group

intervention research design was employed. This study was approved by the University of Texas at Austin institutional review board. The study design included three stages (ie, information gathering, preliminary adaptation design, and preliminary adaptation tests). In the information gathering stage, a literature review and qualitative focus groups were conducted. The findings from this stage were used to design the intervention in the preliminary adaptation design stage. Finally, in the preliminary adaptation tests stage, the intervention was evaluated using a self-report paper survey administered immediately before (pretest) and immediately after (posttest) the intervention. After 3 months, a Web-based self-report survey was administered to all participants (3-month follow-up). Aim 1 was achieved during the information gathering and preliminary adaptation design stages, whereas aims 2 and 3 were achieved during the preliminary adaptation tests stage.

Study Sample

The study sample for the focus groups and intervention evaluation consisted of AA undergraduate college students enrolled at a southwestern US university. Students who participated in the focus groups were also invited to participate in the intervention. AA undergraduate students were selected for this study because of evidence showing greater disparities in treatment among AA young adults. In addition, because depression onset typically occurs in the mid-20s [64], engaging students in undergraduate education may strategically prepare them for potential depression onset in themselves and onset among their peers. Participants were eligible for this study if they (1) were aged 18 to 25 years, (2) self-identified as black or AA, (3) were enrolled as an undergraduate (part time or full time) student during the 2016 to 2017 academic year, and (4) had never been diagnosed with and/or received treatment for a mental health condition. Individuals who have received a diagnosis and received treatment for a mental health condition were excluded from the study because of the intervention purpose and the unique needs of these individuals. The intervention was designed to teach people how to identify mental illness and how to get help. Furthermore, there is evidence that individuals who have had personal experiences in mental health care and have disengaged from treatment require specialized interventions [65]. We determined that a sample of 55 was needed to detect a difference in the prediction of willingness to counsel when adding the cultural variables (alpha=.05, beta=.80, and effect size=0.15), with seven predictors (ie, attitude, subjective norm, perceived behavioral control, stigma, cultural mistrust, self-reliance, and religiosity).

Study Recruitment

There is evidence documenting suboptimal recruitment and participation of AAs in research studies and increased loss to follow-up [66-68]. In an effort to mitigate potential problems, this study leveraged relationships with historically black social fraternities to enroll participants. Local campus chapters hosted specific study segments (ie, focus group sessions and the intervention) as events during their fraternity week at the university. Fraternity weeks are weeks designated to specific fraternities on campus, where fraternities host a variety of events geared toward fraternity initiatives. In fact, one of the fraternities, Omega Psi Phi, has a mental health initiative called *Brother, You're on My Mind: Changing the National Dialogue Regarding Mental Health Among African American Men*, which is featured as part of the National Institute on Minority Health and Health Disparities [69]. In addition to Omega Psi Phi, the local fraternity chapter of Alpha Phi Alpha was also instrumental in supporting this event. Fraternity weeks are heavily attended by the general body of AA college students. Organization leaders received study flyers for distribution to their members and other men and women who met the study criteria. Study flyers were distributed during fraternity week promotion initiatives. Study flyers contained a description of the study and provided the primary researcher's contact information. Interested students were asked to sign up via direct contact with the primary researcher (via email) or electronically through Google forms.

Aim 1: Information Gathering

A literature review was conducted, and several factors impacting AA help seeking were identified, including attitudes toward treatment, influence of family and friends, lack of knowledge, stigma, medical mistrust, self-reliance, and religiosity [10-25]. In addition, three focus groups were conducted to further identify factors that impact help seeking among AA young adults. Saturation was reached after three focus groups. Focus groups used the TPB as a guiding framework to facilitate elicitation of the salient behavioral, normative, and control beliefs associated with seeking help for depression. Questions used to elicit these beliefs were all adapted using a publication by Ajzen [49,70]. Three 60- to 90-min focus groups were conducted with 8 participants per group. As depression is often viewed as a *taboo* topic, a self-write activity was used at the beginning of each focus group to ease students into the discussion. Participants were asked to write or draw a response to the question *What is depression?* and then to share their definitions. Following this, participants were asked questions to assess their behavioral, normative, and control beliefs related to seeking help for depression. Each participant received a US $30 gift certificate for their participation.

Focus groups were audio recorded and subsequently transcribed by a third party. A thematic analysis was conducted in light of the TPB constructs to identify emerging themes related to seeking help for depression using Braun and Clarke's approach for thematic analysis [71]. The primary researcher and a qualitative expert worked together to identify the most frequently mentioned beliefs from the focus group analysis. According to the TPB, these beliefs represent students' modal beliefs, which represent the salient beliefs of the population of interest and, therefore, were used in the surveys. The TPB also suggests that an individual has five to nine beliefs that he or she holds to be salient. This guideline, along with analyses of belief frequencies, was used to determine salient beliefs for this study.

Aim 1: Preliminary Adaptation Design

Knowledge gained in the information gathering stage was used to develop the psychoeducational intervention and a related survey instrument (ie, preliminary adaptation design). The study intervention was developed using MHFA as a guiding framework [40,41]. The first MHFA principle (ie, stigma can

be reduced through awareness raising and education) was central to section 1 of the intervention (Textbox 1), which included activities and presentations to raise awareness and encouraged participants to evaluate how they approach a physical illness versus how they would approach a mental illness. In addition, section 1 included information on depression prevalence, signs, and symptoms as well as available treatments and common culturally related depression myths. The second MHFA theoretical principle (ie, social support is instrumental in reducing the risk of mental illness and assisting a person with a mental health problem) guided how intervention presenters approached intervention materials and topic discussions such that the information provided would be applicable to participants as well as a friend or family member.

Textbox 1. Psychoeducational intervention outline.

Section 1: Pharmacist

- Introduction: Discuss house rules and purpose of the project
- Large group discussions: Participants discuss a time when they were sick. Moderator reveals that participants only referenced physical symptoms and illnesses, sought help from a doctor, and underwent treatment and recovered.
- Active learning exercise: Fact or fiction—the pharmacist moderator reads a statement (eg, antidepressants are addictive), and participants hold up signs that read either fact or fiction. When disagreement occurs, the pharmacist leads a group discussion.
- Depression overview: Medical definition of depression, mental illness in the United States and among African Americans (prevalence and treatment statistics), and causes of depression and available treatments (psychotherapy and medication)
- Active learning exercise: Jelly in a jar—3 participant volunteers are asked to get jelly out of the jar using an oversized spoon. As they struggle to complete the task, the moderator provides commentary (eg, "I don't think you are trying hard enough"). After the task, the moderator tells participants that this exercise illustrates what it is like when you tell someone to "just get over your depression."

