# JMIR Research Protocols

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Protocol

# Using Social Media for the Promotion of Education and Consultation in Adolescents Who Have Undergone Kidney Transplant: Protocol for a Randomized Control Trial

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## Abstract

**Background:** Falling ill represents a traumatic experience especially in adolescence, since in addition to the moments of ambiguity and contradictions that this period brings, there is coping with the disease. Renal transplantation provides a better quality of life but the dependence on dialysis is replaced by the greater responsibility of self-care. With advances in technology, contemporary communication methods are a strategic mechanism for the approximation of the adolescent and the multiprofessional team. In this perspective, our research may provide possible changes and propose alternatives, using social networks for the integration of the multiprofessional team, promoting education within a virtual environment for adolescents who have undergone kidney transplants.

**Objective:** The goal of our research is to compare the knowledge, satisfaction, and self-esteem of adolescent renal transplant patients in 2 groups: patients undergoing conventional treatment versus patients undergoing conventional treatment plus the full-time use of social networks to aid in education and consultation.

**Methods:** Nonblind randomized clinical trial with 128 adolescents (aged 13 to 21 years) divided in 2 groups: the first group will receive conventional care and the second group will be invited to participate in a secret group on the social network Facebook. This group will be used as a new education platform to involve young renal transplant patients to participate in the guidelines provided to them by the multiprofessional team.

**Results:** An environment for learning and exchanging life experiences will be created by using a well-known technology among adolescents. As a low-cost intervention, it will allow a better interaction between the patient and the transplant team. It is expected that the adolescents will improve their knowledge about the disease also increasing their self-esteem and the treatment adhesion.

**Conclusions:** Health professionals need to seek alternatives when educating patients, focusing on easily understandable ways for effective guidance. In the adolescent population, it is understood that the use of technology as support in education is a fundamental tool for this age group. The proposed project will directly benefit adolescent renal transplant patients as it uses language aimed directly at the target demographic. It attempts to overcome the traditional model by being more in contact with the current generation. This approach makes the content easier to assimilate and, consequently, increases understanding.

**Trial Registration:** ClinicalTrials.gov: NCT03214965; https://clinicaltrials.gov/ct2/show/NCT02239354 (Archived by Webcite at http://www.webcitation.org/6wKnYrFGx)

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**KEYWORDS**

transplantation; education; social network; adolescents

## Introduction

### Background

Chronic renal failure is a disease of major impact on the lives of adolescents, with a high morbidity and mortality. It is a worldwide public health problem, and renal transplantation is a therapeutic alternative [1]. In Brazil, the pediatric population is approximately 53 million (according to data by the Brazilian Institute of Geography and Statistics). Brazil has a prevalence of 20 terminal chronic kidney disease cases per million of population and an incidence of 6.6 per million of population [1,2].

According to the Brazilian Association of Organ Transplant, it is estimated that 349 pediatric patients per year are registered on the kidney list. In 2015, 396 children joined the list, and 316 had transplants. The number of kidney transplants for children has changed every year. In 2014, there was an increase of 13.3% compared to 2013. The next year, however, the 532 organ transplants represented a drop of 5% in relation to 2014 [1,2].

Adolescence is a period of life when there are several physiological and morphological changes. It is also the transition phase to adulthood, represented by the struggle for independence and the pursuit for personal identity. Falling ill represents a traumatic experience especially in adolescence, since in addition to the moments of ambiguity and contradictions that this period brings, there is coping with the disease. An important adolescent characteristic is impulsive thought added to the difficulty of predicting the consequences of their actions, relevant factors for the health professional to include in the guidelines for the public of this age [3,4].

The above mentioned factors can compromise adherence to treatment. This problem has been observed more frequently in adolescents aged 11 to 19 years with low self-esteem, depression, and lacking the support of at least 1 adult. Nonadherence to treatment is one of the major problems in adolescence, and the survival of the graft undergoes a sharp drop of 62% in 5 years and 36% in 10 years after transplantation [5,6,7].

Although transplanted adolescent patients are cared for by a multidisciplinary team that helps them face the situation of the disease, minimizing their anguish and orienting them to adapt to changes in their daily lives, we find it difficult to increase the participation of these patients.

With advances in technology, contemporary communication methods are a strategic mechanism for the approach of the adolescent and the multiprofessional team, reducing barriers for education using a language more characteristic of the age. The introduction of new technologies in education has been improving knowledge, in the sense that takes the form of a helpful didactic object in teaching, capable of generating and providing its users with scientific knowledge in a spontaneous manner [8]. Facebook is one of the most popular social networks in the world. It allows social interaction by exchanging and sharing posts, organizing users into groups, and providing an environment to discuss ideas. When used with a well-grounded knowledge source, Facebook may be able to improve the quality of health care [9].

In this perspective, our research may provide possible changes and propose alternatives by using social networks for the integration of the multiprofessional team, promoting education within a virtual environment for adolescents who have undergone kidney transplants. In this way, a means of reference capable of ensuring the expansion of care will be provided.

### Objectives

The goal of our research is to compare the knowledge, satisfaction, and self-esteem of adolescent renal transplant patients, gauged through questionnaires, of 2 groups: patients undergoing conventional treatment versus patients undergoing conventional treatment plus the full-time use of social networks to aid in education and consultation.

## Methods

### Study Design

This study is a nonblind randomized clinical trial. Facebook will be used as a new education platform to involve young renal transplant patients in participating in the guidelines provided to them by the multiprofessional team. It is believed that the use of this tool as an aid in the education of adolescents will cause an improvement in communication and interaction between patients and staff and promote a space for the exchange of experiences between patients of the same age. This will facilitate the expression of feelings and contribute to increased self-esteem, reduced anxiety, and increased adherence to the treatment plan. Considering that Facebook is an already used social network with worldwide coverage, use is possible regardless of location.

The study will be developed with patients from *Hospital da Criança Santo Antônio in the Sistema Única de Saude* (SUS) outpatient clinic. *Hospital da Criança Santo Antônio* is one of the 7 care units of Santa Casa de Porto Alegre.

The inclusion criteria are being between the ages of 13 and 21 years and being in treatment by the nephrology team in pre- and posttransplantation.

The exclusion criteria are patients in pretransplantation who are not registered on the state health department unique kidney transplant list and those who do not wish to participate in the study.

### Intervention

The adolescents will be invited to participate in the study during a routine visit to the outpatient clinic. Educational activities will be provided through the social network for a 3-month period by a multidisciplinary team comprising a nurse, doctor, psychologist, physical educator, social worker, and nutritionist.

The person responsible for the study will create an activity schedule for the team (Multimedia Appendix 1). Each week a professional will have the responsibility of creating educational material related to their specialty. The researcher will follow up with the adolescents daily for questions, answers, and encouragement to post on the social network. Playful and interactive materials will be provided facilitating the adolescent's understanding.

At the beginning of the week, one of the professionals will launch a debatable theme for the week; this debate will be moderated by the author. The postings are of a purely informational nature and will conform to Conselho Federal de Medicina resolution 2133/2015 which, among other things, prohibits the carrying out of consultations, diagnostics, or prescriptions by any means of mass or distant communication [10].

In this study, a group will be created on Facebook. Facebook is a social network launched in 2004 that allows the connection between individuals by sharing their stories. Users customize their profiles that contain photos and lists of personal interests, exchanging messages, private and public, between themselves and participants from groups of friends [11].

To register on Facebook you must be older than 13 years and read and accept the statement of rights and responsibilities. It is prohibited to publish content or perform any act which infringes or contravenes the rights of third parties or the law; Facebook removes any content or information published if judged in violation of this statement or policies. When there are changes to these terms, users receive notifications and have the opportunity to review the revised terms.

On Facebook it is possible to create closed groups (ie, spaces dedicated to share updates, photos, or documents or send messages to a select group of people). Groups can be open, closed, or secret. In this study, we chose the secret group to bring more privacy; it functions as follows:

- Publications are visible only to members of the group
- An administrator is responsible for the creation and maintenance of the group who reviews the members' posts and releases them for all to see
- Only a person invited to participate in the group may take part
- Only current members of the group can see who is in the group
- Only those who are included as part of the group may post comments, view the comments posted, or find the group on Facebook

## Control Group

Traditionally, all transplanted patients are treated as outpatients by a team of nephrologists. Individual consultations are carried out which provide guidance on treatment. Special attention is given to the adherence to the immunosuppressive drugs. The interval between appointments is usually 6 months or less according to clinical criteria. If required, advice is requested from other specialties.

## Randomization

Patients who are receiving medical follow-up treatment in the SUS outpatient clinic will be invited to participate in the study. Those who meet the eligibility criteria and wish to participate will receive a consent form to be completed by the person responsible for the adolescent and one to be completed by the adolescent. The next step will be the completion of the knowledge questionnaire, the satisfaction questionnaire, and the Rosenberg scale. Participants will be advised that the questionnaires will also be completed 3 months after the beginning of the study and that they will be sent a link by email.

The adolescents will be randomly selected by the program randomization.com, which will generate a list through randomization. The list will be held by a person outside the study responsible for sorting the participants according to the order they are drawn into intervention or control group. Study participants will be instructed on the dynamics of the draw, and if they are chosen to take part in the intervention group, the author will send an invitation through Facebook to join the group *Transplantados do Santo Antônio*.

## Outcome Measures

### *Knowledge*

Participants will complete a 10-question multiple choice questionnaire (Multimedia Appendix 2) before and 3 months after the beginning of the study. The items in the questionnaire were taken from the agenda of a transplant patient (the agenda was created by a team of professionals who treat adolescent transplants), which is delivered by the medical team during the orientation consultations with the patient and family before transplantation. The agenda is used in the course of treatment, where the notes on the patient's state of health after transplantation are kept.

### *Self-Esteem*

The Rosenberg Scale (Multimedia Appendix 3) is used in order to evaluate self-esteem. It is based on the adaptation by Dini et al [12] for Brazil. It contains 10 items, 5 referring to a positive vision and 5 to a self-deprecating view of self, with answer choices strongly agree, agree, disagree, and strongly disagree. After completing the inversions and summing the answers, a score between 0 and 30 is obtained on the scale; the lower the score, the greater the level of self-esteem of the individual. The Rosenberg Scale is considered an adequate scale for the evaluation of self-esteem in adolescents because it is composed of a small number of items, uses simple language, and is fast and easy to score [13].

### *Satisfaction*

A structured questionnaire with closed questions used to measure level of satisfaction (Multimedia Appendix 4) will be completed by the participant before and after the end of the study. This questionnaire contains 10 items rated on a 4-point Likert scale from totally unsatisfied to totally satisfied; the higher the score, the higher the level of satisfaction.

### Ethical Conditions

The study was approved by the Ethics Committee of the Institute of Cardiology/University Foundation of Cardiology and Hospital da Criança Santo Antônio. Before the adolescents can participate they will be given 2 copies of a consent form (for the adolescents) and 2 copies of an informed consent form (for the person responsible) in which consent for the participation in the study will be confirmed. The terms of the consent forms will be read together with the participants.

### Sample Size

The self-esteem results were used for the calculation of the sample due to a lack of studies for the other results. For the calculation of the sample, a significance level of 5% with a power of 80% was considered with a standard deviation of 6 points on the Rosenberg Scale that evaluates self-esteem, as in a study by Hutz and Zanon [14], with an expected difference of 3 points between the groups after the intervention, totaling a sample group of 122 participants (61 in each group).

### Statistical Analysis

A chi-square test will be used to analyze the statistics for the comparison of the groups.

## Results

An environment for learning and exchanging life experiences will be created by using a well-known social media technology among adolescents [15]. As a low-cost intervention, it will allow a better interaction between the patient and the transplant team. It is expected that the adolescents will improve their knowledge about the disease also increasing their self-esteem and the treatment adhesion.

## Discussion

### Summary

Innovation in health care doesn't necessarily mean the development of a new technology or the use of a new method. To occur, innovation doesn't need a huge amount of financial resources either. The health care professional can innovate simply by adopting small changes in a traditional process.

In our study, we are seeking a low-cost way to improve quality of life, treatment adhesion, and other aspects related to the follow-up of kidney transplanted adolescents. We decided to use Facebook (a free and well-known resource used by most of our patients daily) to transmit and share transplant-related knowledge, thus using a current technology as a new helper tool for these characteristic patients.

### Conclusion

Health professionals need to seek alternatives when educating patients, focusing on easily understandable ways for effective guidance. In the adolescent population, it is understood that the use of technology as support in education is a fundamental tool for this age group. The proposed project will directly benefit adolescent renal transplant patients as it uses language aimed directly at the target demographic. It attempts to overcome the traditional model by being more in contact with the current generation. This approach makes the content easier to assimilate and, consequently, increases understanding.

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Activity schedule.

[PDF File (Adobe PDF File), 25KB - resprot_v7i1e3_app1.pdf ]

### Multimedia Appendix 2

Evaluation questionnaire.

[PDF File (Adobe PDF File), 31KB - resprot_v7i1e3_app2.pdf ]

### Multimedia Appendix 3

Rosenberg Self-Esteem Scale.

[PDF File (Adobe PDF File), 45KB - resprot_v7i1e3_app3.pdf ]

### Multimedia Appendix 4

Satisfaction survey.

[PDF File (Adobe PDF File), 33KB - resprot_v7i1e3_app4.pdf ]

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## Abbreviations

**SUS:** Sistema Única de Saude (public health system)

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Protocol

# Effectiveness of a Technology-Based Supportive Educational Parenting Program on Parental Outcomes in Singapore: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Supportive educational programs during the perinatal period are scarce in Singapore. There is no continuity of care available in terms of support from community care nurses in Singapore. Parents are left on their own most of the time, which results in a stressful transition to parenthood. There is a need for easily accessible technology-based educational programs that can support parents during this crucial perinatal period.

**Objective:** The aim of this study was to describe the study protocol of a randomized controlled trial on a technology-based supportive educational parenting program.

**Methods:** A randomized controlled two-group pretest and repeated posttest experimental design will be used. The study will recruit 118 parents (59 couples) from the antenatal clinics of a tertiary public hospital in Singapore. Eligible parents will be randomly allocated to receive either the supportive educational parenting program or routine perinatal care from the hospital. Outcome measures include parenting self-efficacy, parental bonding, postnatal depression, social support, parenting satisfaction, and cost evaluation. Data will be collected at the antenatal period, immediate postnatal period, and at 1 month and 3 months post childbirth.

**Results:** Recruitment of the study participants commenced in December 2016 and is still ongoing. Data collection is projected to finish within 12 months, by December 2017.

**Conclusions:** This study will identify a potentially clinically useful, effective, and cost-effective supportive educational parenting program to improve parental self-efficacy and bonding in newborn care, which will then improve parents' social support–seeking behaviors, emotional well-being, and satisfaction with parenting. It is hoped that better supported and satisfied parents will consider having more children, which may in turn influence Singapore's ailing birth rate.

**Trial Registration:** International Standard Randomized Controlled Trial Number (ISRCTN): 48536064; https://www.isrctn.com/ISRCTN48536064 (Archived by WebCite at http://www.webcitation.org/6wMuEysiO)

***(JMIR Res Protoc 2018;7(1):e4)*** doi:10.2196/resprot.8062

**KEYWORDS**

parents; satisfaction; perinatal; self-efficacy; social support

## Introduction

### Background

The addition of a newborn to a family unit necessitates an environment of change and uncertainty [1] as parents are confronted with various new challenges and struggle to adapt to the new dynamics at home [2]. The parenthood experience is largely influenced by many factors including parents' confidence levels, emotional well-being, social networks, and the quality of their support system [3]. Such environmental factors are capable of acting as a security blanket to buffer against the stressors that comes with parenthood, or add on to the stress parents are already facing, and such negative experiences can deter couples from becoming parents again. It is crucial to maintain positive emotional well-being in parents as studies have shown that maternal psychosocial stress can influence dynamics in the family [4-6].

In view of the dipping fertility rate [7,8], the Singapore government has been coming up with attractive incentive packages [9-11]; however, these have proven to be futile in boosting fertility rates. Low fertility rates are associated with multiple factors including an economic drain [12], parental expectations of childbirth, and previous negative birth experiences [13,14]. Previous studies have found that perinatal experiences were one of the major factors affecting birth rate [15,16]. Negative perinatal experiences such as a lack of support during this crucial period may influence a parent's decision to give birth again [17]. In Singapore, perinatal support is mainly provided by maternity hospitals [18]. Unlike certain parts of Western Europe, continuity of care post hospital discharge by community care nurses is lacking in Singapore [19].

To assist parents in transiting smoothly into parenthood, antenatal classes and postnatal educational sessions are available at the hospitals in Singapore [20]. However, because of early discharges [21] and having so much to teach, parents are overloaded with too much information [22], which limits the effectiveness of these educational sessions. In a local study, mothers found that informational support provided by the hospital was unsatisfactory [20] as the most crucial period for parents is usually the first few weeks post discharge, when parents are left to handle stressful situations on their own. Moreover, current perinatal services in Singapore focus much of their attention on supporting women's transition to early motherhood during hospitalization and pay less attention to fathers. A study conducted in Canada revealed that fathers did not feel supported by the hospital environment with regard to promoting their involvement with their newborn [23]. Therefore, there is a need for a theory-based educational program that focuses on facilitating smooth transition to parenthood for both parents.

Previous local studies were mainly focused on first-time mothers [24] or the early postpartum period [25]. There is a limited amount of educational programs that are developed for both first-time and experienced parents across the perinatal period. Support for parents from the antenatal period until the postnatal period is recommended in both international [26-28] and local [25] studies. Additionally, most of the available educational programs are delivered face-to-face, in which information is relayed didactically [27,29]. The shortage of midwives and nurses limits the feasibility of such programs as they are not cost-effective [29].

With the advancement in technology, the use of technology-based educational programs with new parents during the postnatal period both internationally [22,30,31] and in local context [25] have found to be successful in influencing parental outcomes in the postnatal period. However, because of the lack of a rigorous experimental study design [22,31] and limited postnatal focus [25,30,32], there is a need to develop an intensive family-oriented perinatal educational program that is professionally based and provided at a low cost, utilizing technology to enhance accessibility to all parents without compromising its effectiveness on parental outcomes. As such, this study aims to develop a technology-based supportive educational parenting program (SEPP) to support both fathers and mothers across the perinatal period by targeting different variables through the different components of the SEPP.

### Theoretical Framework

The theoretical framework guiding the SEPP is Bandura's self-efficacy theory and Bowlby's attachment theory [32,33]. According to Bandura's self-efficacy theory [33], parenting self-efficacy (PSE) is considered one of the major determinants of competent parenting and the well-being of a newborn and is related to parental emotional well-being such as postnatal depression and the social support available for parents. Bowlby also theorizes that early parent-to-infant attachment provides the foundation of psychological well-being and, later, the development for infants in building social relationships, which can be influenced by PSE, emotional well-being, and social support [32]. Social support is associated with high PSE, which is in turn related to better emotional well-being and enhanced parental bonding with their newborn [24,27,34,35], which may ultimately lead to better parenting satisfaction. Hence, PSE, parental bonding, emotional well-being, and social support are interrelated variables, and the SEPP aims to target these variables to improve parental outcomes. This theoretical framework is represented in Figure 1.

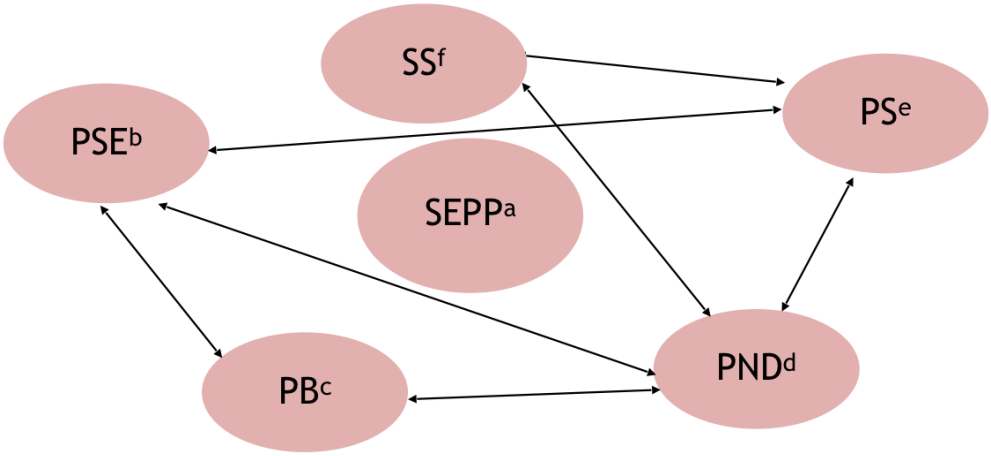
### Aims

The aims of the study were to (1) examine the effectiveness of the SEPP on parental outcomes, including PSE (primary outcome), parental bonding, postnatal depression and anxiety, social support, and parenting satisfaction; (2) evaluate the cost-effectiveness of the SEPP compared with routine perinatal care; and (3) process evaluation of the SEPP by assessing its strengths and weaknesses from parents' perspectives.

### Hypotheses

The hypotheses are (1) When compared with those in the control group receiving routine care, parents receiving the SEPP will report significantly (a) higher levels of self-efficacy in newborn care, (b) higher levels of parental bonding, (c) lower levels of depression and anxiety, (d) higher levels of social support received, and (e) higher levels of parenting satisfaction and (2) It is more cost-effective to provide the SEPP than routine care.

**Figure 1.** Theoretical Framework showing interrelationship between outcome variables. SEEP: Supportive educational parenting programme; PSE: Parenting self-efficacy; PB: Parental bonding; PND: Postnatal depression; PS: Parenting satisfaction; SS: Social support.




## Methods

### Design

A randomized controlled two-group pretest and repeated posttest experimental design will be used. Couples (n=118 participants) recruited from a tertiary hospital will be randomly assigned into the two groups (intervention group receiving the SEPP and routine care or control group receiving only routine care). Data will be collected via questionnaire surveys using locally validated and reliable instruments, medical reviews, semistructured face-to-face interviews, and telephone interviews.

### Components of the Supportive Educational Parenting Program

Parents who are assigned to the intervention group will receive the SEPP and routine perinatal care provided by the hospital. Parents in the control group will receive only routine care. The routine care includes antenatal check-ups with an obstetrician and short postnatal stays in the hospital. During antenatal check-ups, the progress of the pregnancy is assessed via maternal bio-physiological profile, height and weight, and abdominal palpation. Antenatal educational classes are available; however, they are charged and not fully utilized by parents because of their lack of awareness [24]. During postnatal stay, parents will receive care from an obstetrician, nurses, and lactation consultants. Parent-craft educational classes are available. However, because of the short hospital stays, most of the parents are too tired to attend these sessions [24]. The SEPP consists of three main components, as presented in Table 1.

In Singapore, the mobile phone penetration rate was approximately 98% in 2016 [36], which is the highest globally. Moreover, under the smart nation initiative, Singapore is moving toward delivering holistic health care to the population through technological innovations [37]. Hence, delivering the SEPP in the form of a mobile health (mHealth) app is not only feasible but also a sustainable and convenient form of education delivery for health care professionals (HCPs) and parents. All educational contents in the app has been reviewed and approved by the ethics board.

**Table 1.** Details of the Supportive Parenting Educational Program.

| No.[a] | Mode and period of delivery | Approximate duration of the session | Topics covered |
|---|---|---|---|
| 1 | Telephone-based antenatal educational session | 30 min | 1. Parental self-efficacy and bonding (eg, definitions of parental self-efficacy and bonding, why are they important, and how they can be enhanced<br>2. Expectations in the immediate postpartum period<br>3. Emotional needs of parents both during pregnancy and after the child's birth |
| 2 | Telephone-based immediate postnatal educational session | 60 min | 1. Reinforcement on the topics covered during antenatal period, including parenting self-efficacy, parental bonding, and postnatal depression<br>2. Coverage on parent-craft class topics including baby bathing and breastfeeding<br>3. Role of fathers during postnatal period |
| 3 | mHealth[b] app-based follow-up educational session | 1 month access to the mHealth app | 1. A knowledge-based content on topics including newborn and maternal care<br>2. Audio recordings of the knowledge-based content<br>3. Videos on various newborn care tasks such as baby bathing and breastfeeding demonstrated by a trained midwife using a live baby. Each video is approximately 8 min long on average<br>4. A discussion forum<br>5. Push notifications |

[a]Number in series.

[b]mHealth: mobile health.

The knowledge-based content in the mHealth app includes evidence-based information on ways to enhance parental self-efficacy and bonding, newborn care and maternal self-care tasks, emotional challenges and ways of dealing with it, breastfeeding-related information, and insights for new parents for a smooth transition to parenthood. The discussion forum will be a platform for parents to ask any questions they might have. All parental queries will be answered by a trained midwife (research assistant 1, RA1) once a day for the first 4 weeks post childbirth because this period is the most stressful period for new parents in the early post-partum period [38,39]. Additionally, other parents can also provide insights to these queries by sharing their personal experiences. According to Bandura's self-efficacy theory [33], self-efficacy and a help-seeking behavior (social support) can be enhanced when tasks are learned from others in a similar situation; therefore, parents are encouraged to interact with other parents in the discussion forums. Daily push notifications regarding important milestones on parenting will be sent to users. Each notification appears on the user's home screen, which aims to pique the user's interest and serves as a reminder to continue exploring the rest of the content-rich app. Participants' access to the mHealth app will be monitored (by adding the function of time spent in accessing materials) to record the dosage of the intervention each participants receives. The app was developed by an external vendor who is an expert in mHealth app development. The research team and the external app developer have been keeping in close contact for the development of the app. Screenshots of the features of the app as examples are shown in Figures 2-6.

To ensure consistency, the same RA (RA1) will deliver the telephone-based prenatal and postnatal educational component in the SEPP to all the participants in the intervention group. The protocol for the SEPP has been validated by an expert panel consisting of five HCPs (one nursing professor who is experienced in postnatal educational programs, one senior consultant-neonatologist, one senior consultant-obstetrician, and two experienced midwives in perinatal education) and two sets of parents.

**Figure 2.** Screenshot of knowledge-based content.

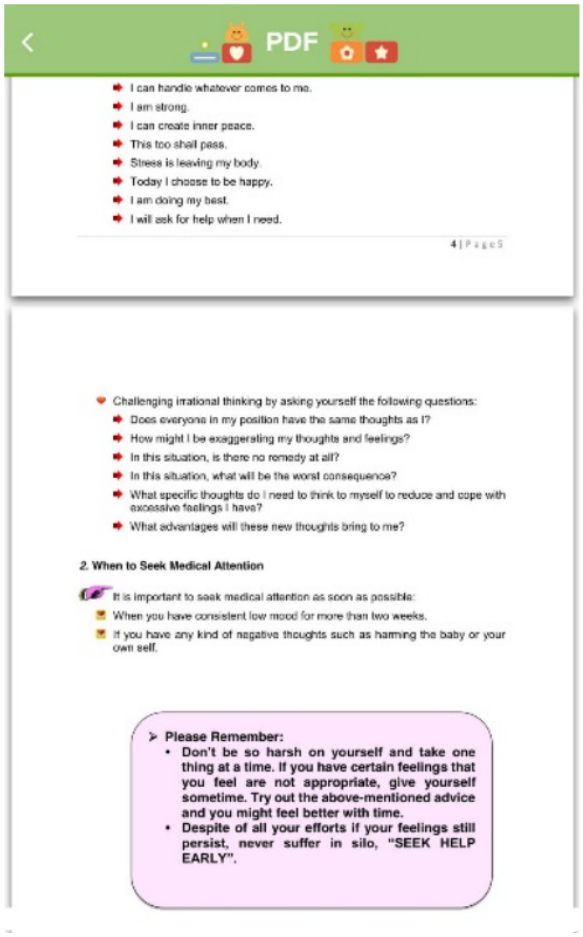



**Figure 3.** Screenshot of audio recordings.

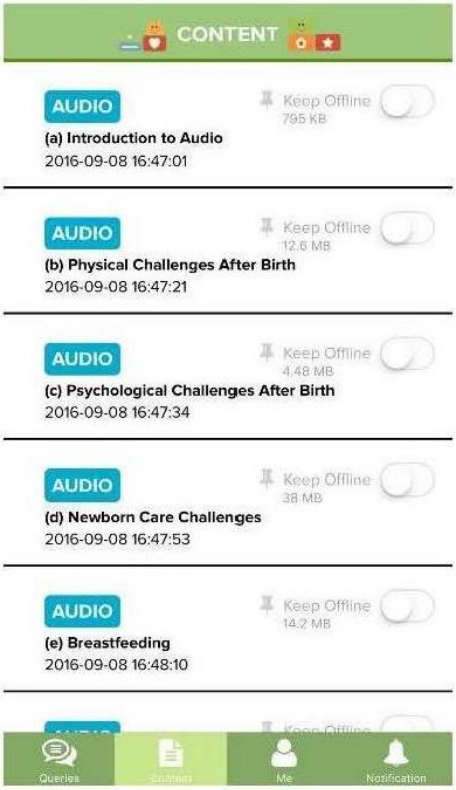


**Figure 4.** Screenshot of discussion forum.


**Figure 5.** Screenshot of videos.

**Figure 6.** Screenshot of push notifications.


**Textbox 1.** Inclusion criteria.

1. Are 21 years and above
2. Are able to read and speak English
3. Have low-risk singleton pregnancy with more than 28 weeks of gestation
4. Have a mobile phone with Internet access
5. Plan to stay in Singapore for the first 3 months post delivery

**Textbox 2.** Exclusion criteria.

1. Have self-reported physical or mental disorders that will interfere with their ability to participate in the study
2. Have high-risk pregnancy, including placenta-previa major, preeclampsia, and pregnancy-induced hypertension
3. Have complicated assisted delivery such as vacuum or forceps with 4th degree perineal tear of the mother
4. Gave birth to a stillborn or a newborn with congenital abnormalities or medical complications, or
5. Are a single parent

## Participants

The participants recruited will be couples (a father and mother dyad is considered one couple). The inclusion and exclusion criteria for participants who are mothers are shown in Textboxes 1 and 2.

The inclusion criteria for fathers are those who (1) are 21 years and above, (2) are able to read and speak English, (3) have a mobile phone with Internet access, and (4) plan to stay in Singapore for the first 3 months post delivery. The exclusion criteria for fathers are those who have self-reported physical or mental disorders that will interfere with their ability to participate in the study and/or are a single parent.

All couples are recruited antenatally and will be told beforehand that they may be excluded from the study if mothers are to experience complication during their pregnancy and the delivery of their newborn.

## Sample Size Determination

On the basis of previous studies, psychosocial and educational interventions in the perinatal period generally produce a medium size effect on outcome variables [27,28]. Hence, the SEPP intervention can also be assumed to have a medium effect size

on outcome variables. A repeated measure analysis of covariance (ANCOVA) will be used to test for differences between two groups (intervention and control) and within four separate time points and for interaction (group x time) effects. The required sample size for the detection of a medium effect size of 0.3 (analysis of variance [ANOVA] *F* value) at a power of 80% and a significance level of 5% (two-sided) is 45 in each group [40]. Considering a 30.0% (30/100) attrition rate based on previous studies [27,29], a minimum of 118 participants (45x2 + 45x2x30%=90 + 28=118), with 59 in each group, is needed. A purposive sample of approximately 16 participants will be needed for the process evaluation. Parents with differing mean parenting efficacy (primary outcome) scores from both the intervention and control groups (8 from each group) will be selected to participate in the face-to-face interviews, until data saturation is attained.

## Randomization

The research randomizer will be used to randomly generate one set of 59 numbers ranging from 1 to 118. Generated numbers are assigned to the intervention group and the remaining to the control group. All 118 numbers will be placed in an opaque envelope. The principle investigator who will not be involved in the recruitment will hold the random numbers and pass it to RA1 for recruitment. After assessing eligibility and obtaining informed consent, the participants will be asked to pick a number from the opaque envelope, in which the number picked will determine the groups assigned.

## Outcome Measures and Instruments

Patients' demographic data (eg, age, gender, ethnicity, and education) will be collected. In addition, the following instruments will be used to measure parental outcomes:

1. Parenting Efficacy Scale (PES): This 10-item PES scale [41] is used to measure parental beliefs on self-efficacy. Nine of the items refer to specific behaviors related to infant care (eg, feeding and bathing), and the last item is a global evaluation of parenting ability. The total score of PES ranges from 10 to 40, with higher scores indicating higher PSE. The Cronbach alpha value of the PES was .74 in the previous study [42].
2. Parent- Infant Bonding Questionnaire (PIBQ): This is an 8-item, 4-point Likert scale used to measure the parental bonding of both parents [43]. The total scores range from 0 to 24, with higher scores suggesting ineffective bonding between mother and infant and vice versa. The cut-off score indicating poor bonding between parent and infant is indicated at 2 [44]. The Cronbach alpha for this questionnaire was .7 in the previous study [45].
3. Edinburgh Postnatal Depression Scale (EPDS): This is a 10-item scale widely used to measure parents' postnatal depression [24,29,46-48]. The total score of the EPDS ranges from 0 to 30. The recommended cut-off score of 12 or 13 is used for screening probable cases of postnatal depression. The sensitivity of the EPDS ranges from 68% to 80%, with 77% specificity and a Cronbach alpha of .88 [49].
4. State Trait Anxiety Inventory (STAI): This is a 40-item 4-point Likert scale used to measure parental anxiety level. The total score for the STAI ranges from 40 to 160, with higher scores indicating greater levels of parental anxiety. The scale has been tested widely in various studies [50-53]. The Cronbach alpha for the STAI was .8 in a previous local study [52].
5. Perceived Social Support for Parenting (PSSP): This is a 4-item scale [42] used to measure the social support parents receive from their partners or others. The score of the 5-point Likert scale ranges from 0 to 20 for the support received from partners or others. The instrument showed high internal consistency and had a Cronbach alpha of .81 in a previous study [42].
6. What Being the Parent of a Baby is Like (WBPL): The evaluation subscale of the WBPL will be used to measure parenting satisfaction [54]. It consists of 11 items, and each item is a 10-point semantic differential scale ranging from 0 (none of the phenomenon) to 9 (a great deal of the phenomenon). In previous studies, the Cronbach Alpha ranged from .91 to .92 [54,55].
7. Health care utilization and program-related expenses sheet: This sheet will be used to capture all direct health systems cost related to health care services utilized antenatally and postnatally because of maternal or infant related health issues such as hospital admissions and outpatient contacts, health professional's time, program-related time, and during pregnancy, for the first and 3rd month after delivery. The study will take an *all-payer* health system perspective in which it will attempt to capture all resources that are used by the participants, regardless of who the payer is (ie, government or consumer), including the program cost. The measurement period begins from entry into the program until 3 months post birth.
8. A semistructured interview guide will be used for the process evaluation. Individual face-to-face interviews will be conducted immediately after the intervention (1 month post birth) to identify strengths and weaknesses and to comment on the content, activities, effectiveness, and delivery methods of the SEPP for participants in the intervention. Parents in the control group will be asked to comment on the current routine perinatal care provided by the hospital. All interviews will be audiorecorded.

## Study Procedure

The study consists of two phases: (1) planning intervention strategies for the intervention group, including the development of the educational content to be covered during the antenatal and postnatal periods and the development of the mHealth app, audio, and videos related to postnatal care, and (2) implementation of the SEPP and investigating its effectiveness on parental outcomes.

This study has been approved by the ethics board, and recruitment at the antenatal clinics has started at the study venue. The principle investigator and her team will inform nurse managers and clinicians at the antenatal clinics before a RA (RA1) commences the process of recruitment. Before contacting potential participants, the attending nurses and/or clinicians will be approached to assess each couple's physical and psychological well-being before inviting them to participate in the research study. The referred couples will once again be

assessed using the inclusion and exclusion criteria. There will be no undue influence or coercion used to recruit couples into the study. Each couple will be given details of the purpose of the study and ample time to ask questions and to consider before deciding to participate. It will be strongly emphasized that their participation is solely voluntary and that they may choose not to participate without any harm or compromise in the care they receive. Verbal and written consent will be obtained from the couple, both mother and father, thereafter. Both first-time and experienced mothers, regardless of their parity, who meet the inclusion criteria, along with their partners, will be recruited. RA1 will visit the antenatal clinics regularly to recruit participants according to the inclusion and exclusion criteria and will be responsible for randomizing the participants.

Once consent has been taken, demographic and baseline data of the participants will be obtained, and randomization will take place. In addition, recruited couples will be asked for their contact details so that they can be contacted for subsequent follow-ups. RA1 will keep in constant contact with the participants to ensure the birth of the newborn. For participants in the intervention group, telephone-based antenatal education session will be delivered by RA1 at the participants' convenience at a prearranged timeslot.

After childbirth, all couples will be reapproached in the postnatal wards by the RA before their day of discharge post childbirth. Before making contact in the postnatal wards, the nurse-in-charge will be approached by RA1 to ensure the physical and emotional well-being of the participants. For participants in the intervention group, the postnatal education session will be delivered by RA1 in the postnatal wards on the day of discharge from the hospital. RA1 will assist parents in downloading the mHealth app and demonstrate the functions of the app before discharge. Participants will also be given individual usernames and passwords for access to the mHealth app. Access to the app will expire automatically in 4 weeks. RA1 will be responsible for answering the queries in the discussion forum and to monitor and correct any inappropriate content shared among parents.

## Data Collection

A single-blind technique will be adopted, in which the RA (RA2) responsible for the collection of data post intervention or post discharge will not be aware of the treatment allocation, which will be conducted by another RA (RA1). RA2 will be responsible for the collection of all interim and postintervention data, including the process evaluation interviews. Outcome measures will take place at the following time points for all parents: (1) during pregnancy, before randomization (baseline); (2) after childbirth, before hospital discharge (interim data); (3) post intervention for the SEPP intervention group and at the end of week 4 post childbirth for the control group (posttest 1); and (4) 2 months after the SEPP for the intervention group and 3 months post childbirth for the control group (posttest 2). The period when parents are prone to facing various challenges is at 1 month post birth. Hence, the rationale for collecting posttest 1 data during that time. At 3 months post birth is when some working mothers return to work, signifying a change in environment relating to the rational for collecting posttest 2 data. Before contacting parents for the posttest data, a message will be sent to ensure parents' availability. In the process of data collection, if either parent feels tired, RA2 will respect the parents' decision to continue or terminate the data collection to ensure parents' comfort. The consolidated standards of the reporting trial flowchart for this study is presented in Figure 7 [56].

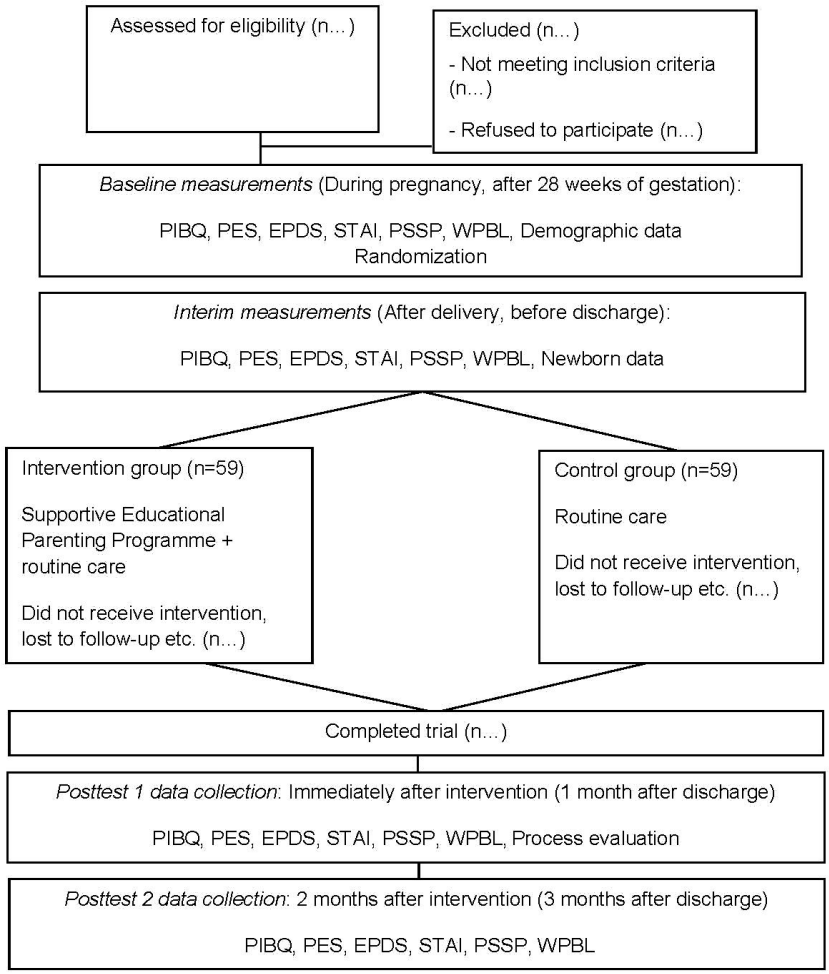
## Process Evaluation

Process evaluation will be conducted with the main objective of obtaining parents' opinions and comments of the SEPP intervention. Purposive sampling of parents will be done based on the parenting self-efficacy scores of parents immediately after the end of the intervention (at 1 month post childbirth). This will be done through a semistructured face-to-face interview. Each interview will take approximately 20 to 30 min and will be audiorecorded. Parents will not be included for interview if they refused to be audiorecorded. The recruitment for process evaluation will continue and will only be terminated once the proposed number of interviews is reached or when data saturation is achieved. The semistructured interview guide has been reviewed and approved by the ethics board.

## Data Analysis

All quantitative data will be analyzed using Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM Corp). Missing data will be replaced (assuming 10%) for intention-to-treat (ITT) analysis. Both ITT analysis and per-protocol analysis will be conducted to compare any differences between groups. Descriptive statistics such as mean, standard deviation, and range for continuous dates, frequencies, and percentages will be used for nominal and ordinal data. Cronbach alpha will be used to test the internal consistencies of the questionnaires. Inferential statistics such as the independent *t* test or ANOVA will be used to compare differences of outcomes between or among demographic subgroups. Presuming that outcomes variables are normally distributed, parametric tests will be used. Repeated measures ANCOVA adjusted for confounding variables will be used to test the effect of intervention on outcome variables across four time points. Univariate ANCOVA will be used to test the differences in outcome variables between two groups at the interim and two posttests data separately.

**Figure 7.** The consolidated standards of reporting trial flowchart. PIBQ: Parent-Infant Bonding Questionnaire; PES: Parenting Efficacy Scale; EPDS: Edinburg Postnatal Depression Scale; STAI: State-Trait Anxiety Inventory; PSSP: Perceived Social Support for Parenting; and WBPL: What Being the Parent of a Baby is Like.




Qualitative data will be analyzed using thematic analysis [57,58]. All recorded audio will be transcribed verbatim by the RA2 concurrently with data collection to capture nonverbal information. Transcribed data will be classified into different categories, with similar ideas grouped in a category highlighted in the same color. Related codes or categories will be collated together to form subthemes, which will be reviewed and combined to form themes [57]. Two investigators will be involved in the analysis process to compare and discuss the categories, subthemes, and themes that are generated and to achieve consensus. Rigor or trustworthiness, including credibility, transferability, dependability, and confirmability, will be considered carefully [58].

### Ethical Considerations

Ethics approval has been obtained from the National Health Group Domain Specific Review Board (NHG DSRB) before the commencement of the study (Ref. No: NHG DSRB: 2016/00651) in June 2016. All participants are given a set of participant information sheets consisting a brief introduction and the purpose of the study, with the advantages and disadvantages of the study conveyed clearly. The participants are guaranteed anonymity and are informed of the right to withdraw at any point of the study without affecting any subsequent care received.

## Results

Phase 1 of the study has been completed. Educational materials for both antenatal and postnatal education, audio and videos files, and the mHealth app have been developed. For phase 2, the recruitment of study participants commenced in December 2016 and is still ongoing. The targeted aim of recruiting 118 couples will be ongoing for a period of 12 months. The total number of participants approached thus far are 211, and 162 were screened (not interested and did not comply to one of the inclusion criteria). The current enrollment is 49 couples (for both the intervention [n=27] and control [n=22] groups). The projected timelines for the completion of the data entry and analysis for investigating the SEPP's effectiveness on parental outcomes is around December 2017.

## Discussion

Theoretical framework–based and technology-enhanced educational programs have shown effectiveness [22,24,25,30,31] in influencing parental outcomes in the postnatal period. Previous studies have used varied technologies including

telephone calls [31], Web-based programs [30], and mHealth apps [22,25] to influence postnatal depression [31], parenting satisfaction, and self-efficacy [30]. The only local study [25] that has used an mHealth app in supporting parents has influenced parental outcomes. However, the effectiveness was tested short-term (1 month post childbirth), and the study showed no influence on parental postnatal depression. A few studies [22,24,25,30,31] recommended the need of providing long-term perinatal educational support to parents. Specifically, the previous local study [25] recommended a long-term evaluation of the effectiveness of the educational program beyond 1 month. As such, this study will address this gap in literature by providing empirical support for the feasibility and effectiveness of the SEPP in enhancing parental outcomes across the perinatal period. This will also be the first study in Singapore that will examine the cost-effectiveness of an educational intervention delivered to parents.

We are hopeful that the provision of this technology-based educational program, which includes telephone calls and an mHealth app, will provide a clinically useful and potentially cost-effective solution to improve parental outcomes. This may eventually lead to more positive perinatal parenting experiences, which may influence the psychosocial well-being of both parents and their newborn, leading to better family dynamics and reducing associated health care and social burdens. It may also impact the future reproductive decisions of parents.

It is worthy to note that this study is being tested in a multiracial population, which enhances its relevance in the local context as participants in the study venue have similar demographic profile to Singapore's general population, with the majority of its population being Chinese, followed by Malays and Indians. However, being a single-centered study, it limits its generalizability to an international population and requires further evaluation.

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## Conflicts of Interest

None declared.

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## Abbreviations

**ANCOVA:** analysis of covariance
**EPDS:** Edinburg Postnatal Depression Scale
**HCP:** health care professional
**ITT:** intention to treat
**mHealth:** mobile health
**PES:** Parenting Efficacy Scale
**PIBQ:** Parent-Infant Bonding Questionnaire
**PSE:** parenting self-efficacy
**PSSP:** perceived social support for parenting
**RA:** research assistant
**SEPP:** Supportive Educational Parenting Program
**STAI:** State Trait Anxiety Inventory
**WBPL:** What Being the Parent of a Baby is Like

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Protocol

# A Tailored Web-based Advice Tool for Skiers and Snowboarders: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Being active in sports has many positive health effects. The direct effects of engaging in regular physical activity are particularly apparent in the prevention of several chronic diseases, including cardiovascular disease, diabetes, cancer, hypertension, obesity, depression, and osteoporosis. Besides the beneficial health effects of being active, sports participation is unfortunately also associated with a risk of injuries. In the case of many sports injuries (eg, winter sports) preventive measures are not compulsory, which means that a behavioral change in sports participants is necessary to increase the use of effective measures, and subsequently prevent or reduce injuries in sports.

**Objective:** The evidence-based Wintersportklaar online intervention has been developed to stimulate injury preventive behavior among skiers and snowboarders. In this article, the design of the effectiveness study will be described.

**Methods:** A randomized controlled trial with a follow-up period of four months during the winter sport season will be conducted. The participants consist of inexperienced skiers and snowboarders. At baseline, skiers and snowboarders in the intervention and control groups are asked to report the injury preventive measures they usually take during their preparation for their winter sport holiday. One and three months after baseline, skiers and snowboarders are asked to report retrospectively in detail what measures they took regarding injury prevention during their current winter sport preparation and winter sport holiday. Descriptive analyses (mean, standard deviation, frequency, range) are conducted for the different baseline variables in both study groups. To evaluate the success of the randomization, baseline values are analyzed for differences between the intervention and control groups (chi square, independent *T* tests and/or Mann-Whitney test). Chi square tests and/or logistic regression analyses are used to analyze behavioral change according to the intention to treat principle (as initially assigned).

**Results:** The project was funded in 2016 and enrolment was completed in 2017. Data analysis is currently under way and the first results are expected to be submitted for publication in 2018.

**Conclusions:** To combat the negative side effects of sports participation, the use of injury preventive measures is desirable. As the use of injury prevention is usually not compulsory in skiing and snowboarding, a behavioral change is necessary to increase the use of effective injury preventive measures in winter sports.

**Trial Registration:** Dutch Trial Registry NTR6233; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6233 (Archived by WebCite at http://www.webcitation.org/6wXZPzjUi)

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**KEYWORDS**

Winter sports, behavior, injury prevention, skiing, snowboarding

## Introduction

Skiing and snowboarding are very popular winter sports worldwide, including among Dutch residents. Nearly one million Dutch snow sport fanatics travel each year to the mountains to spend their winter holidays in the snow, with Austria, France, Germany, Switzerland, and Italy being the most popular destinations [1]. Besides the beneficial health effects of being active, both skiing and snowboarding are also associated with a risk for musculoskeletal injuries and traumatic brain injury (42 injuries per 1,000,000 person-years for skiers and 19 injuries for snowboarders in America or 0.6 injuries per 1,000 skier days in Austria) [2-4]. Although the injury rate among skiers in Austria has decreased in recent years, attention to injury prevention should be encouraged due to the severity of these injuries [2,4].

Known risk factors for the occurrence of snow sport injuries are snow sport experience, rented equipment, weather conditions, speed, fatigue and technical errors [5,6]. The development of safer skiing environments and the use of injury preventive measures—especially a winter sport helmet—might prevent or reduce injury severity among skiers and snowboarders. However, because injury preventive measures such as helmet use for adults and wrist guard use for snowboarders in general are not compulsory on the ski slopes, a behavioral change in skiers and snowboarders is necessary to increase the use of those measures and subsequently prevent or reduce injuries in winter sports.

Accordingly, a scientific research project has started in the Netherlands (funded by ZonMW, the Netherlands Organization for Health Research and Development). The aims of this project are: (i) to develop an evidence-based intervention to stimulate injury preventive behavior among skiers and snowboarders; and (ii) to evaluate the effectiveness of the developed intervention. The effectiveness of the developed intervention will be evaluated through a randomized controlled trial. This article describes the design of this study.

## Methods

The Consolidated Standards of Reporting Trials (CONSORT) statement is followed to describe the design of the study [7]. This statement is a checklist intended to improve the quality of reports of randomized controlled trials.

### Objective and Hypothesis

The objective of the study is to evaluate the effectiveness of the Wintersportklaar intervention (www.wintersportklaar.nl; in Dutch) on injury preventive behavior among skiers and snowboarders. The hypothesis of this study is that the developed intervention would lead to a 10% increase in favorable injury preventive behavior in the intervention group in comparison to the control group.

### Study Design

A randomized controlled trial with a follow-up period of 4 months during the winter sport season will be conducted (see Figure 1). The study is registered in the Dutch Trial Registry (ID: NTR6233).

### Participants and Recruitment

The participants consist of inexperienced skiers and snowboarders. Inclusion criteria are: (i) less than five weeks of winter sport lessons or; (ii) less than two weeks of winter sport holiday per year or; (iii) less than five weeks of winter sport experience or; (iv) low physical fitness. An exclusion criterion is cross-country skiing.

Because of the relatively short duration of the winter sport season, participants can preregister 2 months before the start of the study. Participants are recruited via social media networks (ie, Facebook, websites, Twitter, LinkedIn) of the participating organizations (Dutch Consumer Safety Institute and Dutch Skiing Association). All the preregistered participants will receive the baseline questionnaire.

### Ethics, Consent and Permissions

The study protocol has been approved by the Medical Ethics Review Committee of the Academic Medical Center (W16-335 #16.417; Amsterdam, the Netherlands). Participants willing to take part in the study have to give their informed consent prior to the start of the baseline questionnaire. The flow of the participants is presented in Figure 1.

### Sample Size and Allocation

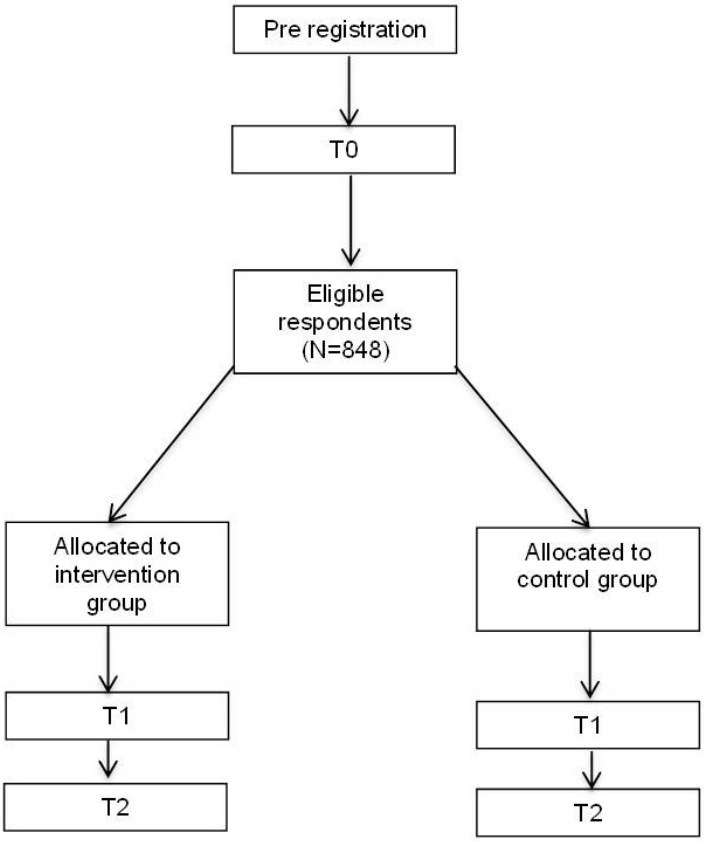
In this study, the assumption is made that a 10% increase in favorable injury preventive behavior in the intervention group compared with the control group can be achieved. To achieve 80% power with a significance level of 0.05, and taking into account a potential loss to follow-up among participants of 10% over the winter sport season, the sample size calculation reveals that 423 skiers and snowboarders per study group are needed in this study. Eligible participants will simultaneously be allocated at random to the intervention or control group after T0, using a computerized random number generator (the ASELECT function in Excel). No restrictions will be imposed for the allocation; simple randomization will be performed. All steps in the randomization process will be done by 1 researcher.

### Intervention

The Wintersportklaar intervention has been developed according to the steps of Intervention Mapping (IM) and Knowledge Transfer Scheme [8-10]. The Fogg Behaviour Model (FBM) to achieve behavior change formed the basis for this development [11]. More information on the development of Wintersportklaar is available in Kemler E, Valkenberg H & Gouttebarge V (under review).

Wintersportklaar will be made available exclusively to the participants within the intervention group, and is an evidence-based intervention developed to stimulate injury preventive behavior among skiers and snowboarders. The development of the intervention was a collaboration between snow sport experts and the target group. According to the Dutch winter sport experts who were consulted, the skill level and the physical fitness level of skiers and snowboarders are the two main dimensions involved in the risk of winter sport injuries.

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




Part one of the intervention is a short questionnaire. Based on 8 single questions, the physical fitness and skill level of the skiers and snowboarders will be determined and classified as: 1) low level of physical fitness and skill level; 2) low level of physical fitness and sufficient skill level; 3) sufficient level of physical fitness and low skill level; and 4) sufficient level of physical fitness and skill level. Depending on their answers, skiers and snowboarders will receive tailored advice on optimal preparation for their winter sport holiday (part two). Examples of advice include taking winter sport lessons, and strength exercises. Furthermore, advice about the use of protective gear and the 10 Fédération Internationale de Ski (FIS) rules for the conduct of winter sport safety are given. After receiving the tailored advice, the skiers and snowboarders can leave their email address on the website in order to receive a personal exercise schedule every week until the start of their winter sport holiday (part three). The Wintersportklaar intervention is made available to the participants within the intervention group. Huge efforts have been made to develop an easily accessible intervention (eg, short questionnaire, quick outcome), with a low threshold, and easily applicable injury preventive advice.

## The Control Group

The skiers and snowboarders in the control group do not have access to the intervention and prepare their winter sport holiday as they normally would.

## Injury Preventive Behavior

In our study, our main outcomes measure injury preventive behavior defined as: (i) taking winter sport lessons; (ii) performing strength exercises; (iii) the use of protective equipment; and (iv) knowledge of the 10 FIS rules for the conduct of safety in winter sport. Each injury preventive topic is divided into preparatory acts like searching for information about injury preventive measures, buying a winter sport helmet, etc, and structural injury preventive measures (eg, wearing a helmet, taking lessons). Taking winter sport lessons consists of two preparatory acts and three structural injury preventive measures. Performing strength exercises consists of two structural injury preventive measures, and the use of protective gear consists of three preparatory acts and three structural injury preventive measures. Finally, knowledge of the 10 FIS rules for the conduct of safety in winter sport consists of three preparatory acts. All injury preventive behaviors are assessed through single questions (eg, Did you buy a winter sport helmet after the start of this study? Yes/No/Not applicable).

## Procedures

At baseline, respondents will be asked about their winter sport demographic characteristics, winter sport skill level, physical fitness, current injuries and physical complaints, winter sport preparation, and winter sport injury preventive measures. Furthermore, skiers and snowboarders in the intervention and control group will be asked to report the injury preventive measures they usually take during their preparation for their winter sport holiday. One month and three months after baseline, skiers and snowboarders will be asked to report retrospectively in detail what they had done up until then regarding injury prevention during their current winter sport preparation and holiday. In the follow-up measurements, respondents will be

asked about any injuries they suffered during their winter sport preparation and holidays. In our study, an injury is defined as an event during skiing or snowboarding after which the participants have to stop their winter sport activities or are unable to participate in another winter sport activity [12-15]).

For all three measurements, an online form will be sent by email by 1 researcher through SurveyMonkey, an online questionnaire system (www.surveymonkey.nl). The first reminder will be sent after 1 week if no response is received. A second reminder will be sent after 2 weeks if no response is received.

The intervention group will be additionally questioned about their use and valuation of the Wintersportklaar intervention. The evaluation of its effectiveness will not take place in an experimental setting; participants in the intervention group will be given access to the intervention, but no further conditions are applied to the use of the intervention. In the questionnaires given at one month and three months, the intervention group will be asked about their use of the intervention, the appeal of the intervention, the behavioral actions they took after being exposed to the intervention, their intention to use the intervention again, and how they would want to be informed about the intervention. If participants indicate that they do not want to use the intervention, they will be asked to explain their decision in detail.

### Statistical Analysis

Descriptive analyses (mean, standard deviation, frequency, range) are conducted for the different baseline variables for both study groups. To evaluate the success of the randomization, baseline values are analyzed for differences between the intervention and control groups (chi square, independent *T* tests and/or Mann-Whitney test).

Chi square tests and/or logistic regression analyses will be used to analyze behavioral change according to the intention to treat principle. According to this principle all participants who were enrolled and randomly allocated to the intervention or control group are included in the analysis and are analyzed in the groups to which they were randomized. In a secondary analysis, behavioral change is analyzed according to the non-intention to treat principle. The proportion of injured winter sport participants is calculated by dividing the number of injured respondents by the total number of respondents in this study and per study group. Differences in the proportion of winter sport injury between the intervention and control groups are assessed using logistic regression analysis (significance level set at $p<.05$).

## Results

The project was funded in 2016 and the funding will end in April 2018. The enrolment was completed in 2017. Currently, data analysis is under way. The first results of this randomized controlled trial are expected to be submitted for publication in 2018.

## Discussion

This article describes the design of a study that will evaluate the effectiveness of an intervention on injury preventive behavior in skiers and snowboarders. A major challenge of this study is related to the recruitment of participants and their adherence to this study. A total of 848 skiers and snowboarders will enroll for this study. To recruit respondents, several strategies are used (eg, social media such as Facebook, LinkedIn, and Twitter, and the possibility to preregister for the study). In a previous study, we also used social media to recruit skiers and snowboarders. Within two weeks, we received 300 responses, without the use of any rewards for participants or paid advertisements on social media. For this study, respondents will be offered a chance to win a money prize if they complete all three questionnaires. The chance to win a reward (€250) is used to enhance the willingness of skiers and snowboarders to participate in the study and the respondents' adherence to the study, even after their winter sport holidays are over. In combination with the possibility to preregister for the study and the use of paid advertisements on (eg, Facebook), we believe that the recruitment of 848 skiers and snowboarders will be challenging, but feasible.

Another challenge is the use of injury preventive behavior and/or a change in injury preventive behavior as a primary outcome measure in a study regarding injury prevention rather than winter sport injuries. Clear definitions of injury preventive behavior are necessary, as well as extensive measurements of injury preventive behavior at baseline and subsequent measurements. Furthermore, we have to determine what a relevant change in injury preventive behavior is. In this study, we limit injury preventive behavior to taking winter sport lessons, performing strength exercises, the use of protective equipment, and knowledge of the 10 FIS rules of conduct. To enhance the measurement of injury preventive behavior, each injury preventive behavior topic will be operationalized in preparatory acts and structural injury preventive measures. To better detect change in our measurements, we use dichotomous answer categories instead of, for example, a 5-point scale. Finally, it is well-known that changing health-related behavior is difficult [16]. It is a lengthy process that requires small steps. Therefore, a relevant change in injury preventive behavior was set at 10%, which we think is an achievable change.

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## Conflicts of Interest

None declared.

## Authors' Contributions

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

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## Abbreviations

**FBM:** Fogg Behaviour Model
**FIS:** Fédération Internationale de Ski
**IM:** Intervention Mapping
**ZonMW:** Netherlands Organization for Health Research and Development

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Protocol

# The Effects of Social Presence on Adherence-Focused Guidance in Problematic Cannabis Users: Protocol for the CANreduce 2.0 Randomized Controlled Trial

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## Abstract

**Background:** In European countries, including Switzerland, cannabis is the most commonly used illicit drug. Offering a Web-based self-help tool could potentially reach users who otherwise would not seek traditional help. However, such Web-based self-help tools often suffer from low adherence.

**Objective:** Through adherence-focused guidance enhancements, the aim of this study was to increase adherence in cannabis users entering a Web-based self-help tool to reduce their cannabis use and, in this way, augment its effectiveness.

**Methods:** This paper presents the protocol for a three-arm randomized controlled trial (RCT) to compare the effectiveness of (1) an adherence-focused, guidance-enhanced, Web-based self-help intervention with social presence; (2) an adherence-focused, guidance-enhanced, Web-based self-help intervention without social presence; and (3) a treatment-as-usual at reducing cannabis use in problematic users. The two active interventions, each spanning 6 weeks, consist of modules designed to reduce cannabis use and attenuate common mental disorder (CMD) symptoms, including depression, anxiety, and stress-related disorder symptoms based on the approaches of motivational interviewing and cognitive behavioral therapy. With a target sample size of 528, data will be collected at baseline, 6 weeks, and 3 months after baseline. The primary outcome measurement will be the number of days of cannabis use on the preceding 7 days. Secondary outcomes will include the quantity of cannabis used in standardized cannabis joints, the severity of cannabis dependence, changes in CMD symptoms, and adherence to the program. Data analysis will follow the intention-to-treat principle and employ (generalized) linear mixed models.

**Results:** The project commenced in August 2016; recruitment is anticipated to end by December 2018. First results are expected to be submitted for publication in summer 2019.

**Conclusions:** This study will provide detailed insights on if and how the effectiveness of a Web-based self-help intervention aiming to reduce cannabis use in frequent cannabis users can be improved by theory-driven, adherence-focused guidance enhancement.

**Trial Registration:** International Standard Randomized Controlled Trial Number Registry: ISRCTN11086185; http://www.isrctn.com/ISRCTN11086185 (Archived by WebCite at http://www.webcitation.org/6wspbuQ1M)

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**KEYWORDS**

cannabis; mental disorders; adherence; social presence; mobile health; cognitive behavioral therapy

## Introduction

### Epidemiology

According to the European Drug Report 2016 [1], approximately 13% of Europeans in the age range of 15 and 34 years have used cannabis in the last year; it is by far the most commonly used illicit drug. Translated into absolute numbers, there are approximately 16.6 million Europeans who use cannabis, with roughly one percent of European adults estimated to use cannabis daily [1]. Within Europe, Switzerland ranks third in the national prevalence of cannabis use: the lifetime prevalence rate of cannabis use is 27.9% (men 32.8%, women 23.2%), whereas the 6-month prevalence rate is 5.4% (men 7.6%, women 3.3%). The highest prevalence is found in the age group between 15 and 24 years. Within this group, the 6-month prevalence rate is 14.4%, with almost one-fifth of users using cannabis daily [2].

Even though these numbers are high, only a minority of cannabis users seem to develop cannabis dependence; in general population surveys, the risk of becoming dependent on cannabis appears to be between 10% and 11% among all cannabis users [3,4]. However, within the subgroup of cannabis users who started using cannabis in early life, the risks of cannabis dependence [5] and cannabis use problems [6] are much higher.

Although cannabis dependence has not been shown to increase mortality in the general population, its impact on the global burden of disease should not be understated. Expressed in disability-adjusted life years (DALYs), which is the sum of years of life lost because of premature mortality and years lived with disability, it has been estimated that, in 2010, cannabis dependence accounted globally for approximately two million DALYs [7].

Furthermore, poorer mental and physical health, lower educational achievement, and decreased cognitive functioning are all commonly seen in daily cannabis users [8]. Numerous studies also point to the associations between a broad range of primary mental illnesses and frequent cannabis use, highlighting the potential for detrimental effects of co-occurring mental health disorders on treatment in problematic cannabis users [9].

Patients who seek treatment for their cannabis use disorder at Swiss outpatient addiction treatment centers are mainly young males in the age range of 15 and 24 years [10]. Data from the monitoring system for addiction counseling and addiction treatment in Switzerland suggest a linear increase in new patients for whom cannabis is the main problem substance from 2004 (8.8%) to 2014 (46.7%) [11], a trend that has also been observed in other European countries [1]. However, it is clear that even though the number of treatment seekers has steadily increased, they still represent the minority of problematic cannabis users (eg, scoring 8 or higher on the Cannabis Use Disorder Identification Test) [12] who could potentially profit from treatment, among whom approximately half develop cannabis dependence [5], and many suffer from comorbid mental health problems [9].

### Accessibility and Reachability

There are various possible reasons why the percentage of problematic cannabis users who seek treatment is still so low. First among them are problems with accessibility: as addiction treatment centers are rare, low accessibility force potential treatment seekers, especially those living in more rural areas, to travel considerable distances. This increase in time required for travel is especially a hindrance, given that most addiction counseling centers operate during normal office hours, rendering attendance for potential treatment seekers almost impossible if they have a job that requires them to work during these hours [10,13]. The second reason pertains to the issue of stigmatization, with the fear of being stigmatized as a drug addict likely preventing many problematic cannabis users from seeking face-to-face treatment. As older individuals generally have greater social responsibilities, it is quite possible that the levels of fear increase as the age of users increase. Consistent with this assumption, users of Web-based self-help tools for the reduction of problematic cannabis use appear to be older and use more cannabis than those who seek help at outpatient addiction treatment centers [10].

Issues relating to self-efficacy also can be problematic, as some users have the desire to quit or reduce their cannabis consumption on their own [14]. Finally, many cannabis users lack insight into the various problems potentially caused by their cannabis use. For example, although many users are aware of some side effects of problematic cannabis use, such as mild depressive symptoms, the physical risks associated with the combustion and inhalation of smoke are often overlooked. These risks include heart disease, lung cancer, and chronic obstructive pulmonary disease [15,16]. Frequent users are more prone to disregard these risks than occasional users, but increased awareness could be advantageous for all, as it has been shown that the more users know about the possible physical risks of problematic cannabis use, the greater their intention to quit or at least reduce their cannabis use is [15,16].

Web-based self-help programs to reduce problematic substance use, such as—in the case of cannabis—CANreduce, could be a great asset in reaching those groups within the general population who would otherwise not seek treatment. Such programs facilitate access by being available around the clock and easily reachable from any home that has a computer and an Internet connection. Nowadays, many Web-based self-help programs also work on mobile devices, making almost any situation a potential treatment session. Apart from this huge improvement in accessibility relative to regular bricks and mortar treatment centers, Web-based programs also solve the fear of stigmatization issue. Allowing for anonymity, as well as enabling self-efficacy, it is often an ideal solution for at least a subgroup of users. Apart from all this, these noninvasive tools are low-cost and, depending on how they are set up (eg, whether or not they have counselors on standby for chat sessions), require

little maintenance effort, lowering the costs once developed to just Web server space, domain name registration, minimal administrative support, and the effort needed to regularly update techniques and design. Naturally, this is of great interest amid the current environment of constantly increasing health care costs, as is the case in Switzerland and other industrialized countries [17].

### Previous Studies and Implications

However, all the aforementioned positive characteristics of such Web-based self-help programs only hold true if they actually are effective in their goal of reducing problematic cannabis consumption. This has indeed been consistently shown for programs aiming to reduce problematic alcohol use [18,19] and also—albeit to a lesser extent and not as consistently—for programs aiming for tobacco smoking cessation [20,21]. The Web-based approach for the most commonly used illicit drug, cannabis, has not been studied as thoroughly. To our knowledge, only two Web-based self-help programs to reduce problematic cannabis consumption have been tested for their effectiveness in appropriate RCTs in adults [10,22].

"Reduce Your Use: How to Break the Cannabis Habit" is an Australian self-help intervention that is fully automated and consists of six modules which are—similar to CANreduce—based on cognitive behavioral therapy (CBT), motivational interviewing (MI), and behavioral self-management. In an RCT, this intervention was shown to be more effective at reducing the frequency and quantity of cannabis consumption than a psychoeducational control condition. Regarding adherence to the 6-week program, two-thirds of the initial participants completed the intervention [22].

In addition, a previous version of CANreduce has been investigated with the objective of determining whether a Web-based self-help tool for reducing problematic cannabis consumption would be more effective if individualized chat sessions with a professional coach are offered [13]. Although the study found that participants who were in the group with the opportunity for individual chat sessions reduced their frequency of cannabis use more than those who only worked with the self-help tool, the effect was also identified among those in a chat sessions group who did not actually make use of the chat offer (ie, who did not reply to chat-based consultation appointments offered by professional chat counselors). Thus, it appears that even just the option of having chat appointments reduced cannabis consumption [10]. With only a quarter of participants who were given the option of scheduling a chat session actually taking advantage of the offer, the question was raised as to whether the same effect could be recreated by simpler means, eliminating the need for professional counselors on constant standby.

With CANreduce 2.0, we try to address this problem by implementing adherence-focused guidance, which has already been documented to be effective at increasing adherence to Web-based self-help relative to Web-based self-help alone [23,24]. The concept of adherence-focused guidance is primarily based on the supportive-accountability model of guidance in Web-based interventions [25] that asserts that unguided self-help programs are often less effective than those that are guided [26]. However, Mohr's model for adherence to electronic health (eHealth) interventions encompasses further factors, which we additionally attempt to address, to strengthen the concepts of accountability and legitimacy with the assumption of thereby increasing the effectiveness of the support in terms of adherence. Specifically, we emphasize the *social presence* factor and those factors that increase program legitimacy as defined by Mohr's model [25].

Furthermore, almost two-thirds of CANreduce participants in the former study screened positive for clinically relevant depression symptoms at baseline [10]. Moreover, even if partakers of intervention programs do not exhibit depressive symptoms at baseline, it is possible that such symptoms could emerge as they decrease their drug use. Comorbidity of depressive symptoms and substance use and its hindrance on positive treatment outcomes has been demonstrated several times before [27]. Furthermore, targeting a reduction in depressive symptoms in patients simultaneously could possibly increase adherence to the program. Therefore, the new version of CANreduce also aims to specifically target issues that potentially help to ameliorate depression and other common mental disorder (CMD) symptoms such as those associated with anxiety and stress-related disorder using CBT [27] and teaching social problem-solving skills [28]. Moreover, we incorporated aspects within modules targeting excessive rumination and worry, as well as difficulties with relaxing.

### Study Aims

The study presented in this protocol seeks to investigate and compare the effectiveness of Web-based self-help interventions at reducing cannabis use in problematic users, while taking into account the most frequently co-occurring mental health symptoms. Moreover, it examines whether adherence to the program can be optimized by emphasizing the social presence factor of adherence-focused guidance, which would only marginally increase costs versus guidance that is less personal.

## Methods

### Study Design

The Web-based self-help program CANreduce will be evaluated within a three-arm RCT, comparing the effectiveness of an adherence-focused, guidance-enhanced, Web-based self-help intervention with a social presence; an adherence-focused, guidance-enhanced, Web-based self-help intervention without a social presence; and treatment-as-usual (TAU) at reducing cannabis use in problematic users. The masking technique will be partially single-blinded—in that participants in either of the two active treatment groups will not know which version they work with. The two versions are neutrally described as two differently optimized variants to prevent participants from having a preference of one over the other possibly resulting in a disappointment when being allocated to the unwished version. However, subjects will know whether they have been assigned to TAU. Any blinding of research and study personnel is not warranted. After successful completion of the baseline assessment (t0), participants will be allocated to one of the three study conditions. Further assessments will take place both 6

weeks (t1) and 3 months (t2) after baseline (Figure 1). The trial has been registered with the ISRCTN registry and is traceable as ISRCTN11086185.

## Recruitment of Study Participants

Recruitment will take place from August 2016 to December 2018 to ensure that the target sample size of 528 participants has been included. Participants will be recruited through the CANreduce website itself [29], which is already established and has links to it on various Internet health portals. Additionally, advertisements will be placed in relevant Internet forums and newspapers (or Web-based versions thereof).

For compensation, all participants who complete 3 months of follow-up from the start of the program will be able to choose between an Web-based voucher worth 30 Euro or donating that amount to charity.

## Registration and Consent Procedure

Participants can register online and will need to provide only minimal personal data, including their email addresses, phone numbers (only to get in contact with if follow-up questionnaires are not filled out), and some basic demographical data (age, gender, and level of education).

Before registration, each participant will be informed online about the study, specifically provided information about the following:

1. Purpose, background, and an overview of the study
2. Inclusion and exclusion criteria (Tables 1 and 2)
3. The difference between the three treatment arms (but no details about how the two active treatment arms differ) and their one in three chance of being allocated to each one of these three arms
4. Financial aspects (no participation fee, compensation for participation)
5. Potential risks of participation and when to contact their general practitioner or, alternatively, a professional they can select from a medical advisory and emergency list that will be accessible at all times merely by clicking on emergency icon
6. The inability of CANreduce to replace face-to-face therapy for problematic cannabis use or abuse
7. The voluntary nature of participation and their right to withdraw from the study at any time without consequences, except for the loss of further compensation
8. Confidentiality and data protection (anonymity is ensured by not recording real names or postal addresses and by deleting email addresses and phone numbers before statistical analysis and data archiving)
9. The approval given by the ethics committee of the Canton Zurich after the committee had reviewed the study

Informed consent will be accepted once participants have activated several check boxes restating important study points and have submitted their consent by clicking a submission button.

## Randomization and Trial Flow

Once participants have completed their baseline assessment, they will be randomized by a computer algorithm in a 1:1:1 ratio into one of three parallel groups, and this assignment will be registered automatically in the background database.

**Figure 1.** Trial flowchart.

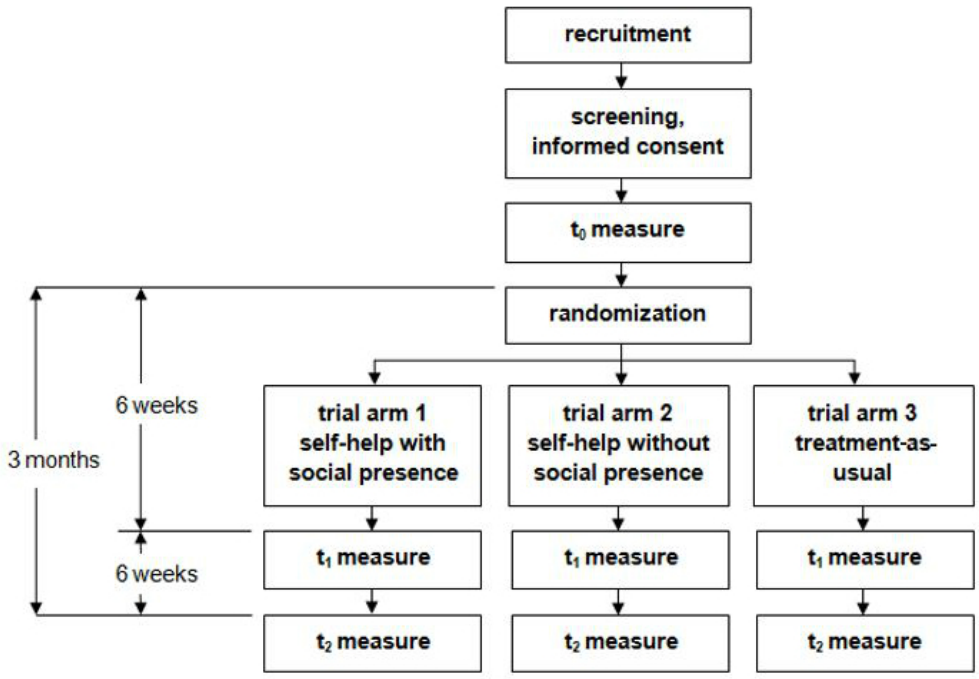


**Table 1.** Inclusion criteria and underlying rationale.

| Inclusion criteria | Reasoning |
|---|---|
| Informed consent via the Web form | To ensure knowledge of procedures and the declaration of consent |
| Minimal age of 18 years | To ensure a minimum age of participation |
| Cannabis use at least once weekly over the last 30 days | To include participants with less than daily cannabis use, increase validity |
| At least once weekly Internet access and a valid email address | To ensure at least some access to the intervention |
| Good command of the German language | To ensure that participants will be able to understand the information provided |

**Table 2.** Exclusion criteria and underlying rationale.

| Exclusion criteria | Reasoning |
|---|---|
| Participation in other psychosocial or pharmacological treatments for the reduction or cessation of cannabis use | To avoid confounding treatment effects |
| Current pharmacologically treated psychiatric disease or any history of psychosis, schizophrenia, bipolar type I disorder, or significant current suicidal or homicidal thoughts | To avoid having subjects with these problems enter the study |

As participants assigned to TAU will immediately become aware of this, we expect that some might try to circumvent their assignment by registering another account, hoping to end up in a different group. If anyone attempts this, he or she nevertheless will be assigned to the original group when they try to register again on the same day based upon his or her Internet protocol address.

Participants will be introduced step by step into the corresponding study arm and, in the cases of study arms 1 and 2, be invited to participate in the program. Participants assigned to study arm 3 will be informed that they will be provided access to the Web-based self-help treatment after 3 months (with TAU until they are 3 months past their baseline assessment). Participants in study arms 1 and 2 will receive automated email notifications to log in and enter their cannabis consumption quantity and frequency into their consumption diary every week.

The two experimental interventions will each last 6 weeks. Follow-up assessments will be 6 weeks and 3 months after the start of the program. As such, there will be a baseline (pretreatment) assessment, a 6-week assessment immediately following the treatment program, and a final assessment 6 weeks posttreatment (3 months postbaseline).

The control condition will be TAU. As these subjects will have access to any other online and offline drug counseling services that are available, they will be asked about their possible use of other treatment services over the course of observation at their final follow-up visit.

Follow-up assessments should be completed online after a reminder is sent by email, in which they also will be reminded that, upon completion of the entire 3-month follow up assessment, they will be compensated with 30 Euro (via either an Web-based voucher or the choice to make an online charitable donation). If the final assessment is not completed within 2 days, the same reminder will be sent out two more times, 2 days apart. If these reminders still go unanswered, participants will be contacted by phone within 1 week after the third email has been sent and offered an interview on the phone with study collaborators to complete the follow-up instruments. Should participants still refuse, they will be asked to answer questions about the primary outcomes only or—should they still refuse—to provide a reason for refusing, which will then be documented.

It is not uncommon for participants of Web-based interventions to take breaks, yet still complete the intervention later. Therefore, there are no dropout criteria relating to inactivity. The only dropout criterion is active withdrawal from the study by the participant, in which case only the data already gathered will be analyzed.

Figure 1 shows a flow chart depicting the flow of subjects through the study.

## Hypotheses

We will test the following detailed study hypotheses with respect to the main outcome: reduction in the number of days of cannabis use over the past week, comparing the baseline, 6-week, and 3-month follow-up assessments:

1. An adherence-focused, guidance-enhanced, Web-based self-help program with a social presence (study arm 1) is more effective than an adherence-focused, guidance-enhanced, Web-based self-help program with no social presence (study arm 2) at reducing cannabis use.
2. An adherence-focused, guidance-enhanced, Web-based self-help program to reduce cannabis use with a social presence (study arm 1) is more effective than TAU (study arm 3) at reducing cannabis use.
3. An adherence-focused, guidance-enhanced, Web-based self-help program to reduce cannabis use without a social presence (study arm 2) is more effective than TAU (study arm 3) at reducing cannabis use.
4. Participants in study arm 1 will demonstrate better adherence than participants in study arm 2 over the 6-week intervention.

We have similar expectations with respect to our secondary cannabis-related outcomes and will explore frequently

co-occurring mental disorders as predictors of adherence and outcomes. Specifically, we also want to explore, for the first time, the influence of attention deficit hyperactivity disorder (ADHD) symptoms on adherence to and outcomes from a Web-based intervention among problematic cannabis users.

## Intervention

CANreduce is an automated Web-based self-help tool developed by the Swiss Research Institute for Public Health and Addiction (ISGF) and and the Arud Centre for Addiction Medicine to reduce cannabis consumption in problematic cannabis users. The Web-based self-help intervention consists of a dashboard, a consumption diary, and eight modules designed to reduce cannabis use based on the principles of MI, self-control practices, and CBT methods. Participants can study all of the modules at their own pace and in whatever order they choose, though a specific order is advised.

As CANreduce 2.0 is regarded as a medical device because of the European Union guidelines 93/42/EWG and 2007/47/EWG, its conformity has been assessed, and potential risks have been evaluated. It is now fully certified in European conformity.

## Active Study Arms

The following elements of CANreduce will be used in both active treatment arms in this study (study arms 1 and 2). The social presence enhancements added just to the program offered to study arm 1 subjects will be described in the *social presence* section below.

### *Start Page*

Before actual registration or log-in, a video is accessible in which the scientific director of the ISGF gives a quick introduction to CANreduce. This introduction can also be read as text and aims to motivate eligible individuals to participate in the study.

### *Dashboard*

The dashboard (see Figure 2) serves as the central hub, displaying useful information at a quick glance. On the dashboard, participants can see the date when they started the program and how many days remain for them in it. It also displays the dates of the two follow-up assessments and indicates when they have been completed. The same is true of the individual intervention modules, and by clicking a link, participants will be taken to the page in the module where they left off the last time they logged in. There is also a way for subjects to directly enter cannabis consumption data over the preceding week, which then displays a consumption graph.

**Figure 2.** Dashboard for study arm 1 (translated from German to English for publication purposes only).

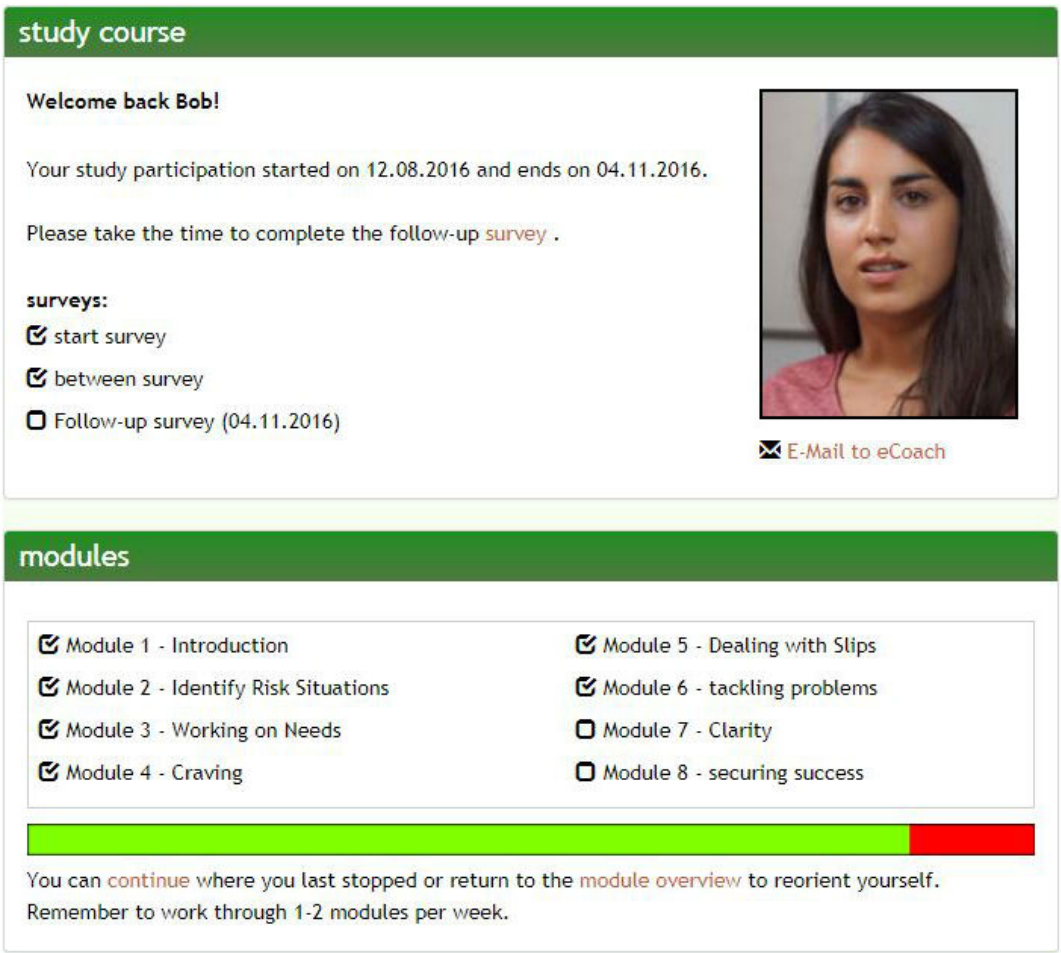
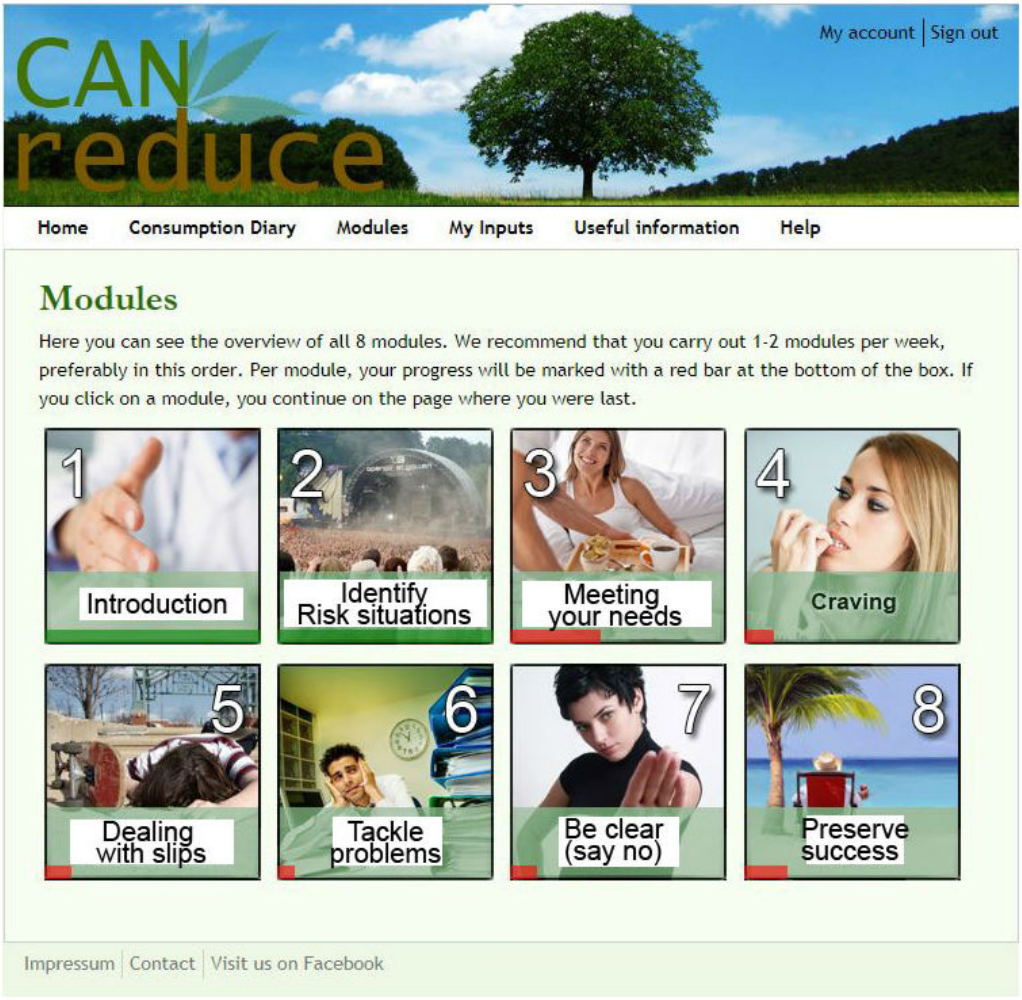


**Figure 3.** Main menu (translated from German to English for publication purposes only).




### *Self-Help Intervention Modules*

There are eight self-help intervention modules that are the same for both active treatment groups in terms of the information presented. They are depicted on intervention website's main menu page (see Figure 3), as well as on the dashboard. Participants are encouraged to complete either one or two of these modules each week and to complete all of the modules in order, though they can access all modules right away. It is also stated that they should feel free to jump directly to modules they feel could be of importance at the moment and to repeat any modules they feel they either especially need to take a second look at, or that they perceive to be especially helpful within the 6 weeks of the program.

A bar in the module overview will indicate the progress they have made with each module; that bar is fully green when the entire module is completed.

The eight modules are summarized in Table 3 and are described below.

#### Module 1: Introduction

In this module, which is largely based on MI techniques, a general overview of the program is given, and fictional companions are introduced. Additionally, participants are encouraged to state their personal reasons for and against their cannabis consumption, which they can review at any time, so they may reflect on what they could gain by successfully completing the program.

#### Module 2: Identifying Risky Situations

Apart from identifying personal situations in which participants could find it difficult to stand by their set consumption goals and working through these scenarios so they are better prepared when they arise, another focus of this module is on seemingly irrelevant decisions and chains of events that can potentially result in unplanned cannabis use. This is an area also explored in traditional CBT.

#### Module 3: Working on Needs

In this module, participants learn skills to help them strengthen their social contacts, decrease possible ruminations, and develop healthier sleeping habits. The importance of sleep and its impact on quality of life is explained. Participants are encouraged to install some rules or rituals to improve their sleeping quality (eg, no big meals or sports in the evening and taking time to unwind the day). Rumination and its impact on well-being is explained, and several techniques are presented to counteract such behavior (eg, thought stop, an audio file with a *passing clouds meditation*, or refocusing on positive things we are grateful for). Finally, social contacts and their link with mood are explained. Participants are encouraged to list people they

wish to be in closer contact with, what they could do about it, and what negative beliefs inhibit them from doing so.

**Module 4: Craving**

Here, the concept of craving is explained with its physical and mental aspects for which participants are encouraged to state examples from their own experience. The key concept of triggers (conditioned stimuli) is explained and its link to risk situations, making module 2 worth a suggested revisit. Five possible ways to deal with craving are presented: distraction, talking about craving, mindful experiencing of craving, envisioning negative consequences of consumption, and self-talk.

**Module 5: Dealing With Relapses**

Temporary relapses can happen, but they should not decrease a person's motivation to achieve their personal consumption goal or be cause for grievance. In this module, participants are taught skills for relapse prevention and to not see relapses as catastrophic events, but rather to learn from them and view their consumption goals as a long-term process.

**Module 6: Working on Problems**

The relationships between cannabis consumption, problems in life, and mild depressive symptoms are highlighted in module 6. Here, participants learn how to deal with problems that they cannot personally affect and are shown problem-solving skills to help them to deal with problems that are seemingly too large to tackle.

**Module 7: Saying "No"; Refusal Skills**

In this module, different ways to strengthen refusal skills are taught to decrease the person's risk of a relapse whenever and wherever they find themselves in high-risk situations.

**Module 8: Preserving Achievements**

In the eighth and final module, participants are encouraged to review their work in the program and then generate a list of five personalized points that can help them to secure their achievements once their participation in the program is completed.

### *Fictional Companions*

Six fictional companions appear within the modules at key points, with the goal of encouraging reflection on certain questions raised by the modules. This is done by the companions thinking out loud, sharing their thoughts on issues raised in written form. Participants can choose one character that best fits their own situation but can also click through the input provided by the other five companions.

### *Consumption Diary*

Participants are encouraged to fill out their cannabis consumption diary completely on at least a weekly basis. They can enter their goal about how much they want to use in upcoming days and how much they actually did use in past days in terms of the number of individually standardized joints.

This individual joint is defined at the start of the program where participants can select between (1) indoor, outdoor, or resin; (2) mixed with or without tobacco; and (3) six different amounts of the substance varying from 67 mg to 500 mg depicted with six photos of unrolled joints corresponding to the type selections from (1) and (2).