Section 2: Licensed Psychologist

- Video and stigma and cultural factors discussion: A young African American celebrity athlete discusses his personal experience with mental illness and his journey to recovery
- Psychotherapy overview and question and answer session: An African American psychologist from the university counseling center leads a discussion on the purpose of psychotherapy and what one might expect from engaging mental health services

Section 3: Consumer Educator

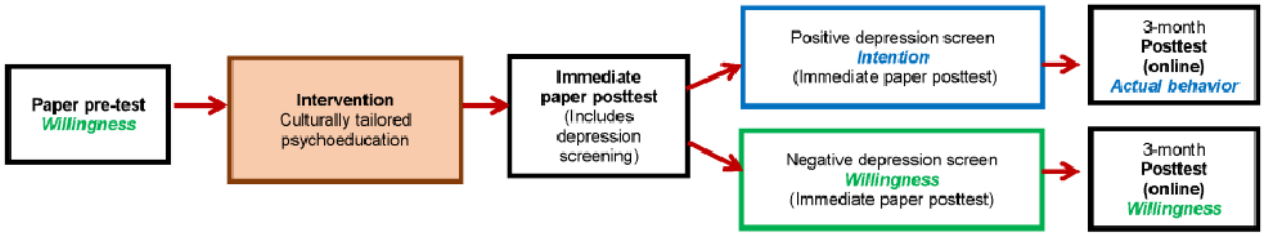
- Presentation and question and answer session: An African American college student living with major a depressive disorder and schizophrenia shares his lived experience with mental illness. He was also a consumer educator representative of the National Alliance on Mental Illness.

Using the aforementioned principles, the intervention consisted of three sections (see Textbox 1). Section 1 was led by the primary researcher, who is an AA and a licensed pharmacist. This section consisted of the introduction, an opening activity, an active learning activity (fact or fiction) designed to highlight and correct common myths about depression, an overview of depression, and another active learning activity (peanut butter in the jar) designed to illustrate what it feels like when someone tells a person with depression to "just get over it." Section 2, led by a licensed AA psychologist (from the university health center and the liaison to black and AA students in the counseling and mental health center), focused on stigma and the unique cultural variables that impact AA help seeking (identified in the information gathering stage). This section also featured a video clip of a young AA celebrity athlete discussing his personal experience with mental illness and his journey to recovery, followed by a group discussion of the video and cultural issues related to depression help seeking and a psychotherapy question and answer session. The last section, section 3, was led by a young AA college student consumer educator from the National Alliance on Mental Illness. He shared his lived experience with schizophrenia and depression, which was followed by an interactive question and answer session. The study intervention lasted 2 hours and 30 min, with multiple active learning activities to facilitate participant engagement and reduce participant fatigue. At the conclusion of this one-time intervention, participants were provided with a list of campus and local mental health resources. This list included campus services specifically for AA students. Furthermore, participants were encouraged to share what they learned in the intervention with their family and other students.

Aims 2 and 3: Preliminary Adaptation Tests

According to Barrera and Castro's [48] framework for cultural adaptation, the preliminary adaptation tests stage involves pilot studies to evaluate the success of the adaptation using both quantitative and qualitative measures. In this study, this stage was completed through implementing and assessing the intervention (Figure 2).

Figure 2. Data collection process.



Data Collection

Quantitative data, which were developed in accordance with the TPB and intervention content, were collected in the pretest, posttest, and 3-month follow-up surveys. Table 1 shows the variables that were collected for each survey. Posttest surveys included evaluation items that were quantitative using Likert-type scales and qualitative using open-ended responses. A pilot test of the questionnaire was conducted to assess the reliability and validity of the instrument with regard to all survey constructs. Feedback from the pilot testing was used to modify the final questionnaire, which was administered to the target population in the preliminary adaptation tests stage. Surveys were linked by a unique code created by each participant using an algorithm, thus rendering all surveys anonymous.

Table 1. Study variables by survey.

Pretest	Posttest	3-month follow-up
Willingness to seek help	Negative depression screening: willingness to seek help	Negative depression screening: willingness to seek help
	Positive depression screening: intention to seek help	Positive depression screening: help-seeking behavior
Attitude	Attitude	Attitude
Subjective norm	Subjective norm	Subjective norm
Perceived behavioral control	Perceived behavioral control	Perceived behavioral control
Depression stigma	Depression stigma	Depression stigma
Cultural variables: medical mistrust, self-reliance, and religiosity	Cultural variables: medical mistrust, self-reliance, and religiosity	Cultural variables: medical mistrust, self-reliance, and religiosity
Demographic and personal characteristics	Selected demographic and personal characteristics and intervention evaluation	Selected demographic and personal characteristics

Demographic and Personal Variables

Participants self-reported demographic (eg, gender identity and ethnicity) and personal (eg, personal and familial mental illness diagnosis, previous mental health course training, stress level, and extracurricular activity involvement) variables as well as depression knowledge. All variables were collected at pretest, and selected variables were collected at posttest and 3-month follow-up (eg, depression knowledge and stress level). Participants were also screened for depression at posttest using the 9-item Patient Health Questionnaire [72]. A cutoff score of greater than or equal to 10 was used for representing moderate depression to severe depression.

Theory of Planned Behavior Variables

Willingness, attitude, subjective norm, and perceived behavioral control were assessed at pretest, posttest, and 3-month follow-up. Willingness was measured at pretest for all participants because of the hypothetical nature of seeking help. Intention was only measured immediately after the intervention at post-test for participants who screened positively for depression. At pretest, although some participants did not have depression, others may not have known that they had depression; therefore, asking about their intention to seek help would have been inappropriate. Furthermore, once participants were screened, asking about their intention to seek help among those who screened negatively for depression would also have been inappropriate. Furthermore, participants who screened positively for depression at posttest were also asked to answer questions created by the authors regarding their help-seeking behavior at 3-month follow-up. All participants who screened negatively for depression were asked to answer questions regarding their willingness to seek help. Attitude, subjective norm, and perceived behavioral control were measured directly and indirectly according to the TPB. These measures were developed by the authors in accordance with the TPB. Direct measures represent a more global evaluation of the variable (eg, “If I screened positively for depression, most people important to me would think I should seek professional help”), whereas indirect measures are belief-based evaluations of the variable (eg, “If I screened positively for depression, my parents would think I should seek professional help”) [73]. Direct and indirect measures were assessed at pretest, posttest, and 3-month follow-up.

Stigma and Cultural Variables

Stigma and the cultural variables measured in this study include medical mistrust, self-reliance, and religiosity. Stigma was

measured using the Depression Stigma Scale [74], and medical mistrust was measured using the suspicion subscale of the Group-Based Medical Mistrust Scale [75]. Self-reliance was measured using the self-reliance and affect regulation subscales of the Strong Black Woman Cultural Construct Scale [76]. Items were modified to be gender neutral. Finally, religiosity was measured using a scale developed for this study, comprising items derived from the literature [77-79].

Intervention Evaluation

Intervention evaluation items were a combination of quantitative and written qualitative measures, as recommended by Barrera and Castro [48]. Quantitative items included items such as "What is your overall rating of the first presenter?" and "What is your overall rating of the course?" Qualitative free-response items included "What was most impactful from the course?" and "How can we improve the course?"

Data Analysis

Primary Outcomes

Willingness, intention, and help-seeking behavior represent the primary outcomes. Intention and behavior were only measured in participants who screened positively for depression at posttest. Intention was measured at posttest, whereas behavior was measured at 3-month follow-up. Willingness and intention scores will be averaged separately, with higher scores representing increased willingness or intention. Behavior will be categorized into professional help and nonprofessional help, then assessed with "yes, sought help" and "no, did not seek help." The impact of the intervention with regard to willingness will be assessed using repeated measures analysis of variance. Descriptive statistics will be calculated for intention and behavior. Data will be analyzed using SAS (version 9.4).

Predicting Willingness to Seek Help

The predictor baseline TPB variables (ie, attitude, subjective norm, and perceived behavioral control), stigma, and the cultural variables will be entered into two hierarchical regression models, as described in our conceptual model (Figure 1). We selected hierarchical regression to allow for comparison of the amount of variance explained in willingness from the cultural variables and stigma while controlling for the TPB variables. Model 1 will pre-test predictor indirect TPB variables (ie, indirect attitude, indirect subjective norm, and indirect perceived behavioral control), cultural variables (ie, medical mistrust, self-reliance, and religiosity), and stigma. Model 2 will consist of these same variables, except it will use the baseline predictor direct TPB variables (ie, direct attitude, direct subjective norm, and direct perceived behavioral control). We hypothesize that attitude, subjective norm, perceived behavioral control, stigma, and the cultural variables would explain a significant proportion of variance in willingness to seek help and that stigma and the cultural variables would significantly add to the prediction of willingness to seek help for depression.

Intervention Evaluation

Descriptive statistics will be calculated for each quantitative intervention evaluation item. Qualitative intervention items will be analyzed via thematic analysis to identify emerging themes regarding the most impactful part of and ways to improve the intervention. The frequency of each code will also be documented.

Results

This is a study protocol. Analysis and presentation of results will be available in 2020. This study was funded in May 2016 and approved by the Institutional Review Board of the University of Texas at Austin in November 2016. Data were collected from November 2016 to March 2016. Of the 103 students who signed up to participate in the study, 70 (67.9%) completed the pre- and posttest surveys. The primary outcome is participants' willingness and intention to seek help for depression. The secondary outcomes include attitude toward seeking help, perceived behavioral control over seeking help, and depression stigma.

Discussion

Significance and Challenges of the Research

This study takes the important initial step in developing a targeted and evidence-based psychoeducational program for young AAs. The findings from this research are expected to improve clinical practice by providing empirical evidence as to whether a culturally relevant psychoeducational intervention is useful for improving help seeking among young AAs. It will also inform future research and intervention development involving the TPB and willingness to seek help by shedding light on the relationship between important factors related to willingness to seek help. Advancing this field of research will be a step closer to improving help-seeking behavior among AAs and reducing AAs' mental health care disparities, which may result in decreased mortality and morbidity and improved quality of life among AAs with untreated mental illness.

Over the course of this study, a significant challenge was recruiting participants. With prior experience and considering evidence documenting suboptimal recruitment and participation and increased loss to follow-up of AAs in research studies, we employed a unique recruitment strategy [66,67]. During the project design, we decided to recruit participants through historically black sororities and fraternities. Initial contact with fraternity and sorority leadership via email was unsuccessful. The primary researcher then joined and engaged with the Black Presidents' Council, an organization of black student organization leaders on campus. Through involvement in the council, the primary researcher learned about fraternity and sorority interests, events, and priorities and developed relationships with organization leaders. Through these relationships, the primary researcher began collaborating with fraternity organization leaders on how to meet organizational priorities and recruit for the study. Through these conversations, the recruitment strategy of using fraternity weeks to host specific study segments (ie, focus group sessions and the intervention) was developed. The relationships and collaborations formed significantly improved our recruitment strategy and retention.

Limitations

This study is not without limitations. Our study sample consists of AA college students at a predominately white institution. Our results may not be generalizable to other AA young adults or AA adults. More research is needed to explore how this intervention may impact AA young adults who are not in college or who may attend a historically black college or university. Another limitation is the absence of a control group. A control group, in which an untailored intervention could have been used, would have strengthened the internal validity of this study. This was the initial study design; however, in the interest of achieving adequate power and in light of literature documenting difficulty in recruitment and retention of AAs in research studies, the authors elected to conduct a one-group intervention study. Therefore, our results may not truly reflect the impact of culturally adapting an intervention and may be similar to results from an unadapted psychoeducational intervention. It may be useful to use a control group when the intervention is further tested in Barrera and Castro's [48] adaptation refinement stage. In addition, it is possible that students with a particular interest in mental health volunteered for the study, resulting in selection bias. Given the sensitive nature of mental illness and this study's self-report surveys, response bias in the form of social desirability may have occurred. However, this may have been mitigated by the unique algorithm that participants created, rendering the surveys anonymous.