**Table 3.** Overview of contents and therapeutic approaches in the modules.

| Module | Contents | Therapeutic approach |
|---|---|---|
| Module 1: Introduction | • General overview<br>• Introduction of fictional companions<br>• Reflection on personal cannabis consumption | Based on motivational interviewing (MI) techniques [30] |
| Module 2 : Identifying risk situations | • Identifying personal high-risk situations<br>• Recognizing seemingly irrelevant but triggering decisions | Cognitive behavioral therapy (CBT) approach to relapse prevention [31] |
| Module 3: Working on needs | • Strengthening social contacts<br>• Decreasing excessive ruminations<br>• Developing healthier sleeping habits | Behavioral activation approach [32] |
| Module 4: Craving | • Concept of craving<br>• Ways to deal with feelings of craving | Based on CBT [33] |
| Module 5: Dealing with relapses | • Relapse prevention<br>• Dealing with relapses | CBT approach to relapse prevention [31] |
| Module 6 : Working on problems | • Relationships between consumption, problems, and depressive symptoms<br>• Skills to deal with solvable and unsolvable problems | Social problem-solving approach [34] |
| Module 7: Saying "no"; refusal skills | • Strengthening refusal skills for use in high-risk situations | Based on CBT [33] |
| Module 8: Preserving achievements | • Review of program<br>• List of five personalized points to help secure achievements after the program is complete | Based on MI techniques [30] |

Overall, there are 36 different photos made for this selection procedure [10,13]. A graph is generated live with these data inputs and provides the participant with visual feedback. The ability to anonymously set daily consumption goals could possibly counteract the self-deception often seen in face-to-face drug counseling and strengthen the self-efficacy of users. By adding this consumption diary to both active study arms, Mohr's accountability factor—*goal setting*—is also integrated into the program.

### *Other Elements*

The CANreduce tool further consists of a section with general useful information regarding cannabis, such as physical risks and harm reduction techniques. Furthermore, in some modules, participants are asked to enter their answers to certain exercises (either by clicking on checkboxes or entering text freely). These data are accessible in the section *My Contribution*.

### *Automated Motivational Email Feedback*

Each week, participants in intervention arms 1 and 2 will be sent automated motivational email feedback that will contain a reminder to fill out their consumption diary and a direct link to the CANreduce log-in site. If participants do not fill out their diary, they will receive a different reminder email 1 and 3 days later.

Additional emails will be sent out, either automatically or triggered by an administrator or moderator, if certain conditions are met—for example, if an increase in a participant's cannabis consumption or stalling of consumption reduction is detected—as well as encouraging emails to work with the self-help tool if only a few modules have been completed after 2 and 4 weeks. These feedback emails will also include module suggestions, depending on how subjects have responded in exercises dealing with high-risk situations, cravings, or the pros and cons of their consumption.

In the first CANreduce study [10], participants sometimes discontinued their use of the Web-based self-help tool simply because they had initially aimed for a minimal reduction in consumption and reached this self-set goal within the first few weeks. Therefore, depending on their goals entered into the consumption diary, participants will receive a message encouraging them to reduce their consumption by at least 20 percent over the first week and, if they succeed, to continue that trend in subsequent weeks. Alternatively, participants who do not succeed at reaching their goal will receive the suggestion that they aim for a more modest goal and continue until their final consumption goal is reached.

Another finding from the first version of CANreduce was that some users seek not only to reduce their consumption, but to become completely abstinent. When this goal was achieved early in the program, some felt less inclined to continue with the program. This will be addressed in this study with an automated email, triggered when actual consumption is recorded as zero for several days consecutively in a subject's consumption diary, encouraging them to nonetheless complete certain modules of importance to their current situation (eg, preventing and dealing with relapses).

One important component of adherence-focused guidance, as defined by Ebert et al [24], is adherence monitoring. Through these mostly automated emails, either encouraging participants to work with the self-help tool or suggesting modules that they have not yet completed, this will be implemented in both active study arms. Another crucial element of adherence-focused guidance is feedback on demand. This too has been implemented in both active study arms by inviting participants at the end of each email to send in any questions that might arise for them during the course of the program. For subjects in the first study arm, this option will also be displayed on the dashboard. Although the content of these nonautomated answers is not specific to either study arm, the format of the emails will differ between study arm 1 and 2, as described next, under *social presence*.

### *Social Presence*

Certain specific enhancements have been implemented in study arm 1 in accordance with points made in Mohr's supportive accountability model [25]. Added social presence aims to give the self-help tool a personal feel, creating a form of alliance between the user and the Web-based self-help tool by replicating that aspect of human support. We aim to recreate rapport similar to what typically is found in client-counselor relationships, without the need to have such a counselor on constant standby. It has been argued by Mohr et al [25] that adherence increases when there is accountability to a coach, who should be seen as trustworthy, benevolent, and having expertise. By introducing a mostly automated eCoach named Deborah, we seek to quite literally give our Web-based tool a face. Although difficult to define one individual who implies the aforementioned attributes to all potential users of the self-help tool, we sought out an eCoach who appears visually friendly and supplemented the representation of benevolence with video scripts and emailed texts that suggest expertise, as well as trustworthiness (see Figure 2).

We created short introduction videos for most of the modules, in which Deborah greets the user, gives her opinion on the importance of certain key points within the module, and finishes by wishing the user an enjoyable time working on the module and acknowledging that they will see each other again in the next module. Additionally, a picture of the eCoach Deborah will be constantly displayed on the dashboard.

She also will personally invite users to write to her should they have any questions or problems. As in the chat version of the first CANreduce study [10], we expect that the number of participants who will actually take her up on this offer will be relatively small. However, we also expect that the assurance that they have the option to write to her will exert a positive impact on their adherence and, thereby, increase their treatment success. Emails written to the eCoach's address will be answered by available study collaborators—if needed after consultation with a certified therapist; consequently, the answer that querying subjects will receive will address whatever issue or issues they have. In this way, however, the task of replying to emails can be spread out among multiple persons, while retaining that element of personal, one-on-one rapport. It is assumed that the content of this feedback will not, in itself, enhance the

effectiveness of the program, but that having the option for direct contact with their own coach will enhance subjects' perception of the coach's benevolence and legitimacy.

Furthermore, automatic email reminders or module suggestions will have a greater personal touch in the adherence-focused, guidance-enhanced version with a social presence (Deborah) than in the version without the social presence (no Deborah). In such correspondence, the participants will be addressed by their username; emails and other written communication from the eCoach will be signed as "your eCoach Deborah"; and all text will be written from a first-person perspective (eg, modules will be recommended by her personally; see Textbox 1).

For technical reasons, only one eCoach has been introduced in this newer version of CANreduce. If the demand for personal feedback by the eCoach proves to be greater than expected, replies will be written by multiple coaches. As it could be perceived as deceitful if they all represented themselves as Deborah, the coaches will each sign those emails as an associate or representative of eCoach Deborah.

Therefore, although participants in both active study arms will receive the same level of support, those in the second study arm will be supported by an undisclosed entity, whereas the form of support provided to those in the first study arm will appear to be more intimate and more closely resembling face-to-face coaching.

### Control Conditions

The control condition will be TAU, as it cannot be ruled out that participants who are allocated to the third study arm will seek out other treatment options during the waiting period. At the last follow-up assessment, participants will be asked if, over the course of their 3 months in the study, they used other treatments and what they were; these data will then be analyzed. After 3 months of follow-up, these subjects' study phase will be finished, at which time they will be offered the opportunity to start the self-help program if they so choose.

A second control condition pertains to the presence versus absence of a social presence. As described above, there will be two active control groups, one with and one without the eCoach Deborah in their version of the self-help tool.

### Technical Specifications

CANreduce 2.0 is based on the content management system Drupal 7, with a MySQL database. It will be administered internally by the information technology (IT) developer at the institution where the principle investigator (PI) works as faculty. All access will be administered via encrypted and password-protected secure sockets layer connections to canreduce.ch [29]. At any time, any participant will have access to his or her own data only. The administrator will have full access to all of the data from all subjects.

All data will be entered online by the users themselves. The website ensures a certain degree of data validation, such as accepting only numbers for number fields, ensuring that users do not mark multiple choices for single choice questions, insisting that certain mandatory fields are filled out, and so on.

**Textbox 1.** Module suggestion on the basis of open text answers for pros and cons for the keywords difficulty with falling asleep, tiredness, social inhibition, feelings of guilt, blaming oneself, and rumination.

With social presence:

*Hello [participant's user name]!*

*You have been using the program for some time now and have already completed a few of the modules. Well done!*

*If I may, I'd like to make a recommendation. I looked at your pros and cons of using cannabis and want to point out module 3 "Working on needs."*

*This module covers three important topics: better sleep, less rumination, and social contacts. Perhaps one of these topics will be particularly helpful in your current situation.*

*Why don't you have a look at it this evening?*

*For questions or difficulties, feel free to contact me.*

*Best regards,*

*Your eCoach, Deborah*

Without social presence:

*Hello,*

*You have been using the program for some time now and have already completed a few of the modules. Well done!*

*On the basis of your pros and cons of using cannabis, module 3 "Working on needs" would be recommendable.*

*This module covers three important topics: better sleep, less rumination, and social contacts. Perhaps one of the topics would be particularly helpful in your current situation.*

*Why don't you have a look at it this evening?*

*For questions, you can write to canreduce@canreduce.ch.*

**Table 4.** Assessment instruments.

| Assessment instruments | Initial assessment ($t_0$) | Week 6 ($t_1$) | 3-month follow-up ($t_2$) |
|---|---|---|---|
| Sociodemographics | X | | |
| Center for Epidemiologic Studies Depression Scale | X | | X |
| Short Screening Scale for DSM-IV[a] posttraumatic stress disorder | X | | X |
| General anxiety disorder-7 | X | | X |
| Adult ADHD[b] Self-Report Scale-version 1.1 | X | | X |
| Quantity of cannabis use | X | X | X |
| Frequency of cannabis use | X | X | X |
| Cannabis Use Disorder Identification Test-Revised | X | X | X |
| Severity of Dependence Scale | X | X | X |
| Fragebogen Substanzanamnese | X | X | X |
| Client Satisfaction Questionnaire-I | | X | |
| Intervention adherence[c] | | X | |
| WAI-TECH[d] | | X | |
| Negative effects according to Rozental | | | X |

[a]DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

[b]ADHD: attention deficit hyperactivity disorder.

[c]Continuous assessment during 6 weeks.

[d]WAI-TECH: Working Alliance Inventory adapted for Web-based interventions.

CANreduce also features a responsive design and can automatically adapt to small screen devices such as tablets and mobile phones. Users can register online by choosing a username and providing a valid email address. To complete the registration process, users will have to click on a verification link sent to the email address specified, which will allow them to create a personal password, while preventing anyone from registering without a valid email address.

All data will be stored on a Web space hosted by an external provider that meets the IT security outsourcing regulations (99/2) of the Swiss Federal Banking Commission. Employees of the Web host will need to identify themselves with biometric data to gain physical access to the infrastructure.

Data will be extracted from the running Web-based database via Drupal and PHPmyAdmin. The data will then be stored at the PI's institution on local computers for further processing and local file servers for archiving.

Each subject's email address and phone number will be deleted after their participation in the study is complete and thereby, not available for either current or future analysis.

The investigator affirms and upholds the principle of every participant's right to privacy and that all personnel involved in the study will comply with applicable privacy laws. No individual data will ever be published or presented at scientific meetings.

## Measurements

Table 4 provides an overview of measurements. Sociodemographic data will include subject gender, age, and level of education.

The primary outcome of interest will be the number of days of cannabis use on the preceding 7 days according to the Time-Line-Follow-Back method [35,36].

Secondary outcomes of interest will include the quantity of cannabis used in the previous week, in standardized cannabis joints (as indicated in the consumption diary as well, as per Schaub et al [10]). Participants can choose between three different cannabis forms presented in photographs and in the second step between five different standard joints for each category (1/10 g, 1/6 g, 1/4 g, 1/3 g, and 1/2 g content pictures). These joints are either pure cannabis or cannabis mixed with tobacco. Finally, every participant has his or her personal standard tobacco cigarette, a ruler with centimeter and millimeter scales, the fraction amount in grams, and an open 10 cm paper prepared to roll a joint and containing the cannabis plant- or resin-tobacco mixture or pure cannabis presented in his or her consumption diary. Further secondary outcomes are the presence and severity of a cannabis use disorder (Cannabis Use Disorder Identification Test-Revised, CUDIT-R); the severity of cannabis dependence (Severity of Dependence Scale, SDS); the use of alcohol, tobacco, or other illicit drugs besides cannabis (Fragebogen Substanzanamnese, FDA); changes in depression, anxiety, and attention deficit symptoms (Center for Epidemiologic Studies Depression Scale, CES-D; general anxiety disorder-7, GAD-7; and Adult ADHD Self-Report Scale-V1.1, ASRS-V1.1); the Short Screening Scale for

Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) posttraumatic stress disorder (PTSD); client satisfaction (Client Satisfaction Questionnaire adapted to Internet-based interventions, CSQ-I); and treatment adherence. The perceived relationship between the user and the eCoach will be assessed at the end of the program using the Working Alliance Inventory [37] adapted for Web-based interventions (WAI-TECH).

The CUDIT-R is a questionnaire containing eight items designed to identify problematic cannabis consumption. Each item is a statement regarding cannabis use, to which respondents are provided with five response options, numbered from 0 to 4, that vary between questions, but for which increasing scores indicate increasing use or cannabis-related problems. As such, possible scores range from a minimum of 0 to a maximum of 32. A score of 8 or more indicates hazardous cannabis use, whereas a score of 12 or more indicates a possible cannabis use disorder [12].

The SDS is a reliable and valid 5-item screening scale, with a score of 4 or more being indicative of cannabis dependence [38].

The FDA asks about a person's years of lifetime consumption, the past month's consumption, and the manner of consumption for the DSM-IV or the International Statistical Classification of Diseases and Related Health Problems, 10th revision substances of abuse. This measure was derived from the EuropeASI, the European version of the Addiction Severity Index [39].

The CES-D Scale is a short self-report scale designed to measure depression symptoms in the general population [40]. All items on the scale are symptoms associated with depression that have been used in previously validated longer scales. CES-D responses rate the frequency at which depression symptoms have occurred over the past week. Possible scores on the CES-D-20 range between 0 and 60, where a CES-D-20 cutoff score of 16 is considered indicative of *significant* or *mild* depression symptoms. This is equivalent to experiencing six symptoms for most of the previous week or a majority of symptoms on 1 or 2 days. Higher scores indicate a higher symptom load.

The GAD-7 is a 7-item, self-report questionnaire to screen for and estimate the severity of GAD and has good reliability as well as factorial and concurrent validity [41]. These items ask about nervousness, inability to stop worrying, excessive worry, restlessness, difficulty relaxing, easy irritation, and the fear of something awful happening. Total scores range from 0 to 21, with a recommended cutoff score of 10 or higher.

The six-item short version of the ASRS-V1.1 can be self-administered easily and quickly [42]. With a total possible score of 24 and a cutoff score of 14, this six-item version has been shown to have strong concordance with clinician diagnoses, while significantly shorter than the full 18-item version.

The short screening scale for DSM-IV PTSD is designed to assess for a lifetime history of PTSD [43]. A score of 4 or more on the seven-symptom screening scale suggests PTSD.

The CSQ-I has been shown to be a suitable measure from the user's perspective in the evaluation of Web-based health interventions. It is scored easily by summing up the individual item scores to produce a score ranging from 8 to 32, with higher scores indicating greater satisfaction [44].

Furthermore, the occurrence of any negative effects will be identified, as in Rozental et al, at the 3-month follow-up assessment [45].

Finally, we will ask all participants if they had used any other treatment than canreduce.ch during the 3 months and if so, to select from a predefined list of services.

As an indicator of treatment adherence, data will be collected on which modules have been completed by the participant and the number of weeks the consumption diary was filled out. Additionally, a script has been implemented that allows us to measure the time that subjects spend on each page. To avoid false data that might result if a participant leaves a Web page open but switches to a different window or leaves the computer, a cutoff time of 10 min inactivity has been set, after which the time spent on the page is disregarded and not saved to the database. These data could potentially lead to insights into how and specifically where to optimize CANreduce to further decrease attrition rates. We also will assess the number of individual emails received by each participant.

## Sample Size Calculation

Anticipating that a Cohen *d* of 0.30 based on our previous study experiences will be realistic for the effect size differences between the unenhanced version of the Web-based tool and the adherence-focused guidance-enhanced version, a sample size of n=176 in each study group would have 80% power to detect this difference based on calculations performed with G*Power software (Faul, Kiel) with an alpha error of 5% and two-tailed testing. Thus, we aim to recruit a total of 528 participants.

## Data Analyses

Data will be analyzed according to the intention-to-treat principle (ITT). To address missing data for the ITT analyses, we will apply multiple imputation procedures with the package Amelia in R (R Foundation for Statistical Computing, Vienna). Amelia uses a bootstrapping-based algorithm that gives essentially the same answers as the standard imputation posterior or expectation maximum approaches according to the authors. We plan to use between 20 and 40 imputed datasets depending on the amount of missing data according to suggestions by Graham [46]. The imputation model will include all primary and secondary outcome variables. Auxiliary variables such as demographic data may be included if they improve convergence of the imputation model.

Differences between study arms in primary and secondary continuous outcome variables at baseline and the follow-up points will be tested using linear mixed models (LMM). LMMs will be specified appropriately to model clusters and repeated measures by defining random effects for study arms and time (repeated measures). For nonnormal continuous outcomes, appropriate distributions (eg, negative binomial and zero-inflated) will be specified. For binary outcomes, a

generalized linear mixed model (GLMM) will be specified that defines an appropriate link-function. In the GLMM fixed effect, coefficients will be interpreted in the context of the subject-specific (nonmarginal) model fit.

### Safety

Potential risks are expected to be minimal as no drugs will be administered and the medical device (ie, the self-help tool) was determined to be of very low risk during the course of its European conformity certification. What we expect to observe is some mild withdrawal symptoms such as craving, mild depressive states, and sleep problems. These issues will be addressed in the psycho-educational modules that are part of the 6-week self-help intervention. At all times, an *instant help* Web page will be available with instructions on what subjects can do if their situation becomes unbearable. These instructions contain psycho-educational self-help instructions, as well as phone numbers to professional health care providers.

## Results

The study will be conducted in accordance with the ethics board–approved protocol and the principles stated in the current version of the Declaration of Helsinki; the CONSORT eHealth Guidelines [47] for studies on medical devices; the European Directive on medical devices 93/42/EEC; and the ISO Norm 14155 and ISO 14971 as well as Swiss Law and Swiss Regulatory Authority requirements. The local ethics committee and regulatory authorities will receive annual safety and interim reports and be informed about study termination, in agreement with local requirements.

The study was approved by the ethics committee of the Canton of Zurich on July 4, 2016 (BASEC-Nr. 2016-00264) and is registered at Current Controlled Trials, traceable as ISRCTN11086185.

Results will be published in a scientific peer-reviewed journal. Anonymized study data will be available on request. Participants will be informed via email about study results via a lay-person-friendly summary of trial findings, if they have requested so at registration.

## Discussion

### Principal Findings

To the best of our knowledge, this study will be the first to assess the effectiveness—in terms of increasing adherence and treatment success—of adding a social presence to adherence-focused guidance by implementing a human element, in accordance with the supportive accountability model [25], all within the context of a Web-based self-help intervention program to reduce problematic cannabis consumption. The results of this RCT could add valuable insights into how to increase adherence to Web-based self-help tools, for which high attrition rates are one of the greatest reported problems. If users do not adhere to the created content, treatment success is unlikely. If these relatively simple techniques are shown to increase adherence, these ideas could be extrapolated further and easily applied to both current and future Web-based self-help tools to aid in reducing problematic substance use of any kind.

Although it must be noted that participants in the first CANreduce study who received at least one chat session still performed better than those in the same treatment condition who did not [10], the offer of being able to contact an eCoach who is perceived as benevolent, trustworthy, and having expertise by email, with any questions or problems, might adequately reproduce this beneficial effect.

Although adherence and treatment success have already been shown to be greater in interventions in which participants have the option of speaking with a therapist [10], the complexity and costs are increased as well, as such sessions need to be scheduled, and therapists must be available. Such increases in cost and complexity should not be a problem with the human element that we will be implementing, as it is a one-time effort to shoot the videos and prewrite emails with a personal feel. We expect that these features alone will increase program effectiveness; and furthermore, that very few actual emails will be sent by subjects seeking answers. If more emails than anticipated need to be answered individually, this task could be handled by multiple people to address less complex issues. Meanwhile, the email format itself should leave enough time for us to gather input from experts to address more complex questions.

To explore the possible effects of the added content addressing CMDs, we will compare outcomes against the study that examined the first version of CANreduce. Another avenue for exploration will be measuring adherence with specific modules that address CMDs.

### Limitations

The following protocol limitations must be considered:

First, cannabis users who are currently receiving other treatments to reduce their cannabis consumption will be excluded. However, CANreduce was designed to access cannabis users who—for personal or practical reasons—would not attend traditional addiction counseling. Second, all measurements will be self-reported. Third, most of the self-report instruments we will be using have not been validated in a Web-based context, though they have largely been validated in other research and clinical settings. Fourth, as found in the previous Web-based intervention [10,22], we expect rather high rates of dropouts. Finally, another possible limitation of Web-based studies is the potential for low adherence rate because of the distant nature of intervention.

### Conclusions

This study will evaluate the effectiveness of an enhanced version of CANreduce, a Web-based self-help intervention to reduce problematic cannabis consumption. If shown effective, the importance of CANreduce as a tool by which to reach users in the general population who otherwise would not seek out traditional mental health care, and addiction counseling services will be documented.

The benefits of the intervention include providing cannabis users with a better understanding of their addictive behaviors,

teaching them psychological tools to handle drug cravings and prevent relapses, and, ultimately, helping them to become free of cannabis dependence.

Furthermore, if adding a social presence to adherence-focused guidance augments the program's effectiveness, valuable insights could be gained into how to more effectively design Web-based interventions. These findings could then be adapted to other Web-based self-help tools, which present poor adherence and high attrition rates.

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## Authors' Contributions

MA and MPS had the initial idea for this study. MA prepared the first draft of the paper and the final manuscript. MA, MPS, AW, and CB developed the intervention of study arms 1 and 2. AW and CB programmed and implemented the study websites of CANreduce 2.0. SH, DDE, TB, LS, and MW provided continuous feedback on the development of the interventions and this study protocol. MA and MPS revised the first version of the study protocol thoroughly. All authors approved the final version of the manuscript submitted for publication. MA is the guarantor.

## Conflicts of Interest

None declared.

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## Abbreviations

**ADHD:** attention deficit hyperactivity disorder
**ASRS-V1.1:** ADHD Self-Report Scale-V1.1
**CBT:** cognitive behavioral therapy
**CES-D:** Centre of Epidemiologic Studies of Depression Scale
**CMD:** common mental disorder
**CSQ-I:** Client Satisfaction Questionnaire adapted to Internet-based interventions
**CUDIT-R:** Cannabis Use Disorders Identification Test-Revised
**DALY:** disability-adjusted life year
**DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders, 4th edition
**eHealth:** electronic health
**FDA:** Fragebogen Substanzanamnese
**GAD-7:** Generalized Anxiety Disorder-7
**GLMM:** generalized linear mixed model
**ISGF:** Swiss Research Institute for Public Health and Addiction
**IT:** information technology
**ITT:** intention-to-treat
**LMM:** linear mixed models
**MI:** motivational interviewing
**PI:** principle investigator
**PTSD:** posttraumatic stress disorder
**RCT:** randomized controlled trial
**SDS:** Severity of Dependence Scale
**TAU:** treatment-as-usual

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Protocol

# Transitions Between Circulatory States After Out-of-Hospital Cardiac Arrest: Protocol for an Observational, Prospective Cohort Study

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## Abstract

**Background:** The post cardiac arrest syndrome (PCAS) is responsible for the majority of in-hospital deaths following cardiac arrest (CA). The major elements of PCAS are anoxic brain injury and circulatory failure.

**Objective:** This study aimed to investigate the clinical characteristics of circulatory failure and inflammatory responses after out-of-hospital cardiac arrest (OHCA) and to identify patterns of circulatory and inflammatory responses, which may predict circulatory deterioration in PCAS.

**Methods:** This study is a single-center cohort study of 50 patients who receive intensive care after OHCA. The patients are followed for 5 days where detailed information from circulatory variables, including measurements by pulmonary artery catheters (PACs), is obtained in high resolution. Blood samples for inflammatory and endothelial biomarkers are taken at inclusion and thereafter daily. Every 10 min, the patients will be assessed and categorized in one of three circulatory categories. These categories are based on mean arterial pressure; heart rate; serum lactate concentrations; superior vena cava oxygen saturation; and need for fluid, vasoactive medications, and other interventions. We will analyze predictors of circulatory failure and their relation to inflammatory biomarkers.

**Results:** Patient inclusion started in January 2016.

**Conclusions:** This study will obtain advanced hemodynamic data with high resolution during the acute phase of PCAS and will analyze the details in circulatory state transitions related to circulatory failure. We aim to identify early predictors of circulatory deterioration and favorable outcome after CA.

**Trial Registration:** ClinicalTrials.gov: NCT02648061; https://clinicaltrials.gov/ct2/show/NCT02648061 (Archived by WebCite at http://www.webcitation.org/6wVASuOla)

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**KEYWORDS**

out-of-hospital cardiac arrest; critical care; hemodynamics; inflammation; biomarkers

## Introduction

### Post Cardiac Arrest Syndrome

Recent advances in cardiopulmonary resuscitation (CPR) have improved the chance of successful return of spontaneous circulation (ROSC) after cardiac arrest (CA) [1,2]. This implies that patients, who previously died during CPR, now obtain ROSC and are admitted to hospitals for further treatment. However, in-hospital mortality is unchanged at around 50% to 70% [3-5]. The post cardiac arrest syndrome (PCAS) is responsible for the majority of in-hospital deaths after CA. PCAS includes (1) brain injury, (2) myocardial dysfunction, and (3) systemic ischemia and reperfusion injury. In addition, the pathological process that caused the CA and other chronic diseases influences the clinical course of PCAS. Circulatory support after CA usually follows recommendations similar to those used for treatment of septic shock [6-9]. Septic shock and PCAS share some characteristics and experiences from the treatment of septic shock, such as emphasis on oxygen deliverance, which may be useful [10,11]. However, PCAS is a different clinical entity than septic shock, and circulatory failure after CA may have special characteristics [4]. This is exemplified by the need to perfuse the postischemic brain without unnecessary strain on the postischemic heart.

### Inflammation and Circulatory Failure

Circulatory failure after CA is both due to cardiac etiologies and systemic inflammatory response elicited by the hypoxic insult and reperfusion, but the relative contribution of each factor is unknown. The balance between pro- and anti-inflammatory cytokine signals is important in the development of organ failure [12]. Several studies have explored cytokine plasma concentrations as biomarkers for severity, risk of organ failure, and mortality in sepsis [13-15]. By comparison, only 4 studies in humans, with data from 2 patient populations, have evaluated the inflammatory response in PCAS [10,16-18], and 2 studies have explored the endothelial activation and injury in relation to inflammation in PCAS [18,19]. Furthermore, none of these studies specifically investigated the relationship between endothelial injury, inflammatory response, and circulatory failure.

In a cohort study from 2002, 73 out of 165 normothermic patients treated for out-of-hospital cardiac arrest (OHCA) developed circulatory instability, with median onset 6.8 hours after OHCA. [20]. Low cardiac output (CO) and filling pressures characterized the circulatory instability. The CO improved after 24 hours but superimposed vasodilatation developed, requiring fluid administration and use of vasoactive medications. Most patients recovered within 3 days, and hemodynamic status did not predict neurologic outcome [20]. In a Norwegian study, these results were confirmed in hypothermic CA patients [21]. In contrast, in the *Target Temperature Management Trial*, which randomized CA patients to either 33°C or 36°C, the circulation of patients in both groups were characterized by vasoconstriction [5,22,23]. However, the variables in studies on circulatory failure after CA are highly dependent on the use of vasoactive medications, and some studies are difficult to interpret because of limited information about the use of these medications.

### Rationale for a New Study

The International Liaison Committee on Resuscitation consensus statement from 2008 acknowledges the lack of knowledge about optimal treatment of PCAS and how to best deliver circulatory support after CA [4].

This protocol describes a study aimed to investigate patients with ROSC after OHCA, regarding (1) characteristics of circulatory failure in PCAS; (2) the endothelial and inflammatory response in PCAS; and (3) the relationship between circulatory failure and the inflammatory and endothelial response in PCAS.

## Methods

### Research Questions

This study will address the following research questions:

- What are the characteristics of circulatory failure in PCAS?
- What are the characteristics of transitions between different clinical circulatory states during PCAS?
- What is the inflammatory response measured by inflammatory and endothelial biomarkers in PCAS?
- Which clinical characteristics and biomarkers predict changes in clinical circulatory states?

### Study Design

This study is a single-center, prospective, observational cohort study.

### Setting

The study will take place at the intensive care unit (ICU) and the coronary care unit (CCU) at the St. Olav's University Hospital, a tertiary referral university hospital in Trondheim, Norway, with a catchment population of 700,000.

## Eligibility

### *Inclusion*

All adult patients who are admitted to either the ICU or the CCU with obtained ROSC after OHCA will be considered for inclusion. Inclusion is performed immediately after arrival to the ICU or CCU.

### *Exclusion Criteria*

Exclusion criteria are age <18 years, CA of septic or anaphylactic origin, sepsis within 24 hours before CA, pregnant women, transferred from other hospitals after OHCA, and decision to not initiate life-sustaining therapy after hospital arrival.

## Censoring

Patients are censored from further follow-up if the patient undergoes acute cardiothoracic surgery or intervention with extracorporeal membranous oxygenation support or a ventricular assist device, at the time of death, if life-prolonging therapy is withdrawn or withheld, or when the patient is transferred to a general ward or another hospital. The reason for censoring is recorded, and all data obtained until censoring will be included in the analysis.

## Sample Size

This is an observational study, and the frequency of abnormal biomarkers, circulatory states, and endpoints are largely unknown; therefore, no formal sample size calculation has been performed [24]. On the basis of a sample size from similar studies describing pathophysiology, we aim at including 50 patients [21,25].

## Routine Post Cardiac Arrest Syndrome Treatment

### *General Consideration*

The treatment of the patients is decided by the physician in charge and will not be changed due to the participation in the study. The routine treatment after OHCA at St. Olav's University Hospital will be applied unless there are specific indications for alternative strategies. Routine care is briefly outlined below.

#### Specific Cardiac Interventions

For OHCA suspected to be caused by disease in the coronary arteries, procedures for revascularization are routinely considered and performed if decided by the cardiologist. All use of medications for cardiac diseases and for anticoagulation is decided by the cardiologist in charge of treatment.

#### Therapeutic Hypothermia

According to the current practice at St. Olav's University Hospital, the target temperature is usually 36°C. Active temperature management is performed for 24 hours.

#### Sedation and Analgesia

Sedation is initiated with either propofol or midazolam, and analgesia with either fentanyl or remifentanil. Sedation is titrated to Motor Activity Assessment Scale (MAAS) 0-1 during active temperature management and later titrated to the lowest dose achieving adequate patient comfort [26]. A muscle relaxant, cisatracurium, is not routinely used, but initiated if shivering during cooling or rewarming, and if needed to achieve adequate ventilation.

#### Cardiovascular Support

The primary treatment goal for circulatory support is to ensure adequate circulation, as evaluated by clinical examination (eg, tachycardia, pallor, cold skin, capillary refill), a mean arterial blood pressure (MAP) ≥65 mm Hg, and a urine output of ≥0.5 $mL \cdot kg^{-1} \cdot h^{-1}$. Generally, circulatory optimization is achieved through fluid and vasopressor administration after the following algorithm: in the presence of hypotension and/or tachycardia, the first step is to assess signs of tissue hypoperfusion (eg, cold, clammy skin and extremities, prolonged capillary refill time, diminished urine output, increasing lactate and decreasing base excess, decreasing central/mixed venous oxygenation, and if not sedated—deteriorating mental status). If the physician suspects tissue hypoperfusion, volume status is assessed through the presence of stroke volume variation >10% (pulsus paradoxus) and/or echocardiographic assessment of the heart and the inferior caval vein. If increased preload is indicated, repeated fluid boluses of 250 mL are given until cardiac output (CO) does not respond. If a fluid load is not indicated or does not improve the perfusion, vasoactive medication is administered. The standard vasoactive medications are norepinephrine and/or dobutamine, depending on whether vasoconstrictive and/or inotropic effects are indicated. If the vasoplegia is not improved by a high dose of norepinephrine ($\geq 0.5$ $\mu g \cdot kg^{-1} \cdot min^{-1}$), vasopressin (0.4 $mU \cdot kg^{-1} \cdot min^{-1}$) is considered.

#### Respiratory Support

Ventilation is administered by a SERVOi ventilator (Maquet Siemens, Germany). Ventilation is either pressure controlled or pressure supported for patients who have adequate spontaneous ventilation. The ventilator settings are adjusted to a positive end-expiratory pressure (PEEP) level, which give the best arterial oxygen partial pressure ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) ratio (usually PEEP is set at 8 cm $H_2O$ at the start of ventilation), a plateau pressure to give a tidal volume of 6-8 mL/kg, a respiratory rate to give a $PaCO_2$ within the normal range, and a $FiO_2$ to give a $O_2$ saturation above 95%. Tracheostomy is considered for patients who are difficult to wean from mechanical respiratory support, usually on days 8-10 of the ICU or CCU stay.

#### Nutrition

No nutrition is given on the day of arrival to the ICU or CCU. Enteral nutrition is given as soon as possible in increasing doses (from 500 kcal/day to 1000 kcal/day to 2000 kcal/day). If enteral nutrition is not feasible or nutrition targets cannot be reached within approximately 4 to 6 days, total parenteral nutrition is gradually introduced on the fourth day (25 $kcal \cdot kg^{-1} \cdot day^{-1}$). Before nutrition is started, the patients receive glucose 100 g/daily. Metabolic control of blood sugar is aimed at 5-10 mmol/L by a continuous infusion of insulin. Patients who use insulin on a regular basis will receive insulin at all times, and hypoglycemia is corrected with increased glucose or nutrition administration.

### Infection Control

Antibiotics are not given routinely, but they are introduced if there is a clinical suspicion of an infection.

### Assessment of Hypoxic Cerebral Injury

Assessment of hypoxic cerebral injury is primarily based on the combination of clinical signs, serum neuron-specific enolase concentrations, and neurophysiological examination of somatosensory evoked potentials. Other examinations, for example, magnetic resonance imaging, are performed when required. The evaluation of potential hypoxic cerebral injury is usually initiated on the third or fourth day after CA.

### Intensive Care Unit Procedures

Airway suction is routinely performed once daily to secure patent airway and as needed if there are signs of excessive airway secretions. Airway suction is performed with a 10, 12, or 14 French scale catheter (depending on endotracheal tube size) through a closed suction system.

Shift of position is routinely performed every third hour.

Spontaneous breathing trials (SBTs) are considered in patients who have spontaneous respiration, airway patency, reversal of the cause of respiratory failure, no uncontrolled infection or metabolic disturbance, heart rate <120, systolic BP 90-180 mm Hg, oxygen saturation >90%, $FiO_2$ <0.5, and positive end-expiratory pressure (PEEP) ≤8 $cmH_2O$. The SBT is performed using pressure-supported ventilation with inspiratory pressure support of approximately 8 $cmH_2O$ and PEEP 6-8 $cmH_2O$ for 10-30 min.

## Study Procedure

### *Screening and Recruitment*

Patients will be screened for eligibility and recruited at the time they are admitted to the ICU or CCU for intensive care after OHCA (Figure 1).

Demographic and clinical data will be extracted from the patient's medical records and documentation from emergency medical service (EMS) personnel involved in the treatment of CA. Registrations of clinical variables, as part of routine critical care from the time of ICU/CCU arrival until inclusion, will be used.

If there is no contraindication to insert a pulmonary artery catheter (PAC), the catheter is inserted as early as possible after inclusion.

### *Baseline Variables*

At time of inclusion the following variables will be registered:

- Patient characteristics: age, sex, ethnicity, weight, height, and premorbid cerebral performance category (CPC) [27,28]
- Charlson Comorbidity Index [29]
- Characteristics related to the CA (*Utstein Style Template*) [30]: location, witnessed arrest, time of emergency call, bystander CPR, time of EMS personnel arrival, initial monitored rhythm, time to first defibrillation, time to ROSC, presumed cardiac or noncardiac etiology, and medications given during or after CPR. End-tidal $CO_2$ results, if applied
- Temperature at admission
- Known pulmonary aspiration during CPR
- Interventions

### *Registrations During the Study Period*

Clinical data are registered in the electronic ICU chart, Picis Critical Care Manager (Optum Inc, USA). After inclusion, the following variables will be recorded:

At the time of inclusion and every minute:

- Basic vital measurements: heart rate and rhythm, invasive arterial blood pressure, pulmonary artery pressure, mixed venous oxygen saturation ($SvO_2$, calibrated twice daily), central venous blood pressure, peripheral transcutaneous oxygen saturation, and temperature
- Central hemodynamic measurements: CO and systemic vascular resistance (SVR), and corresponding indexed values (related to body-surface area)
- Respiratory support: ventilator mode, respiratory rate, $FiO_2$, minute ventilation, PEEP, and plateau pressure

At the time of inclusion and every following hour:

- Fluid balance: fluid administrations, transfusions, and urine output
- All medications

At the time of inclusion and every sixth hour:

- Arterial blood gas analysis, including electrolytes
- MAAS score

After 24 hours:

- Simplified acute physiology score (SAPS) II [31]

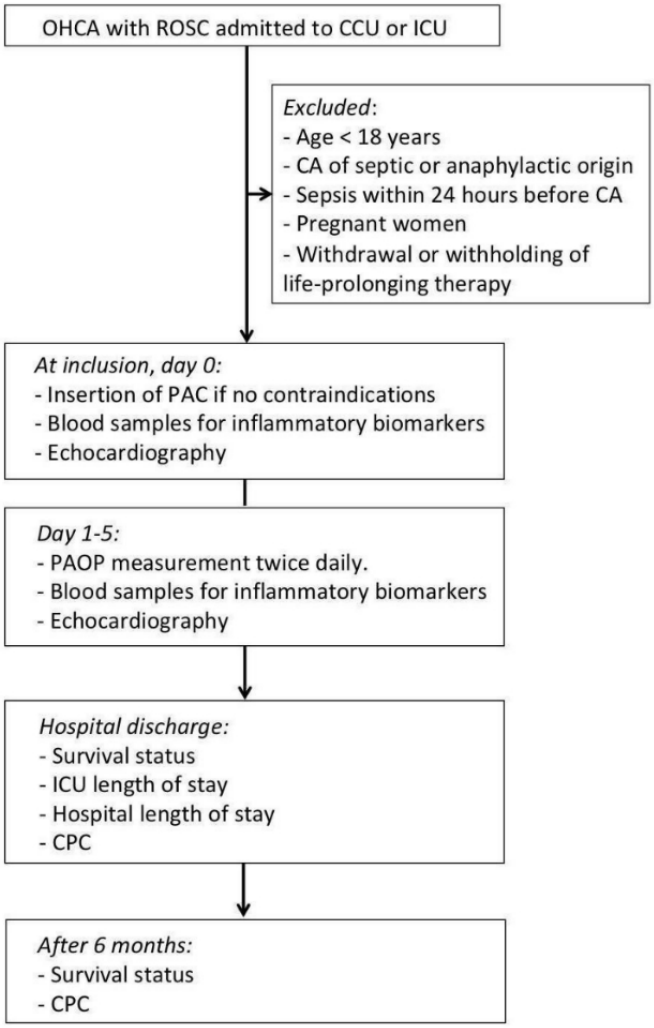
At the time of inclusion and twice daily:

- Pulmonary artery occlusion pressure
- Central venous and mixed venous blood gas

At the time of inclusion and daily:

- Standardized echocardiographic evaluation performed by a trained cardiologist
- Intra-abdominal pressure
- Clinical chemistry: white blood count, thrombocyte count, creatinine, blood urea nitrogen, C-reactive protein, troponin-T, probrain natriuretic peptide, bilirubin, albumin, and haptoglobin
- Blood samples for inflammatory and endothelial biomarkers
- Modified clinical pulmonary infection score (CPIS) [32]
- Sequential organ failure assessment (SOFA) score [33]
- Glasgow Coma Score [34]
- Percutaneous coronary intervention, dialysis, and/or aorta balloon pump
- Results from chest x-ray or other diagnostic imaging tools ordered during the hospital stay
- Other events during the study period (eg, arrhythmias and seizures)

**Figure 1.** Flowchart summarizing patient enrollment and main study procedures. OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation; CCU: coronary care unit; ICU: intensive care unit; CA: cardiac arrest; PAC: pulmonary artery catheter; PAOP: pulmonary artery occlusion pressure; CPC: cerebral performance category.




### *Biomarkers*

As part of the study, we will establish a biobank for analysis of inflammatory and endothelial biomarkers. Blood samples will be taken at inclusion and every morning the 5 following days. After gentle mixing, the blood samples are placed vertical for 30 min in ambient temperature, and then centrifuged at 2200 g for 10 min. The supernatants are stored at −80°C within 1 hour from the time of sampling. During the study period, additional full blood will be drawn and stored at −80°C.

We will analyze the following biomarkers: interleukin (IL)-1β, IL-1 receptor antagonist (IL1-ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, basic fibroblast growth factor, granulocyte-colony stimulating factor, granulocyte macrophage colony stimulating factor, interferon γ, interferon-inducible protein 10, monocyte chemotactic protein 1, macrophage inflammatory protein 1α and 1β, platelet derived growth factor-BB, regulated upon activation T cell expressed and secreted, tumor necrosis factor, vascular endothelial growth factor, syndecan-1, sE-selectin, heparan sulfate, hyaluronic acid, soluble trombomodulin, and sVE-cadherin. Other biomarkers of interest, identified later, may be included in the final analysis.

### *Follow-Up After Discharge From Hospital*

Follow-up after discharge from the hospital will include the following:

- ICU length of stay.
- Hospital length of stay.
- Survival status at hospital discharge and after 6 months.
- CPC at hospital discharge and after 6 months.

## Ethical Considerations

Research on critically ill patients, who are sedated or comatose and, therefore, not able to provide consent, calls for special ethical considerations. For the study, it is vital that clinical information is obtained from the initial critical stage of the disease. This study will not increase the overall risk for the patients, and the study is justifiable according to the *World Medical Association's Declaration of Helsinki* regarding *Ethical Principles for Medical Research Involving Human Subjects*, June 1964, and its later amendments [35]. We will include patients in the study when they are admitted to the ICU/CCU

and at the earliest feasible moment ask for consent from their relatives. Patients, who regain competency to give an informed consent, will later be asked for a deferred consent. This procedure is approved by the Regional Committee for Medical and Health Research Ethics, Central-Norway Health Region (REK Midt, No. 2015/1807).

## Assessment of Safety

Besides establishing and calibrating PAC (Swan-Ganz CCOmbo, Edward Lifescience, USA) and drawing blood for analysis of inflammatory biomarkers at a maximum of 5 time points, the study does not involve other interventions differing from routine care after OHCA. The insertion of PAC induces some benefits and some risks. One of the benefits is the potential of improved circulatory monitoring and support, including a more precise administration of fluids and vasoactive medications. However, complications related to the placement of PAC have also been reported. In a Cochrane report, PAC was neither found to increase mortality or length of stay in the ICU or the hospital (high-quality evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for both the findings). The Acute Decompensated Heart Failure Syndromes Registry compared 502 patients with decompensated heart failure and PAC with 502 controls [36] and observed that the risk of all-cause death was lower in the PAC group than the control group (hazard ratio 0.3, 95% confidence interval (CI) 0.13-0.7). In a large study from Leipzig where 3730 patients with PAC who underwent cardiac surgery, only 0.1% experienced serious complications [37], a similar rate as transesophageal echocardiography (0.2%) [38]. The nursing-staff at ICU and CCU are trained in PAC care and extra lectures in PAC use will be given before and during the study. Only doctors, competent of PAC use, will perform measurements of pulmonary artery wedge pressure. We believe that the patients included will experience neither benefit nor harm by participating in this study.

## Statistical Analysis Plan

### *Statistical Methods*

Descriptive data are presented with either median or interquartile range, or mean with 95% CI, as appropriate. For missing observation of physiological variables (eg, blood pressure), a value corresponding to the mean of the observation before and after this time point will be applied. For biomarkers, the value 0 is attributed if a result is below the detection limits of the assay. Statistical analyses will be performed using Stata or R.

### *Circulatory State Transitions During Post Cardiac Arrest Syndrome*

During critical illness, most patients go through different states of hemodynamic stability. We have categorized the circulatory state after CA in 3 different categories based on data obtained from routine care (Table 1). Every 10 min, a patient is classified according to the least favorable measurement at that time (eg, isolated MAP of 40 mm Hg is sufficient to classify a patient to have severely disturbed circulation).

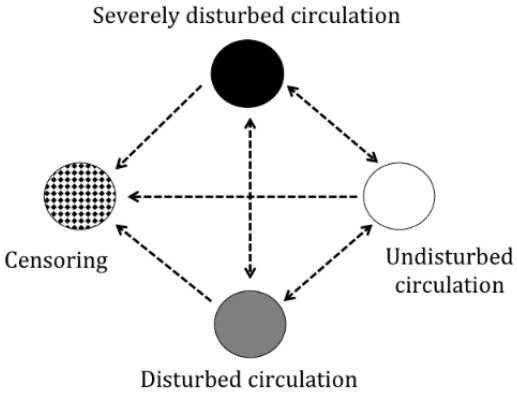
We will validate the appropriateness of the defined categories against the cardiac index.

Patients may go back and forth between the clinical states, defined in Table 1, corresponding to the severity of their illness and its progression (Figure 2), and the changes from one clinical state to another will be recorded. By using survival analysis methodology, we allow for right censoring, which means that the information from patients with limited follow-up time can be included in the analyses. A patient who is in a certain clinical state at time *t* might remain in the same state or change to one of 2 others at time *t* +1. In such multi-endpoint settings, the clinical states compete with each other, and the transitions over time are best studied with methods developed for competing risk analyses.

**Table 1.** Circulatory states.

| Variables | Circulation | | |
|---|---|---|---|
| | Undisturbed | Disturbed | Severely disturbed |
| Mean arterial pressure, mm Hg | ≥65 | 45-64 | <45 |
| Heart rate, bpm | 51-100 | <50, 101-130 | ≤40, >130 |
| Lactate, mmol/L | <2 | 2–4 | >4 |
| $ScvO_2$, % | ≥65 | 50-64 | <50 |
| Fluid resuscitation, L/hours | <0.5 | 0.5-1.9 | ≥2 |
| Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$ | <0.1 | 0.1-0.29 | ≥0.3 |
| Dobutamine, $\mu g \cdot kg^{-1} \cdot min^{-1}$ | No | <10 | ≥10 |
| Vasopressin | No | No | Yes |
| Epinephrine | No | No | Yes |
| Levosimedan | No | No | Yes |
| Aorta balloon pump | No | No | Yes |

**Figure 2.** Possible transitions between circulatory states.




The Kaplan-Meier estimator accurately estimates the transition from one state to another, assuming that these 2 states describe all possible states. To be useful in a competing risk framework, the Kaplan-Meier estimator has been generalized into a matrix version, called the Aalen-Johansen estimator. To describe when, in time, most state transitions occur (ie, transition intensity), we will use the Nelson-Aalen estimator. The Nelson-Aalen estimator is a nonparametric estimator of the "cumulative hazard" of a given event, and it can be applied in a multi-state model.

### *Patterns Predictive of Deterioration in Circulatory State*

We anticipate that not all patients will follow the same circulatory trajectory; during the study, some will deteriorate and some will improve in circulatory status, and during our observation, many will have several state transitions. We plan to analyze events before deteriorations to identify patterns of circulatory and inflammatory response measurements predictive of clinical state deteriorations. These patterns will be compared with those in patients who improve their circulatory status or remain unchanged.

To explore the predictive value of previous measurements to foresee a clinical deterioration, we will use 2 different approaches. The outcome variable will be dichotomized to deterioration versus no deterioration (status quo or improvement). First, we will test different timelags between measurements and deteriorations to see which is more informative (eg, 1 hour, 2 hours, 3 hours). For this analytic approach, we will use univariable and multivariable logistic regression. Second, we will use methods from survival analysis to assess continuous alterations in covariates on the outcome. For this analysis, we will use Aalen's linear model, which is an intensity regression model. Variables from the 2 groups will also be explored in respect to its relation to mortality and CPC at discharge from hospital.

### *Relation Between Distributive Shock and Inflammatory Biomarkers*

We will study the relationship between alterations in inflammatory and endothelial biomarkers and the changes in SVR, in CO, and the need for fluid replacement. As described above, patients with hypotension and low SVR will be treated with norepinephrine. Therefore, we will analyze potential independent biomarkers and other predictors of SVR adjusted for a dose of norepinephrine.

Vasoplegia might also occur as part of an infection, and CA patients are prone to aspiration and pneumonia after CPR. Therefore, we will calculate modified CPIS daily to describe how many patients develop clinical pneumonia.

Circulatory failure might also be due to structural heart defects (eg, mitral valve insufficiency). An experienced cardiologist will perform echocardiogram daily to assess the heart's function.

## Results

Patient inclusion started in January 2016.

## Discussion

### Rationale for This Study

This study will describe the hemodynamic and inflammatory response characteristics of circulatory failure in PCAS. On the basis of the findings, we will develop a prediction model for risk of circulatory failure in PCAS.

PACS after CA is frequent, and it is strongly associated with mortality after CA [4]. However, there is relatively limited information about the detailed circulatory disturbances in PACS, and principles for circulatory supports are partly transferred from other conditions, in particular, in the treatment of septic shock. Moreover, the expected course (eg, improvement or deterioration) of the circulation is not well understood. The clinical trajectory may be 2-phased: first, a low CO state, followed by a low peripheral resistance state, as previously proposed [20]. Alternatively, it may be one-phased: predominantly caused by either an isolated cardiac failure or an isolated vasoplegia. It is also not established which patients are at a higher risk for circulatory failure in the acute phase of PCAS.

Standard critical illness classification systems, such as SAPS II, SAPS III, acute physiology and chronic health evaluation (APACHE) II, SOFA, or New Early Warning (NEW) scores, are not applicable to describe circulatory changes during the acute phase of PCAS. SAPS and APACHE scores are developed to define risk at admission. SOFA and NEWS scores will reach a ceiling effect and not be able to differentiate between various degrees of circulatory failure in this population. Some

researchers have used an extended SOFA circulatory score where 4 further increments are added to the standard circulatory SOFA score [39]. However, this score only includes arterial blood pressure and use of vasopressors, which may not encompass all relevant observations for circulatory stability. Therefore, this study classifies the patients into 3 circulatory groups: *undisturbed*, *disturbed*, or *severely disturbed circulation* based upon predefined values of mean blood pressure, heart rate, serum lactate concentration, $ScvO_2$, use of fluid, vasoactive drugs, and the need for mechanical circulatory devices. Cut-off values were based upon relevant guidelines and clinical practice. All variables were selected because of their known relevance to circulatory failure and because they are easily available during routine monitoring of critically ill patients. More precise measures such as CO or $SvO_2$ were not included, as these are usually not obtained in patients after CA.

The clinical trajectories in the acute phase of PCAS are heterogeneous, as seen from the lack of circulatory stability. Such changes can occur immediately after admittance to the ICU or later, at any time, in the clinical course. Thus, the patients are at constant risk. Limited information exists regarding the factors to identify which patients are at the highest risk of imminent clinical circulatory failure. Such factors may include characteristics of the CA episode or clinical observations in the ICU.

This study will establish which factors—demographic, CA-related variables, or clinical observations— will predict circulatory failure and, thus, assess circulatory stability during PCAS.

## Expected Limitations

We recognize some limitations in this protocol. First, the study will obtain information about long-term outcomes and survival. However, this information will only be used to describe the cohort because of the limited number of patients. It would be of interest to study whether circulatory stability and inflammation during PCAS can also predict long-term outcomes, but such analyses should be done in larger cohorts. Second, this study is a single-center study, which limits the generalization of the findings. Third, the included patients are expected to have considerable variability in demographics and comorbidities, in characteristics of the CA, and thus also in PACS complications (eg, infections). Nevertheless, this is presumably the case in all PACS cohorts, and potential findings must be robust to such confounders to be of potential clinical use.

## Conclusions

This study will obtain longitudinally advanced hemodynamic observations with high resolution during the acute phase of PCAS, and it will analyze the details of clinical transitions related to circulatory failure. Additionally, this study will also examine the relationship between inflammatory and endothelial biomarkers and circulatory failure in PCAS.

## Acknowledgments

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## Conflicts of Interest

None declared.

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## Abbreviations

**APACHE:** acute physiology and chronic health evaluation
**CA:** cardiac arrest
**CCU:** coronary care unit
**CO:** cardiac output
**CPC:** cerebral performance category
**CPIS:** clinical pulmonary infection score
**CPR:** cardiopulmonary resuscitation
**EMS:** emergency medical service
**FiO2:** fraction of inspired oxygen
**ICU:** intensive care unit
**IL:** interleukin
**MAAS:** Motor Activity Assessment Scale
**MAP:** arterial blood pressure

**NEW:** new early warning
**OHCA:** out-of-hospital cardiac arrest
**PAC:** pulmonary artery catheter
**PCAS:** post cardiac arrest syndrome
**PEEP:** positive end-expiratory pressure
**ROSC:** return of spontaneous circulation
**SAPS:** simplified acute physiology score
**SBT:** spontaneous breathing trials
**SOFA:** sequential organ failure assessment
**SVR:** systemic vascular resistance
**TBCS:** transitions between circulatory states

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Protocol

# Effect of a Titanium Tetrafluoride Varnish in the Prevention and Treatment of Carious Lesions in the Permanent Teeth of Children Living in a Fluoridated Region: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Titanium tetrafluoride ($TiF_4$) has regained interest due to new formulations that have been shown to be more effective against tooth demineralization than sodium fluoride (NaF) formulations in vitro and in situ.

**Objective:** The aim of this study is to evaluate the effect of two types of varnishes (4% $TiF_4$ and a commercial 5% NaF) on the prevention of carious lesions and the treatment of noncavitated enamel carious lesions in the permanent teeth of children living in a fluoridated area.

**Methods:** This randomized, controlled, parallel and single-blind clinical trial involves 63 children, 6-7 years old, living in Bauru, São Paulo, Brazil. Children were selected according to their caries activity (ie, presence of at least 1 tooth with a Nyvad score of 1) and randomly divided into the following treatment categories: 4% $TiF_4$ varnish (2.45 % $F^-$, pH 1, FGM); 5% NaF varnish (2.26% $F^-$, pH 5, Duraphat, Colgate) and control (placebo varnish, pH 5, FGM). The varnishes will be applied on all permanent teeth, once a week for 4 weeks and they will be reapplied only once 6 and 12 months after the study begins. Two calibrated examiners will carry out the clinical examination (International Caries Detection and Assessment System [ICDAS] and Nyvad indexes, kappa>.8) at baseline, before the first application, after the 1st, 6th, 12th, and 18th month of the study begins. Furthermore, quantitative fluorescence changes will be measured using Quantitative Light-Induced Fluorescence (QLF). The degree of patient satisfaction with the treatment will also be computed. The data will undergo statistical analysis ($P$<.05).

**Results:** This ongoing study is funded by funding agencies from Brazil (São Paulo Research Foundation, FAPESP-015/14149-1, and National Council for Scientific and Technological Development, CNPq-401313/2016-6). We expect to confirm the efficacy of $TiF_4$ on the prevention and treatment of carious lesions by comparing it to NaF varnish. The subjects are under 1 month evaluation and the dropout was about 8%. No differences between the treatments have been detected at the first month so far ($P$>.05).

**Conclusions:** If our hypothesis is confirmed, $TiF_4$ varnish can be marketed and applied at the individual level and used in community programs to control dental caries.

**Trial Registration:** Brazilian Clinical Trials Registry: RBR-5VWJ4Y; http://www.ensaiosclinicos.gov.br/rg/?q=RBR-5VWJ4Y (Archived by WebCite at http://www.webcitation.org/6wUurEnm7)

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**KEYWORDS**

clinical trial; dental caries; topical fluorides

## Introduction

Fluoride varnishes are a feasible approach for preventing and treating carious lesions at the individual level and in public health programs, due to its good cost-benefit compared to initial carious lesions restorations, when they eventually progress to cavitation and have a significant negative impact in quality of life [1,2].

Due to the polarization of caries [3] and inequality in health services access, treatment is available to only a small portion of the population [3,4]. This fact requires the attention of authorities and appropriate public health interventions [4,5]. Based on this new panorama of the disease, researchers have sought to improve the effect of conventional fluorides or alternatively to test nonconventional fluorides (eg, fluorides [F] containing polyvalent metals, such as stannous fluoride [$SnF_2$] and titanium tetrafluoride [$TiF_4$]) [6,7].

Several in vitro and in situ studies have shown that an experimental 4% $TiF_4$ is more effective than NaF at reducing demineralization and improving remineralization [7-9]. The titanium ions from $TiF_4$ react with dental apatite, forming an acid resistant, glaze-like layer that is rich in hydrated titanium phosphate and titanium dioxide [10]. Furthermore, $TiF_4$ varnish induces a higher deposition of calcium fluoride ($CaF_2$) than NaF varnish on both intact and demineralized enamel surface [10].

Recent in situ study demonstrated that 4% $TiF_4$ varnish was the only treatment capable of improving enamel remineralization regardless of cariogenic activity, while NaF varnish failed in preventing further demineralization under high cariogenic activity [7]. This result supports the hypothesis of the present study that $TiF_4$ varnish could be more effective than NaF varnish in preventing and treating carious lesions in the permanent teeth of children living in a fluoridated area.

The aim of this clinical protocol is to evaluate the effect of 4% $TiF_4$ varnish compared to a commercial 5% NaF varnish on the prevention of carious lesions and the treatment of noncavitated enamel carious lesions in the permanent teeth of children living in a fluoridated area.

## Methods

### Ethical Aspects

The protocol of this study was submitted and approved by the local ethics committee (Number: 59787116.2.0000.5417, Ethics Committee of the Bauru School of Dentistry, University of São Paulo, Brazil) and by the registration of clinical research in the Brazilian Clinical Trials Registry (Number: RBR-5VWJ4Y). The research protocol was also approved by the Municipal Secretariat for Education of Bauru (São Paulo, Brazil) and by the 5 municipal schools (see Table 1) enrolled in the study. Thereafter, the parents and/or guardians responsible for the study participants (eg, children aged 6-7 years) received and signed an informed consent form prior to their involvement in the research. The children also received a consent form, with age-appropriate language, explaining how the research would be conducted. The children were free to accept or reject participation in the study. Upon receiving approval and consent from all involved parties, the study began.

### Study Design

This is a randomized, controlled, parallel, single-blind, and three-armed (ie, 4% $TiF_4$ varnish, 5% NaF varnish and placebo varnish) clinical trial with a duration of 18 months. It involves 63 children (37 males and 26 females) between 6-7 years of age, coming from public schools of Bauru city, an area that is optimally fluoridated. An experimental number of 20 children per treatment group was previously calculated considering an $\alpha$ error of 5%, $\beta$ error of 20%, a dropout rate of 30%, and a caries incidence rate after a period of 2 years of 15% for fluoride group and 42% for control group [11].

Children were selected according to their caries activity (ie, at least 1 active white spot lesion present on the smooth surface of their permanent dentition with a score of 1 according to the Nyvad index [12]) and randomly allocated to one of the 3 treatment options ensuring stratified block randomization into each group: 4% $TiF_4$ varnish (2.45% $F^-$, pH 1, FGM); 5% NaF varnish (2.26% $F^-$, pH 5, Duraphat, Colgate) and control (placebo varnish, pH 5, FGM).

**Table 1.** Distribution of selected schools according to the regions of Bauru city (São Paulo, Brazil).

| Region | Name of school |
|---|---|
| North | EMEF[a] José Romão |
| | EMEF Geraldo Arone |
| South | EMEF Santa Maria |
| East | EMEF Thereza Tarzia - Irmã Rosamaria Tarzia |
| West | EMEF Ivan Engler de Almeida |

[a]EMEF: municipal school of fundamental education.

**Figure 1.** Flowchart of the study.


The treatment was conducted as described below. The teeth were submitted to clinical examination (using the International Caries Detection and Assessment System [ICDAS] and Nyvad indexes), and quantitative fluorescence changes were monitored by a quantitative light-induced fluorescence (QLF) device. The analyses were conducted after the first month and they will be carried out at the 6th, 12th, and 18th month of the study. Figure 1 summarizes the study protocol.

## Baseline Analysis

Two trained examiners (inter- and intraexaminer agreement, kappa>.8), not involved in the treatment application, are responsible for examining the children (NMS and BMS). The children were selected based on the analysis of smooth surfaces using the Nyvad index [12]. Only children aged 6-7 years, presenting at least 1 smooth surface with active carious lesions and the signed consents, were selected. The exclusion criteria were: children under orthodontic treatment; those who participated in another clinical study 3 months prior to the present study; those who underwent professional fluoride application 6 months prior to the present study; those under treatment with antibiotics or some other type of medicine (eg, patients with chronic diseases); or those with periodontal disease.

The distinction between active and inactive carious lesions was done through visual and tactile inspection. The active white spot lesions were defined as having a rough and opaque white surface [13]. All white spot lesions were further analyzed using QLF [14]. Furthermore, all permanent teeth surfaces were analyzed using ICDAS, which is a method of caries detection and evaluation that classifies the stages of the caries process [15]. The decayed, missing, filled teeth index (DMFT) was applied for the primary teeth (this data will be included in the regression analysis to check the influence of other variable on the results).

## Treatment

All children received instruction on cariogenic diets and oral hygiene, and were given supervised tooth brushing. The researchers provided new toothbrushes (Colgate Classic, Colgate-Palmolive), dental floss (Colgate, Colgate-Palmolive), and fluoride toothpastes (Colgate, 1450 ppm $F^-$ as monofluoride phosphate [MFP], Colgate-Palmolive). The oral hygiene kit will be replaced every 3 months during the study.

The varnishes were applied on all permanent teeth once a week for the first 4 consecutive weeks [16] and they will be reapplied once at the 6th and 12th month of the study [17] by ASB. The application was done using a microbrush, under natural light, following the clinical steps:

1. Supervised tooth brushing by DMSS.
2. Relative isolation of teeth area with cotton rolls.
3. Drying of the teeth surfaces using sterile gauze.
4. Varnish application according to the manufacturer's instructions.
5. Waiting for 5 minutes for solvent evaporation.
6. Removal of the cotton rolls.

The treatments were done during the afternoon. The children were instructed not to ingest liquid for 30 min, to have soft meals and to perform oral hygiene 4 hours after the application.

After each application, a visual scale (Figure 2) (Wong-Baker Pain Scale [WBPS]) was applied to assess the degree of patient satisfaction with the treatment. The scale is known to be one of the most effective tools for self-rated child pain [18]. The mean result of the first four varnish applications is described in the Results section.

## Clinical Examination

Clinical examinations were performed after dental hygiene activities, based on the clinical criteria for caries diagnosis outlined by Nyvad et al [19], which were modified as shown in Table 2 [12]. Only the smooth surfaces of all permanent teeth were considered and the clinical examination was carried out in an illuminated environment, using clinical probe and mirror, and sterile gauzes. In addition, the ICDAS index was used to assess all surfaces at baseline and will be applied again at the 18th month (Table 3).

The progression of white spot lesion occurs when the noncavitated lesion becomes a cavity (untreated cavity or restored tooth) or when a healthy surface is transformed into an active lesion (cavitated or not). The regression is defined as when the initial active white spot lesion is transformed into an inactive carious lesion or healthy surface. The data (degrees of freedom [df] = baseline Nyvad's score – 1 month Nyvad's score) was analyzed using a Kruskal-Wallis test.

**Figure 2.** The Wong-Baker Visual Scale (WBPS), where 0 is very good (no pain/discomfort) and 10 is highly dissatisfied (worst possible pain/discomfort).

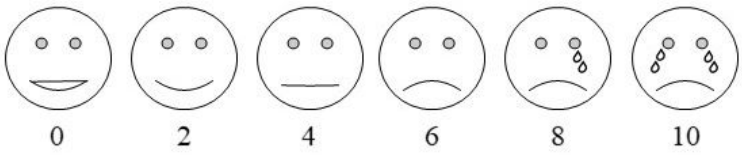


**Table 2.** Modified Nyvad's scores [12].

| Score | Description |
|---|---|
| Score 0 | Sound enamel |
| Score 1 | Active white spot lesion – not cavitated |
| Score 2 | Inactive white spot lesion – not cavitated |
| Score 3 | Cavitated enamel (tooth with cavity, restored, or extracted) |

**Table 3.** International Caries Detection and Assessment System (ICDAS) scores [15].

| Score | Classification criteria |
|---|---|
| 0 | No or subtle change in enamel translucency after prolonged drying (5s) in area of biofilm accumulation |
| 1 | Visible white spot after drying (no loss of surface continuity) or pigmentation restricted to confines of a pit or fissure |
| 2 | White spot visible on wet surface (no loss of surface continuity) or pigmentation that extrapolates confines of a pit or fissure |
| 3 | Localized cavitation (or loss of continuity) in opaque or pigmented enamel |
| 4 | Underlying dark shadow from dentin, with or without cavitation of enamel |
| 5 | Cavitated enamel with exposure of the underlying dentin, involving up to half of the analyzed surface |
| 6 | Cavitated enamel with exposure of the underlying dentin, involving more than half of the analyzed surface |

### Quantitative Light-Induced Fluorescence

QLF is applied to measure the changes in the enamel fluorescence of white spot lesions and to quantify its reversal or progression. A xenon arc lamp is used as a light source, and an optical filter system, producing blue light with a maximum wavelength of 370 nm, is connected to the microscope by a liquid light guide (Inspektor Research Systems BV, Amsterdam, The Netherlands). The fluorescence emitted by the tooth is collected with a charged coupled device (CCD)-video microcamera (Panasonic WV-KS 152, Matsushita Electric Industrial Co, Ltd, Osaka, Japan) equipped with high pass yellow filter ($\gamma$>520 nm) to exclude any excitation or ambient light that may reach the detector and a special dental mirror to reflect the image of the lesion connected to the camera [14].

After drying the tooth surface (for 5 s), images of clinically detected white spot lesions are obtained by QLF, in a completely dark environment. A computer program (Software Inspektor QLF 2.00f; Inspektor Research System BV, Amsterdam, The Netherlands) is utilized to display, store, browse, and analyze the images. The QLF parameters are: 1) the area of the lesion (white spot area [WS], $mm^2$) that is the sum of all points within the lesion with fluorescence loss > 5%; and 2) the mean fluorescence loss (ΔF, %, detection threshold of 5%) [20].

The QLF analysis was performed at baseline and after 1 month. The differences between the 1 month and baseline values were calculated as follows: ΔWS area = WS area baseline – WS area after 1 month (the same for ΔΔF), where ΔWS is the variation of the white spot lesion area and ΔΔF is the variation of the mean fluorescence loss. The data were analyzed using the Kruskal-Wallis test. This analysis will be repeated after the 6th, 12th, and 18th months of the treatment by BMS.

### Statistical Analysis

The data will be subjected to statistical analysis using the GraphPad Instat and Prism (version 5.0 software) for Windows (GraphPad Software; San Diego, CA, USA). Firstly, the data will be checked for normality and homogeneity. A parametric or a similar nonparametric test will be applied to compare the treatments with respect to: 1) the prevention of new carious lesions (ICDAS and Nyvad indexes); 2) regression or progression of previous active white spot lesions using the Nyvad index; 3) regression or progression (gain or loss of fluorescence, respectively) of previously active white spot lesions using QLF (at 0, 1, 6, 12 and 18 months).

## Results

This protocol refers to an ongoing clinical study funded by the São Paulo Research Foundation (FAPESP-2015/14149-1) and the National Council for Scientific and Technological Development (CNPq-401313/2016-6).

Treatment, Clinical Examination and Quantitative Light-Induced Fluorescence

Figure 1 shows the number of children by school enrolled in the research so far. All enrolled children (n=63) were underwent 4 weeks of treatment and almost all of them (n=58) were analyzed after 1 month. Five out of 63 children (8%) dropped out after the first month of analysis (n total=58). No significant differences in caries prevention, regression or progression were found among the treatments at the first month (Tables 4 and 5). The degree of patient satisfaction with the treatment after the varnish applications is displayed in Tables 6 and 7.

**Table 4.** Nyvad's scores [12] at the baseline and after 1 month of treatment (final) for $TiF_4$, NaF and placebo treatments.

| Measures | $TiF_4$ | | NaF | | Placebo | |
|---|---|---|---|---|---|---|
| | Baseline | Final | Baseline | Final | Baseline | Final |
| Nyvad index, mean±SD | 1.0±0.00 | 1.0±0.00 | 0.97±0.15 | 1.03±0.15[a] | 0.99±0.06 | 1.08±0.24[b] |
| Df[c], median (min-max) | 0.0 (0.0 to 0.0) | | 0.0 (–0.7 to 0.0) | | 0.0 (–1.0 to 0.0) | |

[a]One patient presented two teeth that progressed from score 0 to 1 and 1 patient had one lesion that progressed from score 1 to 3.

[b]One patient presented one tooth that progressed from score 0 to 3 and one patient had one lesion that progressed from score 1 to 3.

[c]Df: degrees of freedom. Df = baseline – final value, where positive values indicate regression and negative values indicate lesions progression. Kruskal-Wallis Test ($p$=.39).

**Table 5.** Median (minimum-maximum values) obtained in quantitative light-induced fluorescence (QLF) analysis at the first month compared to the baseline.

| Type of varnish | ΔWS area ($mm^2$)[a,b] | ΔΔF (%)[b,c] |
|---|---|---|
| $TiF_4$ | 0.01 (–9.15 to 1.19) | –1.29 (–16.30 to 4.74) |
| NaF | 0.17 (–2.38 to 1.47) | –0.55 (–5.80 to 6.10) |
| Placebo | 0.19 (–1.14 to 4.36) | –0.23 (–5.17 to 5.10) |

[a]ΔWS: variation of the white spot lesion area. For ΔWS, negative values mean progression (demineralization), and positive values, regression (remineralization). The opposite is valid for ΔΔF.

[b]Kruskal-Wallis Test ($p$=.59 and $p$=.45, respectively).

[c]ΔΔF: variation of the mean fluorescence loss.

**Table 6.** Mean percentage (%) of the degree of patient satisfaction after the first 4 applications of the $TiF_4$, NaF and placebo varnishes using the Wong-Baker Pain Scale.

| Wong-Baker Pain Scale | Type of varnish, mean±SD (%) | | |
|---|---|---|---|
| | $TiF_4$ | NaF | Placebo |
| 0 | 75±8 | 86±6 | 76±11 |
| 2 | 20±5 | 12±6 | 17±9 |
| 4 | 5±4 | 2±3 | 3±3 |
| 6 | 0±0 | 0±0 | 3±3 |
| 8 | 0±0 | 0±0 | 0±0 |
| 10 | 0±0 | 0±0 | 1±3 |

**Table 7.** Number of patients included in the analysis of satisfaction (Wong-Baker Pain scale) after the first four varnish applications.

| Wong-Baker Pain Scale | Number of patients by varnish type | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $TiF_4$ | | | | NaF | | | | Placebo | | | |
| | 1st[a] | 2nd | 3rd | 4th | 1st | 2nd | 3rd | 4th | 1st | 2nd | 3rd | 4th |
| 0 | 18 | 15 | 16 | 14 | 19 | 17 | 19 | 17 | 18 | 16 | 13 | 14 |
| 2 | 3 | 5 | 4 | 5 | 1 | 3 | 2 | 4 | 1 | 4 | 5 | 4 |
| 4 | 0 | 1 | 1 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 20 | 20 | 20 | 20 |

[a]The first (1st), the second (2nd), the third (3rd) and the fourth (4th) varnish application.

We expect to confirm the efficacy of the $TiF_4$ varnish compared to one based on NaF for the prevention and treatment of carious lesions at the end of the present study (18 months) as we have previously found under in vitro and in situ protocols.

## Discussion

Previous systematic reviews have shown no significant differences between the anticaries performances of fluoride (mainly NaF) included in different products such as gel, varnish and toothpaste [1,2]. However, varnish has some advantages over the other products, since it adheres to the tooth surface allowing for a long time of contact between the fluoride and teeth. It also presents low systemic toxicity, and is well tolerated and accepted by patients, especially children [1,2,21]. Therefore, we tested the anticaries effect of an experimental $TiF_4$ varnish.

Incorporating $TiF_4$ into a varnish allows for a longer contact time with enamel, thereby improving the reaction of titanium with the tooth apatite and facilitating the formation of a glaze-like layer on the tooth surface that is rich in titanium dioxide, hydrated titanium phosphate and $CaF_2$[6,10]. Due to its low pH, a $TiF_4$ varnish is able to enhance the enamel fluoride uptake compared to a NaF varnish [10]. The varnish may also reduce $TiF_4$ contact with soft tissues compared to a rinse solution, reducing the possibility of cytotoxicity due to its low pH [22]. A recent study has shown that a $TiF_4$ varnish presents similar levels of toxicity to murine fibroblast lineage (NIH/3T3)

cells as a NaF varnish [22]. To check for possible side effects of the $TiF_4$ varnish, patient satisfaction was evaluated using a simple, but effective tool for self-rated child pain [18].

Previous studies have shown that the application of fluoride varnish once a week for 4 consecutive weeks (4 applications in a one-month interval) has been effective in accelerating remineralization of white spot lesions [16]. On the other hand, biannual applications are effective for the prevention of new carious lesions [17,21]. The focus of the research is preventing and treating carious lesions on smooth tooth surfaces, which is where fluoride varnish is predominantly used [1]. For occlusal surfaces, other treatments are often indicated, such as fissure sealants, despite a recent systematic review has demonstrated positive results using NaF varnish on occlusal surfaces [23].

The most common method for detecting caries is the visual-tactile technique by using the ICDAS, Nyvad and DMFT indexes. However, other noninvasive techniques for the detection of early carious lesions have been developed, such as QLF and DIAGNOdent, which are especially used for research purposes [24]. The traditional DMFT index is based on detecting carious lesions at the cavitated level only, but it is not a good method for identifying these lesions at a very early stage [25]. On the other hand, ICDAS is an accurate and reproducible method for discovering early lesions in enamel and also for detecting changes over time [24]. Braga et al [26] compared two methods of visual inspection (ie, Nyvad and ICDAS), and both presented good reproducibility and validity in regards to identify and estimate lesion depth, which justifies their inclusion in the present study.

The QLF is a sensible quantitative clinical method with good repeatability and reproducibility, requiring a smaller number of participants (that may decrease the impact of dropout for longitudinal studies) compared to the visual analysis [14]. The QLF is able to quantify small mineral changes that might not be detectable in the visual inspection. However, the method is not reliable for detecting the portion of the subsurface lesion where minerals are gained or lost [14,20]. Therefore, we combined the visual inspection with a complementary method (QLF) to better detect and quantify carious lesions at a very early stage [24].

Despite our hypothesis on the effectiveness of the $TiF_4$ varnish, results obtained at the first month of this study demonstrate that the differences between $TiF_4$ and NaF did not reach significance, due to the slight changes in the visual analysis and in the fluorescence loss. If the $TiF_4$ varnish proves to be better at controlling dental caries compared to the NaF version by the end of our study, it shall be marketed and distributed at the individual level and to community programs, in order to prevent and treat dental carious lesions in children in the future.

## Acknowledgments

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## Conflicts of Interest

None declared.

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## Abbreviations

**$CaF_2$:** calcium fluoride
**CCD:** charged coupled device
**CNPq:** National Council for Scientific and Technological Development
**DMFT:** decayed, missing, filled teeth index
**DIAGNOdent:** Brazilian device used for measuring teeth demineralization in vivo.
**EMEF:** municipal school of fundamental education
**F:** fluoride
**FAPESP:** The São Paulo State Research Foundation
**ICDAS:** International Caries Detection and Assessment System
**MFP:** monofluoride phosphate

**NaF:** sodium fluoride
**NIH/3T3:** murine fibroblast lineage
**QLF:** quantitative light-induced fluorescence
**$SnF_2$:** stannous fluoride
**$TiF_4$:** titanium tetrafluoride
**WBPS:** Wong-Baker Pain Scale
**WS:** white spot area
**ΔF:** mean fluorescence loss
**ΔWS:** variation of the white spot lesion area
**ΔΔF:** variation of the mean fluorescence loss

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Protocol

# A Shared Decision-Making Tool to Prevent Substance Abuse: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Substance use disorder (SUD) affects over 20 million adults and costs over $700 billion annually in the United States. It is one the greatest health care challenges we face.

**Objective:** This research project seeks to enhance the standard practice of Screening, Brief Intervention, and Referral to Treatment (SBIRT) through a mobile solution easily incorporated into primary care that will promote shared decision making and increase referral and adherence to specialty care through continued follow-up care.

**Methods:** This research will conduct an Office of Management and Budget (OMB)–approved randomized controlled trial (RCT) in primary care and SUD specialty service providers. The RCT will recruit a total of 500 SUD patients. Recruited patients will be randomized into control and intervention arms. Both arms will take initial baseline and exit (30 days) surveys to evaluate self-reported substance use and specialty service utilization. The control arm patients will receive usual care. The intervention group patients will receive technology-enhanced SBIRT and a mobile follow-up program to track goals and substance use at home. The RCT tracks participants for 30 days after the primary care encounter. We will collect feedback from the patients during the 30 days and count the number of patients who use specialty care services in specialty care programs for tobacco, alcohol, and drug abuse (both from self-reporting and from the service providers).

**Results:** RCT and data collection are underway. We expect to report the data results in 2018.

**Conclusions:** We expect that significantly more intervention group patients will receive specialty SUD care within 30 days following the SBIRT encounter at the primary care clinic compared to the control group. We also expect that the intervention group patients will report a greater reduction in substance use and a greater drop in Drug Abuse Screening Test and Addition Severity Index scores within 30 days.

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**KEYWORDS**

SBIRT; substance abuse; SUD; primary care brief intervention

## Introduction

### Background

Substance abuse is a serious public health concern in the United States, with severe medical, legal, and economic consequences. In 2012, an estimated 23.9 million Americans aged 12 years or older had used an illicit drug or abused a psychotherapeutic medication (such as a pain reliever, stimulant, or tranquilizer) in the past month, and 17.7 million Americans were dependent on or abused alcohol [1]. Recently, there has been a dramatic increase in the misuse of prescription medications, with emergency department visits involving their abuse increasing by 98.4% between 2004 and 2009 and associated increases in overdose deaths [2]. Abuse of alcohol and illicit drugs is costly, with over $30 billion in health care–related costs for alcohol abuse and $11 billion for illicit drugs [3]. Unfortunately, few needing treatment for drug or alcohol abuse get the treatment they need in a timely manner. According to the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health, 23.5 million people aged 12 years or older needed treatment for an illicit drug or alcohol abuse problem in 2009, but of these, only 2.6 million received treatment at a specialty facility [4].

### Substance Abuse Screening and Treatment in Primary Care

The health care landscape for patients with substance use disorders (SUDs) is changing. Recently, there has been a push to incorporate mental and behavioral health treatment into primary care, including screening and treatment for alcohol and drug dependence. The Patient Protection and Affordable Care Act, for example, designates mental health and substance use disorders as essential health benefits to be covered by health insurance plans [5]. The US Preventive Services Task Force (USPSTF) recommends screening for alcohol misuse for adults aged 18 years and older and has found sufficient evidence to suggest that brief behavioral counseling interventions in the primary care setting are effective in reducing heavy drinking episodes in adults engaging in risky drinking behaviors [6]. However, the USPSTF has not found sufficient evidence to assess whether screening for illicit drug use in the primary care setting is beneficial, primarily because the majority of studies have focused on patients already exhibiting clear symptoms of drug abuse [7]. Nevertheless, drug-specific pharmacotherapy and behavioral interventions such as brief motivational counseling for illicit drug use have been proven effective in the short-term [7], and the Centers for Medicare and Medicaid Services provides reimbursement to providers who implement the Substance Abuse and Mental Health Services Administration Screening, Brief Intervention, and Referral to Treatment (SBIRT) model in their practices [8]. The SBIRT model is an evidence-based practice designed to identify, reduce, and prevent problematic use, abuse, and dependence on alcohol and illicit drugs and can be incorporated into a primary care practice with the addition of screening questions into the health history questionnaire and training for health care providers to review the responses and identify high-risk patients.

The implementation of screening and intervention for substance use disorders, such as SBIRT, in the primary care setting has faced several challenges. In the past, physicians have cited barriers such as lack of time, lack of access to treatment, and lack of financial resources—both patient financial issues and reimbursement for the physician from health insurers [9]. The new health care changes will do a great deal in easing some of the cost-related barriers; however, physicians and other health care providers still experience barriers to screening and intervention for SUDs such as lack of time, lack of training, and unfamiliarity with screening tools [10]. Implementation of the SBIRT model has been met with similar concerns, with providers citing lack of time and competing medical priorities in the patient interview as barriers to its use [11].

### Shared Decision Making, Self-Monitoring, and Ecological Momentary Assessment

As the fields of mental health care and substance abuse treatment have changed, there has been a greater emphasis on the importance of patient autonomy and patient involvement in treatment. Active patient participation is a critical component of recovery and enhances the personal meaning, treatment satisfaction, and quality of life for the patient [12]. Shared decision making (SDM) is an interactive collaborative process between the health care provider and the patient in which the practitioner becomes a consultant to the patient, providing information, discussing options, and supporting the patient's autonomy as they mutually decide on treatment options [13]. SDM has been found to be associated with improved outcomes in substance-dependent patients, including increased personal control and reduced drug use [14-15].

One important component of SUD treatment and prevention that contributes to patient autonomy is the use of self-monitoring logs, in which patients are directed to record details about their alcohol and drug use, including their moods and the situations in which use occurred. This practice serves multiple purposes—it provides an opportunity for the patients to talk openly and honestly about their alcohol and drug use, it encourages patients to take responsibility for their own behavior change, and it provides information that providers can use to observe patterns and give feedback about changes in alcohol and drug use over time [16]. Ecological momentary assessment (EMA) is a method in which data are collected in real-world environments as subjects go about their lives. Assessments focus on subjects' current state based on strategically selected moments (eg, occasions when subjects have craving). In EMA, subjects complete multiple assessments over time, providing a picture of how their experiences and behavior vary over time and across situations [17].

The self-monitoring aspect of SUD prevention and treatment lends itself perfectly to EMA, as EMA can minimize recall bias and provide a clear picture of the patterns involved in substance use [18]. Indeed, EMA has been used successfully in the field of substance use research. EMA methods have helped highlight the processes that drive drug use, cessation, and relapse and provide detailed information on mood variations and their relation to substance abuse that is not possible with other data collection methods [19]. Researchers have shown that EMA is

a feasible method for collecting data from methamphetamine-dependent outpatients [20], with recovering alcoholics [21], and with cocaine users [22].

### Technological Approaches to Substance Abuse Disorder Prevention, Screening, and Treatment

In an effort to overcome some of the barriers to screening and prevention of substance use disorders, many researchers have begun to explore novel approaches using Web-based and mobile technology. These mobile technologies often focus on self-help and self-monitoring as an adjunct for traditional, face-to-face treatment in a clinician office setting and in doing so, reduce the time and cost burden on the health care provider.

While the quality of evidence is often inconsistent, there is promising research to indicate that interventions using Web-based or mobile technology for alcohol and other substance abuse can be effective [23-26]. Most recently, brief intervention applications related to substance use have focused on young adult populations and risky drinking behavior. While some studies have shown potential in reducing drinking outcomes [27-28], more research is necessary to determine overall effectiveness and whether the same strategies could be effective for substances other than alcohol. Features such as tailored feedback have shown to be more effective than similar programs without feedback [29], and interventions that combine self-administered therapy in conjunction with therapist-directed interventions show greater reductions in addictive behavior [30]. Future research is needed to determine to what extent such applications can help the primary care physician integrate SBIRT and other substance use screening models into their practice while providing significant outcomes in patient behavior.

## Methods

### Objectives

The main objective of this research will be to conduct an Office of Management and Budget (OMB)-approved randomized controlled trial (RCT) in primary care and SUD specialty service providers affiliated with Washington State University. The RCT will recruit a total of 500 SUD patients from University Health District (UHD) Clinic, a primary care clinic affiliated with the university. The patients will be randomized to receive usual SBIRT care and technology-enhanced SBIRT care. High-risk SUD patients will be referred to university-affiliated specialty providers in the area.

### Hypotheses

The RCT will address 2 primary hypotheses. Hypothesis 1 has 7 secondary hypotheses. Compared with the control group,

1. Significantly more intervention group patients will receive specialty SUD care within 30 days following the SBIRT encounter at the primary care clinic. The secondary hypotheses attempt to explain how and where the increased specialty care utilization occurs in the process.
    a. More intervention group patients are diagnosed with high-risk SUD.
    b. More intervention group patients are subsequently referred to specialty care at the end of the primary care clinic encounter.
    c. More intervention group patients are referred to specialty care during the 30-day following period due to failing to adhere to goals.
    d. Intervention group patients are more satisfied with the care they receive.
    e. Intervention group patients are more knowledgeable about SUD.
    f. Intervention group clinicians are more satisfied with the process.
    g. Intervention group clinicians spend less time on the SBIRT intervention and follow-up.
2. Intervention group patients will report a greater reduction in substance use and a greater drop in Drug Abuse Screening Test (DAST-10) and Addiction Severity Index (ASI) scores within 30 days.

### Trial Process

#### *Timing and Flow of the Randomized Controlled Trial*

We will conduct an RCT with 500 patients with SUD risk in the UHD Clinic, a large academic primary care provider affiliated with a major public university. Recruited patients will be randomized into control and intervention arms. Both arms will take initial baseline and exit (30 days) surveys to evaluate self-reported substance use and specialty service utilization. The control arm patients will receive usual care. The intervention group patients will receive technology-enhanced SBIRT with a mobile follow-up program to track goals and substance use at home. The RCT will be managed by a team of seasoned SBIRT and addiction researchers and practitioners at the research site.

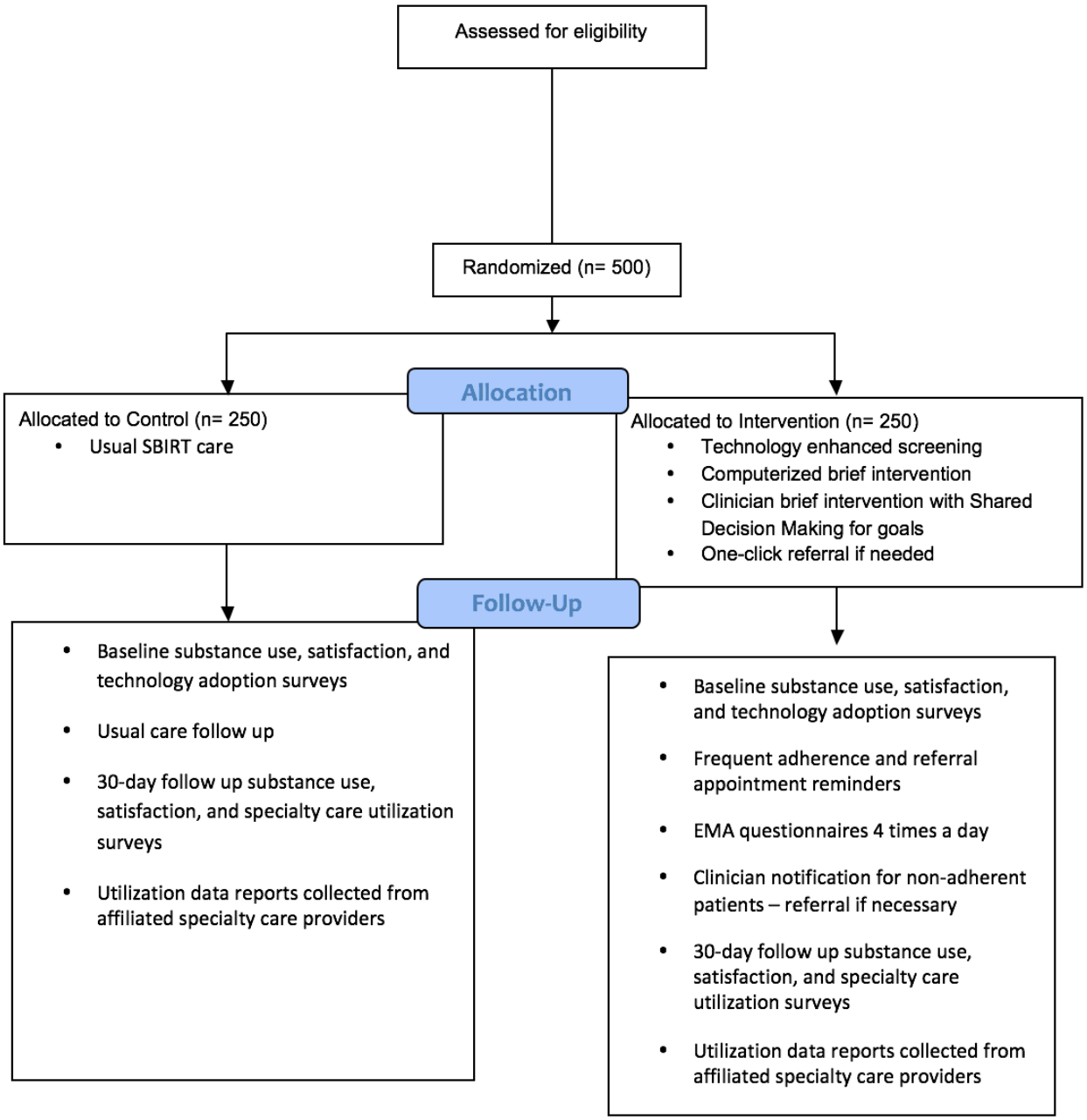
The RCT tracks participants for 30 days after the primary care encounter. We will collect feedback from the patients during the 30 days and count the number of patients who use specialty care services in specialty care programs for tobacco, alcohol, and drug abuse (both from self-reporting and from the service providers).

Since the clinical trial involves more than 9 human subjects, the RCT will be approved by the OMB as well as the university's Institutional Review Board (IRB), which is responsible for research in the university affiliated health care providers. Figure 1 displays the flow of participants.

#### *Recruitment and Consent*

RCT participants will be recruited from patients visiting the UHD Clinic for their regularly scheduled primary care visit. There will be a flyer in the reception area advertising the study. If a patient expresses interest in the study, a study coordinator will come out to greet the patient and lead him or her into a separate waiting room. The study coordinator will speak with the patient and go over the eligibility criteria (see Textbox 1).

**Figure 1.** Study flow diagram.




**Textbox 1.** Eligibility criteria for study.

Inclusion criteria:

- Aged 21 years and older
- University Health District Clinic patient
- Answered positively to single question drug use screener: “In the past year, have you used an illegal drug (including marijuana) or used a prescription medication for nonmedical reasons?”
- Willing to use personal mobile device for 30-day follow-up
- Consents to share personal data from specialty and primary care providers

Exclusion criteria:

- In the clinic for urgent conditions
- Cannot read or comprehend English at 6th grade level

Once the study coordinator decides that the patient is eligible to participate in the study, they will go over the informed consent together. The informed consent is approved by both OMB and the university's IRB. The patient will sign the form and receive a copy of the signed document. Once the patient consents, he or she becomes a study participant.

### *Randomization*

The study coordinator will then use an online random number generator (randomizer.org) to randomize the participant to either the control or intervention group.

The study administrator will then search for the patient name in the SBIRT application's admin console. The admin console searches the connected electronic medical record (EMR) records and retrieves the patient data to populate the study's database. The patient participant's arm will be noted in the database record.

### *Screening*

In this study, we will use a standard set of screening instruments for participants in both arms. Control arm participants will be screened using paper questionnaires. Intervention arm participants will be screened using the dynamically branching iPad mobile app (see Figure 2). Although our recruitment screener only asks about drug use, we will screen for tobacco, alcohol, and drug use in this study, as many drug users have tobacco and alcohol problems that potentially need counseling or treatment. The following screening instruments will be used:

- One question screeners for tobacco, e-cigarette, alcohol, and drug use
- My Own Health Record questionnaire for diet, exercise, and lifestyle
- Patient Health Questionnaire (PHQ-9) for depression screening
- Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire for patients positive for the 1-question alcohol screener
- DAST-10 questionnaire for patients positive for the 1-question drug use screener

### *Brief Intervention*

For control arm participants, usual care will be provided. Screening scores will be manually computed and entered into the EMR by a clinician trained in SBIRT. Clinician will deliver brief intervention to participants who score moderate to high risk in any substance without technology-enhanced intervention.

For intervention arm participants, the brief intervention in the primary care office will consist of 4 steps.

Participant will be asked to rate his or her willingness to quit for all his or her at-risk substances on the iPad app.

For the substance he or she is most likely to quit, the participant completes a brief 2-part intervention using an iPad app: watching a 3-minute educational video about the substance and its risks and completing an exercise to name the pros and cons of quitting this substance (Figure 3).

When the clinician comes into the room, the participant hands the iPad over to the clinician. The clinician now has an overview of screening results, readiness to change for at-risk substances, and the participant's personal pros and cons for the change. The clinician will conduct the brief intervention in person (Figure 4).