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Authors' Contributions

All authors have read and approved the final manuscript. BB, JB, KF, CB, and WL designed the study. BB wrote the first draft of the manuscript, and JB, KF, CB, WL, and KB contributed in the revisions. BB and KB facilitated the intervention.

Conflicts of Interest

None declared.

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Abbreviations

AA: African American
MHFA: Mental Health First Aid
SAMHSA: Substance Abuse and Mental Health Services Administration
TPB: Theory of Planned Behavior

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Protocol

Evaluating Mechanisms of Postoperative Delirium and Cognitive Dysfunction Following Elective Spine Surgery in Elderly Patients (CONFESS): Protocol for a Prospective Observational Trial

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Related Article:

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Abstract

Background: Elderly people are at particular high risk for postoperative delirium (POD) following spine surgery, which is associated with longer hospital stays, higher costs, risk for delayed complications, long-term care dependency, and cognitive dysfunction (POCD). It is insufficiently understood which mechanisms and risk factors contribute to the development of POD and POCD following these major but plannable surgeries.

Objective: This study aims to identify modifiable risk factors in spine surgery. A better understanding thereof would help adapt medical management and surgical strategies to individual risk profiles.

Methods: This is a single-center observational study jointly conducted by the departments of neurosurgery, neurology, and anesthesiology at a tertiary care hospital in Germany. All patients aged 60 years and older presenting to the neurosurgery outpatient clinic or ward for elective spine surgery are screened for eligibility. Exclusion criteria include presence of neurodegenerative or history of psychiatric disease and medication with significant central nervous system activity (eg, antidepressants, antipsychotics, sedatives). Surgical and anesthetic procedures including duration of surgery as primary end point of this study are thoroughly documented. All patients are furthermore evaluated for their preoperative cognitive abilities by a number of tests, including the Consortium to Establish a Registry for Alzheimer's Disease Plus test battery. Physical, mental, and social health and well-being are assessed using the Patient-Reported Outcome Measurement Information System Profile 29 and Hospital Anxiety and Depression Scale. Patients additionally receive preoperative cerebrovascular ultrasound and structural and functional brain imaging. The immediate postoperative period includes screening for POD using the Nursing Delirium Screening Scale and validation through Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, criteria. We furthermore investigate markers of (neuro)inflammation (eg, interleukins, C-reactive protein, tumor necrosis factor alpha). Preoperative examinations are repeated

3 months postoperatively to investigate the presence of POCD and its mechanisms. Statistical analyses will compare delirious and nondelirious patients for predictors of immediate (POD) and delayed (POCD) cognitive dysfunction.

Results: This is the first study to prospectively evaluate risk factors for POD and POCD in spine surgery. Recruitment is ongoing, and data collection is estimated to be finished with the inclusion of 200 patients by mid-2020.

Conclusions: The identification of mechanisms, possibly common, underlying POD and POCD would be a major step toward defining effective interventional strategies early in or even before the postoperative period, including the adaptation of surgical strategies to individual risk profiles.

Trial Registration: ClinicalTrials.gov NCT03486288; https://clinicaltrials.gov/ct2/show/NCT03486288

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KEYWORDS

postoperative delirium; postoperative cognitive dysfunction; spine surgery; neuroinflammation; magnetic resonance imaging; resting-state connectivity; quality of life

Introduction

It is well established that the proportion of elderly people continues to grow at an unprecedented rate in western societies [1]. Older patients are at increased risk for an episode of delirium following major surgery, but the rate of complex interventions such as spine surgery in this population is rising [2,3]. Notably, the increase of anterior cervical fusion procedures is three times greater than that of general surgery in this population based on the National Hospital Discharge Survey from 1990 to 2004 [4]. Other procedures including lumbar fusion, laminectomy, and discectomy exhibit an ongoing and similar progression [3,5].

Postoperative delirium (POD) typically evolves within 72 hours following surgery and is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) as a disturbance in attention and awareness that develops over a short period of time, fluctuates, and is accompanied by a change in cognition [6,7]. It is associated with increased complication rates, nursing times per patient, length of hospital stay, per-day hospital costs, and 1-year health care costs [8-10]. While the full pathophysiology of POD remains to be elucidated, current literature suggests an underlying multicausal model that includes neuroinflammation, brain network dysfunction, endocrine stress response, and neurotransmitter imbalance [11-15]. POD was long considered a reversible condition, but it is now established that affected patients do not return to their prior quality of life and employment [16-18]. Elderly patients are additionally affected by postoperative cognitive dysfunction (POCD) that persists in about 30% to 50% of cases after resolution of POD or develops independently up to 3 months following surgery [7,19,20]. While POCD can develop in the absence of POD, more severe POD increases the likelihood of POCD indicating that both entities share at least some underlying mechanisms [21,22]. Supporting the idea of shared mechanisms, POD and POCD have both been shown to accelerate the rate of cognitive decline and increase the risk of long-term mild cognitive impairment or dementia, which may ultimately lead to long-term care dependency and institutionalization [20,22-26].

Knowledge of risk factors for POD and POCD, particularly modifiable risk factors, is therefore imperative to enhance informed patient consent, adjust anesthetic and surgical strategies to individual risk profiles, and facilitate appropriate postoperative monitoring [27]. Numerous prediction models have been developed to identify patients at risk, yet recent studies highlight that a general application of these models in clinical routine is limited, not least because trajectories of cognitive decline are not independent of the type of surgery [22,26,28,29]. For example, patients who exhibited POCD following cardiac surgery improved cognitive function after 1 year compared with their baseline level, which contradicts results from mixed surgical populations [26,29]. Differences in preoperative cognitive function and mechanisms underlying cognitive dysfunction possibly resolve some of the discrepancy, which highlights that surgical type-specific studies are required to identify mechanisms of POD and POCD unique to these procedures [7,22,28,30].

Five prospective studies evaluated POD following spine surgery and were unable to identify modifiable risk factors other than intraoperative hypotension [31-35]. Retrospective and secondary outcome analyses suggest that less complex and shorter interventions such as simple decompressions could be associated with lower POD and complication rates compared with complex fusion and instrumentation procedures, rendering the surgical intervention itself a potentially modifiable risk factor [34,36].