At the end of the brief intervention, the clinician will ask the participant to rate readiness for change again. They will work together to set up quitting or reducing use goals for at least one at-risk substance. At the end, the participant will sign on the screen and commit to the goals (Figure 5).

**Figure 2.** Dynamic branching screening tool, participant view.

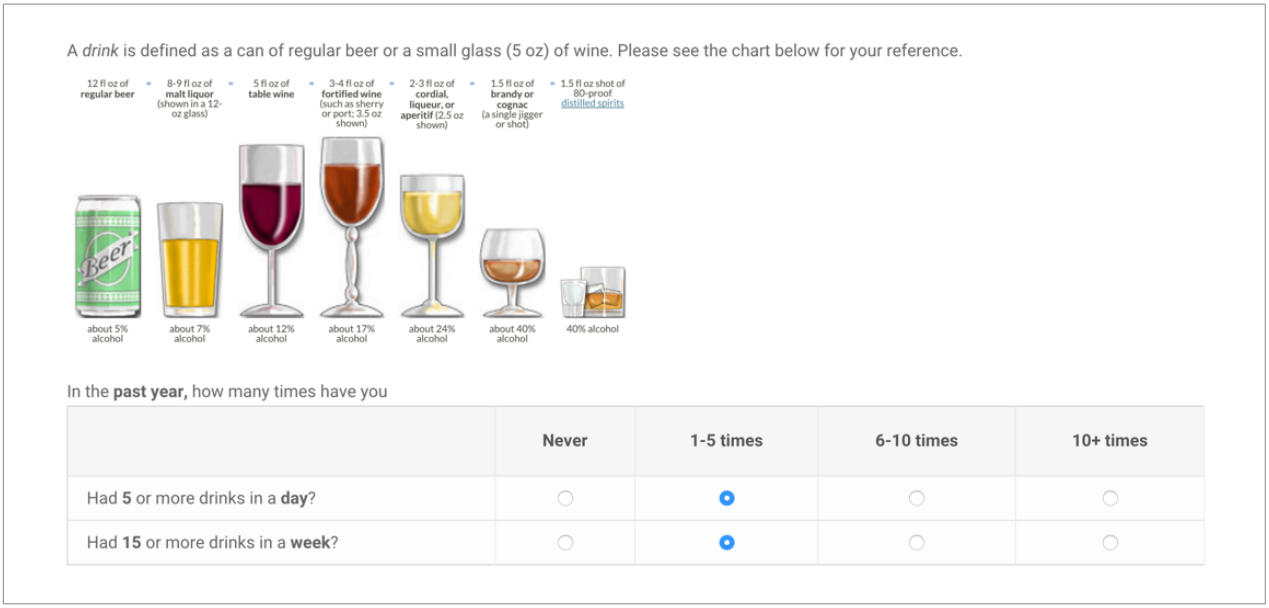


**Figure 3.** Brief intervention, participant view.

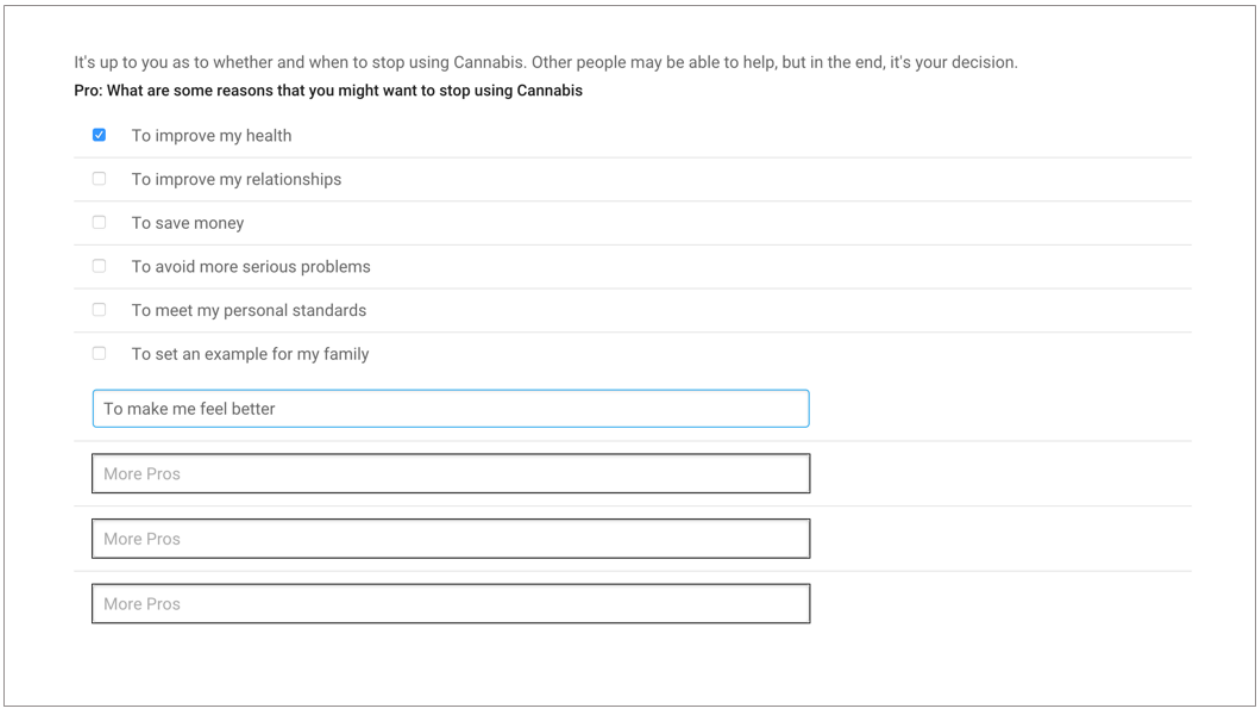
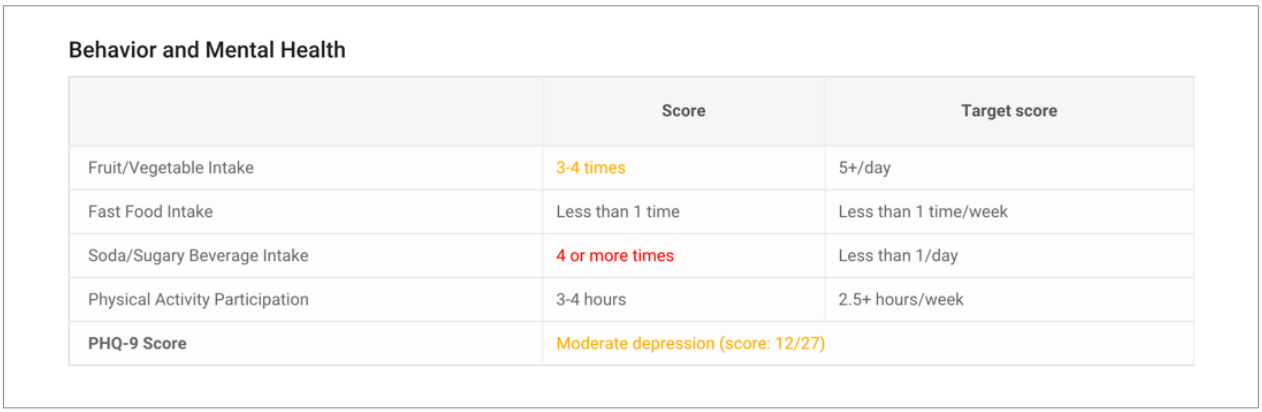


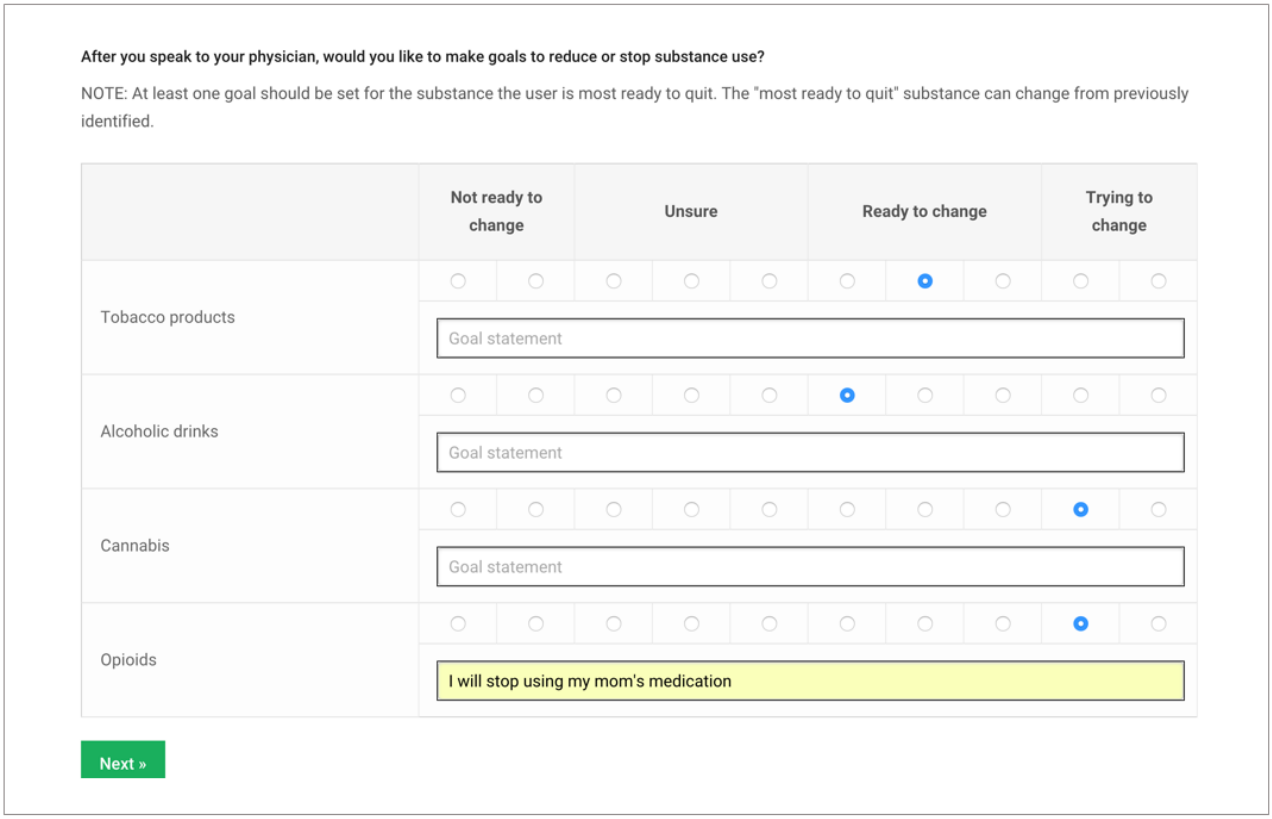

**Figure 4.** Brief intervention, clinician view.



Behavior and Mental Health

| | Score | Target score |
|---|---|---|
| Fruit/Vegetable Intake | 3-4 times | 5+/day |
| Fast Food Intake | Less than 1 time | Less than 1 time/week |
| Soda/Sugary Beverage Intake | 4 or more times | Less than 1/day |
| Physical Activity Participation | 3-4 hours | 2.5+ hours/week |
| **PHQ-9 Score** | Moderate depression (score: 12/27) | |

**Figure 5.** Setting goals, participant view.




### *Referral to Treatment*

If the participant is screened at high risk for any substance and the clinician and participant mutually agreed to specialty follow-up treatment, the clinician can easily refer the participant to a specialty treatment program affiliated with this study from the iPad app. The participant referral data is also integrated into EMR.

### *Follow-Up*

The control arm participants will receive no additional follow-up beyond usual care until the 30 days' end.

The intervention arm participants will receive a once-per-day reminder to answer daily follow-up questions. The questionnaire screen includes:

- Reminder for specialty care appointment the day before the appointment. The user can reschedule the appointment from the questionnaire screen. The questionnaire also asks whether the user went to the appointment on the day after.
- Adherence by participant to each of his or her own stated goals on that day.
- Using items from a drug use self-monitoring log developed by Sobell and Sobell [16], participants will be asked to report details of their drug and alcohol use within the last 24 hours, including drugs used, drinks had, cravings or urges to use drugs or drink alcohol, situations related to drug use (eg, patient was alone, in a social situation), and thoughts or feelings experienced when using drugs or during urges.

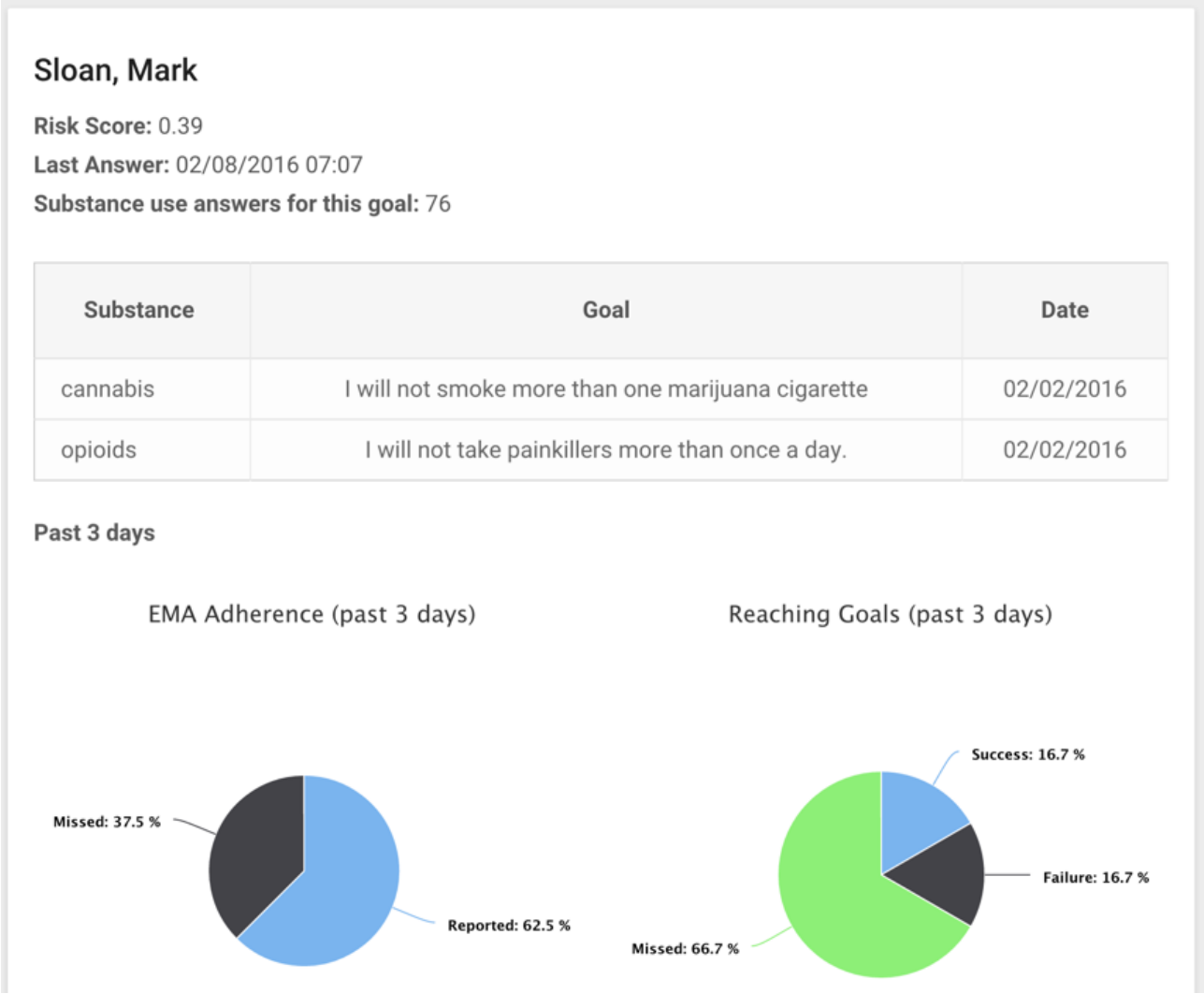
In the event of strong craving or substance use, the user is instructed to access an EMA screen bookmarked on his or her phone. The event-based EMA measures craving and surroundings at the time of craving or substance use.

- Adapted from the 3-item Opioid Craving Scale by McHugh et al [31], participants will be asked to rate on a scale from 1 to 10 how much they currently crave a drug, how strong their desire to use has been when something in the environment reminded them of the drug, and the likelihood that they would use the drug in a specific environment.
- EMA items on psychological mood are adapted from an EMA assessment conducted by Gwaltney et al [32] and are designed to assess the participant's affect state associated with substance use. The items ask participants to rate to what extent they feel happy, stressed, relaxed, bored, irritable, energized, and sleepy.

A risk score will be computed for every intervention participant every day. The score depends on the participant's questionnaire adherence, self reported goal adherence, and substance use. If a participant is at high risk, he or she may be offered the brief intervention video to watch again.

The risk score and individual participant summaries will be made available to the participant's clinicians, including a primary care physician and the study coordinator who also serves as a substance use coach, via a Web-based dashboard (Figure 6). If the clinicians determine that the participant's follow-up pattern or answers indicate high-risk substance use behavior, they may make additional referrals for the participant.

**Figure 6.** Web-based dashboard for intervention or additional referral, clinician view.




### *Surveys*

At the end of the primary care clinic visit, all participants will be asked to complete a survey about their experience with the process and their knowledge about SUDs. The intervention group patients will also be asked about their acceptance of the technology solution. The survey has the following components:

- A 19-item validated computer system usability questionnaire is used to evaluate a computer system's usability [33]. It also allows users to give free form answers on what he or she likes or dislikes about the system. We use it to evaluate the iPad tool in primary care clinics.
- A questionnaire based on the unified theory of acceptance and use of technology (UTAUT) by Venkatesh et al [34] is used to evaluate the technology solution's ease-of-use, perceived usefulness, and the user's social and facilitating conditions to predict the adoption of such technology solutions. The original UTAUT questions will be adapted to reflect our product.
- A 10-item validated patient satisfaction questionnaire will evaluate patient satisfaction with primary care providers [35].
- The ASI–Lite asks for drug use in the previous month, comorbid medical and mental illness, and social and legal outcomes related to drug use [36]. The ASI score is a quantitative measure of the user's substance use.

At the end of the 30-day follow-up period, all participants will be asked to complete the screening, patient satisfaction, and ASI questionnaires again. They will also be asked to report any health care service they received during the 30 days, including any specialty SUD services. They can complete those questions on a computer or on paper. A complete schedule of all participant surveys and questionnaires is listed in Table 1.

### *Clinician Interviews*

At the end of the study, all participating clinicians will be interviewed and debriefed on a one-to-one basis. Some clinicians will have worked on both arms of participants and can provide valuable insights on where the technology solution succeeded and where it still needs improvements. Clinician acceptance is a critical factor for successful commercialization and dissemination of the technology intervention in the future.

**Table 1.** Schedule of survey and questionnaire completion by study arm.

| | Intervention arm | | | | Control arm | | |
|---|---|---|---|---|---|---|---|
| | Screening | End of PCP[a] visit | Follow-up | 30 days | Screening | End of PCP visit | 30 days |
| One question screener | x | | | | x | | |
| My Own Health Record | x | | | | x | | |
| PHQ-9[b] | x | | | | x | | |
| AUDIT-C[c] | Optional | | | x | x | | x |
| DAST-10[d] | Optional | | | x | x | | x |
| Change readiness | | x | | x | x | | x |
| Technology acceptance (UTAUT[e]) | | x | | | | | |
| Computer system usability | | x | | | | | |
| Patient satisfaction | | x | | x | | x | x |
| Addiction Severity Index–Lite | | x | | x | | x | x |
| Goal adherence | | | Daily | | | | |
| Psychological mood | | | EMA[f] | | | | |
| Context/surroundings | | | EMA | | | | |
| Substance use | | | Daily | | | | |
| Substance craving scale | | | EMA | | | | |
| Referral adherence | | | Optional | | | | |
| Specialty care utilization | | | | x | | | x |

[a]PCP: primary care provider.

[b]PHQ-9: Patient Health Questionnaire.

[c]AUDIT-C: Alcohol Use Disorders Identification Test.

[d]DAST-10: Drug Abuse Screening Test.

[e]UTAUT: unified theory of acceptance and use of technology.

[f]EMA: ecological momentary assessment.

## Data Collection and Analysis

### *Data Sources*

In this RCT, we collect data from 2 primary sources: the participant self-reported data through surveys and questionnaires and clinic-reported utilization from reports.

### *Surveys and Questionnaires*

Each participant will complete multiple surveys and questionnaires at various points during this study (see Table 1).

### *Hypotheses Testing*

Since the hypotheses are primarily concerned about the observed differences between control and intervention arms, including referral rates, satisfaction level, knowledge level, and greater reduction in substance use, Student *t* tests will be used.

A chi-square test will be performed on the proportions of participants who receive specialty care to detect the significance in the difference between control and intervention arms. This test will be repeated for participants who have self-reported receiving specialty care. A chi-square test will be performed on the proportions of participants who receive specialty care referral at the end of the primary care encounter and who receive a specialty care referral during the 30-day follow-up period. For each question in the participant satisfaction survey and on the overall computed satisfaction and knowledge score, we will perform a *t* test for the answer's mean value. Clinician interview results will be evaluated qualitatively to determine clinicians' satisfaction with the solution.

Difference in differences regression tests will be performed on the differences in self-reported substance use amount and frequency and DAST-10 scores measured at baseline and 30 days of the study. The correlation coefficients and their confidence levels will be computed. These tests detect difference in drug use changes from control and intervention groups during the intervention period.

### *Exploratory Analysis*

The exploratory analysis will be performed to gain further insights into additional data collected from the intervention participants. We will perform linear regression analysis to associate model technology acceptance factors with the participant's inclination to adopt the technology in the future. This result will inform us on which factors are most important to patients for this tool. We will perform linear regression analysis to associate observed follow-up metrics such as ratio

of missed questionnaires, substance use, and substance craving with participant referral decisions during the follow-up period. The result will inform a model to predict high-priority patients for referral in future interventions.

The association between mood and substance use and craving is inconclusive in existing research literature. In this project, we will collect self-reported mood and substance use/craving data from all intervention arm participants. We will group substance use/craving data into positive and negative mood categories and compare the differences using chi-square or *t* tests of the mean methods as appropriate. Furthermore, we can apply multilevel (also called mixed effect) regression models to EMA data. Mixed effects regression models can be applied to normally distributed continuous and categorical outcomes and nonnormally distributed outcomes such as counts with a Poisson distribution. Mixed effects models are also robust to missing data because time is treated as a continuous variable, the implication being that subjects are not assumed to have the same number of assessments at the same time points. To evaluate the relationship between craving, mood, and substance use, we used a generalized linear mixed model with a binary logistic response function of substance use. Fixed effects included craving for the substance and mood states.

### *Power Calculation*

For primary hypothesis 1, we will perform a chi-square test to evaluate the difference in proportions of participants who receive specialty care in the 2 arms. We estimate that SBIRT intervention [37] could result in 10% to 30% of patients receiving specialty care. We computed power using the following assumptions: chi-square for 2 proportions, 2 samples, and 2-sided test; type 1 error rate of 5%; power of 0.9; control arm with 20% participants receiving specialty care; intervention arm with 35% participants receiving specialty care; and same number of participants in control and intervention. A sample of 197 participants in each of arms will be sufficiently powered to detect such differences between control and intervention arms.

For primary hypothesis 2, we assume that both arms start with the same levels of substance use. Therefore, to test the hypothesis, we will test the mean substance use levels at 30 days for both arms. We computed power for the sample *t* test of the mean using the following assumptions: 2-tailed *t* test for the mean of 2 samples; type 1 error rate of 5%; power of 0.9; medium Cohen effect size; and same number of participants in control and intervention. A sample of 86 participants in each arm will produce sufficient power. Based on the above calculation and considering up to 20% attrition, a sample of 500 total participants will have sufficient power to test both primary hypotheses.

## Results

In phase 1 of this project, we developed and piloted a prototype solution to enhance SBIRT in primary care office and follow up patients intensively for 30 days. The prototype proved feasibility of the technology, including the innovative user interface, dynamic screening logic, computerized brief intervention, shared-screen SDM, and bidirectional EMR connectivity. Our pilot clinicians and patients overwhelmingly determined the tool to be easy to use and not intrusive to normal clinical workflows. Patients with low-risk SUDs were also able to adhere to the shared goals during the follow-up period.

In phase 2 of this project, we supposed that, compared with the control group participants at 30 days, (1) significantly more intervention group patients will receive specialty SUD care and (2) intervention group patients will report a greater reduction in substance use and a greater drop in DAST-10 scores. Our secondary hypotheses include that intervention group patients receive more referrals at the primary care clinic and during 30 days of follow-up, and both clinicians and patients are more satisfied with the technology-enhanced solution.

Data collection for phase 2 is well underway. We expect to report the data analysis results in early 2018.

## Discussion

### Summary

In this project, we propose to demonstrate a technology-enhanced SBIRT process that builds on SDM principles. Our solution provides automated implementation of validated screening measures in an easy-to-use mobile device–based screening tool to be used inside the primary care office. Since it is fully integrated in the clinicians' workflow, the solution improves reliability and efficiency and provides automated EMR documentation. The ease of use and documentation could increase SBIRT-related reimbursement and could increase the number of patients screened for SUDs in primary care settings.

Evaluating change readiness and setting goals are key elements of all cognitive behavioral therapy–based interventions [3]. SDM showed significant improvements with regard to drug use behavior or depression compared with standard decision-making processes [15,38]. Using digital technologies on a shared mobile device inside a primary care office could improve the collaboration between clinician team and the patient, making it easier to use SDM in practice.

Our solution provides ready access to standardized preferred referral resources to use with patients during the brief intervention and/or referral to treatment stages of the process. The primary care provider can easily identify the appropriate referral target, consult with the patient, and complete the referral on the spot. By integrating the primary care and specialty care EMR systems, our system enables providers to follow-up with at-risk patients and potentially create risk profiles for nonadherent patients for early intervention.

Traditional SBIRT practice happens during the clinical encounter, but evidence suggests that following up with patients at home and repeated intervention will improve patient outcomes [39]. Furthermore, the follow-up period provides additional opportunities to identify at-risk patients for referrals if the patient fails to adhere to the shared goals.

## Conclusion

A key objective of this project is an expected deliverable of the National Institute on Drug Abuse: "Demonstrate efficacy to increase significantly the proportion of primary care patients who are successfully linked to and receive indicated follow-up specialty SUD care." This research project seeks to enhance the standard practice of SBIRT through a mobile solution easily incorporated into primary care that will promote SDM and increase referral and adherence to specialty care through continued follow-up care. By conducting an OMB-approved RCT in primary care and SUD specialty service providers, we seek to prove that the enhanced digital SBIRT approach will increase referral from primary care, reduce substance use in the intervention population, and improve SUD patient outcomes compared to the control group.

## Conflicts of Interest

JMY is the CEO of Ringful Health, creator of the software tool used in the study, and could benefit from its commercial use.

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## Abbreviations

**ASI:** Addiction Severity Index
**AUDIT-C:** Alcohol Use Disorders Identification Test
**DAST-10:** Drug Abuse Screening Test
**EMA:** ecological momentary assessment

**EMR:** electronic medical record
**IRB:** Institutional Review Board
**OMB:** Office of Management and Budget
**PHQ-9:** Patient Health Questionnaire
**RCT:** randomized controlled trial
**SUD:** substance use disorder
**SBIRT:** Screening, Brief Intervention, and Referral to Treatment
**SDM:** shared decision making
**UHD:** university health district
**USPSTF:** US Preventive Services Task Force
**UTAUT:** unified theory of acceptance and use of technology

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Protocol

# Smartphone App Using Mindfulness Meditation for Women With Chronic Pelvic Pain (MEMPHIS): Protocol for a Randomized Feasibility Trial

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## Abstract

**Background:** Female chronic pelvic pain (CPP) is defined as intermittent or constant pelvic or lower abdominal pain occurring in a woman for at least 6 months. Up to a quarter of women are estimated to be affected by CPP worldwide and it is responsible for one fifth of specialist gynecological referrals in the United Kingdom. Psychological interventions are commonly utilized. As waiting times and funding capacity impede access to face-to-face consultations, supported self-management (SSM) has emerged as a viable alternative. Mindfulness meditation is a potentially valuable SSM tool, and in the era of mobile technology, this can be delivered to the individual user via a smartphone app.

**Objective:** To assess the feasibility of conducting a trial of a mindfulness meditation intervention delivered by a mobile phone app for patients with CPP. The main feasibility objectives were to assess patient recruitment and app adherence, to obtain information to be used in the sample size estimate of a future trial, and to receive feedback on usability of the app.

**Methods:** Mindfulness Meditation for Women With Chronic Pelvic Pain (MEMPHIS) is a three-arm feasibility trial, that took place in two hospitals in the United Kingdom. Eligible participants were randomized in a 1:1:1 ratio to one of three treatment arms: (1) the intervention arm, consisting of a guided, spoken mindfulness meditation app; (2) an active control arm, consisting of a progressive muscle relaxation app; and (3) usual care (no app). Participants were followed-up for 6 months. Key feasibility outcomes included the time taken to recruit all patients for the study, adherence, and estimates to be used in the sample size calculation for a subsequent full-scale trial. Upon completion of the feasibility trial we will conduct focus groups to explore app usability and reasons for noncompliance.

**Results:** Recruitment for MEMPHIS took place between May 2016 and September 2016. The study was closed March 2017 and the report was submitted to the NIHR on October 26, 2017.

**Conclusions:** This feasibility trial will inform the design of a large multicentered trial to assess the clinical effectiveness of mindfulness meditation delivered via a smartphone app for the treatment of CPP.

**Trial Registration:** ClinicalTrials.gov: NCT02721108; https://clinicaltrials.gov/ct2/show/NCT02721108 (Archived by WebCite at http://www.webcitation.org/6wLMAkuaU); BioMed Central: ISRCTN10925965; https://www.isrctn.com/ISRCTN10925965 (Archived by WebCite at http://www.webcitation.org/6wLMVLuys)

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**KEYWORDS**

randomized controlled trial; pelvic pain; chronic pain; mobile applications; mindfulness; meditation

## Introduction

Female chronic pelvic pain (CPP) is defined as intermittent or constant pain in the lower abdomen or pelvis of a woman for at least 6 months, which is not exclusively associated with menstruation or intercourse, and not associated with pregnancy [1]. CPP affects up to 24% of women worldwide [2], accounts for 20% of gynecological clinic referrals in the United Kingdom [3], and has a considerable impact on patients' quality of life and their income. There are no recent estimates of the cost of CPP, but endometriosis-associated pain alone costs the United Kingdom economy £8.2 billion per year in treatment, loss of work, and health care costs [4], so the cost of general CPP is likely to be even higher. Despite costly interventions, CPP is often resistant to surgical and medical treatment. Both psychosocial causes (such as a history of sexual abuse) and somatic causes (eg, endometriosis, pelvic inflammatory disease, bladder pain syndrome) can contribute to CPP [1]. High levels of depression and anxiety are commonly associated with CPP, but are often not addressed in this population [5].

These multifactorial causes require a multidimensional approach, which is not routinely offered in gynecology clinics [6]. Evidence from randomized controlled trials (RCTs) suggests that a holistic approach using psychological interventions may be superior to primary surgery [7]. Although psychological treatment is provided across the National Health Service (NHS), mostly in the context of the primary care program *Improving Access to Psychological Therapies*, there are problems with capacity, waiting times, and the overall number of patients that are able to access services. Alternatively, supported self-management (SSM) is now recognized as a tool that empowers patients to better cope with their condition [8].

Mindfulness-based therapy is currently creating lively research interest. Two recent systematic reviews report positive effects on somatization disorders [9] and psychological stress [10]. A further systematic review carried out by our research team [11], which examined 15 RCTs for online mindfulness meditation, found small but significant beneficial impacts on depression, anxiety, well-being, and mindfulness, and a moderate effect on stress, with guided programs proving more effective than unguided ones. We are only aware of one ongoing randomized Danish study of mindfulness in patients with endometriosis-specific CPP (NCT02761382).

Our review also found that mindfulness meditation to treat CPP had a promising effect on patient well-being [11], as demonstrated in pilot studies on CPP and larger RCTs on other types of chronic pain. We are therefore investigating the feasibility of a full RCT for mindfulness in CPP, as mindfulness has great potential as a self-management tool that could be used as part of a holistic approach to CPP.

More convenient delivery methods have been called for as an alternative to the 8-week face-to-face sessions required for the standard mindfulness based stress reduction (MBSR) courses [12]. During a patient and public involvement (PPI) session we held to help design our study, CPP patients expressed a preference for receiving the intervention through a smartphone app, as it is portable and could be accessed when and where they liked.

The systematic review showed that mindfulness meditation helps chronic pain patients accept pain better and helps to alleviate anxiety and depression [11], which are particularly common in this population [5]. One of the suggested mechanisms of mindfulness meditation is the uncoupling of sensory aspects from the evaluative and emotional aspects of pain through mindful awareness and meditation. Unlike cognitive behavioral therapy, which is goal oriented, mindfulness meditation relies on nonjudgmental observation. By distancing themselves from painful sensations and thoughts, instead of being alarmed, patients can achieve greater acceptance of chronic pain rather than permanently wanting to control it.

### Systematic Review

Our systematic search and review of the literature on mindfulness meditation in CPP (July 2013; updated May 2017) was designed to investigate prior research in the area before commencing our study. Our systematic review was conducted in line with current standards [13]. We searched MEDLINE (via OVID), EMBASE, PsychINFO, and AMED without language restrictions from database inception to July 2013, and subsequently updated the search in May 2017. The databases were searched for relevant studies using the following key words and word variants: *chronic pain* or *pelvic pain*, and *meditation* or *mindfulness* or *Vipanassa* or *mindfulness based stress reduction* or *mindfulness based intervention* or *mindfulness based therapy*. The reference lists from the obtained articles were examined for additional articles. We also hand-searched all relevant systematic reviews and, if necessary, we approached the authors for missing relevant information.

The first search identified two small, nonrandomized pilot trials investigating the effect of mindfulness meditation on pelvic pain (n=22) [14], and endometriosis (n=10) in particular [15]. Both small studies were uncontrolled. In the study on CPP, significantly improved scores were reported for daily maximum pain, physical function, mental health ($P$=.01), and social function [14]. The mindfulness scores improved significantly in all measures [14]. In endometriosis patients, significant

improvements were reported for bodily pain, general health, and vitality [15].

Since that time, two more studies have been published. Kanter et al investigated the effect of mindfulness compared to usual care in an RCT of patients with bladder pain syndrome (n=20) [16]. Outcome measures relating to empowerment and self-management improved significantly [16]. A small pilot study on military women with CPP (n=15) showed a nonsignificant reduction in pain and increase in mindfulness measures [12]. The authors of this study called for simpler formats of teaching mindfulness than the 8-week standard MBSR, which four studies used [12].

Given this paucity of data on mindfulness in CPP, we expanded our systematic review of mindfulness meditation to include its use in other chronic pain conditions (back pain, headaches, fibromyalgia, and diabetic neuropathy), as we assumed that any benefits in these conditions might also be seen in CPP. Previous systematic reviews of these conditions had a number of limitations, such as not reporting effect sizes [17-19].

We identified 534 relevant citations, and 9 RCTs [20-28] were included in the review [11]. Most studies were of moderate quality, but sample sizes were generally small (from 65 to 259 women). Our results showed mindfulness-based meditation reduced depression levels in chronic pain patients (standardized mean difference [SMD] -0.31; 95% CI -0.52 to -0.10; $I^2$=0%) and anxiety (SMD -0.21; 95% CI -0.45 to 0.03; $I^2$=0%). Pain acceptance was also improved (SMD 0.34; 95% CI 0.09-0.59). No significant changes were seen in quality of life, anxiety, pain scores, or the emotional response to pain.

There are few published robust trials of apps to assist better self-management of chronic conditions. A Cochrane review of apps for asthma found only two studies and concluded there was insufficient evidence to advise patients on their usefulness [29]. Although CPP is as common as back pain and asthma [30], there are no RCTs that are investigating mindfulness meditation in CPP. Mindfulness meditation had shown a promising effect on patient well-being in uncontrolled pilot studies on CPP and larger RCTs on other types of chronic pain [11]. Given the high levels of depression and anxiety in CPP patients, combined with difficult access to psychological treatments, this approach could address a gap both in knowledge and patient care.

### Development of the Mindfulness Meditation App Module

Headspace [31], a company that had already developed and successfully established a mindfulness meditation app, was approached to develop a module for meditation for chronic pain. This module was incorporated into the existing library of app content. The pain module can be accessed after participants have completed the 10-day foundation program.

### Aims and Objectives

The overall aim of this study is to assess the feasibility of implementing a full scale, multicenter RCT to test the efficacy of a mindfulness meditation intervention delivered by a mobile phone app for patients with CPP. The primary objectives are: (1) to provide feasibility data for a large multicenter RCT aimed at rigorously testing mindfulness meditation in patients with CPP (the full-scale trial will assess the effectiveness of the mindfulness meditation app in patients with CPP in a national multicenter RCT); and (2) to determine whether this app can be seamlessly integrated into clinical practice, especially CPP pathways.

## Methods

### Design

Mindfulness Meditation for Women With Chronic Pelvic Pain (MEMPHIS) is a three-arm randomized feasibility trial. Approval was received by Camden and Kings Cross Ethics Committee in February 2016 (15/LO/1967).

#### *Inclusion Criteria*

To be eligible for the MEMPHIS study, women were required to meet the following criteria: (1) aged 18 years or over; (2) have organic and nonorganic CPP lasting for 6 months or more; (3) be capable of understanding the information provided, and be able to understand simple English as is used in the app; and (4) give written informed consent.

#### *Exclusion Criteria*

Patients who met the following criteria were ineligible to participate: (1) no access to a personal computer or smartphone, or (2) current users of the Headspace app content available to the public.

#### *Study Design*

MEMPHIS is a three-arm randomized feasibility trial. All eligible women referred to the CPP clinics at the Royal London and Whipps Cross Hospitals (both new and existing patients) were approached to take part in the study. The setting of the study was NHS Tertiary care hospitals. After informed consent, we randomized eligible women in a 1:1:1 ratio (30 participants in each group) to one of the three treatment groups: (1) *Intervention*, consisting of 60 days of the app delivering mindfulness meditation content (in addition to usual care); (2) *Active control*, consisting of 60 days of the app delivering progressive muscle relaxation content (in addition to usual care); and (3) *Treatment as usual* consisting of usual care. See Figure 1 for a flow chart of the study.

### Outcomes

#### *Feasibility Outcomes Collected From Participants*

Several parameters were collected regarding the participants (Textbox 1).

#### *Participant Focus Groups*

Usability and integration into clinical practice were explored in two postintervention focus groups at each recruiting site: one for each app group. All participants allocated to each app group were invited to a session to take place in a private room at or near the clinic they were recruited from. We aimed to recruit approximately 15 app participants from the study participants. We offered a telephone interview as an alternative to any participant who was unable to attend their focus group.

Discussions were structured around the app System Usability Scale (SUS) and additional questionnaire, and were expected to take two hours to complete. Discussions were recorded and literal themes on integration and usability will be evaluated for in-depth information. This information will be considered, as well as adherence to the app, as an indirect measure of acceptability. We will determine primary and secondary outcomes of interest, from the perspective of patients, for a full-scale trial. This aim will involve asking participants who were randomized to the app groups to discuss and prioritize outcomes. Obstacles to recruitment will also be explored.

### *Health Care Practitioner Focus Groups*

The health care practitioners that were involved with the trial were invited to attend focus groups. A purpose-made topic guide was used to structure focus groups with service providers, which were held in private rooms at the university or clinic, and based on the Normalization Process Theory toolkit [34] and Diffusion of Innovations Theory [35]. Topics were used as a prompt by the facilitator to identify any emergent or residual problems that might act as a barrier to use and effectiveness of the app in the RCT, and implementation into practice.

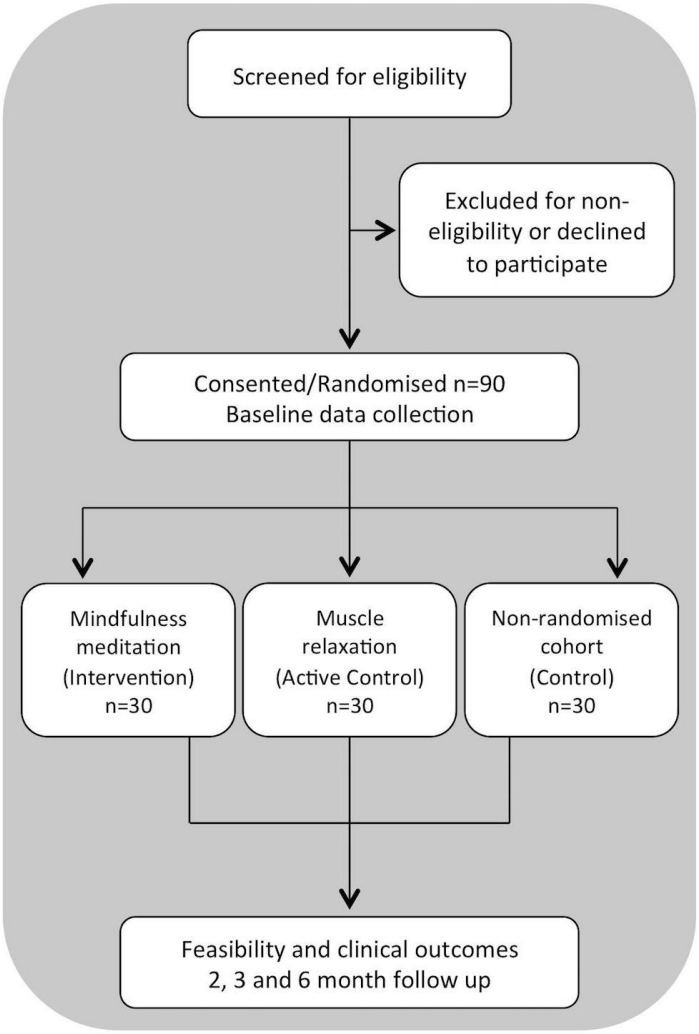
The service providers were asked to consider their role and their organization, to suggest and discuss any issues related to integration, and to also suggest potential solutions (unlike conventional qualitative research focus groups). Discussions considered relative advantage versus existing practices, compatibility with existing practices, simplicity and ease of integration, trialability and reinvention of the process, feedback (eg, can clinicians see that patients benefit?), and peer-to-peer networking. We will use our findings to develop our integration approach to be further explored in the subsequent full trial. Obstacles to recruitment will also be explored.

### *Clinical Outcomes*

Clinical outcomes measures have been selected based on the findings of our systematic review [11] and for their relevance to women with CPP. All scales are validated. We will use the clinical outcomes listed in Textbox 2.

All clinical outcomes were self-reports completed by study participants at baseline, 60 days, 3 months, and 6 months postrandomization (Multimedia Appendix 2).

**Figure 1.** Participant flow showing eligibility, enrolment, randomization and follow-up.



**Textbox 1.** Feasibility outcomes collected from patients

- Time taken to recruit all patients for the study (measured from the day recruitment opens until the day the 90th patient was randomized).
- Estimates to be used for the sample size calculation of the full-scale randmoized control trial:
  - The estimated standard deviation for pain acceptance (as measured by the Chronic Pain Acceptance Questionnaire [CPAQ-8] [32])
  - The dropout rate defined by the proportion of participants who never return or answer a follow-up questionnaire at 6 months postrandomization
  - The proportion of participants who do not return a follow-up questionnaire, but do answer the questionnaire by phone at 6 months postrandomization
- Patient adherence to app use will be investigated using the following outcomes:
  - Number of days (within the first 60 days from randomization) a patient has used the app. The definition of app use was originally defined as having completed 50% of a session. This definition was changed to 90% of a session during the trial (see Multimedia Appendix 1).
  - Whether the patient has used the app on 22 or more days within the first 60 days following randomization
  - Number of weeks (within the first 8 weeks from randomization) during which a patient has used the app on three or more days
  - Whether the patient has used the app on three or more days in 6 or more weeks (within the first 8 weeks from randomization)
  - Whether the patient has used the app on 22 or more days within the first 60 days from randomization, and used the app on three or more days in 6 or more weeks within the first 8 weeks from randomization
- Usability of the app will be measured by:
  - The System Usability Scale [33]
  - A purpose-made nonvalidated questionnaire (Multimedia Appendix 2) developed from patient and public involvement discussion and exploring the issues this group suggested women with chronic pelvic pain might have when using the particular app chosen. For example, we consider its modular format as well as the fit within daily activities, as we had been told from public and patient engagement work that this might be a problem for working women.

**Textbox 2.** Clinical outcomes

- Pain acceptance score (as measured by the Chronic Pain Acceptance Questionnaire [CPAQ-8] [32])
- Quality of life score, Physical Functioning subscale (as measured by the RAND 36-item Short Form health survey [SF-36] [36])
- Quality of life score, Social Functioning subscale (as measured by the RAND SF-36)
- Quality of life score, Pain subscale (as measured by the RAND SF-36)
- Quality of life score, General Health subscale (as measured by the RAND SF-36)
- Depression score (as measured by the Hospital Anxiety and Depression Scale [HADS] [37])
- Anxiety score (as measured by the HADS)
- Mindfulness score (as measured by the Cognitive and Mindfulness Scale - Revised [CAMS-R] [38])
- Pain related disability score (as measured by the Chronic Pain Grade [CPG] disability subscale [39])
- Self-efficacy score (as measured by the Pain Self-Efficacy Questionnaire [PSEQ] [40])
- Sexual Health Outcomes score (as measured by Sexual Health Outcomes in Women Questionnaire [SHOW-Q] [41])
- Subjective outcome score (as measured by Measure Yourself Medical Outcome Profile [MYMOP] [42])

## Recruitment

### *Informed Consent Procedures*

Women were made aware of the study by health care professionals and through promotional materials. Potentially eligible patients received the Patient Information Sheet (PIS) and were given adequate time (at least 24 hours) to consider the trial. Health care professionals and researchers screened eligibility at the time of outpatient clinic visits before offering participation. Women not interested or not eligible were recorded in a screening log. Eligible patients who were seen in clinics other than pelvic pain and endometriosis clinics were given the PIS and contact details for the researcher so they could benefit from participating in MEMPHIS, if they so wished.

### *Randomization Procedures*

After providing informed consent, patients were randomized (maintaining full allocation concealment) in a 1:1:1 ratio to one of the three treatment groups, using permuted blocks without stratification. Block sizes were 27, 30, and 33. Randomization was performed using a centralized Internet service, hosted by the Pragmatic Clinical Trials Unit at Queen Mary University of London.

### *Blinding Following Allocation to Study Arm*

The participant and recruiting staff were aware of allocation to either the *Treatment as usual* group or one of the app groups. The participant and recruiting staff were, however, blinded to allocation to the *Intervention* or *Active Control* app groups.

To preserve blinding of participants within the two app arms of the study, each group used the same app and hearing instructions for the same duration, delivered by the same narrator. Only the content of the instructions differed. In addition, the PIS and consent forms did not explicitly refer to "mindfulness meditation" or "progressive muscle relaxation."

Data on whether any unblinding occured with recruiting staff, or if participants were aware of their allocation, were collected immediately after randomization and after 6 months, respectively. Statisticians will be blinded to individual treatment allocations until required for the final analysis.

## Interventions

The researchers encouraged participants to aim to use the app they were randomized to daily, for as many sessions as they felt comfortable with.

### *The Active Intervention: Mindfulness Meditation App*

The meditation content was delivered via a structured and progressive course, layering in new techniques and concepts over successive sessions. The course was created and narrated by a former monk, Andy Puddicombe, drawing on a secularized version of the techniques he was taught over 10 years in monasteries around the world.

The techniques used in the *Intervention* are shown in Table 1. The first 30 days covered basic techniques, assuming no previous experience of meditation. The second 30 days focused specifically on the use of these techniques with respect to pain. The duration of individual sessions built over time. Days 1-10 involved 10 minutes/day, days 11-20 involved 15 minutes/day, and days 21-60 involved 20 minutes/day. Headspace collected data on adherence to the active intervention.

### *The Active Control App and the Treatment As Usual Group*

The Active Control group used the same app, but the app was configured so that they heard a series of nonmeditative progressive muscle relaxation instructions, also narrated by Andy Puddicombe. These sessions were identical every day, except that their duration increased to mirror the increasing duration of the meditation content being listened to by the Intervention group.

In this way, both Intervention and Active Control groups used the same app, and hearing instructions for the same duration, delivered by the same narrator. Only the content of the instructions differed. Headspace collected data on adherence to the active control.

The control group consisting of treatment as usual (watch and wait, medication, and/or surgery) was included to investigate if any app intervention makes a difference to well-being and to ascertain dropout rates for the full-scale trial in patients who perceive that they are receiving no intervention.

## Schedule of Assessment

Health outcome measures were collected at baseline and immediately after the intervention at 60 days, 3 months, and 6 months. The time points were chosen to obtain information close to finishing the intervention to assess immediate effects, at a mid-point, and after 6 months to assess longer-term effects. App satisfaction/usability measures were collected immediately after the intervention (at 60 days) from app participants. Patients entered the data on paper questionnaires, which was transferred into a purpose-built electronic database. Data management will be carried out using OpenClinica Enterprise v3.12.2.

As an incentive to complete and return the patient questionnaires, a £5 shopping voucher was sent in the post with each follow-up questionnaire, alongside a stamped addressed envelope. In the case that a questionnaire was not received, participants were sent a text message reminder. Nonresponders were then contacted by telephone in order to collect a subset of the questionnaire.

Participants allocated to the app groups were asked for permission to elaborate on the open comment boxes about app satisfaction, and discuss and prioritize clinical outcomes in two focus groups. The focus groups were held after the 6-month follow-up point finished. If participants were unable to attend a focus group, they were given the option to take part in a phone interview.

## Statistical Analyses

A full analysis plan can be found in Multimedia Appendix 3. Thirty participants were recruited to each of the three treatment groups, giving a total of 90 participants. As this is a feasibility study, we have not performed a sample size calculation based upon the power to detect a significant treatment effect on a clinical outcome. However, 90 participants should provide a reliable estimate for the standard deviation (SD) of the primary clinical outcome (likely to be pain acceptance) [43,44], which can be used to inform the sample size calculation of the main trial. Statistical analyses will be carried out using Stata 14.

**Table 1.** Meditation content over 60-day progressive course.

| Series | Techniques involved |
|---|---|
| Take 10/Foundation 1 (first 10 days) | Open monitoring, body scan, breath as anchor |
| Foundation 2 (days 11-20) | As above, plus intention and altruism |
| Foundation 3 (days 21-30) | As above, plus integration of mindfulness with daily activities |
| Pain series (days, 31-60) | As above, plus visualization and enquiry (insight/Tibetan Vipassana) |

### *Baseline*

Baseline variables will be summarized for each treatment group using descriptive statistics.

### *Analysis of Feasibility Outcomes*

The time taken to recruit all patients for the study and the number of participants recruited per month will be presented. An estimate of the SD of pain acceptance (CPAQ-8) in each treatment group at each follow up time point (60 days, 3 months, and 6 months) will be presented.

The proportion of patients in each treatment group who returned data at each follow-up time point (60 days, 3 months, and 6 months postrandomization) will be summarized. Summaries of baseline variables will be presented separately for patients who did and did not return data at each at the 6-month time point. Patient adherence outcomes and outcomes measuring usability of the app will be summarized separately for the intervention and active control treatment groups using descriptive statistics.

### *Analysis of Clinical Outcomes*

For each clinical outcome we will present the number of patients in each treatment group with an observed outcome at each follow-up time point, and the mean (SD) in each treatment group at each follow-up time point. Estimates of treatment effect and 95% confidence intervals will be presented comparing the intervention group (mindfulness meditation app) to the control (treatment as usual) group, the intervention group to the active control (progressive muscle relaxation app) group, and the active control group to the control (treatment as usual) group.

Outcomes will be analyzed using linear mixed-effects models with outcome measurement (at three follow-up time points) as the dependent variable. The model will include fixed time effects, a fixed effect for treatment, time treatment interactions for 3-month and 6-month follow-up time points, and an unstructured correlation matrix for the residuals [45]. The model will include a baseline measure of the outcome as a covariate, assuming a linear relationship between baseline and outcome [46]. The model will be fitted using restricted maximum likelihood. Patient data will be analyzed according to the treatment group to which they were randomized (intention-to-treat). All patients with an observed outcome for at least one of the three follow-up time points (60 days, 3 months, or 6 months) will be included in the analysis [47]. If there are missing values for baseline measures of a clinical outcome, they will be replaced by the mean of the observed baseline values for all participants in all treatment arms (mean imputation) [48].

### *Qualitative Analysis*

We will undertake a literal thematic analysis of the data from the focus group discussions to help us understand usability and implementation of, and response to, the intervention and research protocols [49,50] rather than developing or testing theory [51]. Features of app use and implementation issues will be summarized in a table of app features. For example, we will populate the row labelled *modular design* with comments on this specific feature. Columns of this table will represent more granular themes.

## Results

Recruitment for MEMPHIS took place between May 2016 and September 2016. The study was closed March 2017 and the report was submitted to the NIHR on October 26, 2017.

## Discussion

There are currently no rigorous RCTs that test mindfulness meditation interventions as a therapy for any chronic pain syndrome, including CPP. A previous systematic review [52] and our systematic review [11] identified no RCTs on mindfulness meditation in CPP. However, recent pilot studies [12,14,15] demonstrate promising outcomes and open the door for a large well-designed study with meaningful outcome measures. Given that psychological approaches, when combined with traditional therapies such as surgery, improve outcomes in CPP [7], mindfulness meditation is worthy of further investigation.

The intervention under investigation is novel in that it makes use of mindfulness meditation techniques as a treatment for CPP and it delivers this by means of a smartphone app (rather than traditional face-to-face therapy). Web- and smartphone-based health apps are a burgeoning field and offer the nonmedical population assistance in self-diagnosis, monitoring of long term medical conditions, or learning healthy behaviors. In the pain field alone, 279 smartphone apps were available for download in 2014, but these were simplistic, had unverified efficacy, and lacked the involvement of health care professionals in their development [53]. In our experience, no apps are currently incorporated into widespread routine clinical practice in CPP management. MEMPHIS presents a valuable opportunity to create a partnership between app development and health care professionals.

Not all patients with CPP would be expected to be highly confident in using smartphones and mobile technology, especially since women who are not usually using apps were recruited. Part of our data analysis, collected through focus groups, is directed towards the acceptability and usability of the app and will be valuable for any researcher planning future trials of smartphone technology in clinical interventions.

Given the ubiquity of the app, greater compliance with treatment and less wastage from patients not attending appointments may be expected. The use of the app in local primary, secondary, and tertiary care settings would be introduced in collaboration with general practitioner commissioning groups through local guidelines and protocols. Finally, if the app is shown to be effective in a full-scale trial, there would be benefit from studying how to extend the app to other pain conditions, such as headaches, back pain, and irritable bowel syndrome, in which face-to-face delivery of mindfulness meditation has had positive effects [9].

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## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Amendments to protocol.

[PDF File (Adobe PDF File), 19KB - resprot_v7i1e8_app1.pdf ]

## Multimedia Appendix 2

Case report forms to be used for collection of clinical outcome data.

[PDF File (Adobe PDF File), 434KB - resprot_v7i1e8_app2.pdf ]

## Multimedia Appendix 3

Statistical analysis plan.

[PDF File (Adobe PDF File), 347KB - resprot_v7i1e8_app3.pdf ]

## Multimedia Appendix 4

National Institute for Health Research peer review document.

[PDF File (Adobe PDF File), 131KB - resprot_v7i1e8_app4.pdf ]

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## Abbreviations

**CAMS-R:** Cognitive and Mindfulness Scale - Revised
**CPAQ-8:** Chronic Pain Acceptance Questionnaire
**CPP:** chronic pelvic pain
**HADS:** Hospital Anxiety and Depression Scale
**MBSR:** mindfulness based stress reduction
**MEMPHIS:** Mindfulness Meditation for Women With Chronic Pelvic Pain
**NHS:** National Health Service
**NIHR:** National Institute for Health Research
**PIS:** Patient Information Sheet
**PPI:** patient and public involvement
**RCT:** randomized controlled trial
**SD:** standard deviation

**SF-36:** RAND 36-item Short Form health survey
**SMD:** standardized mean difference
**SSM:** supported self-management
**SUS:** System Usability Scale

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Protocol

# The Effectiveness and Cost-Effectiveness of Web-Based and Home-Based Postnatal Psychoeducational Interventions for First-Time Mothers: Randomized Controlled Trial Protocol

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## Abstract

**Background:** In addition to recuperating from the physical and emotional demands of childbirth, first-time mothers are met with demands of adapting to their social roles while picking up new skills to take care of their newborn. Mothers may not feel adequately prepared for parenthood if they are situated in an unsupported environment. Postnatal psychoeducational interventions have been shown to be useful and can offer a cost-effective solution for improving maternal outcomes.

**Objective:** The objective of this study was to examine the effectiveness and cost-effectiveness of Web-based and home-based postnatal psychoeducational programs for first-time mothers on maternal outcomes.

**Methods:** A randomized controlled three-group pre- and posttests experimental design is proposed. This study plans to recruit 204 first-time mothers on their day of discharge from a public tertiary hospital in Singapore. Eligible first-time mothers will be randomly allocated to either a Web-based psychoeducation group, a home-based psychoeducation group, or a control group receiving standard care. The outcomes include maternal parental self-efficacy, social support, psychological well-being (anxiety and postnatal depression), and cost evaluation. Data will be collected at baseline, 1 month, 3 months, and 6 months post-delivery.

**Results:** The recruitment (n=204) commenced in October 2016 and was completed in February 2017, with 68 mothers in each group. The 6-month follow-up data collection was completed in August 2017.

**Conclusions:** This study may identify an effective and cost-effective Web-based postnatal psychoeducational program to improve first-time mothers' health outcomes. The provision of a widely-accessed Web-based postnatal psychoeducational program will eventually lead to more positive postnatal experiences for first-time mothers and positively influence their future birth plans.

**Trial Registration:** International Standard Randomized Controlled Trial Number (ISRCTN): 45202278; http://www.isrctn.com/ISRCTN45202278 (Archived by WebCite at http://www.webcitation.org/6whx0pQ2F).

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**KEYWORDS**

mothers; education; postpartum period; Internet

## Introduction

The period following a child's birth is considered the most crucial period for mothers as they venture from their current-known reality to an unknown new reality. In addition to recuperating from the physical and emotional demands of childbirth, first-time mothers are concurrently confronted with challenges associated with the demands of adapting to their social roles as new parents [1]. In addition, they are required to pick up new skills to take care of their newborn [2]. The subsequent mastery of these necessary skills at home, without the support from health care professionals, may be challenging for some. This change in role from a nonparent, being only responsible for oneself, to having added responsibility in caring for their newborn could take a toll on first-time mothers if their expectations do not match their experiences [3]. According to the theory of maternal role attainment, a mother's emotional outcome during this phase is very much influenced by the mother's biopsychosocial being, family, and the environment that she is surrounded by [4]. Often, mothers are situated in an unsupported environment and may not feel adequately prepared for motherhood. This presents as a challenge physically, emotionally, and socially, and this is particularly so for first-time mothers [5]. The early postpartum phase presents a critical period where mothers prepare themselves for parenting. A mother's negative psychological status and well-being influence the type of parenting given to their newborn in their developmental stages, consequently impairing the mother-infant relationship and impacting the child's outcome [6].

### Postnatal Services in Singapore and Underused Antenatal Classes

To support mothers, antenatal classes and postnatal support are largely provided by the polyclinics and maternity hospitals in Singapore [7]. Antenatal classes are spread over several weeks and are usually conducted by nurses or midwives from maternity wards or private hospitals. A systematic review revealed that midwifery-led care was associated with better maternal outcomes and should be encouraged [8]. First-time mothers find that being able to communicate with a midwife regarding issues not only helped develop a trusting relationship but also helped to promote choice and control, making them feel more prepared for parenting [9]. Mothers were also satisfied with midwifery-led care [10]. However, antenatal classes usually come with a high price tag in Singapore, which mothers from lower socioeconomic backgrounds may not have access to. In contrast, such classes in certain countries in Western Europe have been offered to mothers without a fee [11]. Research also suggests that the home services provided to mothers are associated with improved emotional maternal outcomes and satisfaction [12].

### Challenges Surrounding Postnatal Period

The average length of hospital stay post delivery is approximately 24 to 72 hours for normal deliveries across all maternity hospitals in Singapore [13]. During the transitional period from hospital to home, mothers face physical challenges, including fatigue from lack of sleep. Mothers often feel a lack of support from 1 to 3 weeks after their discharge [14]. The reality of caring for their newborn only sets in after they are discharged and on their own, and this is when most learning needs are found [15]. Hence, there is a gap in the spectrum of care from the point of discharge back to their homes.

### Postnatal Depression

Postnatal depression (PND) is a depressive illness of mild to moderate severity that occurs during the first postnatal year [16]. It is one of the most common health issues that occurs among postnatal mothers globally, with most mothers experiencing PND in the first 3 months of the postnatal period [17]. In an earlier meta-analysis based on 59 studies, the prevalence of PND was approximately 13% [18]. In a recent meta-analysis of 18 studies, the overall prevalence was 20% [19], whereas another meta-analysis of 78 studies reported an overall prevalence of 3.1% [20]. The prevalence of PND in Singapore is 6.8% [21]. A local study suggested that mothers might be vulnerable to emotional distress cross-culturally regardless of their cultural postnatal traditions [22].

PND is caused by an interplay of a multitude of psychological factors, including societal expectations, social connectedness, child's temperamental challenges, a mother's coping strategies, and many other life stressors [23]. Physiological causes also include neurochemical imbalances in the brain [24]. If left untreated, it can persist for many years [25], leaving detrimental effects on the mother's recovery period. Moreover, there is an association between the mother's mental health status and maternal-child bonding, which subsequently affects the development of depression in adolescence [6]. The father and the family unit are also inevitably affected, which in turn may affect the mother's social relationships [26,27]. These challenges are important in informing health care providers for developing a service that is essential to the promotion of a positive maternal experience. Such strategies may have an impact on future fertility rates, which is important for Singapore, a country with a rapidly aging population and a very low birth rate.

### Social Support, Maternal Self-Efficacy, and Postnatal Depression

Social support refers to interpersonal relationships that provide individuals with emotional support and self-confidence for maintaining maternal and infant psychological well-being. This form of support facilitates a mother's adjustment into motherhood [28]. It acts as a form of buffer for mothers to mediate stress. Parenting can be psychologically stressful for first-time mothers [29], but good social support from various parties can help ease the transition phase into parenthood. The primary sources of support for a mother come mostly from their partner, other family members, and friends. However, providing support for mothers by nurses and midwives during the early postnatal period is also important, as there have been consistent evidence showing that the availability of social support contributes significantly to a person's ability to self-regulate in the presence of stressors [30-33]. A study conducted in Singapore also underlined the significance of providing competent postnatal care to first-time mothers to improve maternal outcomes [22]. Moreover, barriers to mobilizing support were also present and these include fear of judgment and feeling like a burden [34]. Hence, having a variety of support providers can help protect mothers against the harmful

psychological effects of stressors related to parenting by enhancing facilitators and reducing barriers to mobilizing support.

Another crucial component in a seamless transition to parenthood for mothers is maternal self-efficacy. Maternal self-efficacy is the belief that a mother holds of her competence in achieving a set of tasks that produces results related to parenting [35]. According to Bandura's theory of self-efficacy, perceptions of self-efficacy come from four main sources of feedback: mastery experience, vicarious experiences, verbal persuasion, and emotional arousal [36]. For example, in the proposed study, mastery experience means the ability to strengthen self-motivation following successes in performing baby care or self-care tasks. Vicarious experiences refers to acquiring a skill through modeling from peer mothers, hence persuading herself that she, too, is able to carry out the task. Verbal persuasion is the belief that they are able to cope with baby care through encouragement from others. Emotional arousal is the psychological state of mind attributed with performing a task. Bandura's self-efficacy theory postulates that one's self-efficacy operates to reduce feelings of stress and depression and is crucial in determining one's emotional reaction toward a situation.

The amount of social support received and the level of maternal self-efficacy have an impact on a mother's emotional well-being. Inconsistent or low levels of social support have been found to be strongly associated with PND [34]. A study conducted in Canada reported the importance of social support in reducing PND [37]. Other research studies have also found that poor self-efficacy among mothers and a lack of social support are strongly associated with PND [21,38-41]. These studies support that self-efficacy, social support, and PND are associated variables, which are important in determining maternal outcomes. However, only one study has evaluated their relationships in first-time mothers, which confirmed their interrelated relationship and that all three components should be addressed [40].

## Home-Based Psychoeducation Intervention

To combat psychological stressors from parenting, psychoeducational programs aim to address knowledge deficit regarding the postnatal period and build on the participants' strengths and resources to promote emotional coping and parenting skills development [42]. Several studies have shown that psychoeducation programs have been one of the crucial interventions to enhance maternal self-efficacy antenatally and postnatally to improve maternal outcomes [43-45]. In 2012, a preliminary study was conducted in Singapore, which reported self-efficacy improvement and PND reduction in mothers receiving a home-based psychoeducational intervention [46]. Another study exploring women's experiences of midwifery home visits revealed that women felt vulnerable in the early postpartum period but also felt that having a personal relationship with a midwife was important [47]. However, with the shortage of midwives and nurses, a home-based intervention might not be the most accessible and cost-effective method of delivering care.

## Accessible and Cost-Effective Web-Based Psychoeducational Intervention

A Web-based intervention might be able to address the above problem by increasing accessibility and reducing costs associated with home visits without compromising the effectiveness of a psychoeducational intervention on maternal outcomes. A meta-analysis reported the effectiveness of a Web-based intervention in achieving positive outcomes for individuals [48]. Moreover, studies have shown that socioeconomic status, including low education and low income, increases the risk of first-time mothers developing depressive symptoms [49]. Therefore, examining the cost-effectiveness of a Web-based psychoeducational intervention may help to keep costs to a minimum and to make it affordable to all mothers regardless of socioeconomic status while achieving positive maternal outcomes. Moreover, in Singapore, the Home Access Program allows lower income households to be able to afford fiber broadband connectivity and a tablet at a subsidized rate, thereby increasing accessibility to resources online [50].

## Theoretical Framework

The theoretical framework adopted for this study follows Bandura's self-efficacy theory [36], the concepts of social support including functional and structural support that can ease a smooth progression to motherhood [40,51], as well as the interrelationships between self-efficacy, social support, and emotional well-being [52-54]. The framework used in this study is similar to the one used in our preliminary study [46]. The psychoeducation intervention programs, both Web-based and home-based, are developed to promote maternal self-efficacy, social support, and mother's psychological well-being.

## Aims

This study aims to evaluate the effectiveness and cost-effectiveness of Web-based and home-based postnatal psychoeducational programs for first-time mothers on maternal outcomes.

## Hypotheses

The hypotheses are as follows:

1. When compared with mothers in the control group, mothers in Web-based and home-based psychoeducational intervention groups will report a significantly:
   - higher level of self-efficacy,
   - higher level of social support received,
   - lower level of anxiety and depression, and
   - higher level of satisfaction with postnatal services.
2. When compared with those in the home-based psychoeducational intervention group, mothers in the Web-based psychoeducational intervention group will not report significantly poorer aforementioned maternal outcomes.
3. It is more cost-effective to provide a Web-based psychoeducational intervention than a home-based psychoeducational intervention and routine care.

## Methods

### Design

A randomized controlled three-group experimental design was used. First-time mothers (n=204) were recruited from a public hospital in Singapore. Recruited mothers were randomly assigned into any of the three groups: intervention group 1 (receiving the Web-based psychoeducational intervention plus routine care), intervention group 2 (receiving the home-based psychoeducational intervention plus routine care), and the control group (receiving routine care). Research assistant (RA2) who helped with follow-up data collection did not have any knowledge of the treatment allocation of participants, which was completed by another research assistant (RA1).

### Participants

The criteria for inclusion were first-time mothers who: (1) had full-term pregnancy, (2) were 21 years old and older, (3) were able to read and speak in English, (4) had Internet access through a computer or a smartphone, and (5) planned to reside in Singapore for the 6 months post delivery. The exclusion criteria were mothers who: (1) had identified physical or mental disorders (eg, cognitive impairment, schizophrenia, psychosis, or suicidal signs) before and during pregnancy that would hinder their ability to participate in the study, (2) had complicated assisted delivery with 4th degree perineal tear, and/or (3) gave birth to a stillborn child or a child with congenital anomalies or medical complications (eg, pathological jaundice), which required specialized attention in the hospital. A group of participants (15 from each group) were selected to participate in the process evaluation for the purpose of obtaining their opinions and comments on the Web-based, home-based psychoeducational intervention, and routine care.

### Web-Based and Home-Based Psychoeducational Intervention

The Web-based and home-based interventions were developed based on Bandura's theory on self-efficacy [55], social support, findings from previous literature [38-40,43], and local preliminary studies [40,46,55-61]. Both interventions contain similar intervention contents but with different modes of delivery—Web-based or home visits. Table 1 shows the comparison of protocol of routine care, and Web-based and home-based postnatal psychoeducational interventions.

#### *Web-Based Psychoeducational Intervention*

The mothers assigned to intervention group 1 had participants receiving periodic care and a Web-based postnatal psychoeducational intervention with 1-month access. The intervention has been summarized in Table 1. The videos were developed based on current practices in local hospitals. There was a peer discussion forum where the participant could communicate with other participants, or a confidential corner for participants to ask personal questions. Expert advice was also provided by RA2 and other team members when needed. There were also thrice-weekly telephone reminders, which lasted for about 3 min each, solely as a reminder for participants to assess the website without any additional education provided.

**Table 1.** Comparison of protocol of routine care, and Web-based and home-based postnatal psychoeducational interventions.

| Control group: routine care only | Intervention group 1: Web-based intervention (+ routine care) | Intervention group 2: home-based intervention (+ routine care) |
|---|---|---|
| Before discharge: Routine education received in the hospital | Before discharge: Access to website information, and Web-based audio and video materials | Before discharge: Provision of booklet |
| | Main content covered in the website, audios, and videos, which included the following: postnatal experiences; maternal self-care (including physical, emotional, and sexual health); newborn care, and social support | Main content covered in the booklet included the following: postnatal experiences; maternal self-care (including physical, emotional, and sexual health); newborn care, and social support |
| At 2 weeks post-delivery: Follow-up with obstetrician; examination of episiotomy or cesarean wound; wound dressing for cesarean wound; and use of Edinburgh Postnatal Depression Scale (EPDS) | 1st week after discharge: Go through website information, and Web-based audio and video materials | 1st week after discharge: One hour face-to-face education at home |
| | Peer discussion forum, and a confidential corner for personal questions and expert advice | Main content covered in the face-to-face session is the same as in the booklet |
| | Mothers can discuss their concerns related to self-care and newborn care; expert (RA2 and other team members) will access the website and respond to the questions raised daily | |
| At 6 weeks post-delivery: Follow-up with the obstetrician; advice on: breastfeeding; PAP smear; intrauterine contraceptive device upon patients' request; and EPDS for those mothers who have defaulted the 2 weeks appointment | 2nd to 4th week after discharge: Weekly telephone calls x 3; reinforce the use of website resources | 2nd to 4th week after discharge: Weekly telephone calls x 3; reinforcement of the content covered during home visit; find out new challenges faced by the mothers; and provide individualized support as per mothers' needs |

### *Home-Based Psychoeducational Intervention*

Participants assigned to intervention group 2 received periodic care and a home-based postnatal psychoeducational intervention. There was a 1-hour face-to-face psychoeducation via a home visit by a registered nurse (RA1). An educational booklet was also developed based on the one used in the preliminary study [61] with new evidence-based knowledge added, such as mindfulness-based practice and using cold cabbage leaves for managing breast engorgement [61], which were provided to participants before hospital discharge. The main contents in the booklet provided for the home-based intervention were identical to the one from group 1. The contents were validated by an expert panel, consisting of 5 health care professionals (2 professors in Obstetric and Gynecological Nursing, 1 senior consultant in obstetrics, 1 experienced midwife in postnatal care, and 1 postnatal psychologist). There was also a thrice-weekly telephone follow-up to answer mothers' queries.

## Control Group

Participants assigned to the control group only received the routine care provided by the hospital.

## Sample Size Determination

In similar studies, psychosocial and educational interventions have resulted in a medium effect size on outcomes similar to this study [44,52,62]; hence, the study intervention was regarded to have a medium size effect on outcome variables. On the basis of a power analysis, to achieve a medium effect size of 0.55, using a power of 80% and a significance level of 5% (2-sided), 52 participants would be needed in each group [63]. Although a dropout rate of 30% was reported by a previous study [52] and our preliminary study [46], we anticipated a lower dropout rate of 24% in this study because of better communication channels established with participants (eg, using social media such as WhatsApp to remind participants, follow-up questionnaire conducted through a Web-based survey). Therefore, a minimum sample of 204 (52×3/0.76) participants with 68 in each group was needed. For process evaluation, a purposive sampling of 45 participants (15 from each group) with different posttest 1 self-efficacy scores (5 high, 5 moderate, and 5 low scores from each group) were invited to participate in a process evaluation interviews, or until data saturation was achieved.

## Randomization

A random sequence generator was used to generate three sets with 68 unique random integers in each set that ranged from 1 to 204 without being sorted [64]. Three sets of numbers were randomly assigned for intervention group 1, intervention group 2, or control group, respectively. The blinding of the participant was not possible because of the nature of the intervention. All 204 unique numbers indicating the group were placed in an opaque box. After assessing eligibility and obtaining informed consent, participants were assigned randomly to either of the groups by drawing a number from the box. Participants were reminded that there will be no change of groups after numbers are drawn.

## Outcome Measures and Instruments

The outcome measured included are maternal parental self-efficacy (MPSE), social support, PND, anxiety, satisfaction with postnatal care, and cost related to health care services used postnatally. The instruments used to measure the key variables included Perceived Maternal Parental Self-efficacy (PMPSE), the modified Perinatal Infant Care Social Support (PICSS-modified), Edinburgh Postnatal Depression Scale (EPDS), Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), Ordinal Descriptive Scale (ODS), and Questionnaire on Healthcare Service Utilization (QHSU).

### *Perceived Maternal Parental Self-Efficacy*

The PMPSE is a widely used 17-item instrument that measures maternal self-efficacy in the postpartum period. Each item is rated on a four-point Likert scale. The Cronbach alpha values in a previous study and a local study were .91 [65] and .92, respectively [54].

### *Social Support*

The modified PICSS includes the Functional Social Support Measuring Subscale (FSSMS) and Structural Social Support Measuring Subscale (SSSMS). The FSSMS is a 16-item subscale used to measure maternal perceived social support [57] with Cronbach alpha values of .80 in a previous study [57] and .76 in a local study [54]. The SSSMS is a 6-item subscale used to measure the structural dimension of an individual's social network with a Cronbach alpha of .83 in a local study [54].

### *Psychological Well-Being*

The EPDS and HADS-A were used to measure mothers' psychological well-being, including PND and anxiety. The 10-item EPDS has been used to measure PND widely. The recommended cutoff for probable cases of PND is 12 or 13 [66]. The sensitivity and specificity of the EPDS were 68% to 80% and 77%, respectively, and the Cronbach alpha was .88 [67]. The HADS-A is a 7-item instrument that is most commonly used to assess anxiety symptoms [68]. It is rated on a 4-point scale of 0 to 3. The minimum score of 8 determines the presence of anxiety symptoms [69]. The sensitivity and specificity of HADS-A were 93% and 90%, respectively, when it was used for pregnant women from Nigeria [70].

### *Satisfaction With Postnatal Care*

The ODS is a 6-point Likert scale for assessing mothers' satisfaction with the postnatal care they received [46,59].

### *Health Care Service Utilization*

The QHSU was used to capture costs related to health care service usage by the mothers postnatally due to maternal- or infant-related health issues at 1 month, 3 months, and 6 months post delivery. The measurement period for the study was from entry into the program until 6 months. The questionnaire was designed by health economy experts from the Singapore Clinical Research Institute.

## Process Evaluation

Semistructured interviews were conducted for exploring the information regarding the strengths, weaknesses, and perceived

effects of the interventions, and the mothers' opinions on the current routine postnatal care provided by the hospital.

### Study Procedure

Data collection commenced after the ethical approval had been obtained. The nurse in charge was contacted to determine the physical and psychological well-being of potential participants. After confirming the inclusion criteria, the participants were approached at the postnatal inpatient wards. Only after obtaining written consent would the mother be recruited into the study. This was followed by a collection of demographic data and baseline data via a self-administered questionnaire before randomization takes place. Outcomes were measured at the following time points for all participants in all three groups: (1) after delivery and before discharge (baseline data), (2) immediately after the intervention (posttest one, at the end of 1 month post delivery), (3) 2 months after the intervention (posttest 2, 3 months post delivery), and (4) 5 months after the intervention (posttest 3, 6 months post delivery).

RA1 made a visit to the hospital regularly to recruit participants and was responsible for informing all participants of their allocated group, and collection of baseline data for all participants. RA1 provided participants in the Web-based intervention group with Web access (individual username and password) for 1 month. For participants assigned to the home-based intervention group, RA1 provided the educational booklet before discharge and arranging home visits at about 5 to 10 days post delivery, as this is the most crucial period for mothers, as well as 3 telephone calls [71].

RA2 was responsible for the Web-based postnatal psychoeducational intervention (eg, providing expert advice in group discussion forums and confidential corner, and 3 reminder phone calls). RA2 was responsible for the collection of all posttest data, including process evaluation interviews.

### Data Analysis

Quantitative data will be analyzed using IBM SPSS version 24 for Windows (IBM Corp). Descriptive statistics such as mean, standard deviation, and range will be used to report continuous data, whereas frequency and percentages will be used for the nominal and ordinal data. Inferential statistics such as ANOVA will be used to analyze the differences of baseline outcomes among the three groups, whereas chi-square tests will be used to compare the sociodemographics among the three groups.

To answer the hypothesis 1, repeated measures ANCOVA, adjusted for confounding variables (eg, age, ethnicity), will be used to test the effects of both interventions on maternal self-efficacy, social support, postnatal depression, and anxiety across four time points. Univariate ANCOVA will be used to test the difference of each of the three outcomes among three groups at each posttest time point by adjusting for confounding factors (eg, baseline data, age, and ethnicity). Chi-square test or Poisson regression will be used to determine maternal satisfaction with the postnatal supportive care at each posttest time points. To answer hypothesis 2, a 95% CI of the mean difference of maternal self-efficacy scores will be calculated. If the lower boundary is more than −5, the hypothesis will be accepted. To address hypothesis 3, we will calculate the base case incremental cost-effectiveness ratios (ICER) of the two intervention groups compared with the control group. We captured the 6-month costs at three posttest time points: (1) health care system perspectives, including service providers that mothers consumed because of maternal and/or neonatal related conditions such as GP clinic, polyclinic, private clinic, hospital out-patient, hospital Accident and Emergency and (2) participant's out-of-pocket cost of transportation fee for these visits. In addition, fixed costs (also considered health care system perspectives) such as development and implementation of Web-based intervention, delivery of home-based intervention, and training of RAs were also captured. The effectiveness of the intervention on four outcomes (namely self-efficacy, social support, depression and anxiety) will be calculated. The ICERs for each outcome will be plotted in the cost-effectiveness plane to examine the dominance and extended dominance, and then the cost-effectiveness acceptability curves will be generated to demonstrate the cost-effectiveness of the alternatives using difference willingness-to-pay thresholds [72-78].

Qualitative data from the interviews will be analyzed using thematic analysis [79-83]. The audiotaped interview data will be transcribed verbatim by RA2 concurrently with the data collection to capture nonverbal nuances. Transcribed data will be color coded first, which will then be collated to form subthemes, and eventually to form themes [84]. Two investigators will be involved in the analysis process to compare and discuss the codes, subthemes, and themes that are generated and to achieve consensus. Rigor, including credibility, transferability, dependability, and confirmability, will be considered carefully in the study process [85].

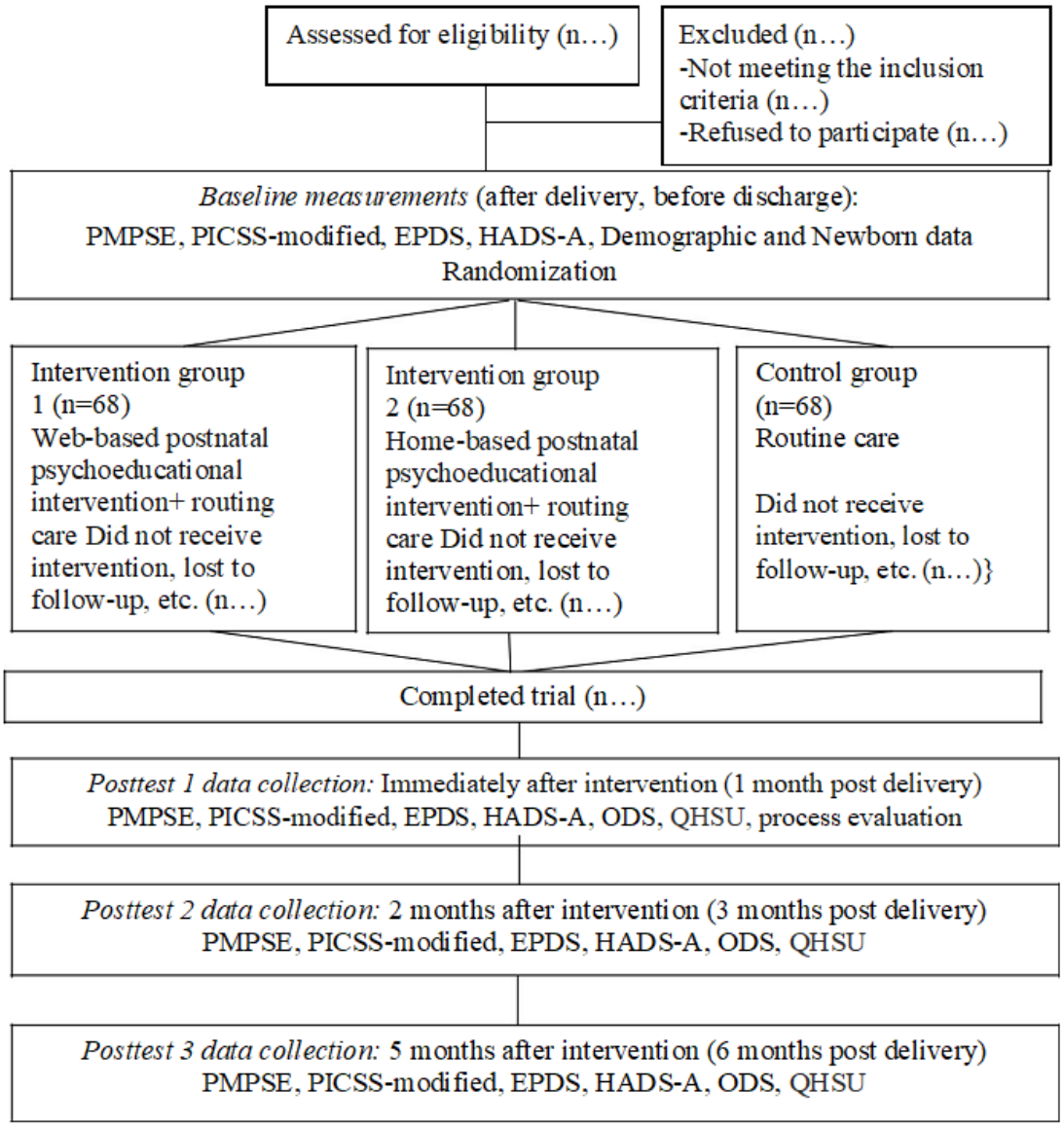
### Ethical Considerations

Ethics approval for the study was received from the relevant ethics review board before commencing the study (Ref: 2015/01189) on 25 January 2016. A participant information sheet, which provides a brief introduction to the study as well as the benefits and risks of their participation in the study was explained. Anonymity and voluntary participation was ensured. Each participant's written consent was also obtained, including consent for audio recording during the process evaluation interview. Participants whose EPDS scores were more than 13 were referred to their obstetrician for further follow-up. A token of appreciation was provided to all participants for their time spent to participate in the study and this is a common practice in the study country.

## Results

The booklet for the home-based intervention group and the website for the Web-based intervention (including the audio and video files) have been developed. The recruitment of participants started in October 2016 and was completed in February 2017 with 68 mothers in each group (n=204). All follow-up data were collected by August 2017. The consolidated standards of reporting trial flowchart can be found in Figure 1. The projected timeline for completion of data entry and data analysis is around March to June 2018.

**Figure 1.** Consolidated standards of the reporting trial flowchart of the study. PMPSE: Perceived maternal parental self-efficacy; PICSS-modified: Modified Perinatal Infant Care Social Support Scale; EPDS: Edinburg Postnatal Depression Scale; HADS-A: Hospital Anxiety and Depression Scale (Anxiety Subscale); ODS: Ordinal Descriptive Scale (satisfaction with postnatal care); QHSU: Questionnaire on Healthcare Services Utilization.




## Discussion

### Principal Findings

This proposed study is based on previous studies conducted by the same research team [22,46,59,60]. With minimal time spent from midwives and/or nurses, this study will provide empirical support and identify a clinically useful and potentially effective and cost-effective Web-based postnatal psychoeducational program in promoting maternal self-efficacy, seeking social support from health care professionals, and family members), and psychological well-being by equipping mothers with knowledge, skills, and support in the postnatal period. The Web-based psychoeducational intervention will reduce the need for face-to-face home-based interventions. If the proposed Web-based psychoeducational intervention is as effective and more cost-effective when compared with the home-based intervention, it will be introduced to the hospital policy maker and be adopted as a standard care to promote the quality of postnatal care for the new mothers and increase mothers' satisfaction with postnatal services, without needing extra manpower to provide postnatal home visits to mothers.

The short term clinical implication of this study is such that a comprehensive and well-designed Web-based postnatal psychoeducational program will be developed for first-time mothers. Following that, an understanding will be established on the determinants of the outcome variables in improving maternal outcomes. These strategies can also be incorporated into the services provided by midwifery-led clinics.

In the long term, the practicality of both interventions will be determined. If the Web-based intervention is reported to be more practical, effective, and cost-effective as compared with

the home-based intervention and the current standard routine care, the learning package adopted in the Web-based intervention can then be provided to first-time mothers to address any doubts and questions. With the implementation of the Web-based intervention, first-time mothers will then be able to effectively allocate their time and resources when it comes to the usage of emergency medical services in addressing minor issues related to maternal and newborn care. Health care professionals will also be able to effectively allocate appropriate resources when it comes to educating new mothers and providing consultations to address queries from mothers. The Web-based intervention can also be beneficial to mothers as it provides continuity of care for new mothers after their discharge from the hospital and enhances the safety of both the mother and the newborn. Empowering mothers with confidence back at home contributes to the overall well-being of mothers and newborns [46]. A positive postnatal experience could also potentially influence future birth plans and eventually contribute to an increase fertility rate in Singapore. In addition, mothers in countries other than Singapore can also benefit from the website resources.

### Limitations of the Study

One of the limitations was the inability to blind the participants from the intervention because of the nature of the interventions. This study was only conducted in a single tertiary hospital in Singapore and all participating mothers were English-speaking mothers. The results tested on mothers from the private hospitals and mothers who speak other languages might be different.

### Conclusions

This randomized controlled trial will provide empirical evidence to support the effectiveness and cost-effectiveness of the Web-based and home-based psychoeducational interventions in promoting maternal outcomes. This study also has potential benefits in reducing health care costs associated with postnatal supportive services. Future studies should include non-English-speaking mothers and mothers from other maternity hospitals in Singapore and other countries to enhance the generalizability of the study findings.

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### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Original peer-review reports.

[PDF File (Adobe PDF File), 2MB - resprot_v7i1e35_app1.pdf ]

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## Abbreviations

**CONSORT:** Consolidated Standards Of Reporting Trial
**CEAC:** cost-effectiveness acceptability curves
**EPDS:** Edinburg Postnatal Depression Scale
**FSSMS:** Functional Social Support Measuring Subscale
**HADS-A:** Hospital Anxiety and Depression Scale
**ICER:** incremental cost-effectiveness ratios
**IUCD:** intrauterine contraceptive device
**MPSE:** Maternal Parental Self-efficacy
**NHG DSRB:** National Health Group Domain Specific Review Board
**ODS:** Ordinal Descriptive Scale
**PMPSE:** Perceived Maternal Parental Self-efficacy
**PND:** postnatal depression
**QHSU:** Questionnaire on Healthcare Services Utilization
**SSSMS:** Structural Social Support Measuring Subscale
**SPSS:** Statistical Package for the Social Sciences

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Original Paper

# Web-Based Training Program Using Cognitive Behavioral Therapy to Enhance Cognitive Flexibility and Alleviate Psychological Distress Among Schoolteachers: Pilot Randomized Controlled Trial

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## Abstract

**Background:** Schoolteachers are known to be faced with various stresses in their work. A simple, less onerous, and effective intervention technique that can enhance the stress management skills, particularly, cognitive flexibility, of schoolteachers is needed.

**Objective:** This study aimed to determine whether stress management training using a Web-based cognitive behavioral therapy (CBT) program is effective for enhancing the cognitive flexibility of schoolteachers and alleviating their subjective distress.

**Methods:** This study was conducted in a random controlled design covering public elementary schoolteachers. Teachers allocated to the intervention group received 120 min of group education and completed homework using a Web-based CBT program that lasted for 3 months. The items of outcome evaluation were cognitive flexibility and subjective distress, and the efficacy of intervention was evaluated at 3 months after intervention.

**Results:** A total of 240 participants were randomly allocated to the intervention group (120 individuals) and the control group (120 individuals). On the basis of the principle of intention to treat, the intervention group and the control group were compared regarding the amount of change from before intervention to after intervention, using a general linear model. Scores of cognitive flexibility and subjective distress were significantly more improved in the intervention group than in the control group.

**Conclusions:** The results of this study suggest that simple stress management training using a Web-based CBT program in elementary schoolteachers enhances cognitive flexibility and alleviates subjective distress.

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**KEYWORDS**

school teachers; education; cognitive therapy; randomized controlled trial

## Introduction

### Stress of Schoolteachers

It is known that schoolteachers are faced with much stress. It is therefore important to seek measures to enhance the stress management skills of schoolteachers. Each schoolteacher in Japan bears the weight of various responsibilities besides lessons in class, including moral guidance, counseling parents, being an advisor to school clubs after class, participating in activities to enhance educational effects, and preparation of reports. Therefore, teachers often feel distress about various areas, and thus, the mental health of Japanese schoolteachers is lower than that of general workers [1,2]. In addition, the number of

Japanese public schoolteachers who are on leave of absence for mental illness is showing an almost consistent upward trend, such that schoolteachers on leave of absence for mental illness accounts for more than 60% of all schoolteachers on leave of absence for any illness [3]. Because poor mental health of teachers affects not only teachers themselves but also their students, this is a socially important problem. Previous studies that examined the relationship between poor mental health or burnout of teachers and various factors have identified less years of experience as a teacher and young age [4-7], insufficient social support [5,8,9], and stress management skills of the individual [10-12] as contributing factors. In particular, a study of young and inexperienced teachers revealed that stress management skills of the individual, rather than job-related stressors, were significantly correlated with mental health [13]. Therefore, it is presumed that policies for not only decreasing stressors but also enhancing stress management skills of teachers are necessary to improve the mental health of schoolteachers.

### Cognitive Behavioral Therapy and Cognitive Flexibility

A preceding study reported that cognitive behavioral therapy (CBT) is useful for enhancing stress management skills of workers [14]. CBT enhances cognitive flexibility, thereby challenging and replacing maladaptive thoughts with more balanced and adaptive thinking [15,16]. According to Dennis and Vander Wal, cognitive flexibility reflects the following 3 aspects: the tendency to perceive difficult situations as controllable, the ability to perceive multiple alternative explanations for life occurrences and human behavior, and the ability to generate multiple alternative solutions to difficult situations [17]. Previous studies in healthy subjects have found that individual differences in cognitive flexibility significantly and effectively predicted good performance on tasks that required carefulness [18], and cognitive flexibility was involved in fluent creativity and new ideas [19]. It has also been reported that persons with a high feeling of happiness have high cognitive flexibility and executed tasks of higher creativity [19]. Therefore, CBT may improve the performance of schoolteachers as well as their stress management skills by improving their cognitive flexibility.

### Effect of Low-Intensity Cognitive Behavioral Therapy

Low-intensity CBT, a program to provide the essence of CBT using simple measures including group education, use of the Internet, and books, is now spreading to use CBT in a wide range of scenarios beyond clinical treatment. It is also reported that stress management education using CBT performed on the Internet (Web-based CBT) alleviated the distresses of general workers and enhanced their cognitive flexibility [20,21]. However, there has been no study that examined whether training programs of schoolteachers using low-intensity CBT would enhance their cognitive flexibility and be effective for reducing their stress.

In this regard, this study provided schoolteachers with simple stress management training using a Web-based CBT program that allowed each of them to complete CBT homework independently, and investigated whether the training would contribute to the enhancement of cognitive flexibility and reduction of stress among teachers.

## Methods

### Participants

This study included 241 schoolteachers serving in public elementary schools in Sagamihara City in Kanagawa, Japan, who were in the fifth year of their career and were prospective participants in a mental health–related training program in 2014. We obtained permission from the board of education of Sagamihara City for the mental health training in 2014 to be performed as part of this study to evaluate the efficacy of a stress management training program using CBT. The board of education recommended that potential participants receive stress management training using CBT; however, there were no exclusion criteria set for study participants.

In a preceding study that used an intervention similar to ours in general workers [21], the effect size (Cohen d) for improvement of cognitive flexibility was 0.37. On the basis of this result, using an effect size of 0.37, an alpha error of .05, and a beta error of .20, the sample size required for this study was estimated to be 116 persons in each group to a total of 232 participants. Because the number of prospective participants in the training program in 2014 was 241, we considered that the necessary number of participants would be secured.

### Ethical Considerations

All potential study participants were instructed orally or in writing by the investigator before the beginning of the study that they could discontinue participation at any time if problems were caused by the intervention, and that this study was to be conducted by an organization independent of the board of education and would have no influence on personnel evaluation. Only the persons who gave consent to this study after this explanation were included in this study. They were also instructed that participation in the study should be completely of their own volition and that not participating in the study would cause no disadvantages. The study protocol was approved by the Ethics Committee of the School of Allied Health Sciences at Kitasato University. Reporting of methods and results of this study are based on the Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth (CONSORT-EHEALTH) guidelines [22]. This study was not registered because it is a pilot study.

### Procedure

The participants in the study were randomly allocated to 2 groups, that is, the intervention group and control group. All participants in the intervention group were given 1 session of group education and a Web-based CBT program lasting for 3 months. The efficacy of the intervention was evaluated based on the results of a self-administered questionnaire survey performed at baseline and 3 months after the completion of the CBT program. For ethical reasons, participants in the control group (waiting-list control) were also given the same group education and Web-based CBT program after the end of the study.

**Table 1.** The contents of the program.

| Program and content | Points addressed |
|---|---|
| **Group CBT [a] education (2 hours)** | |
| Part 1. Lecture | The relationship between cognition, mood, and behavior |
| | What is CBT? |
| | Significance of learning CBT as a stress-coping method |
| Part 2. Group work and discussion for learning cognitive restructuring | How to fulfill the column sheet? |
| | Recognize own inclination in the way of thinking |
| | Cooperate as a team in considering contrary evidence and adaptive thoughts |
| | Use of Web-based CBT program |
| Web-based homework using the Web-based CBT program | Delivering an email 6 times to urge implementation |
| | Implementation of at least 3 sessions recommended |

[a]CBT: cognitive behavioral therapy.

## Intervention

The intervention consisted of 1 session of group education about CBT (lecture on CBT, group session using a column table), homework using the Web-based CBT program for the subsequent 3 months, and 6 emails sent during the self-learning period to stimulate the implementation of the Web-based CBT program (Table 1).

### *Group Cognitive Behavioral Therapy Education*

A specialist in CBT took charge of the group education. One session of group education consisted of part 1 and part 2, taking 120 min in total. In addition, there were 60 participants in one session, and with the therapist was 1 leader (specialist in CBT), 1 coleader (specialist in CBT), and 3 assistants.

Part 1 was a seminar on the basic theory of CBT. Because the participants in this study were healthy, their awareness that CBT is useful for work and daily life was key to enhance motivation for education. Therefore, the purpose of including CBT in mental health education of teachers was clearly specified, such that CBT was not used as a treatment for mental illness but as a method of self-care to cope flexibly with various stress factors. The seminar was devised to use concrete examples and avoid technical jargon as far as possible to make the contents readily comprehensible.

Part 2 comprised group training in cognitive restructuring, the core technique of CBT. Cognitive restructuring helps people identify negative thought patterns, understand that these thoughts are ineffective or disruptive, and learn how to think differently by replacing adverse and illogical thoughts with more rational and adaptive types of thinking. In this part, participants learned about cognitive restructuring by recording the following on a worksheet about a recently experienced familiar (benign) situation: context, mood, automatic thinking, evidence, contrary evidence, adaptive thinking, and change of mood. During practice, participants were divided into groups of 5-7 members. In each group, one member described a recently experienced stressful event (a mild one causing no privacy issues) to the other members and his or her mood and automatic thinking at that time. Then, all members of the group considered evidence, contrary evidence, adaptive thinking, etc to practice completing the columns of the worksheet. Finally, each group presented the contents of the worksheet to all participants to share patterns and to ask a CBT specialist questions that arose during the group work to deepen their understanding of cognitive restructuring. At the end of the group training, the Web-based CBT program was introduced to participants so that they could learn how to manipulate the program.

### *Web-Based Homework Using the Web-Based Cognitive Behavioral Therapy Program*

The homework using the Web-based CBT program lasted for 3 months after the end of the group education. The Web-based CBT program used *Mind Skill Up Training* [23]. This website, developed by a specialist in CBT, is designed for trainees to practice cognitive restructuring by themselves using the guide. This site is open to the public for use with a charge. Each participant in this study was given an ID and password by the investigator to access the website. Self-learning on the Web was feasible in the workplace or at home as long as a proper information technology environment was in place; the place of self-learning varied according to the convenience of the participant. During the homework implementation period, an email from a health nurse who was one of the investigators of this study was delivered to participants 6 times to provide information on CBT and urge them to do homework. Implementation of at least 3 sessions of homework was encouraged.

## Outcome Evaluation

The outcomes were cognitive flexibility and degree of subjective distress. Questions about these items were prepared, and evaluation was performed at baseline and 3 months after the end of the homework period, using self-administered questionnaires. Cognitive flexibility was evaluated in terms of the following 3 points proposed by Dennis and and Vander Wal: "I have a tendency to perceive difficult situations as controllable," "I can perceive multiple alternative explanations for difficult situations," and "I can generate multiple alternative solutions to difficult situations." These items were rated according to 5 grades (1: not at all to 5: completely applicable).

Subjective distress was examined by the question "How much do you perceive stress at work?" and rated according to 10 grades (1: not at all to 10: very strongly).

In addition, participants were examined for their base attributes, including depression, in terms of the Beck depression inventory, which is an index with established reliability and validity developed by Beck et al [24], and the degree of mental health based on the K6, which is a screening questionnaire with established validity and reliability developed by Kessler et al. This questionnaire comprised the following 6 items for screening the state of depression and mood or anxiety disorders in the general population [25]: overtime hours, hours of sleep, marital status, drinking habits, exercise habits, and history of seeking medical advice for mental illness as well as age, gender, and employee number.

### Randomization and Masking

An independent researcher who had no direct contact with the participants used computer-generated randomization with a 1:1 ratio and block size of 6. No stratification was performed and evaluators were masked. Owing to the nature of the intervention, participants were informed of their allocation status.

### Statistical Analysis

A generalized linear model was used for estimation, based on an intention-to-treat (ITT) analysis. To satisfy the ITT requirement that analyses be conducted for all participants, a multiple imputation (MI) method was used on the assumption that data could be considered missing at random. MI allows for uncertainty caused by missing data by generating several different plausible imputed datasets using a set of external covariates and appropriately combining results obtained from each [26,27].

The effect was calculated by subtracting the baseline outcome scores from those obtained after completion of 3 months of homework. Results are shown as changes in the raw scores for outcomes.

To analyze baseline characteristics of the study participants, a test was used for numerical variables and a chi-square test for categorical variables. Statistical significance was set at $P<.05$. IBM SPSS 22 and IBM SPSS Missing Values 22 (SPSS Inc., Chicago, IL, USA) were used for statistical analyses.

## Results

### Participants

The flowchart of this study is shown in Figure 1. Among 241 participants who were prospective participants and who were in the fifth year of their career, 240, excluding 1 who refused participation, gave consent to the study.

**Figure 1.** Study flowchart. CBT: cognitive behavioral therapy.

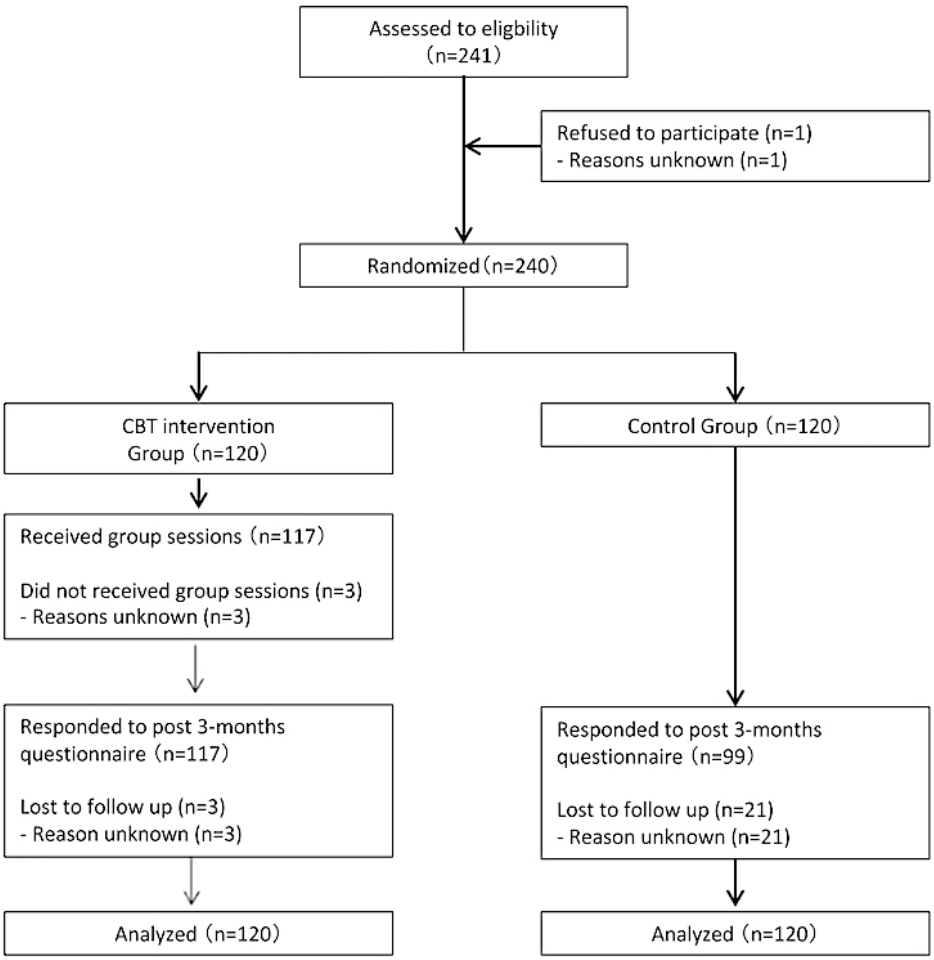

**Table 2.** Baseline characteristics of the participants.

| Characteristics | CBT[a] group (N=120) | Control group (N=120) | Total (N=240) | *P* value |
|---|---|---|---|---|
| **Gender** | | | | .74 |
| Male, n (%) | 39 (32.5) | 56 (46.7) | 95 (38.9) | |
| Female, n (%) | 81 (67.5) | 64 (53.3) | 145 (41.2) | |
| Age in years, mean (SD) | 29.9 (4.3) | 30.5 (6.0) | 30.3 (5.3) | .43 |
| **Monthly mean overtime hours, n (%)** | | | | .85 |
| Almost none | 2 (1.8) | 1 (1.1) | 3 (1.5) | |
| Less than 40 hours | 25 (22.3) | 19 (20.2) | 44 (21.4) | |
| 40-79 hours | 66 (58.9) | 54 (57.4) | 120 (58.3) | |
| 80 hours or more | 19 (17.0) | 20 (21.3) | 39 (18.9) | |
| Missing | 8 (6.7) | 26 (21.7) | 34 (14.2) | |
| **Marital status, n (%)** | | | | .16 |
| Unmarried | 59 (52.2) | 60 (62.5) | 119 (56.9) | |
| Married | 54 (47.8) | 36 (37.5) | 90 (43.1) | |
| No response | 7 (5.8) | 24 (20.0) | 31 (12.9) | |
| **Drinking habits, n (%)** | | | | .53 |
| Not at all | 45 (39.8) | 30 (31.6) | 75 (36.1) | |
| 1-3 days a week | 53 (46.9) | 48 (50.5) | 101 (48.6) | |
| 4-6 days a week | 10 (8.8) | 13 (13.7) | 23 (11.1) | |
| Every day | 5 (4.4) | 4 (4.2) | 9 (4.3) | |
| No response | 7 (5.8) | 25 (20.8) | 32 (13.3) | |
| **Exercise habits, n (%)** | | | | .67 |
| Not at all | 46 (40.7) | 43 (44.8) | 89 (42.6) | |
| 1-2 days a week | 58 (51.3) | 48 (50.0) | 106 (50.7) | |
| 3 or more days a week | 9 (8.0) | 5 (5.2) | 14 (6.7) | |
| No response | 7 (5.8) | 24 (20.0) | 31 (12.9) | |
| **Mean weekday sleep time, n (%)** | | | | .92 |
| Less than 5 hours | 10 (8.8) | 7 (7.3) | 17 (8.1) | |
| 5-6 hours | 77 (68.1) | 66 (68.8) | 143 (68.4) | |
| 7-8 hours | 26 (23.0) | 23 (24.0) | 49 (23.4) | |
| 9 hours or more | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| No response | 7 (5.8) | 24 (20.0) | 31 (12.9) | |
| **Mean weekend sleep time, n (%)** | | | | .42 |
| Less than 5 hours | 2 (1.8) | 0 (0.0) | 2 (1.0) | |
| 5-6 hours | 19 (17.0) | 16 (16.7) | 35 (16.8) | |
| 7-8 hours | 91 (81.3) | 80 (83.3) | 171 (82.2) | |
| 9 hours or more | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| No response | 8 (6.7) | 24 (20.0) | 32 (13.3) | |
| **Poor mental health, n (%)** | | | | .40 |
| Never sought medical advice | 100 (89.3) | 81 (84.4) | 181 (87.0) | |
| Sought medical advice once, but not seeing a doctor currently | 11 (9.8) | 12 (12.5) | 23 (11.1) | |
| Currently seeing a doctor regularly | 1 (0.9) | 3 (3.1) | 4 (1.9) | |
| No response | 8 (6.7) | 24 (20.0) | 32 (13.3) | |

| Characteristics | CBT[a] group (N=120) | Control group (N=120) | Total (N=240) | *P* value |
|---|---|---|---|---|
| K6, mean (SD) | 3.24 (3.80) | 3.83 (4.27) | 3.51 (4.03) | .29 |
| Tendency to perceive difficult situations as controllable, mean (SD) | 3.14 (0.85) | 3.12 (0.80) | 3.13 (0.83) | .86 |
| Ability to perceive multiple alternative explanations, mean (SD) | 3.34 (0.84) | 3.10 (0.86) | 3.23 (0.85) | .04 |
| Ability to generate multiple alternative solutions, mean (SD) | 3.37 (0.91) | 3.28 (0.89) | 3.33 (0.90) | .48 |
| Subjective distress, mean (SD) | 6.03 (1.88) | 6.28 (2.14) | 6.14 (2.00) | .37 |

[a]CBT: cognitive behavioral therapy.

**Table 3.** Effect of intervention by the group cognitive behavioral therapy.

| Variables | Intervention group, mean change (SE[a]) | Control group, mean change (SE) | Mean difference (95% CI) | *P* value | Effect size (d) |
|---|---|---|---|---|---|
| **Cognitive flexibility** | | | | | |
| Tendency to perceive difficult situations as controllable | 0.10 (0.08) | −0.19 (0.11) | 0.29 (0.02-0.56) | .03 | 0.29 |
| Ability to perceive multiple alternative explanations | 0.31 (0.10) | −0.26 (0.11) | 0.57 (0.27-0.86) | <.01 | 0.52 |
| Ability to generate multiple alternative solutions | 0.14 (0.12) | −0.15 (0.12) | 0.29 (−0.03 to 0.60) | .08 | 0.24 |
| Subjective psychological distress | −0.79 (0.24) | −0.13 (0.21) | 0.66 (0.04-1.28) | .04 | 0.28 |

[a]SE: standard error.

The 240 participants were randomly divided into the intervention group and control group, each comprising 120 individuals. Of the 120 participants in the intervention group, 117 received group education. The remaining 3 who did not receive group education did not respond to the follow-up survey performed after 3 months of intervention. Reasons for the lack of response were not obtained, and the number of implementations of the Web-based program was unknown. In the control group, 99 participants responded to the follow-up survey after the intervention, whereas 21 did not (for reasons unknown). This study did not exacerbate any existing psychological problems of any participants.

### Baseline Characteristics

Table 2 shows baseline data. In regard to the male:female ratio of the participants, 39 (32.5%) of 120 individuals were men in the intervention group, whereas 56 (46.7%) were men in the control group. The mean age was 29.9 years (SD 4.3) in the intervention group and 30.5 years (SD 6.0) in the control group. There was no statistically significant difference in lifestyle or base attributes such as gender, age, years of service, position, overtime hours, hours of sleep, marital status, drinking habits, exercise habits, history of seeking medical advice for mental illness, and degree of mental health.

### Effects of the Training Program

Table 3 shows the effect of intervention by the group CBT. On comparing the scores before the intervention and after 3 months of the intervention, scores of outcomes related to cognitive flexibility, that is, “tendency to perceive difficult situations as controllable” and “ability to perceive multiple alternative explanations for difficult situations,” were significantly improved in the intervention group (mean difference 0.29 [95% CI 0.02-0.56], d=0.29 and mean difference 0.57 [95% CI 0.27-0.86], d=0.52, respectively). Although the outcome “ability to generate multiple alternative solutions to difficult situations” was also improved in the intervention group, the difference was not statistically significant (mean difference 0.29 [95% CI −0.03 to 0.60], d=0.24). In addition, the score for the degree of subjective distress was significantly decreased in the intervention group compared with the control group (mean difference 0.66 [95% CI 0.04-1.28], d=0.28).

## Discussion

### Principal Findings

The results of this study suggest that simple stress management training using CBT with elementary schoolteachers contributes to improvement of cognitive flexibility and reduction of subjective distress among these teachers.

Teachers are surrounded by diverse stress factors. Teachers in Japan must cope with various tasks and strive to solve problems of students and their parents. In the context of these diverse issues, it is suggested that reducing the risk of burnout of teachers requires teachers to recognize problems correctly and respond appropriately to a situation. Namely, it is desirable to acquire realistic and adaptive stress-coping behaviors based on high cognitive flexibility [10-12]. Stated differently, cognitive flexibility is the ability or tendency to abandon an unhelpful cognitive strategy and choose a different one when experiencing a problem that is difficult to fix [28]. This ability is indispensable in stress management of teachers who are often faced with student- or parent-related issues that are difficult to resolve. It has also been pointed out that cognitive flexibility contributes to not only prevention of burnout but also nurturing of prompt judgment for difficult tasks and improvement of the ability to recognize even a slight environmental change and to cope with it [18,29]. Teachers are also required to have the ability to promptly cope with consecutive daily problems and to quickly notice and react to changes in the atmosphere of students and the class. Therefore, teachers who have high

cognitive flexibility may prevent a problem from growing through such coping ability, thereby reducing the number of stressors they face. Thus, improvement of cognitive flexibility seems important in the enhancement of stress management skills of teachers.

In this study, greater importance was placed on provision of a feasible program for busy teachers. Regarding mental health measures in the occupational field, previous intervention studies using CBT for individuals or groups have shown beneficial effects such as alleviation of depression or anxiety, reduction of stress [30-32], and improvement of absenteeism [30]. It has also been reported that CBT has a favorable effect on positive dimensions of mental health, such as improvement of the quality of work [30], quality of life [31], work functioning [26], and performance [30,31]. However, intervention programs used in these studies require a lot of time and continuous involvement of CBT specialists, and are, therefore, difficult to implement in the workplace in many cases. In this regard, recent years have seen the implementation of efficacy studies using a simplified CBT program by Internet, email, or telephone in the occupational field. However, most of these programs required much time to complete or frequent exchange of emails or telephone calls [32-37]. This study provided a very simple program consisting of 120-min group education and at least 3 sessions of homework (each session required a run-time of about 30 min) based on a simple Web-based CBT program. This was because we gave importance to the feasibility of the program for a greater number of healthy teachers while minimizing harm to work.

In addition, this study used some mechanisms to maintain motivation for training. Because CBT intervention in healthy subjects may be associated with low motivation for intervention, unlike patients who seek treatment, we emphasized to participants that training based on the principles of CBT in group education would be useful for coping with work stress and for improvement of productivity [38,39]. It has also been reported that reminding increases the implementation rate when CBT is performed on the Internet [40]. Therefore, 6 emails from a health nurse to urge completion of homework were designed to be delivered to each participant during the 3 months of homework. Furthermore, to raise the implementation rate, group education was provided during working hours, and homework was made feasible at home as well as in the workplace. Although the implementation rate of homework was not determined in this study, we presume that these mechanisms contributed to improvement of the implementation rate of homework.

## Limitations

This study had some limitations. First, evaluation indices were our original inquiry items. Although validated scales that evaluate psychological stress are present, and a limited number of scales for cognitive flexibility have been proposed, all these scales include many items. For this study, we chose to use simple questionnaire scales at the stage of study planning. Due to this, a 1-item scale was used for each outcome. Second, participants were limited to teachers in a city who were in the fifth year of their career. To increase the general validity of this study, this issue should be studied in a randomized controlled trial (RCT) design under wider conditions. Third, homework implementation status was not evaluated. This was aimed at reducing burden on the participants. However, because homework is considered to play an important part in CBT, it would have been desirable if we had analyzed in detail how often the participants performed the simplified CBT program and whether and how closely the number of implemented homework sessions was correlated with the effect of CBT. Fourth, evaluation of outcomes was completed only at 3 months after the completion of intervention. The decision to do this was made at the stage of study planning to reduce burden on the participants. However, longer follow-up would have been desirable, considering that the amount of work varies according to the time of year, and for the purpose of examining the long-term effect.

## Conclusions

This study was the first to examine whether an intervention using CBT in teachers would be effective for enhancement of the cognitive flexibility of teachers and alleviation of their subjective distress. The results of this study show that a simple intervention using Web-based CBT enhanced the cognitive flexibility of teachers and alleviated their subjective distress. Because the subjects of this study were busy schoolteachers, the methods of intervention and evaluation were simplified to the maximum possible extent. Therefore, this study had some limitations in its general validity, but it is of major significance that a useful means for stress management of teachers has been proposed. It is desirable that more useful programs using interventions based on CBT be developed and that a number of RCTs be performed to evaluate their effects appropriately.

## Acknowledgments

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## Conflicts of Interest

None declared.

## Multimedia Appendix 1

CONSORT-EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 10MB - resprot_v7i1e32_app1.pdf ]

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## Abbreviations

**CBT:** cognitive behavioral therapy
**ITT:** intention-to-treat
**MI:** multiple imputation
**RCT:** randomized controlled trial


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Protocol

# One Pass Thalamic and Subthalamic Stimulation for Patients with Tremor-Dominant Idiopathic Parkinson Syndrome (OPINION): Protocol for a Randomized, Active-Controlled, Double-Blinded Pilot Trial

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## Abstract

**Background:** Besides fluctuations, therapy refractory tremor is one of the main indications of deep brain stimulation (DBS) in patients with idiopathic Parkinson syndrome (IPS). Although thalamic DBS (ventral intermediate nucleus [Vim] of thalamus) has been shown to reduce tremor in 85-95% of patients, bradykinesia and rigidity often are not well controlled. The dentato-rubro-thalamic tract (DRT) that can directly be targeted with special diffusion tensor magnetic resonance imaging sequences has been shown as an efficient target for thalamic DBS. The subthalamic nucleus (STN) is typically chosen in younger patients as the target for dopamine-responsive motor symptoms. This study investigates a one-path thalamic (Vim/DRT) and subthalamic implantation of DBS electrodes and possibly a combined stimulation strategy for both target regions.

**Objective:** This study investigates a one path thalamic (Vim/DRT) and subthalamic implantation of DBS electrodes and a possibly combined stimulation strategy for both target regions.

**Methods:** This is a randomized, active-controlled, double-blinded (patient- and observer-blinded), monocentric trial with three treatments, three periods and six treatment sequences allocated according to a Williams design. Eighteen patients will undergo one-path thalamic (Vim/DRT) and STN implantation of DBS electrodes. After one month, a double-blinded and randomly-assigned stimulation of the thalamic target (Vim/DRT), the STN and a combined stimulation of both target regions will be performed for a period of three months each. The primary objective is to assess the quality of life obtained by the Parkinson's Disease Questionnaire (39 items) for each stimulation modality. Secondary objectives include tremor reduction (obtained by the Fahn-Tolosa-Marin tremor rating scale, video recordings, the Unified Parkinson's disease rating scale, and by tremor analysis), psychiatric assessment of patients, and to assess the safety of intervention.

**Results:** At the moment, the recruitment is stopped and 12 patients have been randomized and treated. A futility analysis is being carried out by means of a conditional power analysis.

**Conclusions:** The approach of the OPINION trial planned to make, for the first time, a direct comparison of the different stimulation conditions (Vim/DRT, compared to STN, compared to Vim/DRT+STN) in a homogeneous patient population and, furthermore, will allow for intraindividual comparison of each condition with the "quality of life" outcome parameter. We hypothesize that the combined stimulation of the STN and the thalamic (Vim/DRT) target will be superior with respect to the

patients' quality of life as compared to the singular stimulation of the individual target regions. If this holds true, this work might change the standardized treatment described in the previous section.

**Trial Registration:** ClinicalTrials.gov: NCT02288468; https://clinicaltrials.gov/ct2/show/NCT02288468 (Archived by WebCite at http://www.webcitation.org/6wlKnt2pJ); and German Clinical Trials Register: DRKS00007526; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00007526 (Archived by WebCite at http://www.webcitation.org/6wlKyXZZL).

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**KEYWORDS**

Parkinson´s disease, Deep brain stimulation, Dentato-rubro-thalamic tract, Tremor, Ventral intermediate nucleus of thalamus (Vim), Subthalamic nucleus (STN)

## Introduction

Tremor is the most salient symptom of Parkinson's disease (idiopathic Parkinson syndrome [IPS]). Other symptoms include bradykinesia, rigidity, and postural instability. As much as 75% of patients with IPS show resting tremor. Initially, tremor is typically unilateral and might be only visible during stressful situations. In the later stage of the disease it becomes bilateral.

The typical parkinsonian tremor is a resting tremor with or without an additional postural and/or kinetic tremor at the same tremor frequency. This is the most frequent tremor in Parkinson's disease, termed type I tremor. Less than 10% of Parkinson patients develop a resting tremor and a postural tremor of different frequencies, termed type II tremor. A minority of IPS patients present a postural and/or kinetic tremor only, termed type III tremor.

Around 20% of patients with IPS will progress into candidates for Deep Brain Stimulation (DBS) in an advanced stage of the disease. DBS has become a standard treatment for the advanced stages of IPS [1,2,3]. Besides motor fluctuations, therapy refractory tremor (type I and to some extent type II) is one of the main indications of DBS in IPS [4].

First studies have shown that thalamic DBS, which targets the ventral intermediate nucleus (Vim) of thalamus, can effectively reduce Parkinson's disease (PD) tremor (95%). In larger cohorts, this number was reduced to 85% favorable outcome [5,6]. It was also reported that the other symptoms of IPS are not favorably influenced with thalamic DBS and while tremor can be nicely controlled over the years, bradykinesia and rigidity are not well controlled under stimulation [6]. We have recently provided evidence that a fiber structure, the dentato-rubro-thalamic tract (DRT), that traverses the thalamic Vim region is a powerful target of thalamic Vim DBS. This structure can be directly targeted with the aid of diffusion tensor magnetic resonance imaging (DTI) sequences [7]. The use of subthalamic nucleus (STN) DBS shows effects on tremor but typically does not have dramatic initial effects on tremors like Vim-DBS does. However, STN DBS also reduces the other cardinal symptoms of IPS which Vim-DBS does not [8] [9]. There are anecdotal reports on pure STN stimulation's inability to effectively reduce tremor, hence the need to additionally stimulate the thalamic region. However, in recent years, STN stimulation has become the main treatment option for refractory IPS. The main indication for STN-DBS remains fluctuations in movement after long-standing dopaminergic medication [3]. Patients who suffer from tremor on top of these symptoms (equivalent type IPS) and who show some improvement with dopaminergic medication are likely to improve under STN-DBS [8]. However, different considerations apply for tremor-dominant IPS with therapy refractory tremor:

A. In younger patients with tremor-dominant IPS, STN-DBS rather than thalamic (Vim/DRT) DBS appears to be the better option because early onset IPS is known to enter motor fluctuations in a later stage of the disease. These symptoms will likely respond to STN-DBS.
B. Older patients who suffer from tremor-dominant IPS are less likely to develop motor fluctuations. Because of the higher complication rate of stimulation of the STN in this patient group [2], thalamic DBS is typically recommended.
C. Especially older patients receiving thalamic DBS might—in a later stage of the disease—suffer from insufficient symptom control and these patients might benefit from additional STN surgery [10]. At this time, however, these patients might already be in a risk group for STN-DBS [2].

With this study, we will try to understand if patients with tremor-dominant IPS or patients with equivalent type IPS who perceive tremor to be their dominant symptom will benefit from a one-path thalamic and STN implantation of DBS electrodes and, possibly, a combined stimulation strategy for both target regions that is adjustable for the distinct target regions over time. Disease-related quality of life was chosen as the primary outcome. As it has been shown in the EARLYSTIM Study, this allows a global assessment of beneficial and adverse effects in a way that subjectively matters to the patient [1].

### Trial Purpose and Rationale

The proposed trial aims to investigate a combined approach to thalamic/subthalamic DBS for the treatment of patients with tremor-dominant IPS or patients with equivalent type IPS who perceive tremor to be their dominant symptom. As stated above, consensus exists for the application of STN versus thalamic (Vim/DRT) DBS in different age groups. While the younger age group appears to be clear candidate for STN-DBS, the older patient group (>60 years) remains to be problematic because of the above-mentioned reasons.

At the beginning of recruitment we could not detect any controlled study with an intrapatient comparison of thalamic versus STN DBS. We have performed a PubMed search (search as of 15 October 2014) with the search terms "DBS AND tremor

AND Parkinson AND Vim AND STN". In addition, we performed a search for (currently running) clinical trials on the World Health Organization International Clinical Trials Registry Portal (search as of 15 October 2014) with the search terms "DBS tremor parkinson" and "DBS tremor" and we did not find any other comparable trial recruiting and/or treating PD patients. There are case series only describing patients who had previous thalamus operation (Vim/DRT-DBS) and later received additional electrodes in the STN [10,11].

Recently we implanted bilateral octopolar DBS electrodes in the STN additionally traversing the DRT region via a parietal image-assisted approach in two patients allowing compassionate use of a combined stimulation of two tremor targets (STN and DRT) [12]. Both patients showed immediate and sustained improvement of their tremor and the symptoms of the bradykinetic syndrom, bilaterally.

## Methods

### Design

This is a randomized, active-controlled, double-blinded (patient- and observer-blinded), monocentric trial with three treatments, three periods, and six treatment sequences allocated according to a Williams design. The trial flow is illustrated in Multimedia Appendix 1. This monocentric study will be conducted at the Department of Stereotactic and Functional Neurosurgery in close collaboration with the Department of Neurology, both at the Freiburg University Medical Center, Germany.

The primary objective of this trial is to assess whether Quality of Life (QoL), obtained by the Parkinson's Disease Questionnaire (PDQ-39) in Parkinson patients with combined Vim/DRT-DBS and STN-DBS is superior to treatment with either Vim/DRT-DBS or STN-DBS. This will be determined through assessment over a period of three months after implantation of Boston Scientific's Vercise Deep Brain Stimulation System through the Vim/DRT into the STN using a posterior trajectory.

The secondary objectives are:

1. To show advantage of combined STN+Vim/DRT-DBS in tremor reduction in comparison to Vim/DRT-DBS or STN-DBS obtained by Fahn-Tolosa-Marin tremor rating scale (FTMTRS), video recording, the Unified Parkinson's disease rating scale (UPDRS, part III, items 20 & 21), and by tremor analysis
2. To show superiority of combined STN+Vim/DRT-DBS in motor symptoms of Parkinson's disease in comparison to Vim/DRT-DBS or STN-DBS obtained by Unified Parkinson's disease rating scale (UPDRS, part III except items 20 & 21)
3. Psychiatric assessment of patients
4. To assess safety of intervention

### Participant Recruitment

Patients suffering from Parkinson's disease who are referred to our department due to disabling medically resistant resting and/or postural tremor as their major complaint are informed about this study. Patients who give their informed consent are registered in the trial and undergo the screening procedures. Patients who gave their informed consent but do not undergo stereotactic surgery are regarded as screening failures.

Patients with Parkinson's disease of both genders will be enrolled into this trial. No gender ratio has been stipulated. Inclusion and exclusion criteria are listen in Textbox 1.

A sample size of 18 male or female patients was calculated (details below). Recruitment will be stopped after the twelfth patient has completed his/her end of study visit (visit W40, 40 weeks after implantation of DBS system). A futility analysis will be carried out by means of a conditional power analysis. Based on the results of this analysis the study will either be continued or stopped.

### Study Events and Assessments

#### *Screening*

Screening assessments will be performed within 28 days prior to implantation. The patient will be admitted to hospital for this visit and inclusion and exclusion criteria are checked and validated. The complete pretherapeutic work-up includes a physical examination, consisting of a neurological examination and vital signs (including weight and height), medical history, demography, a pregnancy test in women of childbearing potential, Mattis Dementia Rating Scale, PDQ-39, UPDRS, FTMTRS with Video recording, CGI-I, tremor analysis, psychiatric assessment, PD medication, concomitant medication, L-Dopa equivalent dose (LED) and a cranial MRI.

#### *Implantation of the Investigational Medical Device*

The investigational medical device (IMD) for this study is Boston Scientific's Vercise Deep Brain Stimulation System. This device is CE-marked but will not be used within the intended use for this clinical trial. The IMD will be implanted and programmed by the investigator. The investigator or authorized study personnel will document the implantation of each device in the respective forms. The patient will be admitted to hospital and the following assessments will be performed: (1) cranial computed tomography before implantation (planning); (2) cranial computed tomography after implantation (corroboration of electrode position); (3) concomitant medication; and (4) adverse events.

#### *Imaging*

Anatomical and diffusion tensor imaging is performed on a clinical 3 Tesla MRI system (Siemens Magnetom Trio Tim System 3T, Erlangen, Germany) a day before surgery under mild sedation with oral Lorazepam (1 - 2.5mg, Pfizer, Berlin, Germany) using a 12-channel head coil.

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

Inclusion criteria

1. Male or female patients aged ≥ 35 and ≤ 75 years with a life expectancy of at least 5 years
2. Patients with Parkinson's disease according to the criteria of the British Brain Bank as diagnosed by a neurologist specialized in movement disorders
3. Parkinson patients are included with a medical treatment resistant and disabling resting and/or postural tremor as their major complaint and with a less prominent or absent hypokinetic-rigid component of their disease.
4. Absence of postural instability (which could be aggravated under STN DBS)
5. Hoehn & Yahr stage 1-3. After stage 3 patients will show increased incidence of falling that can be aggravated by (typical) STN DBS
6. Disease duration for at least 2 years
   - and routine DAT-scan shows clear indication for Parkinsonism
   - and atypical Parkinson syndromes are ruled out by routine glucose (FDG) PET
7. PDQ-39 to be completed within 42 days prior to surgery
8. Written informed consent

Exclusion criteria

1. Major Depression with suicidal thoughts
2. Dementia (Mattis Dementia Rating Score ≤ 130)
3. Patients with lifetime primary psychotic disorder, schizophrenia, or schizoaffective disorder
4. Patients with acute psychosis as diagnosed by a psychiatrist
5. Nursing care at home
6. Unable to give written informed consent
7. Surgical contraindications like deformed or displaced or not discernable target region, scarring after brain disease (infarction), need for continuous anticoagulation that cannot be bridged in order to obtain normal coagulation
8. Patients with advanced stage cardiovascular disease
9. Patients under immunosuppressive or chemotherapy because of malignant disease
10. Patients who had previous intracranial surgery
11. Patients who are already under DBS therapy
12. Patients with aneurysm clips
13. Patients with cochlear implants
14. Simultaneous participation or previous participation within 30 days prior to start of screening in a clinical trial involving investigational medicinal product(s) or investigational medical device(s)
15. Medications that are likely to cause interactions in the opinion of the investigator
16. Known or persistent abuse of medication, drugs or alcohol
17. Persons who are in a relationship of dependence/employment with the sponsor or the investigator
18. Fertile women not using adequate contraceptive methods, such as female condoms, diaphragm or coil, each used in combination with spermicides; intra-uterine device; hormonal contraception in combination with a mechanical method of contraception
19. Current or planned pregnancy, nursing period
20. Contraindications according to device instructions or Investigator's Brochure:
    - Diathermy: Shortwave, microwave, and/or therapeutic ultrasound diathermy. The energy generated by diathermy can be transferred to the Vercise DBS System, causing tissue damage at the contact site resulting in severe patient injury or death.
    - Magnetic Resonance Imaging (MRI): Patients implanted with the Vercise DBS System should not be subjected to MRI.
    - Patient incapability: Patients who are unable to properly operate the Remote Control and Charging System should not be implanted with the Vercise DBS System.
    - Poor surgical risks: The Vercise DBS System is not recommended for patients who-—because of their primary disease or additional co-morbidities—are not likely to benefit from the DBS system implantation.

1. Anatomical sequences:
   a. Three-dimensional (3D) magnetization-prepared rapid gradient-echo (MP-RAGE), repetition time (TR) 1 390 ms, echo time (TE) 2.15 ms, inversion time (TI) 800 ms, Flip angle 15°, voxel-size 1.0×1.0×1.0 $mm^3$, acquisition time 3:15 min.
   b. 3D T2 SPACE-sequence, TR 2 500 ms, TE 231 ms, echo train length 141, flip angle variable, voxel-size 1.0×1.0×1.0 $mm^3$, acquisition-time 6:42 min.
2. Diffusion tensor imaging:
   a. Single shot 2D SE EPI, TR 10 000 ms, TE 94 ms, Diffusion Values b=0 s/$mm^2$, b=1000 s/$mm^2$, diffusions-directions 61, slice count 69, voxel-size 2.0×2.0×2.0 $mm^3$, acquisition time 11:40 min. Deformation correction of the EPI sequence according to Zaitsev et al. 2004 [13].

Deterministic Fiber tracking is performed on a Linux workstation using StealthViz DTI (Medtronic Navigation, Louisville, Colorado). An internal transfer procedure is used to fuse the line-graphic depiction of the DRT to the DICOM (Digital Imaging and Communications in Medicine) image that further serves for navigation purposes. With this procedure, the DRT becomes part of the stereotactic planning data. Fiber tracking of the cerebello-thalamo-cortical network (DRT) and surrounding structures (cortico-spinal tract) have been previously described [7,14-16].

### *Surgical procedure*

After administration of standard antibiotic prophylaxis, a stereotactic frame (Leksell, Elekta, Stockholm, Sweden) was placed under local anesthesia. A Computed Tomography (CT) scan was performed and the image data were transferred to the planning workstation (Framelink 5.0, Medtronic SNT, Louisville, CO). The previously acquired MRI sequences and the DTI FT rendition of the DRT (as part of the stereotactic DICOM data) were coregistered with the stereotactic CT scan and the trajectories were planned taking into account mid-commissural point (MCP) coordinates (for STN we typically use: x=12; y-2, z=-4) and imaging of the targeted structures (DRT and STN). Where necessary, based on the imaging, the target was refined based on the direct visualization of the structures.

### *Description of the Operation*

After administration of standard antibiotic prophylaxis, a stereotactic frame (Leksell, Elekta, Stockholm, Sweden) is placed under local anesthesia. A CT scan is performed and the image data are transferred to the planning workstation (Elekta, Stockholm, Sweden). The previously acquired MRI sequences are coregistered with the CT scan and the trajectories are planned, taking into account MCP coordinates and imaging of the targeted structures (Vim/DRT and STN).

The bilateral DBS electrode implantation is performed under local anesthesia with the patient in a semisitting position. Using a microtargeting drive (MicroTargeting Star Drive M/E System, FHC Inc, Bowdoin, ME) a test electrode (Cosman Medical, Inc, Burlington, MA) is inserted through a parietal burr hole in the cranium (see Figure 1). Because of anticipated transventricular routes we do not to use sharp microelectrodes for microrecording, but instead rely on the imaging taking into account that the anterior, lateral, and STN (superior sensorimotor or dorsolateral STN) must be targeted [17]. Macrostimulation is performed to confirm a contralateral clinical benefit (tremor reduction at a low threshold for DRT, additional reduction of bradykinesia and rigidity more distally on the trajectory, in the STN) and to test for side effects (at a high threshold) in 2mm steps starting 4 mm above the individual target regions. The definitive DBS electrodes are then implanted under fluoroscopic control. An implantable pulse generator (Boston Scientific, Natick, MA) is implanted under general anesthesia during the same procedure. Postoperatively, all patients undergo a 3D CT scan to corroborate the final DBS electrode localization.

### *1 Month Off Period*

After implantation, the IMD will remain OFF for a period of 1 month. After implantation of a DBS electrode into the thalamic (Vim/DRT) or the subthalamic (STN) target area, most patients will experience a transient alleviation of their symptoms (rigidity, bradykinesia for STN, tremor for Vim/DRT). This is due to a microlesioning effect from electrode placement. This effect can last as short as days but can also last weeks. During this period programming is complicated because it is hard to differentiate between lesion and stimulation effects. Clinical practice shows that an interval of 3-4 weeks is sufficient between implantation and start of stimulation to get rid of most microlesioning effects. In this interval, medication can be expected to be kept unchanged because of the characteristics of the study population regarded here.

## Week 4 (Baseline, treatment start)

Within 7 days prior to treatment start the patient will be randomized.

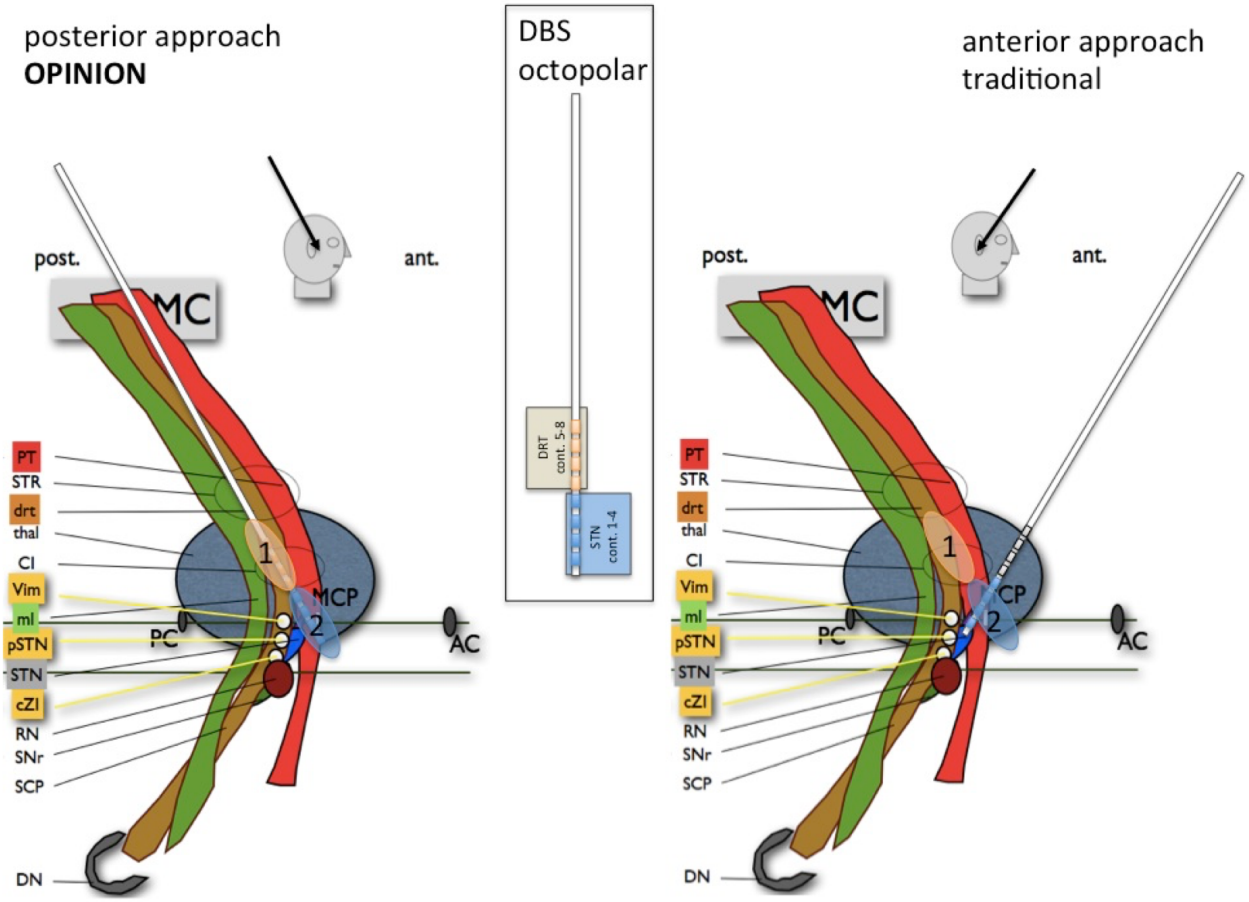
## Assessments at visit Week 4

The patient will be admitted to hospital for this visit. The following assessments have to be performed: PDQ-39, UPDRS, FTMTRS, CGI-I, video recording, tremor analysis, psychiatric assessment, vital signs (including weight), PD medication, concomitant medication, LED, and adverse events.

## Treatment start

Stimulation procedure is conducted by an unblinded investigator, who is not involved in data acquisition. All stimulation contacts will first be checked for impedance as an indicator for cable break, short-circuit or other device-related complications prior to stimulation. Afterwards all eight contacts will be tested for clinical effect on both tremor and hypokinetic-rigid symptoms (rigidity, bradykinesia). Thresholds for side effects and side effects will be evaluated. Therapeutic effects and adverse effects (and between them the therapeutic window) will be noted in a standardized protocol. Stimulation settings will then follow the randomization of the area which has to be stimulated (Vim/DRT, STN or, Vim/DRT-STN). Stimulation parameters are set empirically on the estimation of the investigator based on the testing phase of electrode contacts, with tremor being the primary target symptom.

**Figure 1.** The proposed approach (left) and the traditional approach (right) to the subthalamic nucleus (STN) with dentato-rubro-thalamic tract (DRT) (1) and STN (2) stimulation sites. AC: anterior commissure; PC: posterior commissure; MCP: mid-commissural point; MC: primary motor cortex; CST: cortico-spinal tract; STP superior thalamic peduncle; DRT: dentato-rubro-thalamic tract; thal: thalamus; CI: internal capsule; Vim: ventral intermediate nucleus of thalamus stereotactic target (possibly this is the Vop ventralis oralis posterior nucleus), ml: medial lemniscus; pSTR: posterior subthalamic region; STN: subthalamic nucleus; cZI: caudal zona incerta; RN: red nucleus; SNr: substantia nigra; SCP: superior cerebellar peduncle; DN: dentate nucleus. Figure from [12].




### Week 6, 8 and 12

These visits can be performed either via telephone or at the clinical site. The following assessments have to be performed: PD medication, concomitant medication, LED, and adverse Events.

### Week 16 (first Treatment Switch)

If clinically indicated, the patient will be admitted to hospital for this visit. The following assessments have to be performed: PDQ-39, UPDRS, FTMTRS, CGI-I, video recording, tremor analysis, psychiatric assessment, vital signs (including weight), PD medication, concomitant medication, LED, and adverse events.

Stimulation settings follow the randomization of the area, which has to be stimulated (Vim/DRT, STN or Vim/DRT+STN). Stimulation parameters are set empirically on the estimation of the investigator based on the testing phase of electrode contacts at baseline, with tremor being the primary target symptom.

### Week 18, 20 and 24

These visits will be performed in the same way as visits in week 6, 8 and 12.

### Week 28 (second Treatment Switch)

This visit will be performed in the same way as the week 16 visit.

### Week 30, 32 and 36

These visits will be performed in the same way as visits in weeks 6, 8, and 12.

### Week 40: End of study

If clinically indicated, the patient will be admitted to hospital for this visit. Assessments performed will be the same as those in the week 16 visit.

### Discontinuation criteria

The coordinating investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of a treatment arm or the entire clinical trial.

#### *Premature Termination of One of the Treatment Arms or the Entire Trial*

A treatment arm or the entire clinical trial must be terminated prematurely if:

- The benefit-risk ratio for the patient changes markedly and/or indications arise that the trial patients' safety is no longer guaranteed, defined as: after surgical treatment of the sixth patient, two or more patients experienced severe intra-cranial hemorrhage or ischemia (as diagnosed with computed tomography) or infection and/or severe neurological deterioration (hemiparesis persisting over 24 hours). In this case, recruitment will be stopped and the Data Monitoring Committee (DMC) will discuss continuation of the trial. Bleeding rate is known to be between 1-3% and approx. 0.78% of patients experience a clinically significant bleeding [18] (eg, life changing complications because of persisting disabilities). Therefore, it seems appropriate to temporarily hold the trial if two or more patients out of the first six implanted subjects experience the aforementioned severe complications.
- Following recommendation of the DMC (eg, after futility analysis) the coordinating investigator considers that the termination of the trial is necessary
- The question(s) addressed in the trial can be clearly answered on the basis of an interim analysis
- The questions(s) addressed in the trial can be clearly answered on the basis of results of another trial on the same subject
- An insufficient recruitment rate makes a successful conclusion of the clinical trial appear impossible (eg, less than 3 patients are recruited per year)

### *Premature Discontinuation of Deep Brain Stimulation*

DBS therapy of a patient will be terminated prematurely in the following cases:

- Adverse events (including intercurrent illnesses) which preclude further treatment with the IMD or make further participation in the clinical trial inadvisable because the informational value of the trial results is impaired
- Premature termination of the trial treatment is considered to be medically indicated, eg, because it is subsequently found that inclusion/exclusion criteria were violated
- Continuation of the trial treatment is unacceptable when the risks outweigh the benefits. This is the case if stimulation treatment induces unstable gait and falls or unbearable side effects like severe dyskinesia.
- Pregnancy
- Significant violations of the trial protocol or lack of compliance on the part of the patient
- Logistical reasons (patient changes his/her doctor or hospital or moves to another location)

Follow-up visits will be performed as far as possible.

### *Premature Termination of Trial Participation*

The trial patient can withdraw his/her consent at any time, without having to give reasons, and have his/her entire trial participation terminated prematurely. If a patient withdraws informed consent no further follow-up is possible.

## Biostatistical Planning and Analysis

Before the start of the final analysis a detailed statistical analysis plan will be prepared. This will be completed during the “blind review” of the data, at the latest. This blind review, ie, a checking and assessment of the data, will be performed before the futility analysis and the planned follow-up period without looking at the randomized treatment for each patient. If the statistical analysis plan contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given.

All statistical programming for analysis will be performed with the Statistical Analysis System.

### *Sample Size Calculation*

Based on the standard error of PDQ-39 total score in the EARLYSTIM trial [1], we anticipate a within-person standard deviation of about 14.4 score points for the difference between two treatments. If 18 patients (3x6) are allocated to each of the 6 sequences, a two-sided t-test (analysis of variance for difference of means in crossover designs) at significance level 5% has 80% power to detect a difference if the true mean difference between STN+Vim/DRT-DBS and STN-DBS (or Vim/DRT-DBS) is 10.2 points (effect size: 0.71; nQuery Advisor version 7.0).

### *Randomization*

Fax randomization will be performed within 7 days prior to treatment start. The patient identification code assigned for the trial will be entered on the randomization form and the fully completed form will then be faxed to the Central Randomization Office of the Clinical Trials Unit. Patients will be randomized to 6 treatment sequences. The block-lengths will be documented separately and will not be disclosed. The randomization code will be generated by the Clinical Trials Unit using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigative staff. Patients will be randomized to 6 treatment sequences according to a Williams design. The randomization code will be produced by validated programs based on the Statistical Analysis System.

### *Blinding*

Participating patients and (external) observers and raters are blinded. Since stimulation procedure (eg, start of treatment, treatment switch, adjusting of stimulation parameters/settings) is conducted by an unblinded investigator who is not involved in data acquisition, blinding will be maintained for patients and for observers and raters.

### *Description of the Primary Efficacy Analysis and Population*

Analysis of the primary endpoint will be done by intention to treat in a linear mixed model with baseline score, treatment, period and sequence included as fixed effects [18], and within-patient correlation modelled by a compound symmetry covariance matrix to account for the random subject effect. The sequence effect will be dropped if nonsignificant at the 5%-level. In the final model, treatment comparisons will be based on contrasts estimated by least-squares means with two-sided 95% confidence intervals. For confirmatory analysis, a closed test procedure will be applied: First, the null-hypothesis of equal means in the three arms will be tested at a significance level of 5%. Only if it can be rejected will the three pairwise treatment

comparisons be carried out in a confirmatory fashion. This multiple test procedure assures control of the multiple type I error rate of 5%. In addition, all fixed effects will be tested descriptively at the two-sided 5%-level. Recruitment will be stopped after 12 patients have been randomized and treated. Then, a futility analysis will be carried out by means of a conditional power analysis. The conditional probability to attain a significant result for STN+Vim/DRT-DBS versus STN-DBS and Vim/DRT-DBS, respectively, after recruitment of another 6 patients, given the results of the first 12 patients, will be estimated. Three scenarios will be considered: (1) the effect size for the 6 patients to follow will be estimated from the results of the first 12 patients, (2) the upper (optimistic) limits of the 95% confidence intervals for the treatment effects estimated from the first 12 patients will be used, and (3) the treatment effect for the 6 patients to follow will be assumed to be 10.2 points as anticipated in the sample size calculation. The optional possibility to stop the trial prematurely for futility after this interim analysis does not inflate the type one error rate. If the conditional power is below 30% in all three chosen scenarios the trial will be stopped. If the conditional power of any of the three scenarios is between 30-50%, the DMC will decide on the continuance of the trial. If the conditional power of any of the three scenarios is above 50% the trial will be continued.

### Ethics and Dissemination

An adequate subject insurance contract has been taken out. The study protocol has been approved by the independent Ethics Committee of the University of Freiburg (reference number EK 38/15) and by the Federal Institute for Drugs and Medical Devices (reference number 94.1.04 - 5660 – 9558). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the DIN EN ISO 14155, and applicable regulatory requirements (eg, German Medical Devices Act, Ordinance on Clinical Trials with Medical Devices). The OPINION trial has been registered in the publicly available registries: ClinicalTrials.gov (NCT02288468) and German Clinical Trials Register (DRKS00007526).

#### *Informed consent*

Before enrolment in the clinical trial, the patient will be informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled.

The treating physician will provide the patient with information about the treatment methods to be compared and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatments will be explained to the patient. During the informed consent discussion, the patient will also be informed about the insurance cover that exists and the insured's obligations. The patient will be given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the patient. In addition, the patient will be given a patient information sheet which contains all the important information in writing. The patient's written consent must be obtained before any trial-specific tests/treatments. For this purpose, the written consent form will be personally dated and signed by the trial patient and the investigator conducting the informed consent discussion.

#### *Safety*

Adverse Events will be documented in the case report form and in the patient’s medical chart (source documents). Serious Adverse Events will be reported according to the provisions set forth in the German Medical Devices Safety Plan Ordinance.

### Data Monitoring Committee

The DMC will consist of the coordinating investigator and the unblinded investigators. As stated above, the trial will be stopped if the conditional power is below 30% in all three scenarios; the trial will continue if the conditional power of any of the three scenarios is above 50%. If the conditional power is between 30–50% the DMC will decide on the continuance of the trial. For this purpose, the DMC will receive unblinded trial data and will discuss whether or not continuation of the trial is ethically justified.

The DMC will also receive data on severe intracranial hemorrhages or ischemias or infections and/or severe neurological deteriorations. In case of higher occurrence rates than expected, the DMC will discuss whether the trial should be stopped prematurely.

## Results

Recruitment to the OPINION trial opened in July 2015 and will close in September 2019. At the time of manuscript submission, the recruitment is stopped; 12 patients have been randomized and treated and a futility analysis is being carried out by means of a conditional power analysis.

## Discussion

The approach planned to investigate in the OPINION trial will, for the first time, allow for the direct comparison of the different stimulation conditions (Vim/DRT, STN, and Vim/DRT+STN) in a homogeneous patient population and will furthermore allow an intraindividual comparison of each condition with the outcome parameter “quality of life”. We hypothesize that the combined stimulation of the STN and the thalamic (Vim/DRT) target will be superior with respect to the patients’ quality of life as compared to the singular stimulation of the individual target regions. If this holds true, this work might change the standardized treatment described in the previous section.

### Acknowledgments

This trial receives financial support by Boston Scientific.

## Authors' Contributions

This study was designed by VC, FA, MR and PR. The manuscript was written by PR. VC is the principal investigator of the trial. CJ performed the sample size calculation and planned the statistical analyses. JK made substantial contributions to the organization of this trial. PR, TPi, TPr an MR are involved in trial implementation. CJ, JK, VC critically revised the manuscript. All authors have read and approved the manuscript.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Trial flow of the randomized, active-controlled, double blinded (patient and observer blinded), monocentric trial with three treatments, three periods and six treatment sequences allocated according to a Williams design.

[PDF File (Adobe PDF File), 1MB - resprot_v7i1e36_app1.pdf ]

## Multimedia Appendix 2

CONSORT-EHEALTH (V 1.6.1).

[PDF File (Adobe PDF File), 694KB - resprot_v7i1e36_app2.pdf ]

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## Abbreviations

**CT:** Computed tomography
**CGI-I:** Clinical Global Impression – Global Improvement Scale
**DBS:** Deep brain stimulation
**DRT:** Dentato-rubro-thalamic tract
**DICOM:** Digital Imaging and Communications in Medicine
**DTI FT:** Diffusion tensor imaging fiber tractography
**DTI:** Diffusion tensor magnetic resonance imaging
**FTMTRS:** Fahn-Tolosa-Marin tremor rating scale
**IMD:** Investigational medical device
**IPS:** Idiopathic Parkinson syndrome
**LED:** L-Dopa equivalent dose
**MCP:** Mid-commissural point
**MRI:** Magnetic Resonance Imaging
**PD:** Parkinson’s disease
**PDQ-39:** Parkinson’s Disease Questionnaire -39 items
**QoL:** Quality of life
**STN:** Subthalamic nucleus
**TE:** Echo time
**TR:** Repetition time
**UPDRA:** Unified Parkinson’s disease rating scale
**Vim:** Ventral intermediate nucleus

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Protocol

# Comparing Short Dental Implants to Standard Dental Implants: Protocol for a Systematic Review

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## Abstract

**Background:** Short dental implants have been proposed as a simpler, cheaper, and faster alternative for the rehabilitation of atrophic edentulous areas to avoid the disadvantages of surgical techniques for increasing bone volume.

**Objective:** This review will compare short implants (4 to 8 mm) to standard implants (larger than 8 mm) in edentulous jaws, evaluating on the basis of marginal bone loss (MBL), survival rate, complications, and prosthesis failure.

**Methods:** We will electronically search for randomized controlled trials comparing short dental implants to standard dental implants in the following databases: PubMed, Web of Science, EMBASE, Scopus, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov with English language restrictions. We will manually search the reference lists of relevant reviews and the included articles in this review. The following journals will also be searched: European Journal of Oral Implantology, Clinical Oral Implants Research, and Clinical Implant Dentistry and Related Research. Two reviewers will independently perform the study selection, data extraction and quality assessment (using the Cochrane Collaboration tool) of included studies. All meta-analysis procedures including appropriate effect size combination, sub-group analysis, meta-regression, assessing publication or reporting bias will be performed using Stata (Statacorp, TEXAS) version 12.1.

**Results:** Short implant effectiveness will be assessed using the mean difference of MBL in terms of weighted mean difference (WMD) and standardized mean difference (SMD) using Cohen's method. The combined effect size measures in addition to the related 95% confidence intervals will be estimated by a fixed effect model. The heterogeneity of the related effect size will be assessed using a Q Cochrane test and I2 measure. The MBL will be presented by a standardized mean difference with a 95% confidence interval. The survival rate of implants, prostheses failures, and complications will be reported using a risk ratio at 95% confidence interval ($P$<.05).

**Conclusions:** The present protocol illustrates an appropriate method to perform the systematic review and ensures transparency for the completed review. The results will be published in a peer-reviewed journal and social networks. In addition, an ethics approval is not considered necessary.

**Trial Registration:** PROSPERO registration number: CRD42016048363; https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048363 (Archived by WebCite at http://www.webcitation.org/6wZ7Fntry)

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**KEYWORDS**

dental implants; dental arch; dental restoration failure; postoperative complications/etiology

## Introduction

Dental implants are considered a treatment option to replace missing teeth in edentulous patients. In many clinical situations, insufficient bone volume is a critical limiting factor for dental implant placement and successful osseointegration. Several surgical techniques have been described to obtain adequate bone volume, including bone grafts, sinus lifting, and nerve transposition. These surgeries are technically sensitive and might cause significant postoperative complications such as graft resorptions, severe pain or neurosensory disturbances. Short dental implants have been proposed as a simpler, cheaper, and faster alternative for the rehabilitation of atrophic edentulous areas to avoid the disadvantages of surgical techniques [1-5].

The definition of short dental implants is still controversial in previous research regarding the cut-off length between short and standard implants. Dental implants with intra-bony lengths of less than 10, 8 or 7 mm are defined as short implants in different studies. In this review, implants with lengths of 8 mm or less are considered short because of the available data in research [1,6,7].

Previous systematic reviews have compared short implants with standard implants in the posterior jaws, maxilla or mandible without regards to comparisons between control groups in native or augmented bones [1,7,8]. This comparison may affect outcomes of short implants and two types of control groups with standard lengths [9-12]. Therefore, we not only aim to update existing reviews in more comprehensive databases such as Web of Science, Scopus and clinical trials registries, but also to supplement existing evidence by incorporating the impact of the control group in native or augmented bones.

Our primary objective is to evaluate the marginal bone loss (MBL) of short implants (4 to 8 mm) compared to standard implants (larger than 8 mm) in edentulous jaws. In addition, the survival rate, complications, and prostheses failure of short and standard implants will be assessed as secondary objectives in this review.

## Methods

### Criteria for Considering Studies for This Review

#### *Types of Studies*

This review will include randomized clinical trials which compared short and standard dental implants in the same study. In these studies, patients were randomized according to a split-mouth or parallel group design to receive short and/or standard implants.

#### *Types of Participants*

Studies examining patients rehabilitated with short and/or standard dental implants will be included. The patients were 18 years or older and either female or male.

#### *Type of Interventions*

The intervention of interest is short dental implants of 8 mm or less in length placed in the maxilla and/or mandible.

Comparisons of interest include short dental implants and standard implants.

#### *Types of Outcomes*

The Primary outcomes will to assess the difference in MBL of short implant (4 to 8 mm) compared to standard implant (larger than 8 mm) in edentulous jaws. In addition, survival rate, complication, and prosthesis failure of short and standard implant will be considered secondary outcomes in the review.

### Search Methods for Identification of Studies

#### *Electronic Searches*

We will search PubMed, Web of Science, EMBASE, Scopus, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov with English language restriction. The following strategy will be used to search PubMed, as listed in Textbox 1.

The PubMed search strategy will be adapted to the syntax and subject headings of the other databases. To complete the electronic search, a manual search in reference lists of relevant reviews (included in this review) in the following journals will be carried out: European Journal of Oral Implantology, Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research.

### Data Collection and Analyses

Two investigators will independently perform the data assessment and extraction using a developed data extraction form. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram shows the study selection process (Figure 1).

The extracted data from each included study will include the following:

1. Study characteristics (author/year of publication, duration of follow up).
2. Short dental implants (number of implants, length and diameter, implant system).
3. Standard dental implants (number of implants, length and diameter, implant system, placement in native or augmented bone).
4. Participant characteristics (number and gender of patients, mean age, number of smokers, arch).
5. Statistics for meta-analysis (mean MBL, implant survival, prosthesis survival, complication).

The main effect size measure in each primary study will be the mean difference between MBL in two arms (groups) after intervention on time intervals. The mean differences will be combined in terms of weighted mean difference (WMD) and standardized mean difference (SMD) by Cohen's method. The effect size for implant survival will be calculated in terms of risk ratio.

Discrepancies to reach a consensus will be discussed and one arbitrator will adjudicate unresolved disagreements.

**Textbox 1.** Search methods for the identification of studies.

**Summary syntax**

#1 (short AND implant) OR “short implant”

#2 Maxilla* OR mandible OR jaws OR “Dental Arches” OR (arch AND dental)

#3 #1 AND #2

#4 (short AND dental AND implant) OR (short AND “dental implant”) OR “short dental implant”

#5 (extra AND short AND implants) OR “extra short implants”

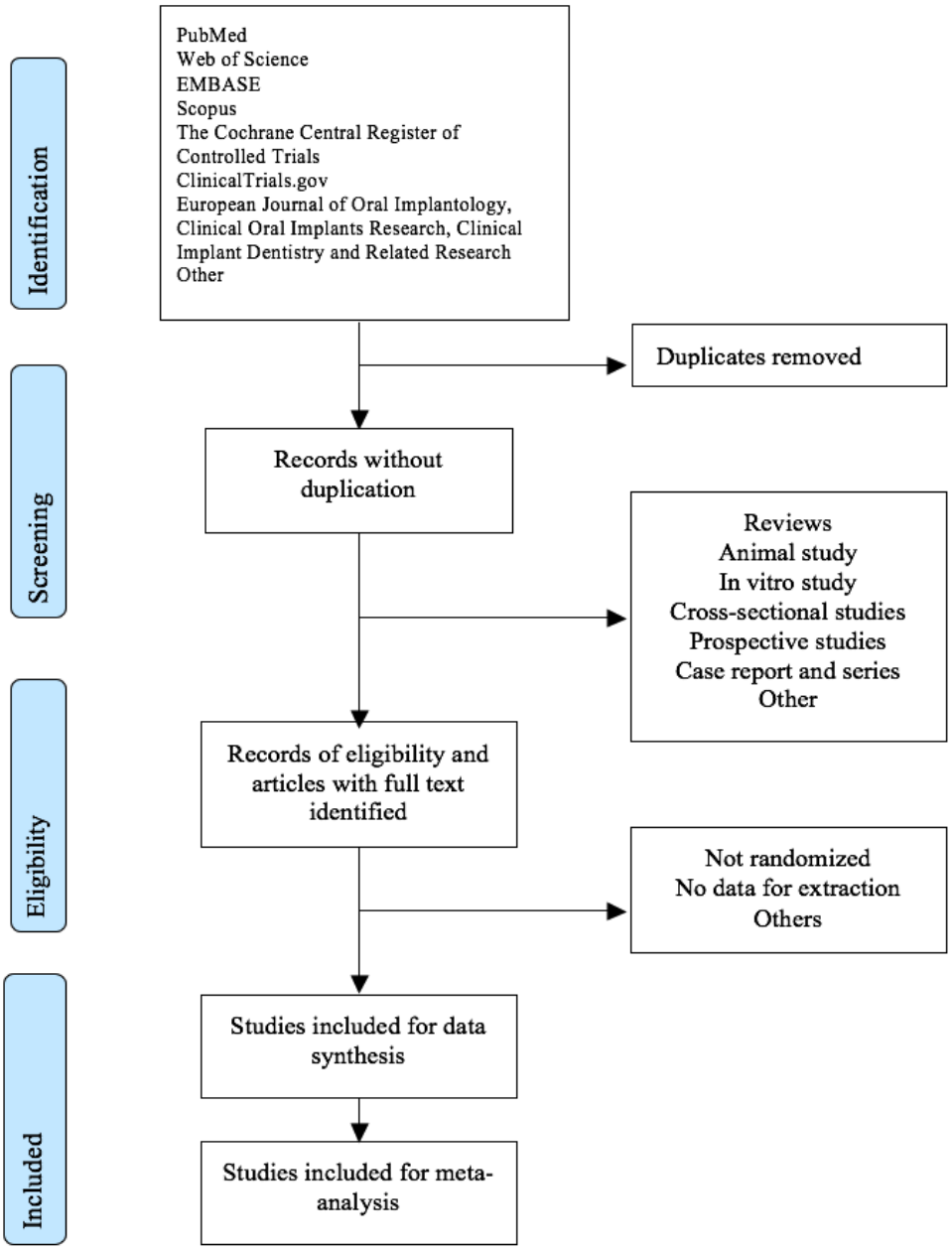
#6 (ultra AND short AND implant) OR “ultra-short implant”

#7 #3 OR #4 OR #5 OR #6

**Complete syntax**

(((short AND implant) OR “short implant”) AND (Maxilla OR mandible OR jaws OR “Dental Arches” OR (arch AND dental))) OR (short AND dental AND implant) OR (short AND “dental implant”) OR “short dental implant” OR (extra AND short AND implants) OR “extra short implants” OR (ultra AND short AND implant) OR “ultra-short implant”

**Figure 1.** Flow diagram of the study selection process based on PRISMA guidelines.



### Assessment of Heterogeneity

The heterogeneity in different effect size measures (WMD, SMD, proportion, etc.) will be assessed by a Q Cochrane test and the related *P* value and $I^2$. The $I^2$ measures will be classified into mild (between 0% and 25%), moderate (between 25.1% and 50.0%), severe (between 50.1% and 75.0%), and highly severe (between 75.1% and 100.0%). The potential sources of heterogeneity will be found by sub-group analysis or meta-regression methods.

### Risk of Bias in Individual Studies

Two investigators will independently evaluate the methodological quality of included articles according to the Cochrane Collaboration tool for risk of bias [13]. The defined questions will be answered as yes, no, or unclear, and the score of each article will be calculated. Disagreements will be resolved by consensus or consulting a third author.

### Strategy for Data Synthesis

The meta-analyses will be carried out using the STATA version 12 by Mantel–Haenszel and Inverse Variance methods. MBL will be assessed by WMD and SMD with 95% confidence intervals. The survival rate of implants, prostheses failures and complications will be evaluated by a risk ratio with 95% confidence interval. The significance level will be set at $P<.05$ and the statistical tests will be two-tailed.

### Analysis of Subgroups or Subsets

The qualitative data will include: author and publication date; length and number of standard implants in native or reconstructed bone; length and number of short implants; number and gender of patients; mean age; number of smokers; evaluated dental arch; outcomes assessed; follow up duration.

The quantitative data will include: first author, MBL, implants survival, prosthesis survival, and complications.

### Assessment of Reporting Biases

The task of assessing publication or reporting bias will be performed by a funnel plot as well as Begg's and Egger's method. If one of the two above-mentioned tests is significant, the Trim and Fill method will be performed to correct the potential reporting bias.

### Sensitivity Analysis

A sensitivity analysis will be used to assess the impact of the outcomes according to the methodological quality items rated by the Cochrane Collaboration tool criteria. Meta-analyses will be performed on high quality studies. The summary table and the review conclusions according to the two meta-analyses will be described. Moreover, the One-Out strategy will be performed by a "metaninf" stata command which is used for assessing impact degree from a specific primary study.

## Results

This protocol of systematic review is aimed at evaluating the MBL of short implants (4 to 8 mm) and standard implants (larger than 8 mm) in edentulous jaws. In addition, the survival rate, complications, and prostheses failure of short and standard implants will be assessed in this review. The outcomes of this review will provide insights on treatment plans that are more preferable and have lower failures and complications. This review is expected to be completed in early-to-mid 2018.

## Discussion

Recently, short dental implants have been proposed as a simpler, cheaper, and faster alternative for the rehabilitation of atrophic edentulous areas to avoid the disadvantages of surgical techniques such as high sensitive technique and postoperative complications. There is no consensus in literature on the performance of short implants compared to standard implants. Some reviews show that MBL, prostheses failures and complication rates of short implants are similar to standard implants. On the other hand, short implants with length less than 8 mm are associated with higher risks of failures due to reduced bone to implant contact [1,5-8].

Other recent systematic reviews were undertaken to compare short implants with standard implants in posterior jaws, maxilla or mandible without comparison between control groups in native or augmented bone [1,7,8]. This protocol updates existing reviews in more comprehensive databases by incorporating the impact of control groups in native or augmented bones.

The primary objective of the study is to evaluate the MBL of short implants (4 to 8 mm) compared to standard implants (larger than 8 mm) in edentulous jaws. In addition, the survival rate, complications, and prosthesis failure of short and standard implants will be assessed as secondary objectives in this review.

### Authors' Contributions

TB, AK, AR, AM and KH were involved in the study design, search strategies development and implantation. TB and KH drafted the manuscript and AK revised it. All authors read, provided feedback, and approved the final manuscript.

### Conflicts of Interest

None declared.

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## Abbreviations

**MBL:** marginal bone loss
**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses
**SMD:** standardized mean difference
**WMD:** weighted mean difference

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Protocol

# Mobile Health Technology Interventions for Suicide Prevention: Protocol for a Systematic Review and Meta-Analysis

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## Abstract

**Background:** Previous research has reported that two of the major barriers to help-seeking for individuals at risk of suicide are stigma and geographical isolation. Mobile technology offers a potential means of delivering evidence-based interventions with greater specificity to the individual, and at the time that it is needed. Despite documented motivation by at-risk individuals to use mobile technology to track mental health and to support psychological interventions, there is a shortfall of outcomes data on the efficacy of mobile health (mHealth) technology on suicide-specific outcomes.

**Objective:** The objective of this study is to develop a protocol for a systematic review and meta-analysis that aims to evaluate the effectiveness of mobile technology-based interventions for suicide prevention.

**Methods:** The search includes the Cochrane Central Register of Controlled Trials (CENTRAL: The Cochrane Library), MEDLINE, Embase, PsycINFO, CRESP and relevant sources of gray literature. Studies that have evaluated psychological or nonpsychological interventions delivered via mobile computing and communication technology, and have suicidality as an outcome measure will be included. Two authors will independently extract data and assess the study suitability in accordance with the Cochrane Collaboration Risk of Bias Tool. Studies will be included if they measure at least one suicide outcome variable (ie, suicidal ideation, suicidal intent, nonsuicidal self-injurious behavior, suicidal behavior). Secondary outcomes will be measures of symptoms of depression. Where studies are sufficiently homogenous and reported outcomes are amenable for pooled synthesis, meta-analysis will be performed. A narrative synthesis will be conducted if the data is unsuitable for a meta-analysis.

**Results:** The review is in progress, with findings expected by summer 2018.

**Conclusions:** To date, evaluations of mobile technology-based interventions in suicide prevention have focused on evaluating content as opposed to efficacy. Indeed, previous research has identified mobile applications that appear to present harmful content. The current review will address a gap in the literature by evaluating the efficacy of stand-alone mobile technology tools in suicide prevention. It is imperative that research identifies the evidence base for such tools in suicide prevention in order to inform policy, guide clinical practice, inform users and focus future research.

**Trial Registration:** PROSPERO International Prospective Register of Systematic Reviews CRD42017072899; https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017072899 (Archived by WebCite at http://www.webcitation.org/6tZAj0yqJ)

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**KEYWORDS**

mHealth; suicide prevention; systematic review; meta-analysis

## Introduction

### Suicide Prevention

Over 800,000 people die due to suicide every year globally, accounting for 1.4% of all deaths worldwide [1]. Suicide occurs regardless of age, and was the second leading cause of death among 15-29 year olds worldwide in 2012. In addition, it is estimated that 25 suicide attempts (100-200 for youth) occur for every death by suicide [2], resulting in more than 400,000 emergency department visits annually in the United States [3]. Suicidal behavior is the result of a complex interaction of psychiatric, psychological, social, and cultural factors [4,5,6]. Prospective studies have attempted to predict which individuals will attempt or die by suicide [7], and a diverse range of risk factors that correlate with suicidal behavior have been proposed to support the identification of those at elevated risk, such as sleep disturbances [8], emotion regulation deficits [9], family history of suicide [10], and chronic pain and illness [11].

Franklin et al [12], in a recent meta-analysis of studies that have attempted to longitudinally predict suicidal thoughts or behavior-related outcomes, found that prediction was only slightly better than chance for all outcomes, and highlighted several fundamental changes needed in future research. They point towards the proliferation of mobile technologies as a means to capture large data sets and to support the expansion of the research-base from a focus on risk *factors* to risk *algorithms*. Furthermore, Kristoufek et al [13], in an attempt to improve the accuracy of suicide estimates, found that estimates drawing on Google search data are significantly better than estimates using previous suicide data alone. Specifically, they found that a greater number of searches for the term "depression" is related to fewer suicides, whereas a greater number of searches for the term "suicide" is related to more suicides.

In parallel, suicide researchers have argued that the Ecological Momentary Assessment (EMA)—high frequency data collection in an individual's usual environment—provides the potential for the development of a temporal, individualized prediction of risk states. Thompson et al [14] tested the ability of EMA to predict individual symptom change in suicidal ideation in a sample of 35 adults diagnosed with interepisode bipolar disorder. The results showed that EMA with Functional Linear Modeling substantially increased the accuracy of predicting study-emergent suicide ideation. By employing measures of negative and positive effects, cross-validated predictions attained 88% sensitivity with 95% specificity for elevated suicidal ideation one week prior to in-person clinician assessment. Such findings indicate that EMA data could sensitively detect the warning signs of suicidal ideation to facilitate improved suicide risk assessment and the timely delivery of preventative interventions [14]. Advances in mobile technologies provide potential opportunities to operationalize EMA research to support the sensitive and timely identification of those at risk of suicide.

### mHealth and Suicide Prevention

Mobile Health (mHealth) is a component of electronic health (eHealth). The Global Observatory for eHealth defines mHealth as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [15]. According to the World Health Organization (WHO), "mHealth involves the use and capitalization on a mobile phone's core utility of voice and short messaging service as well as more complex functionalities and applications including general packet radio service, third and fourth generation mobile telecommunications (3G and 4G systems), global positioning system, and Bluetooth technology" [15].

Mobile devices offer a potentially powerful means of delivering evidence-based interventions with greater specificity to the individual and at the time when the intervention is needed. mHealth programs and interventions use mobile technology for a range of functions, from data collection tools for health care professionals and clinical decision support systems to supporting health behavior change and disease management by patients in the community. Two of the major barriers to help-seeking for individuals at risk of suicide are stigma and geographical isolation [16]. Recent advances in mobile health technology could address these main barriers by directing individuals at risk of suicide, who would not otherwise seek help, to appropriate evidence-based online programs or traditional mental health services [17]. The use of digital technology has been found to be beneficial in the delivery of Web-based suicide prevention interventions [18]. Furthermore, a survey in a psychiatric out-patient setting reported that 69% of respondents and 80% of those aged 45 years or younger indicated a desire to use a mobile application to track their mental health [19]. Brathwaite et al [20], amongst other researchers, have begun to validate machine learning algorithms for social networking data against established measures of suicidality.

Despite the motivation to use mHealth technologies for these purposes, there is a lack of outcomes data on the efficacy of mHealth interventions on suicidal behavior. In 2014, Christensen et al [16] conducted literature review on eHealth and suicide, which involved reviewing the effectiveness of eHealth interventions for suicidal thoughts. The majority of eHealth interventions identified in their search were Web-based as opposed to mobile-based. The researchers concluded that there is some evidence to suggest that suicide interventions via the Web may be effective, but only if they target suicidal content specifically, as opposed to the associated symptoms of depression through cognitive behavioral therapy. Given recent developments in technology, particularly in the area of mHealth technology, there is a need to explore the current research on this subject as it relates to suicide prevention.

Donker et al [21] found that mental health apps evaluated in randomized controlled trials were not publicly available, while those with no research evidence were. Larsen et al [22] conducted a comprehensive content review of currently-available smartphone tools for suicide prevention and reported a lack of comprehensive evidence-based support for the mobile apps evaluated. In addition, mobile apps that presented harmful content were also identified [21]. Perry et al [23] conducted a systematic review of online and mobile psychosocial suicide prevention interventions for adolescents and young adults. The researchers searched four major psychological databases for interventions that explicitly targeted suicidality using a mobile, computer, or Web-based app for individuals aged between 12 and 25 years. However, only one study met the authors' inclusion criteria and therefore, a meta-analysis could not be conducted. Building on the work of Perry and colleagues [23], the current review will aim to address the disparity that exists between the availability of mHealth suicide prevention tools and clinical trial data. The current review will broaden the search strategy to include unpublished studies and ongoing trials of mhealth technology for suicide prevention as previous reviews of digital interventions for suicide prevention have identified a very limited number of mobile apps [23,24] In addition, studies will not be excluded based on participants' age.

### The Importance of This Review

While there has been a rise in the number of mobile technology tools for suicide prevention, there is a dearth of research evaluating the efficacy, and relative strengths and weaknesses of this modality. Research evaluating the content and usability of such tools has been undertaken, but the need to examine outcomes is necessary, particularly given that many of these tools are currently available and utilized. From the perspectives of researchers, policy developers, health care providers, and suicide prevention mobile app users, it is imminently important to assess the effectiveness of this method and to highlight its most efficacious components.

The current review will build upon the systematic assessment of smartphone tools for suicide prevention carried out by Larsen et al [22], which examined the concordance of features in publicly available mobile applications with current scientific evidence for effective suicide prevention strategies. Systematic review methodology was used to screen and assess app content. Therefore, the aim of the current research is to further advance this research by focusing on the efficacy of interventions delivered via mobile technologies for suicide-specific outcomes.

The objective of this review is to examine the effectiveness of stand-alone mobile technology tools in reducing suicide-specific outcomes.

## Methods

### Eligibility Criteria

This protocol has been developed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement [25]. The systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26] and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42017072899). In accordance with the PRISMA checklist recommendations, this review will use the Participants, Interventions, Comparisons, Outcome(s) process for framing and reporting the review criteria, and the study design of the included studies will be reported.

### The Review Team

The review team will manage and conduct the review, and will have experience in systematic review methods, information retrieval, and statistics. A minimum of two researchers will be involved to minimize bias and error at all stages of the review.

In addition to the review team, an advisory group will be consulted at various stages, including health care professionals, experts-by-experience, and experts in research methods.

### Types of Studies

This review is a systematic review of mHealth technology interventions for suicide prevention. As in previous research, which reviewed digital interventions for suicidal ideation and self-harm [24], types of studies included will be randomized controlled trials (RCTs), pseudo-RCTs, and observational pretest/posttest designs that evaluate the effectiveness of mHealth technology in suicide prevention. Due to the expectation of a limited number of publications available, the search strategy will not be restricted to RCTs and will include both published and unpublished trials. Studies will be included if the full report is accessible in English. Only studies that evaluated mobile tools that related specifically to suicide prevention or where suicidality is explicitly mentioned will be included.

### Types of Participants

Participants will be individuals at risk of suicide who took part in a suicide prevention intervention via mHealth technology. No restriction will be placed on the age or gender of participants included in the studies reviewed. Mobile health technology represents a modality that is accessible across the lifespan. However, the review will note the age of participants included in each study where this information is available and use this information to draw conclusions regarding the efficacy of this method for specific age groups.

### Types of Interventions

Included studies must report on a suicide prevention intervention delivered via mHealth technology. That is, interventions must aim to reduce suicide risk by employing mobile communication or mobile computing technology. Studies must report the effects of the intervention on a suicide-specific outcome. The review will include studies with psychological and nonpsychological interventions (eg, psycho-education, diaries, mood monitors, and self-management programs). As defined by Slattery et al [27] in a protocol for a systematic review on eHealth interventions for chronic pain, psychological treatments are those that explicitly deliver a psychological component (eg, psychotherapy for suicidal thoughts). Studies will be included

regardless of treatment intensity or duration. Studies reporting on stand-alone mobile interventions only will be included.

### Types of Outcome Measures

Included studies must have at least one suicide-specific outcome as a primary outcome. This will include suicidal behavior, nonsuicidal self-injurious behavior, suicidal ideation, and suicidal intent. Secondary outcomes will be symptoms of depression, as measured using administered or self-reported scales.

### Search Strategy

All databases will be searched from their start date. Studies will be included if a full-text paper is made available in English, either through databases or through contact with the study authors. The following databases will be searched: MEDLINE, Embase, PsycINFO, CENTRAL (Cochrane Library), and Centre for Research Excellence in Suicide Prevention. The same search strategy will be used for each database; however, appropriate changes will be made to accommodate the different interfaces. Details of the search strategy are provided in Textbox 1. Medical Subject Headings or equivalent and text word terms will be used.

Clinical trial registries will be searched to identify completed and in-progress trials. This will include ClinicalTrials.gov (), the metaRegister of controlled trials () and the World Health Organization International Clinical Trials Registry Platform (). Gray literature will be searched using the OpenGrey database (), which includes technical or research reports, doctoral dissertations, and conference papers from the last 5 years.

The reference lists of relevant systematic reviews and of included studies will be searched in order to identify additional studies that may be relevant.

### Selection of Studies

Studies that are identified by our search strategy will be managed using Endnote X8 [28]. Members of the research team will initially screen the titles and abstracts of publications for duplicates. Members of the research team will then screen for any studies that are not relevant to the review and will exclude them by adding them to a global exclusion folder. All remaining publications will be retrieved for further scrutiny. Two reviewers will independently assess the full text of the remaining studies for inclusion in line with the exclusion criteria. Papers that do not meet the inclusion criteria will be systematically excluded via the exclusion categories and the reason for exclusion will be recorded. Disagreements between reviewers will be discussed until resolved; in the event a resolution cannot be reached, a third reviewer will arbitrate. A record will be kept of all articles excluded at this stage. A PRISMA flow chart will be created to graphically depict the inclusion and exclusion of studies.

### Data Extraction and Management

A data extraction form will be created prior to data extraction. Data will be extracted independently by one reviewer and verified by another reviewer using a customized form, which will be piloted prior to use. The finalized data will be entered into RevMan 5.3 . Where the necessary outcome data are unavailable, the study authors will be contacted. The authors will not be blind to the study author, institution or journal. Data will be extracted relevant to the following categories: (i) study population and design; (ii) intervention; and (iii) outcome. Characteristics of table(s) in included studies' will be created and will include the following information where available:

- Participant characteristics
- Geographic location
- Assessment periods
- Assessment / screening measures
- Description of intervention and comparison interventions
- Primary and secondary outcomes
- Theoretical basis
- Therapeutic content
- Mode of delivery (smartphone application, telephone, text)
- Suicide prevention strategies
- Behavior change techniques
- Control condition
- Intensity and frequency of use
- Treatment engagement (retention and attrition)

### Assessment of Risk of Bias in Included Studies

The reviewers will independently assess risk of bias using the recommended Cochrane Collaboration's Risk of Bias tool [29] for randomized and pseudo-RCTs. The Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) [30] will be used to assess risk of bias for controlled before/after designed studies. The Cochrane Collaboration tool assesses randomization procedures, bias, allocation, outcome assessor, reporting of findings, and losses to follow-up. Studies are then classified having a low, high or unclear risk of bias. The ROBINS-I assesses confounding participant selection, classification of the intervention, departures from the intended intervention, missing data, measurement of outcomes, selection of the reported results, and overall bias. The ROBINS-I classifies studies as being of low, moderate, serious, or critical risk of bias.

**Textbox 1.** Details of the search terms to be used.

| |
|---|
| mobile* OR mobile phone OR cell* or cell phone* OR |
| mobile health OR m-health OR mhealth OR mobile app* OR mobile technolog* OR text messag* OR smartphone OR personal digital assist* OR PDA OR patient monitoring device OR PMD |
| suicid* OR suicide gesture OR suicidal behavio* OR suicidal idea* OR suicide attempt OR self-mutilation OR self harm OR self-harm OR self [-] injury OR suicide OR suicidal intent OR deliberate self-harm OR DSH OR deliberate self poisoning OR self cutting OR self-inflicted wound OR deliberate self cutting |

### Statistical Methods

In the event that only a small number of studies are identified with a large amount of heterogeneity present, a full narrative review will be undertaken using the "Narrative Synthesis in Systematic Reviews" tool [31].

Where a sufficient number of papers are identified that meet the outlined inclusion criteria, the meta-analysis will be conducted. The level of heterogeneity will also be taken into account when considering the suitability of the data for a meta-analysis.

If deemed appropriate, a meta-analysis will be conducted. RevMan 5.3 will be used for all analyses. For continuous data, we will report the mean differences between groups and the 95 % confidence interval (95 % CI). Where no standard deviations are reported, we will calculate the standard deviation using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [29]. Where the same outcome is measured using different measurement tools, we will calculate the standardized mean difference and the 95 % CI for continuous data.

It is expected that many different intervention types, participants and comparators will be examined across studies, sufficient to expect that underlying treatment effects would differ between the included studies. Therefore, a random effects meta-analysis model will be used.

#### *Assessment of Heterogeneity, Sensitivity and Publication Bias*

Statistical heterogeneity will be assessed using $\chi^2$, $I^2$, and $T^2$. $\chi^2$ assesses whether observed differences in results are compatible with chance alone. Statistical heterogeneity will be regarded as substantial if the $\chi^2$ *P*-value is <.01. The $I^2$ statistic represents the percentage of the total variation across studies due to heterogeneity. The Cochrane Handbook [32] suggests that an $I^2$ value of less than 40% is an unsignificant amount of heterogeneity. $T^2$ provides an estimate of the between-study variance in a random effects meta-analysis. A $T^2$ value of greater than 1 indicates substantial heterogeneity. Data will be analyzed using RevMan 5.3.

Sensitivity analysis will be conducted by examining whether the exclusion of studies which were identified as having greater risk of bias affects the effect sizes and comparisons between groups.

Publication bias will be assessed using Egger's test [33] and funnel plots conducted if there are a sufficient number of studies (>10).

#### *Subgroup Analyses*

The inclusion of RCT's and nonrandomized observational studies within a single meta-analysis has become increasingly common [24] as relying on data from RCTs alone can lead to knowledge translation bias [34]. The inclusion of results from pretest/posttest observational studies together with those from RCTs, however, can also lead to over-estimation of the treatment effect size [35]. To address these concerns, RCTs, pseudo-RCTs, and observational pretest/posttest designs will be eligible for inclusion in this review. However, we will not pool data from RCTs together with data from observational studies. Separate subgroup analyses will be conducted by study design to investigate the impact, if any, that study design has on the magnitude of the effect size observed for the included interventions.

## Results

This systematic review is currently underway, with results anticipated by summer 2018. The anticipated findings of this review are likely to inform policy, guide clinical practice, and users, and build on current research in the area of suicide prevention.

## Discussion

### Rationale for This Study

This systematic review will address a significant lack of outcomes research examining the efficacy of mobile technology–based interventions in suicide prevention. The lack of research is pertinent given the recent increase in the development and usage of such tools for this purpose.

This review will be an extension of Larsen et al's [22] review by systematically assessing smartphone tools for suicide prevention by (a) not restricting the modalities reviewed to smartphone apps and including other mobile technology–delivered interventions; and (b) evaluating efficacy using outcomes research in order to complement their comprehensive assessment of content.

Where data is available, a comparison of mobile technology tools across outcome measures (ie, smartphone applications, text etc) would greatly inform clinicians, developers, policy-makers, and researchers on the most effective modes of delivery.

### Limitations

In this study, a limited number of available studies is expected. Including studies examining a broad range of mobile technology tools generally as opposed to smartphone apps specifically will go some way to addressing this. Similarly, including studies which may have a mental health condition such as depression as their primary focus and which include suicide-specific primary outcomes should allow for all relevant data to be collected.

### Implication of the Review

To the best of the researcher's knowledge, no such meta-analysis has been reported that examined the effectiveness of mHealth technology interventions, in particular suicide-specific outcomes. This review will provide guidance for further research, valuable information to clinicians, and support the standardization of practice and policy in relation to the use of mobile technology in suicide prevention.

## Conflicts of Interest

None declared.

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## Abbreviations

**eHealth:** electronic health
**EMA:** Ecological Momentary Assessment
**mHealth:** mobile health
**PDA:** patient digital assist
**PMD:** patient monitoring device
**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses
**RCT:** randomized controlled trial
**ROBINS-I:** Risk of Bias in Nonrandomized Studies of Interventions
**WHO:** World Health Organization


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Protocol

# Migration Influences on the Allostatic Load of Children: Systematic Review Protocol

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## Abstract

**Background:** Migration is a worldwide phenomenon in recent times. Recently, documented studies suggest that the change in environments involved in migration may have an influence on children's allostatic load related to health and well-being.

**Objective:** The aim of this review is to systematically search the extant literature and critically examine the evidence on how migration affects allostatic load in children and describe the relevant methods in measuring allostatic load.

**Methods:** A systematic review will be conducted to recapitulate the evidence on the influence of migration on allostatic load and describe the methods employed in measuring allostatic load parameters among migrant children using the following search terms combinations: 1) allostasis OR allostatic OR allostatic load OR allosta*; 2) migration OR migrant OR immigration OR immigrant OR migra* OR *migra*; and 3) children OR child* OR adolescen*. We will search for peer-reviewed articles in English using a three-step process: title and abstract review, individual article review, and reference hand-searching among the following databases: Medline, CINAHL, ProQuest, PubMed, Science Direct and BioMed Central. Two independent review authors will analyze for data quality, level of evidence and risk of bias; a third review author will be consulted if consensus cannot be met. Data on study details, participant characteristics, allostatic load operationalization and description, methods, and results summary will be extracted. Evidence will be synthesized statistically when possible and narratively clustered into themes.