In this study, we thus investigate the primary hypothesis that the duration of spine surgery is a predictor of POD incidence in spinal surgery, which was not previously tested as a primary end point in a prospective and sufficiently powered study. Evidence in favor of our hypothesis would justify adaptation of surgical interventions to individual risk profiles as a viable means to reduce the incidence and sequelae of POD without withholding necessary surgery from affected elderly patients. This study will also evaluate the relationship between POD and POCD in spine surgery, which has not been done before but was declared one of the most relevant study areas in a recently published multinational and interprofessional delirium research agenda [37]. Additional end points include long-term cognitive function, quality of life, activities of daily living, mood, and frailty. Underlying pathophysiological mechanisms will be investigated through ultrasound of the cerebral vasculature, structural and resting-state functional magnetic resonance

imaging (sMRI, rs-fMRI), markers of (neuro)inflammation, and metabolomics.

Methods

Setting and Registration

The Cognitive Dysfunction Following Elective Spine Surgery in Elderly Patients (CONFESS) study is a prospective single-center observational study jointly conducted by the Department of Neurosurgery and Neurology in cooperation with the Department of Anesthesiology at the University Hospital Greifswald, Germany, a 950-bed tertiary care hospital. The trial was approved by the institutional review board of the University of Greifswald (BB 192/17) and registered at ClinicalTrials.gov [NCT03486288]. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided as Multimedia Appendix 1.

Patient Recruitment and Study Design

Patient recruitment began in February 2018, and the study continues enrolling patients presenting to the Department of Neurosurgery for elective spine surgery. All patients seen in neurosurgery outpatient clinics or inpatient wards are screened for eligibility. Patients can be enrolled if they are at least aged 60 years, scheduled for elective spine surgery without opening the dura, can give informed consent themselves, and are German native speakers. Exclusion criteria comprise any diagnosis of dementia or neurodegenerative disease, psychiatric disease, prescription of central nervous system–active medication (eg, antidepressants, antipsychotics, sedatives, alpha-1-receptor antagonists), inability to participate in follow-up, participation in an interventional trial, electronic or displaceable metallic implants, or active neoplasms. Informed consent to participate can only be given by the patient themself. All baseline examinations are scheduled within 14 days prior to surgery (V0). The day of surgery (V1) includes documentation of routine procedures and a close follow-up of patients in the postanesthesia care unit (PACU) for at least 2 hours or longer depending on the clinical situation. Patients are afterward routinely transferred to the neurosurgical ward or may occasionally require intermediate/intensive care treatment. Postoperative visits (V2) continue for at least 72 hours postoperatively and include detailed documentation of primary and secondary end points. If patients develop POD within 72 hours, daily follow-ups continue until no signs of POD are documented over a period of 24 hours or the patient is discharged (eg, for rehabilitation). Patients are routinely seen in the neurosurgical outpatient clinic 3 months postoperatively and in this context receive additional follow-up examinations (V3). Patients who agreed to be contacted via telephone finally undergo a telephone assessment of their cognitive and functional status 1 year following surgery (V4). A synopsis of the visit plan is provided in Table 1. Recruitment is planned to be completed by December 2019. The last in-hospital follow-up visit is accordingly scheduled for March 2020, and the last telephone interview is anticipated for December 2020.

Table 1. Summary of the recruitment process and visit plan according to the Standard Protocol Items: Recommendations for Interventional Trials checklist.

Event	Study period										
	Enrollment	Preoperative	Intraoperative	Postoperative					3-month follow-up	1-year follow-up
		–7d±7	0	1d	2d	3d	4d	etc	90d±14	365d±14
Eligibility screen	x									
Informed consent	x									
Demographic data		x								
Medical history		x							x	x
Cognitive testing		x							x	x
Quality of life		x							x	
Activities of daily living		x							x	
Bispectral index monitoring			x							
Vital parameters			x							
Delirium		x		x	x	x	*x*	*x*		
Medication		x	x	x	x	x	x	x	x	x
Pain		x		x	x	x	x	x		
Mobilization				x	x	x	x	x		
sMRI/re-fMRI[a]		x							x	
Cerebrovascular ultrasound		x								
Inflammatory markers		x	x	x	x					
Neural injury markers		x	x	x	x					
Brain-derived neurotropic factor polymorphism		x								

[a]sMRI/rs-fMRI: structural magnetic resonance imaging/resting-state functional magnetic resonance imaging.

Routine Surgical Procedures

Patients included in this study suffer from degenerative spinal diseases including cervical disc herniation and stenosis, thoracical and lumbar stenosis, and degenerative instability. All patients are enrolled in elective spinal surgical procedures without an anticipated dural opening and with a minimum scheduled operative time of 60 minutes. All procedures are performed by standard neurosurgical guidelines. The operation is always performed by an experienced spine surgeon. The patients are optimally positioned on the operating table. All patients are operated on in prone position without compression of the abdomen by using proper positioning cushions. Each patient is covered with a thermal blanket throughout the operation. All operations are performed with the help of an operating microscope and a mobile x-ray device. Typical procedures include anterior cervical discectomy and fusion, posterior cervical decompression and fusion, multisegmental thoracical and lumbar decompression, and standard and complex multilevel spinal fusion.

Routine Anesthetic Procedures

The preoperative period before the induction of anesthesia is in accordance with international standards for elective interventions. Food is withheld for a minimum of 6 hours and water for 2 hours before anesthesia starts. Oral premedication is performed with midazolam (0.1 mg/kg) depending on individual levels of preoperative excitement. After placement of a peripheral intravenous line (18- or 20-gauge catheter), anesthesia is induced by intravenous injection of sufentanyl (0.3-0.6 mg/kg) and propofol (1.5-2.5 mg/kg). Muscular relaxation is achieved with intravenous injection of cisatracurium (1.5 mg/kg). Anesthesia is maintained by a balanced anesthesia with sevoflurane. The target range chosen was 0.8 to 1.0 minimum alveolar concentration. Adequate anesthetic depth is verified via continuous monitoring of the bispectral index and real-time electroencephalography waveforms along the scalp. Estimated insensitive fluid losses are replaced isovolemic by intravenous infusion of blood isotonic electrolyte solution without lactate. A convective air warming system is used to keep the body temperature constant and normothermic. Patients are endotracheally intubated and mechanically ventilated (pressure-controlled ventilation, FiO_2 0.4-0.6) at a rate of 10 to 18 per minute and a positive end-expiratory pressure of 5 to 10 cm H_2O. Tidal volume is adjusted individually on the basis of the end-tidal carbon dioxide (capnography) monitoring or blood gas analysis and the measured $PaCO_2$.