**Results:** At present, we have conducted only a preliminary search to test out our search terms. The systematic search, appraisal, synthesis and analysis will be finished by June 2018. It is projected that the manuscript that describes the systematic review will be available by the last quarter of 2018.

**Conclusions:** The results of this systematic review have implications on supporting the concept of allostasis as a mechanism underlying the adaptive processes related to migration. Furthermore, our findings can lead to the development of innovative evidence-informed evaluation and intervention programs aimed at migrant children's needs. Likewise, it is hoped that this review can be an impetus to inform health and sociopolitical policies responsive of migrant children's current contexts.

**Trial Registration:** International Prospective Register of Systematic Reviews (PROSPERO): CRD42017068895; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=68895 (Archived by WebCite at http://www.webcitation.org/6wprRkxvA)

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**KEYWORDS**

migration; allostatic load; allostasis; children

## Introduction

Different areas of inquiry have tackled migration from their own points of view. Herein, we look at migration from a biological perspective, where migration is generally defined as the movement of an individual or group of individuals from one territory to another to establish a new area of residence [1,2]. This entails a change in the environment with respect to one's place of origin and host. The concept of allostasis is intended to be used in this review as a unifying concept to explain the underlying mechanism related to the adaptive processes of migration and its effect on the health and well-being of children. The concept of allostasis stemmed from the earlier research of McEwen [3,4], Sterling and Eyer [5], and McEwen and Wingfield [6]. In allostasis, alteration of the regulatory parameters allows a person to adapt to environmental challenges through the development of a new baseline to maximize the individual's performance [7,8]. Allostasis is responsible for short-term adaptation, survival, and homeostasis, but according to McEwen and Wingfield [6], it can potentially produce permanent changes, termed allostatic load, in a person in prolonged exposures. Allostasis has been widely used to explain the adaptation of migrating animals (ie, birds, fishes) to their environments of habitation using physiological parameters related to the autonomic or neuroendocrine mechanisms [9,10]. Results are congruent in the fact that physiological parameters are regulated upon immigration, and this is related to the survival in the site of resettlement. Among human studies, allostatic load parameters were used to represent regulation of various physiological systems (ie, cardiovascular, metabolic, body composition) using several biomarkers among immigrant adults [11,12,13]. However, as of date, the evidence on the influence of migration on the allostatic load in children has yet to be systematically reviewed.

The allostasis model suggests the interaction mechanisms between individual differences, behavioral responses and physiological responses contextualized within a particular environment can reflect the vulnerability or adaptive functions of individuals [14]. Taken together, the interacting roles of each can presume a child's overall health and well-being. Individual differences may refer to demographic characteristics of individuals (ie, gender, age, ethnicity, genetic predispositions, environment, sociocultural influences, socioeconomic status, family dynamic, place of birth, site of resettlement), which has long been proven to affect the allostatic load [4]. The role of the environment is greatly emphasized in the allostasis model, having the capacity to influence both behavioral and physiological response. The physical environment (ie, temperature, humidity, seasonality, noise, physical landscapes and features) needs to be succinctly accounted for when employing physiological outcomes [15,16,17,18]. Emerging evidence suggests that nativity or place of birth influences the allostatic load [19]. Previous research has likewise implicated sensory-related, temperament and resilience behaviors as possible factors that can shape allostasis [20,21,22,23,24]. The classic paper of Berry [25] provided foundational insight on the factors that can support adaptation among immigrants and has mentioned similar factors. However, these factors mainly focused on psychological adaptation to a new culture and cannot account for salient biological changes related to migration.

In 2015, there were 244 million recorded international migrants, with 20% under the age of 20 [26]. The impact of migration on health has well been studied previously, and recent evidence suggests related long-term physical and mental health issues [27]. Specifically, children ages 6 to 17 may be at risk for psychosocial problems that can have deleterious effects on their health and well-being [28]. However, most of the research done focused mainly on the effects of immigration rather on latent mechanisms which may explain such effects. The concept of allostasis may offer a novel perspective on how a change in the environment influences the regulation of behavior and physiological responses among children, and a better understanding of the mechanisms underlying adaptation, or maladaptation, of migrant children in order to provide relevant healthcare programs and interventions.

In light of the lack of existing systematic reviews, contemporary gaps in knowledge, and the novel application of the concept of allostasis on human migration, the authors of this review seek to systematically review the extant literature that examines how migration influences the allostatic load among children. Specifically, this review aims to answer the following research questions:

1. What is the evidence on the influence of migration on allostatic load among children?
2. What are the allostatic load measures relevant to migrant children?
3. What methods are usually employed in measuring allostatic load parameters among children?

## Methods

The proposed systematic review aims to recapitulate the evidence on the influence of migration on allostatic load; summarize the commonly used allostatic load measures; and describe the methods employed in measuring allostatic load parameters among migrant children. This review is registered on the PROSPERO database with registration number: CRD42017068895, developed and reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidance [29]. The self-assessed PRISMA-P checklist for this protocol is shown in Multimedia Appendix 1.

### Study Selection

This systematic review will consider studies for inclusion based on the following criteria.

#### *Types of Studies*

This review will consider designs including before and after studies, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies for inclusion. Furthermore, we will also consider descriptive epidemiological study designs including case series, individual case reports and descriptive cross-sectional studies for inclusion. In the absence of research studies, other text such as opinion

papers and reports will be considered. The reviewed studies will be summarized based on their typology.

### *Types of Participants and Exposures*

This study will primarily consider studies include migrant subjects between the ages of 2 to 18 years old from typically-developing populations regardless of gender, ethnicity/race, and country of origin/migration, with no known medical, neurobehavioral or psychological history. In this paper, a child will be considered an individual under the age of 18 years old [30]. The lower bound limit was set at age 2 years old to differentiate these groups specifically from infants [31]. In cases, where a clinical group is presented with or without a comparison normative group, the data from these studies will likewise be reported in the final documentation.

The exposure of interest shall be "migration." Several definitions suggest that migration can be classified as either internal or external migration; while migrants can be further categorized as native-born or foreign-born. Due to the exploratory nature of this review, we will consider all of these types of migration exposures and consequently report these data, as well as the operational definitions used in the reviewed studies. However, excluded in the migration category are those results that have experienced forced migration (ie, refugees, victims of famine, disasters, etc). Previous research suggests that adverse life events in childhood may have an influence on a child's neurobehavioral, psychophysiological or physiological development [32,33,34]. Thus, only types of voluntary migration are considered.

### *Types of Outcomes*

Part of the aim of this study is to summarize the common outcome measures to conceptualize allostatic load parameters. Based on the concept of allostasis, we will classify the outcome measures into two categories: 1) behavioral measures (ie, temperament, personality, resilience, health-seeking behaviors, etc); and 2) physiological measures (ie, heart rate, body mass index [BMI], height, weight, etc). Physiological measures may also be in the form of neurobiological or neurophysiological indices (ie, cortisol, hormones, heart rate variability, etc). Data from other outcomes not included in this protocol but emerges from this review shall be succinctly discussed in the final report.

## Literature Search

### *Search Strategy*

Our search strategy aims to find peer-reviewed published studies. A three-step search strategy will be utilized in this review. An initial limited search of the included databases will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe an article by the primary author. A second search using all identified keywords and index terms will then be undertaken across all included databases. Lastly, a reference-searching strategy will be entailed among the primary studies that have gone through the second search level.

For this review, we expanded the search strategy to capture all possible studies using the following databases: Medline, CINAHL, ProQuest, PubMed, Science Direct and BioMed Central. This will be followed by an analysis of the text words contained in the title and abstract and of the index terms used to describe the article. The following databases were chosen based on the recommendation of an experienced librarian in the field of health sciences who likewise helped in validating the search terms of this review paper. The chosen databases include other databases within its system of resources, thus increasing the platform where the search strategy is employed. Studies published in English or which have an English version will be considered for inclusion in this review. The search data will range from January 2007 to December 2017. Initial keywords to be used will be: allostasis OR allostatic OR allostatic load OR allosta*; 2) migration OR migrant OR immigration OR immigrant OR migra* OR *migra*; and 3) children OR child* OR adolescen*. The use of "*" represents truncated terms implemented to increase the scope of the search for articles. This review will likewise consider dissertation papers that meet the previously mentioned inclusion criteria, provided these are appropriately indexed within the abovementioned databases and retrieved during the search. An example of search strategy and results conducted in MEDLINE is shown in Multimedia Appendix 2.

Furthermore, this review will entail contacting authors of the initially identified articles, reference list hand-searching and considering grey literature (ie, existing data sets, unpublished data, theses and dissertations, technical reports) to widen the scope of the search.

### *Screening and Review Process*

Full-text articles retrieved from the three-step search strategy and hand-searched additional articles will be screened and reviewed by two independent review authors for quality appraisal, levels of evidence and risk of bias for potential inclusion in this review. In the event of a disagreement between the two independent review authors, a meeting will be held to reach a consensus; but if a consensus cannot be reached, an independent third reviewer will be consulted. An example of the sample flow diagram of study selection procedures is shown in Multimedia Appendix 3.

### *Data Quality and Level of Evidence*

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI- MAStARI) [35]. The JBI-MAStARI is a comprehensive set of tools that guides researchers in the conduct and preparation of high-quality systematic reviews [35]. The JBI MAStARI appraisal tools are shown in Multimedia Appendix 4.We will use the NHMRC Evidence Hierarchy [36] to assign designations of "levels of evidence" according to the type of research question of the studies appraised. The NHMRC Evidence Hierarchy is shown in Multimedia Appendix 5. Any disagreements that arise between the two assigned independent reviewers will be resolved through discussion or with a third reviewer.

### *Data Extraction*

Quantitative data will be extracted from papers included in the review using the relevant standardized data extraction tool from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument [35]. The data extraction tool to be used in this research is shown in Multimedia Appendix 6. The same review authors that screened and reviewed the primary articles for review shall extract the following data:

1. Study Details: type of study and whenever appropriate, the method of randomization and presence or absence of blinding;
2. Demographic Characteristics: age, gender, ethnicity/race, socio-economic status, number of participants recruited, number of drop-puts/withdrawals whenever possible;
3. Definition and operationalization of allostatic load;
4. Type of outcome measures: behavioral or physiological measures;
5. Details of outcome measure procedures: instrumentation, procedures, methods;
6. Results: details on the role of migration on the autonomic state as it influences child behavior.

When disagreements arise related to data extraction, a discussion will be conducted to reach a consensus on a decision. However, if a consensus cannot be reached, a third review author will be consulted. In the case of missing, incomplete or incomprehensive data, the authors of the reviewed papers will be contacted by email for clarifications and supplement of needed information whenever possible.

### *Risk of Bias*

For assessing the risk of bias within studies, this review will adopt the Cochrane "Risk of bias" [37] tool which included the following criteria:

1. Sequence generation;
2. Allocation concealment;
3. Blinding of participants, personnel and outcome measures;
4. Incomplete outcome data, and;
5. Selective outcome reporting.

The risk of bias tool to be used in this research is shown in Multimedia Appendix 7. Furthermore, the risk of bias across studies shall be reported using the abovementioned criteria from the Cochrane [37] group, with additional criteria added in response to other authors' recommendations [38,39]. On this basis we added two criteria, "Outcome Measure Processes" and "Age Inclusions" using the thresholds for across studies judgment as suggested [39]:

1. Low risk of bias—"Most information is from studies at low risk of bias."
2. Unclear risk of bias—"Most information is from studies at low or unclear risk of bias."
3. High risk of bias—"The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results."

Assessment of risk of bias shall be undertaken by two review authors where discrepancies are identified and resolved through discussion to reach a consensus on results, while a third author will be consulted in case a consensus cannot be met.

### Analysis

### *Statistical Analysis*

Quantitative papers, when possible, will be pooled in a statistical meta-analysis using JBI-MAStARI [35]. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% CI will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different quantitative study designs included in this review.

### *Narrative Analysis*

Where statistical pooling is not possible, the findings will be presented in a narrative form including tables and figures to aid in data presentation where appropriate. This will involve the aggregation or synthesis of conclusions to generate a set of statements that thematically represents such aggregation through accumulating and categorizing these conclusions on the basis of congruency in meaning. The following themes will be narratively reported in the report:

1. Influence of migration on allostatic load;
2. Longitudinal changes and temporal factors related to migration affecting the allostatic load;
3. Allostatic load parameters in migrant children;
4. Methods in measuring allostatic load parameters in migrant children.

## Results

At the time that this systematic review protocol was prepared, the researchers have conducted preliminary literature search suing the abovementioned search strategies. The results of such initial search are shown in Multimedia Appendix 2. This suggests that the search strategy is effective in supporting the objectives of this research. It is intended to replicate the search strategy in other databases. Appraisal, synthesis and analysis of the evidence will be finished by June 2018. It is projected that the manuscript that describes the results of this systematic review will be available by the last quarter of 2018.

## Discussion

Work on this systematic review was initiated last July 2017 and should come into completion by March 2018. Knowledge translation shall include collaboration with international and local affiliates including researchers, decision makers, service providers and migrant families. The major output document shall be the main systematic review which will synthesize the works of the authors, which is aimed to be presented in several media platforms: 1) dissemination of outputs through websites; 2) sharing of outputs through local and international news media outfits; 3) organization of a dialogue between researchers and representatives from embassies and consulates; 4) submission of the article in a peer-reviewed and open-access journal; and 5) presentations at local and international conferences.

We anticipate a limited number of studies on this subject matter, probably due to the overarching theoretical framework applied to describing the influences of migration and the use of allostatic load as parameters of change. Hence, it may likely that we include all available studies despite issues on quality. However, these will be accounted for and reported in succinct detail with respect to the risk of bias involved. Furthermore, the authors will exert the available effort and resources to find other sources of relevant data. Our review may thus be able to map out the scope of the available extant literature relevant to this matter.

The results of this review will not only provide insight on the previously unidentified neurophysiological mechanism underlying the adaptive processes related to migration to a foreign environment of resettlement among children, but has profound implications for understanding the unique health and well-being conditions and needs of this growing population. The potential findings of our review of the evidence can influence the development of innovative evidence-informed evaluation and intervention programs that are empirically relevant and sensitive to the needs of migrant children. Furthermore, the findings of this review have the prospective impetus in guiding the local government to design and enact health and sociopolitical policies responsive of migrant children's current contexts.

## Acknowledgments

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## Authors' Contributions

IG, CL conceived the study. IG wrote the first draft and all authors contributed to the revision of the protocol. The final protocol presented here has been approved by all authors.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

PRISMA-P checklist.

[PDF File (Adobe PDF File), 36KB - resprot_v7i1e29_app1.pdf ]

## Multimedia Appendix 2

Sample search terms.

[PDF File (Adobe PDF File), 20KB - resprot_v7i1e29_app2.pdf ]

## Multimedia Appendix 3

Sample flow of the study.

[JPG File, 77KB - resprot_v7i1e29_app3.jpg ]

## Multimedia Appendix 4

Appraisal instruments.

[PDF File (Adobe PDF File), 263KB - resprot_v7i1e29_app4.pdf ]

## Multimedia Appendix 5

Levels of evidence.

[PDF File (Adobe PDF File), 62KB - resprot_v7i1e29_app5.pdf ]

## Multimedia Appendix 6

Data extraction tools.

[PDF File (Adobe PDF File), 143KB - resprot_v7i1e29_app6.pdf ]

## Multimedia Appendix 7

Risk of bias tool.

[PDF File (Adobe PDF File), 137KB - resprot_v7i1e29_app7.pdf ]

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## Abbreviations

**JBI-MAStARI:** Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument
**NHMRC:** National Health and Medical Research Council
**PRISMA-P:** Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols


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Protocol

# Activating Technology for Connected Health in Cancer: Protocol for a Research and Training Program

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## Abstract

**Background:** As cancer survival rates increase, the challenge of ensuring that cancer survivors reclaim their quality of life (QoL) becomes more important. This paper outlines the research element of a research and training program that is designed to do just that.

**Objective:** Bridging sectors, disciplines, and geographies, it brings together eight PhD projects and students from across Europe to identify the underlying barriers, test different technology-enabled rehabilitative approaches, propose a model to optimize the patient pathways, and examine the business models that might underpin a sustainable approach to cancer survivor reintegration using technology.

**Methods:** The program, funded under the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 722012, includes deep disciplinary PhD projects, intersectoral and international secondments, interdisciplinary plenary training schools, and virtual subject-specific education modules.

**Results:** The 8 students have now been recruited and are at the early stages of their projects.

**Conclusions:** CATCH will provide a comprehensive training and research program by embracing all key elements—technical, social, and economic sciences—required to produce researchers and project outcomes that are capable of meeting existing and future needs in cancer rehabilitation.

***(JMIR Res Protoc 2018;7(1):e14)*** doi:10.2196/resprot.8900

**KEYWORDS**

eHealth; mHealth; consumer health informatics; cancer; cancer rehabilitation

## Introduction

The world of medical science has been waging a war on cancer for decades—a war which is slowly but surely being won. But the victories have been seen on the battlefields for survival, with the goal being life itself, through early detection and aggressive treatments. In short, the mantra to-date has been simple: "save the life, kill the cancer." There were just over 3.4 million new cases of cancer (excluding non-melanoma skin cancers) in Europe in 2012. Mathers and Loncar estimate that by 2030, 20 million people in the World Health Organization European Region will be living with cancer diagnosed five years previously [1].

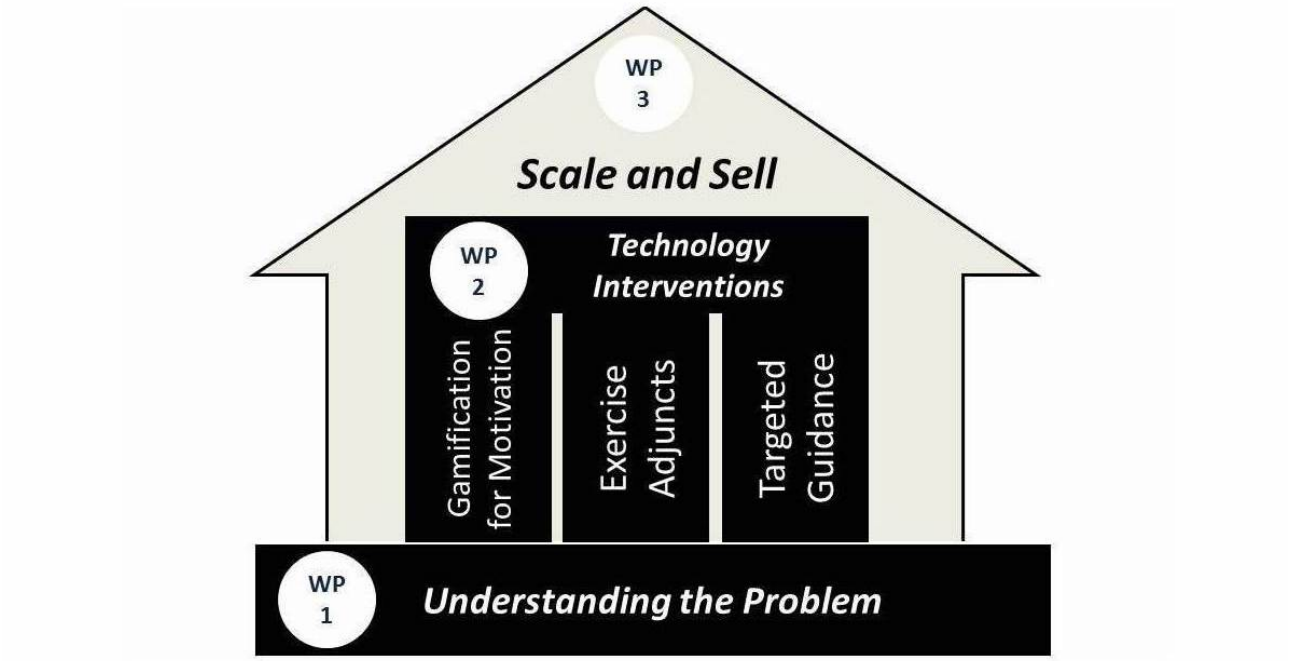
Although the number of cases of cancer is increasing, so are the survival rates of patients in Europe [2] and worldwide [3]. However, cancer and its treatments cause many physical and psychological symptoms and side effects. Physical symptoms include loss of power and function in limbs, muscle wasting, chronic fatigue, and loss of appetite, while psychological symptoms range from depression, anxiety associated with uncertainty, poor body image, and loss of intimacy in relationships [4]. All contribute to reducing the overall QoL (Quality Of Life)[5], the very thing that we are seeking to maximize within cancer-recovery cohorts (see studies in breast cancer [6], [7] and prostate cancer [8],[9]). We know that increased physical exercise within such cohorts has a positive impact on QoL and contributes to the prevention of recurrence [10]–[11]. In addition, increasing physical activity can alleviate long term side effects of new cancer treatment, such as fatigue, offering the "potential to reinstall structure in everyday life." [12]

Cancer: Activating Technology for Connected Health (CATCH) seeks to maximize these restorative powers of physical activity in cancer cohorts while understanding that there are both physical and mental barriers that survivors encounter when seeking to exercise. Therefore, the core objective of the study is to activate technology in bridging the gap between cancer survivors' depleted physical and emotional state and their ultimate ability to return to a fully functional societal role through technology-supported physical exercise.

To achieve the core objective there are three sub-objectives: 1) to understand the nature of the gap (from the patient perspective), 2) to design and test technology-enabled bridging solutions, and 3) to offer routes to market and strategic approaches at both industrial and public actor levels to drive adoption at scale of the proposed solutions and associated care models (see Figure 1 below).

At the same time, CATCH will develop and deliver a program of training to create a cadre of 8 PhD students who, after the training, will be able to implement the required solutions in industry, clinical, advocacy, and academic environments. This paper focuses on the research element of the CATCH program. For further detail regarding the training elements of the program, please see Mountford et al, 2017 [13]. The students' Individual Research Projects (IRPs) will address all the key elements of the objectives. The combined IRPs will drive a new interdisciplinary approach to technology-enabled post-diagnosis rehabilitative solutions and their evaluation and will enhance adoption by healthcare providers, patients, and society.

**Figure 1.** The Cancer: Activating Technology for Connected Health (CATCH) Research Program.



## Methods

Three work packages have been proposed to achieve the three sub-objectives defined for the study and the PhD student training.

### Work Package 1: Understand the Nature of the Problem (Sub-Objective 1)

The first sub-objective consists in understanding, from a patient perspective, the nature of the physical and psychological gap that must be bridged to enable and achieve physical activity. To achieve this, the PhD students will perform the following tasks:

Task 1: An ethnographic analysis of the current care pathway from the patient perspective (PhD student 1). The PhD student will review patient care pathways in cancer treatment literature, including the latest publications, prior to conducting an ethnographic study of the patient care pathways for both men and women. The student will employ ethnographic research methods drawn from the discipline of anthropology [14]—the study of the development of human societies and culture [15]—which is known to more effectively capture patient insights [16] and will:

1. Review patient care pathways in cancer treatment literature.
2. Conduct an ethnographic study of the patient care pathway by observing and interacting with cancer patients to comprehend the lived-experience of particular care pathways.
3. Analyze data to develop a detailed patient pathway that meets the needs of both sexes for all types of cancer.
4. Identify elements of the care pathway where there are opportunities for technology-enabled post-diagnosis rehabilitation.

Task 2: A quantification of health habits and needs of people affected by cancer to improve their QoL through physical activity (PhD student 2). By engaging in ethnographic research with cancer patients involved in various forms of physical exercise, this will result in the design of a digital intervention to maximize the medical, physical, functional, and psychological effects of physical activity programs for men and women with cancer. The PhD student will:

1. Conduct a comprehensive literature review, including the latest publications, focusing on medical, physical, functional and psychological aspects of cancer treatment for both men and women.
2. Undertake qualitative research with male and female patients to identify factors crucial for the design of a digital intervention.
3. Develop guidelines for cancer patient populations regarding health and lifestyle, paying specific attention to physical activity and how to improve patient QoL during the phases of cancer treatment. These guidelines will be tested onsite at the Center of Sport at University of Seville.
4. Design a digital intervention to assist patient adherence to physical exercise regimes.

Task 3: Strategies for increasing mental well-being in patients with cancer (PhD student 3). The PhD student will investigate strategies for using digital health to reinforce and improve psycho-oncology interventions (addressing emotional and mental health issues associated with cancer). Focusing on behavioral and emotional support—increasing motivation and reducing asthenia and fatigue—the student will devise new strategies to improve patients' psychological and physical well-being. The PhD student will perform the following tasks:

1. Review literature to include most recent publications on increasing motivation, supporting positive health behavior, and prior use of technology in mental health support, including a review of psycho-oncology projects that use new technologies.
2. Conduct qualitative research (interviews, focus-groups, workshops) with a diverse group of patients and caregivers with different cancers from both genders. This will provide a detailed and empathic understanding of cancer patients' lived experiences.
3. Develop a motivational framework that maps behavioral and emotional strategies for diverse cancer patients and survivors. Based on the results, a new app will be designed that instantiates the framework which will then be tested to redefine the motivational framework.

### Work Package 2: Design and Test Technology-Enabled Bridging Solutions (Sub-Objective 2)

To achieve this sub-objective, three different technology solutions will be selected and explored to evaluate how they can be matched to specific cancer care scenarios.

Solution 1: Psychological solutions that use gamification and education to empower cancer patients experiencing difficulty regaining their former role in society (PhD student 4). For this study the student will:

1. Perform an up-to-date systematic scoping review of games, techniques, and previous cancer-specific digital solutions. Based on the obtained experience, a gamified application will be implemented.
2. Implement a first version of a social mobile app for prostate cancer patients and survivors.
3. Study and consult with oncology experts regarding the safety, usefulness, and accuracy and refine the app based on this consultation.
4. Evaluation of the app using an A/B based testing protocol with real patients.

Solution 2: Physical solutions, such as electrical stimulation, to help re-educate and strengthen muscle severely weakened as a result of aggressive cancer (PhD student 5). The PhD student will:

1. Conduct a study to understand the exercise rehabilitation needs of patients with breast or prostate cancer.
2. Develop an NMES-mediated hybrid training protocol that meets the specific needs of the two significant cancer survivor cohorts - prostate cancer and breast cancer. This will consist of an evaluation of the acute physiological and subjective effects of applying different variations of a hybrid NMES protocol in a cohort of the target population.

3. Conduct a pilot trial with a group of prostate and breast cancer survivors who are too de-conditioned to meaningfully benefit from standard physical exercise. The trial will require patients to undergo self-directed, home-based NMES training for a period of 8-16 weeks. Approximately 40 participants (equally gender balanced) will be recruited for the prospective trial. The program will be evaluated through clinical and functional outcomes and user experience.
4. Study and understand the potential application of the outputs in the context of care pathways for cancer patients, particularly how this technology can be integrated with drug therapy for cachexia.

Solution 3: Use of motion tracking solutions and interactive biofeedback to monitor performance and improve compliance and quality of patient engagement in rehabilitation exercise programs (PhD student 6). The PhD student will:

1. Conduct a literature review, including the latest publications, on cancer-specific, targeted rehabilitation exercise programs, focusing on the information gap between the patient, consultant, and physiotherapist and the patient's ability to access information about their own care.
2. Gather data from cancer patients performing exercises in a clinical setting to inform the exercise classification model.
3. Develop exercise classification algorithms and a prototype app tailored specifically to each patient's needs by their clinician. This would allow the patient to attain credible information on their rehabilitation progress, regardless of their geographical location.
4. Evaluate the prototype in clinical deployment, and then evaluate and rework it from a 'technology and care' model perspective.

### Work Package 3: Offer Routes to Market and Strategic Approaches (Sub-Objective 3)

The last objective aims to offer routes to market and strategic approaches to drive adoption at scale of the proposed solutions and associated care models at both an industry and public actor level.

To achieve this sub-objective, two different approaches are covered:

Approach 1: Supporting commercialization of technology-enabled cancer solutions through design thinking (PhD student 7). The PhD student will:

1. Conduct an up-to-date systematic review of Service Innovation and related literature, commercialization, and design literature complemented by interviews (cancer patients, researchers, clinicians) to understand how we can mediate between heterogeneous innovators and between internal and external surroundings.
2. Develop preliminary guidelines for how private firms can use design thinking (methods) to qualify the process of developing technology-enabled cancer care solutions (collaboration, innovation, diffusion, and commercialization).
3. Complete workshops with users and partners to assess whether design has strengthened the firms' awareness of different external and internal challenges and how to handle them.

Approach 2: Qualifying private organizations' commercialization efforts through stakeholder interactions (PhD student 8). The student will:

1. Conduct an up-to-date systematic review of Service Innovation and related literature, commercialization, and stakeholder literature on turning health solutions into commercial successes.
2. Study the context in which cancer care solutions are developed including interviews with private and public actors engaged in (Public-Private) Service Innovation.
3. Develop preliminary guidelines for how private firms can use stakeholder interactions to qualify commercialization efforts.
4. Pilot and evaluate the (Public-Private) Service Innovation guidelines and assess whether stakeholder interactions have strengthened private firms' awareness of different challenges and how to handle them.

### Program Management and Ethos

Each sub-objective and its associated work package promote state of the art research in its area. All three work packages are concurrent and will cross-pollinate. Information from work package 1 will provide design input for work package 2 and context for work package 3. Work package 2 will provide case studies and data sources to inform Work Package 3. This will enable a truly interdisciplinary learning environment for the PhD students and a triangulated, defensible approach from an industry-relevance perspective. The tasks will be undertaken by PhD candidates from a range of scientific backgrounds and international locations, as well as across both genders. CATCH will include international, intersectoral secondments to promote interdisciplinary and intersectoral learning and communication, public engagement, and outreach with patients, clinicians, and policy-makers. Building on the core tasks outlined above, an end-to-end technology enabled cancer care research spectrum will be designed from problem definition, to solution design, to implementation and adoption. CATCH will consider the importance of technology not only at the treatment stage, but also during rehabilitation and follow up. Through network-wide events and training modules, the individual research outcomes will synergistically contribute to this complete model. Through diverse means—face-to-face contact in summer schools, electronic communication platforms (e.g. Podio), and physical embedding (secondments)—PhDs will work with non-academic partners to appreciate different perspectives, methods, and approaches. The non-academic sector partners are integral for the development and delivery of the program. Industry partners will recruit and train students, host site visits, host secondments, provide keynote speakers for summer schools, will sit on doctoral studies panels, and will run a transferrable skills module on innovating in an emerging market. Healthcare partners will recruit and host students, run a transferrable skills module on working with patient populations, lead dissemination efforts to clinical audiences, and provide a venue for students to see a clinical setting in practice during the Orientation conference. Patients will contribute as cohorts for studies and participate in

the "working with patients" training module, thus contributing to user experience training. Clinicians from healthcare partners will assist in sourcing cohorts for trials, user-centered design, and membership of supervisory panels for care-led PhDs and attendance at clinician conference.

## Results

This program has now received funding under the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 722012. All eight students have now been recruited and have commenced their PhD programs.

## Discussion

The emerging Connected Health industry is in need of research that combines deep domain-specific expertise and a complementary understanding of how such expertise fits into this intersectoral, interdisciplinary ecosystem. Europe needs to keep up to date with international developments in healthcare (electronic health [eHealth], mobile health [mHealth], telemedicine), but currently, researchers are graduating with narrow mono-thematic, purely academic degrees that limit understanding of the range of solutions possible [17]. CATCH will provide a comprehensive training and research program by embracing all key elements—technical, social, and economic sciences—required to produce researchers and project outcomes that are capable of meeting existing and future needs in cancer rehabilitation. In doing so, CATCH also responds to a fundamental need for a new health care model [18] that can counterbalance the demographic and resource pressures faced by our healthcare systems.

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### Conflicts of Interest

LFL holds shares in the company, Salumedia.

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## Abbreviations

**eHealth:** electronic health
**IRP:** Individual Research Projects
**mHealth:** mobile health
**QoL:** Quality of Life
**CATCH:** Cancer: Activating Technology for Connected Health

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Protocol

# Using the Inflammacheck Device to Measure the Level of Exhaled Breath Condensate Hydrogen Peroxide in Patients With Asthma and Chronic Obstructive Pulmonary Disease (The EXHALE Pilot Study): Protocol for a Cross-Sectional Feasibility Study

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## Abstract

**Background:** Asthma and Chronic Obstructive Pulmonary Disease (COPD) are common conditions that affect over 5 million people in the United Kingdom. These groups of patients suffer significantly from breathlessness and recurrent exacerbations that can be difficult to diagnose and go untreated. A common feature of COPD and asthma is airway inflammation that increases before and during exacerbations. Current methods of assessing airway inflammation can be invasive, difficult to perform, and are often inaccurate. In contrast, measurement of exhaled breath condensate (EBC) hydrogen peroxide ($H_2O_2$) is performed during normal tidal breathing and is known to reflect the level of global inflammation in the airways. There is a need for novel tools to diagnose asthma and COPD earlier and to detect increased airway inflammation that precedes an exacerbation.

**Objective:** The aim of this study was to explore the use of a new handheld device (called Inflammacheck) in measuring $H_2O_2$ levels in EBC. We will study whether it can measure EBC $H_2O_2$ levels consistently and whether it can be used to differentiate asthma and COPD from healthy controls.

**Methods:** We will perform a cross-sectional, feasibility, pilot study of EBC $H_2O_2$ levels, as measured by Inflammacheck, and other markers of disease severity and symptom control in patients with asthma and COPD and volunteers with no history of lung disease. Participants will be asked to provide an exhaled breath sample for measurement of their EBC $H_2O_2$ using Inflammacheck. The result will be correlated with disease stage, spirometry, fractional exhaled nitric oxide (FeNO), and symptom control scores.

**Results:** This study's recruitment is ongoing; it is anticipated that the results will be available in 2018.

**Conclusions:** The EXhaled Hydrogen peroxide As a marker of Lung diseasE (EXHALE) pilot study will provide an evaluation of a new method of measuring EBC $H_2O_2$. It will assess the device's consistency and ability to distinguish airway inflammation in asthma and COPD compared with healthy controls.

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**KEYWORDS**

reexhalation; biomarkers; medical device; asthma; COPD

## Introduction

### Burden of Chronic Obstructive Pulmonary Disease and Asthma

Chronic Obstructive Pulmonary Disease (COPD) is a common and treatable condition that is characterized by predominately irreversible and progressive airflow limitation. COPD is a leading cause of morbidity and mortality worldwide, and its prevalence is predicted to increase substantially in the coming decade [1]. In the United Kingdom alone, COPD affects an estimated 3 million people, with two-thirds remaining undiagnosed [2,3]. Delays in reaching an accurate diagnosis impact on people's quality of life (QoL) and health care resource utilization. COPD is associated with a significant economic and social burden. In 2011, there were over a million in-patient bed days caused by acute exacerbations of COPD, with a severe exacerbation requiring admission to hospital costing up to £1600, therefore having a major impact on health care expenditure [4]. COPD also has a personal burden, causing 24 million lost working days annually, costing the UK economy £3.8 billion [5,6].

Asthma is estimated to affect over 3.5 million people in the United Kingdom, with 250,000 experiencing severe disease with frequent exacerbations [7]. Despite increasing numbers of treatment options, there were still over 900 deaths because of asthma in 2014 [8]. The economic burden of treating asthma is huge, costing in excess of £1 billion per year [4,7]. Like COPD, asthma also has a dramatic personal cost with 1 in 5 asthmatics in the United Kingdom reporting serious concerns that their next asthma attack will kill them [9]. Delays in correctly diagnosing and phenotyping asthma can lead to poor disease control, high emergency health care use, and inappropriate treatment [10,11]. There is a need for additional, widely accessible tools to aid in the accurate diagnosis and phenotyping of both asthma and COPD.

### Rationale for Measuring Airway Inflammation

A common feature of COPD and asthma is chronic airway inflammation, which worsens during exacerbations. These are frequently triggered by infections and inhaled irritants resulting in epithelial injury, neutrophil and eosinophil activation, and release of inflammatory cytokines [10,12]. This all contributes to the bronchoconstriction, smooth muscle hypertrophy, and airflow obstruction that are features of asthma [13]. Where there is prolonged exposure to toxic irritants in COPD, there is ongoing airway inflammation that can continue even after smoking or irritant cessation and begin before the development of clinical symptoms [1,14].

Airway inflammation in asthma and COPD leads to an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to counteract their harmful effects through neutralization by antioxidants; this is termed as oxidative stress [15-17]. Increased expression of ROS by activated inflammatory cells, including neutrophils and eosinophils, can lead to further generation of inflammatory mediators, causing damage to epithelial cells and increased bronchial hyperreactivity [14]. ROS are metabolized in cells to produce highly reactive oxidants such as hydrogen peroxide ($H_2O_2$), which is fat soluble and can move across cell membranes. As $H_2O_2$ is volatile and readily equilibrates with air, its presence can be detected in exhaled breath condensate (EBC). Therefore, measurement of EBC $H_2O_2$ gives a quantitative measure of oxidative stress and airway inflammation [18-21].

### Current Measures of Airway Inflammation

The current *gold standard* tool for assessing airway inflammation and oxidative stress is fiberoptic bronchoscopy with bronchial wall biopsy and bronchial fluid lavage [22,23]. This is an invasive procedure that is not suitable for routine clinical practice or regular repeat sampling. This is because it carries a small but important risk, with complications occurring in up to 4.3% of procedures and a reported procedure-related mortality of up to 0.1% [24]. In patients with underlying asthma and COPD, the risk is even greater, with up to 10% of patients with asthma developing respiratory symptoms post bronchoscopy [24]. Bronchoscopy is also an expensive tool, with British Thoracic Society guidelines recommending a minimum of two qualified nurses present throughout bronchoscopy procedures and one qualified nurse to recover a patient post bronchoscopy [24]. Furthermore, sample analysis requires a series of laboratory measurements, and results can take over 24 hours to become available, causing delays in clinical decision making.

Induced sputum analysis is a semi-invasive means of assessing airway inflammation [25]. However it can be unpleasant, technically demanding, and time consuming, and as a result, is not always possible in patients with more severe airflow obstruction and poor lung function. It is not always well tolerated by patients and is not suitable for repeat sampling [26]. Noninvasive means of assessing airway inflammation presently measure fractional exhaled nitric oxide (FeNO—a specific measure of eosinophilic airway inflammation) [27]. This requires controlled exhalation for at least 6 seconds, making the test unsuitable for patients with significantly impaired lung function and especially those who are tachypnoeic during an exacerbation. Furthermore, FeNO is lowered in current smokers, limiting its diagnostic use, and it also does not measure neutrophilic airway inflammation, a recognized component of COPD and steroid insensitive asthma. It has been reported that up to 50% of patients with severe asthma do not have eosinophilic-driven disease (noneosinophilic) and, as a consequence, FeNO cannot monitor management in this group [28].

### Exhaled Breath Condensate Hydrogen Peroxide

EBC contains aerosolized particles from the airway epithelial lining fluid [29], including volatile water-soluble compounds such as $H_2O_2$. Measurement of EBC $H_2O_2$ therefore gives a direct, quantitative measure of airway inflammation [21,30,31]. In contrast to current measures of airway inflammation, collection of EBC $H_2O_2$ is performed during tidal breathing, making it noninvasive and easy to perform. It can be repeated quickly and is well tolerated even in patients with severe airways disease. It is widely appreciated that EBC $H_2O_2$ measurement

has the potential to improve clinical practice by safely providing vital information on aspects of disease that are currently inaccessible [32].

To date, measurement of $H_2O_2$ in the EBC has required complex, multi-step processing of the collected breath samples to produce a result and as a consequence has largely been used as a research tool [33]. The evidence from these past collection techniques show that EBC $H_2O_2$ levels are significantly higher in COPD patients compared with healthy controls [34]. It has also been demonstrated that the levels rise further during COPD exacerbations, and there is some evidence that EBC $H_2O_2$ levels correlate with COPD disease severity [21]. Within asthma, EBC $H_2O_2$ concentrations were significantly higher in asthmatics who were nonsmokers compared with healthy subjects [30,35]. The level of EBC $H_2O_2$ also correlated with asthma severity and phenotype, being significantly higher in moderate asthmatics compared with those with mild asthma and in asthmatics with neutrophil predominant airway inflammation [36,37]. Furthermore, higher values of EBC $H_2O_2$ were observed in uncontrolled asthma (defined as increased use of short-acting beta-agonist and continued daily symptoms) compared with healthy subjects and controlled asthmatics [31].

Exhalation Technology Ltd. has developed a battery operated, handheld device for point of care measurement of $H_2O_2$ level in exhaled breath—the Inflammacheck device. This test involves simple, relaxed tidal breathing for up to 1 min (20 breaths) into a mouthpiece. The device collects at least 60 µL of EBC in a collection cartridge. A total of 30 µL of the collected EBC is then pipetted by the clinician onto a separate sensor cartridge that measures the level of $H_2O_2$. If this device can be used in a routine clinical setting, it may give clinicians an immediate insight into the inflammatory state of the airways. It also has the potential to identify inflammatory cell specific inflammation (neutrophilic) that would guide treatment decision making. This could aid earlier diagnosis and personalized management plans, ultimately improving patient care. This simple, noninvasive technique may also make repeat sampling and longitudinal monitoring of global airway inflammation a realistic possibility.

We aim to assess whether Inflammacheck can differentiate asthma and COPD from healthy airways and whether its measurement of EBC $H_2O_2$ correlates with other noninvasive methods of assessing airway inflammation and disease severity. Information about the reliability and repeatability of the Inflammacheck sensor also needs to be collected. We will assess Inflammacheck in patients with asthma, COPD, and healthy individuals who do not have respiratory disease.

### Aims and Objectives

#### *Coprimary Objectives*

The coprimary objectives were as follows:

- To determine whether Inflammacheck can differentiate asthma and COPD from healthy controls.
- Whether Inflammcheck can detect EBC $H_2O_2$ levels consistently and in a repeatable manner.

#### *Secondary Objectives*

The secondary objectives were as follows:

- To describe the relationship between EBC $H_2O_2$ and the following:
  - Disease severity (Global Initiative for Asthma [GINA] stage for asthma [38], Global Initiative for Obstructive Lung Disease [GOLD] stage for COPD [1])
  - Disease control (Asthma Control Questionnaire, ACQ score [asthma] and COPD Assessment Test, CAT score [COPD])
  - QoL (Asthma Quality of Life Questionnaire, AQLQ score [asthma])
  - Spirometry (forced expiratory volume in 1 second [$FEV_1$], forced vital capacity [FVC], and ratio), with reversibility where available
  - FeNO (ppb)
  - Atopic status (asthmatics only)
- To determine the reliability and consistency of the Inflammacheck sensor in measuring EBC $H_2O_2$ levels with laboratory reference ranges.
- To determine how frequently patients are unable to perform spirometry, FeNO, and Inflammacheck, or require further attempts.
- To describe any adverse events during the test procedures.
- To explore participants' and health care professionals' (HCPs') experience of Inflammacheck, including *ease of use* and acceptability of the device.

#### *Exploratory Objectives*

To determine whether there is a relationship between EBC $H_2O_2$, as measured by Inflammacheck and FeNO, atopic status (skin prick testing [SPT] result in asthmatics only), exercise, diet, medications, and effects of inhaled therapy. EBC $H_2O_2$ levels will also be compared with peripheral white cell counts, serum biochemistry, and markers of inflammation where available.

## Methods

### Overview

This is a single visit, cross-sectional, feasibility study of EBC $H_2O_2$ levels, as measured by Inflammacheck, and markers of disease severity and symptom control in patients with asthma, COPD, and volunteers with no known lung disease.

### Outcome Measures

Respiratory outcomes were as follows:

- EBC $H_2O_2$ as measured by the Inflammacheck sensor
- EBC $H_2O_2$ as measured by a reference and background sensor
- FeNO
- $FEV_1$, FVC, and ratio.
- GINA stage in asthma patients, GOLD stage in COPD patients.
- ACQ and CAT scores
- AQLQ score

Process outcomes were as follows:

- Number of attempts at each procedure
- Whether patient successfully completed procedure

Safety outcome was as follows:

- Any adverse events reported during any of the study procedures

Experience outcomes were as follows:

- Participant's perception of device
- HCP's perception of device

Environmental and biological outcomes included the following:

- Atopic status (SPT result in asthmatics), diet, exercise, and medication use.

## Study Participants

Three populations of older adolescent and adult patients (all aged ≥16 years) will be invited to participate:

- Asthma patients (n=30)
- COPD patients (n=30)
- Comparator group (n=30)—Volunteers with no previous history of lung disease (our healthy volunteers). These healthy volunteers will be recruited from the hospital staff. This will be facilitated by the hospital and research communications teams. HCPs, who have assisted patients performing Inflammacheck, alongside the standard respiratory tests of spirometry and FeNO, will be invited to participate in an experience outcome questionnaire at the end of the study.

## Inclusion and Exclusion Criteria

Inclusion criteria for the participants are provided in Textbox 1.

HCPs inclusion criteria were as follows:

- Assisted a minimum of 5 patients in performing the collection of EBC $H_2O_2$ levels using the Inflammacheck device during the study.
- Willing and able to give informed consent for participation in the study.

Exclusion criteria for the participants are provided in Textbox 2.

**Textbox 1.** Inclusion criteria for study participants.

- Male or Female, aged ≥16 years.
- Any of the following conditions:
  - A confirmed, clinician-made diagnosis of asthma with symptoms for ≥3 months supported by evidence of any of the following:
    - Airflow variability, with a variability in forced expiratory volume in 1 second ($FEV_1$) or peak expiratory flow of >20% across clinic visits, with concomitant evidence of airflow obstruction ($FEV_1$/FVC ratio <70% on spirometry recorded at any time);
    - Airway reversibility with an improvement in $FEV_1$ by ≥12% or 200 mL after inhalation of 400 µg of salbutamol (or equivalent bronchodilator) via a metered dose inhaler and spacer or nebulizer, recorded at any time;
    - Airway hyper-responsiveness demonstrated by Methacholine challenge testing with a provocative concentration of Methacholine required to cause a 20% reduction in $FEV_1$ (PC20) of ≤ 16 mg/mL or equivalent test, recorded at any time.
  - *OR* a confirmed, clinician-made diagnosis of Chronic Obstructive Pulmonary Disease (COPD) for ≥3 months supported by spirometric evidence of fixed airflow limitation (postbronchodilator $FEV_1$ / FVC ratio <0.7) recorded at any time.
  - *OR* no known history of lung disease (defined as no current clinical diagnosis of, or be receiving treatment for, a lung disease).
- Willing and able to give informed consent for participation in the study.

**Textbox 2.** Exclusion criteria for study participants.

The participant may not enter the study if any of the following apply:

- Existing comorbidities that may prevent them from performing spirometry, fractional exhaled nitric oxide (FeNO), or other study measurements (at the discretion of the clinical investigator).
- Known other lung, chest wall, neuromuscular, or cardiac disease or abnormality (including end-stage disease or cancer) that would confound symptom scores and spirometry.
- Has received treatment for an exacerbation of their respiratory disease within the last 2 weeks.
- In the opinion of the clinical investigator, participant could be put at risk of harm by having to perform any of the study procedures.
- Unable to comprehend the study and provide informed consent, for example, insufficient command of English in the absence of someone to adequately interpret.

## Sampling and Sample Size

The sample size was based on our primary objective of comparing EBC $H_2O_2$ values between each pair of the three main study groups (asthma patients, COPD patients, and controls). This is a feasibility pilot study of the use of a new device. For future, larger trials to be conducted using the device, information is needed to confirm that the Inflammacheck sensor is accurate and can consistently measure $H_2O_2$ in EBC within patients. There are no previous trials using this version of the device that can guide a sample size calculation. As a result, the sample size is based on the research teams' experience of delivering previous trials on novel diagnostic tests.

## Study Procedures

### *Recruitment*

#### Outpatients

Patients attending respiratory outpatient clinics at Queen Alexandra Hospital in Portsmouth will be will be preidentified from upcoming clinic lists and sent a participant information sheet (PIS) and an invitation to participate with their clinic letter. Patients will have adequate time to read this information, and there will be a contact telephone number and email address on the invitation letter so that potential participants are able to discuss the study with a member of the research team before their clinic visit. Patients who are already enrolled in other research trials will be invited and allowed to participate in the study if they so wish. For the recruitment of mild disease, patients will be identified from specialist respiratory clinics held in the community. They will be given a PIS with an invitation to participate in the study.

#### Healthy Volunteers

Posters advertising the study will be placed in staff rest rooms, and an email will be sent to all staff (through the hospital research communications team) to advertise the study. Potential volunteers will be asked to call or email the study team to so that further information (PIS) can be sent via an email and an appointment arranged to discuss the study further.

HCPs

HCPs and members of the research team within the respiratory department, who perform all respiratory tests on the participants, will be asked to participate within the study to answer a questionnaire on their perceptions of the Inflammacheck device. Only HCPs who have assisted a minimum of 5 patients in performing the collection of EBC $H_2O_2$ levels using Inflammacheck will be asked to participate.

## Screening and Enrollment

### *Outpatients*

Those expressing an interest in the study will have eligibility assessed and the opportunity to ask any further questions on their clinic visit. Informed consent will then be taken.

### *Healthy Volunteers*

An appointment will be made with the research team at a convenient time to confirm eligibility criteria and take informed consent.

### *HCPs*

At the end of the study, the research team will approach all HCPs involved in assisting patients in performing the collection of EBC $H_2O_2$ levels using the Inflammacheck device. If HCPs who have assisted at least 5 participants in performing the study breathing tests express an interest in participating, informed consent will be taken.

## Study Assessments

A summary of the study assessments and participant flow is displayed in Figure 1.

### *Participant Characteristics*

Before other study procedures, characteristics of participants that are known to have a potential influence on respiratory test results will be documented. These will include the following:

- Demographics: age, gender, and ethnicity
- Anthropometry: Height and weight (to calculate body mass index)
- Disease severity: GINA stage (asthma), GOLD stage (COPD)
- Medications participants are taking
- Factors that may affect EBC $H_2O_2$ levels including smoking status (current or former or never), time of last cigarette (for current smokers only), number of pack years of smoking (current and former smokers only), use of mouthwash that morning, time of last dose of inhaled medication (asthma and COPD patients only), time of last caffeinated drink, time of last food intake, and time of last vigorous exercise

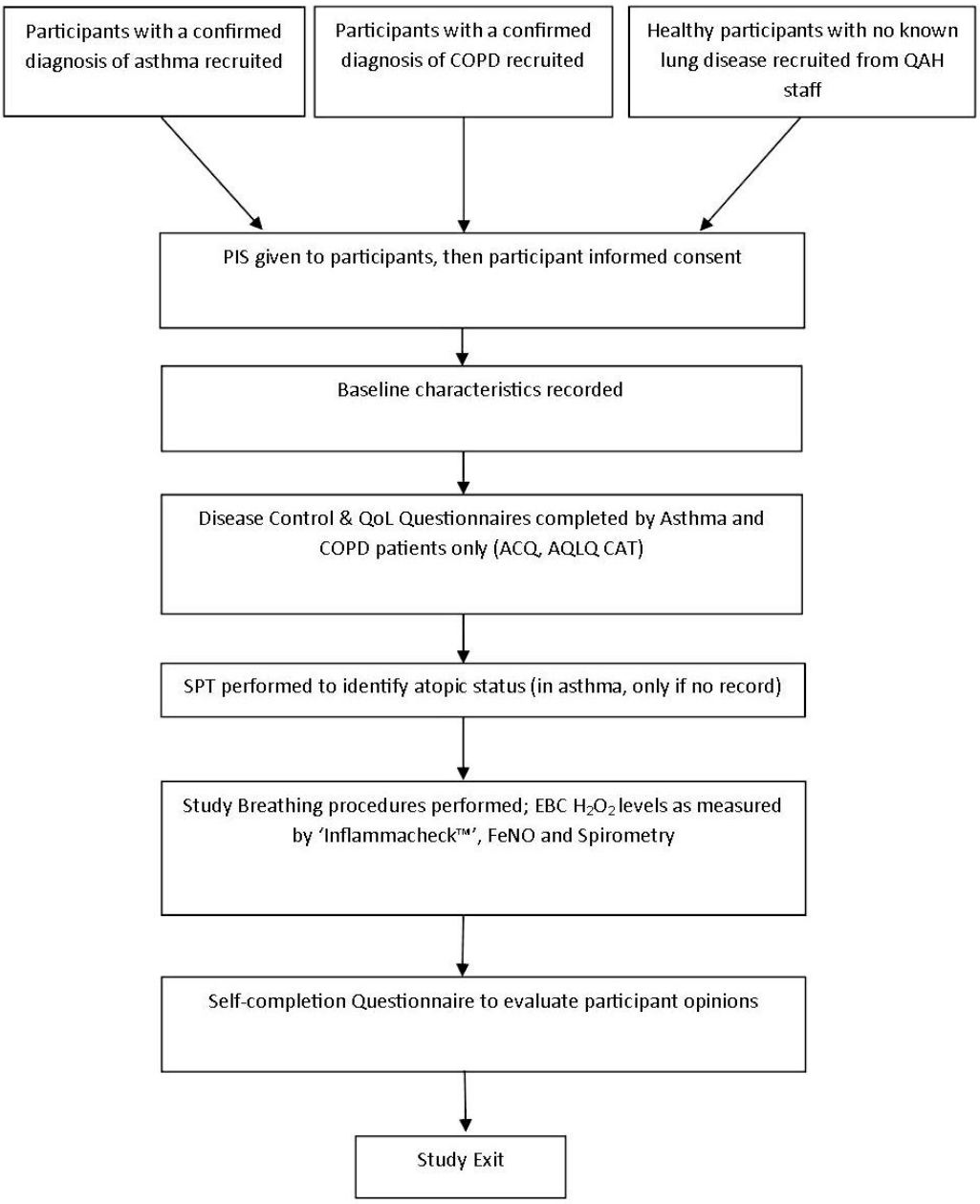
### *Disease Questionnaires*

These will be completed only by patients with asthma and COPD and forms part of their standard clinical assessment in the outpatient setting.

### *Asthma Control Questionnaire*

The ACQ is a validated 7-item questionnaire for assessing the level of asthma control over the preceding 7 days. The questionnaire includes five symptom scores, the frequency of rescue bronchodilator use, and a measure of airway calibre ($FEV_1$% predicted). Responses are given on a 6-point scale, and the overall score is the mean of the responses (0=totally controlled, 6=severely uncontrolled). Scores over 1.0 are considered indicative of poor control [39,40].

**Figure 1.** Summary of study procedures and the participant flow. COPD: Chronic Obstructive Pulmonary Disease; QAH: Queen Alexandra Hospital; PIS: participant information sheet; QoL: quality of life; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; CAT: COPD assessment test; SPT: skin prick test; EBC $H_2O_2$: exhaled breath condensate hydrogen peroxide; FeNO: fractional exhaled nitric oxide.




### *Chronic Obstructive Pulmonary Disease Assessment Test*

The CAT is a validated 8-item unidimensional measure of health status impairment in COPD. It assists patients and their physicians in quantifying the impact of COPD on the patient's health. Responses are given on a 5-point scale with a maximum total score of 40. The higher the score, the greater the impact COPD has on the patient's health; scores of 0 to 9 are considered low impact, 10 to 20 medium, 21 to 30 high, and >30 very high [41].

### *Asthma Quality of Life Questionnaire*

The AQLQ is a validated 32-item questionnaire that measures the functional problems (physical, emotional, social, and occupational) that are most troublesome to adults with asthma. Patients are asked to think about how they have been over the previous 2 weeks and respond to each of the 32 questions on a 7-point scale (7=not impaired at all, 1=severely impaired). The overall score is the mean of all 32 responses [42,43].

### *Skin Prick Testing*

Asthma participants will have an SPT performed to determine their atopic status. If the participant has had an SPT performed and recorded within the last 3 years, then this result will be used. An SPT is a simple and safe method of testing a person to determine whether or not they have an IgE-mediated allergic response to common inhaled allergens [44]. SPT's will be performed by trained and experienced respiratory HCPs, who are also trained in resuscitation techniques. Five common aero-allergens will be tested for: grass, house dust mite, aspergillus, cat dander, and dog dander. Atopic status will be

demonstrated by a positive SPT (wheal diameter ≥3 mm larger than the negative control).

### *Respiratory Tests*

The participants will then continue with the standard respiratory assessment element of their clinic visit, with the addition of the EBC $H_2O_2$ levels measurement performed by the Inflammacheck device, in the order described below. For every test, the following will be recorded:

- the time the test starts and finishes
- the room temperature at the time of the test
- the time of the participants last inhaled medication dose
- the time of the participants last cigarette (if applicable)
- the time of the participants last food and drink intake
- the time of the participants last vigorous exercise
- whether the test was not possible to complete, and the reason for this
- if test was performed, the number of attempts required to complete the test successfully
- any adverse events related to the test that are reported by the patient or noted by clinical staff during the test procedures

### *Exhaled Breath Condensate Hydrogen Peroxide*

EBC $H_2O_2$ will be measured using the Inflammacheck device (Exhalation Technology Ltd., Dereham, Norfolk) as specified by the manufacturer's instructions. For the participant, this involves simple relaxed tidal breathing for 20 breaths into a disposable mouthpiece. Once they have completed this, the research nurse will remove the collection cartridge, which should contain at least 60 µL of EBC. The nurse will then pipette 30 µL onto the Inflammacheck sensor cartridge. The sensor cartridge will be placed back into the device and will give a reading of EBC $H_2O_2$ to the researcher via an attached laptop. The remaining 30 µL will then be pipetted onto a separate reference sensor. This reference sensor will give a separate reading of EBC $H_2O_2$, and will be used to confirm the consistency and reliability of the Inflammacheck sensor. The results of this test will not be disclosed to the patient to avoid bias in effort for subsequent tests. The result will also not be recorded in the clinical notes that are passed to the consulting doctor as they are not intended to inform patient management decisions in this study.

### *Fractional Exhaled Nitric Oxide*

FeNO will be measured using a NIOX MINO device (Aerocrine AB, Solna, Sweden,) or equivalent device for measuring exhaled nitric oxide level, as specified by the manufacturer's instructions and outlined in the American Thoracic Society (ATS) and European Respiratory Society (ERS) standards. This includes collection by controlled exhalation at the recommended expiratory flow rate of 50 mL/s for greater than 6 seconds [45].

### *Spirometry*

Spirometry will be conducted using a spirometer conforming to ATS and ERS standards as specified by the manufacturer's instructions. Participants will inhale rapidly and completely from functional residual capacity, then exhale in an initial blast of exhalation, and then continue exhalation until the end of the test. $FEV_1$ (L), FVC (L), and $FEV_1$/ FVC ratio will be recorded. $FEV_1$ and FVC will be documented as both absolute values and as a percentage of the predicted value [46].

### *Self-Completed Questionnaires*

A brief, self-completed questionnaire will be used to evaluate participant's opinions of the Inflammacheck device on a Likert-type scale. Participants will be asked about ease of use, comfort during testing, perception, and satisfaction of Inflammacheck. They will also be asked to compare Inflammacheck with spirometry and FeNO, stating their preference and which they found easiest to use. At the end of the study, a questionnaire will be used to evaluate HCPs opinions of the different study assessments. Informed consent will be obtained from each HCP to participate within the study. Only HCPs who performed the respiratory tests during the trial on a minimum of 5 patients will be asked to participate. The questionnaire will include a rating for each of the study assessments (spirometry, FeNO, and EBC $H_2O_2$ as measured by Inflammacheck) on a Likert-type scale. HCPs will be asked about "ease of use" of each device, their perceptions of patient experience, and an open-ended question for any further suggestions.

### *Discontinuation of Participants From Study and End of Study*

Participants who are unable to perform EBC $H_2O_2$ measurement with Inflammacheck, spirometry, or FeNO will not be withdrawn. The reason for failing to perform these tests will be documented in the case report form (CRF). The end of study is the date of the last participant completing their study procedures.

## Safety Assessment

### *Adverse Event (AE) Definition*

An adverse event is any untoward medical occurrence in a participant taking part in a clinical trial that does not necessarily have to have a causal relationship with the device under investigation. An AE can therefore be any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of the device, whether or not this has a causal relationship with the device under investigation.

### *Recording and Reporting of AEs*

There are not expected to be any AEs associated with the use of the Inflammacheck device. Only AEs that have a reasonable possibility of being attributable to the device and any other AE considered to be of clinical significance by the principal investigator (PI) as causing harm to the patient will be recorded in the CRF and reported to the sponsor as per their guidelines. We will record all AEs that are observed during all respiratory test procedures as a study outcome. Any AEs that do occur and are considered by the PI to be related to the device will be expedited to the sponsor, research ethics committee (REC), and the device manufacturer within 7 days. Lists of the AEs will be provided to the sponsor when requested.

## Data Handling and Analysis

### *Data Collection and Management*

Enrollment into the study will be documented in each participants' medical notes.

Data collection forms will comprise the following:

- Main CRF, including participant characteristics, SPT results, and respiratory test results.
- Disease control questionnaire (ACQ-7)
- QoL questionnaires (AQLQ and CAT)
- Self-completed questionnaire for participants
- Self-completed questionnaire for HCPs

A bespoke database with preset validation criteria will be created for the study. Data will be entered and checked against the original CRF. Further verification will be done according to frequency and pattern of errors. All data verification will be carried out by the research team and then by the sponsor during their monitoring procedures.

### *Data Analysis*

All participants with an EBC $H_2O_2$ result as measured by Inflammacheck will be analyzed. Subgroup analyses may be carried out if there are sufficient numbers of patients with particular characteristics, for example, smokers versus nonsmokers. Demographics or baseline characteristics of each of the study groups (COPD, asthma, and control) will be produced, as well as summaries for all groups combined. Normally distributed continuous variables will be summarized by the mean and standard deviation, whereas the median and interquartile range will be preferred for non-normally distributed continuous variables. The number and percentage of subjects in each category will be recorded for categorical variables.

### *Primary Analysis*

To establish our primary objective, the primary analysis will be a comparison of EBC $H_2O_2$ values, as measured by the Inflammacheck device between each pair of the three main study groups (COPD, asthma, and control). It is expected that the EBC $H_2O_2$ will have a positively skewed distribution. To allow for the skewed distribution, one approach would be to analyze the data on a log transformed scale and to compare between groups using analysis of variance (ANOVA), with post-hoc tests performed to compare between pairs of groups. It is possible that there may be EBC $H_2O_2$ measurements below the lower detection limit, and thus, the previous approach may not be practical. If there are measurements below the detection limit, this will be dealt with using nonparametric methods. The Kruskal-Wallis test will be used to compare between the three groups, with the Mann Whitney test used to compare between pairs of groups. When comparing between pairs of groups, a Bonferroni correction will be applied to allow for multiple testing.

### *Secondary Analyses*

There will be a comparison of EBC $H_2O_2$ values, as measured by the Inflammacheck sensor and the values measured by the reference sensor. This will determine whether EBC $H_2O_2$ is being measured consistently and reliably by the Inflammacheck sensor, giving confidence for its use in future versions of the Inflammacheck device. The association between the EBC $H_2O_2$ measurements and a number of other parameters will also be examined. Associations will be examined with the following:

- FeNO (both high and low levels)
- Disease severity
- Disease control measures
- Disease QoL measures
- Spirometry measures ($FEV_1$, FVC)
- Atopic status (in asthma participants only)
- Items identified in the pretest checklist

Associations with continuous variables will be examined using either Pearson or Spearman rank correlation (as appropriate). Associations with categorical measures will be assessed using ANOVA (using transformed $H_2O_2$ values) or the Kruskal-Wallis test.

The percentage of attempted tests that *failed* for each test will be quantified. The association between patient characteristics and this outcome will be examined. Assuming patient characteristics are categorical in nature, the chi-square test or Fisher exact test will be used to examine associations with this outcome. The secondary analyses will be performed for all subjects combined and also for each study group separately.

### *Procedure for Dealing With Missing and Spurious Data*

The analysis will include only measured data values, with missing values omitted from the analysis. No imputation of missing data will be performed. The data will be examined for outlying values. Where possible, these will be retained in the data analysis and their influence minimized by a data transformation or a nonparametric approach. If such approaches are not practical, the analysis of the primary outcome will be performed twice, with and without the outlying values.

## Ethics

### *Participant Confidentiality*

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant's ID number on CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorized personnel. The study will comply with the Data Protection Act that requires data to be anonymized as soon as it is practicable to do so.

### *Other Ethical Considerations*

The study will not be initiated before the protocol and all study relevant material such as the informed consent forms and PISs have received approval or favorable opinion from the REC and the respective National Health Service (NHS) research and development (R&D) departments. Any changes to protocol or relevant study documents will be approved by the sponsor. Should an amendment be made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval or favorable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an

apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor amendments as defined by REC as nonsubstantial amendment, may be implemented immediately; and the REC will be informed. All participants will have adequate time to consider participation in the study, as per Good Clinical Practice (GCP) guidelines.

Patients who are already enrolled in other research trials will be invited and allowed to participate in the study if they so wish. This was discussed with our patient and public involvement (PPI) representatives who felt that these patients should also have the opportunity to participate in the study and should not be excluded. There is a possibility that the study procedures reveal potential new, previously unknown disease pathology. This would be more likely to occur in our healthy controls. If such a circumstance occurs, then the participant will be told of the results and immediately referred to the most appropriate NHS department for further review. With the participant's consent, a letter will be written to their general practitioner explaining the findings.

### *Informed Consent*

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each person participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study using the PIS. The consent process will be documented in the participant's notes.

The process for obtaining participant informed consent will be in accordance with the REC guidance and GCP and any other regulatory requirements that might be introduced. The PI or delegate and the participant or any other legally authorized representative shall both sign and date the informed consent form before the person can participate in the study. The participant will keep the PIS and a copy of the signed and dated consent form. The original will be retained in the trial master file. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes of when the PIS was provided and that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty, or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled.

### Patient and Public Involvement

PPI involvement in this study has been sought from patients with first-hand experience of living with chronic respiratory disease. Through face-to-face meetings, email, and telephone contact, we have discussed the concept, impact, and details of the study with our asthma patient representatives from the Wessex Asthma Network and our COPD patient representatives from local British Lung Foundation groups. These people have lived with severe asthma and COPD and been involved in previous research studies. They contributed to developing the key questions and setting our study objectives, ensuring that we answer the questions that are relevant to people suffering from airways disease. They have also helped us with patient recruitment design and the implementation of the Inflammacheck test within a standard clinical visit so as to minimize delays for patients who agree to participate in the study. They have helped design the questionnaire that will be used to record the participant experience of the device, PIS and have coauthored the lay summary.

## Results

Recruitment to the EXHALE pilot study is ongoing. It is anticipated that results will be available by early 2018.

## Discussion

The EXHALE pilot study will provide an evaluation of a new method of measuring EBC $H_2O_2$. It will assess the device's (Inflammacheck) consistency and accuracy of measurement of EBC $H_2O_2$ and its ability to distinguish airway inflammation in asthma and COPD compared with healthy controls. The data collected will allow us to develop the device further in response to participant feedback and prepare for future longitudinal studies that will assess its capability for detecting asthma and COPD exacerbations.

### Conflicts of Interest

None declared.

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## Abbreviations

**ACQ:** Asthma Control Questionnaire
**AE:** adverse event
**ANOVA:** analysis of variance
**ATS:** American Thoracic Society

**AQLQ:** Asthma Quality of Life Questionnaire
**CAT:** COPD Assessment Test
**COPD:** Chronic Obstructive Pulmonary Disease
**CRF:** case report form
**EBC:** exhaled breath condensate
**ERS:** European Respiratory Society
**FeNO:** fractional exhaled nitric oxide
**$FEV_1$:** forced expiratory volume in 1 second
**FVC:** forced vital capacity
**GCP:** Good Clinical Practice
**GINA:** Global Initiative for Asthma
**GOLD:** Global Initiative for Chronic Obstructive Lung Disease
**$H_2O_2$:** hydrogen peroxide
**HCP:** health care professional
**NHS:** National Health Service
**PI:** principal investigator
**PIS:** participant information sheet
**PPI:** patient and public involvement
**QoL:** quality of life
**R&D:** research & development
**REC:** research ethics committee
**ROS:** reactive oxygen species
**SPT:** skin prick testing

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Protocol

# Feasibility and Preliminary Effectiveness of the Homework Intervention Strategy (eHIS) Program to Enhance Male Condom Use: Research Protocol

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## Abstract

**Background:** Although condoms are effective in reducing the risk of sexually transmitted infections (STIs) and unintended pregnancy, they are still often not used consistently and correctly. Negative impact on sensation and pleasure, ruining the mood, causing problems with maintaining erection, and condom slippage or breakage are some of the reasons given by men explaining why they do not want to use condoms. Although many interventions promoting condom use exist, some of them delivered online are complex and time- and resource-intensive. The Homework Intervention Strategy (eHIS) program, adapted from the existing face-to-face Kinsey Institute Homework Intervention Strategy (KIHIS) program, aims to address these issues by encouraging men to focus on sensation and pleasure when trying different types of condoms and lubricants in a low-pressure situation (on their own, without a partner present).

**Objective:** The objectives of this study are to assess the feasibility, acceptability, and users' engagement with the eHIS program, its preliminary effectiveness in increasing condom use frequency and consistency, as well as the feasibility of the program's evaluation approach, including choice of measures and participant recruitment and retaining strategies (primary outcomes). Secondary outcomes include condom use experience, condom use attitudes, condom use self-efficacy, condom use errors and problems, and condom fit-and-feel. All of these will be analyzed in the context of participants' demographics, sexual history, and previous condom use.

**Methods:** The study has a pre-post-test, within-subjects design. Men aged 18 to 69 and living in the United Kingdom are recruited through posters, leaflets, social media, and emails. Study participants are asked to complete T1 (baseline) measures before entering the eHIS website. After completing the T1 measures, they can order a free condoms and lubricants kit and have access to the eHIS website for 4 weeks. During that time they are asked to practice using different types of condoms and lubricants on their own in a no-pressure situation. Following T1, participants are asked to complete the T2 and T3 measures at 4 and 10 weeks, respectively.

**Results:** Data collection for the study is completed. Data analysis is in progress and is expected to be completed by February 2018.

**Conclusions:** This brief, home-based, self-guided program may lead to increased consistent and correct condom use. Online delivery can make the program an easily accessible and low-cost health promotion intervention, which has the potential to reach a wide and diverse audience. If results of the current study show the program's feasibility and preliminary effectiveness in changing condom use related outcomes, a larger scale randomized controlled trial (RCT) will be conducted.

**Trial Registration:** Research Registry: researchregistry2325; http://www.researchregistry.com/browse-the-registry.html#home/registrationdetails/58da6cad1d7ab0314337d076/ (Archived by WebCite at http://www.webcitation.org/6vXs6S9XW)

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**KEYWORDS**

condoms; pleasure; telemedicine; eHealth; risk reduction behavior; sexual behavior; health psychology; behavior modification

# Introduction

## Background

Male condoms remain the single best method of reducing the risk of acquiring sexually transmitted infections (STIs), including HIV [1,2]. Promotion of correct and consistent use of male condoms as an effective method of reducing the prevalence of STIs was recommended in the Global Strategy for Prevention and Control of Sexually Transmitted Infections: 2006-2015 [3]. However, research repeatedly demonstrates that condoms are not used consistently [4-7], and even when used, condom use errors and problems and dislike of condoms are often reported [8,9]. Condom use errors and problems are associated with the reasons men give for not using condoms, such as less pleasurable experience when condoms are used, decreased sensation, poor fit-and-feel, condom breakage and slippage, and difficulties in maintaining erection [10,11].

Many previous interventions aimed to increase condom use but few of them focused on pleasure and fit-and-feel [12], and they were also often resource- and time-intensive. Improving fit-and-feel should lead to reduction in condom use problems and increase consistent and complete condom use. Internet-based behavior change interventions, on the other hand, may be cost- and resource-effective [13-15], easily accessible and acceptable by users, especially when focused on sensitive or stigmatized health-related issues [16-19], and have efficacy comparable with human-delivered interventions focused on condom use [20,21].

The Homework Intervention Strategy (eHIS) program, an online adaptation of the Kinsey Institute Homework Intervention Strategy (KIHIS) [22], combines a focus on pleasure and fit-and-feel in condom promotion with the benefits of an online intervention. In the KIHIS, during the session with the instructor, men are given the correct condom use instruction and are asked to practice condom application on a penile model. The instructor then encourages them to practice using condoms on their own and rate them, highlighting the importance of pleasure and finding the condom that fits and feels best for an individual. The home-based and practice-oriented approach makes the program distinct from most interventions in this area, which are mainly delivered face-to-face, during group workshops, or in individual consultations [23-25]. The results of previous pilot studies [22,26,27], showed the program's potential in improving use experiences, confidence in the ability to use condoms, self-efficacy for condom use, condom comfort, and reduced breakage and erection problems.

The final content and design of the program was developed taking into account participant feedback from the qualitative evaluations of the program prototype (paper-based) and computerized version of the program (M Glowacka, thesis chapter in preparation). The research team adapting the face-to-face version of the program for use in the United Kingdom was also consulted [27].

Mirroring the KIHIS approach, the eHIS addresses the issues related to condom use errors and problems by focusing on correct condom use, pleasure, and developing positive condom use experience. Participants are encouraged to practice correct condom application and explore different types of condoms and lubricants in a low-pressure situation, at home, and without their partners present. Components of the intervention are listed in Textbox 1 and an example of the eHIS webpage is shown in Figure 1.

## Aims and Objectives

The current study aims to evaluate the feasibility of the Internet-based eHIS program. Evaluation of participants' engagement with the program and its acceptability (dimensions of feasibility, primary outcomes) and the potential of the intervention to change targeted behavior (preliminary effectiveness) can provide a "proof of concept" for the approach used in the intervention [28,29]. The primary outcomes of this study are increasing condom use frequency and consistency. The secondary outcomes include reducing condom use errors and problems, enhancing condom use experience, increasing condom use self-efficacy, and improving condom use attitudes and motivation.

The study does not target men based on characteristics such as sexual orientation or condom use history as it has not yet been established for whom the eHIS intervention may be the most useful. Therefore, whether the program's feasibility and preliminary effectiveness are linked to participants' demographic characteristics, sexual history, or previous condom use variables is explored. To inform development of a larger trial, the feasibility of the approach to study evaluation with a focus on recruitment effectiveness, measures completion, and attrition rate is investigated. This will help to verify whether the specific study design and approach employed for the evaluation are appropriate and identifies acceptable outcome measures that should be used as measures of its effectiveness in a full-scale randomized controlled trial (RCT) [30]. The results can also help to estimate the expected effect size of the observed changes, to be used in the calculation of the sample size needed for a full scale RCT [31].

## Research Questions

This study is guided by the following research questions: (1) Is the eHIS program feasible? (2) Does the eHIS program have the potential to be effective in increasing the frequency of condom use, increasing consistent condom use, improving condom use experience, improving condom use self-efficacy, reducing the number of condom-related errors and problems, changing condom use attitudes to more positive ones, and increasing motivation to use condoms? (3) Is the approach to evaluate the eHIS program feasible? (4) Are the program and study feasibility, and the preliminary effectiveness of the program on condom use outcomes associated with participants' characteristics (demographic, sexual history or baseline condom use variables)?

**Textbox 1.** The components of the Homework Intervention Strategy (eHIS) program.

Core pages

- Program's rationale
- Correct condom use skills review
- Tips on how to deal with specific condom use errors and problems
- Information about program procedure and condom kit content
- A home practice guide
- Condom rating forms
- Ratings feedback
- Condoms and lubricants kit order

Optional pages

- Masturbation
- Partner involvement
- Condom effectiveness
- Information where to find support in case of concerns related to condom use
- Condom use instruction in various formats
- Example of condom rating form
- Motivational message (aimed to provide study rationale for specific users' circumstances such as various condom use experience and relationship status or message strengthening program credibility perception)

Additional pages

- Contact form
- Reminders cancellation
- Login
- Exit
- Password reset

Study pages

- Participant Information Sheet
- Consent statement
- Screening questionnaire
- Registration
- Study questionnaires
- Charity donation
- Debriefing sheet
- Information about uncompleted measures
- Next follow-up date/completion of the study

Condoms and lubricants kit

- Six different types of condoms (2 of each) chosen to give a wide range of sizes, shapes, and materials (latex and non-latex)
- Two types of lubricants in 6 single use sachets
- A printed copy of correct condom use instructions with a link to the study website

**Figure 1.** An example of a page on the Homework Intervention Strategy (eHIS) website.


## Methods

### Study Design

The study uses a pre-post test, within-subjects design.

### Participants

A target sample of 139 participants was recruited and data collection is completed. The sample size was estimated on the basis of the calculation of the number of participants required to conduct statistical analysis to evaluate the feasibility of the program and its preliminary effectiveness, possible high attrition (in the region of 60%), more likely in self-guided interventions [32-36], study resources, and numbers of participants recruited to similar studies [31,37-42]. The inclusion criteria for the study are listed in Textbox 2.

### Recruitment

Participants were recruited through self-referral in response to recruitment advertisements (posters, leaflets, business card adverts, Facebook and Twitter posts and paid adverts, emails, and United Kingdom-wide mailing lists for postgraduate psychology students). The adverts included key phrases such as “test and rate condoms,” “improve condom use experience,” “learn more about condoms,” “focus on pleasure,” “enjoy using condoms,” and “get free condoms and lubricants kit.” To ensure wide reach and reduce the risk of recruitment bias (age and geographical location) where possible, study advertisements were distributed in multiple locations (mainly in England, including universities, colleges, sexual health charities, commercial sector employers, community centers, youth organizations), and on social media (Facebook paid posts addressed to specific age groups, for example 26 to 35 years and 36 to 45 years with the United Kingdom chosen as geographical location). People from professional and personal networks were also asked to share the advertisements in their locations and through social media.

### Data Collection

Questionnaires and website usage data were used in the study to collect data. The questionnaires were chosen to mirror as closely as possible the measures used in the face-to-face KIHIS [22,26] and HIS-UK studies [27]. They were reviewed and modified according to the feedback received in a qualitative evaluation of the program during its development phase (M Glowacka, thesis chapter in preparation). Additional measures and items were chosen or developed for this study to allow investigation of the aspects of the program related to its specific mode of delivery. The data collection schedule is presented in Table 1.

### Measures

#### *Eligibility Screening Questionnaire*

The eligibility screening questionnaire included questions assessing the inclusion and exclusion criteria (see Textbox 2).

#### *Registration*

Following screening, eligible participants were asked to provide an email address that the study reminders are sent to and an optional phone number if they would also like to receive text messages with study reminders.

#### *Background Information Questionnaire*

At baseline (T1), participants provided background information such as ethnic background, education, employment, relationship status, first part of the postcode, and computer use proficiency. The ethnic background question categories were adapted from the Census for England [43].

#### *Sexual History*

At T1, participants were asked about their current sexual activity, where they chose an answer from the following options: (1) sex with one partner only, (2) frequent sex with different partners, (3) infrequent sex with different partners, (4)

occasional sex with different partners, (5) not sexually active, and (6) other.

They were also asked about the gender of their sexual partners (women, men, women and men, I have never had sex) [44] and the number of sexual partners.

### *Sexually Transmitted Infections and Unplanned Pregnancy*

At T1, questions about lifetime and last year STI diagnoses and unplanned pregnancies were asked. At T2 and T3 participants provided information about STI diagnoses and unplanned pregnancies in the last 4 weeks.

### *Condom Use and Sexual Activity*

To assess the frequency and consistency of condom use at T1 to T3 participants were asked about the number of episodes of penile-vaginal, penile-anal, or penile-oral intercourse in the last 4 weeks, the number of partners in the last 4 weeks, the number of times a condom was used during penile-vaginal, penile-anal, or penile-oral intercourse in the last 4 weeks, and whether they practiced using condoms in the last 4 weeks. Participants also provided reasons for using condoms (I did not use condoms, to avoid STIs, to avoid HIV/acquired immunodeficiency syndrome [AIDS], to please my partner, to make sex more pleasurable, to make sex last longer, so my partner would not get pregnant, to practice, other) and the type(s) of condoms used in the last 4 weeks (latex, non-latex, I don't know what kind we used, not applicable [I did not use condoms]). In addition, at T1 they were asked whether they were taught how to use condoms, and if so, where they learned to use condoms from (leaflet attached to the condom pack, leaflet given to me, watching condom use demonstration [video], watching condom use demonstration [live], practicing how to use condoms correctly instructed by somebody else [ie, during sex education/in the clinic etc], erotic/porn movie, erotic/porn magazine, have not learnt how to use condoms), and whether they had ever used condoms or practiced using them without a partner present.

### *Condom Use Experience*

This questionnaire was only displayed to those who reported that they had used condoms during sexual intercourse over the last 4 weeks (T1, T2, and T3). The Effect on Sexual Experience subscale from the Condom Barriers Scale [45,46] is a 7-item scale which measures participants' condom use experience at T1 to T3, including condom fit-and-feel, condom mood interruption, and condom impact on climax or orgasm and on the relationship with sexual partner. Items are rated on a 5-point scale from 1 (strongly agree) to 5 (strongly disagree). Higher scores indicate better condom use experience. In previous research this subscale showed good internal reliability with alpha values of .74 [22] and .81 [26].

### *Condom Attitudes*

Five items chosen from the Multidimensional Condom Attitudes Scale (MCAS) [47] assessing pleasure associated with condoms were used to assess attitudes toward condoms at T1 to T3 [26]. Items are rated on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), with higher scores indicating more positive condom use attitude (3 items are reverse scored). An option of "neither agree nor disagree" for the 4th item was added because of participants' feedback in the qualitative study evaluation eHIS program website (M Glowacka, thesis chapter in preparation). The subscale showed good reliability in the previous study evaluating the KIHIS program [26], with an alpha value of .81.

**Textbox 2.** Inclusion and exclusion criteria.

Criteria

- Inclusion
  - Male
  - Aged 18 to 69 years
  - Fluent in English (written and spoken)
  - Have access to the Internet for the duration of the study
  - Living in the United Kingdom
- Exclusion
  - Other than male
  - Below the age of 18 or aged 70 or above
  - Not fluent in English (written and spoken)
  - Allergic or sensitive to latex, non-latex condoms, and/or lubricants
  - Have difficulties using computers and other visual display units equipment requiring use of specialist software to access the website content
  - Have a learning disability requiring third person support to access and use the eHIS website
  - Do not have access to the Internet for the duration of the study
  - Living outside of the United Kingdom

**Table 1.** Schedule of study measures.

| Measure | T1 | T2 | T3 |
|---|---|---|---|
| Eligibility screening questionnaire | Yes | | |
| Study registration | Yes | | |
| Motivation to take part in the study | Yes | | |
| Recruitment information | Yes | | |
| Background information | Yes | | |
| Sexual history | Yes | | |
| STIs[a] and unplanned pregnancy[b] | Yes | Yes | Yes |
| Condom use and sexual activity[c] | Yes | Yes | Yes |
| Effect on Sexual Experience subscale from Condom Barriers Scale[d] | Yes | Yes | Yes |
| Correct Condom Use Self-Efficacy Scale (CCUSS) | Yes | Yes | Yes |
| Condom Use Errors and Problems Survey (M-CUES)[d] | Yes | Yes | Yes |
| Condom Fit and Feel Scale[e] | Yes | Yes | Yes |
| Multidimensional Condom Attitudes Scale (MCAS), selected 5 items | Yes | Yes | Yes |
| eHIS Evaluation Survey | | Yes | |
| Searching for Condom Use Related Information | | Yes | |
| Condom Rating Form (maximum 15 entries) | Yes[f] | Yes | |
| Website usage data are collected throughout the period when the website is available to the participants | Yes[f] | Yes | |

[a]STI: sexually transmitted infection.

[b]At T1 questions are asked about lifetime and last year, at T2 and T3 about the last 4 weeks.

[c]Additional questions asked at T1 (see measures descriptions).

[d]Questionnaires displayed only to those who reported that they had used condoms during sexual intercourse over the last 4 weeks.

[e]Questionnaires displayed only to those who reported that they had used condoms during sexual intercourse or had practiced using condoms over the last 4 weeks.

[f]Between T1 and T2.

### *Condom Use Self-Efficacy*

At T1 to T3 participants' perception of their condom use ability (eg, finding condoms that fit properly, keeping condoms from drying out during sex) were measured by 7 items adapted from the Correct Condom Use Self-Efficacy Scale (CCUSS) [22,48]. These items are rated on a 5-point scale from 1 (very difficult) to 5 (very easy). Higher scores indicate greater correct condom use self-efficacy, which is associated with fewer condom use errors and problems [49]. This scale was demonstrated to have good internal reliability in previous studies with alpha values of .72 [22], .70 [49], and .82 [27].

### *Condom Use Errors and Problems*

The survey was only displayed to those who reported that they had used condoms during sexual intercourse over the last 4 weeks (T1, T2, and T3). The 17-item Condom Use Errors/Problems Survey (M-CUES) [50] assesses condom use errors and problems experienced during the last condom-protected sexual event. Respondents were asked about the presence or absence (yes/no) of problems and errors such as condom breakage and slippage, issues with fit-and-feel, incomplete or incorrect use of condoms, and loss of erection associated with condom use. Separate condom use error and problems scores are calculated, with higher scores indicating more condom use errors and problems. The CUES has good face and content validity [50].

The CUES was modified in line with feedback received from participants in the qualitative study evaluating the eHIS website (M Glowacka, thesis chapter in preparation) and from materials developed for the HIS-UK feasibility study [27]. The form of the questionnaire was simplified, as was the scale instruction and item wording. An item asking about checking a condom expiry date was added to the scale to make it consistent with the condom use instructions given in the program. To make the recollection of events easier the recall time was changed from "last 3 times the condom was used" to "last time you used a condom."

### *Condom Fit and Feel Scale*

The Condom Fit and Feel questionnaire [51] was only displayed to those who reported that they had used condoms during sexual intercourse or practiced condom use over the last 4 weeks (T1, T2, T3). This 14-item scale was completed at T1 to T3. Items include "Condoms fit my penis just fine" and "Condoms are too long for my penis". Answers are given on a 4-point scale from 1 (never applies to me) to 4 (always applies to me) with

some items being reverse scored. An overall score is obtained where higher scores indicate more negative experiences with condom fit-and-feel. Scale validity and reliability have been demonstrated previously, with alpha values ranging from .60 to .86 [52].

### *Condom Rating Form*

Participants were asked to complete this form after each condom use practice. In the first part of the form they gave information about which condom they used during a practice session and whether they had used it before. They indicated what type of sexual activity the condom was used for, whether they stopped testing it before putting it on, and if yes, what was the reason. In the second part of the rating form participants rated condoms on different aspects of fit-and-feel. They were also asked about the use of lubricant and their preference for using the particular condom in the future. Participants were expected to complete at least 6 condom rating forms; a maximum of 15 ratings could be completed across the time when participants had access to the program's website. The condom rating form was adapted from materials used in previous studies evaluating the face-to-face version of the program [22,26,27] and modified in line with feedback received in the qualitative evaluation of the program's computerized version (M Glowacka, thesis chapter in preparation).

### *eHIS Evaluation Survey*

The eHIS Evaluation Survey assessed the acceptability of the program's content and format at the first follow-up (T2). It was developed for this study to explore participants' opinions about the program and the website. A literature search of previous studies using questionnaires to evaluate electronic health (eHealth) interventions, treatment preferences, and measures used to evaluate websites' content and usability [42,53-60] and themes identified in the qualitative phase of the eHIS website development (M Glowacka, thesis chapter in preparation) were used to define key categories and guided item development.

The 24-item survey assessed agreement or disagreement (from strongly disagree to strongly agree) with statements related to relevance of the program for the issues covered, personal relevance, completeness of the information and advice given, willingness to follow the advice given, trustworthiness, clarity of the content, program use enjoyment, website usability, including questions about its structure, navigation, information, organization, and website aesthetics. Participants also had a chance to share their preferences regarding the program's content and design in open text entry questions, as well as provide additional qualitative feedback. For the item "The amount of the information on the page was…" the responses were "just right", "too much", and "not enough".

### *Searching for Condom Use-Related Information*

This is a 3-item questionnaire developed for this study that was completed at T2 only. Participants were asked whether they searched for additional condom use information when they had access to the eHIS website and if yes, where they searched for the information (social media, National Health Service website, other health information websites, sexual health clinic, general practitioner surgery, youth center, friends, other) and what type of information it was (correct condom use instruction, advice on dealing with condom use problems, information about different types of condoms, information about different types of lubricants, other). Answers to these questions, together with the answers from the eHIS evaluation survey, will be used to assess the program's completeness and credibility (dimensions of acceptability).

Website usage data is also used as a measure of participants' engagement with the program [31,35,39,61]; the eHIS website logs are used to analyze participants' activities on the website including time spent on the website, number of visits, and specific pages seen by participants.

Whether participants ordered the condoms and lubricants kit and the number of completed condom rating forms are used as measures of engagement with the program alongside participants' self-reports on the specific items in the eHIS evaluation survey.

The feasibility of the study evaluation approach is also assessed in the context of the recruitment information, motivation to take part in the study, specific outcome measures completion, and attrition rate. At T1, participants were asked how they heard about the study, what were their reasons for taking part (a multiple choice question), and whether they took part in any study at the program's development stage. Measures' acceptance is assessed on the basis of proportion of participants completing specific scales and providing answers to their specific items. Attrition is assessed on the basis of completion rate of baseline and follow-up questionnaires.

## Study Procedure

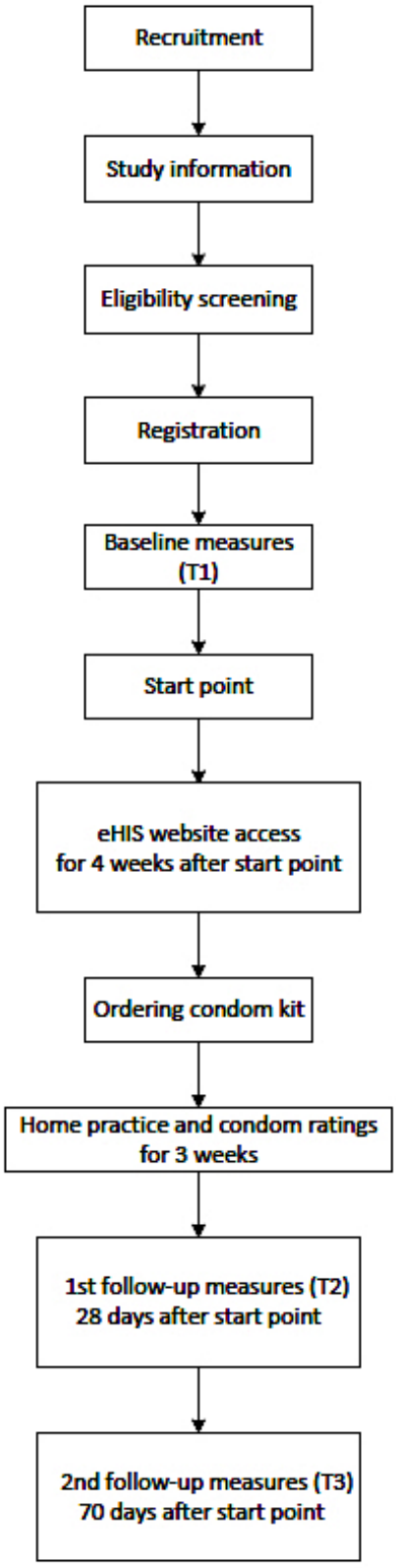
Following the link or QR code from the advertisement individuals were directed to the study website where they were first presented with the Participant Study Information Sheet. Participants indicated their consent to take part and for their data to be used for research purposes by ticking a box next to the consent statement. They then completed the eligibility screening measure; if eligible, they were directed to the study registration page and then to the T1 measures. If ineligible, they were thanked for their interest in the study.

Participants could then access the core eHIS website and were able to order a condom kit to be sent by post or collected from the University of Southampton within 3 working days from placing the order. They had 4 weeks, counting from the date they completed the T1 measures, (hereafter "start point") to practice condom use at home and complete condom rating forms after each practice event. Four weeks from the start point the website was no longer available to participants and at that point participants were asked to complete T2 measures; 10 weeks after the start point they were asked to complete the final T3 measures.

Participants received an email reminder and an optional text reminder on the days the T2 and T3 measures were due to be completed. They also received 2 emails and an optional text per week for the duration of home practice (during weeks 2, 3, and 4) reminding them to complete condom ratings. The condom rating reminders were automatically cancelled for the particular week if at least 1 rating was completed; all reminders were

automatically cancelled if at least 4 ratings were completed. Participants had the option to cancel emails and/or text messages when they visited the program's website regardless of the number of ratings reminders. An overview of the study procedure is presented in Figure 2. Ethical approval from the Department of Psychology Ethics Committee at the University of Southampton was obtained. The study is registered in the Research Registry, Unique Identifying Number researchregistry2325.

**Figure 2.** Study procedure.



### Incentives

After completion of each set of study measures participants chose 1 out of 3 charities that will receive a 50p donation. After completion of the T3 measures participants received a £5 Amazon voucher. Psychology students at the University of Southampton had the option to claim up to 32 research credits for participation.

### Data Analysis

Feasibility of the program and the evaluation approach will be assessed through the analysis of program engagement, acceptability, recruitment, and retention rates. Descriptive statistics will be used to describe the study population, feasibility of the evaluation approach, engagement with the program, and its acceptability. The preliminary effectiveness of the program will be assessed through evaluation of the change on primary and secondary condom use-related outcomes. Within group comparison will be undertaken to assess whether there are any differences between specific subgroups (eg, those who complete the study and those who drop out, those reporting improvement on various dimensions of condom use, and those who do not report change) on characteristics such as demographic variables, sexual history, and/or baseline condom use-related variables where sufficient data will be available. The results of the preliminary effectiveness results will be used to calculate the effect size of changes in condom use related outcomes. SPSS software v.21.0 [62] will be used for data analysis.

## Results

Recruitment for the study is complete and data collection was complete in July 2017. Data analysis is in progress and is expected to be completed by February 2018.

## Discussion

It is expected that this study will provide preliminary information about the feasibility of eHIS, specifically engagement with the program, its acceptability and potential to improve condom use frequency and consistency, reduce condom use errors and problems, improve condom use self-efficacy, improve condom use experience, and improve condom use attitudes. These findings can further direct the program's content and procedure improvements. The results of an exploratory evaluation may support the need for further program development and/or indicate the need for conducting a large scale RCT and provide valuable guidance regarding its optimal design [39,63]. The findings are expected to have scientific and clinical implications, advancing knowledge about the feasibility and preliminary effectiveness of this novel approach to promote consistent and correct condom use and potentially contributing to the development of a tool that could be used in sexual health promotion practice.

### Acknowledgments

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### Conflicts of Interest

To avoid promoting a specific brand of condoms, the choice of condoms included in the condom kit was made from those available in UK shops and/or on the Internet on the basis of their features (size, shape, etc) to provide a variety of choice (essential for the study). There is no particular brand endorsement in any part or at any stage of the program.

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## Abbreviations

**CUES:** Condom Use Errors/Problems Survey
**eHIS:** Homework Intervention Strategy
**KIHIS:** Kinsey Institute Homework Intervention Strategy
**RCT:** randomized controlled trial
**STI:** sexually transmitted infection


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Protocol

# Examining the Frequency and Contribution of Foods Eaten Away From Home in the Diets of 18- to 30-Year-Old Australians Using Smartphone Dietary Assessment (MYMeals): Protocol for a Cross-Sectional Study

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## Abstract

**Background:** Young Australians aged between 18 and 30 years have experienced the largest increase in the body mass index and spend the largest proportion of their food budget on fast food and eating out. Frequent consumption of foods purchased and eaten away from home has been linked to poorer diet quality and weight gain. There has been no Australian research regarding quantities, type, or the frequency of consumption of food prepared outside the home by young adults and its impact on their energy and nutrient intakes.

**Objectives:** The objective of this study was to determine the relative contributions of different food outlets (eg, fast food chain, independent takeaway food store, coffee shop, etc) to the overall food and beverage intake of young adults; to assess the extent to which food and beverages consumed away from home contribute to young adults' total energy and deleterious nutrient intakes; and to study social and physical environmental interactions with consumption patterns of young adults.

**Methods:** A cross-sectional study of 1008 young adults will be conducted. Individuals are eligible to participate if they: (1) are aged between 18 and 30 years; (2) reside in New South Wales, Australia; (3) own or have access to a smartphone; (4) are English-literate; and (5) consume at least one meal, snack, or drink purchased outside the home per week. An even spread of gender, age groups (18 to 24 years and 25 to 30 years), metropolitan or regional geographical areas, and high and low socioeconomic status areas will be included. Participants will record all food and drink consumed over 3 consecutive days, together with location purchased and consumed in our customized smartphone app named Eat and Track (EaT). Participants will then complete an extensive demographics questionnaire. Mean intakes of energy, nutrients, and food groups will be calculated along with the relative contribution of foods purchased and eaten away from home. A subsample of 19.84% (200/1008) of the participants will complete three 24-hour recall interviews to compare with the data collected using EaT. Data mining techniques such as clustering, decision trees, neural networks, and support vector machines will be used to build predictive models and identify important patterns.

**Results:** Recruitment is underway, and results will be available in 2018.

**Conclusions:** The contribution of foods prepared away from home, in terms of energy, nutrients, deleterious nutrients, and food groups to young people's diets will be determined, as will the impact on meeting national recommendations. Foods and consumption behaviors that should be targeted in future health promotion efforts for young adults will be identified.

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**KEYWORDS**

diet; fast foods; young adult; feeding behavior; nutritional status; cell phone

## Introduction

### Background

Overweight and obesity rates continue to rise globally [1]. In Australia, more than 63% of adults are overweight or obese [2]. Increased body weight is associated with the incidence of a number of chronic diseases, and the estimated direct costs of overweight and obesity in Australia is AUD $21 billion per year [3].

Studies have demonstrated that the rate of weight gain in today's young adults has been faster than any other birth cohort [4]. In Australia, males aged 20 to 24 years have the highest annual rate of increase in body mass index (BMI) among all age groups across the life span, and for women, 20 to 29 years is the period of greatest weight gain [5]. Those living in rural areas and of lower socioeconomic status (SES) and lower educational attainment are at higher risk of obesity [6]. The transition from high school to university places students at risk of marked weight gain [7]. The international literature shows that students are likely to gain 1.36 kg in their first 5 months of tertiary education, with more than 60% gaining an average 3.38 kg in the first year [7].

In Australia, young adults are the most frequent consumers of fast foods [8] and spend the largest proportion of their household food budget on fast foods and eating out [9]. In the United Kingdom and the United States, young adults (younger than 35 years) have the highest intakes of foods prepared outside the home [10].

Food environments that promote consumption of highly processed, energy-dense, and nutrient-poor foods and drinks are a major contributor to overweight and obesity levels across all age groups [11]. Frequent consumption of foods prepared outside the home, be it at fast food joints or restaurants, results in poorer diet quality and is associated with weight gain [12-15], insulin resistance [16], diabetes [17], and depression [18-20].

### Knowledge Gaps

Although foods purchased and eaten away from home can impact nutritional status [13,21], the most recent Australian National Nutrition and Physical Activity Survey did not collect data on the source of the food and beverages consumed [22]. Limited research has focused on specific food types that may or may not have been sourced outside the home [23] or on determinants of fast food intake [8,24]. Only one Australian study has been conducted on the consumption of foods purchased outside of home and how this affects the total diet [25]. However, that analysis was conducted using data collected more than 20 years ago, and as Australians' expenditure on fast foods and eating out has been increasing [9], as have the rates of overweight and obesity, it is timely to revisit the role of eating out on diet quality and risk factors for chronic disease. The exact quantities, type, and frequency of consumption of food prepared outside home by young adults and the impact this has on their energy, macronutrient, and micronutrient intakes is currently unknown. To address these gaps in knowledge, the proposed project will collect data on the frequency, type, amount, and place of purchase of foods prepared away from home, together with sociodemographic data in a population sample of 18- to 30-year-old Australians.

## Methods

### Aims

The study will determine how frequently young adults purchase and consume foods away from home in the context of their entire diet, and what types of foods they are purchasing and consuming. The relative contributions of different food outlets (eg, fast food chain, independent takeaway food store, coffee shop, restaurant, cafeteria) to overall food and beverage intake of young adults will be established. Finally, the extent to which food and beverages consumed away from home contribute to the total energy and nutrient intake of young adults will be determined using the complete 3-day food and beverage intake data records.

As a substudy, the comparative validity of data collected by the app will be determined using the 24-hour recalls.

### Study Design

A cross-sectional study of young adults aged 18 to 30 years who reside in New South Wales (NSW), Australia's most populous state [26], will be conducted. Age 30 was chosen as a cut-off, because in Australia the median age of first-time mothers is 28.9 years, and the average age of all women giving birth is 30.3 [27]. The median age of first-time fathers is 33.1 [28]. The age bracket of 18 to 30 years was chosen to capture *young adulthood* —for many, before having their first child.

### Population Sampling

Purposive sampling will be conducted to ensure quotas for different demographics are captured. Individuals are eligible to enroll in the study if they: (1) are aged 18 to 30 years; (2) reside in NSW; (3) own or have access to a smartphone; (4) can read, write, and understand English; and (5) consume at least one meal, snack, or drink purchased outside the home per week. As the data will be collected using a smartphone app in English, it is important that the participants have access to a smartphone

and are proficient in written English. The study is specifically focused on foods eaten away from home, so it is important that participants eat out at least once per week. Participants will be excluded if they do not meet the aforementioned criteria, are not able to commit to 3 consecutive days of data collection, are pregnant and/or breastfeeding, or have ever been diagnosed or treated for an eating disorder. Pregnant women and breastfeeding mothers will be excluded as their nutritional requirements, and potentially eating habits, change during this time. Those who have been diagnosed or treated for an eating disorder will be excluded because of ethical reasons.

A total of 1008 participants will be recruited to the study, across a range of geographic areas and demographic factors, which provides a margin of error of ±3% on all estimates of proportions (with 95% CI). An even spread of males and females will be recruited. The sample will be constituted to ensure an even distribution of participants in the older age bracket (25 to 30 years) and the younger age bracket (18 to 24 years); from metropolitan and regional areas (as defined by the Accessibility/Remoteness Index of Australia (ARIA+) [29] based on the postcode of the area the participant resides, with major cities considered “metropolitan” and all other areas “regional”); and from lower and higher SES areas (as defined by the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) [30] based on the postcode of the area where the participant resides) with “low” SES, including deciles 1-5 and “high” SES deciles 6-10). The sampling diagram is shown in Multimedia Appendix 1.

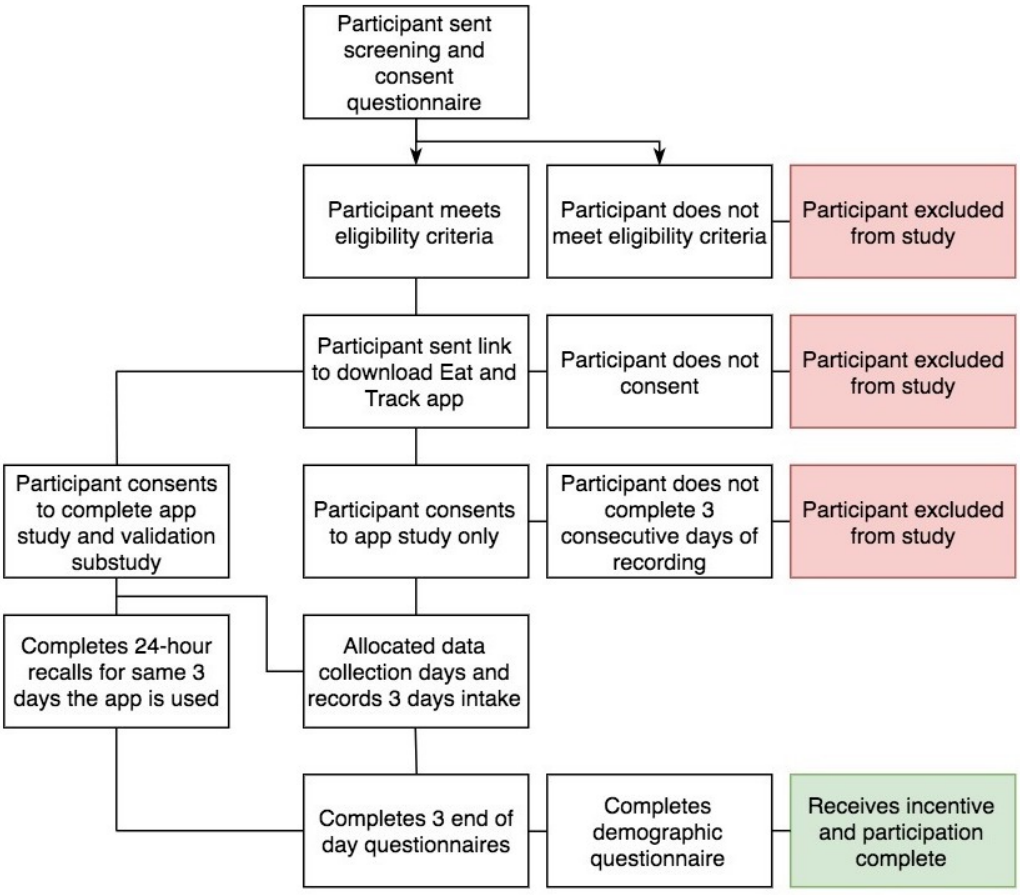
## Recruitment

Participants will be recruited using a range of methods. The study is being conducted in partnership with Cancer Council NSW, a large nongovernment organization that leads a variety of public health research, health promotion, and fundraising activities. Cancer Council NSW has both a head office and a regional structure that allows recruitment across a diverse selection of ARIA+ and IRSAD codes across the state.

One recruitment method will be to recruit through Relay For Life, a community-driven fundraising event, where teams walk or run laps of a running track for 12 to 24 hours [31]. The Relay For Life events are held in both urban and regional centers, and attract approximately 134,000 participants from a broad cross-section of community in Australia annually [32]. During the event, there are other activities and information stands for participants and spectators, where participants will be recruited.

Additional recruitment will be conducted through electronic newsletters, noticeboards, and social media via Cancer Council NSW and The University of Sydney organizational channels. Snowball sampling will also be utilized, with participants encouraged to forward the study details to their own contacts. The recruitment and participation process is summarized in Figure 1.

**Figure 1.** Recruitment and participation flowchart.



## Screening and Consent

The screening survey (Textbox 1) will be administered at recruitment to collect basic demographic data and consent using the Web-based REDCap research management system [33]. The REDCap system will be programmed to screen participant demographics to fill the study's demographic quotas. The REDCap system also allows stratified randomization in the substudy (refer to section below).

After completion of the screening questionnaire and enrollment, participants will be notified of their dietary data collection dates, and emailed instructions on how to download and sign up to use the Eat and Track (EaT) app, and obtain a user guide for the EaT app and a copy of the Australian Bureau of Statistics Food Model booklet [34] to assist with estimating portion sizes. Links to useful information on the study website will also be available, including an electronic version of the Food Model booklet.

The study website (Figure 2) was developed to provide information for those participating in this study and future participants. It contains information about the study, its funding and partners, links to the screening questionnaire, technical guides and videos for participants, and links to the Food Model booklet. Potential participants can also contact the study team via email through the website.

Participants will be taught how to use the app using instructional videos and will have access to these videos at all times throughout the study via the study website. Additionally, participants will need to view 3 tutorial screens in the app before they can start recording their intake. They will then record all food and drinks for 3 consecutive days.

**Textbox 1.** Screening questionnaire.

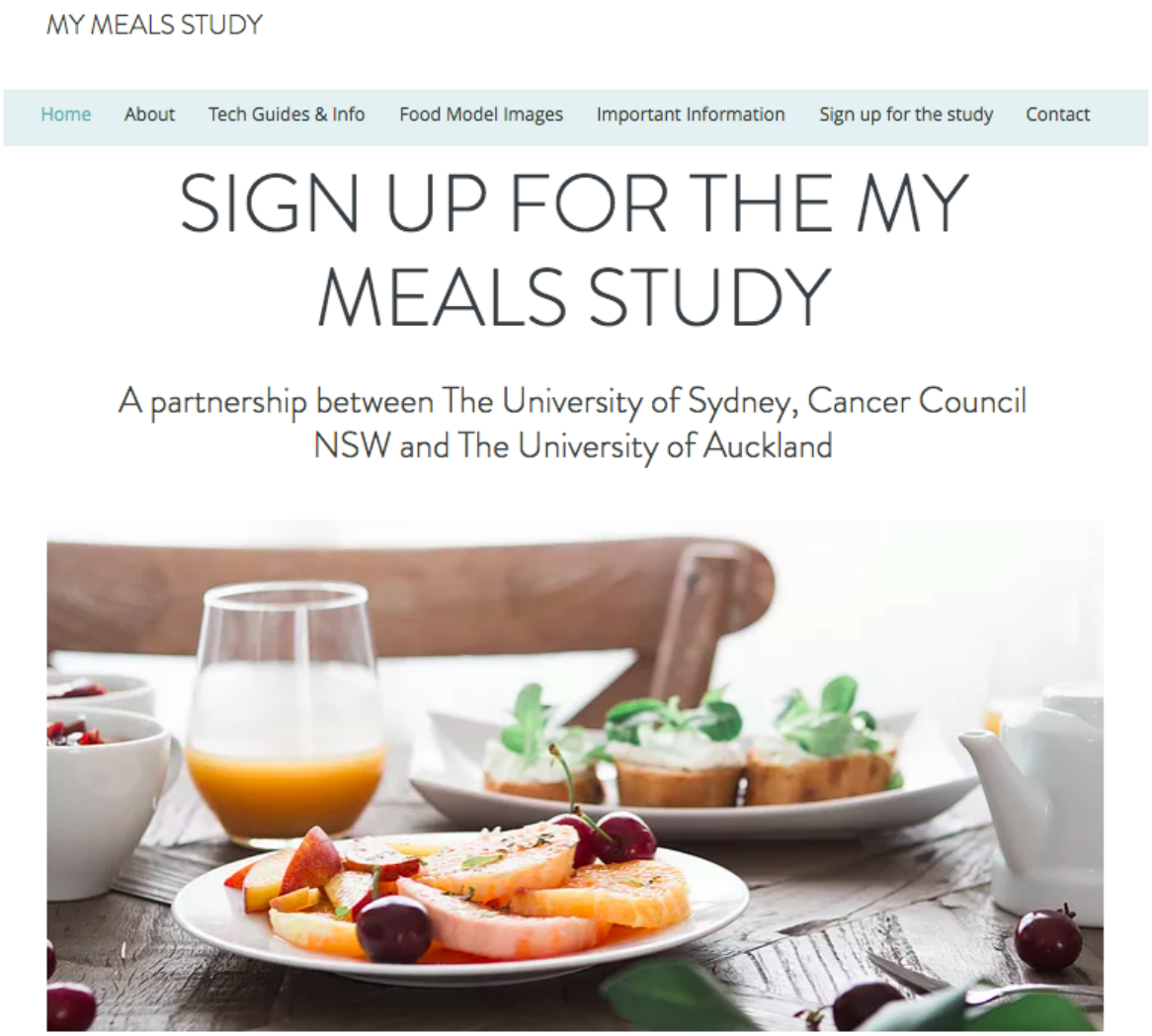
Demographics:

- Age
- Gender
- Aboriginality and ethnicity
- Language spoken at home
- Education attainment
- Postal code of home address
- Living arrangement
- Relationship status
- Employment and study
- Income

Screening questions:

- Do you own a working smartphone?
- On average, do you have at least one drink, snack or meal you buy away from home each week?
- (Females only) To your knowledge, are you pregnant and/or breastfeeding?
- Have you ever been diagnosed or treated for (choose all that apply)?
  - Anorexia Nervosa (screen out)
  - Bulimia Nervosa (screen out)
  - Other eating disorder (screen out)
  - Mental illness
  - Illicit drug use
  - Diabetes
  - None of these

**Figure 2.** MYMeals Study website.

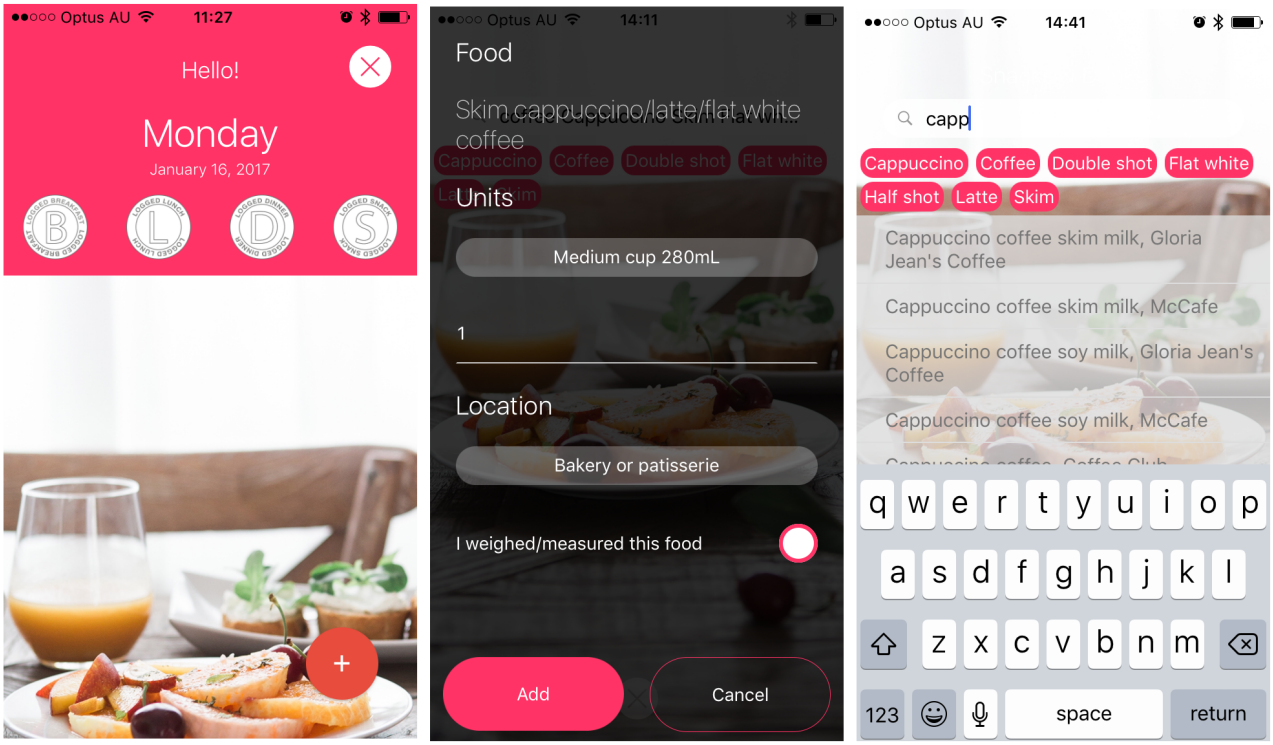



## The Eat and Track Dietary Intake App

Data will be collected using a customized smartphone app, EaT. The EaT app is an updated version of the research team's validated app called electronic Dietary Intake Assessment (eDIA) that uses Australian food composition data [35,36]. The EaT app has an improved user interface and underwent iterative development with usability testing using techniques such as the "Think Aloud" protocol [37]. The EaT app allows participants to record what they eat and drink in real time. Underpinning the EaT app is a customized database containing more than 6200 foods and beverages, including 4046 foods and beverages from the Australian Bureau of Statistics' AUSNUT 2011-2013 database [38] and 2229 fast food menu items sourced from the routinely collected Cancer Council NSW-The George Institute fast food database [39,40]. The EaT app interface supports food searches for many common and commercial brand names to improve the participants' ability to correctly search and identify foods. In addition, for common foods, the interface presents keywords to speed up searches. For example, when a user types "milk," a shortlist of all milk types will appear (Figure 2). Previously added foods remain in a shortlist and create a shortcut in the logging screen. The EaT app also supports freeform text entry of foods so that participants can record what they eat if they are unable to locate it in the database.

Once participants have recorded the foods and drinks they consumed, they then enter the amounts ingested into the EaT app (Figure 3), together with the location from which the food was sourced (Textbox 2). Participants were instructed to choose "home" for all foods not purchased and consumed outside the home. While not mandatory, participants are encouraged to weigh and measure the foods and drinks before consumption, and there is a check button to indicate if foods have been weighed. If not weighed, participants are encouraged to use the Food Model booklet to estimate their amounts in household measures, or they can enter a default portion size. These default sizes are based on typically consumed portion sizes for males and females aged 18 to 30 years based on the latest national dietary survey [41]. If participants cannot find a food listed in the app's database, they will be able to manually enter it as a new food, and this will be flagged to the research team for follow-up. Each entry is time and date stamped, and thereby indicates whether all entries are made at one time or recorded prospectively throughout the day.

**Figure 3.** Eat and Track (EaT) app screenshots showing the landing screen, food logging screen, and pink button filtering of foods.




**Textbox 2.** Locations for food source included in the Eat and Track App.

Fast food chain (Chain outlets selling takeaway foods, such as burgers, pizza, or fried chicken)

- McDonald's, KFC, Pizza Hut, Mad Mex

Coffee chain (Chain outlets selling predominantly coffee and tea)

- Gloria Jean's Coffee, Starbucks

Cold drink chain (Chain outlets selling predominantly cold drinks, including juice, smoothies, or iced tea)

- Boost Juice, EasyWay Tea

Ice creamery/frozen yogurt (Chain or independent outlets selling predominantly ice cream, gelato, or frozen yogurt)

- New Zealand Natural, Yogurberry, local ice creamery

Other takeaway (Independent outlets selling any type of takeaway foods)

- Local fish and chip shop, local pizzeria

Independent café or restaurant (Independent sit-down café or restaurant selling any type of cuisine; may also do takeaway food)

- Asian/Indian restaurant, local café, other restaurants

Bakery or patisserie (Chain or independent outlets selling predominantly baked goods, such as cakes, breads, and sweets)

- Michel's Patisserie, Muffin Break, local bakery

Service station/convenience store (Food bought from service stations or convenience stores, including cafes in these locations)

- 7-Eleven, Wild Bean Café, or BP, Shell or Mobil service stations

Pub or club (Restaurants, bars, cafes or bistros in pubs or clubs)

- Bowling, RSL, sports or community clubs, local hotels

Home (Any food not sourced from the locations above.)

- Includes homemade food, food prepared by friends or relatives, or foods purchased from supermarkets

At the conclusion of each day's recording, participants will complete a short survey. This survey will determine whether the day's food and beverage intake, frequency of eating away from home, physical activity, stress, and sleep levels were higher or lower than usual. Additionally, self-reported healthiness of the day's dietary intake, assessed by a 5-point Likert scale, ranging from "very unhealthy" to "very healthy" was included in the end of day survey.

Data will be collected on 3 consecutive days, and across the entire sample the start days will be spread to capture data for an equal number of weekdays and weekends. In total, data will be collected for 3024 days, including 1512 weekdays (considered Monday to Thursday) and 1512 weekends (Friday to Sunday) to allow for differences between weekdays and weekends to be investigated. Fridays were considered weekend days as previous research has shown that eating habits on Fridays are more like Saturdays and Sundays than weekdays [42].

## Data Cleaning

All app entries will be checked by study investigators in the 2 days following data entry, to allow time for data to be returned from the app server. Participants will be contacted to clarify any freeform text entry food items and inconsistencies such as gross data entry errors and skipped meals. When a recipe is entered by the participant without the quantities of ingredients, the recipe database from AUSNUT 2011-2013 will be used to identify and quantify the individual recipe ingredients and assign the appropriate food codes. If no recipe exists in this database, popular recipe websites Taste Australia and international equivalents will be used.

## Demographic and Usability Questionnaire

Once participants complete the 3 consecutive days of data collection, they will complete the final, extensive demographics questionnaire (Textbox 3). Of the 43 demographic questions included in this questionnaire, 31 (72%) have been previously validated or used in other epidemiological surveys [22,43-45]. The questionnaire will collect self-reported height and weight data, as well as questions on self-perceived health status, and health behaviors such as physical activity and sedentary behavior levels, smoking status, alcohol consumption, stress levels, sleep patterns, and self-rated well-being. Specifically on diet and weight, there will be questions on perceived healthiness of their diet; food avoidance for health, ethical, or religious reasons; frequency of dieting to lose weight, whether participants are trying to lose or gain weight, and how much they care about their weight and appearance. The number of daily meals and snacks and the usual timing of these will be assessed and compared with entries from the app. The self-reported frequency and amount spent on foods purchased and eaten away from home will also be collected over the 3-day study period. Additionally, there will be questions on social factors, such as who they live with, who does the cooking in their household (if anyone), perceived ability to access and cook healthy foods, barriers to accessing and cooking healthy foods, and food security. Participants will be asked about the Australian Dietary Guidelines' [46] recommended number of serves for each of the five food groups to assess their nutrition literacy. Finally, participants will evaluate their perceived usability of the EaT app in the final questionnaire by answering the 4 questions of the Usability Metric for User Experience [47].

## Comparative Validation Substudy

A validation substudy will be conducted with 19.84% (200/1008) of participants to compare the data collected using the app with a structured multiple-pass 24-hour recall method, which is a well-established and valid method of collecting dietary intake data for population groups [48]. The three daily 24-hour recalls will be conducted in accordance with the methods used in the previous validation study for the eDIA app [35,36]. The researcher will administer the recall using the newly developed automated ASA24-Australia system, which is based on the National Cancer Institute system but uses an Australian database of foods [49]. The quantities of food will be estimated from the Food Model booklet provided. Participants will volunteer to complete the 24-hour recalls in the substudy, and those consenting will be randomly selected to participate by the REDCap system aiming for a representative sample from each subpopulation quota.

The mean or median intakes of energy and all macronutrients will be determined with the addition of specific micronutrients of interest, from the 3 days of 24-hour dietary recalls and EaT app records. Food groups for validation include the core foods (grain foods; fruits; vegetables, and legumes/beans; lean meats and poultry, fish, eggs, tofu, nuts and seeds and legumes/beans; and milk, yogurt, cheese, and alternatives) and discretionary foods and beverages listed in the Australian Dietary Guidelines [46]. As per previous research, differences will be determined using paired *t* tests (normally distributed data) or Wilcoxon signed-rank test (skewed data), and correlation coefficients will be calculated on unadjusted, energy-adjusted, and deattenuated values. Cross-classification and Bland-Altman plots will be used to assess agreement between the EaT app and the 24-hour recalls. For all statistical analyses $P<.05$ will be considered the level of significance, but multiple tests will be appropriately adjusted.

## Statistical Analysis

### *Mean Intake of Energy and Nutrients*

Data collected from the EaT app will be used to determine mean, median, and 95% CI of daily intakes of energy, macronutrients, and micronutrients as well as the contribution of each of the macronutrient to energy content. Misreporting of energy intake will be identified using the Goldberg criteria [50], and sensitivity analysis will be undertaken to assess their inclusion or exclusion from the primary analysis. Energy and nutrient intakes will be compared with Australian Nutrient Reference Values [51] applicable for each age and sex group and the usual intakes from the latest Australian Health Survey [6]. Multivariate regression models will be used to determine the various health, social, and environmental factors associated with consumption of energy and nutrients. To control for multiple comparisons, a significance level of $P<.01$ will be considered for these calculations.

**Textbox 3.** Demographics questionnaire.

Anthropometry and diet status

- Self-reported height and weight
- How often the participant attempted weight loss in past 12 months, including currently
- Whether the participant is motivated by eating healthy food, losing weight, staying fit and active, or their appearance

Diet and eating behaviors

- Self-perceived healthiness of their diet
- Food avoidance for health, cultural, or ethical reasons, including vegetarianism
- Supplement use
- Frequency and usual timing of meals and snacks
- Food security
- Adequacy of factors influencing diet, including cooking skills, cooking equipment, time available to cook, and access to healthy foods in their local area
- Quality and variety of healthy foods in their local area
- Who does the cooking in their household
- How often meals and snacks are eaten in front of the television
- Average weekly amount they spend on eating out of home
- Reasons for eating out of home

Nutrition literacy

- Knowledge of the Australian Government's recommended number of serves of the 5 core food groups

Health behaviors

- Alcohol consumption and consumption patterns
- Physical activity and sedentary behaviors at work and during leisure time
- Sleep patterns and duration
- Self-perceived health and well-being
- Tobacco and e-cigarette use

Dietary monitoring

- Whether they would be interested in logging single foods with apps
- What aspects of their diet would participants be interested in logging (if any)

Eat and Track app usability

- Ease of use
- If the app is frustrating to use
- Whether the participant had to make corrections

### *Mean Consumption of Food Groups*

Food consumption data from the EaT app will be classified into their respective food groups to determine mean intakes. Food groups for validation include the core foods (grain foods; fruits; vegetables, and legumes/beans; lean meats and poultry, fish, eggs, tofu, nuts and seeds and legumes/beans; and milk, yogurt, cheese, and alternatives) and discretionary foods and beverages listed in the Australian Dietary Guidelines [46]. Mixed dishes will be disaggregated into their individual ingredients to enable accurate classification, using the AUSNUT recipe database [52]. The proportion of participants meeting the intake for recommended daily number of serves for each food group from the Australian Dietary Guidelines [46] will be determined. Multivariate regression models will be used to determine the health, social, and environmental factors associated with consuming the recommended amounts of each food group.

### *Consumption of Foods Purchased and Eaten Away From Home*

The average frequency of meals, drinks, and snacks (collectively, and by occasion) purchased and eaten away from

home will be calculated. Multivariate regression models will be used to determine the health, social, and environmental factors associated with consumption of foods purchased and eaten away from home. The relative contribution of foods purchased and eaten away from home to total energy and macronutrient intake will be calculated.

### Data Mining

In addition to our usual epidemiological approach, the data will be analyzed using data mining and machine learning techniques employed by information technology scientists. A clustering technique to automatically partition the participant population into groups with similar energy and nutrient intake, and food group consumption patterns will be applied. The resulting clusters of food consumption will be labeled according to their common patterns, for example, high processed meat and takeaway consumption; high fish, fruit, and vegetable consumption. These clusters will then be analyzed for the predominant health, social, and environmental characteristics of each cluster and checked for common associations (such as participants with healthier diets, also exercising regularly, having healthier BMI, not skipping breakfast, and mainly eating at home).

Data mining techniques such as decision trees, neural networks, and support vector machines will be used to build predictive models; for example, to predict the type of diet (high quality or poor quality, assessed by the Healthy Eating Index for Australian adults [53]) based on the frequency and contribution of foods eaten away from home and health, social, and environmental variables. In contrast to standard statistical methods such as multivariable linear regression, these techniques are capable of assessing complex nonlinear relationships and are less sensitive to outliers (data points that correspond to exceptional, nonrepresentative cases). Decision trees offer additional advantage in that they can be represented as a set of if-then rules and are thus easy to explain and use for decision making.

Association rule and time-series mining will be used to find frequent relationships between the variables, for example, what types of foods are typically eaten together at home and away from home by the different groups, whether budget constraints and high stress levels imply fast food consumption regardless of the education level, and whether there are temporal associations.

## Results

Recruitment is underway, and results will be available in 2018.

## Discussion

There is a lack of data on foods purchased and eaten away from home in the context of total dietary intake by young adults in Australia. Our cross-sectional study is designed to determine the frequency and quantity of foods purchased and consumed away from home by young adults in NSW, Australia. The outcome measures will detail the contribution these foods make to young people's dietary intakes, in terms of energy, nutrients, deleterious nutrients, and food groups and its impact on whether diets are compliant with national recommendations. Population monitoring of consumption of foods prepared and eaten outside the home are most usually by short questions on frequency. This study will provide detailed data about the dietary habits of young people and the sources of their food.

### Smartphone Dietary Assessment

Smartphone dietary assessment has emerged as a promising method for increasing participant acceptability and accuracy of the data collected [35,54] and has been shown to be a valid measure for assessing nutrient and food group intakes in population groups [35,36,55,56]. The database underpinning the EaT app assists participants record foods eaten away from home as the commercial fast food chain products are listed by the portions on offer, and we have provided instructions for recording all other foods with weighing or using the Food Model booklet. The extensive usability testing conducted, provision of aids to assist with estimation, and prompts to weigh foods aim to increase the accuracy of portion size estimations.

Although the EaT app has been developed as a research dietary assessment tool and therefore provides no feedback on nutrients consumed to participants, the app could be adapted as a dietary monitoring tool for individual use. As the majority of the available weight management apps have US databases, or hybrid US and local crowdsourced databases, Australian participants have difficulty recording their foods, leading to inaccuracy [57]. There is a need for an app for accurate dietary self-monitoring.

### Conclusions

This study is the first in Australia to provide detailed information on foods purchased and eaten out of home. By incorporating information from the largest fast food chains in Australia in the app's food composition database, it is also the first dietary assessment app internationally to have a specific focus on eating out. The requirement of participants to record where they sourced each food or drink will also provide the first estimation of how often young Australians are eating out, and what proportion of their nutritional intake is derived from such meal occasions. This will enable the identification of foods and consumption behaviors of concern that should become the focus of future health promotion efforts for this target audience. Accurate and detailed measurement is important to ensure evidence-based programs.

### Acknowledgments

The study is funded by an Australian Research Council Linkage Grant (LP15010083) and Cancer Council NSW.

## Conflicts of Interest

Three members of the study team are from Cancer Council NSW and hence have been involved in the review of the manuscript.

## Multimedia Appendix 1

Sampling Diagram.

[PDF File (Adobe PDF File), 111KB - resprot_v7i1e24_app1.pdf ]

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## Abbreviations

**ARIA+:** Accessibility/Remoteness Index of Australia
**BMI:** body mass index
**EaT:** Eat and Track
**eDIA:** electronic Dietary Intake Assessment
**IRSAD:** Index of Relative Socio-economic Advantage and Disadvantage
**NSW:** New South Wales

**SES:** socioeconomic status

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Protocol

# Motivational Interviewing and Medication Review in Coronary Heart Disease (MIMeRiC): Intervention Development and Protocol for the Process Evaluation

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## Abstract

**Background:** Trials of complex interventions are often criticized for being difficult to interpret because the effects of apparently similar interventions vary across studies dependent on context, targeted groups, and the delivery of the intervention. The Motivational Interviewing and Medication Review in Coronary heart disease (MIMeRiC) trial is a randomized controlled trial (RCT) of an intervention aimed at improving pharmacological secondary prevention. Guidelines for the development and evaluation of complex interventions have recently highlighted the need for better reporting of the development of interventions, including descriptions of how the intervention is assumed to work, how this theory informed the process evaluation, and how the process evaluation relates to the outcome evaluation.

**Objective:** This paper aims to describe how the intervention was designed and developed. The aim of the process evaluation is to better understand how and why the intervention in the MIMeRiC trial was effective or not effective.

**Methods:** The research questions for evaluating the process are based on the conceptual model of change processes assumed in the intervention and will be analyzed by qualitative and quantitative methods. Quantitative data are used to evaluate the medication review in terms of drug-related problems, to describe how patients' beliefs about medicines are affected by the intervention, and to evaluate the quality of motivational interviewing. Qualitative data will be used to analyze whether patients experienced the intervention as intended, how cardiologists experienced the collaboration and intervention, and how the intervention affected patients' overall experience of care after coronary heart disease.

**Results:** The development and piloting of the intervention are described in relation to the theoretical framework. Data for the process evaluation will be collected until March 2018. Some process evaluation questions will be analyzed before, and others will be analyzed after the outcomes of the MIMeRiC RCT are known.

**Conclusions:** This paper describes the framework for the design of the intervention tested in the MIMeRiC trial, development of the intervention from the pilot stage to the complete trial intervention, and the framework and methods for the process evaluation. Providing the protocol of the process evaluation allows prespecification of the processes that will be evaluated, because we hypothesize that they will determine the outcomes of the MIMeRiC trial. This protocol also constitutes a contribution to the new field of process evaluations as made explicit in health services research and clinical trials of complex interventions.

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**KEYWORDS**

medication adherence; medication therapy management; pharmacist; coronary artery disease, quality of health care

## Introduction

### Evaluating Complex Health Care Interventions

Complex health care interventions consist of several components that interact or work independently of each other. Trials of complex interventions are often criticized for being difficult to interpret because effects of apparently similar interventions vary across studies dependent on context, targeted groups, and how the complex intervention was actually delivered [1]. The need for complexity is often questioned, since the effects of, or necessity for, the individual parts are seldom reported. Trials of complex interventions are also often difficult to replicate, both because the complexity might make them more sensitive to the context in which they are tested, and because interventions and designs are seldom reported in sufficient detail [1]. However, in the field of behavior change, such as medication adherence, complex interventions are often considered valuable because the determinants of behavior are multifaceted [1,2]. Guidelines for the development and evaluation of complex interventions have recently highlighted the need for better reporting of the development and evaluation of the intervention, including descriptions of how it is assumed to work, how these assumptions informed the process evaluation, and how the process evaluation relates to the outcomes evaluation [3-5]. The protocol for a randomized controlled trial (RCT) of a complex intervention aimed at improving pharmacological secondary prevention practice in coronary heart disease (CHD) is described in a separate paper, Motivational Interviewing and Medication Review in CHD (MIMeRiC) (forthcoming) [6]. In this paper, however, we describe the theoretical framework of the intervention, describe its development, and present the study protocol for our prespecified process evaluation, which will help explain the outcomes of the trial, inform about the generalizability of the trial's results, and highlight barriers and facilitators that are important for successful implementation of the intervention.

### Theoretical Framework and Development of the Intervention

#### *Patients' Adherence Behavior*

Adherence to medical treatment regimens is a complex act requiring both motivation and self-efficacy, and therefore nonadherence can be either intentional or unintentional [7]. Unintentional nonadherence occurs if the patient wants to adhere but is unable to because of difficulties with instructions, costs, remembering administration, or other practical reasons. Intentional nonadherence, on the other hand, occurs when the patient for some reason decides not to follow the recommendations. Factors influencing these types of adherence are different and need different management [8].

Patients' adherence to medicine regimens is influenced by their attitude toward their medications; this can be measured with the instrument Beliefs about Medicines Questionnaire-Specific (BMQ-S) [9,10]. Beliefs are paramount determinants of both intentional and unintentional adherence and changes in beliefs have been linked to changed adherence behavior [9,11-15]. Patients with CHD develop more concern beliefs (ie, are more concerned) during the time after the event [16], which could explain the decrease in adherence in these patients [17,18].

There are several health psychology theories that describe what determines a behavior, and social cognitive theories have often been used to describe the behavior of (medication) adherence [7,19]. The health belief model, the theory of planned behavior, the reasoned action approach (RAA), and Bandura's social-cognitive model all share some ideas about how actual behavior follows from reasoning about expected outcomes of behavior, such as costs and benefits, and perceived control of a behavior (self-efficacy) [20]. According to the RAA, our behavior is determined by our intentions, and our intentions are determined by our attitude, perceived subjective norms, and perceived behavioral control. The subjective norm refers to a person's belief about how important others will view their behavior, and this might be as important in determining intention as their own attitude toward their behavior. The perceived behavioral control refers to a person's belief about their capacity to perform the behavior (very close to the concept of self-efficacy about the behavior), and this also influences their intention [20].

#### *Motivational Interviewing*

Motivational interviewing (MI) is a counseling approach used to elucidate a person's motivation for change of a behavior [21,22]. MI recognizes people's different readiness to change and how this should inform the support offered to a person, and it also recognizes the same determinants of behavior as the RAA. MI is a patient-centered approach which has been shown to be effective in different areas of health behavior change, including medication adherence [23,24]. MI is an approach relying on four main processes: engaging trust, focusing on the problems important to the client, evoking the client's own motivation and perceived resources, and planning specific actions leading to change [22]. All is done under the spirit of MI, which focuses on empathy, partnering with the patient, and emphasizing autonomy. Skills in MI such as affirmations, open-ended questions, and reflections are appropriate to elucidate the status of a patient's medication use, to assess beliefs about medicines, subjective norms and perceived control, and to find the individual resources; all of these aspects are needed to influence the complex behavior of medication adherence. MI can be used to find the patient's specific barriers to adherence and the patient's own solutions for both unintentional and intentional nonadherence, and MI offers a way of giving useful information in an intervention that relies on education about health and medicines. The use of MI or other cognitive methods in adherence interventions increases the likelihood of effect [25].

#### *Secondary Prevention Quality*

Despite established guidelines and widespread access to effective, inexpensive medicines, preventive treatment goals

for blood pressure and cholesterol levels continue to be unmet for many coronary patients [26-28]. This is, in part, also an effect of patients' resistance to the lifestyle changes needed to lower both blood pressure and cholesterol levels [29], but recent cohorts still indicate that the use of evidence-based drug treatments can be optimized to reach treatment targets [26]. Cardiac specialist nurses or pharmacists can help improve blood pressure management [30,31] and might also offer a model for other treatment targets in secondary prevention [32].

### *Medication Review*

Medication review is a structured evaluation of a patient's medicines with the aim of optimizing medication use and improving health outcomes. This entails detecting drug-related problems (DRPs) and recommending interventions [33]. Medication reviews have been evaluated in different settings such as hospitals, care homes, and primary care [34-36], but the diversity of methods and outcomes makes comparison and meta-analyses difficult. However, recommendations are to conduct future trials in high-risk populations, with professionals allowed to change patient medication, and with long-term follow-up [34]. Side effects of drugs are common DRPs and identification of side effects is essential to balance the harms and benefits of secondary prevention medications that are often used for the rest of life. Medication review has been used as part of an integrated medicines management model (LIMM, Lund Integrated Medicines Management) [37,38], which was used as the model for our intervention. We aimed to adapt the LIMM to suit the care process for CHD: a care process characterized by a short hospital stay, polypharmacy initiated in hospital, and follow-up of effects and side effects as outpatients.

### *Theoretical Framework for Intervention Design*

An adherence intervention should be based on what is known about adherence behavior [2,8]. The reasons for nonadherence are multiple and individual, and therefore an intervention must have a broad inventory phase and an individualized problem-solving phase to be effective in a wide group of patients. Our theoretical framework was based on the adherence model described by World Health Organization (WHO), which comprises five dimensions (see Table 1) [8]. The model, which is based on theory and evidence about adherence behavior, formed the basis of how we intend the intervention to work in terms of adherence. We added quality of treatment as one of our intervention targets since a need to improve the quality of pharmacological secondary prevention has been previously highlighted [27,28,39]. It is our core understanding that an ambition to increase adherence to treatment should always be accompanied by an evaluation of the treatment itself, so as not to improve adherence to a treatment that might be harmful. In this way, our theoretical framework for the intervention reflects the concept of pharmaceutical care described by Cipolle and Strand [40]: "Pharmaceutical care practitioners accept responsibility for optimizing all of a patient's drug therapy, regardless of the source…, to achieve better patient outcomes and to improve the quality of each patient's life. This occurs with the patient's cooperation and in coordination with the patient's other health care providers."

The basis of the intervention is that all dimensions should be covered in an inventory of the patient's drug-related needs, and that activities are subsequently undertaken in the dimensions where problems have been identified.

### *Conceptual Model of Change*

On the basis of the adherence model by the WHO, the RAA as a more general model for predicting behavior, and our understanding of how prescribing treatment determines outcomes, we made a conceptual model of how the change processes of the intervention would act to change the outcomes we set out in our RCT [6]. The model in Multimedia Appendix 1 describes how the optimized outcomes follow from full adherence to the optimal treatment, and how the intervention acts by two methods to improve these variables. MI is thought to act on the adherence variable and the medication review on the treatment variable. The intervention can only affect the outcomes if a patient has a problem with adherence (current or expected in the future) and/or treatment quality.

### *Pilot Evaluation: Changes Made From Pilot to RCT*

In a pilot study in 2012, we tested an intervention based on MI and medication review aimed at improving patients' beliefs about medicines and adherence to secondary prevention of cardiovascular disease [41]. The pilot RCT of 21 patients resulted in insights regarding the feasibility of the intervention and study design. Patients with more negative beliefs (BMQ-S) changed toward more positive beliefs, but there was no difference between groups at follow-up. A need to stratify the randomization based on baseline beliefs was identified [41]. We tested a method of categorizing patients according to their beliefs in the pilot study population and found that half of the population (10 patients) had an attitude with a potentially negative impact on adherence [42].

In line with the recommendation from the Medical Research Council (MRC) [3], we have also made a qualitative evaluation of the pilot study (not published). Interviews of 8 patients showed that, overall, the patients were positive about the intervention and felt more informed by it. The interviews also informed us that some patients changed their views on medicines in a positive direction, although it was not enough to categorize them to an attitude group with higher adherence. The care processes for these 8 patients were also compared with the theoretical framework of the intervention, and we found that all the patients were affected by some part of the intervention; patients with a negative attitude toward their medicines were mainly affected in the adherence dimensions, whereas patients with a positive attitude were helped in the area of quality of treatment. However, our evaluation showed that not all the dimensions of adherence were well covered in the identification phase of the intervention and that the pharmacist felt the need for more training in MI.

**Table 1.**

| Target of intervention and dimensions to influence | Activities |
|---|---|
| **Adherence** | |
| Social/economic factors | Reviewing patients' need for social support |
| | Referring to support group |
| Health system/ Health-care team factors | Adding time and competence to the HCT team |
| | Building good patient-provider relationship |
| | More patient-provider contacts |
| Condition-related factors | Identifying and solving other health problems that might affect adherence, ie, depression, stress, pain, pulmonary disease |
| Therapy-related factors | Simplifying regimen |
| | Minimizing side effects |
| | Patient-tailored prescriptions |
| | Continuous monitoring and reassessment of treatment and adherence |
| Patient-related facators | Mutual goal setting |
| | Changing the patient's attitude towards medicine-taking, changing beliefs |
| | Supporting patient's self-efficacy in medicine-taking |
| | Memory aids and reminders |
| **Quality of treatment** | |
| Appropriate medication | Change of prescribing if:<br>• Medicines without indication<br>• Untreated conditions |
| Effective medication | Change prescribing if:<br>• Not prescribed according to guidelines<br>• Unmet treatment goals |
| Safe medication | Change prescribing if:<br>• Any clinical manifestations are due to adverse drug reaction<br>• Risk for future adverse drug reactions |

[a]Five dimensions of adherence, World Health Organization's model for adherence [8].

[b]Pharmaceutical care according to Cipolle and Strand [40].

These results from the qualitative evaluation led us to the following three decisions about the intervention design: (1) all patients should be targeted for intervention regardless of their baseline attitude toward medicines, (2) the intervention needs to be intensified or prolonged for patients with a negative attitude, and (3) a focus on training and applying MI as the basis of the intervention is required.

We also added a second patient consultation in our intervention design before setting up the RCT. This decision was partly based on the experiences of cardiology nurses in another study with prolonged follow-up for this group of patients (not yet published). In the standard care period, patients are discharged from hospital 3 days after admission for an acute event or the day after a planned coronary intervention. At discharge, they receive prescriptions for their secondary prevention medicines to cover 12 months. Patients normally have a follow-up appointment at the cardiology clinic about 2 months after discharge, which includes an evaluation of effects and any side effects of the medicines. Until this follow-up the cardiology clinic is always responsible for the patient’s treatment. Most patients with no need for further adjustments are referred to primary care after their follow-up meeting, but they are rarely summoned for a visit by their primary care facility. In Sweden, patients need new prescriptions after 12 months, and our experience is that patients with little previous contact with their primary care facility often feel unsure about where to turn when they need new prescriptions or have questions about future treatment (qualitative interview study of 18 patients with CHD, not yet published).

Psychological recovery from acute myocardial infarction has been described as occurring in 4 stages, from the acute phase of accepting what has happened to the last stage of living again, or being back to normal [43]. The recovery process can take up to 6 months, and we theorize that the intervention needs to follow the patient until this stage of normality occurs if secondary prevention treatment is to be part of normality. Therefore, we decided to add a consultation at 10 months after discharge to meet all patients when fully recovered, and as a way of supporting the transition from cardiac specialist care at the hospital to the primary care facility.

## Protocol for the Process Evaluation

### *Framework of the MIMeRiC Trial Parallel Process Evaluation Protocol*

As recommended by the MRC guidelines for developing and evaluating complex interventions [3], a process evaluation should be conducted to "explain discrepancies between expected and observed outcomes, to understand how context influences outcomes, and to provide insights to aid implementation". Grant et al, who proposed a framework for the design of process evaluations, highlighted that the purpose of the process evaluation should be explicitly placed along with the original research questions, and that the processes that are not evaluated should be acknowledged [4]. They also proposed a model of prespecified evaluations to quantitatively examine prior hypotheses about trial processes, although post hoc evaluations have the advantage of being flexible for examining unexpected findings. This study includes a protocol for the prespecified evaluation. The logic model of how the intervention is expected to work (Multimedia Appendix 1) underlies our design of the process evaluation [3,4].

Multimedia Appendix 2 shows in detail how we expect the two methods, MI and medication review, to act on different determinants of the adherence and prescribing variables. We intend the MI part to be able to assess determinants such as perceived effects and side effects, beliefs, skills, and values, and also to act on these. In this way, we intend the intervention to work on the adherence variable through an effect on how the patients feel (how they perceive effects and side effects), reason (their values, risk perceptions, and beliefs about medicines and adherence), and act (their skills). The medication review is intended to affect the prescribing variable by increasing physicians' knowledge about the patient and the guidelines. The action on prescribing will also affect DRPs experienced by the patient, which in turn is a determinant of adherence.

When designing the trial, we included process outcomes related to the medication review, that is, the number of DRPs found and quality of prescribing. At that time, we were also informed that it was essential to have some quality control of the MI performance to be a relevant trial in this research field. Therefore, we had prepared for this data collection before the trial started. After the start of the trial and inspired by the aforementioned guidelines, we decided on another four process outcomes that would help us understand any effect of the intervention or any lack of effect [3,4]. Those outcomes are related to cardiologists' and patients' experience of the intervention, patients' beliefs about medicines, and patients' experience of the follow-up care as a whole.

These processes are thought to affect patient adherence and doctors' prescribing, which in turn are thought to affect the trial outcomes (treatment goal attainment, health-related quality of life, and hospital care need) (Multimedia Appendix 2).

### *Study Design of the RCT in Brief*

The MIMeRiC trial is an RCT with 2 parallel groups (N=418) and 12 months follow-up. Patients with CHD identified and followed at the cardiology clinic of Kalmar County Hospital are randomized to usual care (control) or usual care plus a follow-up program with medication review and MI. Ethical approval has been obtained from the Regional Ethics Committee, Linköping (Dnr-2013/236-31). The trial (clinicaltrials.gov, NCT02102503) has been fully described in the forthcoming protocol [6]. Patients in the intervention group meet a clinical pharmacist at the cardiology clinic 2 to 5 times during the year after discharge depending on need, and problems with adherence or prescribing are solved in collaboration with the patient and/or the cardiologist.

The primary outcome of the trial is the proportion of patients reaching the treatment goal for low-density lipoprotein cholesterol. Secondary outcomes involve the effects on blood pressure, patient adherence, quality of life, and health care use. An economic evaluation of the intervention is also planned.

### *Aim and Research Questions*

The aim of this process evaluation is to better understand how and why the intervention was effective or not effective.

Research questions include the following:

1. What was actually delivered in the medication review (DRPs solved and results documented)?
2. How did the cardiologists experience the involvement of and interaction with a clinical pharmacist?
3. Was MI used consistently with MI principles?
4. Did the intervention change how the patients felt, reasoned about, or acted toward their cardiovascular medicines?
5. Did the intervention change the patients' beliefs about medicines (before vs after, and between groups)?
6. How did the intervention affect the patients' experience of their follow-up care after CHD?
7. Did the intervention change the quality of prescribing?
8. Did the intervention change the patients' adherence? This is an outcome measure in the MIMeRiC trial and is described in Multimedia Appendix 2 only for consistency.

In Multimedia Appendix 2, the research questions are shown in relation to the conceptual model to show which intervention processes are not evaluated in this study.

### *Management and Governance*

The process evaluation is to be conducted in parallel with the MIMeRiC trial; some data will be collected together for the two studies. Data analysis for the two studies will also be conducted in parallel. The same researchers are responsible for the RCT, delivering the intervention, and planning and conducting the process evaluation; our small research team and restrictive funding did not allow for any independent evaluators to be involved [3].

Most of the research questions are covered by the ethical approval obtained for the RCT, but a supplemental ethical approval was granted for qualitative study of the patients' experience of the intervention (interviews) and their views on the follow-up care after discharge (questionnaire).

## Methods

### Overall Study Design

The process evaluation is a mixed-method study. Three research questions will be studied using qualitative methods, three using quantitative methods, and one using a mix of qualitative and quantitative methods. This was based on the MRC guidelines: "Hence, when feasible it is often useful to combine quantitative data on key process variables from all sites or participants with in-depth qualitative data from samples purposively selected along dimensions expected to influence the functioning of the intervention" [3].

### Methods for Research Question 1: What Was Actually Delivered in the Medication Review?

This will be studied using a descriptive, quantitative method. The number and type of DRPs will be described using the 7 categories suggested by Cipolle and colleagues: (1) adverse drug reaction, (2) ineffective drug, (3) need for additional drug therapy, (4) dosage too low, (5) dosage too high, (6) unnecessary drug therapy, and (7) noncompliance. If acting on the DRPs has any effects that are documented in the electronic health record (EHR), these will also be described. Data are collected from the pharmacists' documentation in the EHR and from separate study notes about DRPs that pharmacists record during the intervention. Data on the effects of actions on DRPs will be collected from the EHR; the pharmacists' documentation will be used with laboratory results, documentation by primary care or other professionals at the cardiology clinic when relevant.

### Methods for Research Question 2: How Did the Cardiologists Experience the Involvement of and Interaction With a Clinical Pharmacist?

This question will be answered by a qualitative questionnaire to cardiologists with 4 questions: (1) What is your opinion about the patients having a consultation with a pharmacist to discuss their medicine regimen, after the standard follow-up with a physician? (2) What is your opinion about the pharmacists conducting a medication review and contacting you as a cardiologist to consider their suggestions? (3) What is your opinion about the collaboration with the pharmacists in the study? (4) Would you like to add anything else?

Questionnaires will be issued at the end of the intervention period and answered anonymously by the cardiologists. Collected data will be analyzed with inductive content analysis.

### Methods for Research Question 3: Was the MI Used Consistently With MI Principles?

This will be a quantitative assessment of the integrity of MI delivered by the clinical pharmacists. All in-person consultations in the intervention group are audio-recorded if permitted by the patient. A random sample of these recordings, the number corresponding to 20% of in-person consultations, will be coded with the Motivational Interviewing Treatment Integrity behavioral coding system version 4.2.1 (MITI 4.2.1) [44] by an independent coding institute (the MIQA group at the Karolinska Institute, Stockholm). A randomly selected 20 min of these recordings will be coded; for one-third of the consultations, the first 20 min will be coded; for one-third, the middle 20 min will be coded; and for one-third, the last 20 min will be coded. Competency in MI will be described by four global scores: cultivating change talk, softening sustain talk, partnership, and empathy. In addition, the ratios of change talk to sustain talk and questions to reflections will be assessed. These scores and ratios will be related to recommended levels of MI competency. The target behavior of the MI consultations is defined as: start taking medicines regularly or maintain this behavior. Changing a patient's attitude toward their medicines in a positive direction is a strategy for maintaining or reaching the target behavior of regularly taking the medicines. On the basis of our theoretical framework and our pilot evaluation, we assumed that patients with a negative attitude need the MI component of the intervention, and should have this, whereas accepting patients are considered adherent and the need for MI might be less obvious. These patients are targeted by the intervention partly to maintain their target behavior but primarily to solve other DRPs and to improve the quality of prescribing. However, there is no distinct line between these groups; problems with adherence can arise in the group with an accepting attitude as well. To ensure that both groups are equally represented in the assessment of consultations, we will stratify the samples so that 20% of consultations with patients with a negative attitude and 20% of consultations with patients with an accepting attitude are coded. For the latter group, it might be that DRPs make the target behavior undesirable for a particular drug and, if so, only two of the global scores—partnership and empathy—will be used. Such consultations without a target behavior will be valued on a scale for person-centeredness instead of MI competency. The analysis will inform about the frequency of consultations with a target behavior (among the random sample), the fidelity of MI, and the fidelity of person-centered consultations.

### Methods for Research Question 4: Did the Intervention Change How the Patients Felt, Reasoned About, or Acted Toward Their Cardiovascular Medicines?

This will be studied qualitatively by assessing how patients' experiences of the intervention relate to the intended mechanisms of the intervention, as described in the conceptual model (Multimedia Appendix 2) and the framework for the process evaluation. For this question, the method of focus group interviews was chosen because it is an effective method of gathering information and is especially valuable in the evaluation of program experiences. The main advantage of focus groups over individual interviews is the richness and quality of the data that arise, because participants are listening to the answers of others. Comments might trigger memories and thoughts that would not come up in individual interviews, and participants' comments on each other weed out false or extreme views [45].

Three focus group interviews will be carried out with 4 to 6 intervention patients in each group. The interview and discussion will be led by a moderator, a pharmacist who is familiar with the study but is not involved in the care of the patients. Because the intervention is primarily intended to affect beliefs and adherence among those who have a negative attitude and therefore a higher risk of nonadherence, the sample of patients

chosen for the focus groups will be from patients with a negative attitude toward their medicines at baseline. With purposeful sampling among the patients who have taken part in the full intervention, we will try to cover both men and women, those newly diseased and those with a history of CHD, those with acute and those with chronic disease, and those who changed their attitude after the intervention in addition to those who did not.

Questions will be asked about how the patients experienced the consultation with the pharmacist and how they perceived that it had affected their medicine-taking behavior or their reasoning about medicines. The moderator will encourage the patients to describe all aspects by using probing questions. The moderator will also be supported by an observer whose main role will be to record all nonverbal communication in the focus groups. The focus group interviews will be audio-recorded and transcribed verbatim and then analyzed using deductive content analysis. A coding scheme of categories will be constructed based on the conceptual model about how the intervention is intended to work on adherence. The moderator will not be analyzing the interviews but will be accessible for questions about how to read the transcripts.

### Methods for Research Question 5: Did the Intervention Change the Patients' Beliefs About Their Cardiovascular Medicines?

This will be studied primarily quantitatively, but certain aspects will also be illustrated qualitatively by the interviews with patients.

Data on beliefs about medicines will be collected in the MIMeRiC trial with the BMQ-S instrument administered 3 times: baseline (after the standard care follow-up), after 10 months (during the intervention), and after 15 months (after the intervention). In this study, we will ask the patients to consider only their heart medicines as they answer the BMQ-S. The instrument consists of two subscales, one for the perceived necessity for the drugs and one for perceived concerns about the drugs. The two subscales have 5 items each and are assessed by a 5-point verbal descriptor scale ranging from strongly disagree to strongly agree.

As instructed by the originators, numerals (1-5) will then be assigned to each statement of agreement to summarize each subscale with 5 to 25 points. The difference between the necessity and concern scales (range: −20 to 20) will then be related to the cost-benefit analysis for each patient's medications. A positive difference means that the patient perceives the benefit of taking the drugs to outweigh the risks of taking the drugs, and the more positive the difference is, the more adherent the patient is supposed to be [9]. It has also been found that categorization based on high (>15) or low (<15) scores on each scale, yielding 4 categories (accepting, ambivalent, neutral, and skeptical) predicts adherence behavior [46,47]. Because the scales have ordered verbal categories, it is not correct to assign numerals and sum them to a global score, because the data are only ordered within the structure while the distance between the agreement statements or the magnitude of them is not known [48]. Even though the categorization also depends on the global sum of each scale, this is a more correct way of handling the data. Therefore, we chose this as our primary outcome in analyzing the effects of the intervention on beliefs. The stratified randomization of patients in the MIMeRiC trial was also based on these four categories.

In this study, we will:

1. analyze whether there is a difference between the control group and the intervention group in the proportion of patients in each category at follow-up (15 months)
2. describe temporal changes in the 4 categories over the 3 assessments in the control and the intervention groups
3. analyze changes in the sum of each subscale, and differences between the intervention and control groups
4. analyze changes in each item of the scales, and differences between the intervention and control groups
5. analyze the transcribed material from the focus group interviews with intervention patients described above using deductive content analysis methods, based on the 10 items of BMQ-S, as a way of including the results of the quantitative study of beliefs

While item 1 in the list is a primary objective, items 2 to 5 refer to secondary objectives.

Analyses 1 to 3 will be adjusted for variables thought to be influential: sex, age, type of CHD, and history of CHD. In our pilot study, most patients with an ambivalent attitude toward their drugs had a history of CHD [42].

### Methods for Research Question 6: How Did the Intervention Affect the Patients' Experience of Their Follow-Up Care After CHD?

This is a qualitative study of how patients perceive their care after discharge from hospital following CHD. An open question will be enclosed with the questionnaires sent at the 15-month follow-up to all patients enrolled after January 1, 2016. The instructions to these patients will be: *Please take a moment to write freely about your view of the follow-up care you received after your myocardial infarction or angina*

### Methods for Research Question 7: Did the Intervention Change the Quality of Prescribing?

This will be studied using quantitative methods. There are several models for assessing the appropriateness of prescribing or medication use which have been used in intervention studies of medication reviews [49,50]. For this study with a selected group of patients with CHD, we chose to use a tool developed for this diagnosis: the Medication Assessment Tool for evaluation of secondary prevention of CHD (MAT-CHDsp) [51]. The tool is a summary of review criteria based on clinical guidelines and has been developed for use in clinical audits. Compared with the variables in the Swedish Quality Register SWEDEHEART, in which the proportion of patients with a prescription from a certain drug class is registered, MAT-CHDsp has a more individual application where prescriptions that do not follow the guidelines can be justified if the reason is stated in the EHR. The tool was updated in 2014 based on the European guidelines from 2011 and 2012 for myocardial infarction or acute coronary syndrome and the Swedish

guidelines for heart disease from 2011 and was then validated in 22 patients in this study. MAT-CHDsp comprises 28 review criteria for which the assessor chooses *not applicable*, *yes*, *no*, *no information found*, or *no, but this is justified*. As an example, the treatment of a patient with CHD and no left ventricular (LV) dysfunction but with side effects from several statins documented in the EHR would be marked as *not applicable* for the criterion "Patient with CHD with LV dysfunction...is prescribed a beta-blocker" and *no, but justified* for the criterion "Patient with CHD is prescribed atorvastatin or simvastatin."

The MAT-CHDsp will be applied to a random sample of 20% of the patients in each of the intervention and control group. Data on the prescribing 6 months after discharge will be collected retrospectively from the EHR at assessment. Applicable criteria will then be analyzed for adherence to guidelines or justified nonadherence. The results will be compared between the groups in terms of adherence and justified nonadherence, as a measure of the quality of the prescribing for secondary prevention [52].

### Integrating Results of Analysis

Some process evaluation questions will be analyzed before and others will be analyzed after the outcomes of the MIMeRiC RCT are known. This will be determined by time and availability of the data as we prioritize having the results of the RCT ready as soon as all data can be analyzed.

The 7 research questions for the process evaluation will be analyzed by their respective methods and then, when all are complete, the analysis will be combined and applied to the results of the MIMeRiC trial. This will help us understand whether any effects of the intervention are related to the concepts we used in the design. If appropriate, we may carry out additional analyses to test hypotheses generated from integration of the process evaluation data with the trial outcomes; an example of this would be an analysis of the effect of BMQ-S on adherence. The full report of the process evaluation will be published in a peer-reviewed journal and a summary of the findings of and cross-references to the main MIMeRiC trial will aid interpretation of the evaluation.

## Results

Collection of data has been ongoing as part of the MIMeRiC trial, and some process evaluation analyses can start during 2017. The MITI-coding of 64 consultations have been conducted, but the results are not yet analyzed. The method of focus groups and deductive content analysis have been piloted and found to be useful for the question about how patients experience the intervention, and more focus group interviews will be conducted in September 2017.

## Discussion

This paper describes the framework for the design of the intervention tested in the MIMeRiC trial, development of the intervention from the pilot stage to the complete trial intervention, and the framework and methods for the process evaluation. Providing the protocol of the process evaluation allows prespecification of the processes that will be evaluated, because we hypothesize that they will determine the outcomes of the MIMeRiC trial. This protocol also constitutes a contribution to the new field of process evaluations as made explicit in health services research and clinical trials of complex interventions. The two active parts of the intervention, motivational interviewing and medication review, are both quantitatively evaluated with their specific instruments: Motivational Interviewing Treatment Integrity (MITI) coding and categorization of all DRPs acted on, as well as assessment of secondary prevention treatment quality. Qualitative methods are used to inform about patients' experiences of the intervention and to capture any unforeseen effects on the secondary care process experienced by patients.

A limitation might be that we are a small research team and have been the designers, implementers, as well as evaluators of this complex intervention. This may not be in line with the guidelines of the MRC. However, the guidelines for process evaluation of complex interventions issued by the MRC in 2015 have served us well in defining the requirements for properly evaluating our intervention process. We hope that this protocol can inspire other research teams to publish process evaluation protocols so that complex interventions in health services research in general, and medication adherence in particular, can be interpreted with more confidence in the future.

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Conceptual model of change processes in the intervention. The variables we aim to affect are shown in orange, the goal of optimal treatment is shown in yellow, outcomes measured in the randomized controlled trial are shown in green, and the blue lines represent how the two accompanying parts of the intervention act on the variables. The adherence variable is determined by factors identified by the reasoned action approach (The prescribing variable is determined by adherence to guidelines and the level of individualization.). The consequences of inappropriate prescribing are shown in gray boxes; these interact with factors that influence adherence. CHD: coronary heart disease; EBM: evidence-based medicine.

[PNG File, 765KB - resprot_v7i1e21_app1.png ]

## Multimedia Appendix 2

Conceptual model of intervention change processes and what will be covered by the process evaluation. This figure shows more detail of how we expect the motivational interviewing and medication review to act on determinants of adherence and prescribing. More attention, a nonspecific part of any extra follow-up intervention, shown as a blue oval, is thought to act positively on patients' attitudes toward and subjective norms about adherence. Blue arrows indicate what will be assessed by the intervention and red arrows indicate what determinants we think can be influenced by it. The gray boxes contain the research questions for the process evaluation. CHD: coronary heart disease; EBM: evidence-based medicine.

[PNG File, 566KB - resprot_v7i1e21_app2.png ]

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## Abbreviations

**BMQ-S:** beliefs about medicines questionnaire-specific
**CHD:** coronary heart disease
**DRP:** drug-related problem
**EHR:** electronic health record
**LIMM:** LundIntegrated Medicines Management
**LV:** left ventricular
**MAT-CHDsp:** medication assessment tool for evaluation of secondary prevention of coronary heart disease
**MI:** motivational interviewing
**MIMeRiC:** motivational interviewing and medication review in coronary heart disease (trial)
**MITI:** motivational interviewing treatment integrity
**MRC:** Medical Research Council
**RAA:** reasoned-action approach
**RCT:** randomized controlled trial
**WHO:** World Health Organization

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Protocol

# Research- and Practice-Based Nutrition Education and Cooking Workshops in Pediatric Oncology: Protocol for Implementation and Development of Curriculum

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## Abstract

**Background:** Progresses in childhood cancer treatment, diagnosis, and management have resulted in childhood cancer survival rates of over 80%. However, this therapeutic success comes with a heavy price: two-thirds of childhood cancer survivors will be affected by further complications, including cardiovascular and metabolic diseases. Adequate nutrition during cancer treatment is essential to ensure the child's optimal development, improve tolerance to treatments, and can contribute to lower the risk of developing cardiometabolic diseases. Side effects of cancer treatments can negatively impact children's nutritional intake and eating behaviors. Involving the families of childhood cancer patients in educational workshops could be a promising avenue to promote healthy eating during and after cancer treatment.

**Objective:** The objectives of this study were to develop, validate, and implement a family-based nutrition education and cooking workshop curriculum in a pediatric oncology setting that addresses the nutritional issues encountered during treatments while promoting the adoption of healthy eating habits for the prevention of long-term cardiometabolic effects.

**Methods:** The workshops were developed and validated following an 8-step iterative process, including a review of the literature and consultations with a steering committee. An evaluation tool was also developed. A nonrandomized study protocol was elaborated to implement the workshops and measure their impact. The themes of the 6 research- and practice-based lessons are as follows: meal fortification during cancer treatment, changes in taste during cancer therapy and their impact on children, adapting diet to eating-related side effects of treatments, nutritional support during cancer treatment, Mediterranean diet and health, and planning quick and economic meals. The validation process included consultations with the institution's clinical nutrition professionals. Self-administered post questionnaires were developed according to the content of each workshop to measure short-term outcomes, namely, participants' perception of knowledge acquisition, behavioral intention, and satisfaction. Medium-term outcomes that will be evaluated are participants' anthropometric profile, quality of the diet, and circulating biomarkers of metabolic health.

**Results:** The project was funded in 2016 and enrollment will be completed in 2021. Data analysis is currently under way and the first results are expected to be submitted for publication in 2019.

**Conclusions:** This research- and practice-based nutrition education and cooking demonstration curriculum could be a valuable complement to a multidisciplinary lifestyle intervention for the prevention of long-term cardiometabolic complications in childhood cancer.

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**KEYWORDS**

child; diet; education; neoplasms; hospitals; methods

## Introduction

### Long-Term Health Complications in Childhood Cancer Survivors

Progresses accomplished in childhood cancer treatment, diagnosis, and management in the past decades have led to survival rates exceeding 80% [1,2]. Despite these encouraging statistics, it is estimated that about two-thirds of childhood cancer survivors (CCS) will be affected by treatment-related long-term complications [3], including cardiovascular and metabolic diseases [4,5]. Lifestyle practices such as healthy eating and physical activity are well-recognized modifiable factors that contribute to lower the risk of cardiometabolic complications [6]. Particularly, adherence to a Mediterranean dietary pattern has been associated with reduced risk factors related to the metabolic syndrome in survivors of childhood acute lymphoblastic leukemia [7]. In addition to the prevention of long-term sequelae, good nutrition is essential to ensure children's requirements for growth and development during cancer treatments. Adequate nutritional status is also associated with increased tolerance to cancer treatments, better prognosis, and enhanced quality of life [8]. Side effects of cancer treatments such as nausea, mucositis, taste disorders, poor appetite, or increased appetite secondary to steroids intake can impact children's eating behaviors and nutritional status [8]. Furthermore, it is known that eating habits acquired in childhood are likely to persist in adulthood [9,10] and after completion of cancer treatments [11].

### Children's Dietary Habits During Cancer Treatment

Studies on CCS have described similar dietary habits to those of the general population, reflecting a suboptimal diet for the prevention of metabolic syndrome components such as obesity, insulin resistance, arterial hypertension, or dyslipidemia [12]. So, involving families of children with cancer to adopt or maintain healthy habits during and after cancer treatment is essential. Moreover, given that parents often experience time constraints [13] and economic burden related to transportation, accommodation, or loss of work income [14], practical advice for meal preparation should be provided to meet families' needs. Design and evaluation of family-based nutrition and cooking education programs are increasingly reported in the literature, mainly related to the prevention or management of childhood obesity [15-19]. Nutritional interventions for young CCS and their families have been described in the literature [20-22], but, to our knowledge, only few were developed for children undergoing cancer treatment and those that were targeted patients in the maintenance phase of therapy [23-25]. As there is a need to develop and evaluate the feasibility of an early intervention during the course of pediatric cancer treatments, we have developed 6 nutrition and cooking education workshops that aim to increase knowledge relative to the following: (1) children's nutrition during and after cancer treatments; (2) healthy, quick, and economical food preparation, cooking techniques, and food safety specific for children with cancer; and (3) development of food preferences during childhood and parental feeding practices. Here, we describe the following: (1) the development and validation of the workshops; (2) the elaboration of an evaluation tool; and (3) the study protocol to implement the workshops and to measure their impact.

## Methods

### Setting

We have developed a protocol for a nonrandomized controlled study. This study has been developed within the VIE (Valorization, Implication, Education) Program at the Sainte-Justine University Health Center (SJUHC) in Montreal, Canada. This research program consists of a 4-year family-oriented multidisciplinary interventional program integrating physical activity, nutrition, and psychosocial clinical and research teams. The nutritional intervention includes personalized assessment, goal setting, and counseling for behavioral changes with a registered dietitian (RD) as well as group nutrition education and cooking workshops providing complementary information. The SJUHC Institutional Review Board approved the study, and investigations will be carried out in accordance with the principles of the Declaration of Helsinki.

### Curriculum Development and Validation Process

The research- and practice-based curriculum consists of 6 lessons developed by a team of researchers and RD and validated by the hematology-oncology clinical nutrition team at SJUHC. The workshops are designed to provide reliable, up-to-date nutritional information geared to address specific themes and associated to cooking demonstrations facilitated by a RD and a chef.

To develop the curriculum, evidence for common nutritional and behavioral eating problems related to side effects of childhood cancer treatment and their management has been reviewed in the scientific literature published between 2000 and 2017 contained in Medline, PubMed, and Scopus databases. A few core papers published before 2000 have also been considered. Gray literature was searched for Canadian governmental guidelines and family-oriented documentation related to children's diet while on cancer treatment published by recognized organizations, such as the Children Oncology Group and the Canadian Cancer Society. Insight from the SJUHC Centre de cancérologie Charles-Bruneau (CCCB)

clinical nutrition team has also been sought. Recipes for demonstration were developed and standardized to match each of the 6 lesson themes. Nutritional value of recipes was analyzed based on general (for protein, lipid, and sodium content) and theme-specific criteria and was inspired by those of the SJUHC institutional food service, of early childhood nutrition reference [26], and of the Heart and Stroke Foundation program [27].

The curriculum was validated concurrently with its development within an 8-step process (Figure 1). The first 6 steps have already been completed. Subsequent to the literature review, primary themes and specific lesson objectives were elaborated and submitted to a steering committee, composed of SJUHC CCCB clinical RD (n=2) and the Department head of the Clinical Nutrition Services, representing, respectively, 19, 15, and 10 years of experience in pediatric oncology. A consensus on improvements to be made was obtained, and a detailed content of the lessons was then elaborated based on current scientific evidence and common practices by the clinical nutrition team. The modified and detailed content was submitted to the clinicians for a second validation, followed by a final revision of the curriculum. Workshops were pretested with nonparticipants, including CCCB health care professionals, leading to further refinements.

Subsequent steps will be performed before official implementation and intervention evaluation. A validation meeting will be conducted with a committee composed of family members and CCS to better tailor the curriculum regarding the length of the workshop, the timing, and the amount of information delivered. After implementation, we will continually monitor the curriculum and evaluation tools to fine-tune and optimize content delivery.

## Curriculum Description and Content

The developed curriculum consists of 6 themed workshops with specific objectives and key messages (Table 1). The 6 lessons are independent from one another, and there is no specific sequence to attend the workshops. This will increase convenience and allow flexibility according to participants' schedule and needs for information. The nutritional criteria of the recipes are presented in Table 2.

The curriculum will promote a liberalized diet that reinforces food safety guidelines for immunocompromised patients based on Health Canada food safety guidelines for people with a weakened immune system [61] and in line with the SJUHC CCCB standard clinical practices. Patients receiving hematopoietic cell transplantation will be referred to the hematology-oncology RD for personalized diet and food safety guidelines.

**Figure 1.** The 8-step development and validation process of the VIE (Valorization, Implication, Education) Program educational workshops. The dotted line divides the steps that have been completed and those to be performed.

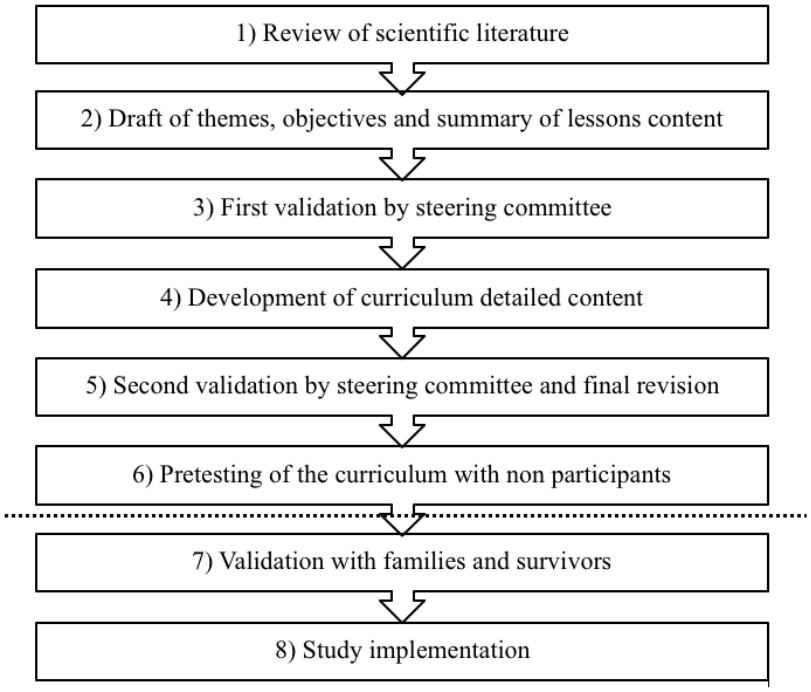


**Table 1.** Themes, objectives, and evidence-based key messages of the nutrition education and cooking workshops.

| Lesson theme | Specific objectives | Learning objectives (specific key messages) |
|---|---|---|
| Meal fortification during cancer treatment | • Understand the role and importance of proteins, calcium, and vitamin D<br>• Learn strategies to fortify usual foods with these nutrients | • Proteins are essential for tissue growth and repair and to support immune system function [28,29]<br>• A source of protein should be included in every meal [30]<br>• Calcium, vitamin D, and proteins are essential for bone growth and play a role in secondary osteoporosis prevention [31,32] |
| Changes in taste during cancer therapy and their impact on children | • Understand the development of taste and food preferences in children<br>• Learn strategies to enhance the flavor of food and to improve meal acceptability during cancer treatment<br>• Understand positive parental feeding practices for optimal taste development and eating behaviors | • Food aversion, neophobia, need for routine and security, need for self-expression, and learning from social modeling are normal behaviors related to the development of taste in children [9,33]. These behaviors can be affected by cancer treatments [34,35]<br>• Parental strategies and attitudes can influence adherence to a healthy diet in children during and after treatments. These include promoting participation in meal preparation when possible [36], maintaining a pleasant atmosphere during meal times, proposing a variety of food, and offering a mealtime structure (where, when, what), while letting the child decide the amount and select the foods from the offering [33]<br>• Some herbs, spices, and acidic food can enhance the flavor of dishes and can be used to mask the perceived metallic taste [37,38] |
| Adapting diet to eating-related side effects of treatments | • Learn how to adapt the child's diet to improve food intake when mucositis, nausea, or vomiting are present<br>• Learn strategies to attenuate diarrhea and constipation secondary to cancer treatments | • Nausea during treatments can be a side effect of the treatment and can be caused by a metallic or a medication taste in the mouth (dysgeusia) [39,40]<br>• Strategies to adapt diet and promote oral intake when the child is experiencing mucositis include serving warm meals and nonirritating foods with soft and moist texture [41]<br>• Soluble fibers, notably psyllium, can be helpful for diarrhea, whereas insoluble fibers and concentrated sugars should be limited [42,43]<br>• Total dietary fibers promote intestinal regularity and help prevent constipation [43] |
| Nutritional support during cancer treatment | • Demystify oral, enteral, and parenteral nutritional support to facilitate their acceptability by patients and families<br>• Understand positive parental feeding practices during nutritional support | • Nutritional support is an adjuvant to cancer treatment in situations when the child's needs are not met with oral eating alone [44,45]<br>• When allowed by the medical team, presentation of food to the child should be encouraged during nutritional support [46,47]<br>• Some strategies can facilitate acceptation of nutritional support [36,48] |
| Mediterranean diet and health | • Learn approaches to integrate principles of the Mediterranean diet into usual meals<br>• Learn the benefits of adherence to a Mediterranean diet for the whole family | • The Mediterranean diet brings health benefits to the whole family, especially for the prevention of cardiovascular diseases [49,50]<br>• The adherence to a Mediterranean diet can be improved with small changes daily (eg, adding a portion of vegetables to usual meals, replacing refined grains by whole grains) [7]<br>• Vegetal and animal proteins offer different health advantages: it is beneficial to diversify protein sources [51,52]<br>• The use of vegetable oils (nonhydrogenated) is preferred to butter or shortening [53,54] |
| Planning quick and economic meals | • Learn planning strategies to remove barriers to cooking at home<br>• Learn tactics to prepare simple and quick meals using accessible and nutritious ingredients<br>• Acquire strategies for eating healthy on a budget | • Meal planning saves time and reduces daily stress [55,56]<br>• Keeping some essential foods in the pantry, fridge, and freezer helps to prepare last-minute balanced meals [57]<br>• Low-cost alternatives can be found in several food categories [58,59] |

**Table 2.** Nutritional criteria for recipes of the nutrition education and cooking workshops.

| Lesson theme | Nutritional criteria[a] |
|---|---|
| Meal fortification during cancer treatment | Recipes rich in proteins that include at least one calcium-rich and one vitamin D-rich ingredient<br>• Protein: >20 g for a meal and >10 g for a snack<br>• Calcium: >165 mg for a meal and >0 mg for a snack<br>• Vitamin D (if possible): >15% of the adequate intake: 90 UI (2.25 mg) |
| Changes in taste during cancer therapy and their impact on children | Recipes include ingredients to enhance the taste of dishes (eg, herbs or spices) while limiting sodium and dietary fat and include ingredients to mask metallic taste (eg, acidic ingredients like lemon juice or vinegar) |
| Adapting diet to eating-related side effects of treatments | Recipes for nausea include:<br>• Cold or warm meals that release less odor<br>• Ingredients to enhance taste and mask metallic taste, such as herbs, spices, or acidic ingredients<br><br>Recipes for diarrhea include:<br>• Meals without irritants (eg, strong spices, insoluble fiber)<br>• Soluble fibers: >2 g<br>• Limited in concentrated sugar: <5 g for a meal and <2 g for a snack<br><br>Recipes for constipation include:<br>• Fiber-rich ingredients (eg, whole grains, vegetables, fruits)<br>• Total fibers >4 g<br><br>Recipe for mucositis include:<br>• Dish with a soft and moist texture<br>• Without irritants (eg, strong spices, acidic ingredients, salt)<br>• Can be reduced in puree if needed<br>• Served at room temperature |
| Nutritional support during cancer treatment | • Recipes rich in proteins (>20 g for a meal and >10 g for a snack)<br>• Meal or snacks also include complex carbohydrates and healthy fats |
| Mediterranean diet and health | • Fish as the main ingredient<br>• Recipes include whole grains and vegetables, or suggest them as side dishes<br>• Include healthy fats (eg, canola or olive oil, nuts or seeds, avocado) |
| Planning quick and economic meals | Recipe includes 2 pantry essentials and costs less than Can $4 per portion |

[a]Nutritional criteria are based on adult portions. Parents will be advised to adapt the portion served according to the child's usual appetite. According to the Satter Eating Competence Model, the parent decides the type of food served while letting the child decide the amount based on his or her internal cues [33,60].

## Study Protocol

### *Recruitment of Participants and Controls*

From January 2018 to December 2020, parents and children newly diagnosed with cancer, treated at the SJUHC, and meeting the inclusion criteria will be offered to participate in the VIE Program. Participant recruitment will be sequential. Inclusion criteria are as follows: (1) being less than 21 years old at diagnosis, (2) being treated with radiotherapy or chemotherapy (including patients receiving hematopoietic cell transplantation), and (3) able to give an informed consent (by parents or legal tutors). Participants who are not receiving radiotherapy or chemotherapy will be excluded from the study. Patients will be followed for 4 years. On average, 140 children per year are admitted at the SJUHC's CCCB, of which about 110 would be eligible. On the basis of earlier studies, we expect an average of 75 patients recruited per year (70.0% recruitment rate), for a total of 150 participants over 2 years. Enrolled participants and their family (parents, grandparents, etc) will be encouraged to attend the nutrition education and cooking workshops. It is to the parents' discretion to attend workshops with or without the child, according to the child's age, interest, and health condition. The control group will be recruited sequentially from patients diagnosed at the CCCB 3 to 4 years ago, who were not exposed to the VIE Program and who fulfill the same inclusion criteria as for the intervention group. No intervention will be offered to control participants. The measures and questions used will be the same as for the end-of-protocol intervention in the patients from the intervention group.

### *Delivery of Educational Workshops*

At first, the workshops will be offered in French considering that a majority of patients treated at the SJUHC CCCB are French speaking, but they will eventually be translated and offered in English. The lessons will be dispensed on a weekly basis. Weekly rotation of the 6 themed lessons and variable scheduled day and time will contribute to maximize participants' exposure and participation. A total of 40 workshops will be offered each year for 4 years. The workshops will take place at the SJUHC CCCB in a room designed for this purpose. Participants will be invited to taste the demonstrated recipes at the end of the workshop, and printed material will be distributed, including recipes and key messages. Because the mean age of patients treated at the CCCB is 7 years old, additional

food-related activities are planned for young children. A signature sheet will be used to record attendance at each session. Videotaped workshops will also be made available to participants on a secure Web platform. Posters will advertise the schedule and topics of the workshops, and the clinical team will receive reminders of the upcoming workshops so they can promote attendance.

### *Workshop Evaluation Tools and Outcome Measurement*

A total of 6 self-administered post-intervention questionnaires were developed to measure short-term outcomes of the workshops, namely, perception of knowledge acquisition, behavioral intention, and satisfaction. At the end of each workshop, adults and children of 12 years and older will be asked to fill out a printed version of the lesson-specific questionnaire available in both French and English. To reduce the burden of participants, the questionnaires contain limited number of items and can be answered in a few minutes. The questionnaires have been reviewed by an expert in the field of program evaluation and were pretested with the target population to validate their comprehension and literacy [62].

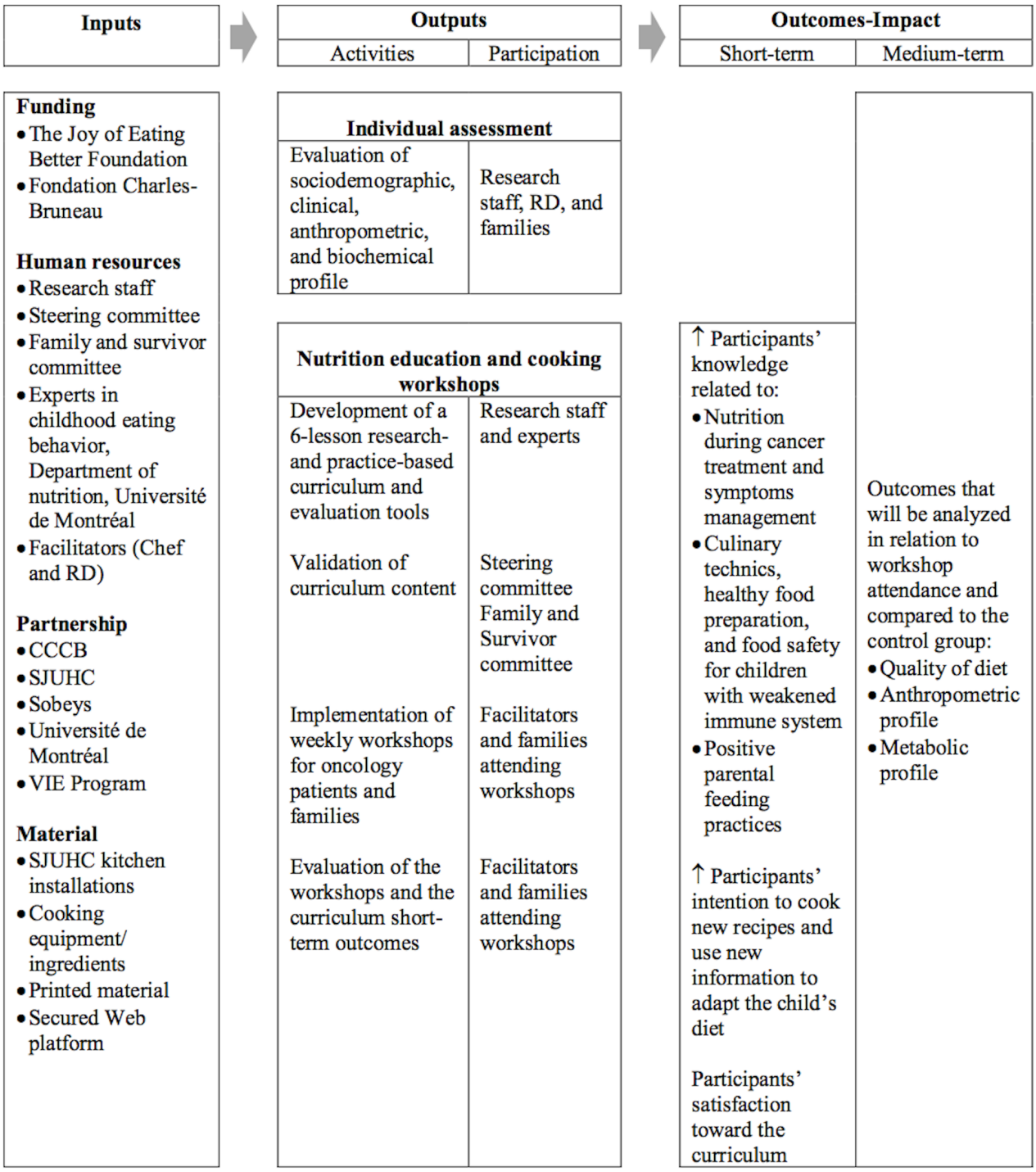
These questionnaires will measure participants' perception of knowledge acquisition based on the corresponding workshop's key messages [63]. This measure based on the perception was preferred to a scholastic questionnaire that measures knowledge to reduce participants' burden. Overall, 3 to 4 items are presented in the form of a statement derived from the learning objectives (key messages) and begin with "I have learned." Participants will answer according to their degree of agreement: "I agree," "I agree more or less," "I don't agree," or "I already knew this information." Additional questions about the intention to try the recipes at home or to use the information to adapt the child's diet [62] are also included. Participants' relationship with the patient (patient, parent, grandparent, etc) consists in the only sociodemographic item captured by the questionnaire. General satisfaction will be measured by asking about the intention to recommend the workshop to others and, if not, to specify why. Finally, a comment section will enquire for qualitative feedback and for suggestions to improve the curriculum.

An activity report to be filled out by the facilitators after each session has also been developed to assess fidelity to the developed curriculum, to record attendance at each session, and to document any adverse event that could have disturbed the group or compromise content transmission. Qualitative feedback from facilitators related to challenges experienced during the workshops will also be sought in the activity report. These short-term outcome data will be used for evaluating the educational workshops.