Continuous recording of vital parameters includes 5-lead electrocardiography, pulse oximetry (SpO_2), and noninvasive blood pressure measurement. Individual patients receive an

arterial catheter placed in the radial artery depending on their preoperative risk profile to enable close monitoring of hemodynamics and arterial blood gas. Hypotensive situations are managed through fluid challenges and continuous medication with norepinephrine. Recovery from anesthesia was monitored in the PACU.

Primary Outcome Measure

This study's primary end points are duration of surgery and incidence of delirium. The hypotheses is that the duration of surgery would predict POD incidence. POD is expected to develop within 72 hours following surgery and screening is performed every 8 hours within this period in every patient using the validated Nursing Delirium Screening Scale (Nu-DESC) [7,38]. Morning and day shift screenings are performed by trained physicians during workdays, other screenings are done by trained nurses. In this study, positive screening results require confirmation by DSM-5 criteria applied by a trained physician to further increase diagnostic specificity [6]. Training of all personnel involved in the study was conducted by a neurologist with expertise in neurocritical care and ample research experience in the field. Sufficient screening performance was guaranteed at the end of the training.

Secondary Outcome Measures

POD severity is evaluated using the Confusion Assessment Method (CAM) scoring system severity scale [39]. Subsyndromal delirium includes Nu-DESC ratings greater than zero that do not fulfill criteria for delirium. Chart-based POD screening is used to complement POD screening beyond the Nu-DESC screening period to estimate the overall in-hospital POD incidence [40].

Preoperative and postoperative cognitive abilities are evaluated at V0 and V3 using the Consortium to Establish a Registry for Alzheimer's Disease Plus (CERAD-Plus) test battery and multiple-choice Mehrfach-Wortschatz-Intelligenztest type B (MWT-B) word test [41,42]. The CERAD-Plus includes assessments of orientation, visual naming, phonematic speed, semantic fluency, verbal episodic memory (encoding, error control, recall, discriminability), nonverbal episodic memory (encoding, recall), visuoconstruction abilities, attention, and executive speed and functions. MWT-B results reflect the general intellectual level.

Systemic inflammation, neuroinflammation, and neuronal injury are assessed with blood samples taken at V0, V1 (immediately after surgery in the PACU), and the first two days of V2 (ie, the first and second postoperative day). Systemic inflammation is characterized by white blood cell count, C-reactive protein, interleukins, and tumor necrosis factor alpha among others that are considered to contribute to the pathogenesis of delirium [15,43-45]. Markers of neuroinflammation and neuronal injury include glial fibrillary acidic protein, neuron specific enolase, and neurofilament levels [46-48]. Neopterin and malondialdehyde levels are established surrogate markers of oxidative (neuronal) stress [49,50]. Given the increasingly recognized role of genetic predisposition for neuronal plasticity, preoperative analysis of brain-derived neurotropic factor polymorphism is intended [51].

Patient-reported quality of life is assessed at V0 and V3 through the 36-item Short Form Health Survey and the Patient Records and Outcome Management Information System 29-item profile (PROMIS-29) [52,53]. Patients' relatives are furthermore handed a proxy version of the PROMIS-29 to evaluate agreements of self- and proxy-reported quality of life regarding individual domains (PROMIS-29 proxy). Proxy reports are a valuable tool to assess patient outcome when cognitive impairment impedes self-report, yet no study previously evaluated if changes of quality of life following surgery are similarly rated by patients and their proxies [54]. Additional patient-related outcome measures include preoperative levels and postoperative changes of frailty as assessed by the Groningen frailty indicator, neck or low back pain–related disability using the Oswestry Disability Index, and anxiety and depression rated by the Hospital Anxiety and Depression Scale [55-57].

sMRI and rs-fMRI have become methods of choice to investigate neuronal correlates of pathology-related cognitive decline in delirium [58]. While there is a promising prospect for electroencephalography biomarkers to facilitate decision making in clinical situations and investigate neurophysiological changes during an episode of delirium, the spatial resolution of MRI enables the detailed investigation of brain structures and network interactions associated with the risk for POD and mechanisms, possibly preventable, leading to POCD and long-term cognitive impairment [13,59].

A recent retrospective analysis found that hemodynamic stenoses of the cerebral vasculature may predict the incidence of POD in spine surgery [60]. This study includes a prospective evaluation of this hypothesis and includes an evaluation of arterial pulsatility that was suggested as an amply available biomarker of cognitive reserve capacity [61].

Sample Size Calculation and Statistical Methods

The primary hypothesis of this study is that the duration of surgery is a continuous predictor for POD in a binary logistic regression model, which has not been previously tested in a prospective study. Five studies performed preliminary evaluations of this relationship treating duration of surgery as a categorical variable and secondary end point. They reported mean delirium incidences of 14% for durations of surgery less than 180 minutes, 33% for 180 to 300 minutes, and 48% for surgeries lasting longer than 300 minutes [31-35]. We extend on these previous findings by using a binary logistic regression model that provides the intriguing perspective to estimate how the odds of becoming delirious change with every minute of surgery. We used a well-established simulation-based approach to estimate an adequate sample size to test our hypothesis [62]. The simulation used a representative population of surgical patients based on information from the hospital's clinical information system, which included duration, type, and frequency of spine surgeries performed by the Department of Neurosurgery in 2016. Samples were randomly drawn from this population and included in repeated study simulations while iteratively increasing sample sizes. This process continued until 80% of simulations run for a given sample size yielded significant regression coefficients in a 2-tailed Wald test at a

5% alpha level. This approach yielded that 182 patients need to be tested so that the power to reject the null hypothesis is 80%. Anticipating a dropout rate of 10%, we plan to enroll 200 patients in this study. Before testing real data, compliance with assumptions of a binary regression analysis needs to be confirmed, including normal distribution of the data and homoscedasticity of residuals.