Medium-term outcomes of the workshops as a component of the nutrition program will be measured as part of the evaluation of the broader controlled study of the VIE Program. Data will be collected by research staff at the beginning, during, and at the end of the intervention for each participant in the program. They will include socio-demographic data (ethnicity and socio-economic status), clinical data (age, diagnosis, age at diagnosis, and treatment protocol), anthropometric profile (body mass index, tricipital and subscapular skinfolds, head circumference [for children <3 years old]), and biomarkers of metabolic health (fasting lipid profile, glucose, insulin, and glycated hemoglobin). Diet will be assessed by an RD using 24-hour diet recalls and food journals. Diet data will be analyzed using the software Nutrific (Department of Food Science and Nutrition, Université Laval, Montreal, Canada). Nutrient values from this application are derived from the 2010 Canadian Nutrient File. Participation in workshops will be assessed using an attendance sheet at each workshop and by questioning participants and their family, at RD follow-up visits, the workshops attended or viewed on the Web platform, and their topics. Quality of diet and anthropometric and biochemical profiles will be analyzed in relation to workshop attendance and will be compared with those of the control group who did not participate in the workshops. Qualitative data regarding usefulness of each workshop will also be collected through focus groups of workshops' participants. They will be leaded by the research RD and will take place at the end of selected sessions for all 6 thematic workshops. Collected data will be subject to thematic analysis to better understand if attendance to specific sessions is related to participants' success.

A logic model [64,65] has been developed describing the resources needed (inputs), the activities achieved or to be implemented, the public reached (outputs), and the expected short- and medium-term outcomes of the VIE Program educational workshops (Figure 2).

**Figure 2.** Logic model of the VIE (Valorization, Implication, Education) Program educational workshops. SJUHC: Sainte-Justine University Health Center; RD: registered dietitian; CCCB: Centre de cancérologie Charles-Bruneau.




## Results

The project was funded in 2016 and enrollment will be completed in 2021. Data analysis is currently under way and the first results are expected to be submitted for publication in 2019.

## Discussion

### Development of the Intervention

With this study, we have developed a family-oriented nutrition education and cooking workshop curriculum specific to pediatric oncology. The elaboration based on scientific evidence and on years of clinical experience, combined with an 8-step validation process, are strengths and features of interest of this study [64,66]. There is a consensus on the value of including field actors and representatives of the target population in the development of lifestyle interventions. Including clinicians in

the development process offers precious insight to enhance the curriculum content and ensures coherence with the medical team. In CCS overweight children, a group lifestyle intervention used interviews and focus groups with health care providers and CCS parents to adapt a curriculum previously shown to be effective in non-CCS overweight children [67].

Some authors suggested that adding a cooking component to nutrition education is a good way to enhance participants' skills and increase application of knowledge [68,69]. In our curriculum, cooking demonstrations will allow observational learning [68] and may enhance participants' familiarity with specific foods [70], cooking techniques, and food safety practices. Moreover, the nutrition education content will focus on practical application as several ideas to apply recommendations and tips to overcome barriers to healthy eating and home cooking will be presented. Furthermore, the developed content aims at reinforcing the messages conveyed by the clinical and research RD during individual follow-up. Therefore, the workshops may serve as a complementary intervention tool to facilitate behavioral change.

### Familial Influence on the Development of Eating Habits

The curriculum was developed based on the social-ecological model, considering that individuals' eating behaviors are influenced by determinants of their environment [71]. Family, as part of their social environment, is one of the most influent determinants of healthy eating in children. Indeed, parents play a crucial role as they usually are responsible for food selection, serve as role models, and use parental feeding practices that impact children's eating behaviors [72]. According to studies designed for obesity prevention or management in children, family-oriented lifestyle interventions are the most effective in noncancer and in CCS populations [15,73]. Therefore, our curriculum targets patients and their families. It will address the use of positive parental feeding practices [74,75] to promote healthy eating behaviors in children during and after cancer treatments, for example, healthy eating role modeling and avoidance of restrictions or control over eating [9,76].

The curriculum will put forward a positive and total diet approach to healthy eating that considers the whole eating pattern, suggests adding healthy foods instead of forbidding specific foods (apart from those restricted for food safety), and avoids categorization of food as "good" or "bad" [77]. The Mediterranean diet pattern is associated with the prevention of cardiovascular diseases [49] that are frequent long-term complications of CCS [4,5]. Therefore, coupled with Canadian Dietary Guidelines [78], this pattern has guided the development of nutrition education content and recipe criteria.

Food safety is a major concern during pediatric cancer treatment due to weakened immune system. It will be addressed throughout all cooking demonstrations when facilitators will model safe food handling practices. Only little evidence support a neutropenic diet to prevent infection for patients undergoing chemotherapy or radiotherapy, as the only few randomized control trials performed used variable methodologies and presented several limitations [79,80]. Indeed, a neutropenic diet may impose unnecessary food restrictions on patients who often consume insufficient dietary intakes [80,81].

### Considerations Related to Childhood Cancer

Further studies need to evaluate the feasibility of implementing workshops for pediatric oncology patients undergoing cancer treatments. The moment surrounding the diagnosis and treatment of cancer has been described as a *teachable moment* for a healthier lifestyle in adult cancer [82]. However, this opportunity window is not well documented in children. Families overwhelmed with the diagnosis might be less interested or find it too challenging to adopt healthy habits while experiencing a distressing life event [83]. However, focus groups with parents of overweight CCS testing a 6-lesson curriculum after completion of their child's treatment revealed that some would have preferred to receive the intervention earlier in the process [67], supporting that the timing of our intervention might be optimal.

The heterogeneity of the target population, which comprises children of various ages, diagnoses, and treatments, was a challenge in the development of the curriculum. Evaluating the implementation of the workshops will inform us on participation rate and will allow to calculate sample size of future nutrition education and cooking program in pediatric oncology. The nonrandomized design is also a limitation of this study. Our study was designed to ensure that every newly diagnosed patient could participate and benefit from this novel lifestyle study. Therefore, control participants will only be recruited among patients who completed the standard treatment before the VIE Program was implemented.

We are confident that this intervention will contribute to increase knowledge about nutrition and cooking in the context of childhood cancer. Hopefully, it will improve children's diet quality while promoting long-term healthy eating habits to prevent cardiometabolic complications. This research- and practice-based nutrition education and cooking demonstration curriculum will be a valuable complement to the VIE Program lifestyle intervention for the prevention of cardiometabolic long-term complications.

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## Conflicts of Interest

None declared.

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## Abbreviations

**CCCB:** Centre de cancérologie Charles-Bruneau
**CCS:** childhood cancer survivors
**RD:** registered dietitian
**SJUHC:** Sainte-Justine University Health Center
**VIE:** Valorization, Implication, Education

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Protocol

# Integrated Decentralized Training for Health Professions Education at the University of KwaZulu-Natal, South Africa: Protocol for the I-DecT Project

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## Abstract

**Background:** The Integrated Decentralized Training (i-DecT) project was created to address the current need for health care in South Africa among resource poor climates in rural and periurban settings. The University of KwaZulu-Natal (UKZN) in South Africa has embarked on a program within the School of Health Sciences (SHS) to decentralize the clinical learning platform in order to address this disparity. Framed in a pragmatic stance, this proposal is geared towards informing the roll out of decentralized clinical training (DCT) within the province of KwaZulu-Natal. There currently remains uncertainty as to how the implementation of this program will unfold, especially for the diverse SHS, which includes specialities like audiology, dentistry, occupational therapy, optometry, pharmacy, physiotherapy, speech-language pathology, and sport science. Consequently, there is a need to carefully monitor and manage this DCT in order to ensure that the participating students have a positive learning experience and achieve expected academic outcomes, and that the needs of the communities are addressed adequately.

**Objective:** The study aims to explore the factors that will influence the roll-out of the DCT by developing an inclusive and context-specific model that will adhere to the standards set by the SHS for the DCT program at UKZN.

**Methods:** Key role players, including but not limited to, the South African Ministry of Health policy makers, clinicians, policy makers at UKZN, clinical educators, academicians, and students of UKZN within the SHS will participate in this project. Once the infrastructural, staffing and pedagogical enablers and challenges are identified, together with a review of existing models of decentralized training, a context-specific model for DCTl will be proposed based on initial pilot data that will be tested within iterative cycles in an Action Learning Action Research (ALAR) process.

**Results:** The study was designed to fit within the existing structures, and emerging framework and memorandum of understanding between the partners of this initiative, namely, the Ministry of Health and UKZN in order to develop health care professionals that are competent and prepared for the changing dynamics of healthcare in a developing world.

**Conclusions:** It is envisioned that this study, the first to include a combination of health professionals in a DCT platform at UKZN, will not only contribute to effective service delivery, but may also serve to promote an interprofessional cooperation within the SHS and tertiary institutions in similar settings.

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**KEYWORDS**

decentralized clinical training, health science, South Africa, health care

## Introduction

### Background

There has been a global debate on the effectiveness of health care education in regards to preparing graduates for the realities of work [1]. In their landmark paper, Frenk et al (2010) [1] call for instructional changes to facilitate more efficient preparation of health professional graduates to ensure improved health outcomes and service delivery, especially within underserved areas. With this, there is a growing need to review how programs address issues of social accountability, where the responsibility of graduates is to serve as advocates for the marginalized and disenfranchised, particularly in rural areas [2,3,4]. In reviewing this, there is a need to explore the relationships and interactions between clinicians, patients and health services, as well as the university and professional expectations to strengthen various curricula [5]. Concurrent policy changes within the South African Ministry of Health call for a review of the strategies and teaching methods presently utilized to prepare health professional graduates for practice.

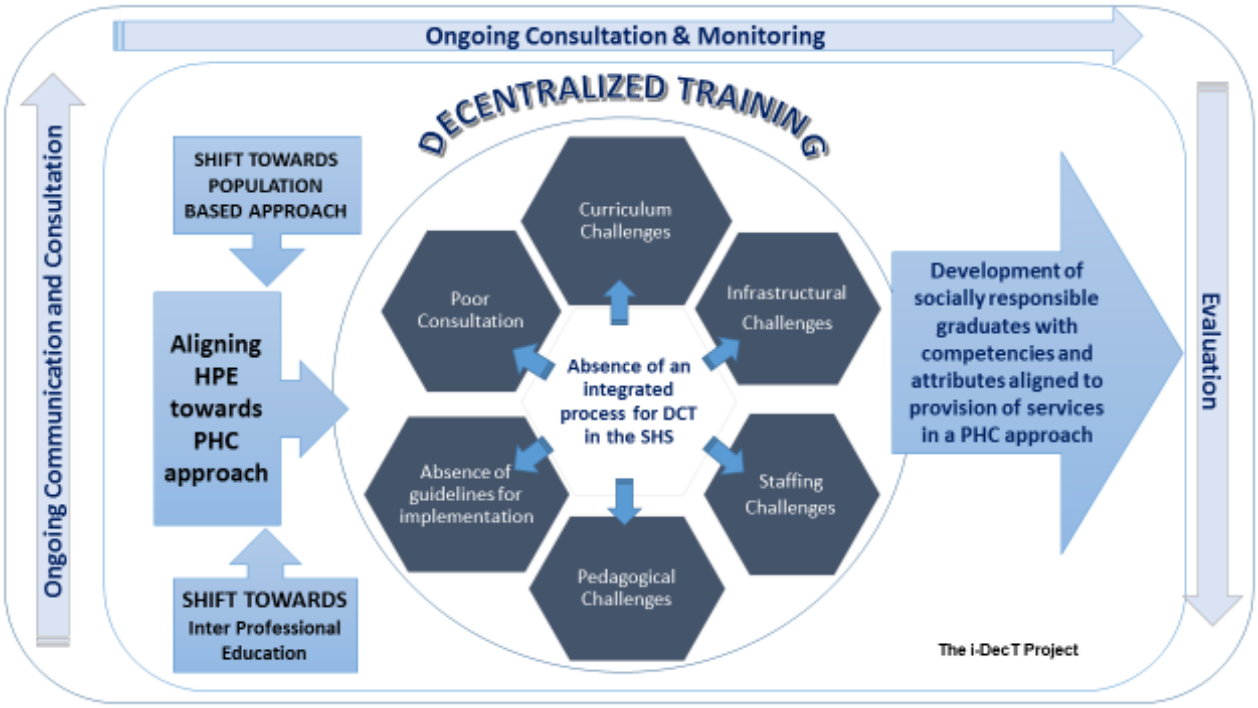
Within the South African context, the National Health Act (2003) [6] was pivotal in establishing a decentralized health system in the country. Within the district health system, hospital-based service delivery is offered at quaternary, tertiary and district levels. Community-based services are delivered through community health care centers and primary health care clinics. In the province of KwaZulu-Natal, the high incidence of disease (eg, HIV, tuberculosis, chronic non-communicable diseases, mental health, injury and violence, and maternal and child mortality) has inevitably placed a high burden on the public health system [7,8]. To address this burden of disease, the Negotiated Service Delivery Agreement [9] was designed to promote intersectoral performance around the delivery of identified outputs. For the health sector, this priority meant improving the health status of the entire population, with four main outputs (ie, increasing life expectancy; decreasing maternal and child mortality; combating HIV and acquired immune deficiency syndrome [AIDS], and decreasing the burden of disease like tuberculosis; and strengthening health system effectiveness). The National Health Insurance (NHI) [10] was introduced to redress the disparity between private and public access to health care. With this, the reengineering of primary health care (PHC) served as a concurrent strategy to the NHI. PHC aims to increase accessibility to health services and redress former inequalities [10]. PHC is an approach to health care that includes health promotion, disease and disability prevention, and rehabilitation [10]. This approach stresses the need to shift from a purely curative approach to health care toward encouraging health care practitioners to consider the impact of the social determinants of health. According to NHI policy [10], PHC services should focus on health promotion and prevention while still ensuring quality curative and rehabilitative services.

Despite the introduction of these policies, implementation at the grassroots level remains a problem, with limited literature around current PHC practice being available. Health professionals are challenged to provide services at both district level hospitals and the PHC level [3]. District level hospitals and PHC clinics are predominantly staffed by community service health professions. Community service is the mandatory year-long service that all South African–trained health care practitioners must undertake following their graduation. Within this community service year, health professionals are expected to work within multidisciplinary teams to deliver context-relevant services to marginalized communities in resource constrained settings in rural and peri-urban South African communities. This highlights the need for health professions educators to ensure that graduates are prepared to meet the demands of their entry into the work field, and that the teaching methods presently used are effective in developing the knowledge and skills required for professional practice.

Health education programs use service learning placements as a platform to facilitate transference of theory into practice. The practice of professional knowledge and skills during service learning placements exposes graduates to authentic working environments and equip them with technical competency, critical reasoning, ethical conduct, social attributes, and a sense of social responsibility so that they are able to serve as advocates for their clients [2,11,12,13]. Transformative learning approaches have thus been suggested as an option to promote acquisition of ethical and socially accountable practice. It is postulated that in using critical reflection of students' experiences, the development of new concepts can be fostered. Moreover, using rational discourse where students' assumptions are challenged and where they are expected to reason though their decisions, help to promote the development of professional reasoning and practice [14]. Within health education programs, there is growing support for decentralized service learning placements or decentralized clinical training (DCT). Current service placements are predominantly in well-resourced tertiary and district hospitals in urban areas. In contrast, rural DCT placements offer students exposure to the realities of rural practice, different levels of care (eg, PHC clinic and community health care centers) and allows for more active engagement with the community [15,16,17,18,19,20]. Van Schalkwyk et al's study [16] revealed that medical students found that DCT placements facilitated positive experiences of working at rural district hospitals and with the local community, and allowed the students to gain confidence in their clinical skills and decision-making abilities. Despite support for DCT placements, there is limited South African literature exploring the factors that promote a successful rural placement and positively influence students learning during DCT.

The University of KwaZulu-Natal (UKZN) offers various health science programs which are housed under the College of Health Sciences (CHS). The CHS has initiated steps to ensure that UKZN produces health care professionals who are competent for practice within a PHC model. Additionally, UKZN and the KwaZulu-Natal Department of Health (DoH) have signed a memorandum of understanding (MOU), which will remain operational over the next five years [21]. UKZN's commitment to the implementation of a decentralized training program for all cadres of health care practitioners is part of this agreement [21]. DCT in primary health care in the context of this study include service placements in DoH PHC sites.

**Figure 1.** Conceptual framework for the i-DECT Project. HPE: health professions education; PHC: primary health care; DCT: decentralized clinical training; SHS: School of Health Sciences.




It is envisaged that this training would enhance students' learning through the development of positive attitudes to rural practice and community engagement. Currently, students who are engaged with family medicine and public health modules as part of their medical degree program participate in a decentralized service learning placement. However, this is executed with a small number of students and in one medical discipline. For the School of Health Sciences (SHS), there currently remains uncertainty as to how the implementation of this program will unfold, especially given the diversity of the school, which comprises of eight disciplines (occupational therapy, physiotherapy, pharmacy, optometry, dentistry, biokinetics and sports science, speech and language and audiology). Consequently, there is a need to establish strategies to ensure successful SHS DCT placements, especially exploration into the factors that need to be considered to ensure that students have a positive learning experience. The Integrated Decentralized Training (i-DecT) project has been initiated in response to this need and aims to explore the factors that will influence the roll-out of DCT placements within the SHS at UKZN in order to construct a model of practice for service learning for the school.

### Research Aims and Objectives

The overall purpose of the i-DecT project is to establish an effective, decentralized training program within the SHS at the UKZN in order to:

1. Develop graduates who are socially responsible.
2. Develop graduates who are able to engage in interprofessional practice to improve service delivery in response to the health needs of the country.

In order to ensure that practical solutions are sought, the research questions are exploratory in nature and are described within the specific objectives.

The overall research question (what factors will influence the roll-out of the DCT for the SHS at the UKZN?) is geared toward the development of an inclusive and context-specific model. Figure 1 highlights some of these challenges from a conceptual perspective towards addressing these via the vehicle of DCT. These will be realized by (i) exploring the pedagogical challenges; (ii) the infrastructural challenges; and (iii) the staffing challenges as well as by (iv) identifying principles and factors for inclusion in the model for DCT.

## Methods

The study is located within South Africa in the province of KwaZulu-Natal. Three decentralized clinical training platforms (CTPs) have already been developed towards the optimization of service delivery and inclusion of these sites to become part of the continuous community and clinical placement service and training platforms for the SHS. This study will take on a multidisciplinary approach with the inclusion of eight health disciplines: audiology, dentistry, occupational therapy, optometry, pharmacy, physiotherapy, speech-language pathology, and sport science. These are the disciplines that are currently housed within the SHS, and hence have been included as a homogenous group.

This study will involve the use of multiple methods as an inclusive approach to knowledge generation and legitimization [22] and will provide the opportunity to utilize the strengths of both qualitative and quantitative approaches within this study.

More specifically, an embedded case study design will be used. The SHS is the case under investigation. The study is structured through three phases: a prepilot, a pilot, and a roll-out phase.

## Prepilot Phase

In this phase, an exploration of the pedagogical, infrastructural and staffing challenges will be explored. To ensure methodological diversity, a combination of desk and field research will be used.

### *Desk Research*

The desk research component will include the following actions:

- Scoping reviews will be conducted in order to establish existing models of DCT as well as principles to be embedded in interprofessional training of health professionals
- Document reviews will be conducted and will include an analysis of curriculum documents to identify the potential for interprofessional learning and methods of supervision required on site in order to address pedagogical challenges
- Policies, processes and procedures that exist between the academy and the health ministry will be reviewed to ensure effective service delivery and principles to be adhered to
- Infrastructural (ie, space, equipment, and other resources) and staffing requirements (ie, supervisors, clinicians, students) will be assessed for effective service delivery according to norms and standards established for each of the professionals in PHC

### *Field Research*

The field research component is outlined as follows:

- Study participants will include clinicians, clinical educators, students, academicians, key stakeholders, and decision makers within the Ministry of Health and the UKZN
- The richness of the data collected will depend on the multitude of perspectives generated from the use of the above sources
- Participants will be recruited based on predetermined selection criteria with purposive sampling techniques
- In order to explore issues of teaching, learning, supervision practices (pedagogy), service delivery through the DCT vehicle of training and human resource and infrastructural challenges, the following methods of data collection [23] will be used:
    - Surveys, focus groups discussions and semistructured interviews with all stakeholders to identify perceptions around DCT and potential challenges, enablers, and opportunities
    - Students will be encouraged to complete blogs as they prepare for the piloting of the DCT
    - Direct observations will occur on site in each of the CTPs to ensure that the infrastructural evaluation is strengthened

## Pilot Phase

In this phase, an exploration of the experiences of students and clinicians will occur within the various CTPs of the DCT program.

### *Action Learning Action Research*

Action Learning Action Research (ALAR) can be considered a cyclic process that includes action and critical reflection stages that in turn produce learning. Within the action research cycle in this study, the following processes and methods will be followed:

- Setting of clear goals and preparation for DCT (eg, identification of needs and setting of faculty learning outcomes, developing student learning outcomes, and performance indicators for each outcome)
- Action stage when placement and supervision occurs at the CTP and reflect on experiences with use of blogs and reflective diaries
- Focus group discussions mid-way through placement to identify revisions and changes to be implemented
- A reflective critique following implementation of changes

### *Co-operative Inquiry*

A co-operative inquiry with educators and clinicians will include the following stages:

- Innovation/Proposition Stage where evaluation of immediate impact and trial strategies are considered for the DCT model
- Investigative/Action Stage where gathering of baseline data and strategic focus for the DCT at the CTP is determined
- Dissemination/Reaction Stage where information is shared and future foci and strategies are determined that will influence the model for DCT
- Reflection Stage where the intermediate impact is evaluated, followed by further refinement and evaluation in preparation for the roll-out phase

## Roll-Out Phase

The data from the prepilot and pilot phases will be merged in order to establish principles that are essential for an appropriate DCT model based on an interprofessional educational rationale. The model for the DCT program will then be implemented within each of the CTPs.

### *Trustworthiness and Rigor*

Techniques for credibility, confirmability, and transferability in this study will include triangulation (methods, source, and analyst triangulation) and member checking / respondent validation in the iterative processes that are inherent in the study. Qualitative and quantitative data will be combined to elucidate complementary aspects of the experiences of the sample in this project. Source triangulation will be ensured by the inclusion of different samples of clinicians, clinical educators, and students. Analyst triangulation will be ensured in the appraisal of the literature and in coding and analysis processes of the qualitative aspects of the research. Reflexive triangulation will also be adopted where reactions and responses of the participants will be recorded. Techniques for confirmability or objectivity will include debriefing, documentation of an audit trail, and reflexivity. Continuous open dialogue with critical readers and mentor will occur [24] in addition to peer debriefing. The researchers in this study occupy an emic (insider) perspective and hence reflexivity and positionality is essential and bracketing of biases may be necessary.

### *Data Analysis*

Semistructured interviews and focus group discussions will be audio-recorded. Transcriptions, together with the reflective blogs and diaries, will be exposed to content analysis through the use of computer-assisted qualitative data analysis software (eg, NVIVO, version 11). Both inductive and deductive reasoning will be used to analyze the data on three levels (codes or nodes, categories and themes). Some of the more specific analytical aspects, namely, constant comparisons between groups, use of the group dynamics as a resource, and use of participants as co-analysts [25,26] will also be considered. The surveys selected for various phases of this project will be analyzed descriptively used MS Excel 10 and SPSS version 24. Data from the qualitative and quantitative phases will be merged and integrated to form conclusions and make relevant assertions.

### Ethical Considerations and Boundaries

Given the emergent nature of this study and the absence of a framework for research within decentralized training programs, the researchers anticipate that there may be power dynamics that will have to be negotiated. It is for this reason that the researchers have attended relevant meetings and have been transparent in the processes that are documented within this project protocol. Moreover, key role players have been approached to form part of the research team in order to contribute to the development of a framework for research in this area. Continued consultation and open communication is identified as necessary towards the ethical principle of beneficence in this study. Gatekeeper permissions have been obtained in addition to approval from a research ethics committee (HSS/0727/017). Written informed consent will be obtained from participants prior to initiating the study. Principles of autonomy and anonymity and the right to withdraw will be observed.

## Results

The project was funded in 2016 with ethical clearance approval granted in 2017. The study is ongoing and researchers are in the process of recruiting postgraduate research fellows as study collaborators as well as reviewing contemporary literature. Currently, the project is in the prepilot phase with data collection underway, and the first results are expected to be submitted for publication in 2018.

## Discussion

The changing landscape of health education and requirements of graduates are the driving force behind the current reengineering of the CHS curriculum towards DCT. This new curriculum aims to ensure that the UKZN produces health care professionals who are competent and prepared for the changing dynamics of health care in a developing world. It also aims to guide the acquisition of graduate competency and proposes that health professionals should demonstrate mastery and/or acquire skills in seven key roles, namely, as practitioner, communicator, collaborator, leader, scholar, health advocate, and professional [27].

Currently, most of the disciplines in the school place students in well-resourced hospitals and disadvantaged communities in urban settings for service learning. The concern is that these placements do not adequately equip students with the ability to assess and treat patients in resource-constrained environments or understand how the DoH system works, including the referral pathways. Additionally, students do not have sufficient opportunity to engage with or consult the community or have the opportunity to deliver programs that address health promotion, and primary, secondary and tertiary prevention of disease and disability. Another criticism is that the current service learning placements in the province are fragmented. Therefore, health professions educators are finding it difficult to create opportunities for interprofessional practice. Anecdotal reports indicate that this results in a lack of understanding of the scope of practice between the various health care practitioners, and decreased intrateam communication and planning, which leads to less favorable outcomes for patients.

In taking this project forward, decentralized service placements can offer a solution where students are exposed to and are allowed active engagement with the communities they serve. Furthermore, the MOU between UKZN and KwaZulu-Natal DoH requires the implementation of DCT in KwaZulu-Natal for the next five years. Although this understanding exists between the two parties, there are currently no formal guidelines or processes in place to guide implementation for the SHS at UKZN. Moreover, the absence of baseline information poses a threat to the successful rollout of this program. For a decentralized learning platform to provide a positive learning experience for students, it needs to be careful planned, monitored and evaluated. However, at present there are many uncertainties that require further exploration to ensure a successful implementation.

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### Conflicts of Interest

None declared.

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## Abbreviations

**AIDS:** acquired immune deficiency syndrome
**ALAR:** Action Learning Action Research
**CHS:** College of Health Sciences
**CTP:** clinical training platform
**DCT:** decentralized clinical training
**DoH:** KwaZulu-Natal Department of Health
**i-DecT:** integrated decentralized training
**HPE:** health professions education
**MOU:** memorandum of understanding
**NHI:** National Health Insurance
**PHC:** primary health care
**SHS:** School of Health Sciences at the University of KwaZulu-Natal
**UKZN:** University of KwaZulu-Natal

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Protocol

# Development of a Maternal, Newborn and Child mHealth Intervention in Thai Nguyen Province, Vietnam: Protocol for the mMom Project

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## Abstract

**Background:** Ethnic minority women (EMW) living in mountainous areas of northern Vietnam have disproportionately high infant and maternal mortality rates as a result of low maternal health knowledge, poverty, and remoteness from low-capacity health centers.

**Objective:** The objective of this study was to describe the protocol for the development and evaluation of the mMom intervention, which is an integrated mobile health (mHealth) system designed to improve maternal and infant health knowledge, and behavior among women in remote areas of Thai Nguyen, Vietnam.

**Methods:** This project featured the following four phases: (1) development of an mHealth platform integrated into the existing health management information system in partnership with the provincial health department; (2) ethnographic fieldwork and intervention content development; (3) intervention piloting and implementation; and (4) evaluation of the intervention's impact on participants' maternal health knowledge, behavior, and interactions with the health system.

**Results:** The mMom project development process resulted in the following: (1) the successful development of the mMom system, including the mHealth platform hardware and integration, the intervention plan and content, and the monitoring and evaluation framework; (2) the piloting and implementation of the intervention as planned; and (3) the implementation of the monitoring and evaluation framework components.

**Conclusions:** This protocol outlines the development of the mMom intervention and describes critical next steps in understanding the impact of the intervention on participants and the wider health system in Thai Nguyen province, Vietnam.

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**KEYWORDS**

mobile health; Vietnam; maternal health; reproductive health; health equity

## Introduction

### Background

Vietnam has made remarkable progress in improving maternal, newborn, and child health (MNCH), but ethnic minority women (EMW) living in mountainous and remote areas still lag far behind. Although Vietnam's overall under-five mortality rate declined from 50.8 per thousand live births in 1990 to 21.7 per thousand in 2015 [1] and the maternal mortality rate dropped from 139 per hundred thousand live births in 1990 to 54 per hundred thousand in 2014 [2], disaggregated data from the last three censuses of Vietnam show that ethnic minority people have higher total fertility rates, higher infant and child mortality rates, lower life expectancies, and are less likely to attend antenatal or postnatal care or to deliver in a health facility than Kinh people (the ethnic majority group) [3,4]. In 2009, the national total fertility rate was 2 children per woman but 5 for H'Mong minority women. H'Mong women also experience the highest infant mortality rate in Vietnam at 46 per thousand live births, whereas the infant mortality rate in Kinh women is 12 per thousand [5]. Undernutrition and stunting rates of children in mountainous areas, which have high concentrations of ethnic minority people, are 3 times higher than those in the wealthier lowland provinces, and maternal mortality rates are also significantly higher among EMW compared with Kinh women, at 316 and 81 per hundred thousand births, respectively [6]. In 2011, 55% of EMW nationwide reported that they had given birth in a health facility, in contrast to over 95% of Kinh women [7]. Although Kinh people have vaccination rates of 73%, the average rate across ethnic minority groups is 38% [3].

Health outcome disparities among ethnic minorities in northern Vietnam are profound, primarily because of sociostructural factors including poor education, low economic and social status, and rural or remote residence [4-6,8-10]. Determinants influencing the substantially poorer MNCH and higher infant mortality rates among EMW and their newborns are limited access to information, low reproductive health knowledge, poor MNCH behaviors, poor access to and uptake of perinatal and postnatal care services, and language barriers [8-11]. In addition, health facilities are unevenly distributed throughout Vietnam, with fewer and lower capacity facilities and staff in remote regions [10,11]. Specific contributing factors include relatively low uptake of tetanus vaccinations among EMW during pregnancy and low uptake of modern contraceptives [7]. In Thai Nguyen province, where ethnic minorities constitute 27% of a population of 1.3 million [12] and where the majority live in mountainous and remote areas, the situation is particularly acute.

### Current Approaches to Global Mobile Health

Over the past decade, mobile health (mHealth) initiatives have burgeoned in both low- and high-income contexts, supported by the high penetration of inexpensive mobile phone services. mHealth has been widely applied to address the stark global inequities in maternal and infant mortality in low- and middle-income countries, as interconnected economic, political and sociocultural factors have impeded progress on MNCH indicators and mHealth may hold the potential to mitigate some of these barriers.

With regard to mHealth acceptability, several recent studies in diverse regions have identified receptive attitudes from target communities toward mHealth projects, ranging from 70% to 90% in different interventions [13-15]. To date, most mHealth initiatives described in the literature are associated with positive health outcomes. A 2014 systematic review of mHealth interventions in low- and middle-income countries found that mHealth has been effective in improving treatment adherence, appointment compliance, data gathering, and developing support networks for health workers [16]. In addition, reviews of recent initiatives show that it has become a powerful tool with the potential to reduce disparities, improve the quality of services delivered by health care workers, and improve access to health services leading to improvement of MNCH in developing countries [17-22]. A review of current mHealth initiatives suggests that mHealth projects are generating benefits in the areas of surveillance of MNCH in India, quality MNCH services in Ghana, MNCH information and education in Tanzania [23], family planning information provision in Kenya and Tanzania [24], and quality health services in Sierra Leone [25]. Among various initiatives using short message service (SMS) for MNCH, the Mobile Alliance for Maternal Action (MAMA), initiated in May 2011, provides critical stage-based information to new and expectant mothers in Bangladesh, India, and South Africa via mobile phones [20]. MAMA has a library providing free adaptable mHealth reminders for programs that are using mobile phones to inform and empower new and expectant mothers.

Available literature indicates high acceptability of mHealth among health staff and that mHealth projects can positively impact community health work and systems. mHealth interventions have been found to increase staff efficiency and improve data entry and monitoring [26-28], though sufficient staff training has been a challenge in some interventions [29]. An SMS intervention in Malawi reduced facility admissions for minor health issues such as fever, thereby decreasing health staff's workload through supporting participants in treating minor conditions at home [26]. A study of health worker perspectives in rural Rwanda found that the use of the RapidSMS mHealth technology to reduce maternal and newborn deaths improved health workers' interactions with mothers and that health workers' knowledge increased, with community health workers reporting improved mobile phone usage skills and increased knowledge of MNCH [29].

Although there has been an increased application of mHealth to support MNCH, evidence of the outcomes of SMS-based interventions for MNCH is still limited [30]. Tamrat and Kachnowski argue that the use of mHealth in MNCH is underdeveloped, and their review suggests that studies of ongoing programs are needed [31]. Furthermore, in comparison with the wider adoption of mHealth in emergency care, point of care support, health promotion, and data collection, there are few studies that examine its use for improving prenatal or neonatal access to health care [31]. Studies in Indonesia and Ghana demonstrated that midwives with low literacy levels could use text messaging effectively to convey information [32,33], and a study in Tanzania found that pregnant women linked to health units by mobile phone had increased contact

with midwives and were more likely to have a skilled attendant at delivery [34].

Vietnam's mobile phone network and market have undergone swift development as the country has experienced rapid economic growth since the late 1980s. Vietnam is categorized as a low-income country, but the number of mobile subscriptions over its population is higher than that of many developed countries. In 2015, there were 130 mobile cellular subscriptions for every 100 people in Vietnam [35] and a total of 122 million mobile subscribers over a total population of 93.4 million [36]. SMS has been used widely for advertisement and commercial services but not for social services, and the application of mHealth in Vietnam is still limited. Mobile service coverage is wide and costs are low (ie, 500 Vietnam dong or US $2.5 cents per SMS sent, and free receipt of SMS) and as such, mHealth holds great potential for affordable provision of social services to hard-to-reach populations, such as ethnic minority groups and people living in remote regions. However, to date, mHealth appears to be underutilized in Vietnam in contrast to other regions in Asia. To our knowledge, mHealth has only been applied to provide health information to internal migrants in Vietnam [37] and has not yet been used to support maternal health with the exception of the mMom project.

Furthermore, although literature on the development of mHealth interventions is growing, certain areas remain understudied. A gap in current literature is the relative absence of studies examining policy and management frameworks to support adoption of mHealth services, with a specific gap related to governance and partnerships with regional and national partners. Issues such as the coordination for mHealth projects among different government bureaus, and protocols for assuring quality of information, require further investigation. This study aimed to address this noted gap through creating multilevel partnerships between commune-, district-, and provincial-level health authorities and documenting the challenges of an integrated, intergovernmental, and interdepartmental project to contribute lessons currently lacking in the literature.

The objective of this paper is to describe the protocol for the development and evaluation of the mMom intervention, which is an integrated mHealth system designed to improve maternal and infant health knowledge and behavior among women in a remote area of Thai Nguyen province in mountainous northern Vietnam.

## Methods

### Development of an mHealth Platform Integrated Into the Existing Health Management Information System in Partnership With the Provincial Health Department

The Government of Vietnam has demonstrated increasing interest in health system strengthening and mHealth over the past decade, creating a favorable policy environment and suitable context for partnerships toward greater integration of mHealth. In 2009, the Ministry of Health established a Central Health Information and Technology Institute, and telemedicine and Web-based electronic medical records systems were subsequently established to strengthen health management information systems (HMISs). In 2012, the Ministry of Health introduced a new set of administrative directives on medical and health information technology (IT), and the Thai Nguyen Provincial Health Department (TNHD) received funds from Atlantic Philanthropy to computerize its HMIS, supported by the Institute of Population Health and Development (PHAD). In Thai Nguyen province, all hospitals and 181 communes in 9 districts are fully integrated into an electronic record management system, and 100% of commune health centers are connected by high speed cables to district and provincial health centers.

Due to the central and provincial government's commitments to use IT to improve health, the mMom project fit well within national and local priorities. The mMom software and its operation was developed and managed by Vietnam electronic health (eHealth) Medical Investment and Communication. The project built a new mHealth component, aimed at health communication, as part of the existing HMIS for maternal and child health. However, this component can also function independently and can be applied to other modules of the HMIS. The mMom database was created as an integrated component of the HMIS through using each patient's unique identity code. The platform aimed to coordinate and add support to commune health workers' existing tasks in monitoring pregnancy and new motherhood in community women. In addition, the project's integration into the HMIS aimed to improve data collection and monitoring, with the goal of supporting future MNCH programming evaluation and improvements due to strengthened data collection systems.

### Ethnographic Fieldwork and Intervention Content Development

Ethnographic fieldwork was conducted at the mMom project outset to identify gaps in current MNCH approaches in the intervention site (Dinh Hoa district, Thai Nguyen, Vietnam) and to inform the mHealth intervention. Fieldwork methodology included focus group discussions (bringing people together to explore their attitudes and experiences on a topic of interest in a group setting); in-depth interviews (guided conversations between a researcher and an individual, which collect specific information on their perceptions and experiences) with the target populations of currently pregnant women, new mothers, their families, and health workers; and document review. Focus groups and interviews were selected as the methods most suited to achieving the fieldwork goals of assessing the extent of mobile phone use in the district, literacy barriers, social and cultural issues affecting phone ownership and use, health service utilization, capacity and response of health workers, organizational factors that may impact mHealth promotion, and technical constraints such as mobile signal coverage.

The intervention was developed based on several well-known conceptual frameworks for mHealth and maternal health. These included the following: (1) the World Health Organization (WHO) framework and standards for country health information systems, which emphasizes reliable and timely health information as an essential foundation of effective public health systems and provides guidelines for strengthening the key components of health information systems [38]; (2) the Philbrick

strategic framework on mHealth for MNCH, which proposes 3 strategic objectives that lead to improving MNCH in low- and middle-income countries and 5 operational priorities for public health professionals and policy makers to conceptualize how mobile technology can be harnessed to improve MNCH and to increase its effective use [17]; (3) the Mobile Alliance for Maternal Health Global Monitoring and Evaluation Framework, a tool for planning, management, monitoring and evaluation (M&E) of mHealth projects to ensure that programs meet the needs of the target population [20]; and (4) the WHO mHealth framework for assessing the impact of MNCH mHealth interventions on health systems, which describes the value of mHealth solutions in strengthening health systems across reproductive, maternal, neonatal, and child health areas and combines metrics on health system functions and needs and matches them to appropriate mHealth strategies [39]. These frameworks were used as reference or for guidance during development of the project intervention, logical framework, and indicators under a results-based management accountability framework and will be used for project impact assessment. The mMom project was developed by a team of local and international experts and was funded by the International Development Research Centre (IDRC)—a Canadian funding organization that supports research on capacity development in low- and middle-income countries. The project aimed to build on prior successful collaborative work on HMIS among the PHAD, Population Council, and TNHD.

The intervention consists of 2 SMS message programs designed to support women's health during pregnancy and new motherhood. The mMom SMS messages were developed using MAMA [20] materials as a primary reference. From the MAMA templates, messages that were applicable to the context of northern Vietnam were selected and then further adapted for local acceptability among the project's target population. Additional messages based on the Vietnam Ministry of Health guidelines on MNCH were added. The TNHD and external experts provided feedback on the message content, and the messages were piloted with members of the target population in nonstudy sites before being finalized for the intervention. The first SMS program was focused on prenatal care and offered actionable tips on how to remain healthy throughout pregnancy and promote healthy fetal development. Topics included what to expect during each stage of pregnancy, danger signs, antenatal care visits, nutrition, supplements, and immunizations. The program featured a total of 75 SMS messages, which were delivered 2 to 3 times per week from the 5th to 42nd week of pregnancy. The second program was initiated once the infant was born and provided information on women's postpartum care and infant development. Topics included breastfeeding, danger signs, immunization for baby, and contraception. The program included 71 messages, which were delivered 1 to 2 times per week for the first year of the baby's life. The mMom messages were brief, written in accessible language, and sent automatically by the database to all participants.

Each SMS program was designed to include the following 4 types of messages: informational and educational, reminder, interactive, and scanning. Informational, educational and reminder messages provided one-way information and reminded women to take critical actions, such as getting a tetanus immunization. Interactive or three-way messages requested women to respond to monitoring questions, such as whether the participant has recently visited the health center. If women do not respond, or if their responses suggest a risk, the database automatically informs that individual participant's health worker so that they may reach out to the woman. Within each SMS program, approximately 15% (12/75) of all messages were interactive messages. Finally, the program linked the interactive messages to the HMIS database of the TNHD to scan for relevant information and take the next action appropriately. For instance, if the system scans the HMIS and learns that a woman already obtained her polio shot, the system will then skip the reminder message for the polio immunization. Each type of message was sent at the appropriate time for the stage of a woman's pregnancy; the timing was customized within the program algorithms.

## Intervention Piloting and Implementation

The intervention site was determined through discussion with the Dinh Hoa District Health Center. All communes in Dinh Hoa district were stratified into centrally located, middle and remote communes, and then random selection was applied to choose 8 project communes and 4 control communes in the district.

The mMom intervention target population included EMW living in Dinh Hoa district who had a current pregnancy or who had a child aged less than 1 year. The sampling frame within the project communes included all pregnant women, new mothers, and women of childbearing age who were known by and under the care of a village or commune health worker. All women were individually invited to participate in the project by the commune health worker in charge of her specific village. Introduction to the project and seeking informed consent for participation took place during a woman's first prenatal visit, where a health worker described the mMom project and asked for the woman's consent to receive SMS messages over the course of her pregnancy and participate in project evaluation activities. If she agreed, she was asked to sign a consent form and complete the preintervention survey. Her phone number and unique identity code were then added to the database, and she began to receive messages based on her estimated week of pregnancy. Once she had delivered her baby, the participant was switched to the new mother SMS program. The study was approved by an institutional review board at PHAD, which was registered with and used ethical protocols of the Office for Human Research Protections of the United States Department of Health and Human Services. Project data were subject to privacy and security protocols of the Office for Human Research Protections and the TNHD.

The mMom platform and intervention were developed over 6 months, piloted for 2 months, and implemented for 24 months. Project wrap-up occurred over the final 10 months; project data are currently under analysis, and dissemination of results is forthcoming.

### Evaluation of the Intervention's Impact

The project evaluation framework included the following 4 major components: (1) initial ethnographic fieldwork, (2) pre- and postintervention surveys in intervention and control communes, (3) regular M&E site visits, and (4) extended mid-term and final evaluations. Each of the four components of the project evaluation framework were planned and designed at the project outset. As described earlier, ethnographic fieldwork was carried out in Dinh Hoa district at the beginning of the intervention development phase to learn about project feasibility and potential challenges and to further contextualize and refine project details. The team included experts (in obstetrics and gynecology, MNCH, public health, IT, and M&E) from Simon Fraser University (Canada), PHAD, National Hospital of Obstetrics and Gynecology (Hanoi), Hanoi Medical University, and TNHD. Focus group discussions and in-depth interviews were carried out with staff of the district and commune health centers, pregnant women and women with an infant aged less than 1 year, and family members of these target population women, especially their husbands and mothers-in-law.

Preintervention questionnaires were developed and piloted at the beginning of the project. All pregnant women and women with infants aged less than 1 year in 8 intervention and 4 control communes were invited to respond and provide information on their knowledge, attitudes, and practices around MNCH. The questionnaire was formulated to evaluate participants' knowledge of food sources for specific nutrients, what types of experiences merited medical attention during pregnancy or new motherhood, and their attitudes toward MNCH; and to assess participants' current mobile phone use habits, their family income, prior health care experiences, health insurance status, and other demographic details. When participants delivered their infant or experienced a miscarriage (for the pregnancy program) or when their child reached 1 year of age (for the new motherhood program) or when they wanted to cease participation for any reason, they were asked to be interviewed using a postintervention questionnaire. The postintervention questionnaire was formulated to mirror the preintervention questionnaire to assess changes in knowledge, attitudes, and practices over the course of the intervention. It is expected that this intervention-control survey design will allow us to control for confounding factors and learn about net effect of the mMom intervention with appropriate techniques, such as difference-in-differences analysis. Additionally, participants living in the 8 intervention communes were asked about their experiences with and attitudes toward the mMom project. Commune health center staff were trained to administer the questionnaires under the supervision of PHAD project officers. EpiInfo (Centers for Disease Control and Prevention, Atlanta, US) was used to develop data entry forms, and double-entry protocol was employed to control data entry quality.

Regular M&E trips were conducted by project management teams from PHAD, TNHD, and Dinh Hoa district health center to participating communes for monitoring the intervention's progress and for anticipating and addressing any issues that arose. The mid-term and final evaluations were carried out in May 2014 and May 2016, respectively, and were led by mixed teams of semiexternal evaluators, who knew the project well but did not take part in implementing the intervention, and external evaluators (including MNCH and IT experts) to gain objective project insights. Qualitative data collection guidelines (focus group and interview guides, Multimedia Appendix 1) were developed to elicit responses from mMom stakeholders on their experiences with and perceptions of the project. Focus group discussions and in-depth interviews were carried out (by international and Vietnamese evaluators and with Vietnamese translators) with TNHD officials, district health center staff, project beneficiaries, and their families. All participants involved in evaluation activities had provided their written consent upon joining the intervention and received a small honorarium for providing their insights on the project. The focus groups and interviews were tape-recorded and transcribed. These mid-term and final evaluations provided ample qualitative data, the analysis of which is expected to support a deeper understanding of the project's implementation and impact. Analysis of the quantitative data provided by the pre- and postintervention surveys is expected to result in quantitative evidence of the impacts of the mMom intervention on participants' MNCH knowledge, behaviors, and interactions with the health system.

## Results

The results of the mMom project development process were as follows: (1) the successful development of the mMom system, including the mHealth platform hardware and integration into the HMIS, the intervention plan and content, project personnel, and M&E framework; (2) the piloting and implementation of the intervention through multistakeholder partnerships as planned; and (3) the implementation of all planned M&E activities.

## Discussion

The mMom project's design and research protocol aim to contribute several lessons on multilevel stakeholder partnerships and the integration of mHealth systems with existing electronic population and health record systems, which are relatively lacking in the global mHealth literature.

The mMom system focused on development through partnerships at local, provincial, and national levels to enhance the sustainability of the intervention. One of its anticipated strengths is that the project was informed by global-level frameworks, guidance, and best practices on the application of mHealth to improve MNCH outcomes, but it was also highly context-specific because of careful attention to the local relevance of the SMS message content, a piloting phase in the Dinh Hoa district, and local implementation through existing community health work systems. The project's high level of integration with local partners, including TNHD, the Dinh Hoa district health center, and the local commune health centers that carried out daily project activities, was anticipated to present challenges because of the significant communication necessitated by this approach. To ensure effective coordination, two dedicated project officers at PHAD communicated routinely with all partners, and the project team met the TNHD, the district health center, commune health staff, and a number of

participants on at least a biannual basis to discuss the progress of the intervention and share perspectives on its future. It is expected that this consistent engagement will promote partners' commitment to the project over the longer term.

The enabling policy and technological environment in Thai Nguyen is expected to promote this intervention's continued integration and uptake among high-level decision makers in Dinh Hoa district and at the TNHD. As previously described, Thai Nguyen province has adopted a HMIS and has increasingly applied technology in improving health service delivery over the past two decades. In terms of technological integration, Thai Nguyen is advanced relative to other provinces in Vietnam, and officials at several health system levels have engaged with and received training in health information technologies in recent years. It was expected that this material context (ie, eHealth information components that are already in place) and a social and policy context which is committed to exploring and applying mHealth to improve health outcomes, would create an environment of high readiness for a project such as mMom and would enable the project's effective implementation.

It was also anticipated that the mMom project would be innovative and sustainable because of its integration into the local HMIS and its implementation by the local health workers at district and commune levels. Furthermore, the TNHD was engaged in comanaging and overseeing operation of the intervention from its initiation and also took ownership of the mMom system at the official end of the project period. It was expected that continuous involvement of the health centers and government bodies at the district and provincial level would support the project's integration into current systems and will boost the likelihood of its permanent adoption.

## Conclusions

This protocol outlines the research tools and process of the mMom project in northern Vietnam, which aims to examine the feasibility and impact of implementing an integrated mHealth intervention to improve maternal and child health knowledge and behavior among EMW living in a remote area in Vietnam. The project is likely to provide important lessons on the challenges of a highly integrated multistakeholder partnership and insights on coordination between the international project team, the provincial health department, and the district and commune health center levels, which took place as part of implementation. The project may also contribute lessons on factors that may enable or present challenges to integrating a novel component into an existing HMIS and lessons on district management of mHealth implementation. These potential contributions can provide valuable insights into currently existing gaps in the mHealth literature and are expected to support the increased integration of mHealth for MNCH projects in other contexts.

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## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Qualitative data collection guidelines, mMom project evaluation.

[PDF File (Adobe PDF File), 97KB - resprot_v7i1e6_app1.pdf ]

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## Abbreviations

**eHealth:** electronic health
**EMW:** ethnic minority women
**HMIS:** health management information system
**IDRC:** International Development Research Centre
**IT:** information technology
**M&E:** monitoring and evaluation
**MAMA:** Mobile Alliance for Maternal Action
**mHealth:** mobile health
**MNCH:** maternal, newborn and child health
**PHAD:** Institute of Population, Health, and Development
**SMS:** short message service
**TNHD:** Thai Nguyen Provincial Health Department
**WHO:** World Health Organization

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Protocol

# Effects of Psychiatric Comorbidity in Immune-Mediated Inflammatory Disease: Protocol for a Prospective Study

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## Abstract

**Background:** Immune-mediated inflammatory diseases (IMID), such as inflammatory bowel disease (IBD), multiple sclerosis (MS), and rheumatoid arthritis (RA), are highly prevalent in Canada and the United States and result in substantial personal and societal burden. The prevalence of psychiatric comorbidities, primarily depression and anxiety, in IMID exceeds those in the general population by two- to threefold, but remains underdiagnosed and undertreated. Furthermore, the effects of psychiatric comorbidity on IMID are not well understood.

**Objective:** The objectives of this study were (1) to compare health-related quality of life and work ability in persons with IMID and psychiatric comorbidity with those of persons with IMID without psychiatric comorbidity and with those of persons with depression and anxiety disorders alone, and (2) to validate existing case identification tools for depression and anxiety in persons with IMID to facilitate improved identification of depression and anxiety by clinicians. To achieve these objectives, we designed a prospective 3-year longitudinal study. In this paper, we aim to describe the study rationale and design and the characteristics of study participants.

**Methods:** Between November 2014 and July 2016, we recruited 982 individuals from multiple clinic and community sources; 18 were withdrawn due to protocol violations.

**Results:** The final study sample included 247 participants with IBD, 255 with MS, 154 with RA, and 308 with depression or anxiety. The majority were white, with the proportion ranging from 85.4% (IBD [210/246]; MS [217/254]) to 74.5% (114/153, RA; *P*=.01). There was a female predominance in all groups, which was highest in the RA cohort (84.4%, 130/154) and least marked in the IBD cohort (62.7%, 155/247). Participants with depression or anxiety were more likely to be single (36.0%, 111/308) than participants in any other group (11.8% [30/255]-22.7% [56/247], *P*<.001).

**Conclusions:** This paper presents the rationale for this study, describes study procedures, and characterizes the cohort enrolled. Ultimately, the aim is improved care for individuals affected by IMID.

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**KEYWORDS**

inflammatory bowel disease; multiple sclerosis; rheumatoid arthritis; depression; anxiety; epidemiology

## Introduction

Immune-mediated inflammatory diseases (IMID), such as inflammatory bowel disease (IBD), multiple sclerosis (MS), and rheumatoid arthritis (RA), are highly prevalent in Canada and the United States, and substantially burden affected individuals and society [1-4]. Persons with IBD, MS, and RA report poorer health-related quality of life (HRQOL) as compared with the general population [5-8]. They are also at increased risk of leaving the workforce early due to disease-related disabilities [9-11].

### Psychiatric Comorbidity

Increasingly, psychiatric comorbidity, including depression and anxiety disorders, is recognized as common among individuals with IMID, with a prevalence exceeding that in the general population by two- to threefold. Psychiatric disorders are commonly associated with adverse health outcomes, including impaired HRQOL and missed work [12,13]. The effects of psychiatric comorbidity on HRQOL and work ability in those with IMID, beyond the impact of the IMID itself, are not well understood. Most studies have focused on the impact of the IMID on cessation from paid work, but this fails to capture the spectrum of functional work impairment. Presenteeism (reduced productivity while at work due to illness) and absenteeism (missed work due to illness) have received much less attention, including how they are affected by psychiatric comorbidity [14-16]. Moreover, prior studies have often been cross-sectional and included small samples.

Several potential mechanisms may underlie the association between psychiatric morbidity and adverse outcomes. Psychiatric comorbidity may lead to changes in health behaviors such as poorer diet or sleep hygiene, lower adherence to treatment, and increased smoking [17]. Complex bidirectional relationships exist between psychiatric disorders, such as depression and anxiety, and immune function [18]. Stress may play a role in psychiatric comorbidity and poor chronic disease outcomes [19-21].

Despite the adverse effects of depression and anxiety disorders on chronic disease outcomes, these psychiatric disorders are undertreated when they co-occur in IMID [22-26]. Improved detection of these disorders in IMID is a necessary step to better management. Case identification instruments (screening tools) may promote detection of depression and anxiety disorders. However, tools developed for the general population may not translate well to use for people with IMID. For example, somatic symptoms of depression (depressive affect), such as fatigue, difficulty sleeping, and poor appetite, captured in screening tools are also common somatic symptoms of IMID, which may lead to criterion contamination [27]. Similar issues arise when screening for anxiety. Therefore, screening tools must be validated in the IMID populations. To date, these validation efforts have been limited to a few tools, and evaluation of psychometric characteristics of these tools has been limited [28-30].

### Aims

We designed a prospective 3-year longitudinal study of persons with IMID with 2 principal aims. The first aim was to compare HRQOL and work ability in persons with IMID and psychiatric comorbidity with those of persons with IMID without psychiatric comorbidity and with those of persons with depression and anxiety disorders alone. The second aim was to validate existing screening tools for depression and anxiety in persons with IMID to facilitate improved identification of depression and anxiety by clinicians. We expect that improved identification and management of these disorders would positively affect patient-centered outcomes such as HRQOL.

This paper describes the study design, recruitment of participants, and the characteristics of the established cohort.

## Methods

### Design

We enrolled participants with any of the following 5 diagnoses: (1) IBD—Crohn disease or ulcerative colitis [31,32]; (2) MS—definite diagnosis according to the Poser or revised McDonald criteria [33-36]; (3) RA—definite diagnosis based on the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Rheumatoid Arthritis Classification Criteria [37]; (4) major depressive disorder meeting the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria [38]; and (5) any anxiety disorder meeting the DSM-IV criteria [38]. As DSM-IV rather than DSM-5 was in place at the time of the study inception, post-traumatic stress disorder and obsessive compulsive disorder were included as anxiety disorders, in keeping with the DSM-IV classification scheme.

All participants were required to be aged 18 years or older (without an upper age limit), able to provide informed consent, willing to participate in the study for 3 years, and to have an adequate knowledge of the English language to complete questionnaires (this latter criterion did not exclude anyone). Diagnoses of IBD, MS, and RA were confirmed by medical records review and by querying treating physicians directly if needed. Diagnoses of depression or anxiety were confirmed by structured clinical interview as delineated below. The presence of comorbid psychiatric disorders was not an exclusion criterion.

We obtained ethics approvals from the University of Manitoba Health Research Ethics Board and research committee approval from the Winnipeg Regional Health Authority, Winnipeg Health Sciences Centre, St. Boniface Hospital, Seven Oaks Hospital, and Victoria General Hospital. All participants provided written informed consent. In addition to consenting to core study activities, participants were also asked to agree to blood sample collection at each visit and to linkage of the collected data to health administrative data records.

### Recruitment

We used general and targeted strategies to recruit participants from the community and tertiary care settings. General strategies included the placement of posters in local hospitals, private medical and psychology clinics, and academic institutions within

the Winnipeg region; use of social media outlets (tweets and Facebook posts) through the largest tertiary center (Winnipeg Health Sciences Centre); and self-help groups for mental health concerns. The targeted strategies used for each group are described below.

For IBD, research assistants directly approached individuals attending gastroenterology clinic visits using a standardized script and contacted participants in a population-based IBD research registry via email. The registry was established in 1995 by one of the investigators (CB) and includes nearly half the provincial IBD population [39].

For MS, research assistants contacted participants in the Winnipeg MS Clinic registry by phone and mail. This clinic was established in 1998 and is the sole source of care for Manitobans with MS being treated with disease-specific therapies, although the clinic population is not limited to those receiving such therapies. A research registry was established in 2011, and most of the individuals with MS attending the clinic have agreed to participate.

For RA, research assistants directly approached individuals attending scheduled clinic visits at the University of Manitoba Arthritis Centre, the tertiary care clinic for rheumatologic disease in Manitoba, using a standardized script. The University of Manitoba Arthritis Centre also contacted individuals with RA in their clinic database by mail, as did one other local community rheumatology clinic.

For depression and anxiety disorders, information about the study was included in appointment letters sent to individuals referred for psychology or psychiatry consultation at tertiary care centers within the Winnipeg region. Information letters were also mailed by primary care clinics operated in partnership by the Winnipeg Regional Health Authority and the University of Manitoba and at a local primary care practice to patients with diagnoses of depression or an anxiety disorder identified using their electronic medical records. Research coordinators also presented information about the study to individuals attending psychoeducational classes for cognitive behavioral therapy held by the Psychiatry Program at the Health Sciences Centre.

## Data Collection and Measures

We collected information regarding sociodemographic characteristics, height, weight, blood pressure, physical function, cognitive function, psychiatric morbidity, and self-reported smoking status, stress, pain, fatigue, HRQOL, and work disability from all participants. Disease-specific measures tailored to each disease group were also collected. Unless otherwise specified, each of these measures was collected at study enrollment and will be collected at 3 annual study-specific assessments thereafter for a total of 4 assessments. Annual assessments will be booked within ±1 month of the enrollment date.

### *Sociodemographic Characteristics*

Using questionnaires, participants reported sex, date of birth, ethnicity, total number of years of formal education, highest level of education attained, annual household income, marital status, whether they had any children (yes vs no), and current or most recent occupation. Ethnicity was captured using the categories specified by Statistics Canada in regular surveys. Highest level of education completed was reported using the following categories: elementary school, junior high school, high school diploma or General Education Diploma (GED), college, technical/trade, university bachelor's degree, university master's degree, university doctorate, and other. Annual household income was reported as less than Can $15,000, Can $15,000-29,999, Can $30,000-49,999, Can $50,000-100,000, more than Can $100,000 or "I do not wish to answer." Responses for marital status included single/never married, married, common law, divorced, widowed, and separated. Occupation was categorized using Statistics Canada's categories as management; business, finance, and administration occupations; health occupations; occupations in education, law, and social, community, and government services; occupations in art, culture, recreation, and sport; sales and service occupations; trades, transport and equipment operators, and related occupations; natural resources, agriculture, and related production occupations; and occupations in manufacturing and utilities [40].

### *Body Mass Index*

Research assistants measured height and weight to derive body mass index ($kg/m^2$).

### *Blood Pressure*

Blood pressure and heart rate were measured in the seated position using an automatic blood pressure machine.

### *Physical Function*

We assessed lower limb function and ambulation using the timed 25-foot walk test [41-43]. This tool is considered to be a quick, reliable measure of functional capacity in older populations [44,45] and has been validated for use in MS. Upper limb function was assessed using the 9-hole peg test, a validated measure used in MS [41-43] and the Arthritis Hand Function Test for RA [46]. The timed 25-foot walk test and 9-hole peg test constitute 2 of the 3 components of the Multiple Sclerosis Functional Composite [41-43], which all research assistants were certified to perform.

### *Cognitive Function*

We selected validated neuropsychological measures to assess cognitive domains of processing speed, working memory, and verbal learning, which are often found to be affected in MS [47], RA [48], and IBD [49] as well as in depression (processing speed, working memory) and generalized anxiety disorder [50]. The measures included the Symbol Digit Modalities Test (processing speed) [51]; Wechsler Memory Scale-III Letter-Number Sequencing subtest (working memory) [52]; and California Verbal Learning Test II (verbal learning and memory) [53]. We also included the Wechsler Test of Adult Reading as a measure of premorbid intellectual functioning [54]. The extent of cognitive testing was constrained by the length of study visits and the potential for participant fatigue. Research assistants who administered the cognitive measures were trained by a psychometrician, under the supervision of a registered neuropsychologist (JDF).

### *Smoking Status*

We assessed smoking status because smoking may confound associations between psychiatric status and study outcomes, such as HRQOL [55-57]. Individuals who reported ever smoking ≥100 cigarettes were defined as ever smokers [58] and were asked to report current smoking status (not at all, some days, every day), the age at which they had started smoking, how many cigarettes they currently smoked per day, and the number of days in the past 30 days that they had smoked. Ex-smokers reported the age at which they quit smoking cigarettes and the average number of cigarettes smoked per day during the years that they smoked.

### *Comorbidity*

To assess self-reported physical and psychiatric comorbidities, we used questions derived from a survey validated for the general population [59] and for use for people with MS [60]. Participants reported whether a doctor has ever diagnosed them with any of the following conditions: high cholesterol, high blood pressure, heart trouble, disease of arteries in the legs, lung trouble, diabetes mellitus, cancer of the breast, cancer of the colon or rectum, cancer of the lung, skin cancer, other cancers, migraine, thyroid disease, lupus, osteoarthritis, osteoporosis, fibromyalgia, kidney disease, peptic ulcer disease, liver problems, irritable bowel syndrome, epilepsy (seizure disorder), depression, anxiety disorder, bipolar disorder, or schizophrenia. For any condition indicated as present, participants reported the year of diagnosis and whether it is currently being treated.

### *Psychiatric Morbidity*

We assessed psychiatric morbidity at enrollment using the structured clinical interview for DSM-IV-TR Axis I Disorders—Research version (SCID), a semistructured interview to identify anxiety, mood, and substance use disorder DSM-IV diagnoses [61], all of which were captured in this study. The interviews were conducted by graduate students in clinical psychology, nurses, and research coordinators who were trained to conduct the interviews by a registered clinical health psychologist (JRW) with extensive experience with SCID. Training included review of the SCID users guide, observing video examples of interviews, detailed review of the modules, role-playing interviews, observing an interview, and being observed when administering an interview. Team members met to review interviews regularly, and consultation with more experienced team members was available when diagnostic questions were encountered.

Participants also completed several case identification (screening) instruments for depression and anxiety (Table 1) [62-68]. These instruments were selected because they were brief, easy to self-administer, and available in the public domain for clinical purposes, making them feasible to use in clinical settings. In the general population, they share features of moderate to high sensitivity and specificity [62-68]. In addition, the "Perceived Need Question" was included, which queries patients' perceived need for treatment and can improve specificity of depression screening. Responses are "no," "yes, but not today," or "yes" [69].

### *Stress*

The Perceived Stress Scale (PSS) is widely used to measure the degree to which individuals are experiencing stress, the underlying concept being that stress is the extent to which perceived demands exceed the perceived personal resources to cope [70]. The 10-item version (PSS-10) has high internal consistency reliability and test-retest reliability, good construct validity, and predictive validity [71-74]. Scores range from 0 to 40, with higher scores indicating greater perceived stress.

### *Pain*

The Pain Effects Scale assesses pain, and it was originally developed and validated for the Medical Outcomes Study [75]. A reduced 6-item version (Modified Pain Effects Scale) was included in the MS quality of life inventory, and is valid and reliable [76,77]. Scores range from 6 to 30, with higher scores indicating greater pain.

### *Fatigue*

Fatigue was evaluated using the Fatigue Impact Scale for Daily Use (D-FIS), a brief validated instrument adapted from the Fatigue Impact Scale that includes 8 items that reflect daily fatigue [78]. Each item is scored ordinally from 0 (no problem) to 4 (extreme problem), and total scores range from 0 to 32. The D-FIS has good psychometric properties [79].

### *Health-Related Quality of Life*

We measured HRQOL using the Short Form-36, a generic measure of HRQOL validated in the general population as well as in multiple IMID populations [80-83]. The 2 summary scales capture physical HRQOL (the physical component score [PCS]-36) and mental HRQOL (the mental component score [MCS]-36). Scores on the PCS-36 and MCS-36 range from 0 to 100, with a mean of 50 and standard deviation of 10; higher scores indicate better quality of life.

### *Work Impairment*

We used the Work Productivity and Activity Impairment Questionnaire (WPAI), a 6-item questionnaire to measure work and activity impairment. Impairment due to a specified health problem during the past 7 days is reported, where higher scores indicate greater impact of health. Outcomes include percentage of work time missed (absenteeism), percentage of impairment while working (presenteeism), percentage of overall work impairment, and percentage of activity impairment due to health problems. The first 3 outcomes are calculated for persons who are working for pay, and the last outcome is calculated for all persons. In a clinical trial for IBD, the WPAI had adequate discriminative validity, reliability, and responsiveness [84]; it has good construct validity in RA [14], and it has been used in MS studies [15].

### *Disease-Specific Measures*

The disease-specific measures were chosen to describe disease activity and disease progression or functional status.

**Table 1.** Case identification (screening) instruments for depression and anxiety.

| Screening instruments for depression and anxiety | Construct | Number of items | Scoring | Published cut points | Possible range of values |
|---|---|---|---|---|---|
| Patient Health Questionnaire—brief (PHQ-2) [63] (based on the first 2 questions in this scale) | Depression (presence of) | 2 | Items scored 0-3, summed | 3 | 0-6 |
| Patient Health Questionnaire (PHQ-9) [62] | Depression (presence of) | 9 | Items scored 0-3, summed | 10 | 0-27 |
| Generalized Anxiety Disorder 7-Item Scale [64] | Anxiety, generalized (severity of) | 7 | Items scored 0-5, summed | 10 | 0-21 |
| Overall Anxiety and Severity Impairment Scale [65] | Anxiety (severity of) | 5 | Items scored 0-4, summed | 8 | 0-20 |
| Hospital Anxiety and Depression Scale [66] | Depression (severity of), anxiety (severity of) | 14 (7 for anxiety, 7 for depression) | Items scored 0-3, summed | 8, 11 | 0-21 |
| Kessler-6 Distress Scale [67] | Nonspecific distress | 6 | Items scored 1-5, summed | 19 | 6-30 (alternative scoring) |
| National Institutes of Health Patient-Reported Outcomes Measurement Information System—emotional distress depression—Short Form 8a [68] | Depression (severity of) | 8 | Items scored, summed, and then converted to T score | T-score 60 | 8-40, T score 38.2-81.3 |
| National Institutes of Health Patient-Reported Outcomes Measurement Information System—emotional distress anxiety—Short Form 8a [68] | Anxiety (severity of) | 8 | Items scored, summed, and then converted to T score | T score 60 | 8-40, T score 37.1-83.1 |

### Disease Activity

We characterized disease activity using the Powell Tuck Index (PTI) for ulcerative colitis [85], the Harvey Bradshaw Disease Activity Index (HBDAI) for Crohn disease [86], annualized relapse rate for MS, and Clinical Disease Activity Index (CDAI) [87] for RA. The PTI and the HBDAI inquire about symptoms over the previous week and are administered by research staff. The HBDAI includes a score for the presence or absence of an abdominal mass as assessed by an abdominal exam conducted by trained personnel. A score of ≥5 is considered active disease on each index. The CDAI is a composite obtained by summing 28 tender and 28 swollen joint counts and disease activity according to the patient (0-10) and the physician (0-10) [88]. It has the advantage of not requiring any laboratory tests. A score of 0-2.8 indicates remission, 2.9-10.0 indicates low activity, 10.1-22.0 indicates moderate activity, and 22.1-76.0 indicates high activity [89].

### Disease Progression

Participants reported the year of symptom onset and the month and year of diagnosis of their IMID. Dates of symptom onset and diagnosis were verified using medical records. Current disease-modifying therapies were also captured from medical records. We characterized disease phenotype and progression in IBD using the Montreal Classification [31,90], which identifies 4 key variables in Crohn disease including age of onset, disease behavior (inflammatory, stricturing, or fistulizing disease), disease location (ileal only, colon only, small bowel and colon, and upper gastrointestinal tract), and whether perineal fistulas are present or not. In ulcerative colitis, the Montreal Classification identifies age of onset and extent of disease (either rectal, left-sided, or pancolitis). For MS, we used the Expanded Disability Status Scale (EDSS) [91], which is an ordinal measure of disability based on the neurological examination. Total EDSS scores range from 0 (no disability) to 10 (death due to MS), and are derived from scores on visual, brainstem, pyramidal, sensory, cerebellar, sphincter, and cerebral functional systems, as well as an observed walk of up to 500 meters. In RA, we used the modified Health Assessment Questionnaire (mHAQ) [92,93]. The mHAQ is a patient-reported measure that assesses functional status, specifically the degree of difficulty (without difficulty, 0; with some difficulty, 1; with much difficulty, 2; unable to do, 3) to perform 8 daily activities (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities). Responses are averaged to yield scores ranging from 0 to 3. Where available, x-rays obtained at annual clinic visits will be used to determine the presence of joint erosions.

## Sample Collection

At the end of each assessment, consenting participants provided a blood sample collected by venipuncture using a straight needle into an EDTA tube and into a Paxgene (Qiagen) deoxyribonucleic acid (DNA) tube. Samples collected in EDTA tubes were centrifuged at 1500-2500 × g for 15 min at room temperature. The resulting plasma layer and buffy coat layers were aliquoted separately into 2 mL cyro vial tubes for storage at −80°C. DNA was extracted using a Paxgene DNA kit using a single tube procedure according to the manufacturer's (Qiagen) instructions and stored at −80°C.

## Data Management

Study data were managed using REDCap electronic data capture tools hosted at the University of Manitoba [94]. REDCap (Research Electronic Data Capture) is a secure, Web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry, audit

trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources [94].

### Sample Size

The required sample size for the 2 principal aims was determined as follows. For the first aim, to test the baseline association between psychiatric comorbidity and either HRQOL or work disability in each IMID group, we assumed that at least 30% of the sample will experience any psychiatric comorbidity [95-97], confounders will explain 10% of the variation in the data, a 10% difference in HRQOL (MCS-36/PCS-36), a 10-point difference in work impairment for the 2 psychiatric disorder (depression/anxiety) groups, a pooled standard deviation of 10, and alpha=.05. For longitudinal analyses, we assumed an annual attrition rate of 3% [98], an average annual rate of decline of 3% in HRQOL and work impairment, a pooled between-group variance of 10, and a pooled within-group variance of 5. On the basis of these assumptions, each IMID and psychiatric group would need a minimum sample size of 150, for a total of 750.

For the second aim, which sought to test the performance of the case identification (screening) tools for depression and anxiety as compared with the SCID in the IMID groups, we assumed a lower bounds sensitivity=0.75 and specificity≥0.85 [62,99], precision=0.15, and alpha=.05, for which the required sample size per group was 247. To detect a kappa (κ) for agreement ≥0.60 between the SCID and the screening tools, assuming alpha=.05, beta=.20, a null hypothesis of kappa≥.46, and that depression or anxiety affects ≥15% of the IMID cohort, the required sample size per group was 250.

Therefore, we sought to recruit 250 participants for each IMID group, and 150 each for the depression and anxiety disorder groups.

### Current Analysis

We summarized the characteristics of the sample at enrollment for the purpose of assessing the potential generalizability of the findings. We summarized categorical variables using frequency (percentage) and continuous variables using mean (standard deviation) or median (25th-75th percentiles). Each of the disease groups was also reviewed relative to samples in other studies of those disease groups, to consider representativeness and generalizability of the samples. Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary, NC).

### Future Analyses

We will assess the impact of changes in psychiatric status on change in these HRQOL and work ability outcomes over the 4 measurement occasions (3-year period) using generalized linear models with generalized estimating equations to account for the dependence among the repeated measurements. We will select the distribution to model each outcome using a combination of empirical (eg, ratio of model deviation to its degrees of freedom) and theoretical considerations. We will choose a correlation structure for the repeated measurements by examining the pattern of empirical correlations. The independent variables of interest will be IMID type and psychiatric status. Psychiatric status will be determined based on the SCID-determined diagnoses (at enrollment) and symptom severity based on whichever screening instrument has the best performance characteristics (as described below). Potential confounding covariates will be age, sex, disease duration, education, smoking, body mass index, physical comorbidity, and disease activity status.

On the basis of published cut points, we will compare depression and anxiety status based on the SCID and the screening instruments using sensitivity, specificity, positive predictive value, and negative predictive value. We will also use receiver operating curve analysis to understand the relationship between sensitivity and the false positive rate, which allows an optimal cut point to be assigned depending on the requirements in a specific context. We will assess internal consistency reliability using Cronbach alpha [100]. In a subgroup of ~150 participants in each IMID group, we will determine the test-retest reliability of these instruments using an intraclass correlation coefficient.

## Results

### Recruitment

Between November 2014 and July 2016, we enrolled 982 individuals. Of these, 18 were later withdrawn; 6 did not meet inclusion criteria after review of their medical records because they did not have confirmed diagnoses of IBD (3) or RA (2), or had 2 of the IMID of interest (1). A total of 11 individuals enrolled as members of the psychiatric cohort were withdrawn as they did not have a confirmed diagnosis of depression or anxiety disorder following SCID administration. Finally, 1 individual in the IBD cohort withdrew from the study and that person's data were destroyed shortly after enrollment. Therefore, the final study population included 247 participants with IBD, 255 with MS, 154 with RA, and 308 with depression or anxiety (172 with depression, 136 with an anxiety disorder as self-identified at enrollment) for a total of 964. As expected, participants were recruited from multiple sources (Table 2). A higher proportion of participants with MS were recruited through targeted contacts, reflecting the delivery of MS care in Manitoba through a single specialty clinic, whereas care for other conditions is less centralized.

**Table 2.** Recruitment sources for study participants.

| Source | Inflammatory bowel disease (N=247), n (%) | Multiple sclerosis (N=255), n (%) | Rheumatoid arthritis (N=154), n (%) | Depression/anxiety disorder (N=308), n (%) |
|---|---|---|---|---|
| Targeted email/mail[a] | 98 (39.7) | 222 (87.0) | 52 (33.8) | 59 (19.1) |
| Clinic/CBT class[b] | 133 (53.8) | 30 (11.8) | 80 (51.9) | 60 (19.4) |
| Poster (paper/electronic) | 5 (2.0) | 3 (1.2) | 10 (6.5) | 60 (19.4) |
| Tweets/Facebook/Internet | 5 (2.0) | 0 (0) | 0 (0) | 15 (4.9) |
| News article | 1 (0.4) | 0 (0) | 0 (0) | 2 (0.6) |
| Clinician referral | 0 (0) | 0 (0) | 0 (0) | 7 (2.3) |
| Word of mouth | 1 (0.4) | 0 (0) | 12 (7.8) | 18 (5.8) |
| Unknown | 4 (1.6) | 0 (0) | 0 (0) | 87 (29.2) |

[a]Some participants in the MS Clinic registry were contacted by telephone rather than by mail.

[b]Cognitive behavioral therapy (CBT) classes served as a recruitment source only for those with depression/anxiety.

Sociodemographic characteristics of the participants are shown in Table 3. Several differences were apparent across disease groups. The percentage of participants who were white varied across groups, being highest among those with IBD or MS and lowest among those with RA. We observed a female predominance in all groups, but this was least marked in the IBD cohort. Participants with depression or anxiety were more likely to be single than participants in any other group. Annual income also varied across groups, being highest in the IBD cohort.

## Individual Immune-Mediated Inflammatory Diseases Cohorts

As has been observed in other IBD cohorts, participants were more likely to be females than males (Multimedia Appendix 1) [101-103]. The proportion of individuals reporting white background was higher in this study than that of a national US study [101], but lower than that seen in a previous Manitoba study [102]. The level of education was generally high, consistent with other studies [101-103]. Participants in the present MS cohort were older than those in 3 other Canadian MS study cohorts [104,105], and a slightly higher proportion of females was observed also (Multimedia Appendix 2). The age at MS onset was slightly lower in this study than in the other cohorts. The proportion of female participants in the present RA cohort was higher than that reported in other RA cohorts, and the proportion with white ethnicity was lower (Multimedia Appendix 3) [106-108]. The second most common ethnicity in our cohort was First Nations and other Indigenous ethnicities (not specified).

The proportion of women in the depressed/anxiety disorder cohort was higher than that in a previous cohort from the Canadian Community Health Survey—Mental Health (CCHS) in 2012 (Multimedia Appendix 4). The percentage with more than a high school education level was similar in both cohorts. The proportion who smoked was lower in our cohort than in the CCHS cohort.

**Table 3.** Cohort demographics stratified by disease group.

| Characteristics | Total (N=964) | Inflammatory bowel disease (N=247) | Multiple sclerosis (N=255) | Rheumatoid arthritis (N=154) | Depression/anxiety disorder (N=308) | *P* value |
|---|---|---|---|---|---|---|
| Age in years, mean (SD[a]) | 49.2 (14.2) | 47.4 (14.8) | 51.1 (12.9) | 59.5 (11.7) | 43.9 (13.0) | |
| **Sex, n (%)** | | | | | | <.001 |
| Male | 235 (24.4) | 92 (37.2) | 47 (18.4) | 24 (15.6) | 72 (23.5) | |
| Female | 729 (75.6) | 155 (62.7) | 208 (81.6) | 130 (84.4) | 235 (76.6) | |
| **Ethnicity, n (%)** | | | | | | |
| White | 786 (81.9) | 210 (85.4) | 217 (85.4) | 114 (74.5) | 245 (79.8) | .01 |
| Other | 174 (18.1) | 36 (14.6) | 37 (14.5) | 39 (25.5) | 62 (20.2) | |
| Missing | 4 | 1 | 1 | 1 | 1 | |
| **Education, n (%)** | | | | | | .06 |
| Elementary school | 5 (0.5) | 0 (0) | 1 (0.4) | 3 (1.9) | 1 (0.3) | |
| Middle school | 44 (4.5) | 8 (3.2) | 9 (3.5) | 11 (7.1) | 16 (5.2) | |
| High school or GED[b] | 268 (27.8) | 68 (27.5) | 78 (30.6) | 37 (24.0) | 85 (27.6) | |
| College | 253 (26.2) | 51 (20.6) | 72 (28.2) | 45 (29.2) | 85 (27.6) | |
| Technical or trade | 107 (11.1) | 32 (13.0) | 29 (11.4) | 19 (12.3) | 27 (8.8) | |
| Bachelor’s degree | 215 (22.3) | 60 (24.3) | 56 (22.0) | 27 (17.5) | 72 (23.4) | |
| Master’s degree | 54 (5.6) | 21 (8.5) | 7 (2.8) | 10 (6.5) | 16 (5.2) | |
| Doctoral degree | 18 (1.9) | 7 (2.8) | 3 (1.2) | 2 (1.3) | 6 (1.9) | |
| **Annual income, n (%)** | | | | | | <.001 |
| Less than Can $15,000 | 100 (10.4) | 14 (5.7) | 20 (7.8) | 19 (12.3) | 47 (15.3) | |
| Can $15,000-29,999 | 88 (9.1) | 14 (5.7) | 24 (9.4) | 19 (12.3) | 31 (10.1) | |
| Can $30,000-49,999 | 162 (16.8) | 29 (11.7) | 37 (14.5) | 32 (20.8) | 64 (20.8) | |
| Can $50,000-100,000 | 341 (35.4) | 104 (42.1) | 99 (38.8) | 48 (31.2) | 90 (29.2) | |
| More than Can $100,000 | 189 (19.6) | 68 (27.5) | 47 (18.4) | 25 (16.2) | 49 (15.9) | |
| I do not wish to answer | 84 (8.7) | 18 (7.3) | 28 (11.0) | 11 (7.1) | 27 (8.8) | |
| **Marital status, n (%)** | | | | | | <.001 |
| Single or never married | 217 (22.5) | 56 (22.7) | 30 (11.8) | 20 (13.0) | 111 (36.0) | |
| Married or common law | 569 (59.0) | 160 (64.8) | 182 (71.4) | 93 (60.4) | 134 (43.5) | |
| Divorced or separated | 150 (15.6) | 24 (9.7) | 39 (15.3) | 31 (20.1) | 56 (18.2) | |
| Widowed | 28 (2.9) | 7 (2.8) | 4 (1.6) | 10 (6.5) | 7 (2.3) | |

[a]SD: standard deviation.

[b]GED: General Education Diploma.

## Discussion

This paper presents the study rationale, describes study procedures, and characterizes the cohort enrolled. The ultimate goal of the study was to compare and contrast the impact of psychiatric comorbidity on outcomes in IMID that affect different organ systems but share the issues of immune dysregulation and inflammation. We hope to gain more specific insights into the role of psychiatric comorbidity in IMID, with the aim of improved care for individuals affected by IMID. These analyses will be conducted once the cohort completes follow-up.

When selecting the measures for this study, we sought standardized measures appropriate for the domains of interest. Where possible, we chose instruments with good criterion and construct validity, and high reliability, which had been demonstrated in one or more of the disease groups of interest. If this was not possible, we favored validated measures used in Canadian national data collection efforts to offer the opportunity for comparisons of this cohort with national cohorts.

### Participants

Our recruitment strategy precluded the determination of a participation rate, as it was designed to reach potential participants from a broad range of settings using general and

targeted strategies. For all of the groups except for the RA group, we were able to recruit the desired number of participants; the time period for recruitment was limited by the need to complete 3 years of follow-up by the end of the funding period. It has been noted that participation rates in cohort studies and surveys have declined over the last 3 decades [109]. Several factors have been suggested to contribute to this decline [109]. These include an increasing array of research and marketing studies, a decrease in volunteerism, and the complexity of study demands. The latter is likely to be a particular issue in our study given the length of study visits, which range from 1.5 to 3 hours depending on the disease group, and the requested duration of participation (3 years). Nonetheless, our sample size remains large enough to meet the study's main objectives.

Retention of study participants will be critical, and we aimed to minimize attribution by employing several strategies that have been successful in other studies [110,111]. First, participants are offered gift cards to recognize their contributions to the study at each study visit as this has been shown to improve response rates [112]. Second, retention is carefully tracked. All participants receive reminder phone calls or emails for study appointments depending on their preference. Study coordinators are flexible about rescheduling appointments and follow-up with all participants who miss appointments. Third, a study newsletter is distributed semiannually. The newsletter provides information about study team members, progress, and findings, as well as information about relevant research news and wellness. We hope that annual face-to-face contact will also aid retention. Finally, when participants move out of province or become too ill to attend study visits, they are offered the opportunity to maintain participation by completing some of the study assessments such as questionnaires by telephone or mail.

The characteristics of participants enrolled in our study are similar to those enrolled in other studies after accounting for differences in how variables were measured, supporting the representativeness of the sample across the disease groups. However, some differences with respect to other cohorts and the general IMID populations of interest are worth noting. Participants in the MS cohort were older than those in some other cohorts, likely reflecting recruitment efforts aimed at capturing the full spectrum of individuals with MS. The proportion of participants with MS who were women was slightly higher than expected, even when considering that women are affected by MS two to three times more often than men [113]. Similarly, the proportion of individuals with RA or depression/anxiety disorder who were women was also somewhat higher than expected. The proportion of individuals reporting white race/ethnicity was lower in our RA cohort than that observed in other cohorts, but this may better reflect the local demographics, as there is a large First Nations (Indigenous) population in Manitoba [114], and there is a high risk of RA in this group. There was a very high proportion of participants with RA who were actively being treated with disease-modifying antirheumatic drugs, potentially reflecting oversampling of participants from a tertiary care center relative to community sampling. The level of education in all recruited cohorts was relatively high.

## Limitations

Selection bias is a potential limitation of any study. As reviewed elsewhere [109], certain demographic characteristics are associated with participation in research. Women are more likely to participate in research studies than men. Findings regarding age are inconsistent, as are findings regarding race/ethnicity. Individuals with higher levels of education and higher socioeconomic status are more likely to participate. However, in studies focused on a particular health condition or exposure, health status and relevance of the study subject to the potential participant also influence participation and may modify these demographic patterns [109].

In addition to potential selection biases, attrition may occur despite the use of appropriate retention strategies due to death, loss to follow-up, or other reasons. As noted, we did not achieve the desired sample size for the RA cohort, and this will reduce statistical power for RA-specific analyses. To minimize participant burden, we included only a single measure of pain and of fatigue, although these are multidimensional concepts that may be better evaluated with multiple instruments that capture different dimensions. We did not capture all potential confounders such as the life events (eg, pregnancy, menopause) that may be unique to subgroups of the study population and that may be associated with disease activity and psychiatric status in IMID [115-117].

## Conclusions

Nonetheless, this study has several strengths including the establishment of representative cohorts of those with IMID and depression and anxiety disorders, which will support comparative work, as well as careful attention to retention and stakeholder engagement. We expect this comprehensive prospective longitudinal study to provide valuable new knowledge about the impact of psychiatric comorbidity on IMID, including on outcomes important to affected individuals and society, such as HRQOL and work disability. We also expect that this study will contribute to improved diagnosis of psychiatric comorbidity by identifying validated instruments which can be used in clinical practice. For health care providers, an understanding of the relationships between psychiatric disorders, symptoms of pain, and fatigue and outcomes should encourage more attention to the identification and treatment of psychiatric disorders and change the approach to disease management to improve outcomes in IMID. The analytical methods used will support future research regarding patient-reported outcome measures. Focusing on three IMID with similarities and differences will support the generalizability of our findings to other IMID and provide policy makers with the evidence base to make decisions regarding health services for IMID broadly.

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## Conflicts of Interest

RAM has conducted clinical trials for Sanofi Aventis. CAH has research funds for unrelated studies from UCB Canada. JS holds stocks in Johnson and Johnson. CNB has consulted Abbvie Canada, Ferring Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada, and Napo Pharmaceuticals and has consulted Mylan Pharmaceuticals. He has received unrestricted educational grants from Abbvie Canada, Janssen Canada, Shire Canada, and Takeda Canada. He has been on speaker's bureau of Abbvie Canada, Ferring Canada, and Shire Canada. All other authors have no conflicts of interest to declare.

## Multimedia Appendix 1

Characteristics of participants with inflammatory bowel disease (IBD) and those of participants in other IBD cohorts.

[PDF File (Adobe PDF File), 30KB - resprot_v7i1e15_app1.pdf ]

## Multimedia Appendix 2

Characteristics of participants with multiple sclerosis (MS) and those of participants in other Canadian MS studies.

[PDF File (Adobe PDF File), 26KB - resprot_v7i1e15_app2.pdf ]

## Multimedia Appendix 3

Characteristics of participants with rheumatoid arthritis (RA) and those of participants in other RA cohorts.

[PDF File (Adobe PDF File), 30KB - resprot_v7i1e15_app3.pdf ]

## Multimedia Appendix 4

Characteristics of participants with depression or anxiety disorder and those of participants in other depression or anxiety disorder cohorts.

[PDF File (Adobe PDF File), 25KB - resprot_v7i1e15_app4.pdf ]

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## Abbreviations

**ACR/EULAR:** American College of Rheumatology/European League Against Rheumatism
**CCHS:** Canadian Community Health Survey
**CDAI:** Clinical Disease Activity Index
**D-FIS:** Fatigue Impact Scale for Daily Use
**DNA:** deoxyribonucleic acid
**EDSS:** Expanded Disability Status Scale
**GED:** General Education Diploma
**HBDAI:** Harvey Bradshaw Disease Activity Index
**HRQOL:** health-related quality of life

**IBD:** inflammatory bowel disease
**IMID:** immune-mediated inflammatory diseases
**MCS:** mental component score
**mHAQ:** Modified Health Assessment Questionnaire
**MS:** multiple sclerosis
**PCS:** physical component score
**PSS:** Perceived Stress Scale
**PTI:** Powell Tuck Index
**RA:** rheumatoid arthritis
**SCID:** structured clinical interview for DSM-IV-TR Axis I Disorders—Research version
**SD:** standard deviation
**WPAI:** Work Productivity and Activity Impairment Questionnaire

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Protocol

# The Role of Ethnicity and Environment in the Regulation of Response to Sensory Stimulus in Children: Protocol and Pilot Findings of a Neurophysiological Study

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## Abstract

**Background:** The ability to regulate the response to sensory stimuli has been associated with successful behavioral patterns necessary for daily activities. However, it is not known whether a child's ethnicity and environment can influence autonomic regulatory mechanisms.

**Objective:** This study aims to explore the role of ethnicity and environment in the regulation of responses to sensory stimuli in children.

**Methods:** In this study, we intend to recruit 128 children from different ethnic groups or environment contexts as follows: (1) 32 typically developing Chinese children living in Hong Kong; (2) 32 typically developing Filipino children living in Hong Kong; (3) 32 typically developing Filipino children who are living in urban areas; and (4) 32 typically developing Filipino children who are living in rural areas in Philippines. Autonomic activity (heart rate variability [HRV] and electrodermal activity [EDA]) will be measured and recorded using Polar H2 heart rate monitor and eSense GSR skin response sensor. Autonomic activity (HRV-low frequency, HRV-high frequency, and EDA) at different conditions between pairwise groupings will be tested using multivariate analysis of variance (MANOVA). All significant levels will be set at $P \leq .05$.

**Results:** We present the research protocol of this study, as well as a short discussion of the preliminary findings from our pilot data, with consequent power and sample size analysis that informs the appropriate sample needed to test our hypothesis.

**Conclusions:** This study will increase the understanding on the role of individual differences related to a child's ethnicity and environment in the regulation of response to sensory stimuli. The findings of this research may further shed light on the evaluation and treatment planning for children across and within cultures.

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**KEYWORDS**

ethnicity; environment; children; autonomic nervous system; parasympathetic nervous system; sympathetic nervous system

## Introduction

### Background of the Study

The response to sensory stimuli can be defined as an individual's reactivity to sensory inputs [1]. Sensory information from the environment is processed and regulated by the individual to support behaviors in everyday situations and development [2,3]. The regulation of response to sensory stimuli entails adjustments of internal measures as a reaction to external demands. Difficulty in the regulation of response to sensory stimuli has been suggested to be prevalent in 40-80% of children with disabilities and in as much as 5-16.5% among typically developing children [4]. The literature that examines the regulation of response to sensory stimuli seems to largely use behavioral and physiological measures [5]. Preliminary evidence suggests that atypical sensory-related behaviors are related to underlying physiologic autonomic regulation [5-9]. Individual differences (ie, age, gender, ethnicity, environment, etc) have been suggested to impact both behavioral and physiological responses [10]. In this research, we examine the role of ethnicity and environment in the regulation of response to sensory stimuli in children using a neurophysiological framework, conceptualized to reflect the information-processing model, which assumes that sensorial information from the environment is subject to underlying physiological processes [11,12].

The theory of allostasis and the allostatic load model is intended to be used in this research to theorize the role of ethnicity and environments in the regulation of response toward sensory stimulus. Foundations of the theories on allostasis were supported by evidence from the studies of McEwen [13,14], Sterling and Eyer [15], and McEwen and Wingfield [16]. In allostasis, alteration of the regulatory parameters (eg, by increasing or decreasing the set point of a homeostatic physiological mechanism) allows a person to adapt to environmental challenges and can create a new baseline to maximize the individual's responses [17,18]. Individual differences shape how individuals respond to external challenges [10,13]. Such individual differences have been categorized to involve expressive-dependent information appraisal and biological embedding [10,13,19]. Expressive-dependent information appraisal suggests that one's life history, which includes environmental, cultural, social, or economic backgrounds, shaped our abilities to make sense of situations and instilled in us a set of codes that determine how we react or appraise a situation. In this research, expressive-dependent information is conceptualized to be the influences related to one's environment, due to the geographic niche or the physical landscapes to which a child has been exposed to. Biological embedding is related to the physiological expression of genetic traits exemplified by our body's condition [10,13]. These individual differences can account for variations in how individuals successfully adapt to the incessant stimulation or challenges in the environment. In this research, these biologically embedded traits are conceptualized to be the influence brought about by a child's ethnic origins.

The mechanisms underlying the allostatic response draw from physiological perspectives of how the body responds to and regulates itself from external challenges [10,13,17]. In response to environmental challenges (ie, stress, sensory information), mediators of allostasis effected by multiphysiological systems (ie, hormones, parasympathetic nervous system [PNS], sympathetic nervous system [SNS]) are activated in different modes of control (ie, increase, decrease, no change) to meet the needed demands [20]. Although allostasis is responsible for short-term adaptation, survival, and homeostasis, according to McEwen and Wingfield [16], it can potentially produce permanent changes in a person after prolonged exposures termed as allostatic load.