Secondary end points will be analyzed using appropriate summary measures depending on the distribution of data. Categorical data will be presented as absolute and relative frequencies. Continuous data will be presented as mean or median values with 95% confidence intervals. Global tests will be performed using analysis of variance for categorial data; binary and continuous data will be analyzed using generalized linear models with a suitable link function. Post hoc tests will be performed using Student *t* tests for normally distributed data, Wilcoxon signed-rank test for paired observations, or Mann-Whitney *U* test for unpaired observations. Categorical values will be compared using $\chi 2$ or McNemar. A *P* value of <.05 is denoted statistically significant. Corrections for multiple comparisons and alpha error accumulation will be performed. Statistical analysis will be performed using SPSS Statistics 25 (IBM Corp) and MATLAB 2018a (The MathWorks Inc).

MRI analysis will include quantification of brain atrophy through estimations of pre- versus postoperative changes of tissue volumes. To assess the impact of cortical atrophy, brain grey matter volume will be included as an additional covariate in statistical analyses [63]. Preoperative extent and postoperative changes of white matter lesions will be quantified using the age-related white matter changes score [64]. Resting-state analyses will be conducted as previously published and particularly include the default mode network (DMN), task-positive network (TPN), salience, and dorsal attention network [13,65,66]. Regression analyses will be used to correlate network changes with alterations in domains of cognitive dysfunction.

Results

Recruitment began in April 2018, and the study is currently enrolling patients. Data collection is expected to be finished by April 2020. This study does not receive funding from third party organizations but is supported through research budgets of involved departments. This approach was chosen to expeditiously establish a status quo supporting applications for subsequent interventional trials since the burden of POD significantly impacts clinical routine.

First results of primary end point evaluations are expected between June and July 2020. If the primary hypothesis turns out to be true (ie, duration of surgery is a predictor of POD), funding for an interventional trial will be applied for by the third quarter of 2020 and, if funding is granted, a corresponding trial to be started in 2021.

Discussion

Significance of This Study

This is the first study to prospectively evaluate risk factors for POD and POCD in spine surgery including comprehensive pre- and postoperative assessments of cognitive function, markers of systemic and neuroinflammation, metabolomics, cerebral vasculature, and structural and functional neuroimaging. There are no other ongoing registered studies with a similar focus [67]. The few prospective studies that evaluated risk factors and mechanisms of POD in the context of spine surgery were already discussed [31-35], however neither of the studies assessed associations of POD and POCD, which is required to disentangle pathways that promote either one or both postoperative cognitive disorders. Available retrospective studies do not resolve this issue given diagnostic inaccuracies [36,40]. Yet identification of possibly common mechanisms underlying POD and POCD would be a major step toward defining effective interventional strategies early in or even before the postoperative period, including the adaptation of surgical strategies to individual risk profiles [37]. Despite the exciting prospect for the application of possible findings from this study, there are important methodological and conceptual issues that require close attention concerning data acquisition, analysis, and interpretation.

Diagnostic Challenges to Identify Delirium

Accurate diagnosis of POD is a major concern in all studies in the field. While diagnosing the patient using DSM-5 criteria applied by a trained specialist (eg, psychiatrist, neurologist, intensivist) is considered the method of choice, this approach is impractical in clinical routine and challenging even in study environments given the high prevalence of delirium and its fluctuating character that requires multiple assessments per day [6,68,69]. The use of screening tools, which are time efficient and can be applied by trained nurses or physicians, is hence an important step toward timely diagnosis and effective treatment of delirious patients [27,70]. A recent review of established delirium screening tools found psychometric properties to be best for the Nu-DESC and CAM, and both tools are recommended to be used by the European Society of Anesthesiology guideline on POD [70,71]. This study uses the Nu-DESC since the CAM was recently shown to be difficult to implement in practice and the Nu-DESC can be performed in less than 2 minutes and is suitable for screening by trained nurses [71-73]. Interrater reliability is not a concern using the Nu-DESC since it was reported to be substantial to excellent [71].

In order to achieve a balanced trade-off between feasibility and accuracy of diagnostic tools, we chose a combination of methods for the detection of POD regarding our primary end point. Screening for POD is performed using the Nu-DESC with a cutoff of 2 points, which provides a sensitivity and specificity of about 80% [71]. Lack of specificity is counterbalanced by subsequent confirmation of positive screening results by DSM-5 criteria [6]. While this strict approach may miss subsyndromal and mild cases of POD, we argue that it will provide robust results that are not susceptible to confounding variance introduced by cases of marginal delirium. In this context, it is

important to note that current diagnostic criteria are based on phenotypes and do not reflect neurobiological endotypes, which inevitably includes the possibility that none of the available diagnostic methods will sufficiently discriminate POD endotypes from variants of physiological brain states or altered brain states of other causes [37,74,75]. Given this uncertainty, we will run secondary analyses on subsyndromal cases of POD based on Nu-DESC screening and chart-review and evaluate whether associated pathophysiological changes are continuous with endotypes of full POD.

Contribution of Anesthesia to Neuronal Injury

Anesthesia is considered one of the major contributors to the development of POD and POCD and therefore requires close attention in every study in the field [76,77]. It is well established that the cumulative dose of anesthetics applied during surgery and the depth of sedation are modifiable risk factors for perioperative brain injury [78]. This study therefore includes continuous bispectral index monitoring for depth of anesthesia, which allows retrospective adjustment of the statistical model for confounding variance [79]. Possible mechanisms underlying nocuous effects of anesthetics include disruption of neuronal oscillations, importantly those associated with amyloid cleavage [80], induction of tau hyperphosphorylation [81], initiation of apoptotic cell-death pathways via caspase activation [82], and disruption of cholinergic transmission regulating microglia activity [83,84]. While these mechanisms were identified using single anesthetics, there is no proven benefit from using one drug over another (eg, sevoflurane or propofol) on the incidence of POD [85,86]. In the context of this preliminary evidence, we chose to standardize the anesthetic procedure using the same drugs in all patients unless the regimen needs to be changed for medical reasons (eg, due to allergies or contraindications).

Role of Inflammatory Pathways

Investigating the role of mediators of systemic and neuroinflammation has become one of the cornerstones of POD and POCD research [37]. Research in animal models brought about exciting results, including upregulation of several inflammatory pathways and decreased neuronal plasticity in hippocampal regions while cortical regions were generally spared, which is in line with cognitive deficits observed in humans [14,15,30,87,88]. This motivated studies in humans that assessed the association of markers of inflammation with POD and POCD, yet findings were ambiguous. While some studies reported that systemic levels of interleukins, particularly interleukin-6, and C-reactive protein were predictors of brain injury, delirium, and subsequent cognitive impairment [44,89], others did not find similar associations [44,90,91]. Possible reasons for this discrepancy are that some studies included cases of intensive care unit (ICU) delirium, concentrations of markers of inflammation vary substantially between types of surgery [30,92], and neuroinflammatory effects seem to depend on the extent of preexisting neurodegeneration, which was rarely controlled for [14,93]. Another unresolved issue is how systemic and neuroinflammation interact to cause brain injury [84]. Several possible mechanisms were studied in animal models and include passive diffusion through leaky blood brain barrier [94], carrier-mediated transport [95], and de novo central production mediated through vagal afferents [96,97]. While opening of the blood barrier induced by anesthesia is an intriguing and prevailing explanation, cerebrospinal fluid levels and serum concentration of markers of inflammation are not correlated, suggesting additional involvement of other mechanisms that remain to be elucidated [47,98].

Structural and Functional Imaging

Studying the pathophysiology of POD and POCD using MRI provides numerous opportunities to asses brain structure and function. Previous studies investigating sMRI changes found that preoperative white matter hyperintensities (WMH) were predictors of POD [99-101]. These studies, however, evaluated patients undergoing cardiac surgery or being treated in ICU, which limits their generalizability. As outlined above, cognitive trajectories in cardiac surgery can be expected to differ from other conditions given their unique hemodynamic situation that possibly affects cerebrovascular autoregulation [7]. Development of ICU delirium is associated with several risk factors that are rarely present in patients following spine surgery such as continuous sedation, ventilation, noisy environment, sleep deprivation, compromised hemodynamics, and repeated painful invasive procedures, all of which limit the interpretation of WMH as an independent risk factor [20,102]. In support of this limitation, Cavallari et al [103] examined WMH as a risk factor in a surgical population that mainly comprised orthopedic patients not treated in ICU and found no significant association with delirium. A recent review concluded that prospective studies are needed to resolve current uncertainties regarding the significance of structural abnormalities, particularly vascular abnormalities, in sMRI [104]. The situation is similar concerning the role of preexisting cortical atrophy on the risk of developing POD. Some studies reported that generalized or focal (temporal lobe, limbic system) grey matter atrophy increases the risk for delirium while others did not find this association [105,106]. A recent review interpreted differences in structural imaging to be mainly due to the focus on cardiac surgery and ICU patients, who are difficult to generalize [58]. Our study provides several potential benefits regarding mentioned limitations. We focus on a population less confounded by critical illness and also include pre- and postoperative imaging to overcome variance in the general population that limits cross-sectional comparisons to controls. We expect that these benefits and concomitant evaluations of cognitive and inflammatory profiles will help elucidate the role of sMRI changes for POD and POCD.

There are no studies that performed fMRI before surgery to identify brain network properties that predispose for the development of POD and POCD [58]. This is surprising given the broad acceptance of models that consider cognitive resilience a relevant protective mechanism and that fMRI is the method of choice to investigate neurobiological substrates underlying resilience [107-109]. This study aims to fill this gap by correlating functional data with perioperative cognitive profiles. The combination of pre- and postoperative rs-fMRI will furthermore help to disentangle brain networks that are affected by the surgical procedure and lead to sequel cognitive deficits [74]. There are currently only a few studies that provide cross-sectional data and allow for a hypothesis of involved networks including a loss of anticorrelation between the TPN

and DMN, decreased DMN functional connectivity, reduced functional network integration and efficiency, and decreased functional connectivity between the posterior cingulate and superior frontal gyrus [13,110-112].

Investigation of Perioperative Cognitive Function

The association between POD and POCD is an ongoing matter of debate [22]. While POD may accelerate the trajectory of cognitive decline, it is also possible that POD is a marker of rapid cognitive decline but does not accelerate it or that both conditions are unrelated [113]. Recent consensus statements suggest studies in the field should include investigations of both POD and POCD to elucidate their relationship and disentangle shared mechanisms [37,70]. Cognitive testing should comprise pre- and postoperative assessments to account for baseline differences, examine a broad spectrum of cognitive domains, and account for ceiling effects in good performers and floor effects in bad performers [114,115]. This study uses the MWT-B, which allows for adjustment for baseline intelligence. The CERAD-Plus test battery enables repeated measurements of cognitive abilities in multiple domains, and normative age-, education-, and gender-specific databases are available [41].

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Authors' Contributions

JM, SN, AV, SR, TU, AF, JUM, and RF designed the study and wrote the initial protocol. BvS, ER, SS, HK, KH, and HWSS provided advice and input into the protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials checklist.
[PDF File (Adobe PDF File), 188 KB - resprot_v9i2e15488_app1.pdf]

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Abbreviations

CAM: Confusion Assessment Method
CERAD-Plus: Consortium to Establish a Registry for Alzheimer's Disease Plus
CONFESS: Cognitive Dysfunction Following Elective Spine Surgery in Elderly Patients
DMN: default mode network
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICU: intensive care unit
MWT-B: Mehrfach-Wortschatz-Intelligenztest type B
Nu-DESC: Nursing Delirium Screening Scale
PACU: postanesthesia care unit
POCD: postoperative cognitive dysfunction
POD: postoperative delirium
PROMIS-29: Patient Records and Outcome Management Information System
rs-fMRI: resting-state functional magnetic resonance imaging
sMRI: structural magnetic resonance imaging
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TPN: task-positive network
WMH: white matter hyperintensity

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Corrigenda and Addenda

Correction: Evaluating Mechanisms of Postoperative Delirium and Cognitive Dysfunction Following Elective Spine Surgery in Elderly Patients (CONFESS): Protocol for a Prospective Observational Trial

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In the original published paper "Evaluating Mechanisms of Postoperative Delirium and Cognitive Dysfunction Following Elective Spine Surgery in Elderly Patients (CONFESS): Protocol for a Prospective Observational Trial" (JMIR Res Protoc 2020;9(2):e15488), published on February 13, 2020, there was an error in the order of authors: Robert Fleischmann was listed as the second author. The correct order of the authors is provided above, with Robert Fleischmann named last on the author list.

The correction was made in the online version of the paper on the JMIR website on February 14, 2020. Because this change was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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