Ethnicity refers to the biomedical origins and genetic similarities among individuals [21-23]. Ethnicity represents biologically embedded genetic traits and its expressions that have been suggested to influence behavioral and physiological responses related to adaptation [19]. A child's response to sensory information within his environment seems universal and stable across ethnicities. Royeen and Mu [24] implicated no significant differences in the sensory responses between North American and multiethnic European children situated in the United States and Germany, respectively. Conversely, other researchers counter-argued and found influences of ethnicity on children's regulation of sensory stimuli using behavioral measures [2]. Caron et al [25] obtained some differences on the responses to sensory information between North American and Israeli children in their responses to sensory experiences. Although Tirosh et al [26] suggested that ethnicity can account for significant differences in the regulation of sensory response between 2 different ethnic groups of children living in the same environment, older children from different ethnic-cultural groups exhibit differences in regulatory responses. The evidence on the influence of ethnicity on the regulation of response to sensory stimuli appears to be inconsistent and inconclusive. Furthermore, it is unclear whether such differences are influenced by inherent ethnicity or the environment in context. In this research, we look at the regulation of response to sensory stimuli among a group of children from different ethnicities, while controlling for environment variables. Specifically, to represent such ethnic differences, we recruit Hong Kong-Chinese and Filipino school-aged children living in Hong Kong and the Philippines, respectively.

The environment is the geographic range where a group of individuals exists [27]. Expressive-dependent information appraisal suggests that the responses of an individual are shaped by similar sociocultural traits and experiences shared by a category of people that set apart one group of people from another, who are embedded within similar geographic environments [10,13,19]. Similar sociocultural traits and experiences embedded within comparable geographic environments result in behavioral responses that are shared by a category of people that set apart their group from another [28,29]. These factors within the geographic environments have been implicated to account for differences or associations between individuals from that of a different one [30]. Thus, the geographic environment, such as the country of abode, is likely to influence the response to sensory stimuli among children, suggesting that the geographic environment where a child develops may have the ability to override ethnic influences [31].

The experiences encompassing within the child's environment, which include the sensory events and stimuli, possibly shape their responses consequently. Previous researchers suggested that differences in beliefs, practices, behaviors, culture, parenting practices, physical landscapes, and sociocultural and economic aspects can explain these differences [10,13,19,28-31]. However, the experiences related to the sensory information within a particular geographic environment may be different. Furthermore, there is a dearth of evidence that further supports this notion. In this research, we conceptually define environment on 2 levels, that is, geographic environments and physical environment, and explore their influence on a child's ability to regulate sensory stimulus.

The physical environment is defined herein as the objective characteristics of the physical context related to habituation and gradients of man-made or natural structures and components [32]. This is exemplified in the dichotomous characteristics of urban and rural settings, further operationalized by Perloff [33]. An urban physical environment describes a developed metropolitan setting characterized by a density of man-made human structures (ie, houses, buildings, bridges, railways). On the other hand, a rural environment may be viewed as an open strip of natural environment (ie, agricultural, coastal, mountainous) inhabited by fewer humans with lesser man-made infrastructures. The physical environment can greatly impact how individuals regulate responses to the external world [34]. In comparing urban and nature environments, it was found that the latter produces less physiological arousal and attentional demands [35,36]. Among Taiwanese children, Lin et al [37] proposed that urban and rural children have different performances in the regulation of responses to sensory stimuli. Tirosh et al [26] similarly found urban-rural differences and specifically suggested sociocultural influences (ie, maternal education, cultural differences) as a moderating factor in the regulation of response to sensory stimuli among rural-dwelling children. On the other hand, a different group of researchers suggested that the physical features of the dwelling spaces of children can facilitate better regulation of response to sensory information among urban-dwelling children as reflected by significantly superior perception, perceptual-motor, and cognitive performance [38]. The physical characteristics of the living environment, which include the noise level, visual stimuli related to infrastructures or nature landscapes, pollution, topography, and space, to name a few, have been previously suggested to contribute to possible differences [10,13,19,34-37]. At this time, it is uncertain whether the variation of responses toward sensory stimulation in people of the same ethnicity across regions is related to their physical environment or other factors.

The findings of previous researchers on the influence of ethnicity and environment appear inconclusive. One caveat of previous studies is that the measurement of responses toward the stimuli was not under a controlled environment. The environmental conditions when one experiences sensory stimulation may be varied between levels of the environment (ie, physical space, sound environment, visual stimuli in the environment). In this research, we classify environments on 2 levels: geographic and physical environments. Geographic environments refer to the geographic range where a group of individuals exists [27]. The physical environment is defined herein as objective characteristics of the children's physical context related to habituation and gradients of man-made or natural structures and components represented by urban and rural settings in this research [32]. Thus, the findings of previous studies may have a limitation on explaining the influences of ethnicity and environment. Another limitation of previous studies concerns their methodology, which has adopted mainly behavioral measures as measuring instrument. Behavioral outcomes, whether through clinical observations or parent reports, are unable to provide precise information about the regulation of response to sensory stimuli [5]. Previous research has found initial evidence that associates SNS [39] and PNS autonomic functions [40] to the regulation of response to sensory stimuli. Indexing physiological responses can offer a more sensitive and objective measure of the underlying mechanisms of internal state regulation in response to external sensory challenges [41]. A child's environment is contextualized within the sensory events and stimuli that are embedded in it, which makes it a variable of interest. To examine the influence of ethnicity and environments on the regulation of response to sensory stimuli, objective neurophysiological outcomes are needed. In this research, the authors examine the regulation of PNS and SNS autonomic measures in response to sensory stimuli among a group of children.

Autonomic regulation refers to the underlying physiological mechanisms mediated by the autonomic nervous system (ANS) and its parasympathetic and sympathetic branches that support regulation of internal responses in the face of external demands to maintain homeostasis [42]. Empirical evidence that supports autonomic regulation of response to sensory stimuli stemmed out from a series of research that hypothesizes differences in PNS or SNS functions in response to a laboratory paradigm that presents a series of sensory stimuli among children with and without known problems in the regulation of response toward sensory stimuli. In a systematic review that explores the extant literature in the behavioral and physiological regulation of response to sensory stimuli among children, Gomez et al [43] have suggested methodological inconsistencies. For instance, the prevalent use of a single autonomic physiological measure was commonly observed. The group of Schaaf [40,44,45] has suggested PNS functions, specifically the cardiac vagal tone, whereas Miller's group [46-48] worked on the SNS functions using electrodermal activity (EDA) as an autonomic measure in their research. Even when the same autonomic measure was used, specific parameters and its operational definition appear to vary across studies. However, the use of a single physiologic measure to represent the complexity of autonomic functions should be approached carefully. Thus, researchers need to refocus the choice of autonomic measure to represent the dynamic and interrelated allostatic relationship between the PNS and SNS [45]. Another observation noted was on the choice of laboratory paradigm across various studies. The Sensory Challenge Protocol (SCP), as initially described by Miller and colleagues [46], is a child-friendly laboratory paradigm suggested to be a reliable measure to quantify a child's physiologic regulation of response to multisensorial stimuli and has been recommended for its ability to reliably quantify physiologic regulation of response to sensory stimuli [49].

However, the use of a multidomain sensory paradigm may not always be suitable. Our recent literature review urges the use of modality-specific measurements to improve the sensitivity of measures [43]. The auditory modality seems to offer a more sensitive stimulus to elicit physiological responses [6,50]. In any case, studies that refer to SCP must modify with caution and decisions must be rationale driven, supported with evidence from the physiological literature. Additionally, autonomic activity is influenced by external environmental factors related to temperature, humidity, and noise level, among others [51-53]. In this study, we use an auditory paradigm to represent external challenges to elicit a multiphysiological response as indexed by the SNS and PNS allostatic mediators. Furthermore, environmental factors during the experimental procedures are discretely controlled during the laboratory paradigm experiment and explicitly reported.

Measures for ANS could provide an objective measure of internal state and the capacity in regulation. In this study, heart rate variability (HRV) and EDA will be measured. Both measures are recommended to be safe, efficient, and noninvasive and objective measures of autonomic activity. HRV has been considered as a promising marker for autonomic activity [51] and has been an increasing outcome option in providing insight into individual differences in autonomic response [41]. HRV indices of low frequency (LF) and high frequency (HF) bands represent the activity of SNS and PNS, respectively. Because HRV can measure both SNS and PNS simultaneously, this study will use HRV as one of our measures. Nevertheless, it has been argued whether the value of LF is a pure measure of SNS functions [52]. Therefore, other than HRV, EDA will also be a supplementary measurement in this proposed research. EDA is a well-recognized sensitive indicator of SNS activity and has been used in identifying physiologic activities related to sensory stimuli responses [53]. Considering the nature of data processing, the measurement of HRV and EDA is suitable for an experiment using block design as in this proposed study.

Sensorial input from the external environment is regulated through neurophysiological mechanisms where reactivity is determined, conventionally, in the form of adaptive responses. The ANS response is conceptualized in this research to include the child's physiological capacity to receive sensory information, react to such information, and recover thereafter. The capacity to receive sensory information can be represented by the resting baseline (sometimes called as resting, basal, or baseline) condition of the ANS activity and is indexed to establish basal levels to which changes in experimental conditions can be referred to [54-56]. The doctrine of autonomic constraint, as initially proposed by Berntson et al [20], suggests that the ANS activity capacity of magnitude change depends on the set starting point. This starting point, as represented by the resting autonomic functions of PNS and SNS, may be involved in regulation of responses. Exposure to sensory stimuli entails physiological reactions from ANS, which has been previously suggested to be the first system to respond to external challenges. This is characterized by the physiological reactivity during the stimulation condition where patterns of magnitude changes from resting baseline conditions to the point of stimulus presentations are referred to [54-56]. During stimulation conditions, the ANS function levels are measured, but other measures are likewise suggested, such as the mean difference between values at the stimulation and resting baseline conditions [57] or the magnitude of change [58]. The recovery condition is roughly described as the temporal point at which experimental stimulation ceases and conditions similar to the resting baseline conditions are used. To an extent, this condition can indicate adaptability of the child after stimulation. In this research, the concept of allostasis is used to better explain the adaptation that is manifested during the recovery condition. Allostasis allows adapting one's self to the changes in their environment [59] through autonomic responses that can be facilitated by mediators of allostasis.

ANS is the first physiological axis to be activated in response to an environmental challenge. Mediators of allostasis can include heart rate, respiratory rate, blood pressure, cardiac output, and EDA [60,61]. The activity of allostasis mediators is integrated and cross-regulated and reflects components of a single functional system even with anatomical and physiological differences [62-64]. Thus, regulatory mechanisms involved in the allostatic process are described as a sequential or synchronized event between different mediators [65,66]. However, previous research seems to index singular mediators (ie, PNS or SNS only) of allostasis and may not reflect the inherent nature of how subsystems are interrelated with each other. We apply such concepts in this research by looking at the multivariate combination of HRV and EDA to represent allostasis, the mechanism related to the regulation of response toward sensory stimulus in children. The allostatic load is used to represent the influence of ethnicity and environments among the groups of children recruited in this study.

Sensory information from the environment is processed and regulated by the individual to support behaviors in everyday situations and development. The concept of allostasis suggests that adaptation to external demands entails internal regulation of physiological parameters. Individual differences shape how individuals respond to external challenges. Such individual differences have been categorized to involve expressive-dependent information appraisal and biological embedding. Ethnicity represents a proxy measure of biologically embedded genetic traits that differentiates one ethnic group from another (ie, Chinese, Filipino). The environment represents 2 levels of experience-dependent information based on (1) geographic environments, which take on the geographic niche of habituation represented by the country of living (ie, Hong Kong and the Philippines), and (2) physical environment, which explains the physical landscape features of the environmental habituation represented by urban and rural settings. In this research, we recruit children from similar ethnic origins (ie, Filipino) living in different geographic environments (ie, Hong Kong and the Philippines) and physical environments (ie, urban and rural Philippines). Neurophysiological measures of HRV and EDA that represent the interrelated activities of PNS and SNS will be primarily measured, alongside usual behavioral measures of how children adaptively regulate responses to sensory stimuli.

### Research Question and Motivation

The motivation for this research stems from the dearth of evidence in the literature that supports the role of individual differences in the regulation of response to sensory stimuli in children that use neurophysiological outcomes. Our research question, therefore: *do ethnicity and environments influence the regulation of response to sensory stimuli in children?* The findings in this research can have implications in cross-culturally appropriate evaluation measures and intervention procedures that are relevant to the regulation of responses to sensory stimuli.

### Research Hypothesis

This research study is an exploratory inquiry on the role of ethnicity and environments in the regulation of response to sensory stimuli among children by using neurophysiological outcome measures. Supported by behavioral studies and the concept of allostasis as applied in this research, the researchers hypothesize that there is significant difference in the regulation of response to sensory stimuli in (1) children from different ethnicities living within the same geographic and physical environments, (2) children from similar ethnicities and physical environments living in different geographic environments, (3) children from different ethnicities and geographic environments living in similar physical environments, and (4) children from similar ethnicities and geographic environments living in different physical environments.

### Research Aims

Considering the available evidence in the current literature and our perceived gaps in the knowledge related to our topic, in this study, we study the role of ethnicity and environment in the regulation of response to sensory stimuli among children from a neurophysiological perspective by applying the theory of allostasis. We aim to explore differences in the regulation of response to sensory stimuli in children through their ethnicity (as proxy measure of genetic influence) and environments (as a general measure of beliefs, practices, behaviors, culture, parenting practices, physical landscapes, and sociocultural and economic aspects). Specific to this manuscript, the authors also aim to determine the ample sample size needed for the main study, based on the pilot data presented.

## Methods

### Ethical Considerations

Ethical approval was obtained from the Hong Kong Polytechnic University, Human Subjects Ethics Sub-committee (Hong Kong, SAR), with reference number HSEARS20150316001, and from the University of Santo Tomas-College of Rehabilitation Science (Philippines) with protocol no: FI-2015-02. Before the data-gathering procedure, assent forms and parental consent forms will be distributed to the participants of the study and their respective parents. Whenever the discomfort could not be tolerated by the child, the testing procedure was stopped.

### Participants

Using a cross-sectional study design, this study compares the autonomic activity in different experimental conditions (resting baseline condition, stimulation condition, and recovery condition) among 4 groups of participants, comprising 2 groups of typically developing children, (1) from different ethnicities (Chinese children in Hong Kong, Filipino children in the Philippines-Urban area); (2) from different geographic environments (Filipino children in Hong Kong, Filipino children in the Philippines-Urban area); (3) from different ethnicity and geographic environments (Chinese children in Hong Kong and Filipino children in the Philippines-Urban area); and (4) from different physical environments (Philippines-Urban area, Philippines-Rural area). Participants will be typically developing boys and girls, aged 7-12 years with no known developmental, neurological, or medical condition. The sample size of n=32 for each group was initially estimated based on the mean change of ANS indices of a previous study with similar but not the same experiment [67] by using the effect size of 0.8 for group differences with the alpha level at .05.

### Assessments and Measures

#### *Behavioral Measures*

To measure a child's behavioral patterns in response to sensory stimulus in his daily activities, the original Sensory Profile [2] and Chinese Sensory Profile [68] are used. The original Sensory Profile, which was developed and validated by Dunn [2], is a 125-item questionnaire that is completed by the caregiver. The Chinese Sensory Profile is a 100-item parent-report measure used among children and uses the same rating scale as the original one. We extracted the similar items from these 2 versions; the computed total and subscale scores will be subjected to intraclass correlation coefficient computation later on. The Sensory Profile has been used in both normative and clinical population in screening for sensory modulation disorders. Higher scores indicate lesser sensory behavior issues, whereas lower scores, typically seen in clinical populations, suggest the prevalence of sensory issues. Because the recruited participants in this study are assumed to be typically developing, statistical analysis may be confounded. We will further use other behavioral measures that can represent behavioral responses. Temperament and resilience were chosen, as this gives unbiased composite scores from which we can ascertain whether sensory behavior responses are deemed to be issues or just a trait pattern.

To measure temperament, the Temperament in Middle Childhood Questionnaire [69] and Early Adolescent Temperament Questionnaire [70] will be used. Both are psychometrically sound measures that are answered by parents to describe their children's traits [70,71]. We will use the translated and validated Chinese version (personal communication by Samuel Putnam, 2015) for the relevant populations. Three factors will be used in the group analysis: negative effect, surgency, and effortful control.

To measure resilience, the Child and Youth Resilience Measure (CYRM) [72], which was established through a process of interviews with youth and adults in countries around the world, was completed by the participants' parents. Previous research has suggested that ethnicity and environmental experiences influence the development of resilient behaviors [73,74] and that it is likely moderated by autonomic activity [75-77]. We included resilience as a behavioral outcome measure to

determine whether group differences in autonomic activity across conditions can be explained by our main dependent variables (DVs, ie, ethnicity, environment), or other factors, for which we may try to control. This research uses the 28-item (>10 years of age) or the 26-item (5-9 years of age) Person-Most-Knowledgeable questionnaire version, which was developed and validated by Ungar and Liebenberg [78]. The similar items between the 2 versions will be used for analysis. Although CYRM is originally in English, a translated Chinese version was recommended and provided by the authors and was used among Chinese participants in this research (personal communication, Linda Liebenberg, 2015).

### *Neurophysiological Measures*

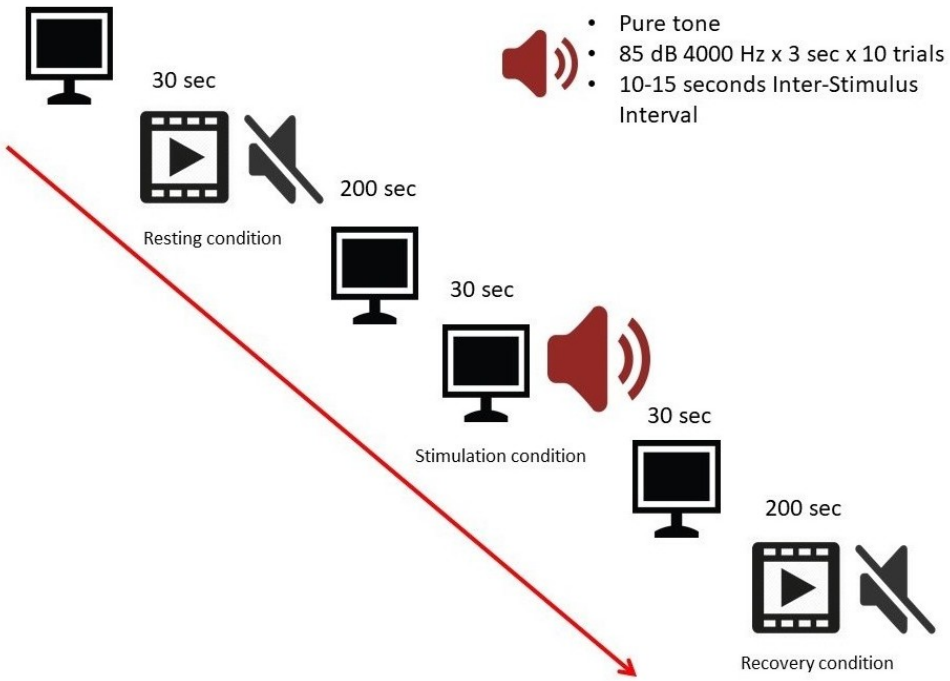
HRV enables this research to look at the activities of PNS, SNS, and their interactions across different experimental conditions (ie, resting baseline, stimulation, recovery conditions). For this study, Polar H2 Heart Rate Monitor (Polar, Finland) is used to measure HRV at 5 kHz sampling rate. There is some evidence that supports the use of Polar heart rate monitors as a valid instrument to measure HRV [79], and ultimately follow the set guidelines for HRV measurement and research [51].

EDA is an autonomic measure of SNS. Because LF bands of HRV have been contested as a true measure of SNS activity, EDA is used as an adjunct measure in this research. The eSense Skin Response-GSR sensor (Mindfield, Germany) measures skin conductance level (SCL) and response (SCR) with a sampling rate of 5 Hz and a resolution of 18 bit, using direct current. The device performs exosomatic measurement with a direct current of 0.50 V through two 5-mm silver-silver chloride (Ag/AgCl) electrode. Although fairly new, the specifications of eSense meet the general publication recommendations for EDA research [52,53].

## Procedures and Paradigm

The experimental protocol used in this part of the study is adapted from SCP, first employed by Miller et al [46], with a few modifications based on a systematic review by Gomez et al [43]. Figure 1 presents the experimental paradigm used in this study. Instead of using various multisensory stimuli, we opt for an auditory stimulus to represent external challenges to the allostatic response. Furthermore, we use 3 conditions, instead of the original resting baseline and stimulation conditions. A 3-min resting baseline period is used to allow sufficient data time points necessary for analysis of autonomic responses (HRV-HF [normalized units (n.u.)] and LF (n.u.); EDA-SCL) [51-53]. During this time, a silent cartoon movie is shown to the child for 200 seconds. At the condition of sensory stimulation, the screen turns blank and the participant receives a block of passive auditory sensory stimulation (a block of 10 trials of a 4 KHz pure tone at 85 dB; each trial lasting for 3 seconds) with a pseudorandomized interstimulus interval of 10 to 15 seconds to avoid adaptation to stimuli. The auditory stimulation condition lasts for approximately 160 seconds. The use of a pure tone is another modification of this research, used from the original fire engine sound, to reduce any emotional responses to familiarity with the stimuli. The loudness is reduced from the original 95 dB to 85 dB to ensure that the intended physiological response is recorded and no other internal events related to louder auditory stimuli [80]. At the recovery condition, the same silent cartoon movie is played for 200 seconds. Previously, the recovery condition was not a part of the original SCP; however, it has been added and adapted in more recent literature. Such recovery conditions may represent physiological regulation related to adaptation, further described in the concept of allostasis. This entire procedure takes around 12 min. The experimental protocol, including the generation of the pure tone for auditory stimuli, is developed and executed using LabView (National Instrument, USA).

**Figure 1.** Laboratory paradigm.



ANS measures are strongly affected by environmental factors. Thus, in all studies, regardless of the country (Hong Kong or Philippines) where the research is conducted, the same procedures are implemented. Similarly, other factors that influence physiological responses can likewise influence the ANS response. To control for this, parents of the participants are instructed with experiment preparatory reminders: no intake of caffeinated drinks 4 hours before the scheduled testing; no intake of food 1.5 hours before the scheduled testing; no rigorous physical exercise before the scheduled testing; and no treatments/interventions (ie, sensory integration therapy, craniosacral therapy, acupuncture, or any other procedures that could influence ANS activity) 24 hours before the scheduled testing.

During the experimental testing, the body mass index (BMI) is ascertained through measurement of the participants' height and weight. The Polar H2 chest strap is securely fastened just below the chest muscles. The finger cuffs are fixed around the medial phalanx of the index and middle fingers, opposite the laterality of the participant's hand. The child sits on a comfortable child-sized chair, facing a 19-inch monitor 3 feet away from him. A set of over-ear open headphones is placed over the child's ears. During the actual experimental conditions, the room is dimmed to 10 lux (illumination level), temperature set to 23 to 25°C, humidity level at 60 to 80%, and background noise level at 40 to 45 dB. The researcher is located 60 to 80 cm away to the left of the participant, keeping interaction to a minimal. Testing procedures in this research are adapted from a similar previous study by Lai [63] and a systematic review by Gomez et al [43]. These conditions are kept constant across all testings.

## Data Analysis

### *Neurophysiological Data*

HRV is acquired using Polar H2 heart rate monitor, recorded in real time, and simultaneously stored using the Polar Trainer 5, directed through infrared signals. The software for HRV analysis used was aHRV (Nevrokard, Slovenia), which uses the current guidelines for HRV analysis [47]. Raw data were converted into aHRV tachogram files. Using the researcher's observation notes, tachograms are subjected to visual analysis, identifying ectopic beats, movement artifacts, and abnormal noise signals. HRV files are then epoched into specific time events in the experimental paradigm. The epoched tachograms are subjected to correction of artifacts following the guidelines used by Task Force of the European Society of Cardiology [51]. In identifying artifacts for the short-term recordings, aHRV compared values to 20% under or over the mean of the preceding 25 beats [51]. Identified noise artifacts are then edited using proper interpolation, keeping as much of the integrity of the data sample. Data with more than 3% correction from the total normalized HRV data samples were discarded from the analysis. A 512-point Fast Fourier Transform was generated using a Hanning window to minimize spectral leakage at truncated data segments. Frequency domain analysis covered low (LF: 0.04-0.15 Hz) and high (HF:0.15-0.40 Hz) frequency components in its normalized units. The normalized units of LF were used as representatives of sympathetic modulation activity (predominantly), whereas the normalized units of HF were used as representatives of parasympathetic modulation activity using the following formula: LF *or* HF/(total power−VLF)×100, where VLF stands for very low-frequency band.

Ledalab version v.3.2.9, a MATLAB-based computer program, is used to extract EDA using a continuous decomposition analysis (CDA) method [81]. Epoched EDA data are then preprocessed individually using visual analysis and subsequent data grooming to reduce noise, which includes manual smoothing using a 5-second Hann window [82,83] and a filter of a unidirectional first-order Butterworth low-pass filter with a similar cutoff frequency of 5 Hz [83,84]. The traced EDA artifacts are then corrected using a spline interpolation within a 5-second pre/post parameter [85]. The CDA method uses parameters based on the previous works of Benedek and Kaernbach [81], which optimizes the EDA data and applies a 0.2-Hz Gaussian smoothing window within a 10-second grid size to detect significant peaks of >0.05 µS [86]. For the resting baseline and recovery conditions, SCL is extracted by using the *CDA.Tonic* parameter, which computes for the mean tonic EDA within the epoched response window (150-second block), in an aggregated 10-second moving within-window averaging method. In the case of processing the EDA stimulation condition data, a similar CDA method is used (Bateman functions comprising onset, amplitude, 1 and 2 parameters). The software can identify significant peaks of >0.05 µS [87], within a response window of 1 to 4 seconds poststimulus [82,88] across the stimulation condition block that consisted of 10 trials. To represent the sympathetic activity in the form of EDA, *CDA.SCR* was identified [82,87], which was then averaged across trials (0 responses not included) within the stimulation block condition as estimate of mean sympathetic activity, reflecting the individual's amplitude of responsiveness to sensory stimulus. To remove the impact of within and between-subject variance, analysis was performed using z-transformed individual *CDA.SCR* scores [82]. Furthermore, to correct for skewed distribution of skin conductance data scores and to meet assumptions required for parametric statistical analyses, normalization of SCL and SCR data for each intersection was performed using square root transformation [83,89-91]. This logarithmic transformation is determined as follows: $\sqrt{(CDA.Tonic)}$ and $\sqrt{(CDA.SCR+1)}$.

### *Statistical Data*

Descriptive statistics involving measures of central tendencies, variation, and dispersion are used to describe the salient characteristics of the data gathered. Demographic data related to participant gender, age, BMI, type of school (ie, public, private), number of parents working, primary caregiver, highest educational attainment of caregiver, family income, and parent's occupation will be gathered and considered in further statistical analyses. The Shapiro-Wilk test of normal is used to determine normality at baseline of the characteristics of the participants included in the study. Univariate and multivariate tests are likewise used to determine whether there are group and subgroup baseline similarities at critical alpha=.05. Variables deemed as non-normally distributed or significantly different at baseline are used as covariates. General linear modeling is used to

determine whether effects of ethnicity or environment (used as the independent variables [IV] in this study) can explain differences in the behavioral measures of the participants at a critical value of alpha=.05. Autonomic regulation is represented in this research as HF (n.u.) and LF (n.u.) of HRV and mean EDA (SCL/SCR) values as multivariates. Multivariate analysis of variance (MANOVA) tests will be used to determine whether effects of ethnicity or environment (used as IV in this study) can explain differences in the multivariate set of DVs, across the different research aims, with the different pairwise combinations in between 3 events (resting baseline, stimulation, and recovery). Effect size is interpreted using the values of Cohen *d*. Statistical analysis will be computed using SPSS version 23.0.

Specific to this report, sample size and power analysis are performed using G*Power version 3.1.9.2 [91,92]. Post hoc analysis of computed achieved power of the pilot data will be ascertained to determine the needed effect size for a subsequent a priori computation of required sample size for MANOVA tests.

## Results

For this report, we present data from our pilot data which include 30 participants (n=30) of 2 groups of children with controlled ethnicity (Filipino) but living in different physical environments (urban and rural settings) during the resting baseline phase of our experimental paradigm. The pilot samples are controlled for gender and age-matched. Table 1 presents a summary of the demographics and statistics of the variables included in the analysis for this paper.

### Group Differences: MANOVA

Preliminary data from 30 gender-controlled and age-matched participants with a mean age of 8.667 (SD 1.759) are analyzed for the influence of physical environments on the neurophysiological regulation of response to sensory stimuli using the HF (n.u.) and LF (n.u.) bands of HRV and EDA-SCL during the resting baseline condition as DVs. On the basis of the Shapiro-Wilk test and independent samples *t* test, BMI was normally distributed (*P*=.149) and similar at baseline (*P*=.57) between urban- and rural-dwelling participants.

The mean HF (n.u.) for the resting baseline condition was computed at 62.301 (SD 15.903) for urban-dwelling children, which is higher than the rural-dwelling group (mean 52.096, SD 15.125). This is the other way around for the LF (n.u.), where the rural-dwelling group (mean 29.228, SD 10.639) fared better than the urban-dwelling group (mean 24.171, SD 9.370). EDA-SCL showed almost similar values, with the urban group having slightly higher values (mean 1.929, SD 0.600) compared with their rural group (mean 1.900, SD 0.363).

**Table 1.** Summary of demographics and statistical results.

| Demographics | Urban (N=15) | Rural (N=15) | Total (N=30) | Shapiro-Wilk test | *t* test | *F* test | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Pillai *V* | *F* | *P* | *d* |
| **Type of school, n (%)** | | | | | | | | | |
| Public school | 12 (80) | N/A[b] | N/A | | | | | | |
| Private school | N/A | 15 (100) | 17 (57) | | | | | | |
| **Number of parents working, n (%)** | | | | | | | | | |
| Both parents | 10 (67) | 13 (87) | 23 (80) | | | | | | |
| **Primary caregiver, n (%)** | | | | | | | | | |
| Mother | 13 (87) | 12 (80) | 25 (83) | | | | | | |
| **Primary caregiver's highest educational level, n (%)** | | College degree | College degree | | | | | | |
| College degree | 8 (53) | 10 (67) | 18 (60) | | | | | | |
| Age in years, mean (SD) | 8.667 (1.759) | 8.667 (1.759) | 8.667 (1.759) | | 1.000 | | | | |
| BMI[c], mean (SD) | 16.145 (3.722) | 15.467 (2.683) | 15.806 (3.207) | 0.149 | 0.572 | | | | |
| HF (n.u.)[d], mean (SD) | 62.301 (15.903) | 52.096 (15.125) | 57.199 (16.108) | 0.504 | | 0.107 | 1.033 | .394 | 0.692 |
| LF (n.u.)[e], mean (SD) | 24.171 (9.370) | 29.228 (10.639) | 26.700 (10.181) | 0.448 | | | | | |
| SCL[f] (μS), mean (SD) | 1.929 (0.600) | 1.900 (0.363) | 1.914 (0.488) | 0.397 | | | | | |

[a]N/A: not applicable.

[b]BMI: body mass index.

[c]HF (n.u.): high frequency (normalized unit).

[d]LF (n.u.): low frequency (normalized unit).

[e]SCL: EDA-Skin Conductance Level.

**Table 2.** Sample size analysis protocol.

| Analysis[a] | Results |
|---|---|
| **Input** | |
| Effect size $f^2(V)$ | 0.0625 |
| α err prob[b] | 0.0500 |
| Power (1- β err prob)[c] | 0.8000 |
| Number of groups | 4 |
| Response variables | 3 |
| **Output** | |
| Noncentrality parameter λ | 16.5000 |
| Critical *F* | 1.9171 |
| Numerator df | 9.0000 |
| Denominator df | 252.0000 |
| Total sample size | 88 |
| Actual power | 0.8094 |
| Pillai *V* | 0.1765 |

[a]Computation was based on *F* tests–MANOVA: Global effects with analysis of a priori to compute for the required sample size.

[b]This is the critical value.

[c]This is the specific formula to compute for the power.

Using physical environment (urban or rural setting) as IV and the values at resting conditions of the LF (n.u.), HF (n.u.), and SCL as DV, a multivariate analysis of covariance (MANCOVA) test, specifically Pillai *V*, was performed using BMI as a covariate. In the series of analyses of variance (ANOVAs) performed, results of the multivariate tests confirm that the differences in the measures of autonomic regulation considered as DV among the 2 sampled ethnic groups in this study are not significant using a critical alpha of .05 ($V$=0.107, $F_{3,26}$=1.033, $P$=.39, $d$=0.692). A univariate analysis of individual DVs reveals similar nonsignificant differences between LF (n.u.) ($F_{1,30}$=1.909, $P$=.18, $d$=.523), HF (n.u.) ($F_{1,30}$=3.243, $P$=.08, $d$=0.681), and SCL ($F_{1,30}$=0.025, $P$=.87, $d$=0.063) of the sampled groups. It remains unclear whether the sample size in our pilot findings confounded the influence of the physical environment of the participants in explaining differences in the autonomic regulation of response to sensory stimuli.. Thus, a subsequent power analysis of the sample reported is performed.

### Power and Sample Size Analysis

A post hoc analysis using the results of the MANOVA test for the reported sample population on our preliminary data was conducted using G*Power version 3.1.9.2. Statistical power was computed using a sample of n=30 and the identified 3 DVs at resting baseline condition. Alpha level was set at alpha=<.05. The results of our post hoc analyses suggest that our effect size ($f^2$=0.120) is considerably in the medium range [93], whereas power was low at 0.283. This is considerably different from the initial set sample size of n=32 (alpha=.05, $d$=0.80, $P$=.80). With this in mind, we then recomputed the required sample size using a priori methods, setting a moderately large effect size of $f^2$=0.625 and a power of 0.80 for the needed 4 groups among 3 response variables to be used as DVs. Our post hoc analysis suggests that the current samples (n=15 per group) included in our pilot findings are underpowered; hence, significant effects may not yet be seen. On the basis of our results, the needed sample for this research is computed at n=22 per group (Table 2).

## Discussion

Our initial data suggest that ample sample size is needed to demonstrate our concepts and prove our hypothesis, given our methods. Although our initial findings currently yield nonsignificant results, the lack of differences in the regulation of response between our sampled groups might be due to underpowered sample size; hence, the researchers shall be guided with the recommended ample sample size in the offing.

Although there is much that remains to be done, our work has future important findings in the field. The development of the ability to regulate responses to sensory stimuli does not occur in a vacuum, and some other variables (ie, cultural, anthropological, socioeconomic) may likely account for variations. Although we will collect several measures of socioeconomic status (ie, school attended, whether public or private; number of parents working; primary caregiver; highest educational attainment of caregiver; family income; and parent's occupation) and proxy cultural measures (ie, parent-reported behavioral profiles of the child) and try our best to control for their confounding effects through sample stratification and statistical measures, their main effects are beyond the scope of this research. In this research, we mainly aimed to explore the influence of ethnicity and environment to explain differences in the regulation of response to sensory stimuli among typically

developing school-aged children through indexing physiological autonomic measures from a biomedical and neurophysiological perspective.

Regulation of sensory responses from the environment is essential in daily activities. Some children may have difficulty in processing sensory information. However, the underlying mechanism contributed to the regulation of behavior toward sensory stimulation is not clearly understood yet. The answer that our research will eventually provide has several implications. First, our findings may further strengthen the role of individual differences on behavioral and physiological responses, adding to the body of literature that supports the theory of allostasis. Second, our future findings may influence the reconceptualization of the neurophysiological mechanisms behind the regulation of response to sensory stimuli. Third, if our hypotheses are correct, then our findings may influence the review and further development of behavioral outcome measures of regulation of response to sensory stimuli to constitute questionnaire constructs related to physiological symptoms, rather than on purely behavioral ones alone. Finally, this research may further inform clinical practice on the importance that a child's external environment may play in the regulation of response to sensory stimuli, and consequently, consider these factors in intervention planning for children from clinical populations with diverse ethnic environments.

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## Authors' Contributions

ING and CYYL conceived, designed, and wrote the initial drafts of this study. CCHC and HCWT made significant contributions to the planning and design of the study and contributed to the revision of the manuscript. All authors read and approved the final version of the manuscript.

## Conflicts of Interest

None declared.

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## Abbreviations

**Ag/AgCl:** silver-silver chloride
**ANOVAs:** analyses of variance
**ANS:** autonomic nervous system
**BMI:** body mass index
**CDA:** continuous decomposition analysis
**CYRM:** child and youth resilience measure
**DV:** dependent variable
**EDA:** electrodermal activity
**HF:** high frequency
**HF (n.u.):** high frequency (normalized unit)
**HRV:** heart rate variability
**IV:** independent variable
**LF:** low frequency
**LF (n.u.):** low frequency (normalized unit)
**MANCOVA:** multivariate analysis of covariance
**MANOVA:** multivariate analysis of variance
**PNS:** parasympathetic nervous system
**SCL:** skin conductance level
**SCP:** Sensory Challenge Protocol
**SCR:** skin conductance response
**SNS:** sympathetic nervous system

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Original Paper

# mHealth Intervention Promoting Cardiovascular Health Among African-Americans: Recruitment and Baseline Characteristics of a Pilot Study

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## Abstract

**Background:** Mobile health (mHealth) interventions are promising avenues to promote cardiovascular (CV) health among African-Americans (AAs) and culturally tailored technology-based interventions are emerging for this population.

**Objective:** The objectives of this study were to use a community-based participatory research (CBPR) approach to recruit AAs into a pilot intervention study of an innovative mHealth CV health promotion program and to characterize technology use patterns and eHealth literacy (EHL).

**Methods:** Community partners from five predominately AA churches in southeast Minnesota collaborated with our academic institution to recruit AA congregants into the pilot study. Field notes as well as communications between the study team and community partners were used to design the recruitment strategy and its implementation with a goal of enrolling 50 participants. At its core, the recruitment strategy included community kickoff events to detail the state-of-the-art nature of the mHealth intervention components, the utility of CV health assessments (physical examination, laboratory studies and surveys) and the participants' role in advancing our understanding of the efficacy of mHealth interventions among racial/ethnic minority groups. Detailed recruitment data were documented throughout the study. A self-administered, electronic survey measured sociodemographics, technology use and EHL (eHEALS scale).

**Results:** A total of 50 participants (70% women) from five AA churches were recruited over a one-month period. The majority (>90%) of participants reported using some form of mobile technology with all utilizing these technologies within their homes. Greater than half (60% [30/50]) reported being "very comfortable" with mobile technologies. Overall, participants had high EHL (84.8% [39/46] with eHEALS score ≥26) with no differences by sex.

**Conclusions:** This study illustrates the feasibility and success of a CBPR approach in recruiting AAs into mHealth intervention research and contributes to the growing body of evidence that AAs have high EHL, are high-users of mobile technologies, and thus are likely to be receptive to mHealth interventions.

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**KEYWORDS**

mHealth intervention; community-based participatory research; cardiovascular disease; cardiovascular health; health disparities; African-Americans; faith-based intervention

## Introduction

African-American (AA) participation in mobile health (mHealth) studies is expanding in parallel to their increased adoption of mobile technologies [1-6]. Recent studies have integrated culturally tailored web-based platforms [7,8], monitoring technologies [9], and text-messaging [10-12] strategies to address key cardiovascular disease (CVD) risk factors among AAs, but few have attempted to translate existing effective evidence-based, community-based behavioral interventions into mHealth interventions within this population. Furthermore, there is a need to better understand the technology use patterns of AAs and their eHealth literacy (EHL) (perceived skills to effectively utilize and apply electronic health information) as these factors have been associated with healthy lifestyle behavioral change[13-15].

AA faith communities offer a promising avenue to foster recruitment into and deliver mHealth interventions as technology integration into health promotion activities at church may facilitate their implementation, dissemination and sustainability [9,16]. In addition, community-based recruitment approaches have cultivated trust between researchers and increased enrollment and retention rates in AAs [1,17,18]. We previously created a face-to-face, community-based, CVD prevention program among AA congregants in Minnesota (MN) which was successful in improving cardiovascular (CV) health knowledge and promoting CV health [19]. Post-intervention analyses revealed keen interest in translating the face-to-face program into an mHealth intervention to increase its accessibility and reach within AA faith communities [20]. Use of a community-based participatory research (CBPR) strategy bolstered our intervention recruitment and implementation efforts and fostered acceptability of the overall program by the AA community members[18,20]. Thus, we hypothesized that the ongoing use of a CBPR approach as a means to engage AAs in the translational design and development of an mHealth intervention, acting to springboard from a face-to-face program, would maximize recruitment within the AA community.

In this report, we describe our recruitment strategy design incorporating a CBPR approach in addition to its effectiveness and challenges. We also report participant baseline characteristics, technology use patterns, and EHL.

## Methods

### Study Design and Description

The Fostering African-American Improvement in Total Health (FAITH!) program is a behavioral theory–informed, culturally tailored, community-based CV health and wellness program implemented as an academic-community partnership with our institution and local AA churches [19,20]. As previously reported, the FAITH! face-to-face intervention targeted multiple CV risk factors (ie, hypertension, dyslipidemia, diabetes) among AA faith communities. Participants demonstrated improvements in CV health literacy and CV health metrics (blood pressure, body mass index [BMI]) along with positive trends between self-efficacy and health behaviors. Participant evaluations indicated an interest in integrating mobile technology or the Internet into the program to optimize dissemination and sustainability [20]. In response to the program's demonstrated effectiveness and its overall participant acceptability, the study team and community partners mutually decided that design of an mHealth intervention would enhance the program's reach to the AA community while creating a less resource-intensive yet effective tool for AA churches. Using a CBPR approach with community partners from five predominantly AA churches in the Rochester and Minneapolis-St Paul (MSP), MN areas, we jointly developed an innovative, interactive, on-demand lifestyle intervention in the form of an app through an iterative and formative research design process to ensure its usability, satisfaction and cultural relevance for the AA faith community. The purpose of the app as a whole was to deliver health education and motivational support to users to improve CV health. The app-based intervention (*FAITH! App*) included a 10-week core series of multimedia education modules addressing key CV risk factors as well as interactive self-quizzes, self-monitoring (diet and physical activity) and social networking (discussion sharing board). The intervention was intended for participants to follow a weekly schedule of each education module concentrating on each CV behavior or risk factor.

Within the current *FAITH! App* pilot study, health assessments were conducted at baseline and 6-months post-intervention at local community health clubs (in Rochester and MSP, MN) with the assistance of a trained nursing team. These assessments included collection of CV health risk factors: anthropometrics (BMI, waist circumference), blood pressure measurements (average of three sitting readings, by oscillometric automated blood pressure monitor, Bp TRU BPM-100) and laboratory studies (total cholesterol, glucose by fingerstick). Electronic surveys were administered at baseline, mid-intervention, post-intervention and 6-months post-intervention including further measures of CV health behaviors (measured by an adapted version of the National Cancer Institute fruit and vegetable all-day screener [22] and the International Physical Activity Questionnaire-short form [23]). Primary outcomes included self-efficacy (diet and physical activity [24,25]), CV health knowledge and CV health (risk factors and behaviors [19]). Additional survey items included self-reported mobile technology use, Internet access, and EHL [13-15]. EHL was evaluated using the eHealth Literacy Scale (eHEALS) which consists of eight items scored on a 5-point Likert scale which assesses an individual's perception of their ability to understand and apply electronic health information [13]. The sum of all items ranges from 8 to 40 with higher scores reflecting a higher

level of EHL. Similarly to other studies, eHEALS scores were dichotomized into high EHL (≥26) and low EHL (<26) [13]. Participants received incentives (cookbook, cash card [US $50], heart health book, personal physical activity monitor (Fitbit Charge) at enrollment and were provided with an iPad mini tablet device installed with the app software for use throughout the study. Two one-hour, hands-on instructional training sessions on the app log-in access and the basic app features and navigation were delivered by the study team (one held each in Rochester and MSP, MN). Participants were provided with an instructional manual including step-by-step screen shots to support their independent use.

Inclusion criteria were the following: AA, aged ≥18 years, basic Internet navigation skills, at least weekly Internet access (such as at home, a family member's or friend's home, church, library/community center, school/university, Internet café, etc), active email address, minimal fruit/vegetable intake (less than 5 servings/day), no regular physical activity program (less than 30 minutes/day of moderate physical activity), able to engage in moderate physical activity (such as brisk walking, dancing, aerobics, gardening, weight lifting without restrictions including physical disability, use of a wheelchair daily or serious medical condition). Individuals were ineligible if they were unable to walk up at least two flights of stairs or walk at least one city block without assistance or stopping, pregnant, had visual/hearing impairment or mental disability that would preclude independent use of the app or were past participants of the face-to-face CVD prevention program [19]. The three partnering Rochester churches were small in congregation size (varying from 50 to 100 members) and together they constituted approximately 200 congregants (range 50% to 75% adults aged ≥18 years). The two MSP churches were larger in congregation size (varying from 100 to 200 members) constituting approximately 400 congregants (range 50% to 75% adults aged ≥18 years). Thus, as a combination of all five churches, an estimated 300 members comprised our recruitment pool. The Mayo Clinic Institutional Review Board approved the study protocol.

## Community-Based Participatory Research Recruitment Strategy

A series of jointly-led meetings were held over a 6-month period to outline a clear and culturally appropriate plan for recruitment from five local churches. Participating churches designated church liaisons (FAITH! Partners) to engage in these meetings to design and tailor a recruitment strategy. We collaborated with eight FAITH! Partners (seven which were AA women). Each church had at least one FAITH! Partner with three churches designating two representatives. Community kickoff events were suggested by the FAITH! Partners to serve as our primary recruitment tools to outline the study timeline and specific expectations of potential study participants. The FAITH! Partners highly suggested that the study team provide an overview of the mHealth intervention with an emphasis on how the *FAITH! App* was designed and rigorously tested by AA community members to increase its cultural relevance, credibility and uptake. Also, a demonstration of the *FAITH! App* 's key components was recommended to show their "cutting edge" nature and aim to improve CV health as this was viewed as a way to stimulate excitement among the kickoff event attendees. The study team and FAITH! Partners also felt that connecting CV health promotion to the health assessments was fundamental by highlighting them as a means to "know your numbers" and track them for anticipated improvements over the course of the study. During the kickoff events, it was deemed necessary that the study team clearly describe the requirements of the health assessments and make the events convenient in terms of time and location for our participants (community venues). Furthermore, the health assessments were held at local community health clubs in an aim to increase participant comfortability, awareness, and familiarity with health promotion facilities within their communities.

The FAITH! Partners also recommended that interested participants complete a "Registration/Program Interest Form" at the events. The form included contact information and questions corresponding to inclusion/exclusion criteria. Use of the interest form was affirmed as an essential recruitment tactic by our community partners in order for potential participants to better understand the eligibility requirements and for the study team to gauge the number of eligible participants from each church. The FAITH! Partners also suggested that we utilize self-administered, electronic surveys (rather than written) throughout the pilot study for participant convenience and to facilitate more thoughtful responses. They also felt that participants would find this appealing and would aid in their willingness to enroll in the study.

To remain in alignment with CBPR principles, the group mutually agreed upon stressing the importance of research participation among AAs to advance knowledge on the efficacy of mHealth lifestyle interventions in racial/ethnic minority groups. Efforts were made to underscore how their participation in the study would contribute to the AA community at-large and society as a whole. The presence of the study principal investigator and church leadership (ie, church pastor or FAITH! Partner) at the events was deemed critical by our FAITH! Partners for full transparency and to demonstrate a collaborative and equitable partnership in all research phases—a central CBPR tenet [18,21].

The study team and FAITH! Partners developed uniform recruitment tools including church announcement scripts, flyers and a promotional video containing testimonials from prior study participants and FAITH! Partners regarding the program benefits with integrated motivational spiritual messaging (see Multimedia Appendix 1). Lastly, the group solidified a communication plan to promote the kickoff events, as well as enrollment and attendance at the baseline health assessment through a variety of means of contact (ie, church announcements, flyers, telephone calls and emails). We collectively set a recruitment goal of 50 participants to evaluate the feasibility of our recruitment and intervention approach.

## Pilot Study Recruitment Procedures

FAITH! Partners promoted kickoff events through church announcements and flyers. Three kickoff events were held in June 2016 (two at churches in MSP, MN, one at a community health club in Rochester, MN) and were led by both the study principal investigator (LB) and FAITH! Partners. The events

were approximately two hours in duration and held at the convenience of the participating churches (ie, following Sunday worship service or integrated into weekly evening Bible Study). Each event included an introduction to the study team, prior research study findings/accomplishments, an overview of the current research project (timeline, intervention components, health assessments, etc) including the promotional video and open discussion. Healthy refreshments were provided at all events. Interested participants completed the "Registration/Program Interest Form" which was returned to the church designated FAITH! Partner and then forwarded to the study team. Subsequently, the study coordinator contacted the interested participants to reiterate study details and complete eligibility screening. Upon confirmation of eligibility, participants were then invited to the baseline health assessments (two held in July 2016 at community health clubs) and to complete the baseline electronic survey. All participants provided written informed consent at the baseline health assessments.

## Results

Approximately 100 individuals attended the three kickoff events. Figure 1 summarizes the recruitment process. Seventy-five individuals completed interest forms and were assessed for eligibility. Of these, 51 (68%) were eligible for participation and enrolled in the baseline health assessment (more than 100% achievement of recruitment goal). Of the 51 enrolled, 100% completed the baseline health assessment and 50 completed at least one education module and form the basis of this report. Of the 24 excluded from the study, 13 (54%) were deemed ineligible by study criteria and 11 were uninterested or unable to be reached by study personnel. The most common reason for ineligibility was lacking basic Internet skills or access (n=4).

Participants were predominately women (70% [35/50]) and employed full time (64% [34/50]) with mean age of 49.6 (SD 12.7) years (Table 1). Nearly all participants used some form of mobile technology (smartphones were the most common, at 92% [46/50]) and reported primary use at home (100%) with typical use in the evening (91.8% [45/49]). The mean EHL score (eHEALS) was 30.4 (range 21-40; SD 4.6), with 84.8% (39/46) having high EHL (score ≥26). There was no difference in mean EHL scores by sex ($P$=0.75). Forty-six out of 50 participants (92%) rated their own ability to use the Internet as 'fairly skilled to expert' levels. Only 26% (13/50) reported 'very often' downloading apps and 42% (21/50) reported 'very often' social media use (data not shown).

**Figure 1.** Recruitment process and participant flow. Reasons for exclusion are not mutually-exclusive. One participant withdrew from intervention due to difficulty with the technology.

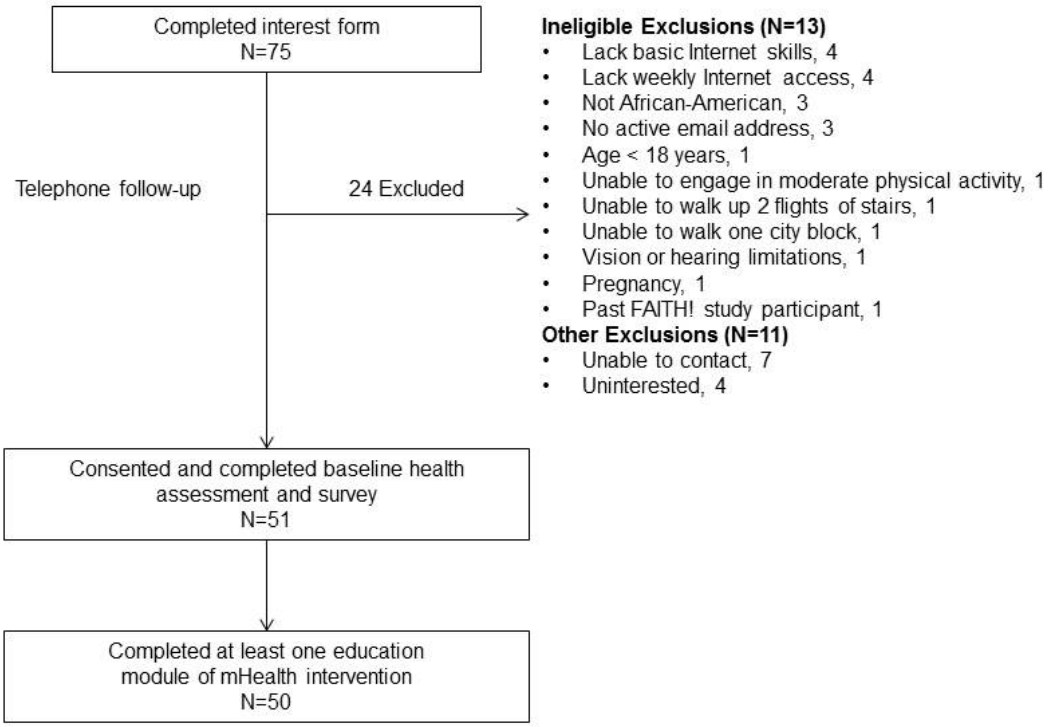

**Table 1.** Participant demographics and self-reported mobile technology use.

| Characteristic | Total (N=50 unless otherwise noted) |
|---|---|
| **Sex, n (%)** | |
| Female | 35 (70.0%) |
| **Age** | |
| Mean (range), years | 49.6 (26.0-72.0) |
| **Marital status, n (%)** | |
| Single | 9 (18.0%) |
| Divorced | 7 (14.0%) |
| Widowed | 2 (4.0%) |
| Married/in committed relationship | 32 (64.0%) |
| **Highest level of education, n (%)** | |
| Some high school | 1 (2.0%) |
| High school graduate or GED equivalent | 5 (10.0%) |
| Some college | 12 (24.0%) |
| Technical degree or Associate's degree | 11 (22.0%) |
| College graduate/advanced degree | 21 (42.0%) |
| **Employment status, n (%)** | |
| Employed, full-time (32+ hours/week) | 34 (68.0%) |
| Employed, part-time (less than 32 hours/week) | 3 (6.0%) |
| Unemployed | 17 (34.0%) |
| **Annual household income (N=49), n (%)** | |
| Less than $20,000 | 5 (10.2%) |
| $20,000 to $34,999 | 9 (18.4%) |
| $35,000 to $49,999 | 10 (20.4%) |
| $50,000 to $74,999 | 9 (18.4%) |
| ≥$75,000 | 12 (24.5%) |
| Chose not to disclose | 4 (8.2%)) |
| **Mobile technology use, n (%)** | |
| Smartphones | 46 (92.0%) |
| Tablet | 37 (74.0%) |
| Laptop | 36 (72.0%) |
| Personal physical activity monitor | 13 (26.0%) |
| No mobile technology use | 1 (2.0%) |
| **Mobile technology use locations (N=49), n (%)** | |
| Home | 49 (100.0%) |
| Family member's home | 16 (32.7%) |
| Friend’s/neighbor's home | 12 (24.5%) |
| Work | 34 (69.4%) |
| Library/community center | 6 (12.2%) |
| Internet cafe | 11 (22.4%) |
| School/university | 13 (26.5%) |
| Church | 26 (53.1%) |

| Characteristic | Total (N=50 unless otherwise noted) |
|---|---|
| **Most frequent locations for Internet use (N=49), n (%)** | |
| Home | 40 (81.6%) |
| Family member's home | 1 (2.0%) |
| Work | 7 (14.3%) |
| Church | 1 (2.0%) |
| **Average daily mobile technology use (N=49), n (%)** | |
| 0 to 2 hours | 10 (20.4%) |
| 2 to 4 hours | 13 (26.5%) |
| 4 to 6 hours | 8 (16.3%) |
| 6 to 8 hours | 4 (8.2%) |
| 8 or more hours | 14 (28.6%) |
| **Level of comfort with mobile technology, n (%)** | |
| Very comfortable | 30 (60.0%) |
| Somewhat comfortable | 18 (36.0%) |
| Neither comfortable nor uncomfortable | 2 (4.0%) |
| **Home Internet access, n (%)** | |
| Yes, wireless | 47 (94.0%) |
| Yes, non-wireless | 4 (8.0%) |
| No access in home | 1 (2.0%) |
| **Sources primarily used to access health information on the Internet, n (%)** | |
| Government websites | 15 (30.0%) |
| Non-profit organization websites | 17 (34.0%) |
| Hospital/Clinic websites | 31 (62.0%) |
| Commercial websites | 26 (52.0%) |
| Non-Medical websites | 11 (22.0%) |
| Do not access health information on the Internet | 4 (8.0%) |
| **How useful do you feel the Internet is in helping you in making decisions about your health? (N=46), n (%)** | |
| Not useful | 1 (2.2%) |
| Unsure | 7 (15.2%) |
| Useful | 30 (65.2%) |
| Very useful | 8 (17.4%) |
| **How important is it for you to be able to access health resources on the Internet? (N=46), n (%)** | |
| Not important | 3 (6.5%) |
| Unsure | 2 (4.3%) |
| Important | 25 (54.3%) |
| Very important | 16 (34.8%) |
| **eHealth literacy score (possible range 8-40, N=46)** | |
| Mean (SD) | 30.4 (4.6) |
| Range | (21-40) |
| Low (<26), n (%) | 7 (15.2%) |
| High (≥26), n (%) | 39 (84.8%) |

| Characteristic | Total (N=50 unless otherwise noted) |
|---|---|
| **How would you rate your own ability to use the Internet?, n (%)** | |
| Not very skilled | 4 (8.0%) |
| Fairly skilled | 17 (34.0%) |
| Very skilled | 22 (44.0%) |
| Expert | 7 (14.0%) |

## Discussion

This paper outlines the successful application of a CBPR approach to "re-design" a highly accepted, yet resource-intensive face-to-face program to promote CV health within an mHealth intervention to support broader dissemination capability for the AA community. Leveraging the expertise and insights of our community partners in development of the intervention and the recruitment strategy was crucial to the success of our recruitment efforts. By doing so, we were able to keep the needs of our prioritized population at the forefront which facilitated our participant enrollment. Our investment of resources in face-to-face engagement through kickoff events was important to this community and enhanced transparency and mutual understanding of the intervention goals. Consistent with prior studies of AA adults [2,6], nearly all of our participants reported use of mobile technology (specifically, a high usage of smartphones), a desire to have access to Internet-based health information, and demonstrated high EHL; these factors likely facilitated their enrollment.

A recent systematic review revealed the low representation of AAs in mHealth research [1]. Culturally insensitive recruitment methods and retention strategies have been postulated as potential root causes to low enrollment over apathy from AAs. The review also highlighted the challenge of engaging AA men in these studies and a general increased willingness by AA women to participate in mHealth studies. To overcome this barrier, AA women could serve as advocates to increase AA interest in digital interventions and mHealth research. Our study incorporated the input and active presence of church liaisons (FAITH! Partners) whom were mostly AA women, into designing a culturally relevant intervention and recruitment plan. Their positive influence undoubtedly contributed to us meeting our enrollment goals. The predominance of AA women in our study is reflective of the demographics of the partnering church congregations, and suggests that additional efforts may be needed to reach AA men. It is also noteworthy that the principal investigator is an AA woman and CV medicine specialist; her involvement likely conveyed authenticity, personability and cultural relevance to potential participants. This is in direct congruence with the preferences of racial/ethnic minority groups to include culturally-matched research personnel in leadership roles within clinical studies [26].

To foster recruitment of racial/ethnic minority populations into clinical research whether technology-based or not, it takes an in-depth understanding of their multifactorial, perceived barriers and facilitators to research participation. Having the intent at conception and design of a study to enroll minorities and not having to make midstream adjustments to recruitment efforts have been associated with minority recruitment success rates among study principal investigators [27]. In a recent systematic review of shared barriers and facilitators to research participation among minority groups, the most commonly reported perceived barrier was mistrust in relation to purposeful mistreatment or experimentation by the study investigators [26]. AAs in particular have reported a fear of being treated as "lab rats" or "guinea pigs" which stems from lingering effects related to dark historical unethical and exploitative research practices (eg, US Public Health Services Syphilis Study at Tuskegee, Henrietta Lacks "immortal" cell line) [26,28]. Our study team and community partners wholeheartedly recognized these unfortunate events, but sought to overcome this eroded trust in clinical research and medicine by instilling full transparency and involvement of the community for which our intervention was originally developed into the entire research process. We also made it our goal to underscore the altruistic benefits yielded by the community and future generations from our participants' research involvement—an articulated facilitator to research participation by minority groups. We devoted a great deal of time explaining the "big picture" of eradicating CV health disparities through our innovative mHealth intervention. We made it clear that there was a growing body of evidence showing the benefits of mHealth interventions in CVD [29], but unfortunately these were not being designed and tested specifically for AAs and others who need them most—underserved racial/ethnic minority populations. From our observation and anecdotally from our community partners and participants, it seemed as if our participants enrolled not only to improve their individual CV health, but also to avoid creating disparities themselves by not participating in a study that was potentially on the frontier of new discoveries within their communities.

When translating community-based, face-to-face health programs to mHealth interventions, it is advantageous to have community "buy in" for trust-building and to overcome challenges to enrollment [1]. The AA church is one of the pillars of the AA community and has a rich legacy central to addressing health disparities among AAs through effective health promotion programming with many engendered through academic-community partnerships [18]. Our ongoing relationship with the AA faith community generated a joint motivation to advance the reach of our CVD prevention program through mobile technology as an mHealth intervention promoting CV health. The collective feedback received from our partnering church leaders and FAITH! Partners assisted in

framing a recruitment strategy that was attentive to the facilitators of enrolling AA congregants into our study. The congregations' established social networks and infrastructure were undoubtedly crucial to our recruitment success as they were the basis for and enabled our community engagement.

### Limitations

We acknowledge limitations to our recruitment methods. We did not collect detailed data on the time and number of attempts required by our study coordinator to reach prospective participants, yet this information would assist other investigators seeking to recruit from AA faith communities by providing them with an estimate of the time allocation required [17]. In the future, we plan to integrate these assessments into our recruitment evaluation strategies. Furthermore, we did not evaluate satisfaction with the recruitment strategy and process from the church pastors or FAITH! Partners immediately following recruitment. These data will be collected in subsequent assessments including focus groups. However, based on their input, a study-specific community steering committee comprised of community and faith-based organizations as well as past study participants has been established to enhance future recruitment strategies. Moreover, we did not include an objective measure of skill assessment to use mobile technologies. However, the fact that our intervention was born out of a community-originated recommendation to develop an mHealth intervention suggests that the group possesses a strong interest in increasing its skillset to use these technologies. In addition, our app was designed through a rigorous formative research process with preliminary usability testing with AA community members of similar demographics to those we intended to recruit into the pilot study. We plan to assess these skills and proficiencies with previously validated tools in future studies.

### Conclusions

Our study supports the effectiveness of integration of a CBPR approach to translate culturally relevant mHealth lifestyle interventions to AAs to maximize recruitment success. Our results also contribute to the growing evidence that AAs have high EHL, are high-users of mobile technologies, and thus are likely to participate in mHealth interventions.

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## Conflicts of Interest

None declared.

## Multimedia Appendix 1

FAITH! program promotional video.

[WMV File (Windows Media Video), 30MB - resprot_v7i1e31_app1.wmv ]

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## Abbreviations

**AA:** African-American
**BMI:** body mass index
**CV:** cardiovascular
**CVD:** cardiovascular disease
**CBPR:** community-based participatory research
**EHL:** eHealth literacy
**eHEALS:** eHealth Literacy Scale
**FAITH:** Fostering African-American Improvement in Total Health
**mHealth:** mobile health


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Original Paper

# The Use of Facebook Advertising to Recruit Healthy Elderly People for a Clinical Trial: Baseline Metrics

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## Abstract

**Background:** This report provides data on the use of social media advertising as a clinical trial recruitment strategy targeting healthy volunteers aged 60 years and older. The social media advertising campaign focused on enrollment for a Phase 1 clinical trial. Traditional means of recruiting—billboards, newspaper advertising, word of mouth, personal referrals, and direct mail—were not producing enough qualified participants.

**Objective:** To demonstrate the effectiveness of using targeted advertising on the social networking site Facebook to recruit people aged 60 years and older for volunteer clinical trial participation.

**Methods:** The trial sponsor used a proactive approach to recruit participants using advertising on social media. The sponsor placed and monitored an Institutional Review Board-approved advertising campaign on Facebook to recruit potential candidates for a Phase 1 clinical trial. The clinical trial required a 10-day residential (overnight) stay at a clinic in Michigan, with one follow-up visit. The sponsor of the clinical trial placed the advertising, which directed interested respondents to a trial-specific landing page controlled by the Contract Research Organization (CRO). The CRO provided all follow-up consenting, prescreening, screening, and enrollment procedures. The campaign was waged over an 8-week period to supplement recruiting by the CRO.

**Results:** A total of 621 people responded to a Facebook advertising campaign by completing an online form or telephoning the CRO, and the clinical trial was fully enrolled at 45 subjects following an 8-week Facebook advertising campaign.

**Conclusions:** An 8-week Facebook advertising campaign contributed to 868 inquiries made regarding a Phase 1 clinical trial seeking to enroll healthy elderly subjects. Over the initial 11 weeks of recruitment, 178 inquiries were received using traditional methods of outreach. Respondents to the Facebook advertising campaign described in this report engaged with the sponsored advertising at a higher rate than is typical for social media-based clinical trial recruitment strategies. The older adults' engagement rate of 4.92% was more than twice as high as click-through rates of younger adults engaged with social media advertising in other clinical trial recruitment studies. Advertising placed on the social media platform Facebook is effective with the healthy volunteer population aged 60 years and older. This approach can quickly and cost-effectively reach qualified candidates for clinical trial recruitment as a supplement to traditional means of recruiting.

**Trial Registration:** ClinicalTrials.gov: NCT02840279; https://clinicaltrials.gov/ct2/show/NCT02840279 (Archived by WebCite at http://www.webcitation.org/6wamIWXAt)

***(JMIR Res Protoc 2018;7(1):e20)*** doi:10.2196/resprot.7918

**KEYWORDS**

clinical trial recruitment; medical research; older people; social media; Facebook; research subject recruitment; advertising; elderly

## Introduction

### Background

Sponsored advertising on social media as a clinical trial recruitment strategy is relatively new. Informed by known barriers to successful enrollment [1,2], Contract Research Organizations (CROs) and sponsors of clinical trials are now using Internet-based outreach to augment traditional ways of recruiting elderly subjects, such as doctor referrals, print advertising, and television advertising [3-5]. In the last few years, there has been increasing research measuring the effectiveness of social media outreach [6], including the use of Facebook [7,8]. Although an increasing number of published articles provide metrics of successful Facebook advertising campaigns [9-11], few discuss Facebook-based recruitment of older adults for participation in clinical trials [12,13].

This report provides an example of clinical trial recruitment of healthy elderly people using Facebook advertising. Older adults are using Facebook in increasing numbers; in 2016, of all online adults, 62% of those aged 65 years and older used Facebook [14]. In 2017, 67% of adults aged 65 years and older said they went online, with 45% of seniors under the age of 75 using social networking sites, along with 20% of those aged 75 and older [15]. There are ample and recent calls to implement social media-based recruitment strategies as an effective and cost-saving approach to clinical trial recruitment [16-19]. The Michael J. Fox Foundation's Facebook-based recruitment of older Ashkenazi Jews provides an anecdotal success story [20].

This study provides data on an outreach method targeted to healthy elderly adults (age 60 years and over) for enrollment in a Phase 1 multiple ascending dose clinical trial assessing safety, tolerability, and preliminary cognitive benefit of a compound being developed for the treatment of Alzheimer's disease (NCT02840279). This report presents examples of paid (sponsored) Institutional Review Board (IRB)-approved advertising on Facebook, and the response to the recruitment effort compared to traditional methods. This study demonstrates the cost effectiveness of a targeted advertising campaign over a short duration for a sponsor with no established social media presence prior to the advertising launch.

### Context

The Facebook advertising campaign was launched due to low enrollment by the CRO. The CRO had begun clinical trial recruitment in early June 2016 using the following methods: (1) personal referral; (2) direct mailer (quantity of 6000) sent to surrounding postal ZIP codes, age 60 and older; (3) billboards placed near the clinical site; (4) bus advertising in the city where the clinic is located; (5) newspaper ads in three regional and free "shopper" newspapers; and (6) outreach events.

This outreach, conducted over a period of 11 weeks, resulted in 6 enrolled subjects. The enrollment goal was 45. Due to the low enrollment, three additional strategies for recruitment were implemented: (1) the study fee for the participants was raised from US $2500 to US $4000, (2) outreach from the sponsor increased to include personal contact with leaders of area churches and senior groups, and (3) the sponsor launched a Facebook advertising campaign to direct interested people to the CRO through completion of an online form or by telephone inquiry.

The social media campaign was an intense, immediate, and directed effort to enroll in the trial. The comparative effectiveness of the different social media recruitment strategies against traditional media was made weekly, with adjustment as needed. The Facebook advertising campaign was run by the sponsor, rather than the CRO, and the CRO controlled all contact with respondents. The objective of the Facebook campaign was to enhance awareness and create a trial-unique pathway that allowed potential volunteers to discover and learn more about the clinical trial, and ultimately contact the CRO for further information.

## Methods

### Clinical Trial Design

The clinical trial was a Phase 1 study of a memory drug at a single clinical site. Details of the clinical trial design have been registered at ClinicalTrials.gov (NCT02840279). The study protocol required a 10-day/night stay (residential) in a clinic in Michigan, with one follow-up visit. Participants stayed in dormitory-style rooms, with no visitors permitted. Candidates for the study were required to be nonsmokers, free from any central nervous system medications, with age-normal lab values, well managed diabetes (if diabetic), no history of cancer, healthy blood pressure, and were asked to complete a cognition battery. Recruitment was planned to reflect the demographics of the region surrounding the clinical site, which for Kalamazoo County, Michigan are 51% female and 81.7% white [21].

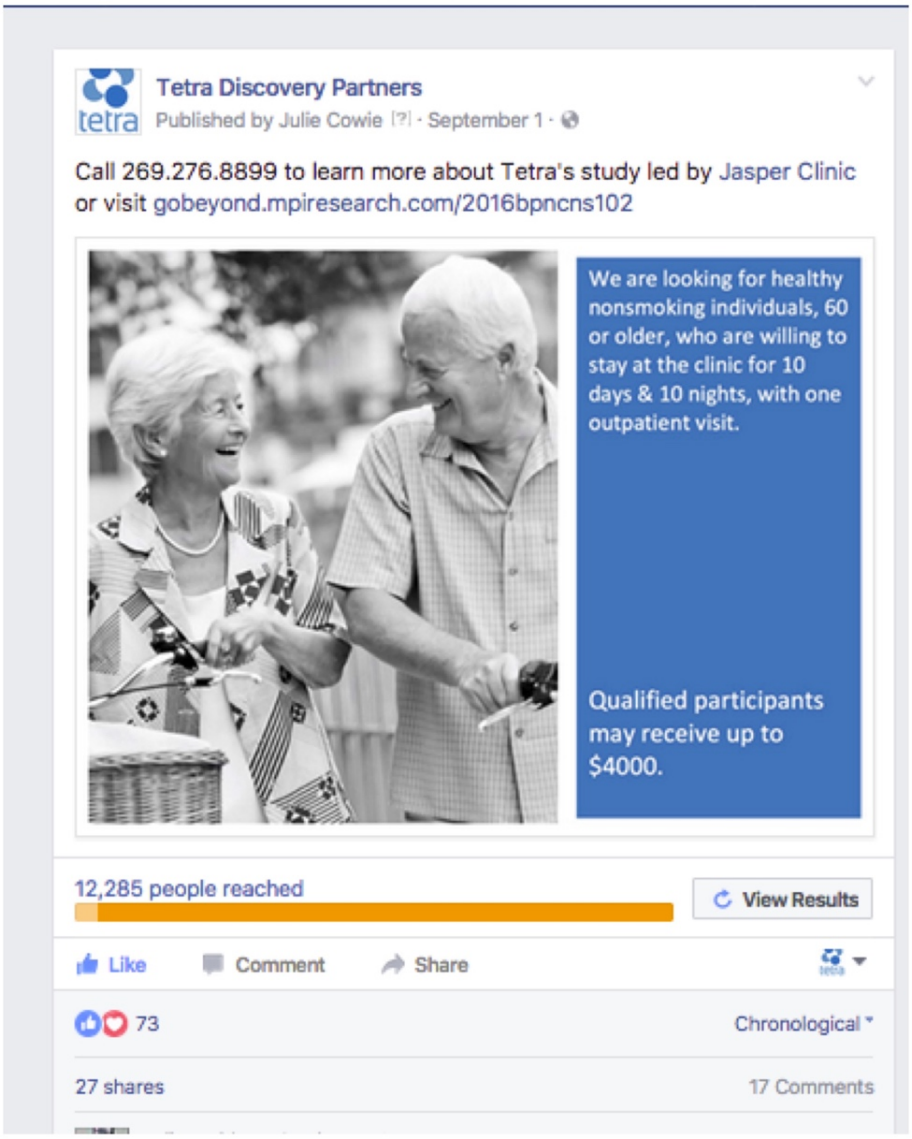
### Approach

#### *Social Media Campaign #1*

The initial social media outreach used the same words and images as the traditional campaign. The advertising placed on Facebook used artwork and text that had been approved by the IRB and used for outreach in the prior three months of the recruitment period. The CRO had implemented a recruitment campaign consisting of: billboards, a direct mailing of 6000 postcards sent to local area residents aged 60 years and older, regional newspaper ads, announcement of the trial on the CRO's website and Facebook page, advertising on buses, recruitment events (including talks at senior centers), and flyers and posters.

The sponsor had no social media presence prior to the start of the trial. Day one of this Facebook advertising campaign consisted of establishing a company page for the sponsor. On the second day of the campaign, Facebook posts were boosted or paid to reach a wider audience. At this early stage of the social media campaign the approach reinforced the advertising already distributed throughout the region. The initial post, a black and white image with text, is shown in Figure 1.

**Figure 1.** Initial boosted Facebook post using black-and-white image.




Targeting [22], a tool available to Facebook advertisers, was used to direct this post to Facebook users with the following interests: (1) Alzheimer's disease research, (2) medical research, and (3) the Alzheimer's Association. Ads were targeted to individuals aged 60 years and up, with a focus on geographic communities within a 60-minute drive of the clinical site.

The campaign was actively managed, with staff from the clinical trial sponsor monitoring the social media engagement throughout the day and evening. The initial spend was US $150/day for the first four days. Following this initial period, advertising placements and expenditures varied relative to the CRO's capacity to follow up on inquiries in a timely manner.

Posted comments were acknowledged, usually with a reply to contact the CRO for additional information. Advertising was updated if posted questions or comments suggested that the advertising text was not clear. The CRO provided Health Insurance Portability and Accountability (HIPAA)-compliant feedback to the sponsor about the reasons for failed prescreening. This feedback informed the next iteration of advertising recruitment.

### *Social Media Campaign #2*

The sponsor has a track record as an innovative startup, using lean methods [23] to rapidly adjust and experiment as a way of solving problems. In this case, the innovative approach taken was to launch advertising on Facebook and focus on the potential clinical trial participant as a *customer*. The customer segments principle [24] and the use of keywords within Facebook advertising guided the remainder of the advertising campaign.

Two distinct customer segments or Facebook audiences were targeted in the second iteration of the social media campaign. One advertising strategy focused on older adults who would be content with the low level of stimulation a 10-day/night stay would offer and who would be healthy enough to qualify for the study; this was the "typical" campaign. A second advertising strategy was oriented to people who would be altruistically motivated to enroll. This campaign targeted older adults interested in helping to advance scientific progress regarding the treatment of Alzheimer's disease and memory loss; this was the "altruistic" campaign. Both segments reflect known

motivations for participants in clinical trials [25]. The advertising strategy hypothesized that these two customer segments had the distinct attributes shown in Textbox 1.

Facebook advertising provides the ability to target by age, geography, income level, and keywords. These qualifiers were used to narrow the outreach to either the typical or the altruistic customer segments. Keywords can also be used for exclusion. The use of keywords for exclusion narrows the targeted audience even further. The Facebook algorithm seeks to match only one of the keywords, not all. Keywords employed in the advertising campaign are outlined in Table 1.

As the social media campaign evolved, the sponsor submitted for IRB-approval of additional text and photographs more suited to social media. The campaign was configured so that the sponsor paid only for link clicks. All links in the Facebook ad connected to the CRO's trial-specific landing page. The landing page offered a form to be completed by potential participants expressing interest in the trial. An advertisement representative of the typical campaign is shown in Figure 2. An advertisement representative of the altruistic campaign is shown in Figure 3.

**Textbox 1.** Description of customer segments.

Characteristics of the "typical" recruit:

- Sedentary but healthy
- Willing to forego exercise/outdoors for 10 days
- Enjoys television or reading
- Available for a 10-day/night stay with short notice
- Not involved in providing daily care for another

Characteristics of the "altruistic" recruit:

- Civic-minded
- Oriented to philanthropy or religious stewardship
- Motivated to give of oneself and one's time for a greater good
- Engaged in Alzheimer's disease awareness or touched by Alzheimer's disease
- Interested in scientific advancement, medical research, and/or clinical trials

**Table 1.** Keywords used for targeted advertising on Facebook.

| Parameter | Typical campaign | Altruistic campaign |
|---|---|---|
| Geography | • Communities within 90 minutes' drive of clinical site<br>• At or just below median income level for the county (2015 census)<br>• Engagements from initial ad were reviewed for geography, with advertising concentrated in communities showing higher rates of engagement | • University regions within two hours' drive<br>• Affluent communities within two hours' drive |
| Income Level | $100,000 or less | $100,000 or above |
| Keywords | Clinical trial, Reading, WebMD, Widow, Frugality, Fixed income, Single person, Retirement, Social security, or solitaire | Neuroscience, Clinical trial, Alzheimer's disease research, Philanthropy, Mind games, Costco, Altruism, Medical research, Lumosity, or Lifelong learning |
| Exclusions | National Cancer Survivors Day, Diabetes mellitus type 2 awareness, Hypertension Awareness, Allergy, Prehypertension, Cancer signs and symptoms, Diabetic diet | National Cancer Survivors Day, Diabetes mellitus type 2 awareness, Hypertension Awareness, Allergy, Prehypertension, Cancer signs and symptoms, Diabetic diet |

**Figure 2.** Example of advertising placed for the typical campaign.

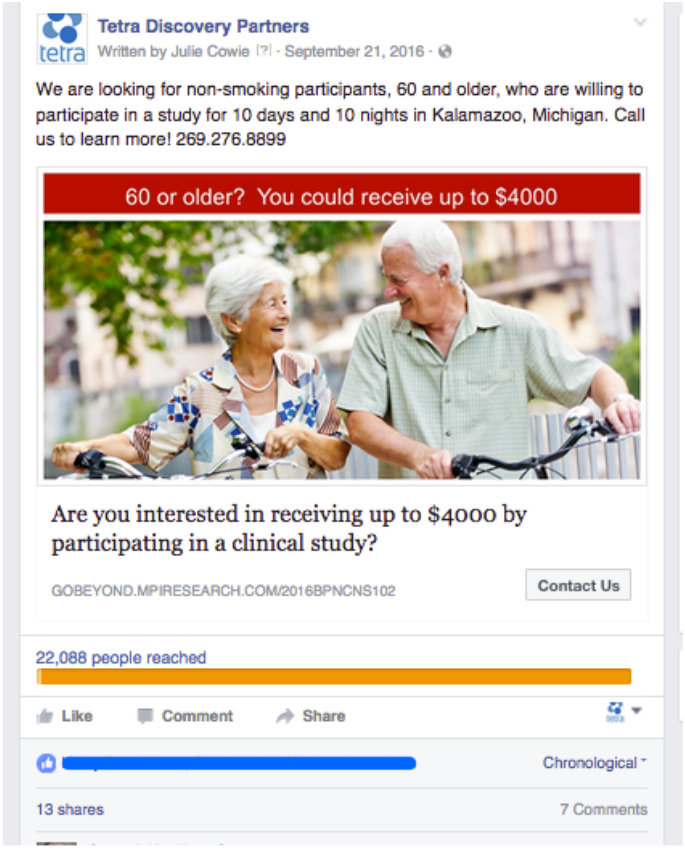
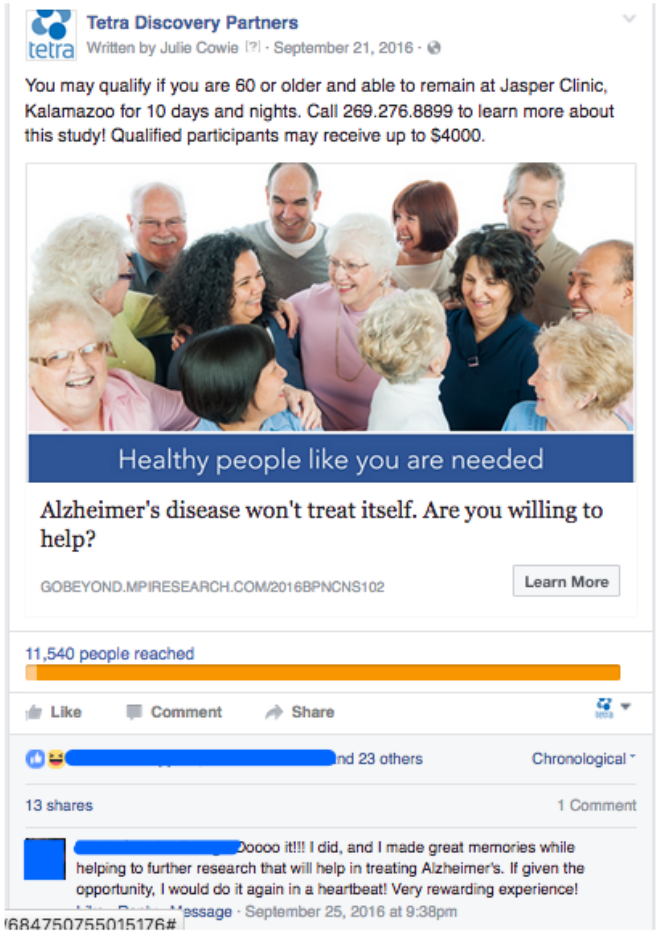



**Figure 3.** Example of advertising placed for the altruistic campaign.



## Results

The Facebook advertising campaign was conducted over a period of approximately 8 weeks. The campaign concluded when the trial was fully enrolled with 45 subjects.

### Social Media Campaign #1 Results

The initial post, a black and white image with text, received a "1" relevance score on a scale of 1 to 10, with 1 being low. This finding indicated that the ad was not well designed for the target audience [26]. The full set of metrics for the initial ad from social media campaign #1 is shown in Table 2.

In this post, the result rate was 1.9%, representing the ratio of engagements to impressions. Engagements are clicks, likes, shares, or comments. Impressions refers to an ad appearing in a newsfeed. The reach (11,052) represents the number of unique people who viewed the content. Of the 126 unique clicks, approximately 30 online contact forms were completed on the CRO landing page in the first five days. The initial advertising run, which included a three-day holiday weekend, resulted in 27 shares, 73 reactions, and 17 comments. This run also showed cost effectiveness, with a cost per engagement of US $1.23, compared to an industry average for medical campaigns of US $1.32 per click [27]. The clinical site reported results from the media outreach on a weekly basis during the recruitment period. Table 3 shows the results at the end of this initial week of paid Facebook posts.

Despite the high contact rate, most subjects failed the stringent inclusion and exclusion criteria for the study. However, this first iteration of the social media campaign successfully enrolled eight subjects and two alternates in the next dose cohort.

### Social Media Campaign #2 Results

The typical and altruistic campaigns shown in Figure 2 and Figure 3 produced the results shown in Table 4.

The ads from social media campaign #2 used color images, wording specifically chosen for social media, and keyword targeting. This campaign produced click-through rates of 2.79% for the typical campaign and 2.01% for the altruistic campaign.

### Total Campaign Results

Table 5 summarizes the metrics from the entire Facebook advertising campaign.

The overall campaign click-through rate of 3.37% shown in Table 5 exceeded the typical click-through rate range for clinical trial recruitment, which is 0.5-1.2% [28]. The CRO reported the following demographics for participants in the healthy elderly clinical trial, shown in Table 6.

With 29 women and 16 men participating, the study enrolled 64% women. The study overenrolled white subjects. White participants represent 81% of the southwest Michigan population in which the clinical site was located, whereas whites comprise 76.9% of the US population [29].

Table 7 summarizes the total number of inquiries made of the CRO about the trial by outreach form, as reported by the CRO. Of 857 inquiries into the clinical trial, Facebook outreach produced 72.5% (621/857) of them.

**Table 2.** Facebook metrics for initial boosted post shown in Figure 1.

| Metric | Total number |
|---|---|
| Impressions | 27,496 |
| Reach | 11,052 |
| Link clicks | 524 |
| Shares | 27 |
| Comments | 17 |
| Click-through rate, % | 1.9 |
| Cost per click, US$ | $1.23 |
| Frequency | 2.49 |
| Unique clicks | 126 |

**Table 3.** Summary of responses by medium in the first week of active Facebook advertising. CRO: Contract Research Organization.

| Promotional medium | Responses, end of week #1 |
|---|---|
| CRO website | 1 |
| Referral | 2 |
| Word of mouth | 2 |
| Facebook | 134 |
| Newspaper ads (3 papers, 3 cities) | 6 |
| Billboard | 4 |

**Table 4.** Facebook advertising results for typical and altruistic campaigns.

| Metric | Typical campaign | Altruistic campaign |
|---|---|---|
| Impressions | 44,659 | 31,080 |
| Reach | 22,288 | 11,488 |
| Link clicks | 1246 | 627 |
| Shares | 14 | 12 |
| Comments | 10 | 4 |
| Click-through rate, % | 2.79 | 2.01 |
| Cost per click, US$ | $0.91 | $1.27 |
| Frequency | 2.0 | 2.71 |
| Unique clicks | 1084 | 534 |

**Table 5.** Facebook metrics for advertising campaign targeted to healthy elderly people.

| Metric | Total number |
|---|---|
| Impressions | 454,284 |
| Reach | 142,228 |
| Link clicks | 15,322 |
| Shares | 140 |
| Comments | 87 |
| Click-through rate, % | 3.37 |
| Cost per click, US$ | $0.45 |
| Frequency | 3.19 |
| Unique clicks | 7004 |

**Table 6.** Demographics of enrolled subjects.

| Parameter | Total number |
|---|---|
| Enrolled subjects | 45 |
| Age range | 60-78 |
| Number of women | 29 |
| Number of men | 16 |
| White ethnicity, % | 90 |

**Table 7.** Total inquiries sorted by method of outreach. CRO: Contract Research Organization.

| Clinical trial inquiries | Number |
|---|---|
| CRO website and intranet | 81 |
| Facebook | 621 |
| Word of mouth/referral/event | 64 |
| Print/newspaper ads | 61 |
| Poster/flyer/direct mail/billboard | 30 |

## Discussion

The purpose of this report is to demonstrate the effectiveness of using sponsored advertising on Facebook to recruit people aged 60 years and older for clinical trial participation. Initial metrics showed that even with a low relevance score, the initial black and white ad used for social media campaign #1 (and shown in Figure 1) was twice as effective as average health care online advertising. The average click-through rate for health care marketing online is 0.83% [30] and this result rate was 1.9%. Moreover, the Facebook advertising tool proposed a potential reach of 7000, and the actual reach of 11,052 exceeded

this estimate by over 50%. Analysis of social media campaign #2 by gender shows that women slightly favored the altruistic campaign, and men favored the typical campaign. Results are shown in Table 8.

When considering the whole campaign, the engagement rate of men was slightly higher than the engagement rate of women, meaning that men were more likely to click on the advertisement than women. The advertising appeared to more women than men, with Facebook reporting that 71% of the impressions were to women. The results in Table 9 show this distinction of click activity by gender.

Facebook advertising can be a cost-effective method to recruit people aged 60 years and older into Phase 1 clinical trials. Respondents to the Facebook advertising campaign described in this report engaged with the sponsored advertising at a higher rate than younger adults engaged with social media advertising in other clinical trial recruitment studies [31].

In Table 10, metrics for this study are contrasted to two others: one involving young adults up to age 25 for a smoking cessation intervention [32]; and one aimed at young women, aged 16-25, regarding sexual health [21]. In contrast to people of younger ages, sponsored advertising for this campaign geared to healthy people aged 60 years and above prompted a notably high proportion of unique clicks to campaign reach. This finding affirms what other researchers have shown: people aged 55-64 are twice as likely to engage with sponsored Facebook advertising than younger adults [31].

The amount of commenting and sharing also exceeded typical standards. This advertising campaign received positive comments (posted on more than one ad) from a person who had completed the study. The effects of this are immeasurable and certainly rare [28]. The ads were monitored several times per day throughout the campaign, with most comments receiving some kind of timely acknowledgment or reply. Negative comments were unusual but did occur.

Minority enrollment in the study was not proportional to the US population and lagged behind the demographics of the population surrounding the clinical site. Reasons for low enrollment are not known but may relate to the demographics of Facebook users regionally, the images used for the Facebook ad campaign (which predominantly depicted white ethnicity subjects), and the gap in recruitment rates of minorities when recruiting older people in general [4].

**Table 8.** Comparison of responses by gender, and typical and altruistic campaigns.

| Response | Women | Men |
|---|---|---|
| **Typical campaign** | | |
| Reach, n (%) | 15,344 (69.48) | 6740 (30.52) |
| Clicks, n (%) | 827 (70.74) | 342 (29.26) |
| Click-through rate, % | 5.38 | 5.07 |
| **Altruistic campaign** | | |
| Reach, n (%) | 10,116 (88.92) | 1260 (11.08) |
| Clicks, n (%) | 587 (94.22) | 36 (5.78) |
| Click-through rate, % | 5.80 | 2.86 |

**Table 9.** Engagement and cost by gender for the Facebook advertising campaign.

| Total campaign | Women | Men |
|---|---|---|
| Impressions, n (%) | 322,185 (71.52) | 128,266 (28.48) |
| Reach, n (%) | 98,721 (70.04) | 42,227 (29.96) |
| Cost, total US$ (%) | 5200 (76.81) | 1570 (23.19) |
| Cost per click, US$ | $0.0526 | $0.0371 |
| Engagement rate, % | 3.06 | 3.29 |

**Table 10.** Comparison of engagement rates for advertising targeted to elderly and younger adults.

| Age groups | Campaign reach | Unique clicks | Clicks per reach (%) | Cost per click (US$) | Overall cost (US$) | Number of subjects needed |
|---|---|---|---|---|---|---|
| Healthy Age 60+ | 142,228 | 7004 | 4.92 | $0.45 | $6828 | 45 |
| Smokers age 18-25 | 961,131 | 5895 | 0.61 | $0.34 | $2024 | 230 |
| Females age 16-25 | 469,678 | 7940 | 1.69 | $0.67 | $5400 (estimated) | 200 |

**Table 11.** Inquiries made of a clinical trial, with and without Facebook advertising.

| Recruitment period | Number of weeks[a] | Facebook advertising campaign | Inquiries from all advertising[b] | Enrolled subjects |
|---|---|---|---|---|
| June 13 - August 28 | 11 | No | 178 | 6 |
| August 29 - October 25 | 8 | Yes | 691 | 39 |

[a]Approximated.

[b]Results provided by Contract Research Organization.

Other gaps in data stem from the relationship between the CRO and the sponsor. The Facebook advertising campaign was initiated by the sponsor, without extensive coordination with the CRO. The recruitment process was parallel but distinct, and specific recruitment data tracked by the CRO was not shared with the sponsor. In this study, the following are not known: how many people completed the online form compared to telephoning their interest, how many of the 621 responses attributed to the Facebook campaign were contacted for prescreening, the subjects' precise reasons for enrolling in the study, and how much money was spent by the CRO on more traditional forms of recruitment. Data that showed how the enrolled subjects learned of the clinical trial opportunity was not provided to the sponsor, so a cost-per-compliant participant from this Facebook campaign cannot be ascertained.

In this discussion, a sponsor with no prior presence on Facebook completed recruitment for a single-site, Phase 1 clinical trial following a Facebook advertising campaign. The Facebook advertising was used in addition to other forms of outreach and demonstrated effectiveness in recruiting qualified candidates, as shown in Table 11.

This study showed that interest in (and response to) a clinical trial focused on healthy elderly participants can be increased through a targeted Facebook advertising campaign.

## Conclusion

Results from this Facebook advertising campaign show that a sponsor who placed advertising on Facebook targeted to healthy people aged 60 years and older prompted enough interest in the clinical trial to successfully recruit a full cohort in a period of less than two months, thereby closing the gap created by clinical trial recruitment outreach using traditional methods alone.

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## Authors' Contributions

JMC conducted the Facebook ad campaign. MEG provided input on strategy for the ad campaign and had overall responsibility for the conduct of the clinical trial. JMC and MEG coauthored the manuscript.

## Conflicts of Interest

JMC and MEG own stock options in Tetra Discovery Partners, which is the sponsor referred to in this study. MEG is the founder, CEO and Chairman of Tetra. JMC is a consultant holding a long-term contract with Tetra.

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## Abbreviations

**CRO:** Contract Research Organization
**IRB:** Institutional Review Board

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Corrigenda and Addenda

# Correction for: Opening the Black Box of Electronic Health: Collecting, Analyzing, and Interpreting Log Data

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The authors of "Opening the Black Box of Electronic Health: Collecting, Analyzing, and Interpreting Log Data" (JMIR Res Protoc 2017;6(8):e156) would like to make a correction to Reference 42. The first author's name was incorrectly rendered as "van MT". The full reference should read:

42. van Mierlo T, Li X, Hyatt D, Ching AT. Demographic and indication-specific characteristics have limited association with social network engagement: evidence from 24,954 members of four health care support groups. J Med Internet Res 2017 Feb 17;19(2):e40

The corrected article will appear in the online version of the paper on the JMIR website on January 17, 2017, together with the publication of this correction notice. Because this was made after submission to PubMed or Pubmed Central and other full-text repositories, the corrected article also has been re-submitted to those repositories.

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